**Endocrinology**
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Paolo Sbraccia
Nicholas Finer *Editors*

# Obesity

## Pathogenesis, Diagnosis, and Treatment

Springer

# Endocrinology

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Within the health sciences, Endocrinology has an unique and pivotal role. This old, but continuously new science is the study of the various hormones and their actions and disorders in the body. The matter of Endocrinology are the glands, i.e. the organs that produce hormones, active on the metabolism, reproduction, food absorption and utilization, growth and development, behavior control, and several other complex functions of the organisms. Since hormones interact, affect, regulate and control virtually all body functions, Endocrinology not only is a very complex science, multidisciplinary in nature, but is one with the highest scientific turnover. Knowledge in the Endocrinological sciences is continuously changing and growing. In fact, the field of Endocrinology and Metabolism is one where the highest number of scientific publications continuously flourishes. The number of scientific journals dealing with hormones and the regulation of body chemistry is dramatically high. Furthermore, Endocrinology is directly related to genetics, neurology, immunology, rheumatology, gastroenterology, nephrology, orthopedics, cardiology, oncology, gland surgery, psychology, psychiatry, internal medicine, and basic sciences. All these fields are interested in updates in Endocrinology. The aim of the MRW in Endocrinology is to update the Endocrinological matter using the knowledge of the best experts in each section of Endocrinology: basic endocrinology, neuroendocrinology, endocrinological oncology, pancreas with diabetes and other metabolic disorders, thyroid, parathyroid and bone metabolism, adrenals and endocrine hypertension, sexuality, reproduction, and behavior.

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Paolo Sbraccia • Nicholas Finer
Editors

# Obesity

## Pathogenesis, Diagnosis, and Treatment

With 66 Figures and 31 Tables

Springer

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# Series Preface

Is there an unmet need for a new MRW series in Endocrinology and Metabolism? It might not seem so! The vast number of existing textbooks, monographs and scientific journals suggest that the field of hormones (from genetic, molecular, biochemical and translational to physiological, behavioral, and clinical aspects) is one of the largest in biomedicine, producing a simply huge scientific output. However, we are sure that this new Series will be of interest for scientists, academics, students, physicians and specialists alike.

The knowledge in Endocrinology and Metabolism almost limited to the two main (from an epidemiological perspective) diseases, namely hypo/hyperthyroidism and diabetes mellitus, now seems outdated and closer to the interests of the general practitioner than to those of the specialist. This has led to endocrinology and metabolism being increasingly considered as a subsection of internal medicine rather than an autonomous specialization. But endocrinology is much more than this.

We are proposing this series as the *manifesto* for "**Endocrinology 2.0**", embracing the fields of medicine in which hormones play a major part but which, for various historical and cultural reasons, have thus far been "ignored" by endocrinologists. Hence, this MRW comprises "traditional" (but no less important or investigated) topics: from the molecular actions of hormones to the pathophysiology and management of pituitary, thyroid, adrenal, pancreatic and gonadal diseases, as well as less common arguments. Endocrinology 2.0 is, in fact, the science of hormones, but it is also the medicine of sexuality and reproduction, the medicine of gender differences and the medicine of wellbeing. These aspects of Endocrinology have to date been considered of little interest, as they are young and relatively unexplored sciences. But this is no longer the case. The large scientific production in these fields coupled with the impressive social interest of patients in these topics is stimulating a new and fascinating challenge for Endocrinology.

The aim of the **MRW in Endocrinology** is thus to update the subject with the knowledge of the best experts in each field: basic endocrinology, neuroendocrinology, endocrinological oncology, pancreatic disorders, diabetes and other metabolic disorders, thyroid, parathyroid and bone metabolism, adrenal and endocrine hypertension, sexuality, reproduction and behavior. We are sure that this ambitious aim,

covering for the first time the whole spectrum of Endocrinology 2.0, will be fulfilled in this vast Springer MRW in Endocrinology Series.

Andrea Lenzi M.D.
Series Editor

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Series Co-Editor

# Volume Preface

Obesity is now the leading cause of preventable disease worldwide and continues to increase in prevalence. The ever-increasing list of complications of obesity affects every organ system in the body, from type 2 diabetes to nonalcoholic steatohepatitis and dementia. Increasingly it is recognized as a disease in its own right. Yet despite the importance of obesity as a disease, people with obesity are still underdiagnosed and undertreated and are subject to bias and stigma not just from society at large but also health-care professionals. The past decade has seen a major shift in the perception of obesity from being simply a matter of excess weight with largely mechanical complications to a chronic disease characterized by chronic low-grade inflammation driven by the active secretion of cytokines, hormones, and other factors from adipose tissue. Obesity is a true endocrine disease, and adipose tissue is the largest endocrine organ.

It is with this background that the editors have drawn together experts in the field to provide a timely and comprehensive resource to those wanting to expand their understanding of this twenty-first-century disease. There is much to learn in this rapidly evolving area of basic science, physiology, and translational medicine, with a growing number of treatment options for people with obesity. In the USA, Board Certification is well established as a specialty and the numbers of bariatric physicians growing in numbers and strength. Elsewhere, it is endocrinologists who are seen taking on this role, but they are often poorly resourced to provide the multidisciplinary and long-term care that patients with obesity need and should expect. We hope this book will enthuse endocrinologists, in particular but not only, into the exciting field of obesity medicine and encourage them to develop and strengthen their research and clinical involvement. The ultimate goal is to benefit every single patient with obesity and the public health at large.

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Professor Sbraccia is also currently serving as President of the Italian Federation of Endocrinology, Diabetology, Andrology, Metabolism and Obesity and as Vice President of the Italian Barometer Diabetes Observatory. In addition, he is Past President of the Italian Society of Obesity and a Member of the European Medicines Agency's Scientific Advisory Group on Diabetes/Endocrinology.

In 2011, on behalf of SIO, he coordinated the Steering Committee for the Italian Guidelines for the Management of Obesity, and in 2016 he was Editor of the book *Clinical Management of Overweight and Obesity: Recommendations of the Italian Society of Obesity (SIO)*.

Professor Sbraccia is also a Member of the editorial boards and reviewer panels of various scientific journals; in particular, he was recently Editor of the book "Clinical Management of Overweight and Obesity, Recommendations of the Italian Society of Obesity (SIO)" and coordinated an SIO steering committee for the Italian Guidelines for the Management of Obesity.

**Nicholas Finer** has been since 2016 Senior Principal Clinical Scientist with Novo Nordisk, Global Medical Affairs. He is also Honorary Clinical Professor in the National Centre for Cardiovascular Prevention and Outcomes within the Institute of Cardiovascular Science at University College London. Qualifying in Biochemistry and Medicine at University College London, Finer has held senior clinical and academic appointments as an Endocrinologist and Obesity and Internal Medicine Physician at UMDS Guy's and St Thomas' Hospitals, Luton and Dunstable Hospital NHS Trust, University of Cambridge, and University College Hospital London. Nicholas Finer is an elected Fellow of the US Obesity Society and of the UK Association for Nutrition; in 2013 he received the Bisset Hawkins Medal "for work in advancing sanitary science or in promoting public health" awarded by the Royal College of Physicians. Finer chaired World Obesity – Clinical Care until 2015, developing the SCOPE educational program. He is Past Chair of the UK Association for the Study of Obesity. Finer coauthored the Royal College of Physicians report "Action on Obesity: Comprehensive Care for All" and was a Member of the UK Government Advisory Group on Obesity, the Clinical Reference Group that advised NHS England on commissioning of specialist obesity services, and the NICE Public Health Advisory Group. Finer is Editor-in-Chief of Clinical Obesity and has published more than 200 peer-reviewed papers and lectured extensively on obesity and its complications as an internationally invited speaker.

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# Epidemiology of Obesity

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W. P. T. James

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**Abstract**

Obesity, although recognised millennia ago as an unusual feature and a societal handicap, only since the 1980s has it become a major clinical and public health problem. Originally a disease of affluence it became evident in poorer countries in the 1990s with children then showing increasing evidence of their excess weight gain with all its propensities to premature disease and death. Obesity rates are

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rising rapidly in poor countries with clear evidence that many societies are more prone to obesity's amplification of diabetes and hypertension rates than in Western Europe and North American. These differences probably relate to the impact of poor fetal and early nutrition as well as infections on development and the epigenetic control of metabolism. The epidemic was precipitated by dramatic rises in the mechanisation and computerisation of labour, household work and home entertainment combined with a huge drive to market readily prepared high energy dense fatty, sugary and salty foods and drinks. Now dietary factors dominate global health burdens and obesity overwhelms health services with the global societal cost estimated as $2trillion a year, approximately the same as the cost of all warfare and conflicts. Only coherent government initiatives can reverse these burdens with little evidence so far of any appropriate national or international response.

**Keywords**
Anthropometric indices · Obesity · Morbidity · Mortality · Prevalence · Burden of disease · Economic cost · Prevention

## Introduction

In this chapter there will be a focus on the overall societal patterns of obesity and how we are seeing a shift in the spectrum of the human body's structure linked to both immediate environmental factors and those long-standing effects which have led to both genetic selection and involved epigenetic programming as well as generational structural changes in the composition of the body with associated morbidity and epidemiological effects. The societal health burdens and their economic implications will be outlined before finally considering the implications for the key potential components of prevention stemming from this epidemiological understanding.

## History

This has been exceptionally well covered by Bray (1997) who pointed out that there were images of obesity perhaps as deities in Europe from prehistoric times about 23,000–25,000 years ago with further images in the early agricultural period 5000–6000 years BC in Mesopotamia and later in Egypt by which time obesity was already seen particularly in the ruling classes and was considered objectionable rather than representing a wonderful god-like status. Chinese and Indian medicine also dealt with obesity as a problem condition before the Roman Galen distinguished between "moderate" and "immoderate" obesity. So for centuries physicians have sought to engage with the problem of obesity and its causes with attention paid to genetic factors by assessing the familial propensity to obesity and then twin studies. But it was Quetelet in 1835 who assessed man's size on a population basis by

developing the idea of standardizing people of different sizes by deriving the index $W/H^2$ in metric units, now termed the body mass index, whereas Livi later that century suggested the cube rather than the square of height should be used since weight reflected a three-dimensional being. This ponderal index was simply converted to a corpulence measure (not index) $W/H^3$ by Rohrer and is now often called the ponderal index.

## BMI and Mortality Risk

The health implications of being too heavy were first made coherent with analyses of the mortality risk from the insurance industry in the USA published in 1915. Large tables were developed with weights and heights given in imperial units where weights corresponding to the appropriate low mortality range quoted for the individuals' height (with the men and women measured lightly dressed and wearing shoes). Repeated analyses by the Metropolitan Life Insurance Company followed with the analyses being divided at each height into adults of small, medium, and large frame sizes. By the 1960s population analyses were being assessed for the relative benefits of different indices, but by 1972 Ancel Keys, using some of his and colleagues' Seven Country data and other small surveys, concluded that the $W/H^2$ measure was suitable for general use. At the same time the BMI measure was being assigned to the USA insurance mortality data and checked in relation to the very large Build Study from the USA by a UK Government group (James 1976) which assigned BMI "normal" weights as between 19.1 and 24.6 for women and 19.7–24.9 for men, these BMIs corresponding to the lowest mortality values with obesity conventionally taken as 20% above the normal weight. These figures were then simplified by Garrow using BMI 20–25 as a normal BMI for clinical use as was then proposed by the US Fogarty Conference in 1973 (Bray 1976).

By 1983 the importance of a distinction being made between smokers and nonsmokers was evident in the analyses of the London Royal College of Physicians working party (Black 1983; Fig. 1) which showed that smoking men of normal weight had a mortality rate which was equivalent to that of nonsmoking obese men. It was also recognized that smokers were usually thinner than nonsmokers because smoking induces an increase in metabolic rate as well as reducing appetite (Dallosso and James 1984). Therefore ignoring the different relationship between BMI and mortality in smokers leads to the common finding that the lowest mortality rate seems to be when BMIs are about 27–30, because the thinner smokers in the lower BMI ranges have an increased mortality. Since then large detailed integrated multinational studies taking account of smoking and involving almost a million individuals from 54 international studies have confirmed that a BMI of 25 is an appropriate crude upper limit of normal or what should more accurately be termed "acceptable" body weights (Prospective Studies Collaboration 2009).

This approach to the health impact of excess weight assessed as BMI has for many decades been recognized as crude, and clinicians and body composition experts have always highlighted the crude nature of the correlation between BMI

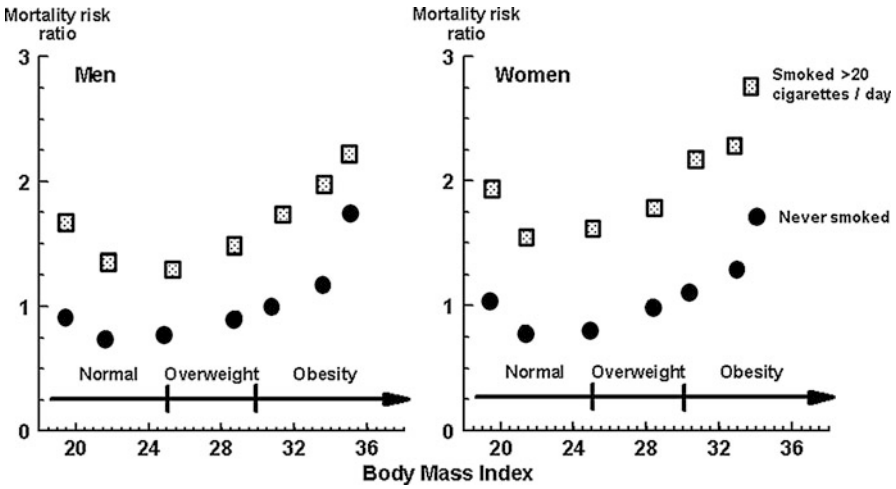


**Fig. 1 The need to differentiate the effect of smoking and body weight on mortality**. The mortality risk of those smoking >20 cigarettes/d (in red) is compared with those who have never smoked (blue) in relation to their respective body weights (Data taken from the London Royal College of Physicians Report on Obesity (see Black 1983))

and body fat. Ancel Keys and his colleagues were highlighting 60 or so years ago how the presence of blood pressure, smoking, and high blood cholesterol levels were far better predictors of deaths from coronary artery disease with the contribution of BMI making little extra difference (Keys et al. 1972). More recently the stronger association with other risk factors than with the crude measure of BMI together with assessments of any progressive organ damage has been shown to produce a far better classification of mortality (Sharma and Kushner 2009; Padwal et al. 2011).

## BMI and Morbidity

The relationship between BMI and the health impact of excess weight has often been confused with the original BMI criteria relating to mortality risk. The "normal" range of BMIs, e.g., 20–25, does not give a suitable range for the lowest risk, for example, for hypertension, diabetes, coronary artery disease, or cancer, as these conditions not only depend on other environmental factors, e.g., salt in relation to hypertension or excess intakes of specific saturated fatty acids for coronary heart disease and a multiplicity of environmental factors leading to cancer, but also is roughly linearly related to BMI levels down to about 20. This implies that there are environmental factors which often combine to promote both weight increase and the concomitant disease, and indeed weight loss can often ameliorate the disease but whether this is the loss of body fat per se with all its hormonal and metabolic consequences or in part the parallel effects of the dietary changes needed to reduce the severity or impact of the concomitant disease is often not clear.

Nevertheless some of the conditions do seem to depend to a substantial extent on clear factors linked to body weight, e.g., the propensity to develop diabetes seems to relate to the duration of being overweight/obese as well as the magnitude of excess weight, (Abdullah et al. 2016) and reducing body weight has been found to be a critical factor in limiting the development of diabetes in those overweight/obese individuals at high risk of diabetes (He et al. 2015). Furthermore hypertension can be ameliorated by weight loss, and this may not just reflect the reduction in food intake and therefore sodium ingestion but also the change of diet with more potassium-rich fruit and vegetables. Nevertheless there are clear hormonal factors involving the angiotensin-renin system that also play a part.

## Refining the Anthropometric Indices of Excess Weight and Their Relationship to Disease: The Value of Waist Measurements

For decades the importance of body shape as well as size as a predictor of disease risk has been highlighted with an original emphasis on the selective increase in the dimensions of the waist or hips. Then attempts were made to simplify clinical approaches by focusing on the waist measurements with the Scottish clinical management committee stimulating Han and colleagues to develop a set of waist measurements corresponding epidemiologically with the BMI 25 and 30 measurements in a population of young Dutch adults (Han et al. 1995). These values were incorporated tentatively into the first comprehensive World Health Organisation (WHO) report on obesity (WHO 2000) and have been widely used and incorporated, e.g., by the US National Institutes of Health (NIH) into appropriate body weight and shape standards relating to risk (National Institutes of Health 1998). Later the INTERHEART international study revealed that waist and waist/hip (W/H) ratios were a better index of the risk of coronary heart disease than BMI (Yusuf et al. 2005) with marginally better statistical if not practical predictability with the use of W/H values as increased hip values seem to be a protective of heart disease, perhaps relating to the body's ability to store fat safely. This has been repeatedly confirmed with some suggestion that waist for height in metric units with a simple ratio cutoff of 0.5 rather than hip circumference is a better predictor of disease risk factors, e.g., dyslipidemia, increased blood glucose levels, or higher blood pressures (Ashwell and Gibson 2016).

## Broadening the Acceptable BMI Limits and the Greater Sensitivities to the Morbidity Impact of Weight Gain in Non-Caucasian Communities

By 1995 it had been accepted by WHO that the normal lower limit of adult BMI should be reduced to 18.5 in the non-Western world, i.e. the majority of the global population adults were much thinner but seemed healthy and able to sustain beneficial manual work, e.g., in agriculture at BMIs of 17–18.5, but evidence from South

American, African, and Asian analyses of morbidity showed an increased susceptibility to infections and time off work when BMIs were below 17.0. Mortality rates were observed to be increased when BMIs were below 16.0 so these became the BMI cut-off measures for undernutrition in adults (James et al. 1988; Ferro-Luzzi et al. 1992). The cutoff of 18.5 was chosen because it was shown that this seemed reasonable because populations with a median BMI of 20 had only about 10% of adults (but in practice with slightly more women than men) with BMIs of less than 18.5 and about 10% of adults with BMIs more than 25 (this time with more men than women). Yet concerns relating to obesity were still dominated by assessments in Western, i.e. European and North American, communities so when the international technical expert group met in WHO in 1997 to consider the problem of obesity (WHO 2000) the Japanese and other Asian experts' proposal to have the upper acceptable BMI limit reduced from 25 to 23, on the grounds that Asian communities were much more prone to the comorbidities associated with weight gain at much lower BMIs, was rejected. So, in the absence of coherent evidence to support the Asian proposition, the "acceptable" BMI range was maintained at 18.5–25.0. WHO then did hold an expert discussion in Singapore (WHO 2004) where attempts were made to see if one could define different societies by their relative body fat content in the usual BMI range of 18.5–24.9 as it seemed that many Asian communities had a smaller skeletal but a larger fat mass at the same BMI (Deurenberg et al. 2002; Deurenberg et al. 2003). However, it was recognized that not only were there few nationally representative data on the body composition of different ethnic groups but in addition Chinese children in Beijing and in Singapore had different body fat contents as did the rural and urban Thailand adults. This suggested that the differing body composition in similar ethnic groups was not an intrinsic ethnic feature but in some way reflected the response to some environmental factors. Nevertheless the WHO group in Singapore suggested that an upper normal BMI limit of 23 rather than 25 might be adopted by at least some Asian governments as the operational norm, and the Japanese and Indian governments now use these criteria. However, the newly formed Chinese obesity collaborative group led by the Prime Minister's advisor, Chen Chung Ming, concluded, after their own health analyses, that a BMI of 24 was most suitable in China (Chen 2008).

The basis for the concern that Asians in general were more sensitive to the comorbidities of weight gain already had been demonstrated in an earlier small UK study showing that the selected South East Asians were more prone to diabetes at lower degrees of obesity than British Caucasian adults (McKeigue et al. 1991). Then a major analysis of about 263,000 adults across Asia including the Chinese, Koreans, Japanese, Indonesians, Thais, and Indians showed that Asians, when considered as a group, were more prone to diabetes and indeed their waist or waist/hip ratios or waist/height ratios were better predictors of diabetes and hypertension than BMI with the Asians more prone to abdominal obesity at the same BMI (Huxley et al. 2008). This same phenomenon was then observed in Mexicans when compared with USA non–Hispanic whites (Sanchez-Castillo et al. 2005; see Fig. 2) and in the African diaspora. African Americans not only have higher BMIs than whites or Hispanics but their diabetes rates are even higher than one would expect for

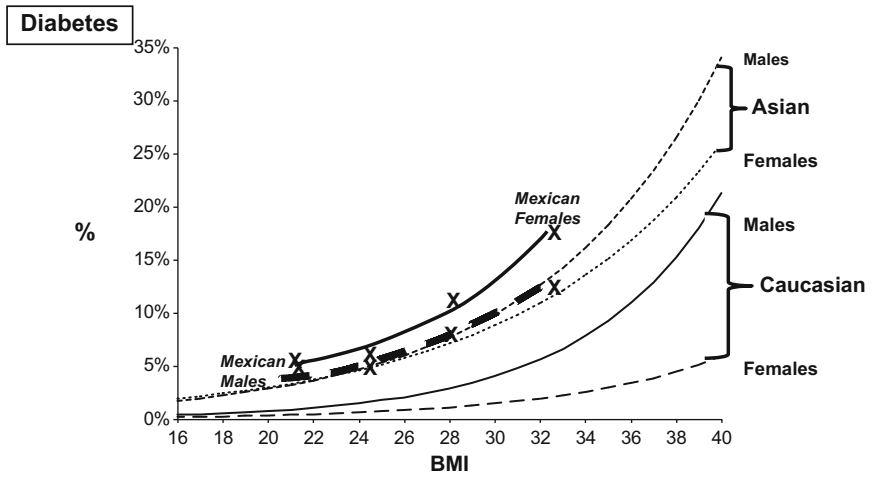


**Fig. 2 The relationship between the BMI of Asians and Mexicans when compared with Caucasians**. The comparison of the Asians with Caucasians (mostly Australasians) was set out by Huxley et al. (2008) and the representative Mexican data are derived from the 2000 national survey and compared with representative measured data from the age-matched US non-Hispanic white population (Sanchez-Castillo et al. 2005). The US data for non-Hispanic whites, used for the comparison with Mexican analyses, are almost identical to the Caucasian data shown and therefore have not been included in the graph

their greater size (Shai et al. 2006). Attempts to identify a genetic basis for this have so far been unsuccessful (Yako et al. 2016) with studies of the African diaspora also showing marked differences in glucose metabolism in different communities eating different diets and with objectively measured differences in physical activity (Atiase et al. 2015). However, studies even of the seemingly genetically obesity prone PIMA Indians from Mexico and Arizona in the USA show that with similar genetic profiles their dramatic national differences in BMI and diabetes prevalences were largely environmentally determined (Schulz and Chaudhari 2015) with very low obesity and diabetes rates in the hard working, home farming Pima Mexicans consuming a 25% fat, high fiber diet with a negligible sugar content (Chaudhari et al. 2013).

## Secular Trends and Sex Differences in Obesity's Prevalence

Although, as noted earlier, adult obesity had been recognized as a clinical problem for centuries it did not emerge as a substantial health issue until the second half of the twentieth century when an appreciable number of middle-aged adults (usually women) started complaining about their inability to lose weight with doctors noting that they had a number of disabilities including back ache, arthritis, and breathlessness, i.e., comorbidities understandably linked to their excess weight. National or employee surveys in the UK suggested that the average BMI of men and women started to rise first in late middle age, i.e., the 50–65 year group from about the early

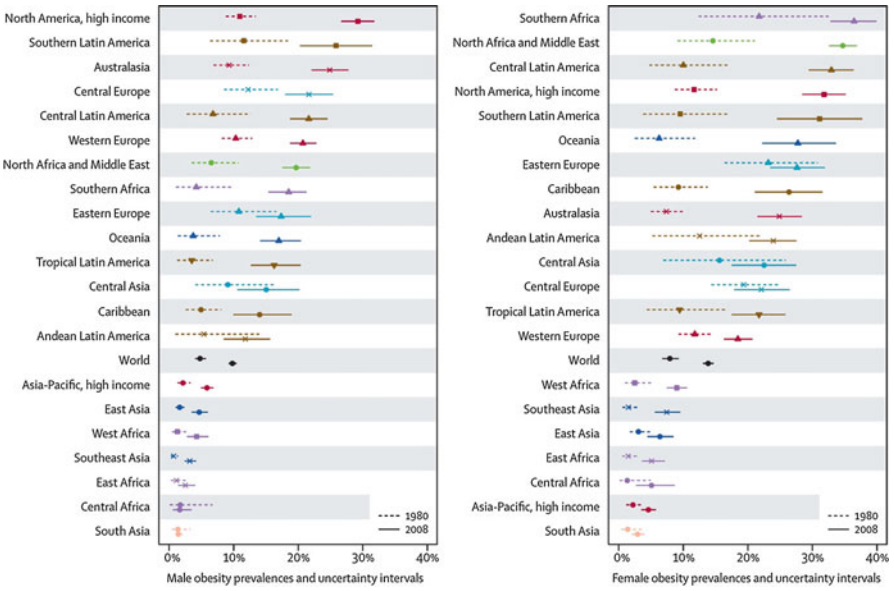


**Fig. 3 The global epidemic of obesity in adults)** Figure taken with permission from Finucane et al. (2011) showing the regional age standardized prevalences of obesity in men and women measured first in 1980 and again in 2008

1960s, but in the USA postwar data from the 1959 Build and Blood Pressure Study of the Society of Actuaries was already showing evidence of obesity although the terms for their definition at that time included adults with BMIs over about 27.5 and therefore would have included some more muscular males involved in the manual work common at that time. Internationally it was also clear that some societies, e.g., the Polynesian women and African women in South Africa and the Caribbean, already had high obesity rates in the 1960s by the time they were middle aged (Christakis 1975). By the 1980s, however, obesity as a public health problem was becoming very evident and since then there have been numerous studies and analyses across the globe showing the escalation of obesity globally (Finucane et al. 2011; Fig. 3). Note the sex differences in the responses to the new "obesogenic" environment and that lower-income regions are now often showing much higher obesity rates than Western Europe, for example, particularly in women.

Although there was widespread concern about the prevalence of obesity in the year 2000 recent analyses clearly show that the greatest increases in the prevalence of obesity are in proportion to the previous prevalences, i.e. countries with the highest prevalences have been showing the greatest increases (Dobbs et al. 2014; see Fig. 4). So clearly there is a need to understand the underlying forces for such a marked relationship. When national data are now considered in detail it also becomes clear that the populations in lower-income countries and particularly in Asia are currently seeing explosive increases in obesity with women's obesity rates usually exceeding those for men (Stevens et al. 2012). Although these sex

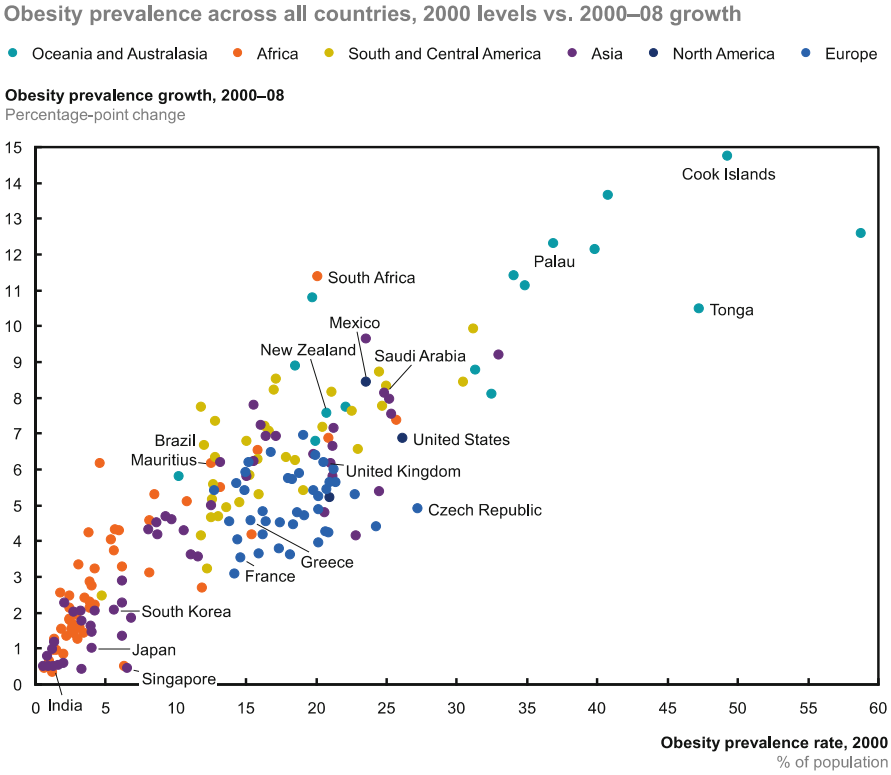


**Fig. 4 Obesity prevalence growth has momentum: countries with the highest prevalence in 2000 experienced the most subsequent growth in prevalence.** (Taken from the McKinsey Institute report on obesity (Dobbs et al. 2014)

differences in the propensity to obesity are usually ascribed to environmental factors, it is also evident that women are more prone biologically to develop obesity when energy imbalance occurs because their capacity to accrete lean tissue, e.g. muscle with its increased 24 h resting energy demands, means that sustained excess energy has to be accumulated as more fat in women (James and Reeds 1997).

## Children's Criteria for Normal Weight Gain and Obesity

Childhood obesity was recognized early on in seemingly genetically distinct and often unusual cases but children in society as a whole only began to display marked weight gain from about the early 1980s. When the WHO group met in 1997 to deal with obesity in general it had to focus on adults as at that time there seemed no clear readily accepted definitions of obesity in children although an earlier WHO group, set up originally to deal with anthropometric issues relating to childhood malnutrition, had arbitrarily used the conventional WHO 2 SD cutoff points for designating

abnormal findings (WHO 1995). Therefore the International Obesity Task Force (IOTF) established a group which assessed the options and recognized that the use of the BMI as a measure of appropriate body proportions in children was crude. The choice of 2 for the power of height in the BMI calculations was shown not to be really appropriate except at about the age of 6 and ideally should have been different at younger and older ages (Franklin 1999). Nevertheless the BMI was agreed as the best simplified option, and the IOTF developed criteria by linking the percentile curves of BMIs of children from age 2 to 18 years to adult BMI cutoffs at the age of 18 with BMIs of 25 and 30 and then finding the corresponding percentiles for boys and girls at each age in an integrated set of nationally representative data for children from six countries where there were meticulous measurements of children at a time when obesity was not considered a problem, i.e., in early USA and British data, plus survey data from the Netherlands, Hong Kong, Brazil, and in addition in Singapore where there was some concern and where ideally these data should perhaps not have been included in the reference percentile curves (Cole et al. 2000). This set of age- and sex-specific reference points then made the analyses of population obesity rates coherent and multiple analysts have used these criteria for several years.

Assessments of childhood overweight and obesity prevalences, using the IOTF cut-points on representative or community surveys in Australia going back over a century[iii](38), clearly show that obesity suddenly emerged in the early 1980s in Australia and also in lower income countries after a short interval. The childhood epidemic is now evident in all 5 continents (see Fig. 5; Lobstein et al. 2015) and has continued to escalate particularly in poorer countries where there is little or no effort as yet to combat the problem.

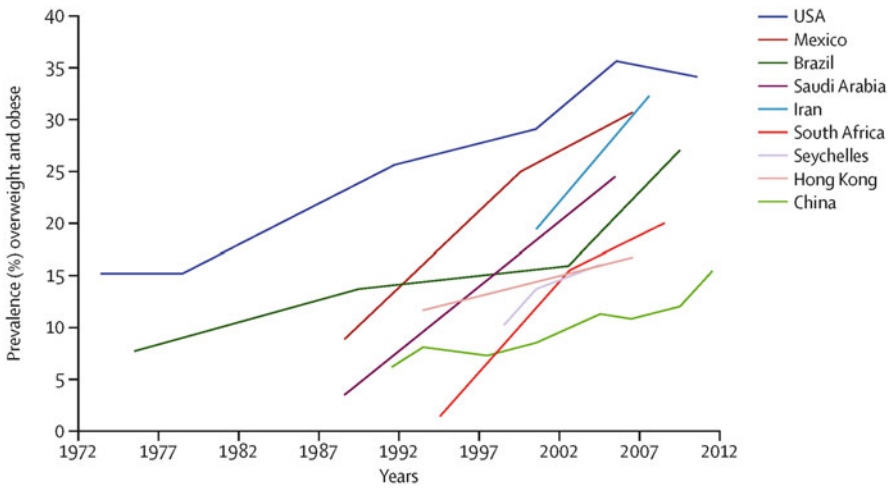


**Fig. 5 The childhood obesity epidemic**. New analyses of the emergence of obesity in children in lower-income countries compared with the USA (Taken from Lobstein et al. 2015)

More recently WHO established their own criteria for childhood overweight and obesity and used the birth to 5-year-old data from a meticulously organized six-nation international study of normal weight babes at birth who were then exclusively breast fed for the WHO specified optimum time of 6 months before being weaned onto appropriate diets and then followed up. The astonishing finding was the babes born in Norway, India, Oman, Ghana, Brazil, or the USA had amazingly similar growth rates with no discernable national differences at all (WHO 2006; WHO and Multicentre Growth Reference Study Group 2006). So these could now provide not just arbitrary reference cutoffs but a standard specifying how children anywhere in the world should grow optimally. Then WHO staff took adjusted old 1977 USA BMI values with some selection for 5–19-year-old children as the reference values so that the one standard deviation (ISD) of the USA data reference corresponded to BMIs of 25 at 19 years and the 2SD BMI value was about 30. Unfortunately WHO then specified as "overweight": only those children below 5 years with BMIs >2SD above the median whereas this "overweight" designation from 6–19-year-old was so designated when the BMI was above >1SD not 2 SD, with the latter limit now being designated as "obese" and therefore roughly corresponding to a BMI of 30 when adult. The differences of the new WHO BMI reference points and those of the IOTF and CDC seemed small, but the WHO approach has been heavily criticized by Cole and Lobstein who also developed a complete profile of percentiles corresponding to all the degrees of overweight and obesity as well as underweight designated for adults by WHO but based on their six nationally representative global data sets (Cole and Lobstein 2012). On this basis the different degrees of childhood obesity and underweight can be calculated for all societies.

## Intergenerational Amplification of Obesity and Cohort Effects on Childhood Obesity

The probability that an overweight or obese child remains in the same category when adult rises markedly the longer they remain too heavy as adolescents. This then amplifies their future risk of both diabetes and cardiovascular disease (Baker et al. 2007). More recently it has become evident that mothers entering pregnancy when overweight and then putting on substantial amounts of weight in pregnancy are more likely to produce larger babies who then more readily become overweight in early childhood with further tracking of the excess weight into early adult life (Institute of Medicine 2009). This then means that cohorts of bigger babies and more overweight children are now emerging and one can now distinguish between the cohort effects and the impact of an adverse "obesogenic" environment in each age group in a population study – see Fig. 6 (Allman-Farinelli et al. 2008). However, when these overweight children/adolescents mature and themselves conceive there is then developing an intergenerational cycle of increasing childhood obesity within a population and this problem is going to be very difficult to reverse. These analyses are now being applied in several countries, e.g. the USA, (Reither et al. 2009) and are emphasizing the impact of early fetal changes reflecting the epigenetic and perhaps physiological

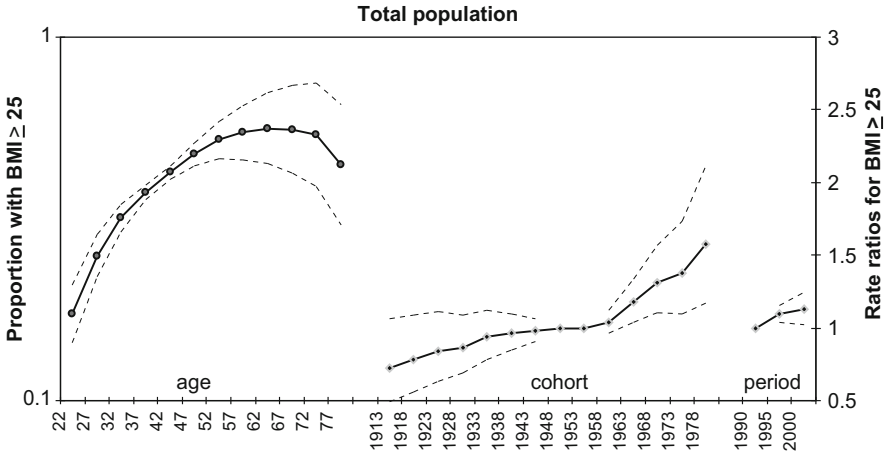


**Fig. 6 An analysis of repeated surveys of children in Australia analyzed to distinguish between the age relationship (in months), the cohort dependent, and the secular (period) effects on the degree of overweight** (Taken from Allmann-Farinelli et al.) On the *left* is the age (in months)-related increase followed by the cohort effect which is set out in terms of the cohorts born in different years (between 1913 and 1978) and on the *right* is the period effect showing the change in impact of the environment between 1990 and the year 2000

programming of generations at the early phases of fetal development, particularly during the setting of the trajectory of fetal growth. The basis for these epigenetic changes is now under intense investigation but these changes imply that the physical as well as the metabolic and nutritional state of young women is also very important at the time when they conceive. These findings also imply that the future epidemic may only be prevented long term if we focus on the well-being and BMI status of young women as a whole. Given the prevalence of unplanned pregnancies the general well-being of young women within the whole population becomes important.

This intergenerational effect not only relates to a successive amplification of the maternal overweight problem but studies from lower-income countries show that maternal malnutrition also has profound effects on the fetus with, in the Indian subcontinent, a reduction in the growth of lean tissues within the fetus with an excess body fat content even if the baby is born small (D'Angelo et al. 2015). There is also a marked tendency to abdominal obesity with its amplified risks of glucose intolerance and hypertension (Yoo 2016). This maternal malnutrition therefore may in part explain the ethnic differences in the propensity to diabetes on weight gain in different communities.

## The Burden of Disease Associated with Obesity

The handicaps associated with obesity are many with several more continuing to be added as careful studies document the extent of the obesity handicap. So, for example, it is becoming clear that obese individuals are more susceptible to

infections sometimes for mechanical reasons, e.g., their greater difficulty with breathing, increased gastric reflux leading to lung infections, and their greater skin infection problems. In addition there seem to be changes in immune function with a greater intrinsic susceptibility to the acquisition of an infection and to the development of greater complications when infected with a greater resulting need for more frequent hospitalization. So there is an increased risk of urinary tract infections, of gastric helicobacter pylori infection, and pancreatitis as well as a greater risk of severe infections in obese subjects when suffering from trauma. Objectively the failure to mount an appropriate immune response is also shown by the far poorer antibody responses to vaccination with most vaccines although the response to influenza vaccine is not necessarily poorer in the obese (Tagliabue et al. 2016).

In addition to a greater susceptibility to infections in obesity there is also the well-documented increased risk of developing diabetes, hypercholesterolemia, and high blood pressure with therefore an increased propensity to coronary heart disease and strokes (see ▶ Chap. 11, "Obesity, Hypertension, and Dyslipidemia"). These increased risks are amplified by the usual finding that overweight/obese individuals also have a poor diet which also influences their tendency to increased blood uric acid levels and the risk of gout. There is also an increased likelihood of nonalcoholic fatty liver (see ▶ Chap. 4, "Roles of Gut Hormones in the Regulation of Food Intake and Body Weight" Van Gaal) and when sugary diets are consumed of more dental caries.

## Weight Gain, Obesity, and the Risk of Several Cancers

It has also long been recognized that excess weight gain increases the likelihood of developing several cancers. These have been carefully characterized by the World Cancer Research Fund (WCRF) in exhaustive and systematically updated epidemiological analyses (World Cancer Research Fund/American Institute of Cancer Research 2007) backed usually by an understanding of a clear plausible mechanism. Some cancers are considered "convincingly" linked to excess weight gain and others are "probably" linked (see Table 1). The degree to which one can be confident that these relationships apply biologically was in practice based on the consistency of multiple cohort studies. This approach is, however, fraught with problems of interpretation, because they depend on the accuracy of dietary measures such as food frequency questionnaires often made many years beforehand and even if repeated are very subject to systematic as well as random measurement errors as well as secular changes in eating habits. Few long-term studies are available with biomarkers of dietary intake. There are the additional problems that when comparing two groups with different diets there may be several other characteristics that in part explain their different outcomes, and it is not always possible to identify these adequately. There is also the issue of how to cope with the intrinsic biological differences in the way in which individuals respond to the same intake or change in diet. This has long been recognized as exceptionally important when considering, for example, the blood low density lipoprotein (LDL) cholesterol responses to a

**Table 1** The World Cancer Research Fund/International Cancer Research Fund analyses of the relationship between excess weight gain and its effect in inducing cancers

| |
|---|
| Convincing evidence of weight gain inducing cancers of: |
| Esophagus (the adenocarcinoma type associated with gastric reflux) |
| Pancreas |
| Colorectum |
| Postmenopausal breast |
| Endometrium |
| Kidney |
| Liver |
| Advanced prostate cancer |
| Evidence of a probable induction of cancers of: |
| Gallbladder |
| Ovaries |
| Cardia part of the stomach |
| Probable decreased risk |
| Premenopausal breast |
| Cancer survival: |
| Increased risk of mortality in premenopausal and postmenopausal women when overweight or obese once breast cancer is diagnosed |

Data taken from the original WCRF/AICR 1997 (Yoo 2016) analyses but updated from their continuing analyses see: http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports

defined intake of saturated fats where some individuals will show a fivefold greater increase in LDL cholesterol levels than others. Therefore a cohort study with perhaps at most a two to threefold range in diets within a community usually is unable to show a relationship between saturated fatty acid intakes and coronary heart disease even when it is clearly established that an increase in LDL cholesterol is causally linked to the development of coronary heart disease. This is but one example of the range of individual metabolic responses to the same intake of many different nutrients, these responses being determined by both genetic factors and the magnitude of enzyme systems which may in part be determined by the mass of that organ conditioned by physical activity in the case of muscle or by a sustained change in intake inducing a substrate amplification of the relevant pathway. So the problem with the analysis of cancer risks is that we do not often have a really good understanding of the causal mechanisms so we can see which environmental factors interact with this mechanism and either amplify it or inhibit it.

The magnitude of the potential environmental impact on the development of cancers can be seen when one compares the 10-fold differences in the age- and sex-matched differences in the incidence of, for example, breast and colorectal cancer in Japan versus the USA when first measured 50 years ago by cancer registries. Furthermore studies within Japan showed a fourfold increase in colon cancer over a period of 30 years, and migrant studies also clearly show the increasing propensity to both breast and colon cancer when Japanese migrate to the USA. Subsequent

**Table 2** World Cancer Research Fund updated estimates of preventability (PAF%) of cancers of which body fatness is a cause in the UK, USA, China, and Brazil

| Cancer type | USA | | UK | | Brazil | | China | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| Esophagus (adenocarcinoma) | 37 | 30 | 35 | 20 | 26 | 14 | 19 | 7 |
| Stomach (cardia) | 18 | 27 | 18 | 20 | 13 | 14 | 10 | 8 |
| Pancreas | 17 | 20 | 14 | 16 | 8 | 13 | 5 | 10 |
| Gallbladder | 11 | 28 | 8 | 21 | 3 | 15 | 2 | 10 |
| Liver | 27 | 28 | 22 | 19 | 11 | 13 | 6 | 7 |
| Colorectum | 17 | 15 | 15 | 13 | 10 | 11 | 8 | 9 |
| Breast (postmenopausal) | – | 17 | – | 16 | – | 14 | – | 12 |
| Ovary | – | 5 | – | 4 | – | 3 | – | 1 |
| Endometrium | – | 50 | – | 38 | – | 5 | – | 4 |
| Prostate (advanced) | 11 | – | 9 | – | 5 | – | 4 | – |
| Kidney | 20 | 28 | 17 | 21 | 10 | 16 | 6 | 10 |
| Total of these cancers | 21 | 21 | 16 | 17 | 12 | 14 | 12 | 10 |

Using numbers of new cases of cancer diagnosed annually from GLOBOCAN 2012 for both men and women combined this translates to about 117,000 cases of cancer in the USA, about 23,000 for the UK, about 17,000 for Brazil, and about 99,000 for China being preventable if everyone had a healthy weight

Based on the WCRF 2009 approach but updated see: http://www.wcrf.org/int/cancer-facts-figures/preventability-estimates/cancer-preventability-estimates-body-fatness

generations display cancer rates which increasingly converge with those in USA Caucasians. Yet in cohort studies we only seem to be able to discern a 50% increased propensity to breast or colorectal cancer with particular diets. This probably means that not only are the dietary studies flawed but also that we have not begun to take account of the differences in the propensity of different individuals to have a fivefold or more differences in those reactive metabolic processing pathways which lead to cancer for reasons both genetic and epigenetic relating to both paternal and maternal environmental factors. So we probably have grossly underestimated the dietary and perhaps the BMI-related effects on cancer propensity. Table 2 illustrates the results of an approach to distinguishing the contributions of an increase in BMI to the risk of the cancers in different affluent and middle-income countries based on the approach set out by WCRF in 2009 (World Cancer Research Fund/American Society for Cancer Research 2009) but now updated on the basis of new analyses.

## Functional Impairments

Although it has long been recognized that diabetes, hypertension, and some cancers are much commoner in the overweight and obese, it is the constraints on people's

mobility that they first notice with their very high prevalence of backache and the greater extent and degree of arthritis especially of the knees, hips, and ankles induced at least in part by their excessive weight gain. However, there is also evidence that arthritis of the hands is more common – perhaps another sign of the impaired immune response in the obese. The pain on movement and patient's breathlessness explains a substantial part of their everyday immobility and distress.

However, there is the additional mental burden often induced by their sense of failure to reduce weight accompanied by the widely recognized public disapproval in affluent societies. Candidates for a job appointment or for promotion within almost any field are likely to fare worse if they are overweight or obese. Obese individuals have therefore, perhaps not surprisingly, been documented to be less productive when at work and to have more time off work. They also often feel depressed and suffer from a greater sense of isolation from society. To add to their personal burden they are likely to retire early, to remain isolated from society, and to suffer earlier the first stages of brain aging with earlier signs of cognitive decline with later dementia in part seemingly related to the brain's considerable sensitivity to insulin (Kullmann et al. 2016) and the increasing brain insulin resistance as weight gain occurs. This brain insulin resistance brings functional handicaps which are also evident in those overweight/obese individuals who have progressed to type 2 diabetes. Patients with type 2 diabetes display impaired mental performance in almost all neuropsychological tests with the greatest impairments being found in memory, information-processing speed, and executive function. These problems are in part reversed rapidly with bariatric surgery (Handley et al. 2016) implying that the insulin resistance effect may be important. However, there is also more progressive brain atrophy with aging with obesity, and the accompanying impact of atherosclerotic changes in the cerebrovascular circulation contribute substantially to the progressive cognitive decline in obesity.

## Calculating the Burden of Disability and Premature Mortality

The standard approaches used by WHO and others to estimate the overall burden of disease in a society involves calculating the number of years of life lost (YLL) by premature deaths. This was originally taken by WHO as the number of years lost before the age of 75 years, but more recently Murray and colleagues in Seattle (GBD 2015 DALYs and HALE Collaborators 2016) have simply taken the longest life expectancy of any group of more than 5 million within a particular geography. To these YLL lost can then be added the years during which individuals were handicapped by disabilities to give the total number of years of disability and yours of premature death. This sum is called the Disability Adjusted Life Years (DALYs) lost. Then the proportion of the total DALYs that are accounted for by different diseases is estimated. In practice, the DALY calculations of the impact of, for example, diabetes or coronary heart disease usually deal with each risk factor separately without accounting for how these risk factors might interact in a synergistic or inhibitory manner with amplification or a reduction in each factor's impact

on the total burden of disability. So the total of the factions of DALYs accounted for by diabetes, heart disease, and cancers, etc., usually adds up to over 100% of the observed total DALYs but allows one to rank the importance of different conditions in any one society.

This estimation of DALYs attributed to different diseases does not take into account the risk factors such as weight gain, high blood cholesterol levels, and high blood pressure which are simply seen as risk factors and so are not displayed in the DALY calculations which in any case do not include the whole range of functional disabilities noted above. However, separate analyses can be made for risk factors where one assigns a proportion of a disease which is attributable to a particular risk factor with the estimates usually based not on clear clinical trial data but on inferences from cohort studies.

When these BMI analyses were first included in a risk analysis by WHO for the Millennium analyses of risk on the basis of a need to estimate the extent to which the disease burden was preventable, it was necessary to identify the optimum levels of each risk factor. Thus for blood pressure the optimum systolic blood pressure was not the clinical cutoff of 140 mmHg but 115 mmHg, for total cholesterol levels it was 3.8 mmol/L (later rounded up to 4.0 mmol/L), and for smoking it was to have never smoked. Similarly for the BMI the optimum weight status on a global level was a BMI of about 21 (which was later changed by US investigators to a BMI of 23 perhaps because they could not cope with the implications for the USA of a global standard set on the basis of mortality, morbidity, and functional criteria). A high blood glucose and diabetes were not set as risk factors at that time because the global evidence on its prevalence was inadequate, but with the accumulation of data blood glucose was added with minimum optimum values for health being set at 5.3 mmol/L (Afshin et al. 2015) whereas WHO in a more cautious mode has taken a higher glucose value of 7.0 mm/L (World Health Organisation 2014). Originally WHO using these optimum values showed that the top risk factors for the DALY burden of what they then termed "developed" countries in descending order were smoking, high blood pressure, alcohol consumption, and a high blood cholesterol with overweight coming in as the fifth biggest risk factor for the whole disease burden in these relatively rich countries (World Health Organisation 2002). The point that cholesterol levels and blood pressure are magnified by obesity and smoking reduces the obesity rate was not explicitly considered. Nevertheless in the so-called low mortality developing countries, i.e., representing a variety of countries including, for example, Mexico, South America, and the Caribbean as well as many other countries, e.g., China, overweight was still the fifth biggest risk factor. So this was the first time that WHO and national governments really recognized the magnitude of ill-health stemming from the problem of overweight and obesity.

Since then the Gates funded Seattle/Boston/London group, often collaborating with WHO, has assessed both the disease burden and the accompanying risk factors in different parts of the world with updates being made on a continuing basis. Analyses of the disease burden usually still consider obesity as a risk factor not a disease outcome, but more recently the risk factor analyses have been extended to include dietary factors and physical inactivity based primarily on the authors'

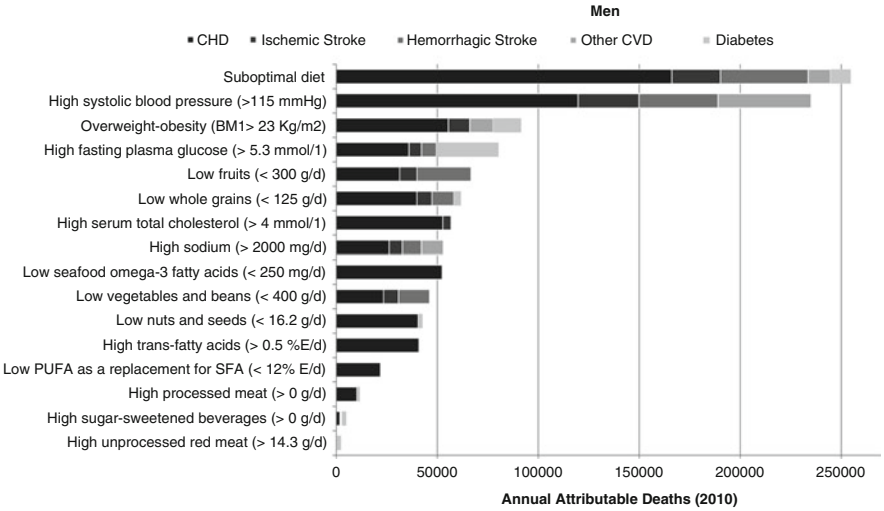


**Fig. 7 The impact of different risk factors on the mortality rates from diabetes and cardiovascular disease in the Middle East and North Africa** (Taken from Afshin et al. (2015))

interpretation of the proportion of risk factors accounting for particular diseases. These involve meta-analyses of cohort studies on diet, physical inactivity, and disease combined with a huge collation of dietary studies and then complex mathematical analyses of the proportions of risk attributed to the different risk factors. The estimates also often involve a crude extrapolation to countries where dietary measures and disease data are either hopeless or nonexistent. With these major caveats in mind Fig. 7 shows more recent analyses relating in this example to the Middle East where excess weight gain is the third most important risk factor after a suboptimum diet and high blood pressure.

## Economic Impact of Obesity

These functional and societal handicaps impose a burden that can now be quantitated by economists in financial terms and these so-called indirect costs add to the widely recognized increased direct costs of medical services through the cost of medical consultations in the community, hospitalization, and the cost of any pharmaceutical treatments provided at home. Doctors, familiar with the immediate costs of really heavy patients, usually do not realize that the incremental costs of obesity are evident even in the overweight group, i.e., in those with BMIs of 25–29.9. So when analyses of the direct medical service costs are linked to the proportion of adults in a society with different degrees of overweight/obesity then the total direct medical costs of the overweight in a country are appreciable (Withrow and Alter 2011) accounting for about 1–3% of a country's total healthcare expenditures but with obese individuals costing about 30% more than their normal weight peers. Figure 8 shows, however,

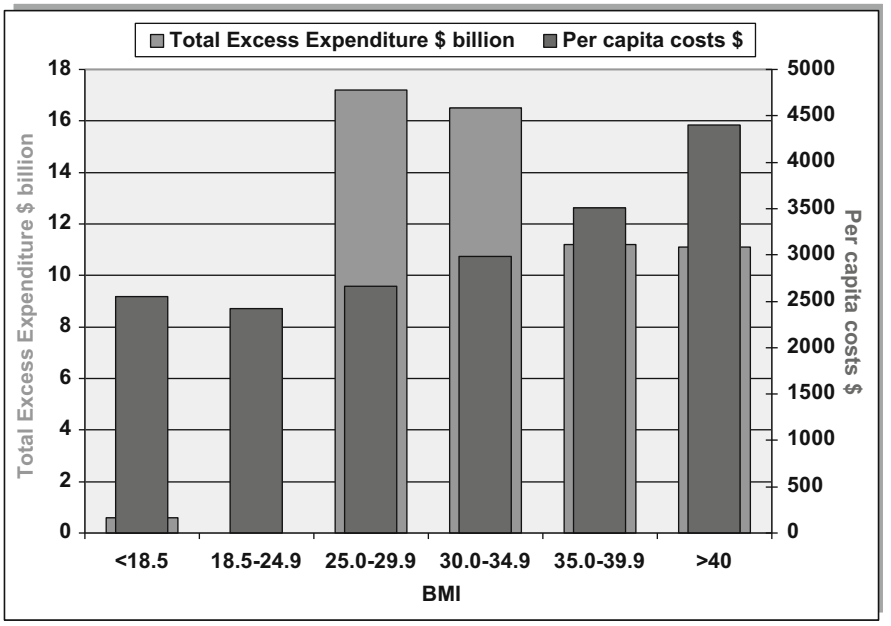


**Fig. 8 The cost of different degrees of excess weight in the USA**. The data on the average annual medical costs of adults with different BMIs is taken from Arterburn et al. (2005) but then the prevalence of the distribution of BMIs was found from NHANES statistics corresponding to the same time. The prevalence multiplied by the individual cost of each BMI group gives the total national burden in $billions per year for each BMI group

that if we take some crude USA estimates of the direct medical costs of individuals of different weights then there is a progressive increase in costs from a normal weight status to extreme obesity (Arterburn et al. 2005). Then if one considers the prevalence of these different degrees of overweight on a national basis at the time of the cost analyses then the total costs for a country from adults just being overweight with BMIs 25–<30 then the small incremental personal cost for the overweight individual translates on a national basis to a substantial health care cost. These costs are either paid personally by the large numbers of individuals or by the state if there is a national health service. This means that if the state is directly or indirectly responsible for the health costs then clearly a focus only on the most obese cases is inappropriate and the actual costs of being overweight should not be neglected.

Most analyses of the costs associated with obesity reveal, however, that the indirect economic costs of disability, absenteeism, and early retirement are even greater than the direct medical costs and amount to about 60% of all costs in advanced economies (Dee et al. 2014). Fewer estimates of the economic costs of obesity have been made in lower-income countries, but in many countries most individuals cannot afford medical consultations, tests, or drug therapy so their condition is neglected until they incur serious illness with its major costs. In poor countries ill health then induces poverty not only because people are unable to work

and have no welfare benefits but also in addition they usually have to pay for the costs of their treatment (World Bank 2014). In India and several other Asian countries these costs have long been known to induce catastrophic debts with households effectively locked into intergenerational repayments of debt in a manner akin to slavery. The amplification of risks from diabetes exacerbated by even modest weight gains therefore becomes important in the economic analyses of different health systems in Asia, Mexico, and probably in many other countries where the propensity to weight gain with additional sensitivities to diabetes, hypertension, and other noncommunicable diseases is rising rapidly.

The burden of disease in more affluent countries is also usually greater in the lower socioeconomic groups and the healthy life expectancies differ between the rich and poor by up to 20 years (Marmot 2010). The McKinsey Institute (Dobbs et al. 2014) also estimated using OECD statistics that the societal burden of obesity usually ranked as one of the top five social burdens in both rich and middle-income countries. Using the disease burden analyses on a global basis and recent analyses of obesity's economic costs based on World Bank data, the McKinsey Institute estimated the total global economic costs of obesity as $2trillion per year – only just below the $2.1 trillion costs of smoking and all armed conflicts and terrorism in the world.

## The Drivers of Obesity: Epidemiological Implications for Population Prevention and Economic Benefits

Analyses of the health costs of obesity illustrate the dimensions of the challenge because although the focus of the public and of policy makers is on how to prevent obesity in children it becomes clear that a reduction in health costs becomes evident in a society within months if the number of overweight and obese in the adult, not children, population could lose weight whereas combatting childhood obesity brings economic benefits only about 40 years later if one considers the major costs, e.g., of diabetes as one of the great medical expenses relating to excess weight gain. This is shown in Fig. 9 taken from the UK Chief Scientists Foresight obesity analysis with its microsimulation studies involving actual health costs of diabetes in England (Foresight 2007). To prevent any further increases in total health care costs relating to obesity would require the average BMI of the adult population in England to fall by 8 BMI units i.e. bringing it back to an average of BMI 20-21, a fiigure which matches the original analysis of the optimum BMI for a population. So given this perspective and the well-recognized continuing escalation on obesity rates globally in adults, one can consider which major risk factors are or were responsible for the epidemic from an epidemiological point of view and then use a variety of analytical methods to quantify the potential impact of different measures.

Clearly a marked reduction in physical activity has occurred over the decades, and this automatically means that we need far less food to maintain energy balance. This secular change in demand may have amounted to an average reduction of 500–1000 kcal or more per day, and if we consider the old data from the Baltimore

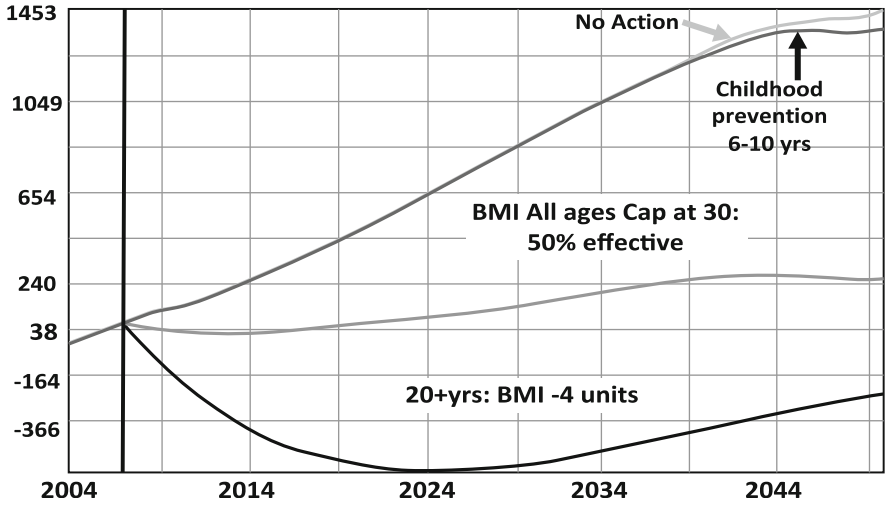


**Fig. 9 The predicted future health care costs of diabetes in £millions from 2004 to 2050 in England in relation to the potential changes in the prevalence of obesity induced by different strategies either in children or by reducing the obesity rate by 50%, i.e., with a cap on the number of those with BMIs30+ or by having all adults reduce their BMI by 4 units** (Taken from the UK Foresight report on obesity 2007)

aging study where they monitored men at the age of 25 and 70 years and then use current updated analyses of different ranges of physical activity (see Fig. 10) the fall in energy expenditure with age is dominated by the reduction in activity in sport and general activity (James et al. 1989). There were some early secular changes at that time in the USA as well as the very small intrinsic aging effect, but the overall cause of the decline in energy needs is the age-related fall in general and sports activities. So adults needing to maintain their energy balance will have to either subconsciously or deliberately reduce their food intake by anything from 500 kcal–1800 kcal/day. Most men are now by the age of 25 years only undertaking moderate activity so the average man of 70 kg would still need to reduce their intake by about 1200 kcal/d over their life time with similarly active average women needing to reduce their intake by perhaps 800 kcal/d.

This implies the need to rethink the whole strategy for maintaining physical activity throughout life. But the mechanization of work is unlikely to be reversed as it brings huge economic benefits and the idea of removing all the household aids that minimize work in the home would mean many more hours of housework and would be totally unacceptable in most if not all societies. Urban design to amplify walking, cycling, and minimize the public's use of cars for everyday activity is now seen to be valuable as is the provision of parks and other spaces and facilities for leisure time sports (Sallis et al. 2016). Nevertheless the major focus needs to be on factors that promote unnecessary food intake.

Detailed analyses of the factors promoting weight gain were set out by WHO in 2003 (WHO 2003) and are set out in Table 3 with additional updates by WHO on the

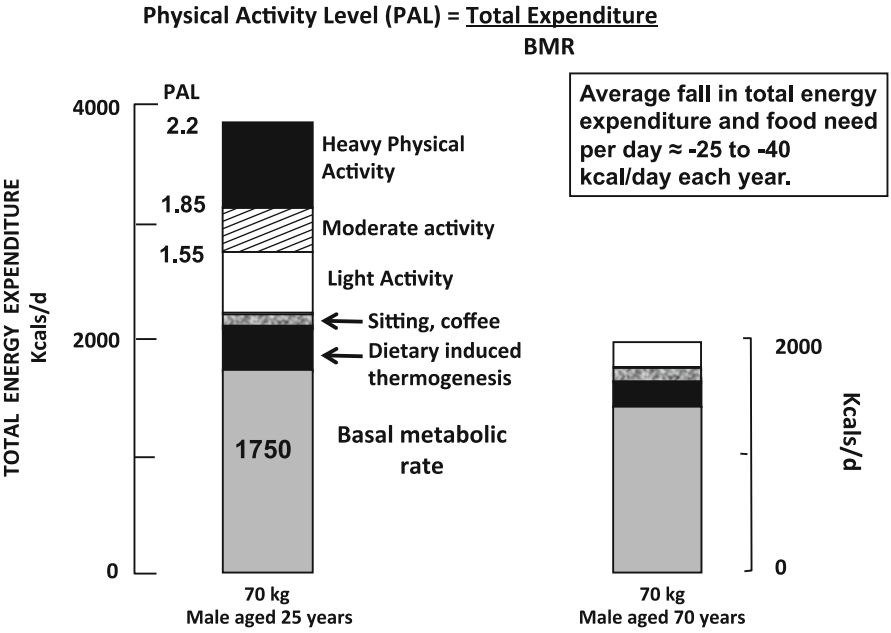


**Fig. 10 The fall in energy needs with age as shown by repeated measures of body weight, body composition, and basal metabolic rate in the same men when 25 years and 70 years of age**. (Data adapted from the USA Baltimore Ageing Study but preserving the body weight as constant to illustrate the aging effects). The different degrees of potential energy needs were taken from the original FAO/WHO/UNU 1981 analyses of energy requirements at different activities and the impact of reducing physical activity as observed with aging: so a 1000 kcal–1800 kcal fall in daily energy expenditure occurs from youth to old age depending on the degree of physical activity so if the young men were moderately active the fall in energy needs is equivalent to the need to reduce energy intake by about 30 kcals/day each year on average, but this may vary from about a 25 kcal to 40 kcal/day decline each year from the age of 25 years to 70 years (Adapted and redrawn from James, Ralph and Ferro-Luzzi (1989))

need to restrict sugar intakes (WHO 2015) and on the basis of their recent updated systematic analyses to reduce total fat intake (Hooper et al. 2015). These careful analyses relate to the original WHO proposition that the foods' energy density was the key to promoting inadvertent, i.e. "passive overconsumption" of kcalories. This emphasis on energy density fits with the recent UK government's scientific advisory committee on nutrition highlighted the need to substantially increase the intake of dietary fiber (SACN 2015). WHO highlighted the effects of food marketing on energy intake and more recently in the UK Public Health England (PHE) has found that 40% of all foods purchased are in response to special marketing promotions which almost always involve the promotion of high fat, high sugar, and salty foods as well as sugary drinks (Public Health England 2015). The traditional approaches of trying to induce behavior change in a population by health education has been repeatedly tried for over 30 years and has clearly failed even if backed by subtle techniques such as the "nudge" manipulation of purchasing circumstances

**Table 3** The causes of excess weight gain and obesity as assessed by the World Health Organisation based on its original 2003 analyses but updated by their new expert analyses of the impact of total fat and free sugars on the propensity to weight gain

| Strength of evidence | Decreases risk | No relationship observed | Increases risk |
|---|---|---|---|
| **Convincing** | (a) regular physical exercise<br>(b) high NSP (dietary fiber) intake | | (a) High intake of energy dense, nutrient poor foods. (New confirmatory analyses[a]: high total fat and sugar intakes)<br>(b) Sedentary lifestyles<br>(c) Heavy marketing of energy dense foods[b] and fast food outlets.<br>(d) Adverse socioeconomic conditions in developed countries (especially for women)<br>(e) Sugar sweetened soft drinks and fruit juices |
| **Probable** | (a) Home and school environments that support healthy food choices for children[b]<br>(b) Promoting linear growth<br>(c) Breastfeeding | | (a) Large portion sizes[c]<br>(b) high proportion of food prepared outside the home (western countries)[a] |
| **Possible** | (a) Low glycaemic index foods | Protein content of the diet | (a) "Rigid restraint, periodic disinhibition" eating patterns |
| **Insufficient** | (a) Increasing eating frequency | | (a) Alcohol |

Note:
[a]This table is set out as in the original WHO 916 report (2003) (World Health Organization 2003) except that new analyses by Hooper et al. (2015) for WHO have now confirmed the importance of a high fat diet and separate WHO (2015) and (SACN 2015) analyses, with systematic reviews of total free sugar intakes, have also highlighted their role in promoting weight gain but still probably through an effect on the energy density of foods.
[b]This designates what the experts for WHO in 2003 considered was a reasonable set of judgments based on associated evidence and expert opinion. Since then further analyses usually support these propositions
[c]This signifies that portion sizes and the proportion of prepared foods outside the household has been moved up from a "possible" cause to a "probable" cause on the basis of more recent analyses

(House of Lords 2011). This in part is because no government can match the sophistication, intensity, pervasive, and endlessly repeated effects of marketing by food companies and supermarkets (Cohen et al. 2015). These approaches involve a variety of remarkably subtle and well-researched methods including the development of methods that help to evade normal conscious decision-making. Such techniques also involve the constant siting of food outlets and vending machines to stimulate impulse buying, the manipulation of subconscious registered eye catching labels, the length and position of each item's display in supermarkets, and the

unrecognized increasingly routine use of synthetic flavors chosen on the basis of molecular responsive laboratory plates incorporating huge numbers of distinct olfactory receptors. These distinct flavors have been shown experimentally to appeal separately to men and to women including those taste preferences in young women at different physiological phases of their menstrual cycle. This as well as brain imaging techniques to identify those flavors which trigger the brain's pleasure sensors in effect amplify the pleasurable experiences of the foods and therefore their chances of being repurchased. These often-unrecognized marketing techniques are very difficult to combat by any policy process.

The other major factors impacting on food choice and the magnitude of food intake involve marketing by offering lower priced products. Although in the medical field this has not received much analysis, economists for decades have understood and estimated mathematically the impact of price changes on purchasing habits. This price elasticity was used to vary the subsidy or tax on specific foods and therefore the consumers' choices. This then systematically changed the consumption and reinforced the costs of eating more or less fruit and vegetables as well as meat and fish. These items have proved to be very price responsive whereas the intake of fats and oils and sugary products are less readily affected by small price changes.

The actual ranking of the price of these different foods has changed substantially over the decades in large part because subsidies induced major changes in the primary cost of commodities. Thus farm prices have traditionally been dramatically affected by multibillion-dollar farm subsidies in most parts of the world but particularly in the USA and Europe where subsidies have differentially favored meat, fats, oils, and sugar production with horticultural products receiving much less favored treatment. This has led to major changes in commodity prices with new calculations demonstrating that to purchase a healthy diet costs a household about three times the cost of buying cheaper fat and sugar rich foods with few vegetables and fruit (Wiggins et al. 2015).

As the production of fats, oils, and sugar has risen markedly and with it the total food energy being produced the farmers then have to do everything possible to sell their products to food manufacturers who in turn do their utmost to increase their volume as well as their price turnover in complex negotiations with supermarkets undertaking the same exercises. So the whole food chain in Western societies and increasingly in lower-income countries is locked into an intense effort to encourage people to buy more food when in practice they need to consume less. This relationship between the drive for profits and health relates to the tobacco and alcohol industries as well as the fast food industry (Moodie et al. 2013). It is little wonder therefore that there is a relationship between the total food kcalories available in a country and the development of obesity. So now in practice in the UK 30–40% of all household food purchased is discarded as food waste compared with about 2% in the straightened times of the 1950s.

To combat all these factors means that policies need to be developed right across different branches of government with the need for multiple steps rather than

assuming crudely that a single "magic bullet" will suffice. This has been emphasized repeatedly by many government sponsored analyses as well as by independent analysts such as the OECD (Sassi 2010) and the McKinsey Institute which estimated the strength of evidence and cost effectiveness of 60 different measures (Dobbs et al. 2014). If the United Kingdom were to deploy all 60 interventions, the analyses suggest that these multiple but modest measures could reverse the rising obesity rates and bring about 20% of overweight and obese individuals back into the normal weight category within 5–10 years with an estimated total economic saving on health, employment, and social costs of $25billion a year (including a $1.5 billion saving for the UK NHS). These analyses combined with a variety of systematic reviews of cost-effective measures and national experience relating to both food and physical activity allowed the Eastern Mediterranean Region of the WHO to set out priority actions for combatting obesity in the region (see Table 4) where obesity and diabetes rates are among the highest in the world (WHO (EMRO) 2017). Regulatory backed progressive food reformulation will be a higher priority in Western societies where a greater proportion of food is already sold as food products or prepared meals.

**Table 4** Policy strategies for obesity prevention based on numerous systematic analyses of cost-effectiveness and national experience

| |
|---|
| 1. Reformulation: |
| National progressive mandatory reductions in fat sugar and salt every 3 years |
| Apply to total fat, saturated fat, free sugars, and salt |
| Audit, publicize |
| Include street traders and fast food outlets |
| Include reduced portion sizing |
| 2. Fiscal measures: |
| That is, taxes and subsidies of food (but also relate to socioeconomic policies to reduce inequality). Taxes best used as a commodity tax on fat, sugar, sugary drink and not a product-based VAT measure |
| 3. Public procurement: |
| Introduce mandatory nutrition standards in all publicly funded institutions (and progressively involving private providers with nutrition standards for types of food served) |
| Aim for progressive reductions in dietary fat to 25%, free sugar to 5 g%, and salt to 2.0 g/1000 kcal |
| Provide training to catering companies on appropriate catering methods in public institutions to reduce the use of frying and sweetening of foods and help/training with menu redesign |
| 4. Physical activity interventions with wide variety of policies throughout life with (a) media, (b) multiple school actions, worksite, transport, civic recreation opportunities, and urban redesign; transport changes crucial |
| 5. Food supply and trade |
| Establish mandatory national food standards thereby overcoming free world trade regulations by affecting local production as well as imports |

(*continued*)

**Table 4** (continued)

| |
|---|
| Take Finnish canteen experience of "free" salad bar/vegetables; city planning, e.g. controlling public adverts, density/location of fast food outlets |
| Sign up to/implement Milan urban food pact and sustainable food plan |
| 6. Marketing |
| Children <18 years focus for 1st phase only with application of WHO-agreed ban on marketing. Then: |
| Apply restrictions to all marketing of high fat, sugary, salty (HFSS) foods to population by all means |
| Abolish food promotions of HFSS foods in its many forms by legal means |
| Establish a national and then regional legal process with potential global agreement on liability of food companies for their advertising effects in other countries – thereby setting internet/cable TV standards |
| 7. Labeling with traffic light labeling shown to be most effective. Need standard display as a mandatory requirement on all packaged foods/menu displays; consider related supermarket layouts |
| 8. Breast feeding. Many national practices very poor so implement: |
| Mandatory baby-friendly hospitals and clinic facilities |
| Implement WHO bans on breast milk substitutes anywhere associated with pregnancy |
| Provide and promote facilities for breastfeeding at work/in public/mandatory maternal leave for 6 months |
| 9. Mass media campaigns: Their main purpose is to build support for the other policies and actions; a few of the more receptive public will change their living patterns as a result |
| 10. Health sector: |
| Prepregnancy counselling and management crucial |
| Community-based/GP screening for high-risk groups with early interventions |
| Integrated focus on dietary improvements, tobacco use cessation, exercise, and their life-long benefits |

Policies adapted for general use in countries with very developed industrialized food system from the WHO EMRO analyses of policy needs for obesity and diabetes prevention (2017) (WHO (EMRO) 2017)

Unless there is a coherent approach to government-led regulatory measures then most experts find it difficult to foresee any reduction in the epidemic of obesity because of the modest improvements attained in some countries in the children's prevalences of obesity. Small changes can be induced by tackling individuals within the community at risk of diabetes and then instituting substantial changes by specific advice and monitoring over a prolonged time with a 5% reduction in weight and falls in fat intake to 25%, with increases in fruit and vegetable and fiber intake together, of course, with little or no sugar added to the diet, and with some increase in physical activity. If this is coordinated on a state or national bases then the distribution of BMIs within a community can be changed a little as well as helping to prevent diabetes, but the impact on obesity as such is very modest and few countries are yet able to undertake the major interventions on a national individual basis that Finland is engaged in (Salopuro et al. 2011).

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# Neuroendocrinology of Energy Balance

2

Antonio Giordano and Enzo Nisoli

## Contents



**Abstract**

In the past decades, the spiraling obesity epidemic has renewed the interest of basic scientists in the control of hunger and satiety, food intake and energy expenditure, and body weight regulation by the central nervous system. The discovery of the adipose-derived satiety hormone, leptin, in 1994 greatly advanced the neuroscience of obesity by enabling detection and characterization of the – largely hypothalamic – neurocircuits that underpin feeding behavior and energy balance regulation. A number of circulating factors that affect the energy

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balance at the central level have subsequently been discovered in the adipose organ, the gastrointestinal tract, and the endocrine pancreas or their mechanisms of action have been characterized. Although several major pieces of the picture are still missing, the available data suggest that energy balance homeostasis is achieved at the central level by hypothalamic and brainstem neurocircuits which integrate metabolic stimuli with cognitive, hedonic, and emotional cues, regulating energy use and storage and body weight homeostasis through behavioral, autonomic, and endocrine responses. These extremely complex and closely integrated neurocircuits are mainly peptidergic and give rise to a highly redundant system. They operate continuously in response to stimulatory or inhibitory hormonal and metabolic inputs coming from the periphery of the body through the circulation. Such crosstalk between "center" and "periphery" is currently a major area of energy balance research. Its elucidation is expected to provide in the near future novel druggable targets for the effective treatment of obesity and related diseases in humans.

**Keywords**
Hypothalamus · Arcuate nucleus · Solitary tract nucleus · Circumventricular organs · Leptin · Insulin · Ghrelin · Cholecystokinin · Peptide YY · Glucagon-like peptide-1 · Amylin

## Introduction

In the whole animal kingdom, the search for nutrients is key to survival. During evolution, animals have developed complex biological systems to search for food, maintain a homeostatic internal metabolic environment, and store energy, mainly in the form of fat, to overcome periods of fasting and to sustain energy-intensive behaviors such as reproduction. Conceivably, a greater ability to store energy and withstand prolonged fasting has also played a role in the differentiation of mammalian brain and behavior, partly releasing individuals from the constant quest for food to pursue increasingly complex tasks, including exploration of the physical environment and social interaction.

More than 50 years ago, the "thrifty genotype" hypothesis suggested that genes favoring energy storage and reduced energy expenditure were positively selected during the evolutionary history of mammals, including humans, and enhanced survival in an energy-poor environment (Neel 1962). Thus, despite marked differences among species and individuals, the mammalian genotype is evolutionarily geared to a highly efficient use of food-derived energy (Sellayah et al. 2014). However, in the modern obesogenic environment these genetic advantages have become a problem, since the virtually limitless availability of calorie-rich food and the diffusion of sedentary lifestyles have led to a severe epidemic of obesity, type II diabetes, and metabolic disease. From a therapeutic viewpoint, overriding this highly efficient evolutionarily selected system has proved extremely difficult.

The central nervous system (CNS) plays a crucial role in all energy balance-related processes, from the hunger sensation and search for food up to energy expenditure and/or accumulation. This review begins with a historical section describing the identification of the main brain areas and molecules involved in mammalian energy balance regulation; it then examines the brain areas most closely involved in energy balance control; and finally presents a systematic overview of the most important peripherally produced hormones which, by acting at distinct brain sites, regulate different aspects of the energy balance. Understanding the mechanisms underpinning energy balance regulation has helped devise some obesity treatments and is likely to prove even more useful in the future. Yet, there are at present few and only mildly effective pharmacological treatments for human obesity, and the sole therapeutic option available to the morbidly obese is bariatric surgery. In the past few years, a greater understanding of body weight homeostasis and appetite regulation has provided an impressive list of potential druggable targets. This knowledge and the intense research effort currently under way are likely to lead to the development of successful single or combination treatments for obesity.

## The Birth of the Neuroendocrinology of the Energy Balance: A Historical Perspective

In the mid-nineteenth century, pituitary tumors were known to lead to obesity and hypogonadism; this clinical condition was called Frohlich's syndrome. At the time, the excessive fat accumulation in such patients was attributed to endocrine abnormalities due to pituitary gland dysfunction. The general belief that obesity was primarily related to pituitary dysfunction was the prevailing view until the first decades of the twentieth century, when it was first found that obesity often developed in patients with tumors at the base of the brain, near but not extending to the pituitary. In the same years, further challenges came from experimental studies showing that in dogs and rats, lesion of the basomedial hypothalamus often resulted in obesity, whereas hypophysectomy without additional hypothalamic damage did not (Elmquist et al. 1999; King 2006).

It is generally accepted that the modern era of brain research in feeding behavior began in 1939, with the adaptation of the Horsley-Clarke stereotaxic instrument for use in rat studies. This apparatus allowed reaching specific sites of the brain of anesthetized animals to introduce fluids or implant cannulae. Thus, bilateral electrolytic lesions of the rat hypothalamus, sparing the adjacent pituitary gland, demonstrated that bilateral damage to the ventromedial portion of the tuberal hypothalamus induced hyperphagia and obesity (Hetherington and Ranson 1940). A few years later, bilateral lesions in the adjacent lateral hypothalamus were shown to result in severe anorexia, weight loss, and even death by starvation (Anand and Brobeck 1951). These studies firmly established a crucial role of the hypothalamus in body weight regulation, and the hypothesis that obesity was the result of a pituitary dysfunction was shelved. Moreover, these investigations suggested the presence in the hypothalamus of two centers regulating food intake and energy balance and

exerting opposite actions: the satiety center, corresponding anatomically to the ventromedial hypothalamus, and the feeding center, corresponding to the dorsal and lateral hypothalamus. These seminal experiments sketched a massive, complex, bilateral, and redundant role of the brain in energy balance regulation. In 1954, the discovery of the hypothalamic satiety and feeding centers suggested to Eliot Stellar his dual-center hypothesis for motivated behavior, where the vast majority of motivated behaviors, including hunger, thirst, reproduction, and aggressiveness, would be produced by the reciprocal and opposing action of excitatory and inhibitory brain centers (Stellar 1954).

In the mid-twentieth century, Gordon Kennedy was the first to suggest that circulating signals generated by peripheral organs in proportion to their energy stores could influence food intake and energy expenditure in a coordinated manner to regulate body weight (Kennedy 1950). The hypothesis obtained some experimental evidence from parabiosis studies, complex experiments where sharing of the blood supply between two animals was achieved through a surgical connection. In particular, lesion of the ventromedial hypothalamus (the "satiety center") of one animal of the pair resulted in its gaining weight, while the other animal refused food and eventually died; however, lesion also of the second animal's ventromedial hypothalamus resulted in its overeating and ultimately in obesity (Hervey 1959). Collectively, these experiments were the first to suggest that as yet unidentified blood-borne satiety factors produced by the obese animal affected food intake and that an intact hypothalamus was required for their action.

The question remained as to which signal(s) the hypothalamic centers could sense in the blood in order to regulate food intake and body weight. Jean Mayer advanced a highly popular theory involving glucose as the signal (Mayer 1955). According to this hypothesis, glucose metabolism in certain hypothalamic cells generates a signal to the brain areas controlling appetite and food intake. When, after prolonged fasting or physical exercise, glucose levels decrease, the impaired glucose metabolism in these cells induces the hunger sensation and the animal begins to search for food, and eats if food is available. As eating progresses, blood glucose progressively augments and is again metabolized by the same hypothalamic neurons, which elicit the satiety sensation and halt the eating. At the experimental level, important support for Mayer's glucostatic theory was provided by the voracious eating of animals administered 2-deoxyglucose, a toxic molecule that enters cells along with glucose but cannot be oxidized to produce ATP, thus impairing cellular energy metabolism (Smith and Epstain 1969). We now know that mammals feed well before blood glucose declines, and it is generally believed that glucose levels have little to see with the physiological regulation of feeding. However, it should be noted that glucoprivic eating is an acute emergency response to a severe energy deficit of the body, and that it also occurs in pathological conditions such as severe diabetes, where intracellular glucose reduction prompts an urgent search for sugar-rich food.

In the 1960s, stereotaxic studies involving the ablation of hypothalamic connections or injection of neurotransmitters into hypothalamic sites showed that extrahypothalamic areas also play an important role in the central regulation of the energy

balance and demonstrated the role of the neurotransmitters acetylcholine and noradrenaline in the neural regulation of feeding.

A pivotal discovery in 1973 showed that the duodenal peptide cholecystokinin (CCK) acted as a meal-generated circulating satiety factor (Gibbs et al. 1973). CCK was thus the first gut hormone found to have an effect on appetite. In subsequent years, the characterization of its mechanism of action highlighted the role in feeding regulation of brainstem centers, which are now defined as the dorsal vagal complex (DVC) of the brainstem.

In the late 1960s, Coleman had identified a naturally genetically obese (*ob*/*ob*) and a naturally genetically diabetic (*db*/*db*) mouse strain. Their phenotype was characterized by massive overeating, obesity, insulin resistance, and impaired sexual maturation leading to infertility. Parabiosis experiments establishing cross-circulation between the two strains allowed Coleman and his colleagues to infer that the *ob*/*ob* mouse lacked a circulating compound capable of preventing obesity, while the *db*/*db* mouse lacked the receptor for such factor (Coleman 1978). In the early 1990s, the advent of molecular genetic techniques allowed identifying the gene of Coleman's factor, whose product induced a strong satiety effect by acting on the CNS: the factor was named leptin (Zhang et al. 1994). This discovery spurred intense experimental work on the neural mechanisms of energy balance regulation, leading to the identification and characterization of mammalian neuronal circuits and neurotransmitter systems regulating energy intake and expenditure at the hypothalamic and extra-hypothalamic level and ensuring energy balance and body weight homeostasis. Importantly, the discovery of leptin also changed the scientists' view of the adipose organ, from a mere energy depot to an active endocrine organ (see ► Chap. 3, "The Adipose Organ").

## The "Central Anatomy" of Feeding Behavior and Energy Balance Control

Feeding is a highly complex behavior that massively involves the brain by recruiting sensory, motor, attentive, cognitive, emotional, and reward neuronal systems. This also applies to humans, where recent advances in neuroimaging techniques, such as functional magnetic resonance, allow recording the activity of distinct brain areas during different phases of feeding. Exposure of fasted healthy humans to food-related cues involves activation of brain regions commonly associated to reward and motivation (striatum, pallidum, and midbrain), of areas held to encode visual processing and attention (visual cortex and anterior cingulate cortex), and of areas involved in gustatory (insula, frontal operculum) and oral somatosensory (postcentral gyrus) processing (Burger and Berner 2014). Notably, the reduced activation of reward areas seen in obese subjects exposed to food-related stimuli has generated the notion of hedonic obesity, where defective reward-related responses to food intake may in some patients override the body's energy balance regulation, resulting in overeating, excess fat deposition, and obesity (Lee and Dixon 2017).

In the orchestrated action of the several interconnected brain areas that are involved in such diverse feeding-related functions, the hypothalamus plays the

"conductor," directing, integrating, and blending visceral, endocrine, and behavioral inputs to respond to contingent situations and ensuring the homeostatic control of metabolism.

The hypothalamus, one of the smallest and most ancient parts of the mammalian brain, is found in all vertebrates. It contains highly conserved neural circuits that control a number of basic life functions and behaviors, including the energy balance, fluid and electrolyte balance, thermoregulation, sleep-wake cycles, stress responses, and reproduction. From an anatomical point of view, it is most easily described from the ventral surface of the brain, where it is bounded anteriorly by the optic chiasm, laterally by the optic tracts, and posteriorly by the mammillary bodies. It is divided in two identical halves by the third ventricle, which is located along the midline. Functionally, the hypothalamus is usually divided from rostral to caudal into three portions: (i) the preoptic area, which mainly contains the integrative circuitries for thermoregulation, fever, electrolyte and fluid balance, the wake-sleep cycle, and reproductive behaviors; (ii) the tuberal hypothalamus, with a stalk connecting it to the pituitary gland, which mainly contains the neural circuits for energy balance regulation and endocrine and vegetative responses; and (iii) the mammillary portion, which is believed to be involved in wakefulness and stress responses. Most functions involve a single side of the hypothalamus, whereas some homeostatic functions, such as feeding behavior and energy balance control, recruit the neural circuits bilaterally. The tuberal hypothalamus is thus the most important portion of the hypothalamus for feeding behavior and energy balance homeostasis. It is divided by the fornix into a medial and a lateral part. The medial part contains well-demarcated neuron groups, such as the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the ventromedial nucleus (VMH), and the dorsomedial nucleus (DMH), whereas neurons in the lateral part are more dispersed, do not form distinctive nuclear groups, and are collectively referred to as perifornical and lateral (LH) areas of the hypothalamus.

Besides the tuberal hypothalamus, some brainstem centers in the hindbrain are also crucially involved in feeding behavior and energy balance regulation. They are found on the border between the medulla and the pons and collectively form the DVC. The DVC comprises: (i) the nucleus of the solitary tract (NST), the main sensory relay for the viscera, including the gastrointestinal tract; (ii) the dorsal motor nucleus of the vagus (DMX), which is the source of vagal efferents controlling such visceral responses as gut motility and secretion; and (iii) the area postrema, a circumventricular organ.

The NTS receives afferent fibers from the facial, glossopharyngeal, and vagus nerves which convey gustatory, mechanical, hormonal, and metabolic visceral information. It is reciprocally connected to other brainstem centers, including the area postrema, the DMX and the lateral parabrachial nuclei, and with the hypothalamus, especially ARC and PVN neurons. Thus, the hypothalamic and brainstem feeding centers are anatomically and functionally interconnected.

The circumventricular organs are called "the windows of the brain." They are distinctive areas located in periventricular position, where the absence of the blood-brain barrier (BBB) involves that circulating factors such as hormones and metabolites quickly cross the fenestrated wall of their capillaries and diffuse some way into the extracellular space, affecting the activity of neurons located in circumventricular

organs or in the adjacent brain parenchyma. Interestingly, both the tuberal hypothalamus and the DVC contain a circumventricular organ, respectively the median eminence and the area postrema. Recent experimental evidence has highlighted the role of these two circumventricular organs in regulating the delivery of circulating hormones and metabolites to the ARC and the NTS, respectively.

The nuclei of the tuberal hypothalamus and the DVC are nodal centers in feeding behavior and energy balance regulation and have strong integrative functions. They receive body energy status information from circulating metabolites and hormones – through the circumventricular organs and/or specific carriers in the BBB – and a wide range of sensory inputs such as taste and gastrointestinal information through the vagal afferents to the NTS. Comparison of these inputs to basic references prompts activation of adequate autonomic, endocrine, and behavioral responses to ensure metabolic homeostasis and to meet the energy requirements of the body.

The strong involvement of the tuberal hypothalamus and the DVC in energy balance regulation is clearly demonstrated by c-Fos immunostaining in fasted animals. Feeding is essential for survival, and prolonged fasting involves strong activation of brain activity. c-Fos is the product of an immediate early gene, whose expression in the brain is elicited by a wide range of stimuli (Sheng and Greenberg 1990). Its detection by immunohistochemistry has been extremely useful in identifying the CNS pathways that are activated by several peripheral stimuli. Whereas fed mice display very low, almost undetectable levels of brain c-Fos in neuronal cell nuclei, fasted animals exhibit strong c-Fos nuclear staining in numerous neurons of both the tuberal hypothalamus (Fig. 1) and the DVC (Fig. 2).

## Hormonal Signals Involved in the Control of Energy Homeostasis

In the past few years, a large number of circulating hormones, metabolites, and peptides with a role in the energy balance have been characterized. These factors exert a short- and/or long-term regulatory activity on feeding behavior through a concerted action on several distinct areas of the tuberal hypothalamus and/or the DVC. They also affect other brain areas and are involved in other brain functions, a fact that often hampers the characterization of their true role in energy balance regulation. They come from at least three sites: the adipose organ, the gastrointestinal tract, and the endocrine pancreas. Here, the discussion is confined to those factors that in the past few years have been seen to play substantial roles in energy balance homeostasis and whose mechanism of action have proved paradigmatic to understand how the brain regulates feeding behavior, energy consumption, and body weight.

### Leptin

Leptin is a peptide hormone produced and secreted by white adipose cells in proportion to the body's fat energy stores (Zhang et al. 1994). Although under certain conditions, it is also produced by other organs and tissues, including

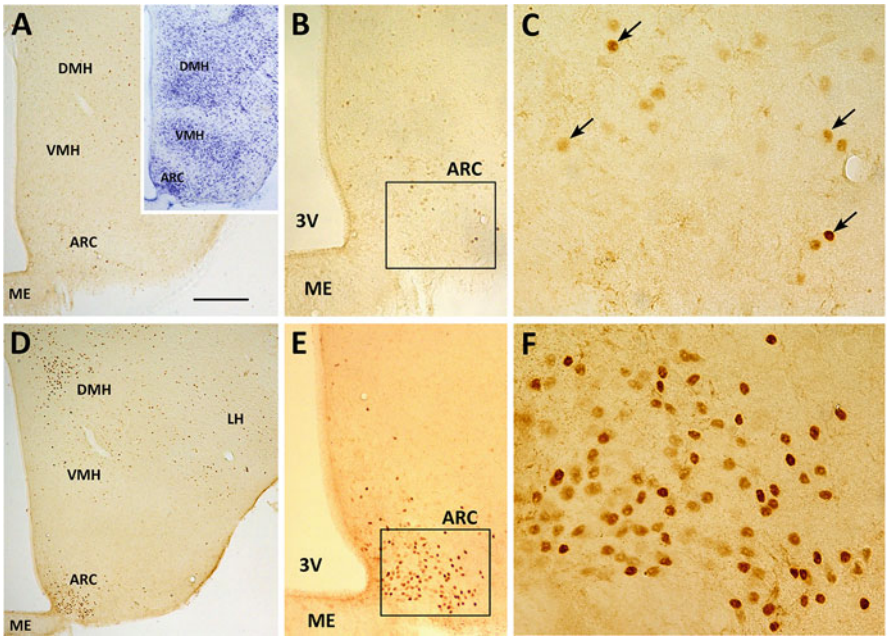


**Fig. 1** c-Fos immunohistochemical expression in the tuberal hypothalamus during fasting. In a normally-fed mouse (**a**–**c**), only few and spared neurons located in some hypothalamic nuclei exhibit c-Fos immunoreactivity in their cell nucleus (arrows in **c**). In a mouse fasted for 24 h (**d**–**f**), c-Fos immunoreactive neurons are very numerous and mainly located in medial structures of the tuberal hypothalamus, such as the medial part of the ARC and the DMH, collectively forming what was known as "the feeding center" of the hypothalamus. **c** and **f** are enlargements of the corresponding areas framed in **b** and **e**, respectively. 3V, third ventricle; ME, median eminence. Bar: **a** and **d** 350 μm; inset of **a** 600 μm; **b** and **e** 150 μm; **c** and **f** 30 μm

placenta, mammary gland, stomach, and skeletal muscle, its blood levels closely depend on the secretory activity of white adipocytes and are proportional to their lipid content (Considine et al. 1996). Leptin is a potent satiety factor whose genetic deficiency leads to massive obesity, as seen in *ob*/*ob* mice. Indeed, administration of mouse recombinant leptin to *ob*/*ob* mice reduces food intake and body weight and redresses all the endocrine abnormalities observed in these mice, including hypogonadism, insulin resistance, hypercorticosteronemia, and low levels of thyroid hormones (Ahima et al. 1996). The discovery of leptin was rapidly followed by cloning of its receptor (LepR) (Tartaglia et al. 1995), of which six alternatively spliced isoforms have been identified in mammals. The long isoform (LepRb) contains a fully signaling-competent intracellular domain and is required for most of the central and peripheral effects of leptin. Importantly, the diabetic obese syndrome affecting *db*/*db* mice is due to a mutation of the *LepRb* gene (Chen et al. 1996), which confirms that leptin is the satiety factor hypothesized by Coleman based on his parabiosis experiments. Binding of leptin to LepRb-bearing cells modulates a number of cellular signaling pathways, including phosphatidylinositol

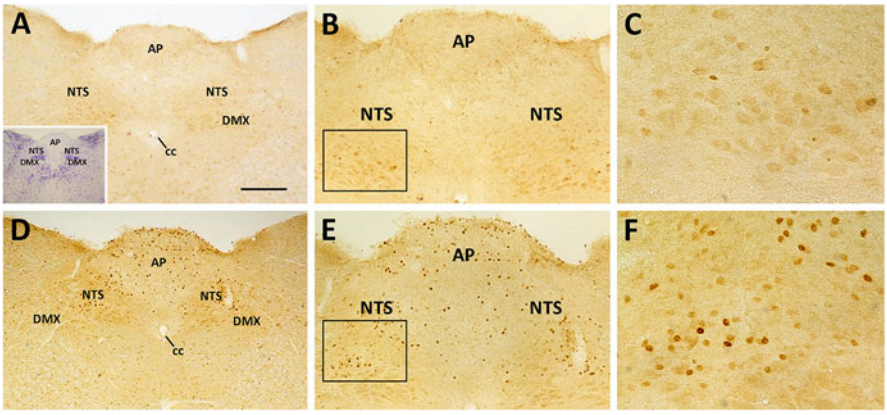


**Fig. 2** c-Fos immunohistochemical expression in the DVC of the brainstem during fasting. In a normally-fed mouse (**a**–**c**), c-Fos immunoreactivity is almost undetectable. In a mouse fasted for 24 h (**d**–**f**), numerous c-Fos immunoreactive neurons appear in both the area postrema (AP) and the NTS. **c** and **f** are enlargements of the corresponding areas framed in **b** and **e**, respectively. cc, central canal. Bar: **a** and **d** 300 μm; inset of **a** 900 μm; **b** and **e**: 180 μm; **c** and **f** 35 μm

3-kinase, mammalian target of rapamycin, and AMP-dependent protein kinase. Activation of Janus kinase 2 (Jak2), leading to tyrosine phosphorylation, dimerization, and nuclear translocation of the signal transducer and activator of transcription 3 (STAT3), is the main signaling system activated by leptin and is required for accurate regulation of the energy balance (Villanueva and Mayers 2008). In situ hybridization and immunohistochemical studies have documented that LepRb is widely expressed in the hypothalamic and brainstem nuclei involved in energy balance regulation (Mercer et al. 1996; Schwartz et al. 1996; Fei et al. 1997; Elmquist et al. 1998). In experimental animals, intraperitoneal leptin injection induces a rapid increase in its blood levels, strongly activating the Jak2-STAT3 pathways in several neurons of the tuberal hypothalamic nuclei (Fig. 3) and the NTS of the brainstem (Fig. 4).

Studies aimed at characterizing the satiety action of leptin in the hypothalamus have stressed the crucial role of two populations of ARC neurons exerting opposite effects in feeding behavior: the neurons co-expressing neuropeptide Y (NPY) and agouti-related protein (AgRP) are found in the medial part of the ARC and are orexigenic, whereas the proopiomelanocortin (POMC) neurons are located in the lateral portion of the ARC and are anorexigenic (Aponte et al. 2011; Krashes et al. 2011; Zhan et al. 2013). Circulating leptin, reaching these neurons through the median eminence or the cerebrospinal fluid, or carried through the BBB by specific transporters, inhibits the orexigenic NPY/AgRP neurons and stimulates the anorexigenic POMC neurons (Kim et al. 2014). This well-characterized mechanism is followed by numerous and still poorly understood interactions involving leptin and neurotransmitter (dopamine, serotonin, and glutamate) and neuropeptidergic neuronal systems. “First order” leptin-responsive NPY/AgRP and POMC ARC

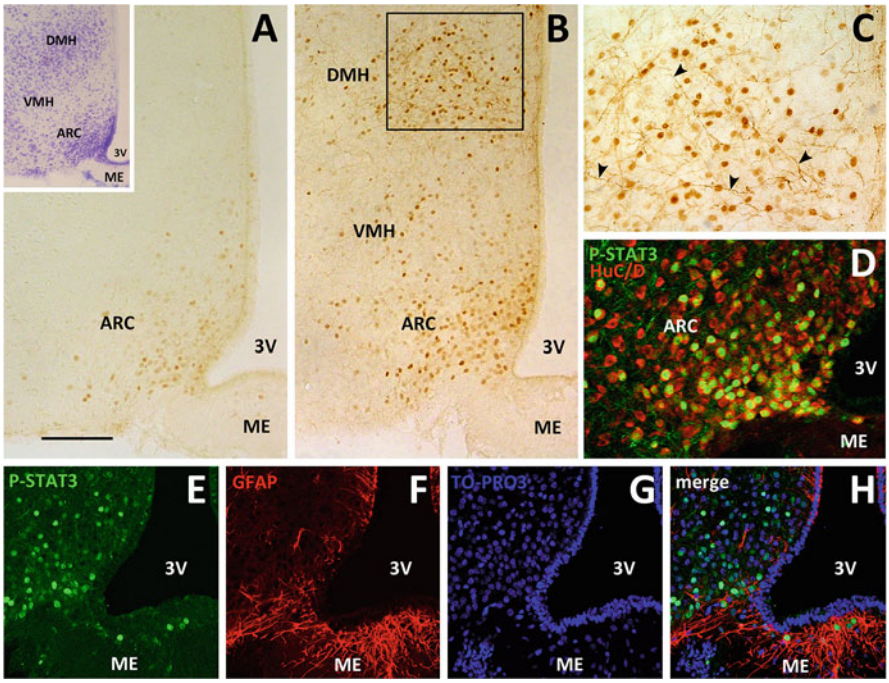


**Fig. 3** Activation of the Jak2-STAT3 signaling pathway in the tuberal hypothalamus by circulating leptin. In a control mouse (**a**), phospo-STAT3 (P-STAT3) immunoreactivity is only slightly detectable in a few neurons of the medial part of the ARC. In a mouse intraperitoneally treated with leptin for 40 min (**b** and **c**), numerous P-STAT3 immunoreactive neurons appear in the ARC, the DMH and, to a lesser extent, in the VMH. C is the enlargement of the area framed in **b**, showing that also neuronal projections do express P-STAT3 (arrowheads) following leptin treatment. Double immunostaining experiments and confocal microscopy analyses in leptin-treated mice show that nuclear P-STAT3 immunoreactivity is located in neuronal cells (**d**), expressing the neuronal marker HuC/D, but not in the glial cells (**e**–**h**), visualized through the glial marker GFAP. TO-PRO3 is a fluorescent nuclear counterstaining. 3V, third ventricle; ME, median eminence. Bar: **a** and **b** 150 μm; inset of **a** 400 μm; **c** 60 μm; **d** 45 μm; **e**–**h** 100 μm

neurons project to "second order" neuronal populations located in medial structures of the tuberal hypothalamus (PVN, DMH, and VMH), where they stimulate anorexigenic peptidergic systems (e.g., brain-derived neurotrophic factor, BDNF), and in the lateral tuberal hypothalamus (perifornical area and LH), where they inhibit orexigenic peptidergic systems (e.g., orexin) (Morton et al. 2014). Importantly, the POMC neurons act on downstream neurons through melanocortin 3 and 4 receptors (MC4R) (Waterson and Horvath 2015). The medial structures are the "satiety center" and the lateral structures "the feeding center" of the stereotaxic approach. From the tuberal hypothalamus, the "satiety message" conveyed by circulating leptin spreads to other hypothalamic and extra-hypothalamic neurocircuits to induce the satiety sensation, halt eating, and promote energy-intensive responses and behaviors such as thermogenesis, immunity, locomotion, growth, and reproduction (Park and Ahima 2015).

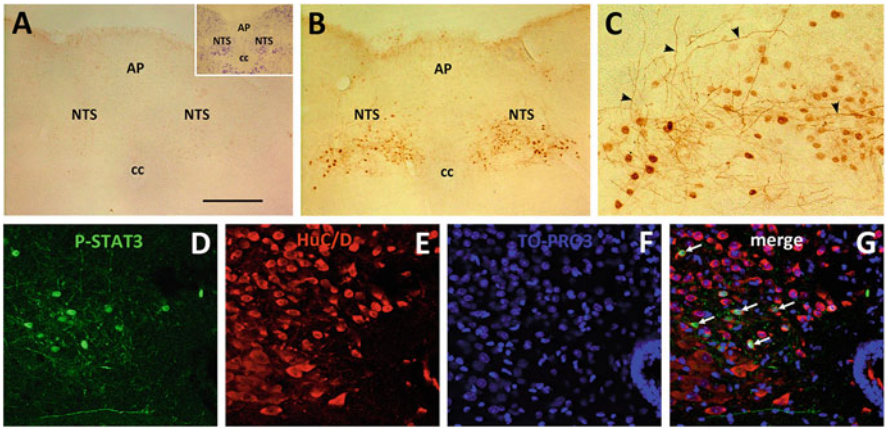


**Fig. 4** Activation of the Jak2-STAT3 signaling pathway in the DVC of the brainstem by circulating leptin. In a control mouse (**a**), phospo-STAT3 (P-STAT3) immunoreactivity is not detectable in the DVC (see text for details). In a mouse intraperitoneally treated with leptin for 40 min (**b and c**), numerous P-STAT3 immunoreactive neurons appear in the NTS, where also neuronal projections are positive for P-STAT3 (arrowheads in **c**). Double immunostaining experiments and confocal microscopy analyses (**d**–**g**) show that P-STAT3 immunoreactivity in the NTS is located into neuronal cells expressing the neuronal marker HuC/D (arrows). TO-PRO3 is a fluorescent nuclear counterstaining. cc, central canal. Bar: **a** and **b** 150 μm; inset of **a** 400 μm; **c**–**g** 40 μm

The discovery of leptin, more than a decade ago, was hailed by the scientific community as the solution to the treatment of human obesity. Unfortunately, it soon emerged that, except for very rare leptin-deficient individuals (see below), obese humans are minimally responsive to exogenous leptin: they develop leptin resistance in the brain and even high levels of circulating leptin are unable to reduce feeding and body weight. Several mechanisms have been proposed to account for the leptin resistance seen in the obese, including defective leptin transport across the BBB (Banks 2003), impaired leptin intracellular signaling (Munzberg and Morrison 2015), and endoplasmic reticulum stress in leptin-sensitive neurons (Ozcan et al. 2009). The neurobiological basis of leptin resistance is a very active area of research with the potential to lead to the development of molecules that act as leptin sensitizers to treat obesity.

## Insulin

Insulin produced and secreted by pancreatic beta cells regulates blood glucose and glucose metabolism by acting on peripheral organs. However, insulin also exerts effects on the brain, where it controls food intake and the energy balance. Glucose-induced insulin secretion is proportional to body fat stores (Bagdade et al. 1967), and circulating insulin enters the brain through a specific transport machinery (Baura et al. 1993). Intracerebroventricular administration of insulin reduces food intake in

experimental animals (Woods et al. 1979). Insulin receptors are diffusely expressed in the brain, especially in the hypothalamic and brainstem areas that are crucial for food intake regulation (Perry and Wang 2012). The anorectic effect of insulin is mainly due to inhibition of orexigenic NPY/AgRP neurons and stimulation of anorexigenic POMC neurons (Dodd and Tiganis 2017). Thus, its satiety action converges to a significant extent on the hypothalamic neurocircuits that are targeted by leptin, although its satiety action is less effective and involves different intracellular signaling systems. Notably, in the hypothalamus of morbidly obese patients, leptin resistance is often associated to insulin resistance.

## Ghrelin

Ghrelin, first discovered as the endogenous ligand of the growth hormone secretagogue receptor 1a, is a peptide hormone produced and secreted into the blood by the stomach (Kojima et al. 1999). Only its acylated form is able to bind to ghrelin receptor in the brain and in peripheral organs and to cross the BBB (Kojima et al. 1999). Serum ghrelin concentrations are augmented by fasting and reduced by refeeding, and central or peripheral ghrelin administration strongly increases food intake, adiposity, and body weight in experimental animals (Tschöp et al. 2000; Nakazato et al. 2001) as well as humans, where it also enhances appetite (Wren et al. 2001). In the brain, ghrelin receptors are found in several hypothalamic and extrahypothalamic areas, such as hippocampus, substantia nigra, ventral tegmental area, and all three DVC components in the brainstem (Zigman et al. 2006). They are also highly abundant in NPY/AgRP neurons of the hypothalamic ARC, where selective re-expression of ghrelin receptor in fully ghrelin receptor-deficient knockout mice has been shown to restore the orexigenic response to administered ghrelin and to normalize the lowered blood glucose induced by caloric restriction (Wang et al. 2013). Based on these data, the orexigenic action of ghrelin is therefore held to be closely linked to the depolarization and activation of orexigenic NPY/AgRP neurons of the hypothalamic ARC. Overall, ghrelin stimulates eating and helps to maintain normal blood glucose levels upon fasting or calorie restriction. For this reasons, it is often referred to as the "hunger hormone." To date, it is the only known orexigenic hormone produced by the gastrointestinal tract. A role for ghrelin in feeding behavior has been documented by an action not only on the hypothalamus but also on the DVC of the brainstem (Suzuki et al. 2010). Furthermore, by interacting with several neurotransmitter and peptidergic systems of the brain, it also regulates complex energy-intensive processes and behaviors such as stress responses, growth, and reproduction (Al Massadi et al. 2017).

## Cholecystokinin

CCK is a small peptide secreted from specific enteroendocrine cells of the duodenum, the first segment of the small intestine, and plays well-established roles in

digestive processes. The fatty and/or amino acids contained in the chyme entering the duodenum stimulate the release of CCK, which induces delivery into the small intestine of digestive enzymes from the pancreas and bile from the gallbladder. As noted above, in 1973 its circulating levels were found to increase rapidly in response to meals and it was demonstrated to act as a satiety factor (Gibbs et al. 1973). Subsequent studies confirmed its acute satiety effect also in humans (Kissileff et al. 1981; Beglinger et al. 2001). CCK receptors are widely distributed in the brain both in the tuberal hypothalamus and in the DVC of the brainstem (Ballaz 2017). However, attempts to correlate its blood levels to its anorectic effect have not been conclusive, CCK does not appear to be able to cross the BBB and, most importantly, central administration of CCK receptor antagonists does not blunt the satiety effect of peripherally administered CCK (Corp et al. 1997). The search for other ways by which CCK could act has led to the discovery that its satiety effect depends on a local and paracrine action on the gastrointestinal vagal sensory terminals that innervate the intestinal mucosa and project into the NTS. The anorectic effect of CCK is abolished by lesion of vagal afferent nerves by surgery (subdiaphragmatic vagotomy) or chemical treatment (using capsaicin, which selectively destroys small unmyelinated visceral sensory fibers) (Iwasaki and Yada 2012). Importantly, POMC neurons are not only found in the lateral part of the hypothalamic ARC, but also in the NTS of the brainstem, where a further POMC neuronal population is involved in energy balance regulation (Zhan et al. 2013). The CCK-sensitive vagal afferents activate NTS POMC neurons, which in turn recruit satiety brainstem neurocircuits through MC4R (Fan et al. 2004), thus mirroring the action of leptin and insulin in the ARC POMC system of the tuberal hypothalamus. Collectively, these studies show that the peripheral terminals of vagal afferents play an important role in energy balance regulation by sensing meal-evoked gut-derived peptides and acting on the DVC. Notably, a similar gut-to-brain satiety pathway has been hypothesized also for other gastrointestinal and pancreatic hormones that regulate feeding and metabolism, such as peptide YY and glucagon-like peptide-1 (GLP-1).

## Peptide YY and Pancreatic Polypeptide

The NPY family of peptides comprises three highly homologous 36-amino acid peptides: NPY, peptide YY, and pancreatic polypeptide (PP). Whereas NPY is chiefly expressed by neuronal cells in the brain, peptide YY is primarily produced by enteroendocrine cells of the ileum and colonic mucosa, and PP by pancreatic islet PP cells (Ekblad and Sundler 2002). All these peptides act through at least five widely distributed functional receptors: Y1, Y2, Y4, Y5, and Y6. Nutrient ingestion stimulates gastrointestinal production and secretion in the blood of PP and peptide YY. A potential role for PP as a circulating satiety factor was first surmised based on the observation that meal-induced PP secretion was blunted in children with Prader-Willi syndrome, a rare childhood genetic disorder characterized by obesity, diabetes, cognitive impairment, and infertility (Zipf et al. 1981). Subsequent animal and

human studies confirmed its satiety effect. PP regulates food intake by acting on hypothalamic Y4 receptors, although its mechanism of action does not seem to involve primarily the ARC. It inhibits the orexin orexigenic pathway in the LH and simultaneously stimulates the BDNF anorexigenic pathway in VMH (Sainsbury et al. 2010).

Peptide YY is found in the blood in two forms, $YY_{1-36}$ and $YY_{3-36}$, the latter form being the more effective (Chelikani et al. 2005). The mechanism of action of peptide $YY_{3-36}$ is very different from that of PP. As described in Y2 receptor-deficient mice, where peripheral administration of neuropeptide $YY_{3-36}$ evokes no anorectic response (Batterham et al. 2002), this satiety factor acts through Y2 receptor, not Y4 receptor. Y2 receptor is widespread in the body. In the hypothalamus, circulating neuropeptide $YY_{3-36}$ may diffuse over the median eminence, reach the NPY/AgRP neurons of the ARC, and inhibit the electrical activity of the NPY orexigenic system by acting through Y2 receptors (Batterham et al. 2002). However, Y2 receptors are also found in peripheral vagal afferents, and bilateral subdiaphragmatic vagotomy reduces the anorectic effect of intraperitoneal neuropeptide $YY_{3-36}$ (Abbott et al. 2005; Koda et al. 2005). These data indicate that neuropeptide $YY_{3-36}$ acts both on hypothalamic ARC neurocircuits and on peripheral vagal afferents, where it likely evokes as yet unknown neural circuits that inhibit feeding behavior.

## Glucagon-Like Peptide-1

The gut neuroendocrine cells that produce peptide YY also synthesize pre-proglucagon, a large precursor protein that is further processed to produce numerous biologically active peptides, including glucagon, GLP-1, GLP-2, and oxyntomodulin. All these peptides are secreted in the blood during feeding and play interconnected and redundant roles on digestive processes and metabolism, such as gastric emptying, gut motility, nutrient absorption, and insulin secretion (Spreckley and Murphy 2015). For many of them, a true action on the nervous system to reduce food intake is still debated. GLP-1 is the peptide that has attracted the most attention in the past few years, also because of its therapeutic potential for diabetes (see chapter ▶ "Roles of Gut Hormones in the Regulation of Food Intake and Body Weight"). It is an incretin hormone, whose primary effect is to enhance glucose-stimulated insulin release by pancreatic beta cells and to reduce blood sugar, but it also has satiety effects (Vilsbøll and Holst 2004). Gut vagal sensory terminals express GLP-1 receptors, whose stimulation evokes action potentials in vagal nodose ganglion neurons (Kakei et al. 2002). Importantly, the anorectic effect seen after peripheral administration of GLP-1 is abolished by abdominal vagotomy in rats (Abbot et al. 2005) and by capsaicin pretreatment in mice (Talsania et al. 2005). Altogether, these data suggest that the satiety effect of GLP-1 is to a large extent due to activation of the vagal-NTS brainstem route. However, GLP-1 receptors are also found in key brain areas for energy balance regulation, including hypothalamus and brainstem (Merchenthaler et al. 1999). Recently, circulating GLP-1 has been shown to exert an inhibitory effect on eating through direct activation of GLP-1 receptors in

the DVC of male rats (Punjabi et al. 2014), suggesting that the satiety effect of secreted GLP-1 is likely due to an action on both peripheral vagal terminals and brainstem feeding centers through as yet unknown mechanisms.

### Amylin

Amylin, also known as islet amyloid polypeptide, is a 37-amino acid peptide co-secreted, together with insulin, by pancreatic beta cells in response to nutrient ingestion (Cooper et al. 1987). After its discovery, circulating amylin was shown to be involved in gastric emptying and in glucagon and digestive enzyme secretion (Hay et al. 2015). However, in rats food intake involves a rapid increase in blood amylin that correlates with meal size, and intraperitoneal administration of recombinant amylin reduces food intake in a dose-dependent manner (Lutz et al. 1995). In addition, intravenous administration of the amylin receptor antagonist AC187 stimulates eating in rats through increased meal size (Reidelberger et al. 2004). For these reasons, amylin is regarded as a physiological circulating satiety factor in both rodents and humans. Interestingly, its mechanism of action primarily involves the area postrema, the brainstem circumventricular organ. Amylin receptor is highly expressed in neurons of the area postrema (Becskei et al. 2004), and stereotactic injection of amylin in the area postrema inhibits eating, whereas injection of the amylin receptor antagonist AC187 stimulates it (Mollet et al. 2004). Finally, the satiety effect of amylin is abolished in animals with area postrema lesion, whereas it is maintained in capsaicin-treated rats and in animals subjected to subdiaphragmatic vagotomy (Lutz et al. 2001). The brainstem neurocircuits engaged by amylin have not yet been elucidated. However, in the area postrema, it activates a substantial population of noradrenergic neurons (Potes et al. 2010) that affect the excitability of NTS neurons, including POMC neurons, where the satiety message conveyed by amylin converges with that of other gastrointestinal satiety factors including CCK, peptide YY, and GLP-1.

## Conclusion and Future Directions of Research

Our knowledge of the neuroendocrinology of the energy balance, gained in the past few decades, comes mainly from animal models. Albeit still largely incomplete, the evidence collected to date allows to make some general considerations on how hormones act on the brain to regulate feeding behavior, energy expenditure, and, ultimately, body weight.

Numerous hormones produced by peripheral organs affect energy balance regulation through such an action. Their metabolic information reaches the brain through at least four different routes: interaction with specific BBB transporters (insulin, leptin); diffusion to adjacent brain areas through the circumventricular organs (ghrelin); direct action on neurons in the circumventricular organs (amylin); and, finally, stimulation of peripheral vagal sensory afferents (CCK, peptide YY,

and GLP-1) and activation of gut-to-brain pathways. Importantly, these routes are not mutually exclusive and a hormone can often reach its brain targets through multiple routes. For instance, the area postrema is crucially involved in mediating the effect of amylin but also contains neurons and glial cells that sense several other circulating signals related to energy homeostasis, like ghrelin, CCK, and GLP-1 (Young 2012).

Each hormone involved in energy balance homeostasis likely regulates distinctive, subtly different features of feeding behavior, metabolism, and energy homeostasis. However, knowledge in this area is still very limited.

The vast majority of such hormones are satiety factors. Only one feeding factor, ghrelin, has been identified to date, possibly indicating that the brain's default setting is to search for food and to feed, and that circulating satiety cues keep the feeding neurocircuits inhibited and the satiety neurocircuits activated between meals.

Some energy balance hormones, including leptin, insulin, and ghrelin, seem to have a predominantly longer-term metabolic regulatory action, providing to the brain information on the body energy stores and playing a permissive or restrictive role on energy-intensive behaviors, such as growth and reproduction. These hormones primarily act on the neurocircuits of the tuberal hypothalamus. Other energy balance hormones, including CCK, neuropeptide YY, GLP-1, and amylin, appear to be more suited to playing a short-term action on satiety and feeding behavior and primarily act on brainstem feeding neurocircuits.

Emerging evidence indicates that mammalian energy balance hormones can affect feeding behavior through multiple parallel neurocircuits in different hypothalamic and brainstem areas involving diverse neurotransmitter and neuropeptidergic systems. At the same time, each neurocircuit is targeted by several energy balance hormones, giving rise to an extremely complex, overlapping, distributed, and redundant neuronal system. Thus, it is not surprising that, for instance, ghrelin knockout in adult mice affects neither feeding nor body weight (McFarlane et al. 2014) or that CCK-knockout mice exhibit a normal feeding behavior (Lo et al. 2008). From a physiological viewpoint, the redundancy may be explained with the need to ensure a normal or normal-like feeding behavior even in extreme environmental conditions, whereas from a pathological viewpoint it explains why it is very difficult to obtain significant and durable changes in body weight and to find effective drugs to treat human obesity.

However, basic neuroendocrinology research in this area has the potential to lead, in the near future, to the discovery of more effective anti-obesity drugs. Importantly, investigation of mutations homologous to those causing obesity in mouse models has allowed to identify some human monogenic obesity syndromes related to leptin deficiency (Farooqi et al. 1999) and dysfunctional mutations of *POMC* (Krude et al. 1998) or *MC4R* (Hinney et al. 1999) genes. Although these monogenic forms of obesity are rare, they indicate that the energy balance neurocircuits are evolutionarily highly conserved among species. Murine models are therefore suitable to study the central mechanisms of energy balance regulation and to identify novel molecular targets for the treatment of human obesity.

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# The Adipose Organ

3

Saverio Cinti

## Contents



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**Abstract**

White and brown adipocytes form tissues (WAT and BAT, respectively) contained in a dissectible organ formed by subcutaneous and visceral depots. WAT and BAT have almost opposite roles in partitioning energy between two fundamental needs for survivals: metabolism and thermogenesis. All organs in mammals are composed by different tissues acting with different physiology to reach a common finalistic purpose. The plasticity of adipocytes, i.e., their reversible physiologic transdifferentiation ability, offer an explanation to their common membership to adipose organ, but imply a new physiologic ability for mature cells: the physiologic reversible transdifferentiation property. This conversion ability of mature adipocytes is supported also by the plasticity of mammary glands during pregnancy, lactation, and postlactation periods when white adipocytes convert reversibly to milk-secreting glandular cells (pink adipocytes). During chronic positive energy balance, the adipose organ undergoes a whitening phenomenon with hypertrophic adipocytes. Hypertrophic adipocytes show several alterations of their organelles including those able to activate the inflammasome system. Stressed adipocytes die leaving conspicuous debris that must be removed by macrophages. This last cell surrounds debris and form crown-like structures (CLS) responsible for a chronic low-grade inflammation that link obesity to T2 diabetes. The plasticity of adipocytes could be used to reverse the phenomenon.

**Keywords**

Adipocytes · WAT · BAT · Pink adipocytes · Obesity · T2 diabetes · Hypertrophic adipocytes

## Adipocytes of White Adipose Tissue of Obese Animals and Humans Are Hypertrophic

Adipocytes are large spherical cells allowing to store high levels of energy in minimum space. A total of 90% of their volume is formed by a single lipid droplet contained into the cytoplasm (unilocular adipocytes). The nucleus is squeezed at periphery and the thin cytoplasmic rim contains all normal organelles found in other cell types. Quite specific for adipocytes are numerous pinocytotic vesicles on the cell membrane and a distinct external lamina on its outer side. A variable amount of collagen fibrils is also present on the interstitial side of external lamina. Mitochondria are thin and elongated with sparse and randomly oriented cristae (Cinti 2017).Their energy, under the chemical form of triglycerides, is essential for survival in the intervals between meals that can be prolonged up to several weeks if the number of adipocytes in the organism is sufficient. In order to guarantee the maximal energy reserve, adipocytes are able to increase their size (hypertrophy) and number (hyperplasia) during positive energy balance periods (Faust and Miller 1981). In genetically obese mice and humans, the size of adipocytes can be seven (subcutaneous in mice, 1.6 in humans) or six (visceral in mice, 2.6 in humans) times larger

than lean controls; thus, the large adipocytes can become gigantic in obese mice and humans (Camastra et al. 2017; Murano et al. 2008).

Unilocular adipocytes are also called white adipocytes because they form a white tissue (WAT, yellow in humans) that is supplied by nerves (mainly unmyelinated noradrenergic fibers) and vessels.

White adipocytes secrete a series of adipokines (leptin, adiponectin, adipsin, resistin, etc.) with many direct endocrine properties playing important roles also in the regulation of animal behavior mainly regarding food search and intake and glucose and lipid metabolism (see Giralt et al. 2015 for recent review of this topic).

## Hypertrophic Obese Adipocytes Are Stressed

Electron microscope analyses revealed that hypertrophic adipocytes in genetically as well as in diet-induced obese mice have several abnormalities in their organelles. Mitochondria become smaller and reduced in number, with some hypertrophic irregular mitochondrion. Golgi complex become hypertrophic, rough endoplasmic reticulum dilates, and often glycogen cumuli are present. Some dense small crystals resembling calcium aggregates have been found at the lipid droplet surface where the proteins (e.g., perilipin1) regulating lipolysis are usually located. Some hypertrophic adipocytes resulted so rich in calcium crystals that were positive for the calcium-specific von Kossa histochemistry reaction at light microscopy (Giordano et al. 2013). In some obese adipocytes, cholesterol crystals were described in line with the well-known positive correlation between size of adipocytes and their cholesterol content. Obese adipocytes with signs of cytoplasmic degeneration and lipid extrusion were also found with both transmission electron microscopy and high-resolution scanning microscopy. Macrophages close to these altered obese adipocytes were frequently found. These techniques also revealed an increased amount of collagen associated to the external surface of the external lamina.

Quantitative analyses revealed that all the above-described alterations (with the exception of calcium crystals) in obese adipocytes were more represented in visceral than in subcutaneous fat.

## Hypertrophic Obese Adipocytes Die

Specific features denominated crown-like-structures (CLS) are frequently found in the adipose tissue of obese animals and humans (about 30 times more frequent in obese than lean fat) (Fig. 1).Each single CLS is formed by active (MAC2 immunoreactive) macrophages surrounding debris of death adipocytes (Cinti et al. 2005). The debris is mainly composed by a gigantic free lipid droplet liberated in the interstitial space by the dead adipocyte. More than 90% of all MAC2 positive macrophages formed CLS. Electron microscope revealed that the lipid droplet is surrounded by active macrophages in direct contact with the surface of the lipid droplet. In most cases, the side of cytoplasm in contact with the lipid droplet resulted

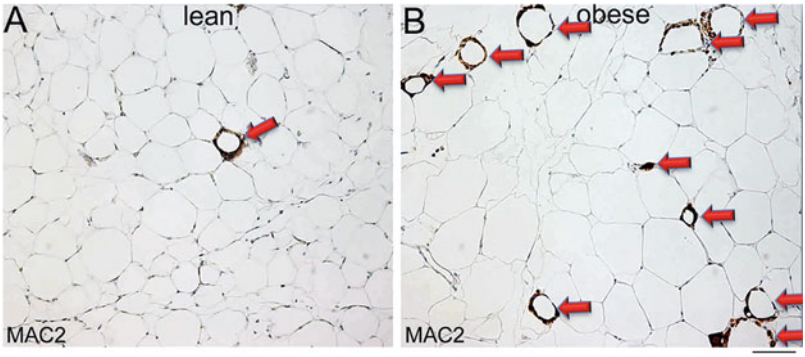


**Fig. 1** Immunostaining of active macrophages (MAC2) in visceral WAT of lean (**a**) and obese (**b**) mice. Note the presence of crown-like structures (CLS, arrows) apparently surrounding adipocytes. CLS density is about 30 times higher in obese fat. Bar = 100 μm in both panels (From Cinti et al. 2005)

filled by reabsorbed lipids. On the opposite side (toward the interstitium), an irregular basal membrane is often observed; thus, the macrophages layer result in the space between the basal membrane and the lipid droplets (Fig. 2). Importantly in most CLS no cytoplasm of adipocytes is visible between the lipid droplet and the basal membrane, allowing to speculate that this part of adipocytes was completely lost probably due to a degenerative phenomenon. In line with this hypothesis, residual cytoplasmic debris were found into phagosomes inside the cytoplasm of macrophages. Furthermore, electron microscope revealed all morphologic transformative steps between normal adipocytes and degenerating adipocytes. These last types of cell were often surrounded by macrophages and lipid droplets extruding or just extruded from degenerating adipocytes surrounded by cytoplasmic projections of macrophages or inside their cytoplasm were also observed. Perilipin1 (Plin1) is an adipocyte-specific protein localized at lipid surface of metabolically active adipocytes. Immunohistochemistry with anti-Plin1 antibodies revealed absence of signal from CLS supporting the death of adipocytes (Fig. 3).These observations offered an explanation to the cause of the well-known chronic low-grade inflammation due to the macrophage infiltration of obese adipose tissues.

## Death of Adipocytes Is due to Hypertrophy and Not Linked to the Obesity Per Se

In order to verify if hypertrophy per se is sufficient to induce CLS, the adipose tissues of mice lacking hormone sensitive lipase was studied. This enzyme is important to allow lipolysis in adipocytes; thus, it absence induce adipocytes hypertrophy. Adult $HSL^{-}/^{-}$mice are lean, but their adipose tissues resulted rich of CLS (same density as in obesity) with all the morphologic and immunohistochemical characteristics of CLS found in obese fat (Cinti et al. 2005). Thus, hypertrophy of adipocytes is sufficient to induce a histopathology very similar to that found in obese adipose tissue. In line with

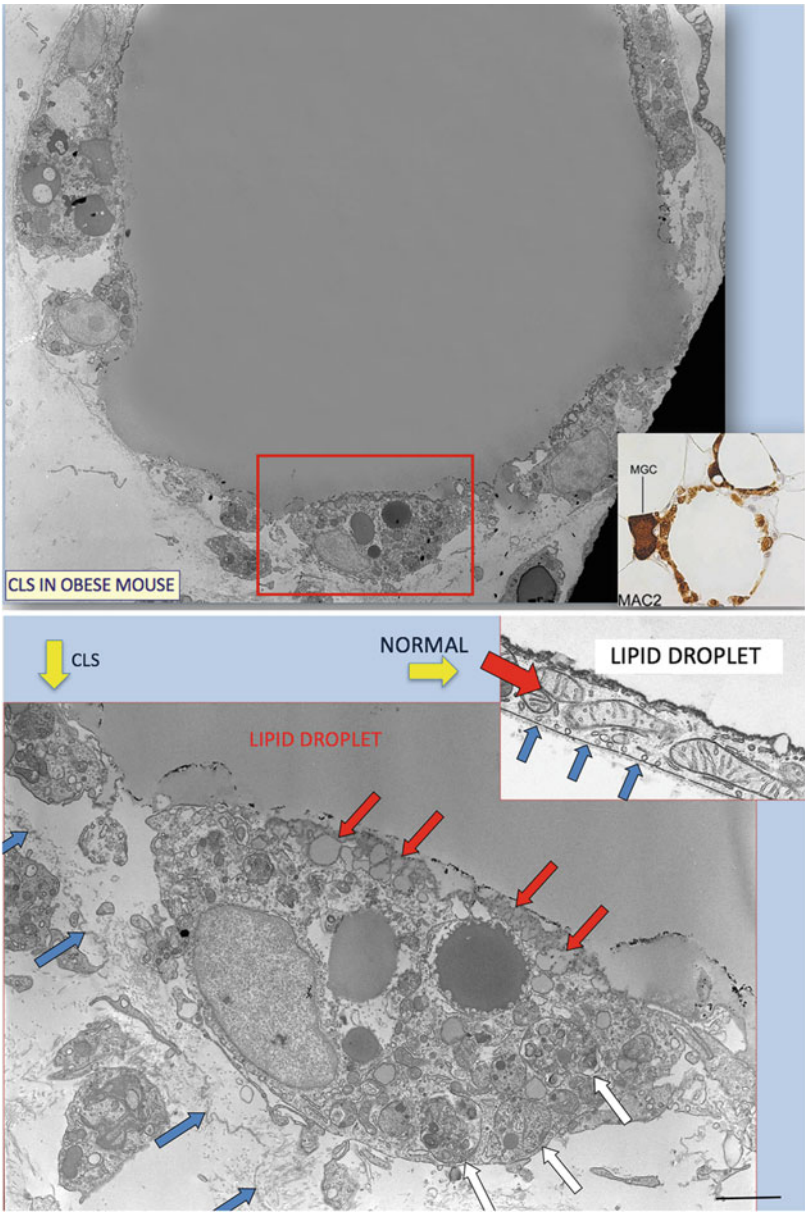


**Fig. 2** Electron microscopy of a CLS. Note the classic ultrastructure of macrophages surround in the lipid droplet (upper panel). MAC2 immunohistochemistry of a similar CLS is shown in the small frame of upper panel. The red framed area of upper panel is shown in lower panel. The normal ultrastructure is shown of small frame in lower panel. Note that the macrophage is located between the lipid droplet and the basal membrane (blue arrows). The cytoplasm of adipocyte is not visible in CLS (compare with small frame), and residual structures of degenerating cytoplasm are visible inside phagosomes into macrophage (white arrows). Reabsorption lipid vacuoles are visible on the side facing the residual lipid droplet (red arrows). Bar = 5 μm in upper panel and 1.7 μm in lower panel (From Cinti et al. 2005)

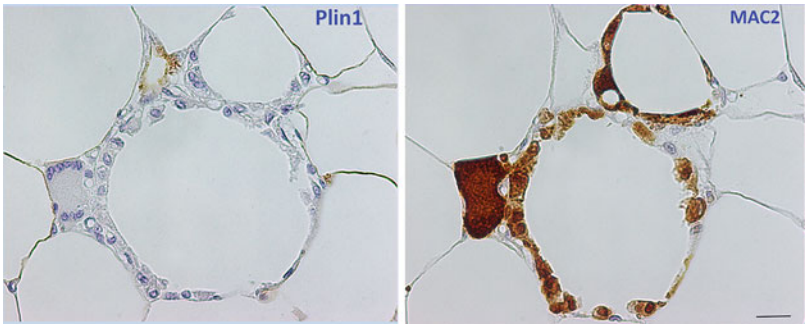


**Fig. 3** Serial sections of a CLS in obese mouse visceral fat. Perilipin1 (Plin1) immunostaining is present only in adipocytes surrounding the CLS. Most macrophages of CLS are MAC2 immunoreactive, including giant multinucleated cells. Bar = 28 μm in both panels (From Cinti et al. 2005)

the hypothesis that CLS are important to induce insulin resistance and T2 diabetes is the old notion that there is a positive correlation between size of adipocytes and insulin resistance. Furthermore, it is interesting that most obese persons and animal models with hyperplastic obesity (increased number of small adipocytes) do not develop a metabolic phenotype. In line with these data, a higher number of CLS are present in lean and obese patients with larger adipocytes (Cinti et al. 2005).

## Induced Death of Adipocytes in FAT-ATTAC Transgenic Mice Give Rise to CLS

In order to verify if CLS truly represent sites of dead adipocytes, the well-characterized model of mice in which specific death of adipocytes (apoptosis by caspase 8 activation) can be induced by dimerization of the transgenic construct (FAT ATTAC model)has been studied. The time course study of morphologic effects on two different fat depots of dimerizer injection showed an acute response (first days) characterized by infiltration of adipose tissues by granulocytes and lymphocytes followed immediately by MAC2 not-immunoreactive (negative) macrophages infiltration. MAC2 is an index of phagocytosis activation. The next step at day 4–5 after injection showed areas of Plin1 negative adipocytes (i.e., dead adipocytes) surrounded by Plin1 immunoreactive adipocytes (i.e., metabolically active alive adipocytes). In the next day macrophages invaded the areas of apoptotic adipocytes and number of MAC2 immunoreactive adipocytes increased progressively. After 10–15 days after injection the vast majority of macrophages resulted MAC2 positive and all dead adipocytes formed typical CLS. Of note, the acute inflammatory cells disappeared after the first postinjection days. Electron microscopy revealed the same morphologic alterations of adipocytes described above in obese hypertrophic adipocytes including all phases of progressive organelles damage till the evidence for frank degeneration of adipocytes (Murano et al. 2013).

Thus, this time-course study demonstrated that CLS are indeed sites of dead adipocytes surrounded by active reabsorbing macrophages.

## Hypertrophic Adipocytes Die by Pyroptosis

Short after the hypothesis of death of adipocytes (Cinti et al. 2005), an elegant study by Spalding et al. showed that human adipocytes die after a lifespan of about 10 years, thus confirming that adipocytes die in physiologic conditions (Spalding et al. 2008). In this work, it was also shown that in obese fat the rate of death is not changed, but due to the higher number of adipocytes the dead adipocytes were indeed higher than in fat of lean persons. The mechanism inducing death of adipocytes was unknown, but morphologic data suggested a stressed status of hypertrophic adipocytes described above. Furthermore, stressed hypertrophic adipocytes contain calcium and cholesterol crystals. These crystals are known inducers of the NLRP3 inflammasome system activation that produce active caspase 1. Caspase 1 is responsible for IL18 and IL1β activation that induces death of the cells. This type of cell death is called pyroptosis. Interestingly NPRP3 has been shown to be activated in obese fat with local production of inflammatory IL18 and IL1β activation. In order to prove that stressed adipocytes had activated, the NLRP3 system several markers (including NLRP3, ASC, TNPIX, and caspase1) have been checked both as gene expression in the tissue and as protein expression inside the cytoplasm of hypertrophic adipocytes (Giordano et al. 2013). Immunohistochemistry for caspase1 resulted in an unusual staining of cytoplasm of adipocytes, i.e., the staining was not uniform as resulted for other proteins such as, for example, Plin1 (Murano et al. 2013) or Leptin (Cinti et al. 1997) or S-100b (Barbatelli et al. 1993) but formed small spherical structures recalling the spherical shape of NLRP3 protein complex. Furthermore, caspase 1 immunostaining is absent in the tissues of the FAT ATTAC model of fat-specific apoptosis described above.

## Macrophages and Multinucleated Giant Cells Reabsorb Debris of Dead Adipocytes and Stimulate Adipogenesis

The size of hypertrophic obese adipocytes that die by pyroptosis is gigantic in proportion to that of normal macrophages infiltrating obese fat. Because residual debris of dead adipocytes are close to the same gigantic size, it is not surprising that macrophages form syncytia similar to those formed in foreign body reactions. The size of CLS in obese fat is variable; the largest approach that of surrounding hypertrophic adipocytes the smallest are almost exclusively composed by macrophages with the central residual lipid droplet barely visible. These data allow to think that CLS are sites of reabsorption of debris derived from hypertrophic adipocytes death. In line with this hypothesis, a time course study of fat inflammation in visceral fat of HFD treated mice showed that CLS number progressively increase in this fat depot of these animals in parallel with the increase of fat and of the size of adipocytes

(Strissel et al. 2007). At week 16 of HFD, about 70% of epididymal depot was occupied by CLS and after 4 further weeks of HFD the % of tissue occupied by CLS dropped to less than 20% with a parallel decrease in weight of the depot. These data suggest a renewal of the tissue and recently Lee et al. (2013) identified CLS an adipogenic niche. In particular they found that clusters of proliferating PDGR-α-marked preadipocytes where in close connection with CLS. Furthermore, they showed that CLS-macrophages produce osteopontin and a subpopulation of PDGR-α-marked preadipocytes express CD44 that is the receptor for osteopontin.

Further data supporting the reabsorbitive-clearing role of CLS macrophages have been recently produced by Haka et al. (2016) that showed an extracellular digestive activity of CLS macrophages denominated exocytosis.

## In Humans, Cyst-Like Structures Are Gigantic CLS

Hypertrophy of adipocytes seems to be the prerequisite for CLS formation. In a case series study of 28 obese patients undergoing bariatric surgery, two patients with extreme hypertrophy of adipocytes have been described (Camastra et al. 2017). Their adipocytes resulted about 30% larger than any other obese patient studied. Only in these two cases rare gigantic CLS denominated cyst-like structures (CyLS) were found (Fig. 4). Their anatomical composition was similar to classic CLS, i.e., they were composed by CD68 immunoreactive macrophages surrounding a lipid-like structure Plin1 negative. In some CyLS, macrophages formed syncytial structures. Their size was approximately ten times that of the largest CLS found in those as well in all other patients of this case series. This size excludes the possibility that CyLS represent debris of single death adipocyte and the hypothesis shown in Fig. 5 was proposed: the very thin rim of cytoplasm, pushed by the expanding lipid droplet, is damaged and imaging a confluence of enormous lipid droplets extruded by ruptured adipocytes it can be supposed the formation of very large oil-like lipids free in the interstitium. As a matter of fact, olive oil injections in inguinal fat for vitamin A administration reproduced very similar structures. Gigantic lipid droplets represent gigantic debris requiring reabsorption as those smaller deriving from death of single adipocytes; thus, it is not surprising to see CD68 immunoreactive macrophages (also syncytial) surrounding the lipid structure.

## Visceral Adipocytes Have a Lower Critical Death Size

Since the original clinical observations, it became evident that accumulation of fat in humans is different in males and postmenopausal females (abdominal or central body forming apple shape) and premenopausal females (gluteo-femoral or lower body forming pear shape). This different distribution has important health consequences because the metabolic associated disorders affect only the apple shaped obesity (central or visceral obesity) implying important differences in the fat site distribution (Bjorntorp 1997). As a matter of fact, fat localize at two compartments of the body:

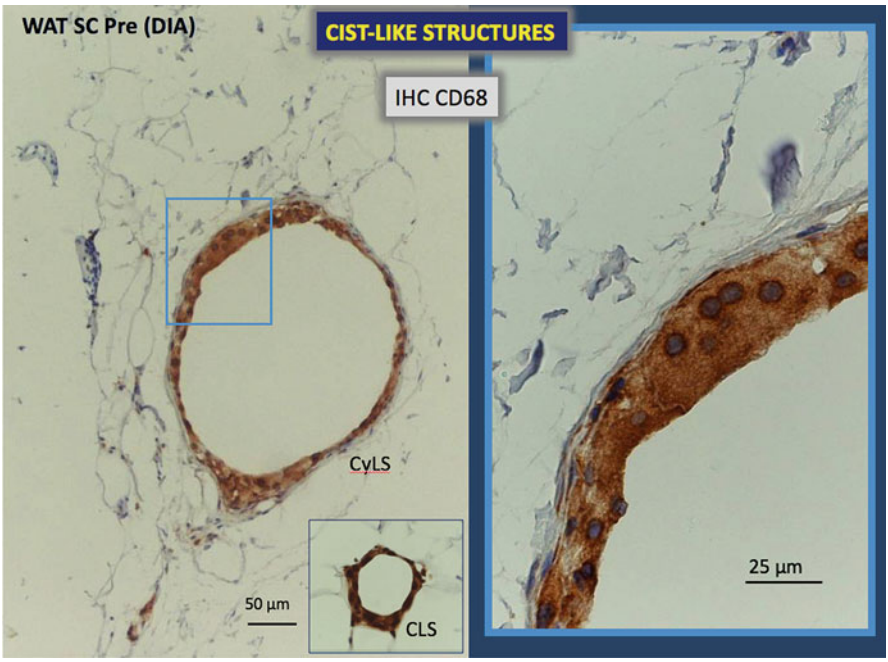


**Fig. 4** CD68 immunostaining of macrophages forming CLS and cyst-like structures (CyLS: giant CLS) in subcutaneous fat of obese diabetic patient. Note the difference in size between CLS and CyLS (same enlargement in the left panel). The blue framed area is enlarged in the right panel showing the multinucleated giant macrophage. Bars as indicated (From Camastra et al. 2017)

subcutaneous and visceral. The first is contained in the space between skin and muscle superficial fascia, and the second inside the trunk.

In order to understand why visceral fat accumulation is more dangerous for health than subcutaneous fat, the two depots in two different models (ob/ob and db/db) of genetic murine obesity have been studied. The size of adipocytes resulted increased six to seven times both in subcutaneous and in visceral fat, but subcutaneous adipocytes were larger than visceral adipocytes. The CLS density in both compartments was higher in visceral fat. This was unexpected result because of the well-established positive correlation between size of adipocytes and number of infiltrating macrophages. These data suggested a lower critical death size (CDS, size triggering death) for visceral adipocytes (Cinti 2009).

## Fat Inflammation Causes Insulin Resistance

The prevalence of visceral inflammation is relevant because it has been shown a temporal association between fat inflammation and insurgence of insulin resistance. The molecular mechanism linking macrophage infiltration of obese fat and insulin resistance is incompletely known, but several cytokines and factors produced

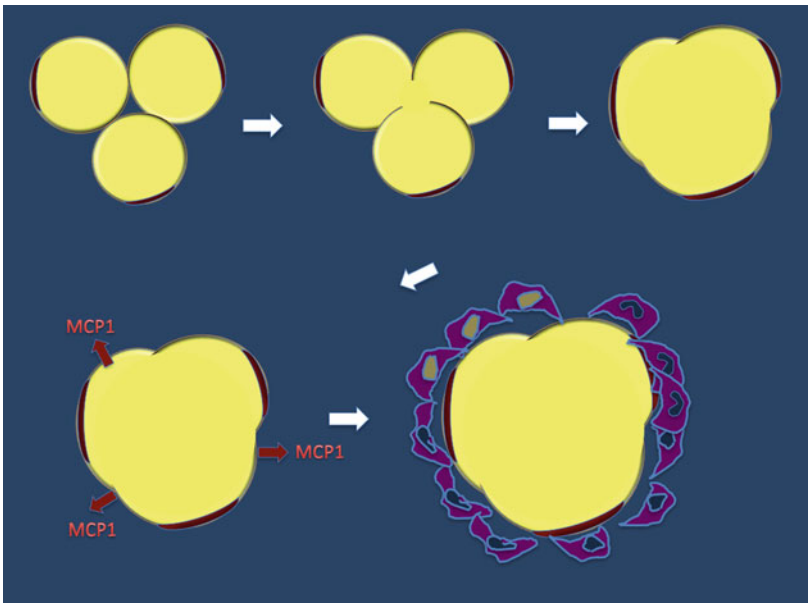


**Fig. 5** Hypothesis for CyLS formation: Very large adipocytes with breakage of their very thin cytoplasmic rim coalesce forming very large lipid droplets remnants ready to be reabsorbed by macrophages attracted by secreted chemoattractant (From Camastra et al. 2017)

by macrophages could play an important role. Since the discovery of a direct link between TNFα hyper production in obese fat and insulin resistance, a causal link between obesity and T2 diabetes was carefully searched for (Hotamisligil 2006). TNFα direct interference with insulin receptor normal signaling was well established, but subsequent other works suggested that several other molecules could also play a role. In 2003 two independent laboratories evidenced the great role for a low grade chronic inflammation mainly due to macrophage infiltration of obese fat (Weisberg et al. 2003; Xu et al. 2003). In these papers, the coincidence between macrophages infiltration and appearance of insulin resistance was established. Furthermore, most of the cytokines with potential role in insulin resistance were found to be present in the stroma-vascular fraction of the tissue implying that its source would be different from that of mature adipocytes as previously thought and macrophages were indicated as the most probable source. Furthermore, stressed hypertrophic adipocytes can cause insulin resistance before their death and obese adipocytes reduce their production of adipsin that exert a positive role on pancreatic β-cells (Lo et al. 2014).

In synthesis, the sequence of events in WAT induced by a chronic positive energy balance possibly linking obesity to type2 diabetes could be (Fig. 6):

1. Hypertrophy of adipocytes
2. Stress of adipocytes with reduced secretion of adipsin, adiponectin, and increased secretion of chemo attractants (mainly MCP1)

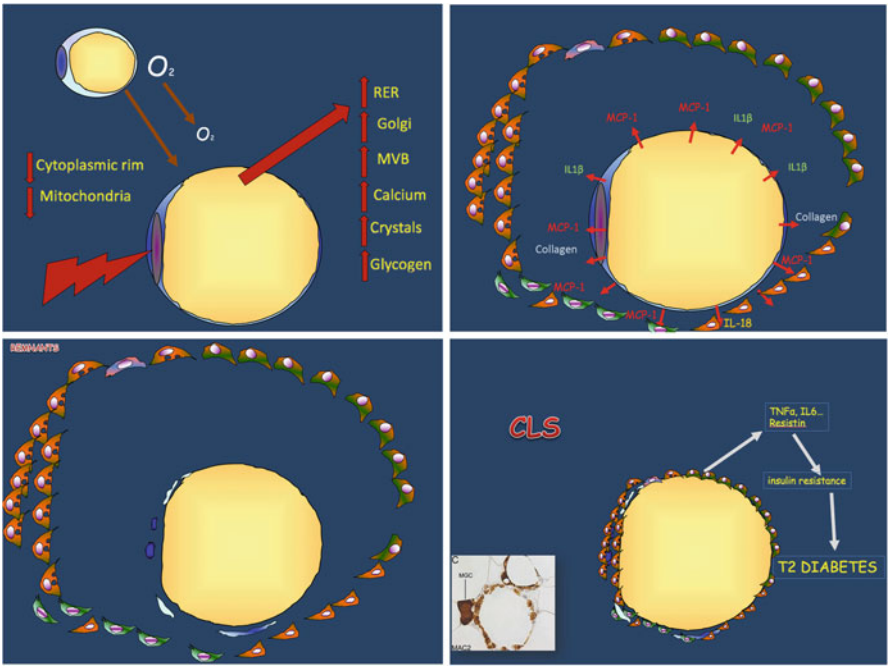


**Fig. 6** Summary of events possibly linking hypertrophy and death of adipocytes to T2 diabetes

3. Death of adipocytes by pyroptosis (with lower critical death size in visceral fat)
4. Formation of gigantic debris (mainly represented by residual free lipid droplets)
5. Formation of CLS or eventually (very hypertrophic cases) CyLS
6. Reabsorption of debris by macrophage phagocytic activity in CLS (by exocytosis, eventually with syncytia formation)
7. Macrophage secretion of cytokines with toxic effects on insulin receptor signaling (including TNFα, resistin, Il-6, and iNOS)
8. Insulin resistance
9. T2 diabetes

## Weight Loss Induces CLS Density Reduction with Amelioration of Metabolic Parameters

Several histopathologic data from fat of patients with obesity treated by bariatric surgery that lost significant amount of fat, showed a reduction in size of adipocytes with a reduction of CLS number. In parallel with these inflammatory parameters reduction, an improvement of metabolic parameters was shown. Interestingly, in spite of a drastic reduction of fat inflammation a persistence of an obesity signature or

incomplete restoring of pancreatic β-cells glucose sensitivity was detected in these patients (Camastra et al. 2017; Cancello et al. 2005, 2013).

## Adipose Tissue Is Organized in Subcutaneous and Visceral Depots

Together with WAT, all adult mammals (humans included) have variable amounts of brown adipose tissue (BAT). BAT is formed by polygonal cells smaller than white adipocytes (about 1/3) with central roundish nucleus and several cytoplasmic small lipid droplets (multilocular adipocytes) (Fig. 7). Brown adipocytes have numerous large mitochondria containing a protein that is uniquely found in this cell type and that is responsible for its function: thermogenesis (Cannon and Nedergaard 2004; Ricquier 2017). When mammals are exposed to cold (temperature under thermoneutrality, i.e., under the temperature not requiring thermogenesis), the sympathetic nervous system (SNS) induces noradrenalin (NE) secretion at the terminal end of sympathetic nerve fibers that directly reach brown adipose tissue (BAT). NE activates cAMP signaling through the specific β3 adrenoceptor. The signaling ends with activation of protein kinase A and subsequent activation of lipases and neo-synthesis of UCP1. This protein is located in the inner mitochondrial membrane (cristae) and acts as protonophore, thus nullifying the proton gradient derived from the beta oxidation of fatty acids and transforming all the energy liberated by the oxidative process into heat. Thus, BAT is composed by cells completely different in anatomy and functions from those of WAT, but we call both these cells adipocytes only for historical reasons essentially due to their old descriptions as lipid loaded cells well before the discoveries of their functions.

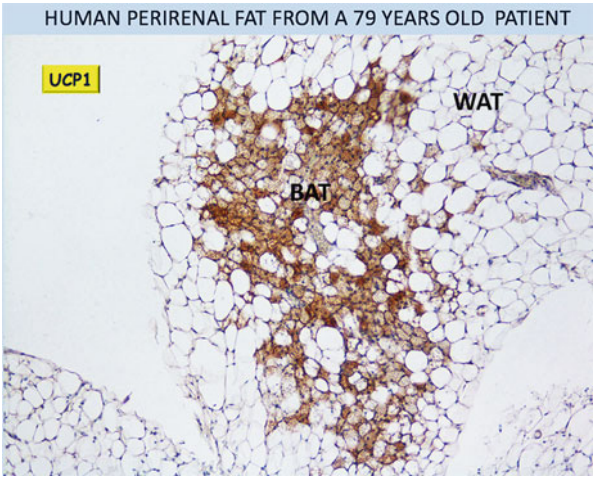


**Fig. 7** UCP1 immunoreactive brown adipose tissue (BAT) mixed to white adipose tissue (WAT) in perirenal fat of a 79-year-old man (From Cinti 2017)

## Adipose Organ of Mice and Humans Is Mixed and Contains also BAT

In spite of their different morphology and physiology, WAT and BAT are contained together in a dissectible organ composed by subcutaneous and visceral depots in all adult mammals (Fig. 8).

In small mammals (mice, rats, ferrets), 60–70% of this organ is located in the subcutaneous and intermuscular compartment, i.e., between skin and skeletal muscles fasciae, with some projections in deeper intermuscular areas. Two main subcutaneous depots are dissectible in these small mammals: anterior and posterior subcutaneous depots (Cinti 1999, 2000, 2001a, b, 2002, 2005). The anterior subcutaneous depot (ASC) is more complex than the posterior (PSC). ASC is mainly dorsal and located in interscapular area with several symmetrical projections (lateral, cervical, axillary, and subscapular). Each of these parts is mixed: formed by BAT and WAT, i.e., within these areas pure BAT lobules are located near pure WAT lobules with mixed tissue at the boundaries. Thus, ASC is mixed with pure WAT near pure BAT and near areas composed by the two cell types. PSC is mainly WAT and located symmetrically in the inguinal area with dorso-lumbar and gluteal extensions. In the inguinal area is always visible a lymph node. Small mixed depots are present in the

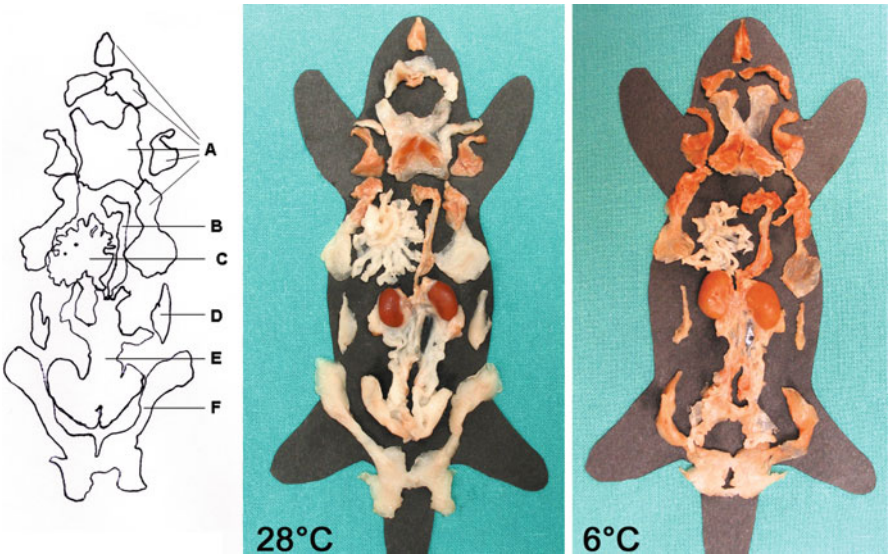


**Fig. 8** Gross anatomy of Adipose Organ of adult female Sv129 mice maintained at 28 °C (left) and 6 °C (right) for 10 days. *A* = anterior subcutaneous depot (formed by interscapular, subscapular, axillo-thoracic, and cervical parts), *B* = mediastinal-periaortic visceral depot, *C* = mesenteric visceral depot, *D* = retroperitoneal visceral depot, *E* = abdomino-pelvic visceral depot (formed by perirenal, periovarian, parametrial, and perivesical parts), *F* = posterior subcutaneous depot (formed by dorso-lumbar, inguinal, and gluteal parts) (From Murano et al. 2005)

limbs. Visceral depots are contained into the trunk: thorax and abdomen. In thorax, fat occupies the mediastinal area with projections following all main aorta branches. In abdomen, a unitary structure denominated abdominopelvic depot surrounds abdominal aorta and its main branches forming perirenal, mesenteric, retroperitoneal, periovarian, parametrial, and perivesical fat in female mice. In male mice, abdominal fat mainly forms the perirenal and retroperitoneal fat. Pelvic fat in male mice forms the perivesical and epididymal depots. Visceral fat is also present in omentum that is very small in mice. Mediastinal and perirenal fat are the richest in BAT and a gradient BAT-WAT is present from aorta to its peripheral branches, i.e., all described depots are close (surrounding) to aorta and its main branches. The fat closest to aorta is usually BAT and a gradual transition toward WAT is found following the peripheral part of the branches. Epididymal fat and omentum (both far away from aorta) are always pure WAT. This anatomy is finalistically easy to explain: heat produced by BAT is quickly transferred to the close aorta and its main branches in order to diffuse thermogenesis to all organisms.

In humans, the anatomy of this organ is quite similar to that described above for small mammals.

Major differences are: (1) subcutaneous compartment is more diffuse and continuous also in the limbs, (2) the interscapular area is less developed, (3) most tissue is formed by WAT, (4) BAT is restricted mainly in peri subclavian and perirenal areas, and (5) BAT is rarely pure (usually lobules of BAT are mixed with WAT). In a case series of about 45 adult patients biopsied in the peri subclavian-peri carotid area, UCP1 immunoreactive BAT in about 1/3 of them have been described (Zingaretti et al. 2009). Furthermore, positron emission tomography with deoxy-fluoro-glucose (PET) showed active uptake signal in the same area, which increased in intensity after cold exposure or in patients with pheochromocytoma (a benign tumor od adrenal gland secreting high levels of catechol amines in the blood) (Saito et al. 2009).

Thus, the human adipose organ is mixed and its BAT component can be activated in adult humans (Cypess et al. 2009; van MarkenLichtenbelt et al. 2009; Virtanen et al. 2009). A recent paper showed that a new β3AR agonist drug (mirabegron) approved for hyperactive bladder is able to activate BAT as visualized by PET in young lean voluntary patients (Cypess et al. 2015).

## BAT Is an Antimetabolic Syndrome Tissue

The presence of BAT in adult humans is of clinical interest because the energy dissipated by BAT thermogenesis could help to treat patients with obesity (Cypess and Kahn 2010). It has been shown that lack of BAT activity favors obesity and T2 diabetes in small mammals (Bachman et al. 2002; Lowell et al. 1993) and treatment of obese animals with β3AR agonists rescue obesity and related disorders (Ghorbani and Himms-Hagen 1997, 1998). Furthermore, BAT activity improves insulin sensitivity (Seale et al. 2011), lipid metabolism (Bartelt et al. 2011), atherosclerosis (Berbee et al. 2015), and increase longevity (Ortega-Molina and Serrano 2013). It

has also been shown that cold exposure of adult patients improves the insulin sensitivity (Chondronikola et al. 2014).

## WAT Can Be Converted into BAT

A major question deriving from the anatomy of adipose organ is related to the finalistic common purpose of WAT and BAT. By definition an organ must be dissectible, containing at least two different tissues, and these tissues should cooperate for a unitary finalistic purpose. Thus, the stomach (widely accepted as an organ) is dissectible and formed by different tissues such as mucosae and smooth muscles. These tissues cooperate with different functions to the unitary finalistic purpose of digestion: mucosae by gastric juice production and smooth muscle by peristalsis. In order to search for the unitary finalistic purpose of WAT and BAT in adipose organ, the dynamic changes of this organ during several physiologic stimuli such as cold exposure and pregnancy have been studied. After just 10 days of cold exposure, the color of the organ changes dramatically (Fig. 8) from mainly white (mice maintained at 28 °C) to mainly brown (mice maintained at 6 °C) both in B6 and Sv129 adult mice. Detailed quantitative measurements of adipose organs in these experiments showed that after cold exposure in both strains the total number of adipocytes was unchanged, of course, as expected, the number of brown adipocytes increased but surprisingly the number of white adipocytes decreased exactly of a number of cells equivalent to the increased number of brown adipocytes (Fig. 9) (Vitali et al. 2012). These data suggested a conversion of WAT to BAT in line with other experiments performed since 2000 when a direct conversion of white into brown adipocytes in old rats treated with β3AR agonists was showed (Granneman et al. 2005; Himms-Hagen et al. 2000) (Figs. 10 and 11).

The ideal technique to demonstrate this conversion is lineage tracing where cell tagged by the cell specific activation of a gene induces irreversible production of β-galactosidase (β-Gal or other reporter gene) that persists in the converted cell independently by the new phenotype and gene expression. β-Gal expression can be visualized at light microscopy level by histochemistry (X-Gal reaction) as a blue cytoplasm adding to the genetic precision the cell specific morphology precision. With this powerful technique, Christian Wolfrum group demonstrated the reciprocal conversion of WAT-BAT in 2013 (Rosenwald et al. 2013).

With the same lineage tracing technique, it was also demonstrated that white and brown adipocytes derive from the same stem cell reinforcing the concept of possible interconversion (Tran et al. 2012).

Browning can be obtained mainly by cold exposure, administration of β3ARs agonist drugs, and physical exercise (Bostrom et al. 2012; De Matteis et al. 2013; Frontini and Cinti 2010).

Thus, the answer to the major question could simply be: the unitary finalistic purpose is repartition of food-derived energy into functions for survival (short-term homeostasis) – thermogenesis (BAT) and metabolism (WAT) – but in special occasions such as chronic cold exposure WAT converts to BAT to respond to the

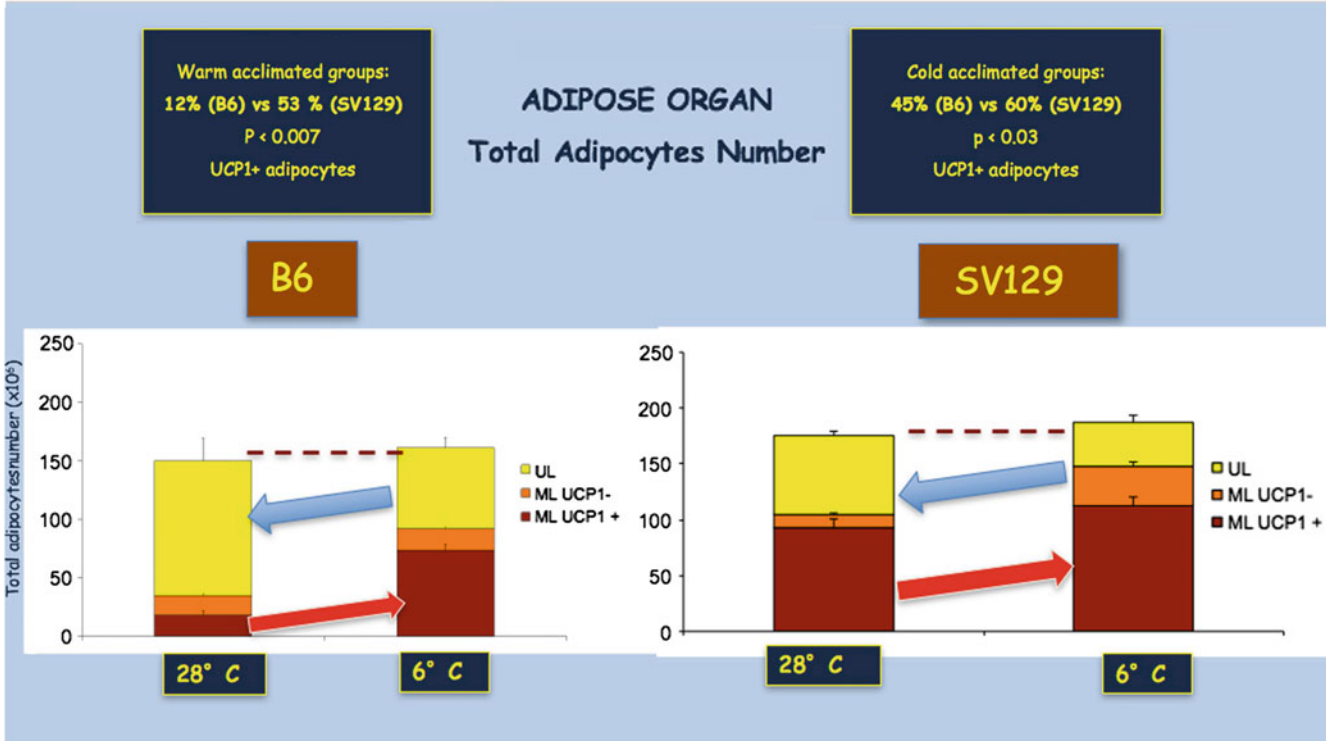


**Fig. 9** Quantitative assessment of adipocytes number in the adipose organ of adult female Sv129 and C57/BL6J mice maintained at 28 °C and 6 °C for 10 days. After cold acclimation, in absence of change in total number, brown adipocytes increase of a number equivalent to that of white adipocytes decrease (From Vitali et al. 2012)

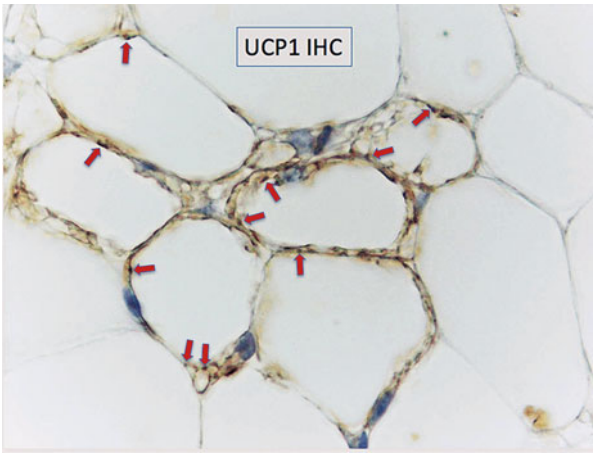


**Fig. 10** UCP1 immunoreactive paucilocular adipocytes found in anterior subcutaneous WAT of cold exposed C57/BL6J adult female mouse. Note the immunoreactivity at periphery of the cells, roundish small immunoreactive structures with size and shape of mitochondria (arrows) are visible, suggesting an early stage of white to brown transdifferentiation

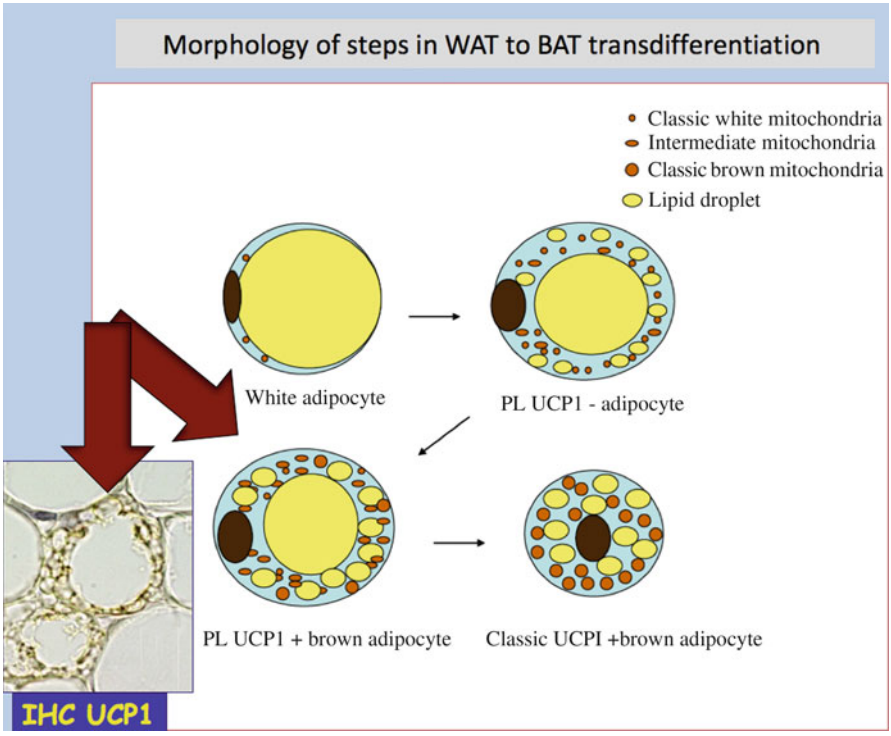


**Fig. 11** Proposed morphology of steps during white to brown transdifferentiation. The UCP1 immunoreactive paucilocular step is shown also in the original immunohistochemistry analysis (arrows) (From Barbatelli et al. 2010)

extra need for thermogenesis. On the other hand, in the case of chronic positive energy balance, the organ cannot refuse the precious energy of extra food because of lack of any guarantee for future food availability.

## Pink Adipocytes Integrate the Transdifferentiation Triangle of Adipose Organ

This theory explains the mixed anatomy and the need of cooperation between WAT and BAT, but implies a new basic property of mature cell: the physiologic ability of reversible transdifferentiation. In search for new examples of this property, it has been shown that subcutaneous WAT of female mice is able to reversibly convert to milk-secreting epithelial glands during pregnancy and lactation. It is well known that the alveolar component of mammary glands develops during pregnancy and progressively substitutes for the mammary WAT. Early alveoli (day 17–18 of pregnancy) are diffusely formed by glandular cells with cytoplasm occupied by large lipid vacuoles (Masso-Welch et al. 2000; Richert et al. 2000; Smorlesi et al. 2012). Thus, parenchymal cells of adipose organ during pregnancy fulfil the definition of adipocytes that were denominated pink adipocytes because the color of the organ during pregnancy is pink (Giordano et al. 2014). Lineage tracing and explant experiments showed the reversible white to pink transdifferentiation (De Matteis et al. 2009; Morroni et al. 2004). Recently it has also been showed that pink adipocytes (milk secreting glandular cells), in the postlactation period, not only convert to white adipocytes but also to UCP1 immunoreactive brown adipocytes in the dorsal area of ASC (Giordano et al. 2017). Molecular mechanisms underlying this triangle of transdifferentiation (Fig. 12) are under investigation, but comparative microarrays analyses between cleared fat pad (mammary fat after surgical removal of ductal tree) and contralateral normal glands at various period of pregnancy showed that osteopontin secreted by the ductal cells and the master transcription factor Elf5 could play key roles in the white to pink transdifferentiation (Prokesch et al. 2014).

Thus, physiologic reversible transdifferentiation of adipocytes could be the specific property explaining why cells with different anatomy and physiology are mixed to form a well-defined organ. White, brown, and pink adipocytes in the adipose organ respond not only to the need of partitioning energy between thermogenesis (browning) or metabolism (whitening) for short-term homeostasis (survival of the animal), but also for the needs of offspring survival (pinking) for long-term homeostasis.

## Browning Can Curb Obesity and Related Disorders

A growing body of evidences suggest that browning of adipose organ can be used to treat the metabolic syndrome (Nedergaard et al. 2011). Since several decades it was evident that obese animals treated by β3AR agonists undergo browning of adipose

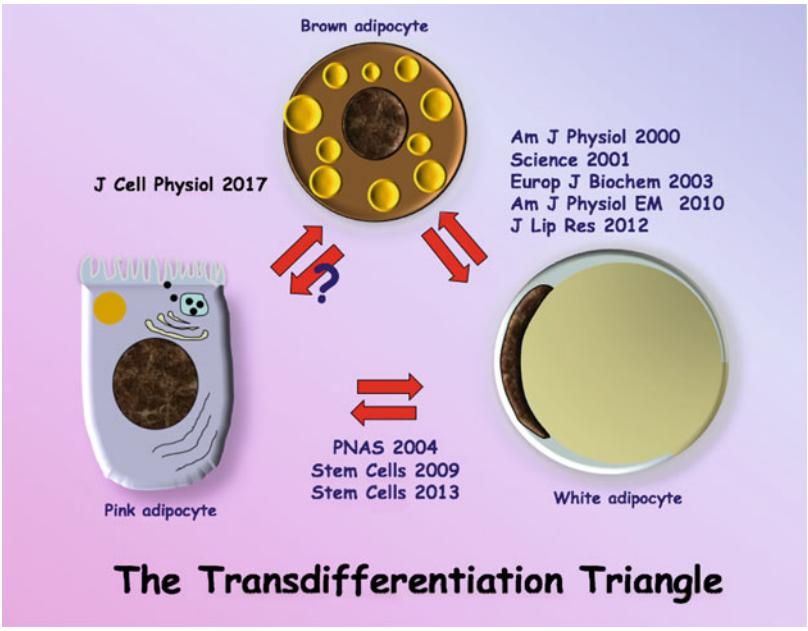


**Fig. 12** The transdifferentiation triangle. All published data supporting the physiologic reversible conversions of adipocytes are indicated (From Cinti 2017)

organ and weight loss (Guerra et al. 1998; Tseng et al. 2010). Several data also support positive effects on glucose and lipid metabolism and recently most data have been confirmed in humans (Yoneshiro et al. 2013).

## BAT Is Mainly Visceral in Humans

It must be outlined that most BAT in humans is located in visceral fat. PET analyses (Kuji et al. 2008) and biopsy studies (Cinti 2006; Zingaretti et al. 2009) showed that in humans BAT is mainly located in the neck visceral areas (in contact with the visceral and with the neurovascular units) and in the perirenal fat (Cinti 2017).

## Visceral BAT Converts into WAT in Obese Mice and Humans

Brown visceral fat convert to WAT with age and weight gain, and this BAT-derived WAT is responsible of most of the adverse effects in obese patients mainly for its low critical death size (Giordano et al. 2016) (see above).

## Specific Drugs Able to Convert White Visceral Adipocytes into Brown Adipocytes Are Needed

Thus, specific drugs able to convert visceral WAT to BAT would be very useful not only for their intrinsic potentiality to increase energy expenditure so favoring weight loss, but also because the specific reduction of visceral fat would prevent the adverse effects of visceral fat expansion (Giordano et al. 2016). The general belief that visceral fat is resistant to WAT to BAT transdifferentiation is probably wrong. This idea likely derives from experimental data on visceral fat using epididymal depot as paradigm of visceral tissue. Epididymal fat is indeed resistant to browning, but several other, less studied, visceral depots are much more prone to browning: mediastinal, periaortic, perirenal, periovaric, parametrial, and mesenteric depots showed a high proneness to browning (Vitali et al. 2012).

## The Partial WAT-BAT Conversion Could Be Sufficient to Improve the Metabolic State

All data reported above seem to suggest that size of white adipocytes is very important to trigger the adverse metabolic effect of a chronic positive energy balance. The increase in size of adipocytes is particularly dangerous in visceral fat. Pointing to browning of visceral fat could be a strategy to combat the adverse metabolic effects of obesity (Giordano et al. 2016). The most efficient way to obtain browning in small mammals is through the activation of β3ARs. The last generation of β3AR agonists mirabegron activate BAT in humans (Cypess et al. 2015), but its approval only for bladder hyperactivity allows to suspect that clinical trials for the treatment of obesity failed or showed adverse collateral effects. Considering that the first steps of WAT to BAT conversion is the reduction in size of white adipocytes (Fig. 11) and considering the importance of cell size for adipocytes, it could be concluded that a mild activator of β3ARs could realize healthy cell size reduction avoiding collateral adverse effects. The pharmacologic research should point to this direction or to all other emerging alternative mechanisms of browning (also mild browning) not involving this receptor such as natriuretic peptides, BAIBA, irisin, FGF21 (for a recent review see Giordano et al. 2016).

## Conclusions

A deep knowledge of anatomy and physiology of adipose organ is very important to understand the physiopathology of obesity and its related disorders. Furthermore, the extraordinary plasticity capacities of this organ offer possible innovative therapeutic strategies that may overcome these pathologies and include unexpected fields of

applications such as those involving the developmental properties of mammary gland.

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# Roles of Gut Hormones in the Regulation of Food Intake and Body Weight

4

Lidia Castagneto Gissey, James Casella Mariolo, and Geltrude Mingrone

## Contents



**Abstract**

The gastrointestinal tract is extremely rich in endocrine cells and secretes a myriad of hormones, including ghrelin, glucagon-like peptide 1(GLP1), gastric inhibitory peptide (GIP), cholecystokinin (CCK), amylin, peptide YY (PYY), oxyntomodulin, and leptin. Mechanical distention of the stomach elicits mechanoreceptors within the gastric wall sensing tension, stretch, and volume, which then send brain signals through vagal and spinal sensory nerves.

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Both stomach and gut are tightly connected with the central nervous system where the fullness sensation is elaborated. Peripheral signaling hormones regulate appetite in the hypothalamic arcuate nucleus through anorexigenic and orexigenic signals. The gut–hindbrain axis is sufficient to drive the satiation sensation, although hindbrain also communicates with the forebrain where sensory and cognitive processes linked to meal anticipation and learned associations play a relevant role in the anticipation of food reward and pleasure.

We report an overview of the intestinal mechanisms regulating satiety and body weight with particular emphasis to the effects of drugs and bariatric/metabolic surgery on gut hormonal secretion.

**Keywords**
Gastrointestinal hormones · Nervous system · Satiety · Appetite

## Introduction

Food ingestion promotes satiation trough two mechanisms: stomach distension and hormone release. The gastrointestinal tract is tightly connected with the central nervous system (CNS) where the fullness sensation is elaborated. Peripheral signaling hormones regulate appetite in the hypothalamic arcuate nucleus (ARC) through anorexigenic and orexigenic signals. The former are mediated by neurons expressing the neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), while the latter are mediated by neurons expressing the neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY). Projections of these neurons transmit the signals to secondary neurons located in the dorsomedial and paraventricular nuclei, in the lateral hypothalamus, and in the prefornical area.

The gut–hindbrain axis is sufficient to give the satiation sensation, although hindbrain also communicates with the forebrain where sensory and cognitive processes linked to meal anticipation and learned associations play a relevant role in the anticipation of food reward and pleasure.

Mechanical distention of the stomach elicits mechanoreceptors within the gastric wall sensing tension, stretch, and volume which then send brain signals through vagal and spinal sensory nerves (Ritter 2004).

When vagotomy was used, years ago, as a therapeutic approach to cure peptic ulcers, it was associated with a decline of appetite and consequently with weight loss (Irving et al. 1985). Therefore, the vagus nerve was regarded as a possible target for the treatment of obesity. The Maestro System (Enteromedics) has been recently approved by the Food and Drug Administration and consists of a subcutaneously implanted rechargeable battery connected with two electrodes that are laparoscopically implanted in the trunks of the vagus nerves just above the junction between the esophagus and the stomach. The leads are placed on the anterior and posterior intra-abdominal nerve trunks. Clinical studies have shown that Maestro System implantation determines a significant weight reduction of around 3 kg in 1 year (Shikora et al. 2013).

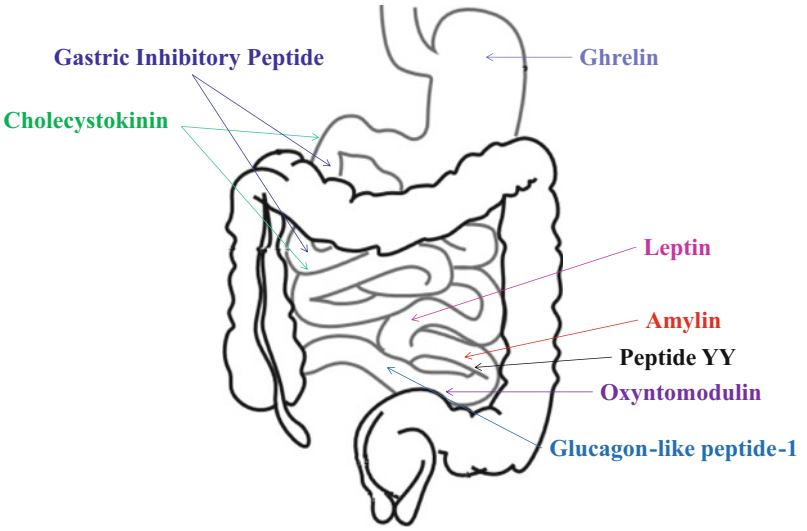


**Fig. 1** Major hormones produced by the gastrointestinal tract

Nutrient delivery in the small intestine is able to reduce food intake (Powley and Phillips 2004) through the secretion of satiation hormones by entero-endocrine cells.

## Entero-Endocrine Cells

Entero-endocrine cells (EECs), derived from pluripotent stem cells and located within the epithelial cells of the intestinal mucosa, sense the intraluminal nutrients and produce a series of hormones that regulate many functions including appetite, digestion, gut motility, and metabolism. Importantly, these cells are connected with nervous terminations and, thus, they can dialogue with the central nervous system.

At least 12 types of entero-endocrine cells have been identified until now and their location and type of hormone produced are summarized in Fig. 1. Single types of EECs are able, however, to produce more than one hormone as shown in transgenic CCK-eGFP mice, where six functionally different peptides (CCK, GLP1, GIP, PYY, secretin and neurotensin) can be coexpressed (Egerod et al. 2012).

In the following sections, the action of the major entero-hormones will be underlined.

## CCK

Cholecystokinin (CCK) is produced by I endocrine cells of the duodenum and jejunum, but it is also produced in the enteric nervous system and in the brain. When injected before meals, CCK promotes satiety, but it has a short life (Lieverse

et al. 1995). Injection of CCK in the hypothalamus induces satiation. Long-term administration of CCK in both animals and humans is associated with ending of anorectic effects within 24 h.

CCK-1 receptors are expressed in the pancreas as well as in some sites of the brain (Hill and Woodruff 1990), while CCK-2 receptors are present in the gastrointestinal tract and are widely distributed throughout the brain (Hill and Woodruff 1990).

Otsuka Long-Evans Tokushima fatty (OLETF) rats, a model of congenital CCK1 receptor deficiency, develop hyperphagia and obesity (Takiguchi et al. 1997). In contrast, CCK1 receptor knockout (KO) mice are not hyperphagic or obese (Bi et al. 2004). These findings probably depend on the fact that in mice CCK2 receptors are predominant. In fact, $CCK2R^{(-/-)}$ mice develop obesity associated with hyperphagia (Clerc et al. 2007).

Few years ago, after the negative results, in terms of weight loss and cardiometabolic risk markers, of a 6-month phase II trial in 701 obese subjects using the selective CCK-A agonist GI181771X, GlaxoSmithKline terminated the development of this drug (West et al. 2008). However, interestingly, CCK shows a synergic satiation action with leptin enhancing weight reduction at least in experimental animals. Therefore, a combination of leptin and CCK might represent a promising pharmaceutical approach to obesity.

Studies investigating the changes in CCK levels after bariatric surgery are few and controversial. Rubino et al. (2004) did not find significant changes of CCK levels in the bloodstream after Roux-en-Y gastric bypass (RYGB). In another study, in contrast, RYGB patients had four time higher plasma CCK concentrations after a test meal than weight-matched control subjects (De Giorgi et al. 2015). In rats which underwent RYGB or sham operation, no difference in CCK circulating levels was found (Suzuki et al. 2005).

## GLP1

Glucagon-like peptide-1 (GLP-1) is secreted by the enteroendocrine L cells distributed throughout the entire intestine but with a higher density in the ileum and colon (Gibbs et al. 1973; Jordan et al. 2008). It derives from proglucagon that is cleaved by the prohormone convertase 1/3 (PC1/3) (Fig. 2). In L cells, GLP1colocalizes with oxyntomodulin and peptide YY (PYY).

For the first time in 1987, Kreyman et al. (1987) found gut GLP-1 7–36-like immunoreactivity in humans and showed that GLP1 infusion enhanced insulin secretion. Similarly to glucose-dependent insulinotropic polypeptide (GIP), GLP1 is rapidly inactivated in the circulation by dipeptidyl peptidase-4 (DPP4).

GLP1 enhances insulin secretion and inhibits glucagon secretion; in addition, it stimulates β-cell proliferation and neogenesis, and inhibits β-cell apoptosis. Its inhibitory action on insulin secretion seems to be mediated by somatostatin (de Heer et al. 2008).

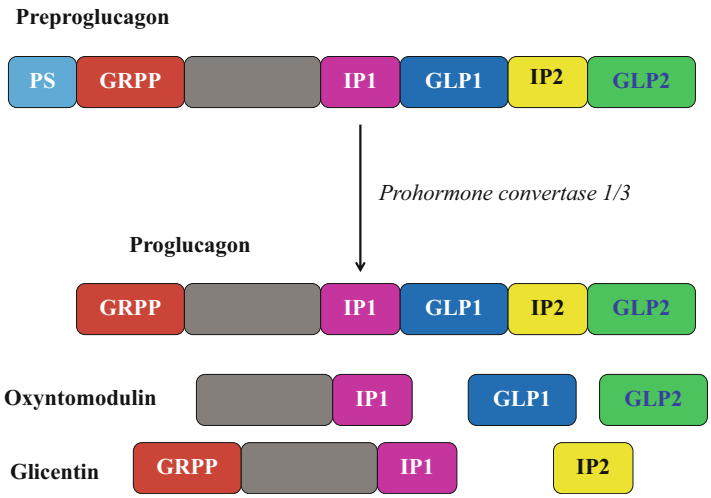


**Fig. 2** Incretin synthesis pathway

Several reports show that GLP-1 reduces food intake in animals and humans, while blocking the GLP-1 receptor with exendin 9–39 determines hyperphagia in rodents (Williams et al. 2009).

The presence of GLP-1 receptors on neurons in the human hypothalamus, medulla, and parietal cortex has been recently demonstrated (Farr et al. 2016). Exenatide, an injectable GLP1 agonist, infusion increases activation in appetite- and reward-related brain areas in normoglycemic obese and in type 2 diabetic, obese subjects as compared with lean volunteers. Very recently, it has been shown that exenatide increases electrical activity of the dorsal raphe serotonin neurons (Anderberg et al. 2017).

Similarly to exenatide, liraglutide, another GLP1 agonist, decreases the activation of the parietal cortex in response to highly desirable visual food cues (Farr et al. 2016).

In a 56-week, double-blind trial involving 3731 patients with a BMI 38.3 $\pm$ 6.4 (Pi-Sunyer et al. 2015), 63.2% of the patients in the 3 mg once daily Liraglutide (commercial name, Saxenda) arm lost at least 5% of their baseline body weight as compared with 27.1% in the placebo arm ($P < 0.001$), while 33.1% and 10.6%, in the two groups respectively, lost more than 10% of their basal body weight ($P < 0.001$). The mid-term (3 years) results of this RCT in terms of transition from prediabetes to diabetes, published in February 2017 (le Roux et al. 2017), showed that 2% of the patients in the 3 mg daily liraglutide group progressed to diabetes versus 6% in the placebo group; the weight loss difference between liraglutide and placebo was −4.6 kg (95% confidence interval − 5.3 to 3.9 kg, $P < 0.0001$) with 49.6% of patients who lost $\geq$5 kg, 24.8% who lost $\geq$10 kg, and 11% who lost $\geq$15 kg in the liraglutide arm.

## Oxyntomodulin

Preproglucagon is a polypeptide containing 179 amino acids; its fraction near the N-terminal contains glicentin while its fraction close to the C-terminal is the major proglucagon fragment (MPGF) (see Fig. 2). The latter contains GLP1 and GLP2. While in the pancreatic α-cells it is processed to the 29 amino acid glucagon and MPGF, in the intestinal L cells it forms glicentin, GLP1, GLP2, and oxyntomodulin (Fig. 2).

In experimental animals, oxyntomodulin injection reduces food intake and increases energy expenditure while its chronic administration reduces body weight gain (Wynne et al. 2005). Oxyntomodulin infusion for 4 weeks in humans reduces meal size by at least one-fourth, while its chronic administration determines a 0.5 kg/week average weight loss higher than with placebo (Brown and Pederson 1970).

It has been shown that oxyntomodulin binds the GLP1 receptor, although with an affinity 100 times lower than that of GLP1 itself (Wynne et al. 2005). Its action is at least partially mediated by GLP1 receptors; in fact, it does not modify appetite in GLP1 receptor knockout mice (Brown et al. 1970), and exendin 9–39, an antagonist of GLP1 receptor, blocks the effects of oxyntomodulin (Wynne et al. 2005). However, oxyntomodulin elicits anorexia in equimolar dose as GLP1 suggesting that it has a direct effect other than that mediated by its GLP1-R agonist action (Wynne et al. 2005). A possible direct action is that on the ventromedial hypothalamic satiety center (Wynne et al. 2005).

Oxyntomodulin linked at its N-terminus to a linear polyethylene glycol (PEG) chain is under study with the name of MOD-6031. Contrary to oxyntomodulin which has a very short half-life, MOD-6031 is a long-acting GLP-1/glucagon dual receptor agonist under development by OPKO Health Inc.

## Gastric Inhibitory Peptide

Scientists noted that some nutrients, in particular fat, inhibit gastric acid secretion in a mechanism of negative feedback. In 1969, John Brown and Raymond Pederson (1970) published a paper in which two preparation of CCK, purified at 10% or 40% on the basis of gallbladder-stimulating potency, were studied on in vivo denervated stomach preparations of dogs. 40% purified CCK was more effective than 10% in stimulating gastric acid secretion suggesting that a gastric stimulant hormone was removed. In 1970, at the Karolinska Institute in Stockholm, Sweden, Brown et al. (1970) isolated the gastric inhibitory peptide (GIP) whose sequence was identified the following year. Later on, it was shown that the infusion of GIP during an oral glucose tolerance test potentiated insulin secretion. Indeed, the action of GIP on β-cells was found to be glucose dependent, a characteristic of the incretin action (Pederson and Brown 1976). Both GIP and GLP1 concur to the incretin effect, which is the much larger insulin secretion driven by an oral as compared with an intravenous glucose administration.

Similarly to GLP1, GIP is degraded by the enzyme DPP4. GIP, however, covers also a relevant action on modulating insulin sensitivity. In fact, genetic knockout of the GIP receptor protects from obesity-related diabetes (Miyawaki et al. 2002). Furthermore, chronic administration of ($Pro^3$GIP), a specific and stable GIP receptor antagonist, can prevent or reverse many of the established metabolic alterations, including insulin resistance associated to type 2 diabetes (Gault et al. 2002).

## Peptides from the Pancreatic Polypeptide Family

The pancreatic polypeptide family includes the pancreatic peptide (PP), the peptide YY (PYY), and the neuropeptide Y (NPY).

PYY is cosecreted with GLP1 by endocrine L-cells. Circulating levels of PYY peak within 2 h of eating and are proportional to meal size and composition, with proteins having a stronger stimulating action than fat and carbohydrates, and fat larger that carbohydrates (Hill et al. 2011). PYY is an antilipolytic hormone as shown by Labelle et al. (1997).

The PYY response to meal ingestion is attenuated in obese subjects (Brownley et al. 2010).

PYY binds and activates at least three different G-protein-coupled receptor subtypes ($Y_1$, $Y_2$, $Y_3$, $Y_4$, and $Y_5$) dislocated in the brain, the subtype $Y_5$ is particularly expressed in the hypothalamus.

NPY is a 36 amino acid peptide with an anorexic action. It binds to $Y_1$ receptor that mediates its antilipolytic effect in the adipose tissue (Reichmann and Holzer 2016) and it is cleaved by dipeptidyl peptidase IV forming $NPY_{3–36}$ that can bind to the receptor $Y_5$ (Reichmann and Holzer 2016).

$PYY_{3–36}$ infusion reduces food intake in lean and obese individuals and decreases ghrelin levels in the bloodstream (Batterham et al. 2003).

PP acts by reducing food intake and delaying gastric empting; it is possible that PP transmits satiety signals to the satiety center via the vagus nerve (Wang et al. 2008). In fact, vagotomy reduces PP's satiation effects (Wang et al. 2008). Stomach distention during eating stimulates stretch receptors connected with vagal fibers. Therefore, PP can act by reducing gastric emptying and thus stimulating stretch receptors and vagal fibers, and also directly through PP receptors on the vagal afferents signaling to hypothalamus satiety center (Wang et al. 2008).

## Amylin

In 1900, Opie described a hyaline degeneration of the Langerhans islets (Opie 1900) which later was recognized as a typical feature of type 2 diabetes and identified to be an accumulation of aggregates of fibrillar islet amyloid polypeptide (IAPP) or amylin.

Amylin, a member of the peptide calcitonin family, is mainly expressed by the pancreatic β-cells where it is stored together with insulin in 1:100 molar proportions,

but its expression has been also evidenced in the gut as well as in the hypothalamus and basal ganglia (Westermark et al. 2011).

Amylin is excreted in the urine but it is also degraded by the insulin degrading enzyme (IDE) (Gebre-Medhin et al. 1998); in fact, the in vitro addition of the IDE inhibitor bacitracin impairs amylin degradation. Another enzyme able to catabolize amylin is a type II zinc-containing metallo-protease known as neprilysin, which is mainly located in the β-cells (Gebre-Medhin et al. 1998).

Amylin has an action opposite to insulin; in fact, it inhibits insulin-mediated glucose uptake and glycogen synthesis in rat skeletal muscle. However, this effect is obtained with supraphysiological concentrations; thus, amylin cannot be considered as the hormone responsible of insulin resistance.

Amylin knock-out mice have an enhanced insulin response and a rapider plasma glucose clearance than wild-type controls (Gebre-Medhin et al. 1998). Amylin inhibits gastric emptying acting centrally in the brain (Gebre-Medhin et al. 1998).

Gastric bypass was not associated with amylin changes in nondiabetic patients (Jacobsen et al. 2012).

## Leptin

Leptin is a 167 kDa polypeptide secreted by the adipocytes; it was discovered in 1994 by the Friedman's team (Zhang et al. 1994). Until now six different leptin receptors (ObR) have been identified, although $ObR_b$ is considered to be the main functional receptor of leptin (Thon et al. 2016) and it is highly expressed in the hypothalamus.

In the central nervous system, leptin inhibits NPY/AgRP neurons and activates pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART) neurons located in the arcuate nucleus (Thon et al. 2016), thus inducing satiety.

Through its receptor $ObR_b$, which belongs to the class I cytokine receptor family, leptin activates Janus kinase signal transducer and activator of transcription (JAK-STAT), the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathways (Thon et al. 2016).

Leptin regulates the autonomic nervous system circadian command mechanism. In fact, it is also secreted by the stomach (Liu et al. 2015) being stimulated by gastric wall distension and intragastric nutrients as well as by the CCK level raise. It potentiates the satiating effects of CCK and GLP1. Gastric overstretching, which is promoted by large and repeated meal ingestion, decreases leptin secretion, and this mechanism of action has been advocated in the reduced satiation of obese subjects (Mingrone et al. 2005). Adipose tissue leptin secretion contributes to signal to the satiety brain regions; in fact, feeding enhances leptin secretion from adipocytes (Thon et al. 2016).

Leptin counteracts the lipogenic and anabolic action of insulin and reduces fat ectopic deposition in the liver, skeletal muscle, and pancreas. Through the

sympathetic nerve system, it stimulates diet-induced thermogenesis by enhancing uncoupling protein (UCP1) gene expression in the brown adipose tissue (Thon et al. 2016).

As far as body weight increases during overeating, subjects become leptin resistant. In the leptin-resistant state, there is an excess of the suppressor of cytokine signaling 3 (SOCS3), which downregulates STAT3 (Mori et al. 2004) and thus reduces the effect of leptin on satiety. In fact, SOCS3-deficient mice show increased leptin-induced STAT3 phosphorylation in the hypothalamus. Protein tyrosine phosphatase 1B (PTP1B) inhibits leptin signaling by dephosphorylating JAK2. Adipose tissue PTP1B knockout mice increase body weight, while neuronal $Ptpn1^{(-/-)}$ mice are hypersensitive to leptin (Bence et al. 2006).

Leptin ultradian rhythm was studied before and after a malabsorptive type of bariatric surgery, biliopancreatic diversion (BPD), showing that the maximum leptin diurnal variation, i.e., the acrophase, decreased ($10.27 \pm 1.70$ vs. $22.60 \pm 2.79$ ng $\cdot$ $ml^{-1}$; $P = 0.001$), while its pulsatility index increased ($1.084 \pm 0.005$ vs. $1.050 \pm 0.004$ ng $\cdot$ $ml^{-1} \cdot min^{-1}$; $P = 0.02$) (Mingrone et al. 2005). Leptin changes negatively correlated with the changes of insulin sensitivity. It was suggested that insulin resistance reversion that follows BPD might allow reversal of leptin resistance and restoration of leptin pulsatility, thus increasing satiety (Mingrone et al. 2005).

Drugs improving leptin resistance have been proven to reduce body weight at least in rodents under a high fat diet and to lower hepatic fat deposition. Among these molecules, there are celastrol, a pentacyclic triterpene extracted from the roots of *Tripterygium Wilfordii* (thunder god vine) plant (Liu et al. 2015), and withaferin A that were shown to reverse leptin resistance in mice and to ameliorate the metabolic features linked with obesity.

## Ghrelin

Ghrelin is a 28 amino acids acylated peptide mainly produced in the stomach and named after its ability to stimulate the secretion of growth hormone (GH). It is the only known orexigenic hormone; in other words, it stimulates food intake and is, therefore, associated with weight gain.

The binding of octanoic acid to the gherlin's serine 3 residue in its N-terminal confers to this hormone the capacity to bind its receptor, the GH secretagogue receptor 1 (GHSR1). This active form of ghrelin is promptly degraded to desacyl-ghrelin; in fact, the half-life of the acyl-ghrelin is only 10 min. Ghrelin circulates also bound to the immunoglobulins (IgG); in fact, ghrelin-reactive IgG are natural autoantibodies (Takagi et al. 2013) and protect ghrelin from acyl degradation.

In humans, ghrelin levels rise before a meal and fall after food intake. In addition, food proteins have a larger inhibitory effect than carbohydrates and fat on ghrelin secretion.

Ghrelin stimulates the dopaminergic regions of the limbic system, but it acts also on the amygdale and the orbitofrontal cortex, two brain regions that control eating

behavior addressing food choice toward high density energy, fat-rich food. Conversely, visual stimuli of hedonic foods stimulate ghrelin secretion.

Ghrelin, directly or through the vagus nerve, stimulates the neurons of the arcuate nucleus, which secrete NPY and AgRP, and inhibits the anorexigenic neurons secreting pro-opiomelanocortin and α-melanocyte-stimulating hormone.

The effect of ghrelin on appetite is larger in obese than in normal weight subjects. Nevertheless, total ghrelin plasma concentrations were found to be low and acyl-ghrelin to be normal in obese individuals, thus excluding a causative role of ghrelin in the pathogenesis of obesity. However, IgG seem to protect more ghrelin from degradation in ob/ob mice and in Zucker rats than in normal rodents, thus permitting the circulation of its active form in higher amounts.

Acylated ghrelin has also a strong gastric effect in increasing gastric secretion and motility.

Weight loss induced by dieting is associated with an increased ghrelin secretion, while gastric bypass dampens ghrelin secretion possibly contributing to the large weight reduction and marked appetite suppression observed after this kind of bariatric operation (Cummings et al. 2002). In contrast, after biliopancreatic diversion, a malabsorptive type of bariatric surgery that leads to massive lipid malabsorption and weight reduction without appetite changes, 24 h circulating ghrelin levels were unmodified from before surgery but its ultradian rhythm was disrupted (Mingrone et al. 2006). It is likely, therefore, that ghrelin secretion reduction after gastric bypass can contribute to the appetite reduction and weight loss observed after this type of bariatric surgery, while the weight loss observed after biliopancreatic diversion might be mainly driven by its associated massive lipid malabsorption.

## Mechanisms Stimulating Gut Hormone Secretion

After food ingestion, its gastric presence is detected by vagal afferent fibers in the mucosa sensitive to mechanical touch, while the stretching of the gastric muscle layer due to stomach distention is sensed by vagal afferents in the external gastric musculature. The vagus nerve mediates the effects of many gut-satiating hormones which can however act also directly on the brain by stimulating the satiety center. In addition, enteroendocrine cells possess chemosensors, which belong to the family of G-protein-coupled receptor, that determine sweet (T1R) and bitter (T2R) taste in the mouth, as well as their common G-protein, α-gustducin (Mace et al. 2007).

In the rat jejunum, T1Rs regulate glucose uptake mediated by the sodium glucose cotransporter SGLT1. TIR2 and TIR3 have been found in entero-endocrine cells producing GLP1 and those producing GIP; while α-gustducin colocalize with PYY (Jang et al. 2007).

Food fats exert a potent satiating effect by stimulating the release of satiating hormones, including PYY, CCK, GLP1, and oxyntomodulin. However, fatty acids need to have a chain length longer than 12 carbon atoms and they act trough the binding to the GPR120 receptor (Hirasawa et al. 2005).

Interestingly, GLP1 producer L cells express receptors for leptin and insulin, the two long-acting adiposity hormones that control body weight, that stimulate GLP1 secretion. However, also L cells are subject to the phenomenon of leptin and insulin resistance.

## Conclusion

The gastrointestinal tract communicates with the brain via the rich vagal mechanosensory innervation and by releasing entero-hormones to modulate appetite and satiety.

Efforts have been and are currently made by scientists to better characterize the molecular basis of the transduction cascades leading to gut hormone secretion, at both transcriptional and posttranscriptional level.

In addition, a better characterization of the nutrients stimulating satiety hormone synthesis and release is needed to choose those dietary nutrients with highest satiating effects and to design new drugs that reduce appetite and, thus, induce a long-lasting weight loss.

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# Obesity Pathogenesis

5

Roberto Vettor and Scilla Conci

## Contents



**Abstract**

Obesity represents a complex chronic disease; likewise, its pathogenesis is characterized by a multifactorial, intricate interplay between environmental, genetic, and epigenetic factors. A sedentary lifestyle together with an excess calories intake set on a genetic predisposing background, which can be further modulated through epigenetic modifications. Among genetic mutations, the most important *FTO* region was found to correlate with obesity and its complications development, together with several other genes involved in food intake and body weight regulation. Moreover, the concept of a circadian clock disruption, induced by the gradual change in lifestyle habits, seems to strongly contribute to those metabolic and endocrine alterations which favor obesity development.

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The mechanisms regulating hunger and satiety in our body are extremely complex, involving several organs and systems which in turn interact with the external environment integrating different kind of inputs. The central nervous system (CNS) communicates to the peripheral organs, sending and receiving a whole range of signals including mechanic, hormonal, and nervous stimuli, which mediate a cross-talk not just with the central brain but also between lower systems. In the CNS, the main regions involved in food intake regulation are located in the hypothalamus; the mesolimbic hedonic pathway carries out a different kind of food intake control which involves the more instinct drivings. Several hormones secreted by gastrointestinal tract, adipose tissue, and pancreatic-liver axis, such as glucagon-like peptide (GLP-1), leptin, and insulin, are well-known factors acting on this fine regulation system. Other central regulators, identified more recently, are represented by the big family of the skeletal muscle produced hormones, the myokines, and the gut microbiota, whose alteration seems to be crucial in obesity development.

Adiposity does not represent a pathologic condition per se; indeed, the concept of "sick fat" refers to all those local modifications occurring in adipose tissue and gradually involving the body systemically, which set at the cell site, and finally lead to disease. Adiposopathy is typically characterized at the cell level by adipose cell hypertrophy, visceral fat accumulation, tissue fibrosis, and low-grade inflammation. These alterations could lead to the preferential challenging of fatty free acids (FFA) towards other organs outside adipose tissue with an ectopic lipid and fat accumulation, a phenomenon called lipotoxicity which is strongly related to the appearance or worsening of insulin resistance. At this final step, the obesity-associated complications develop. Indeed, pathological obesity typically correlates with metabolic syndrome, i.e., type 2 diabetes mellitus, hypertension, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and cardiovascular complications.

**Keywords**
Obesity pathogenesis · Multiorgan cross-talk · Adiposopathy

## Introduction

Obesity is a deadly epidemic disease and a major public health concern since it associates with many comorbidities such as type 2 diabetes, hypertension, cardiovascular disease, psychiatric and psychological disorders, osteoarthritis, and several types of cancer. It is a multifactorial disease determined both by environmental and genetic factors. Among the environmental factors, an excessive energy intake, a sedentary lifestyle, and circadian rhythm sleep alterations are probably the most important determinants.

## The Gene-Environment Disequilibrium as a Trigger for Obesity Development

One of the most intriguing hypothesis in the pathogenesis of obesity is related to the existence of a "thrifty genotype" favoring the accumulation of calories excess as fat, but none of the genes discovered so far fully support this theory as a major determinant factor. Moreover, the environment can directly influence the genome through epigenetic modulation of gene expression without altering the underlying base pair sequence. The early life "maternal" interactions and the "paternal" influence are now widely accepted as potential epigenetic mechanisms influencing offspring development. Nutrition and in particular the high-fat diet (HFD) play a crucial role in inducing epigenetic changes not only in the directly exposed organisms but also in subsequent generations through the transgenerational inheritance of epigenetic traits. The exposure to HFD during fetal life, particularly if combined with the same insult during the suckling period, was reported to correlate with the type 2 diabetes phenotype, which can be directly transmitted to the progeny even in the absence of additional dietary insults (Gniuli et al. 2008). Recent studies suggest that a parental HFD challenge can additively render female offspring more obese, with approximately equal effect strengths from maternal and paternal gametes. All these observations are consistent with epidemiological studies showing that an offspring's body mass index is significantly associated with the degree of parental obesity, whereas reduced glucose tolerance appears to be more prominently associated with maternal than with paternal impaired glycemic control (Fox et al. 2014). Many epigenetic variations occurring in the genomic methylome, the histone code, the proteome, and the metabolome, are potential carriers of epigenetic information at the germline level. Moreover, several recent studies have shown that the microinjection of specific sperm-derived small RNAs into zygotes can elicit persistent gene transcriptional effects and contribute to the observed metabolic phenotype in the first generation (Huypens et al. 2016). The epigenetic phenomena are dynamic and reversible processes and a prolonged exposure to a safe environment and lifestyle changes could potentially result in a complete recovery of a normal gene function.

Despite the impact of these epigenetic alterations due to environmental changes, obesity appears to manifest preferentially in genetically predisposed individuals and a high level of interindividual variation has been observed among exposed populations (Wardle et al. 2008). Genetic and epigenetic changes may be silent or alter the quantity, structure, and function of RNA and proteins, which ultimately can influence fat mass and distribution. Both genetic and epigenetic variations across individuals can thus alter adiposity phenotypes and lead to variation in traits across individuals. Moreover, heritability of obesity-related traits can be modulated by lifestyle factors such as diet, physical activity, and other environmental factors.

If the discovery of leptin in adipose tissue has revolutionized the way we interpret the function of this organ, likewise the finding in humans of the same single-gene alterations that justified the obese phenotype in mice gave a tremendous boost to

research on obesity genetics. Several loss-of-function mutations causing monogenic obesity were identified to be determined by genes responsible for appetite regulation in central nervous system (CNS); of particular relevance are the genes coding for leptin, POMC-derived peptide melanocortin, leptin receptor, and melanocortin 4 receptor (MC4R). These phenotypes are characterized by hyperphagia, which can be reversed after leptin supplementation. The huge advancements given by the genome-wide association studies (GWAS), along with the availability of larger biobanks, have further fueled the research in this field. This lead to the identification of several genes mostly expressed in specific areas and in integrated neuro-peptidergic and functional networks in the CNS, playing a prominent role in synaptic function and in neurotransmitter signaling (*ELAVL4*, *GRID1*, *CADM2*, *NRXN3*, *NEGR1*, and *SCG3*), in energy homeostasis control (*HNF4G*, *TLR4*, *BDNF*, *POMC*, *MC4R*, and *ETV5*) with an important influence in food intake and body weight regulation.

Among them, the most important identified *FTO* locus was found to be associated with both BMI and diabetes and their cardiovascular complications. The strongest effect of the *FTO* locus was observed in individuals younger than 50 years and it is noteworthy that its effect on adiposity can be modified by physical activity (Frayling et al. 2007).

The obesity-associated noncoding sequences within FTO are functionally connected with the homeobox gene IRX3. The obesity-associated FTO region directly interacts with the promoters of IRX3 as well as FTO in the human genomes. Furthermore, long-range enhancers within this region recapitulate aspects of IRX3 expression, suggesting that the obesity-associated interval belongs to the regulatory landscape of IRX3. Consistent with this, obesity-associated single-nucleotide polymorphisms are associated with expression of IRX3, but not FTO, in human brains (Smemo et al. 2014). IRX3-deficient mice showed a significant reduction in body weight and fat mass and an increased basal energy expenditure due to, at least in part, the activation of browning of white adipose tissue. IRX3 is also overexpressed in adipocytes after weight loss, suggesting its importance in weight regulation. It has been shown that FTO SNP rs1421085 disrupts the binding site of the ARID5B repressor leading to the increased expression of IRX3 and IRX5 during adipocyte differentiation, thus inducing the whitening of beige adipocytes (Claussnitzer et al. 2015). Similarly as for the FTO gene, most part of the genes involved in the regulation of energy expenditure, in the control of food intake, and body weight are expressed in the CNS. On the contrary, there are a few genes which have been studied at the peripheral level with a substantial influence on the genesis of obesity. Among them, of relevance, the genes involved in adiponectin signaling, insulin sensitivity and glucose levels regulation, skeletal growth, angiogenesis *(STAB1*, *WARS2*, *MEIS1*, *FGF2*, *SMAD6*, *VEGFA*, *VEGFB*, *RSPO3*, *PLXND1*, and *CALCRL*), transcriptional regulation (*CEBPA*, *PPARG*, *HOXC*, *ZBTB7B*, *JUND*, *KLF13*, *MSC*, *SMAD6*, *NKX2-6*, *HOXA*, *MEIS1*, *RFX7*, and *HMGA1*), and adipose tissue development (*CEBPA*, *PPARG*, *BMP2*, *HOXC-mir196*, *SPRY1*, *TBX15*, and *PEMT*, WNT10B). However, the obesity pathogenetic processes could be understood only by putting together the relative weight of genes with their tissue expression along with the environmental influences (Fall et al. 2017).

In recent years, genetic research on syndromes associated with obesity has increased considerably and in a recent wide meta-analysis, 79 obesity syndromes have been reported in literature. Of the 79 syndromes, 19 have been fully genetically elucidated, 11 have been partially elucidated, 27 have been mapped to a chromosomal region, and for the remaining 22, neither the gene(s) nor the chromosomal location(s) have been identified yet. Interestingly, 54.4% of these syndromes have not been assigned a name, whereas 13.9% have more than one name (Kaur et al. 2017).

## Obesity Development as a Disruption of the Nature Harmony: A Question of Rhythm

Although obesity is considered to result from an imbalance between energy intake and energy expenditure, the therapeutic strategy based on dietary changes and physical exercise has failed to tackle the global obesity epidemic. In search of alternative and more adequate treatment options, research has aimed at further unraveling the mechanisms underlying this excessive weight gain. These simple considerations raise a crucial question on what could be considered the series of event leading to the development and exacerbation of obesity.

In the era of system biology and medicine, the concept of obesity as a simple result of a disruption in the thermodynamic laws appears to be an oversimplification.

Moreover, the use of the classical research approach, studying separately the single cell, tissue, organ, or organism, could lead to misrepresentative conclusions. Indeed, they could lead to completely different results if we take into account their fundamental interrelationships investigating them as a whole.

Any organism is a system capable of regulating both the internal relationships between organs and the influence of environmental factors, not only through an exchange of fuel substrates and energy but also through an exchange of information. The unifying theory of the organization of the living beings has been interpreted within a hierarchical system of control, which integrates the separate subsystems possessing autonomous mechanisms of self-regulation.

The most important control system is related to the harmonic interaction among the biological systems with the environment and is characterized and determined by periodic processes. Our body is part of the universe and everything that happens in the universe ultimately affects the physiology of our body. Biological rhythms are an expression of the rhythms of the earth in relationship to the entire cosmos, and just four rhythms – daily rhythms, tidal rhythms, monthly or lunar rhythms, and annual or seasonal rhythms – are the basis of all the other rhythms in our body.

An increasing amount of chronobiological studies have started to raise consciousness concerning the crucial role of the circadian system in the development of obesity and its complications. Biological clock is expressed in periodic changes in respiration, body temperature, and other vital processes. The nature of biological rhythms is still essentially unclear, but it is reasonably acceptable considering periodicity as an essential characteristic of the biological system occurring at each

of the levels of the living system; disruption of these biorhythms results in a disruption of all or part of the system.

There is evidence for a cross-talk between the circadian rhythm and metabolic changes during the day and the disruption of body clocks due to frequent time zone traveling, shift work, or continuous consumption of high calories and high-fat foods, can induce metabolic impairment predisposing to obesity and its complications development. The day-night rhythm and the light-dark cycle act as the most potent synchronizing signals for the control master present in the hypothalamus. The central clock can further synchronize the clocks in the periphery by means of neural and humoral signaling. Likewise, the rhythm of food and the pace at which you take your meals during the day conditions, such as in a perfect orchestra, induce synchronous changes of all the clock genes at the periphery which must be ready to cope with the arrival of nutrients and their use in energy purposes. The circadian oscillations that are displayed by numerous metabolically relevant hormones could be altered by the disruption of several clock genes and hormones which regulate metabolism and are able to induce or reset circadian rhythms. The integrity of the clock machinery and the relative genes Per1 and Per2 is not only important for the proper circadian adaptation of gut hormones secretion but also for the rhythmicity in the gut microbiome which is influenced by feeding rhythms (Thaiss et al. 2014; Zarrinpar et al. 2014).

Obesity could be seen as the result of a circadian system disruption. The term "chronodisruption" has been coined to indicate the desynchronization between external environmental cues and internal physiological processes with a loss of rhythmicity among the environment, the CNS, and the peripheral clocks. Flying across time zones, shift work, disturbed eating patterns, and consumption of a high-fat diet have been recognized as the most threatening conditions able to induce disruption of the internal rhythm leading to metabolic and endocrine abnormalities which are the basis for obesity development (Laermans and Depoortere 2016).

## The Complex Dialogue Between Systems: Brain and Peripheral Organs

In a hierarchical control system, the CNS has assumed the most important role because it is the perfect integration between environmental changes and the body internal needs. CNS control of metabolism includes energy balance regulation coordinating the individual contribution of white adipose tissue (WAT) and brown adipose tissue (BAT), the gastrointestinal tract, liver, pancreas, and muscle. Any alteration of these organs or an incorrect communication among these organs could be the early step triggering the cascade of events leading to obesity and its complications.

The concept of a complex "brain-peripheral organs dialogue," central for energy homeostasis maintenance between food intake and energy expenditure, has developed over the past decades. Indeed, the past concept of a hierarchical from top to bottom control of the brain on several, separate systems has been gradually

reconsidered, leading to the present view of a complex and multidirectional dialogue between deeply related entities. The central nervous system (CNS) receives several afferent signals through neural circuits and humoral stimuli sent from the periphery, such as gut, adipose tissue, liver-pancreatic axis, and muscle. The dialogue takes place through a central homeostatic pathway, which integrates these signals with another complementary drive for food intake balance: the hedonic or reward-based pathway mediated by the mesolimbic dopamine system (Batterham et al. 2007). The main "homeostatic" centers locate in hypothalamus including the arcuate nucleus (ARC) and the periventricular nucleus (PVN), dorso- and ventromedial nuclei, and lateral hypothalamic area peptidergic neurones. They dialogue in response to different peripheral stimuli through the secretion of several neuropeptides, such as neuropeptide Y (NPY) and the Agouti-gene related peptide (AgRP), the pro-opiomelanocortin (POMC), precursor of the α-melanocyte stimulating hormone (α-MSH), the melanin-concentrating hormone, and orexin, which differently promote or inhibit energy expenditure responses via the efferent autonomic nervous system. The melanocortin POMC neurons in the ARC are part of the "first-order" catabolic system; they strongly inhibit food intake through the direct action of the α-MSH on the melanocortin-4 receptor (MC4r) located in the "second order" periventricular hypothalamic neurons. Counterparts in the ARC are the "first order" anabolic neurons, containing NPY and the coexpressed AgRP, antagonist of the MC4r, which stimulate food intake. These two neurons systems are potent sensors of the metabolic status: The NPY/AgRP one is activated by fasting, whereas POMC neurons are activated after the meal (Morton et al. 2006).

## The Brain-Gut Axis

The hormonal signals from the gut to the brain have been well characterized during the past century by recognizing that they seem to deeply communicate to each other mediating both acute and long-term responses. Indeed, gut hormones were identified in the brain, as well as their receptors, widely expressed in different brain regions (Dockray 2014). Moreover, the "gastrointestinal microbiota" has been recently identified as a key mediator of immune responses and energy metabolism control. In the satiety/hunger balance, mechanical and humoral signals are involved as well: gastric distention or contraction and nutrient absorption or fasting status could directly or indirectly act on the brain centers mediating behavioral reactions. Gulatory landscape of IRX3. Consistent with this, obesity-associated single nucleotide polymorphisms are associated with expression of IRX3, but not FTO, in human brains.

In the cephalic phase of appetite control, the information about food availability and palatability is conveyed into the brain by visual, olfactory, and acoustic signals through complex sensory pathways, increasing hunger levels. During food consumption, taste and olfactory signals influence eating behavior by short positive feedback. After entering the stomach and gastrointestinal tract, food components stimulate secretion of several hormones from enteroendocrine cells. These hormones function as a negative short-term satiety signals to elicit satiation and satiety. In the

postabsorptive state, food-derived fuel substrates further promote satiation and satiety both directly through brain nutrient-sensing systems and indirectly by promoting secretion of long-term adiposity signals from adipose tissue and the pancreas. The description of multiple taste receptors in gastrointestinal cells suggests that there are nutrient-sensing mechanisms in the gut. Oral sensing seems to mainly influence food discrimination and nutrient appetite, while post-oral chemosensors may relate to nutrient utilization and inhibition of appetite. The most common accepted view is that taste receptors and other taste-related genes present in enteroendocrine cells sense the arrival of the different nutrients and generate appropriate response signals that evoke gut hormones and vagal nerve responses (Psichas et al. 2015).

Several gut hormones are involved in food intake regulation; among them, the most recently described glucagon-like peptide (GLP-1), cholecystokinin (CCK), enterostatin, and polypeptide Y 3–36 reduce food intake, whereas ghrelin and orexin-A increase it. GLP-1 is a small peptide hormone secreted by L-cells in the ileum and colon especially in response to nutrient ingestion. It enhances glucose-induced insulin secretion and inhibits both gastric emptying and glucagon secretion. In CNS, GLP-1 acts as a neurotransmitter involved in satiety circuits (Turton et al. 1996). Studies in mice recently demonstrated that GLP-1 analogues, such as liraglutide, directly bind on GLP-1 receptors located on the POMC-CART (cocaine- and amphetamine-regulated transcript) neurons in the ARC, inhibiting indirectly the NPY/AgRP neurons and thereby explaining the weight loss effect described for these molecules. GLP-1 analogues probably reach the hypothalamic ARC and PVN through fenestrated capillaries; the PVN presents the highest capillaries density in the hypothalamus and the ARC works through the tanycytes, specialized glial cells which seem to mediate a peculiar neurons-capillaries interaction (Secher et al. 2014). CCK is a peptide synthesized by enteroendocrine cells, I cells, mostly localized in the duodenum; its demonstration in CNS neurons as well corroborated the hypothesis of a brain-gut cross-talk. CCK inhibits gastric emptying and stimulates the secretion of pancreatic enzymes and bile salts, thereby balancing the quote of hepato-pancreatic secrete and of ingested substrates. The CCK-mediated food intake inhibition arranged by the brain was demonstrated to work through vagal afferent fibers. The selective destruction of the vagal afferent branch with capsaicin significantly decreased the gastric motility attenuation induced by CCK. Ghrelin is released by gastrointestinal cells of the stomach and duodenum during fasting, while it is inhibited by food intake with gastric stretching. It represents the ligand of the growth hormone secretagogue receptor (GHSR), which was found in the same CNS neurons as the leptin receptor, with opposite functions (see below). Ghrelin acts on hypothalamic cells both directly and via vagal afferents, mediating hunger and increasing gastric motility and acid secretion; it is involved in the reward dopamine-mediated pathway as well. Its increase after diet-induced weight loss seems partly to explain those compensatory energy expenditure modifications which impair long-term weight loss maintenance (Schwartz et al. 2000) (Cummings et al. 2002).

Vagal afferent neurons are key players in the brain-gut dialogue; interestingly, they behave not just as mere signal transducers, being able to switch their

neurochemical phenotype in response to fasting or satiety status. CCK was shown to mediate this receptor switch, moreover, inducing a neuropeptide transmitters modulation in the vagal neurons through the differential increase/decrease of CART and MSH which respectively inhibit and increase food intake. Ghrelin was shown to inhibit CCK actions, whereas leptin, a potent food intake regulator protein from adipose tissue, potentiates it, demonstrating the mutual influence of different peripheral systems, i.e., gut and adipose tissue, in brain signaling mediation. Finally, a recent interesting observation suggested a decreased vagal afferent phenotype switch in obese subjects, being the response to CCK and leptin reduced, whereas that to ghrelin increased, partly explaining the energy intake increase observed in obesity (De Lartigue et al. 2010).

The microbial population resident in gastrointestinal tract, also known as "gut microbiota," consists of trillions of bacterial cells which colonize the gut from birth, being peculiar for each individual and whose composition depending on the subject's lifestyle, nutrition, and further diseases. Indeed, microbiota changes could occur after food intake variations or with the onset of several diseases. Equally, a microbiota dysfunction leads to the onset of several disorders as well, such as inflammatory bowel diseases, autoimmune and allergic diseases, and the metabolic syndrome. Physiologically, gut microflora mediates important functions: it is involved in dietary carbohydrate digestion, transforming nondigestible polysaccharides in volatile substances and short-chain fatty acids (SCFA); thereby, they not only mediate energy balance but also provide defense systems through the intestinal pH acidification, mediated by fatty acids synthesis, and functioning as a physical barrier. Microbiota is made up by two major bacterial families: Bacteroides and Firmicutes (Tremaroli and Bäckhed 2012). A prevalence of the latter one was observed in human obesity and obese animal models with an increased energy production through SCFA extraction from fibers. Interestingly, after weight loss in ex-obese subjects the proportion of the Bacteroides was shown to increase positively. The microbiota influences the vagal activity especially in conditions of infections or inflammation: the low-grade inflammation observed in obese subjects leads, through different mechanisms, to the inhibition of leptin or CCK action, contributing to the vagal phenotype switch mentioned above (Ley et al. 2006).

## The Brain-Adipose Tissue Axis

The concept of adipose tissue (AT) as a static organ for fatty acids storage has been reconsidered; indeed, it is involved in important dynamical processes as endocrine organ and hormonal source and moreover as thermogenic regulator which make it one of the key players involved in brain cross-talk. The evolution of the concept of AT as an active organ originated also from the description of three different adipose subtypes with selective functions and variable involvement in pathology: white and brown adipocytes and the more recently described beige AT. White adipocytes consists of large cells with unilocular lipid droplets and low mitochondrial levels, while brown cells are smaller with multilocular lipid droplets and a high number of

mitochondria and vascularization. Their functions differ from each other, being the white cell a main energy storage (triglycerides) and hormone producer and thereby a hunger/satiety balance regulator, where the brown one works as heat producer through the uncoupling protein-1 (UCP-1) expression. They originate from different precursors: the Myf-5 positive cell which gives rise to the myogenic lineage, and thereby brown AT, and the Myf-5 negative cell which is committed to an adipogenic lineage, leading to white adipocytes. Interestingly, they also communicate to brain differently: white tissue works principally through adipokines, while brown through the adrenergic system. Beige adipocytes represent a third intermediate population with variable morphologic and function's features; indeed, they are able to switch their phenotype from a white to brown one depending on environment conditions, precisely on heat/cold exposure and beta-adrenergic stimulation. In vivo they present as multiloculate cells able to express high UCP-1 levels in response to specific stimuli. If the beige cell originates from a transdifferentation process from white adipocytes or from a de novo differentiation from a different population, this was a main issue of debate. The observation that under specific conditions, i.e., PPAR-y agonists (thiazolidiediones) treatment, just some white cells underwent a white-to-brown transformation, supported the hypothesis of a separate precursor subpopulation. The mean of an AdipoChaser transgenic mouse model further suggested a plausible origin from different precursors (Rosen and Spiegelman 2014).

One important molecule involved in brain-adipose tissue signaling is represented by leptin, the first adipokine described in mice in 1994 as the ob gene product; the gene encodes for a peptide hormone mainly expressed in adipose tissue. It works as a peripheral fat stocks sensor for CNS, acting as an "adipostatic" signal to reduce energy intake in overnutrition conditions. Leptin receptor was widely identified throughout the body; in the brain, it is well represented in hypothalamic regions, contributing to the energy balance regulation system. In the ARC, it binds to the POMC cells stimulating α-MSH secretion and thereby working as a satiety stimulator; at the same time, it inhibits the NPY/AgRP neurons action, thereby promoting hunger inhibition. The observation that leptin-deficient mice (ob mice) correlated with a severe obesity phenotype with insulin resistance and that leptin administration completely reversed it didn't reflect the real majority obese subjects' status. Indeed, just some rare obesity cases are due to a real leptin deficit, whereas obese individuals normally show higher levels of circulating leptin compared to lean, due to their more represented fat mass; exogenous leptin administration results just in minimal weight loss. Obese phenotype correlates with a central and peripheral leptin resistance. Plausible explanations seem to be a leptin receptor signaling change especially in the ARC with an increasing leptin resistance and a consequent fail in hunger control; moreover, a decrease in leptin cerebrospinal fluid levels was demonstrated in obese subjects, suggesting an alteration in leptin central brain barrier crossing rather than a receptorial dysfunction (Considine et al. 1996).

Brown adipocytes, and more recently beige adipose cells, were shown to represent key contributors to body thermogenesis in response to external stimuli. For both, the direct inductor of the cellular thermogenic cascade is the sympathetic nervous system which operates on beta-3 receptors through noradrenalin released

by amyelinic fibers. Beta-adrenergic agonists induce thermogenesis as well, whereas cold exposure activates it indirectly. Brown adipose tissue (BAT) is well represented in rodents and infants, whereas its more recent description in human adults occurred through 18-FDG PET studies; it was identified as intercepting areas located in interscapular, perirenal, cervical, periaortic, and carotid regions. If these "brown areas" described in humans represent real constitutive brown tissue or beige cells, this is still matter of debate. Indeed, in postmortem studies conducted in young adults, cells collected from BAT regions showed a gene expression profile comparable to murine beige tissue, whereas other in vivo studies showed the coexistence of both classical brown and beige cells (Cypess et al. 2009). Beside catecholamines and PPAR-y agonists, beige islands in WAT were shown to appear in response to other stimuli as well: biliary acids, fibroblast growth factor-21, atrial and ventricular natriuretic peptides (ANP, BNP). Bone morphogenetic protein (BMP-4 and 7) are able to induce beige differentiation through several mechanisms. The "browning" of white adipose tissue (WAT) represents a new therapeutical target in obesity treatment, leading to UCP-1 iperexpression and thereby to heat production and energy dissipation. The identification of all those factors involved in this process could represent a revolutionary step in obesity management.

## The Liver-Pancreatic Brain Axis

The pancreatic gland, through insulin and glucagon secretion, represents not just the main glucometabolic profile regulator, but also a central player for food intake control. More precisely, it carries out such functions together with liver, communicating with brain through hormonal signals secreted proportionally to glucose levels and glycogen storages which in turn depend from the nutritional status.

Insulin is an anabolic peptide hormone, released by pancreatic beta-cells in response to high blood glucose levels. It promotes glucose absorption into cells especially in liver, adipose tissue, and skeletal muscle building glycogen via glycogenesis or triglycerides via lipogenesis. In regard to its central action, insulin works similarly as leptin, sensing the adiposity degree and sending a lipostatic signal to the brain. Its central action in food intake regulation is less efficient than leptin, but in a similar way, its levels increase proportionally to adipose mass growth. Moreover, insulin improves leptin synthesis and secretion in adipose tissue by an adipo-insular cross-talk (Kieffer and Habener 2000). In CNS, insulin binds to its receptors localized in central areas involved in food intake regulation; it seems to reduce food intake and thereby body weight by inhibiting the NPY/AgRP neurons (Gray et al. 2014). First studies performed in baboons demonstrated that intracerebroventricular (ICV) insulin administration markedly decreased food intake, whereas intravenous administration in humans did not influence it significantly in acute. Insulin was thereby shown to be centrally involved in nutritional behavior and energy storage regulation; moreover, it probably influences cognitive and memory-involved areas in hippocampus. Another interesting parallelism with leptin is the insulin resistance status

establishing in response to the increased adipose degree, despite higher insulin levels. Presumed mechanisms explaining this observation involve cellular insulin sensitivity decrease and insulin receptor dysfunction, which both mediate the development of prediabetes and diabetes often associated with obesity.

The central role of insulin in mediating satiety explicates through peripheral mediators as well; since the late 1970s, liver was shown to play a central role as food intake brake through its crucial position, which sets it as ideal nutrient sensor in peripheral-brain dialogue. Glucose infusion directly in central portal vein of rats induced a spontaneous decrease in nutrient ingestion, more than what observed by jugular vein infusion. The liver represents a constant oxidizable substrates supplier, interchanging phases of energy storage, in the form of glycogen and triglycerides, and substrates degradation during fasting. The main signals involved in this catabolic-anabolic regulation are glucose, insulin, and glucagon which influence the activity of enzymes involved in carbohydrate and fatty acid metabolism. Insulin stimulates glycogenesis and lipogenesis suppressing gluconeogenesis, whereas glucagon counteracts insulin actions. Liver metabolic processes are finely regulated both by hormonal and neuronal inputs. Indeed, the sympathetic nervous system stimulates hepatic gluconeogenesis promoting a substrate mobilization, whereas the parasympathetic inhibits it, promoting energy storage; both systems directly innervate the liver (Seoane-Collazo et al. 2015). Insulin mediates its actions on liver both directly and indirectly through a brain circuit, involving neurons located in the hypothalamus. The hormone binds to its receptors and mediates the hepatic glycogen synthesis and gluconeogenesis suppression through several intracellular cascades, such as PI 3-kinase/Akt pathway activation in the brain, and through vagus nerve stimulation as well. The hepatic insulin action of gluconeogenesis interruption is impaired after insulin receptors deletion on AgRP neurons (Könner et al. 2007). As mentioned above, brain action on liver is performed not just through hormonal stimuli but also through a direct vagal stimulation mediated by plasmatic substrates levels, which inhibits the hepatic glucose production.

Again, if in a simplistic view, these central to peripheral axes operate as bidirectional interlocutors, concretely the dialogue between systems builds on a complex inputs integration which connects them in a unicuum.

## The Brain-Skeletal Muscle Axis

Similarly to liver, skeletal muscle has the ability to store glucose in the form of glycogen. Glucose deposits allow the muscle to begin contraction by a rapid substrates breakdown and energy production; moreover, by storage mobilization skeletal muscle provides substrates to other organs as well, operating as a metabolic organ especially during fasting. In extreme conditions and starvation, the muscle is able to catabolize proteins as well, providing amino acids for gluconeogenesis. Muscle glucose uptake is tightly regulated by CNS and more

precisely by the sympathetic efferent branch via the ventromedial hypothalamic nuclei. Nevertheless, skeletal muscle takes part to body energy homeostasis not just as mere effector; indeed, it was recently identified as an endocrine organ, since it was shown to produce myokines, hormones produced and identified in the tissue. Several myokines have been described; most part of them is released after exercise and functions either locally with paracrine effects or on target organs. Beneficial local effects observed after exercise, such as increased insulin sensitivity, glucose uptake and fatty acid oxidation, are partly mediated by myokines. Moreover, they mediate the muscle-target organs cross-talk, promoting a rapid and a long-term metabolic regulation (Schnyder and Handschin 2015). The first described myokine was interleukin-6 (IL-6) but the effective myokine number seems to reach 600; among them, of relevance are interleukin-8 (IL-8), interleukin-15 (IL-15), brain-derived neurotrophic factor (BDNF), fibroblast growth factor 21 (FGF21), and the more recent irisin, BAIBA, and meteorin-like.

As prototype myokine IL-6, classically described as proinflammatory cytokine, is physiologically released after exercise and increases circulating anti-inflammatory cytokines. In muscle, through the AMPK and PI3K activation, it increases glucose uptake and fatty acid oxidation; a similar effect was observed in adipose tissue. Among other target organs were observed the activation of hepatic glycogenolysis and gluconeogenesis and GLP-1 production, with an enhanced insulin secretion. IL-8 muscular specific function is still not fully understood, even if it seems involved in neovascularization of muscle during and after exercise. IL-15 is another pro-inflammatory cytokine which is supposed to provide an anabolic action in muscle, inducing an in vitro muscle cell hypertrophy; it is also associated with adipose mass loss, through muscle-mediated mechanisms but also through the hepatic lipogenesis inhibition and fatty acid production.

In 2012, a new myokine family was described with particularly relationship to the "browning" process induction; it included irisin, BAIBA, and meteorin-like. Irisin is part of a bigger protein, FNDC5, which is bound to cell membrane and induced by exercise. Its extracellular domain could be shed, forming irisin. Irisin was shown to work on beige cell precursors, activating the thermogenic program by UCP-1 induction. Interestingly, irisin was able to induce the browning program just in "beige" precursors, whereas white primary cells did not change their basal thermogenic status (Boström et al. 2012). FNDC5 is enriched not just in skeletal muscle but also in heart and in brain. Interestingly, during chronic exercise, FNDC5 levels increase in hippocampus; this process was related to the concomitant hippocampal increase of another myokine, expressed both strongly in CNS and to a lesser extent in skeletal muscle, the BDNF. This molecule plays pivotal roles in neurons growth, maintenance, and survival; it mediates synaptic plasticity and contributes to learning and memory circuits. Finally, it is expressed in hypothalamic areas involved in energy homeostasis regulation. The FNDC5-induced BDNF expression, mediated by exercise, improves neurogenesis and represents a fine example of the direct skeletal muscle-brain dialogue.

## The Adipose Organ Disease: Adiposopathy

Adiposity, meant as adipose tissue expansion, does not represent a pathologic condition per se. Indeed, if adiposity often associates with other metabolic disorders, such as diabetes, dyslipidemia, or high blood pressure, some obese subjects show a metabolically healthy phenotype (Denis and Obin 2013). The concept of adiposity differs deeply from the concept of adiposopathy or "sick fat," which identifies a condition of adipose cell and adipose tissue dysfunction. The primum movens of both conditions is a positive energy balance, usually linked to genetic and environment/lifestyle predisposing factors (Bays 2014). Nevertheless, "metabolically protected obese" do not show all those anatomic alterations which normally characterize the pathological adipose tissue. Indeed, they show a reduced visceral depot with a relative subcutaneous WAT expansion, which correlate with an improved insulin sensitivity status, and smaller size adipocytes. Moreover, their adipose tissue showed a reduced inflammatory cells infiltrate with a consequent low proinflammatory cytokines secretion profile and a positive extracellular matrix (ECM) remodeling. Starting from these observations, adipose tissue sets between health and pathology; its "healthy" or "dysfunctional" expansion depends on a complex network of intrinsic and extrinsic factors, not fully understood yet.

## Adiposopathy: Anatomic Manifestations

### Adipocyte Hypertrophy

Adipose tissue shows an extraordinary ability to change rapidly its dimensions, as otherwise just neoplastic tissues do. This ability occurs through two principal mechanisms of growth: cell size enlargement (hypertrophy) and cell number increase (hyperplasia). From recent studies, both mechanisms seem to coexist in the adult adipose tissue, even if from previous observations the adipocyte number was suggested to become fixed between childhood and early adulthood, being the hypertrophic cell growth a prerogative of the adult adipose tissue (Spalding et al. 2008). Depending on the study, different and contrasting theories have been proposed over the years, trying to explain the location, the timing, and the causal factors involved in adipose cell growth. Definitively, hypertrophy correlates with a unfavorable metabolic profile; the abnormal cell growth leads to a relative hypoxic environment, which in turn leads to an increased cellular death and to an inflammatory milieu with immune cell infiltration and fibrosis (Rosen and Spiegelman 2014). In humans, adipocyte size correlates positively with hyperinsulinaemia and glucose tolerance dysfunction. SAT and omental VAT of non-diabetic subjects show smaller adipocytes compared to diabetic obese ones.

### Visceral Adiposity

Adipose tissue develops in different specific depots, whose behavioral differences have been largely demonstrated. Visceral fat (VAT) is associated with metabolic disease development and a higher overall mortality, whereas subcutaneous fat (SAT) seems to reduce the disease risk, correlating with insulin sensitivity improvement. To a certain extent, this distinction results simplistic; the subdistinction among VAT

depots is likewise relevant and the comparison between human and mice compartments turns out to be not always possible. Nevertheless, SAT and VAT show recognized differences, such as differential adipokine profiles or lipolysis and triglyceride synthesis rates (Tchkonia et al. 2013). What is still controversial is the full comprehension of the factors leading to VAT-SAT different behavior. Indeed, SAT and VAT microenvironments appear different from each other, owning a specific depot vascularization, innervation, and matrix composition; for example, the venous visceral fat system collects blood and its substrates into liver differently from subcutaneous fat. At the same time, the preadipocyte itself exhibits a site-specific gene pattern expression which is able to condition its behavior even after isolation and several in vitro culture passages.

### Hypoxia and Fibrosis

Adipose tissue expansion through hypertrophic growth correlates with oxygen tension alteration. Even if, depending on study, the absolute oxygen tension value in obese adipose tissue was found reduced, normal, or even elevated, pathologic AT expansion is characterized by an environment hypoxia. Critical conditions in this process are a lower capillary density, an increased adipocyte-capillary distance due to adipocyte hypertrophy, and an increased cell oxygen consumption. AT hypoxia leads to HIF-1α activation, an oxygen-sensitive transcription factor, which is involved in a profibrotic program induction in precursor adipose cells (Lee et al. 2014). Fibrosis represents another hallmark of the dysfunctional AT. ECM proteins normally surround, support, and mediate the cellular signaling in healthy AT. The disruption of the fine balance between fibrillar components synthesis and degradation leads to the building of a rigid matrix network which limits adipose cells healthy growth and properly nutrient excess storage. Collagen VI represents one of the most studied profibrotic ECM proteins involved in adipose tissue rigidity and secondary metabolic dysfunction in rodent models (Sun et al. 2013).

### Adipose Cell Apoptosis, Immune Cells Infiltration, and Low-Grade Inflammation

All the local mechanisms involved in pathology development, such as hypoxia, fibrosis, and low-grade inflammation, do not follow each other in an organized sequence; they rather contribute simultaneously to a vicious circle establishment, which grows boosting itself. Nevertheless, the fibrotic process associated with hypoxia seem to set at earlier steps compared to macrophages infiltration and related inflammation. Adipocytes encored in fibrotic matrix lose their proper functions and undergo cellular death through apoptosis or cell necrosis. The description in VAT of "crown-like structures" identified such dying adipocytes surrounded by infiltrating macrophages, which, together with other immune cells, such as neutrophils, lymphocytes, and mast cells, promote a local proinflammatory environment (Cinti et al. 2005). Macrophages normally exist in healthy AT as M2 polarized cells, secreting anti-inflammatory cytokines and mediating positive functions. With obesity progression, AT infiltration changes progressively toward a M1 polarized population, responsible of TNF-α, IL-6, and IL-1 beta secretion and thereby worsening inflammation

and insulin resistance mediating cytotoxicity and tissue injury. Injured adipocytes release chemokines as well, including MCP-1, TNF-α, IL-1, IL-6, and IL-18; they contribute to immune cell further activation probably acting as antigen-presents cells and thereby recruiting resident T-cells.

### Ectopic Fat Deposition

VAT shows a limited tissue plasticity potential compared to SAT; as mentioned above, it grows predominantly though hypertrophy. Visceral fat accumulation in obese subjects was shown to correlate with ectopic lipid deposition, probably mediated by the cellular storage capacity exceeding and the cell growth impairment induced by ECM rigidity. This ectopic deposition was described especially in liver and skeletal muscle and is implicated in insulin resistance and diabetes development and more in general to other obesity-related disorders. Moreover, it could involve myo- and pericardium, pancreas, brain, and several peripheral organs, mediating lipotoxic effects on target cells, such as cell dysfunction and cell death. The increased cardiovascular risk observed in obesity results not just from indirect effects of metabolic diseases but also from local direct adiposopathic and atherogenic mechanisms (Shimabukuro et al. 2013).

## Adiposopathy: Pathophysiological Manifestations

Obesity was shown to correlate with adipocytes differentiation impairment. Depending on study, different mechanisms have been suggested, explaining how it could establish. In SAT of obese adults, a reduced number of preadipocytes was found to differentiate into adipose cells. Other studies, however, described a pre-adipocyte differentiation impairment rather than a real precursors number decrease. More recently, SAT preadipocytes from morbidly obese were shown to down-regulate the "stemness" genes profile, to show a stronger adipose commitment and to upregulate inflammatory genes compared to lean subjects (Oñate et al. 2013). During hypertrophic expansion, after reaching a certain expansion level, the cell begins to exhibit signs of stress. Cell membrane undergoes mechanical stress, endoplasmic reticulum and mitochondria work dysfunctionally, the latter ones producing reactive oxygen species (ROS). ROS can damage several cellular components (Chattopadhyay et al. 2015). Plasmatic free fatty acids (FFA) elevation represents another central event in obesity-related metabolic disorders development. The increased FFA oxidation demand in obesity cannot be satisfied by the dysfunctional adipose cell. FFA can directly enter the liver via the portal circulation and can lead to an increased hepatic lipogenesis, gluconeogenesis, and insulin resistance. They can bind to the toll-like receptor 4 (TLR4) complex mediating cytokine production by macrophages. Beyond the well-known low-grade inflammation status (already mentioned above), which sets in the obese environment through increased proinflammatory responses mediated by adipose and immune system cells, adiposopathy also correlates to adipokine signaling alterations. Circulating leptin levels increase, whereas adiponectin ones decrease, reflecting a progressive insulin resistant metabolic profile.

## Adiposopathy: Clinical Manifestations

Obesity is associated with several diseases, correlating especially with metabolic and cardiovascular complications; in the 1980s, the relationship between body fat accumulation and metabolic disease was seen more as an "association" rather than a causal events concatenation. It was just in the following decades that the entity of the metabolic syndrome was coined, changing the concept of obesity as a separate condition. Among the several clinical manifestations described, insulin resistance, with the development of prediabetes and type 2 diabetes mellitus, adiposopathic dyslipidemia and ectopic fat accumulation, with its main manifestation of non-alcoholic fatty liver disease (NAFLD), represent frequent obesity complications related to cardiovascular disease development.

Obesity-related insulin resistance, firstly believe to arise in response to a reduced receptor affinity or receptors number decrease, establishes subsequently to insulin-signaling cascade defects in the target organs, such as liver, adipose tissue, and skeletal muscle (Jung and Choi 2014). In diabetes development, it combines with insufficient insulin secretion from the pancreatic β-cells. FFAs, spilled over to other tissues when the adipose cell storage capacity is exceeded, contribute to insulin resistance of tissues. Adiponectin decrease could contribute to this process as well. NAFLD typically correlates with a reduced insulin response, leading to an increase in hepatic gluconeogenesis (Seppälä-Lindroos et al. 2002). On the other hand, the insulin resistant status of adipose cell fails to inhibit properly the lipolysis process thereby enhancing the adipose FFAs secretion. Their deposition in muscle also mediates glucose uptake impairment and at further extent they finally result lipotoxic for cells, for example, contributing to the pancreatic β-cell exhaustion. Another central mechanism involved in insulin-resistance onset is the low-grade inflammation which sets at the AT level. Especially some cytokines, such as TNF-α, induce an increase in triglycerides hydrolysis and an impaired gene expression of factors involved in insulin signaling and adipocyte differentiation. Partly caused by these same mechanisms, obesity-related dyslipidemia is a recognized risk factor for cardiovascular disease. It is characterized by high plasma levels of FFAs and triglycerides, decreased high density lipoprotein (HDL), and altered low-density lipoproteins. The primum movens in dyslipidemia development is the uncontrolled release of FFAs from the adipose cell induced by the impaired hypertrophic growth and by the local proinflammatory environment. As mentioned above, FFAs reach the liver through the portal vein and promote the synthesis of very-low-density lipoproteins (VLDL), which in turn inhibit chylomicrons lipolysis and induce hypertriglyceridemia. Hypertrigliceridemia is responsible for the triglycerides-cholesterol esters exchange observed between VLDL, rich in triglycerides, and LDL/HDL, rich in cholesterol esters. This leads to a decrease in HLD-cholesterol levels and to the formation of small, dense LDL, a relevant risk factor for cardiovascular disease. The insulin resistance and the systemic inflammatory state observed in obesity, together with increased FFAs plasma levels, reflects in a similar hepatic condition; the liver becomes insulin resistant, secretes proinflammatory cytokines, and stores circulating FFAs (Dowman et al. 2010). This condition configures the

NAFLD, which is defined as a hepatic fat content over 5% of total liver volume or weight. In NAFLD, liver increases gluconeogenesis, despite the high glucose plasma levels, releases more VLDL produced from FFAs contributing to hypertrigliceridemia, increases hepatic cytokines but also thrombotic factors secretion.

Not all obese subjects meet this spectrum of comorbidities. Again, just a dysfunctional fat growth, especially in its visceral depot, triggers all those detrimental phenomena which finally lead to pathology.

## Summary

Obesity pathogenesis comprises a complex spectrum of pathogenetic conditions, including environmental, genetic, and epigenetic factors, which variably contribute to the disease setting. Considering the diseases complexity, most of the etiopathogenic mechanisms leading to obesity are far to be clarified and new causal factors are brought to light. Since obesity is a deadly epidemic disease with severe complications, the further elucidation of the pathogenic factors bearing it represents a crucial step in order to solve one of the major health problems in the so-called modern society.

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# The Microbiota and Energy Balance

6

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## Contents



**Abstract**

Human gut microbiota consists of trillions of microorganisms which participate actively in host metabolism. Recent advances in bioinformatic and molecular biology (bacterial genome sequencing) have allowed for exploring in depth the relationship between gut microbiota and obesity-associated metabolic disturbances. A large number of studies in animal models and humans indicate that gut microbiota is linked with the onset and development of metabolic disorders, such as obesity. The abundance and the composition of the gut microbiota are conditioned by metabolic state of the host, including the degree of obesity and

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insulin sensitivity, and by exogenous factors, such as diet and medication. Experiments in rodents demonstrated that the microbiota can modulate both energy balance and energy stores through the production of specific molecules. In this chapter, we will summarize the existing evidence supporting the possible role of gut microbiota and energy balance in both – animal and human – models, the pathophysiological mechanisms underlying these effects and potential novel therapeutic targets in obesity.

**Keywords**
Gut microbiota · Energy balance · Obesity

The human body is a complex group of organs and systems, and also contains more than 500 different species of microorganisms that accompany human from birth to death. Human biological entity is a stable symbiosis of two equal autonomous systems: macroorganism (host) and symbiotic microorganisms that are evolutionarily adapted to life in relatively open human organs on the basis of mutually beneficial relations (Round and Mazmanian 2009; Ley et al. 2008).

Human gut microbiota consists of trillions of microorganisms and thousands of bacterial phylotypes, which are deeply involved in a different function of host metabolism. During phylogenesis, the symbiosis of host and microflora was steadily improving, resulting in transformation of microbiota into a kind of vital regulatory body. The collective genomes of our gut microbes (microbiome) may contain >150 times more genes than our own genome (Qin et al. 2012). Eighty to ninety percent of the bacterial phylotypes are members of two phyla: the *bacteriodetes* (Gram negative) and the *firmicutes* (Gram positive), followed by *actinobacteria* (Gram positive) and proteobacteria (Rosenbaum et al. 2015; Turnbaugh et al. 2009). Each patient has a specific gut microbiota, but a core human gut microbiome is shared among family members despite a different environment (Turnbaugh et al. 2009). Recent studies described that dietary intervention impact on gut microbial gene richness (Zhang et al. 2010). Initial studies on gut microbial composition and function were limited by the difficulty to culture all intestinal microbes. The introduction of bacterial genome sequencing and "metagenomic" analysis has contributed to increase the knowledge about uncultivable microbes, gut microbial functions, its cross-talk with the host, and the potential pathogenic role related to host's diseases.

The pathophysiology of obesity is complex and involves a combination of both genetic and environmental factors (Hill 2006). Ingestion of food is a major environmental exposure. According to the fact that ingested food is processed through the filter of the intestinal microbial community, it is not surprising that gut microbiota should be considered an environmental factor that modulates host metabolism and capable to contribute into metabolic diseases.

Mounting evidence in animal models and humans is accumulating showing that gut microbiota is linked with the onset and development of metabolic disorders, such as obesity. The metabolic state of the host, diet, and medication exert significant effects on the abundance and the composition of the gut microbiota (Fig. 1).

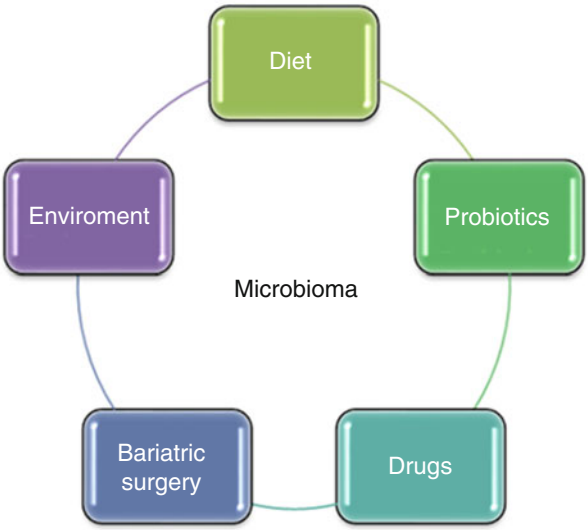


**Fig. 1** Factors capable of modifying microbiome

Experiments in rodents demonstrated that the microbiota can modulate both energy balance (weight gain and loss) and energy stores (fat mass) through the production or the secretion of specific molecules (such as short-chain fatty acids) (Rosenbaum et al. 2015). In this chapter, we will summarize the existing evidence in both – animal and human – models, the pathophysiological mechanisms underlying this association, how diet interact with gut microbiota, and how these findings may give rise to novel therapeutic targets in obesity.

## Altered Composition of Gut Microbiota in Obesity

Recent evidence suggests that gut microbiota is involved in the control of body weight, energy homeostasis, and inflammation, and thus plays a role in the pathophysiology of obesity.

The development of obesity is the result of a dysbalance between energy intake and energy expenditure. In this complex process, genetic susceptibility, environmental, and lifestyle factors are involved. Recent advances in next-generation sequencing technology and mechanistic testing in gnotobiotic mice have identified the gut microbiota as an environmental factor which influences whole-body metabolism (Devaraj et al. 2013). Gut microbiota affects energy balance, inflammation state, and gut barrier function, as well as integrates peripheral and central food intake regulatory signals leading to an increase in body weight. Underlying mechanisms of the gut microbiota contribution to host metabolism were revealed from studies on germ-free mice which were protected against developing diet-induced obesity.

In rodents, obesity is associated with an increase in the relative size of the *Firmicutes* versus *Bacteroidetes* populations in the gut (Rosenbaum et al. 2015;

Ravussin et al. 2012), and a decrease in the diversity of the microbiota that is due to both weight and diet composition. However, a recent study demonstrated that cold exposure led to dramatic changes of the microbiota composition, increasing *Firmicutes* vs. *Bacteroidetes* relative abundance (Chevalier et al. 2015). Interestingly, this shift in microbiota composition is associated with a phenotype of increased capacity of energy extraction, characterized by increased intestinal absorptive surface area and browning of the white adipose tissue (Chevalier et al. 2015). This phenotype prevents obesity and insulin resistance (Chevalier et al. 2015). In line with this, a recent study demonstrated that brown bears during their active phase (summer) become obese, but remain metabolically healthy, in parallel to increased *firmicutes* relative abundance; whereas during hibernation, brown bears had reduced gut microbial diversity, reduced levels of *firmicutes* and *actinobacteria*, and increased levels of *bacteroidetes* (Sommer et al. 2016). Transplantation of the bear microbiota from summer or hibernation to germ-free mice demonstrates that summer microbiota (increased ratio of *Firmicutes/Bacteroidetes*) promoted adiposity and slightly improved glucose metabolism (Sommer et al. 2016).

In humans, there is much greater variability in the relationship between gut microbiota composition and obesity. Some studies report a similar increase in the ratio of *Firmicutes/Bacteroides*, as well as a decrease in the gut biodiversity in obese humans, but there are also numerous studies reporting contradictory findings in obese versus lean humans (Sze and Schloss 2016). A recent meta-analysis of 10 independent studies that investigate gut microbiota composition in obese human subjects demonstrates that the ratio of *Firmicutes/Bacteroides* and the relative abundance of *Firmicutes* were not significantly associated with obesity (Sze and Schloss 2016). However, intervention studies (diet- or bariatric surgery-induced weight loss) in animals and humans can shift gut microbiota toward health-associated composition (Martinez et al. 2017).

Otherwise, an increased ratio of *Firmicutes/Bacteroides* is associated with significantly increased energy harvest (Jumpertz et al. 2011), while a significant reduction in bacterial species from *Firmicutes* phylum and increased relative abundance of bacterial species from *Proteobacteria* and *Bacteroidetes* phyla are linked to insulin resistance and type 2 diabetes (Qin et al. 2012; Pedersen et al. 2016; Haro et al. 2016; Fugmann et al. 2015; Korem et al. 2015; Karlsson et al. 2013).

## Pathophysiological Factors Linking Gut Microbiota, Obesity, and Energy Balance

Taking into account that the obese phenotype is associated with differences in the gut microbial composition compared with lean counterparts (Rosenbaum et al. 2015), several mechanisms have been proposed to explain the influence of the microbiota on obesity, such as metabolic endotoxemia, modifications in the secretion of the incretins, and SCFA production (such as acetate, propionate, and butyrate). We here summarize the main pathophysiological mechanisms by which intestinal microbiota

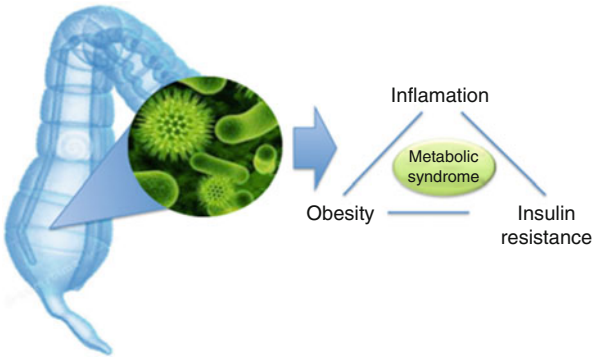


**Fig. 2** Pathophysiological factors linking gut microbiota and energy balance

could promote obesity (Fig. 2), although the exact mechanism through which intestinal microbiota alter systemic homeostasis is just beginning to be dissected.

## Short-Chain Fatty Acids

The gut microbiota has profound effects on metabolism of several dietary components and produces numerous metabolites that can be detected in the circulation. One of the most widely studied metabolites is short-chain fatty acids (SCFAs). Intestinal microbes ferment nondigestible carbohydrates in order to yield energy, leading to the production of SCFAs in the form of acetate (60%), propionate (25%), and butyrate (15%) (Rosenbaum et al. 2015). The concentration of fecal SCFAs is highly dependent on the amount of daily dietary fiber intake and is readily absorbed in the plasma of the host via the intestinal epithelium, serving as an energy source, predominantly via metabolism in the liver. The role for intestinal bacteria in the production of SCFA is clearly demonstrated by the observation that germ-free rats and mice are characterized by reduced levels of intestinal SCFAs with a concomitant increase in fecal excretion of nondigestible carbohydrates. Moreover, mice models (ob/ob) and human disease states (e.g., metabolic syndrome) characterized by obesity and insulin resistance also tend to have decreased intestinal SCFAs levels with a concomitant reduced excreted energy content in their feces (Qin et al. 2012; Karlsson et al. 2013). Gut microbial-derived SCFAs have been demonstrated to improve insulin sensitivity through the enhancing of fat oxidation and energy expenditure (van der Beek et al. 2016; Shirouchi et al. 2016; Canfora et al. 2015). For instance, acetate seems to exert a crucial role in brown adipocyte differentiation through the induction of mitochondrial biogenesis, leading to increased oxygen consumption rate in white and brown adipocytes and in skeletal muscle and increasing the browning of subcutaneous adipose tissue in parallel to increased insulin sensitivity in mice (Hu et al. 2016; Sahuri-Arisoylu et al. 2016). In fact, exogenous acetate administration also resulted in increased expression of browning genes in 3 T3-L1 cells and in white adipose tissue in parallel to increased whole-body oxygen consumption and enhanced fat oxidation (Canfora et al. 2015; Hanatani et al. 2016; Lu et al. 2016). Reduced ratio of

*Firmicutes/Bacteroides* has been associated with decreased serum acetate and impaired insulin sensitivity, measured as glucose infusion rate during a hyperinsulinemic euglycemic clamp (Carvalho et al. 2012). The recovery of serum acetate levels (using antibiotics or acetate administration) led to improved insulin sensitivity and attenuated adipose tissue macrophage infiltration in adipose tissue (Carvalho et al. 2012). Interestingly, a recent study reported the importance of some bacterial species of Firmicutes phylum in acetate biosynthesis (Goffredo et al. 2016). In humans, distal colonic acetate infusion resulted in increased whole-body fat oxidation (van der Beek et al. 2016). However, further intervention studies in humans are required to demonstrate the relationship between gut microbiota-induced SCFA biosynthesis and metabolic phenotype. Mechanistically, SCFAs interact to two orphan G protein-coupled receptors, GPR41 (also termed free fatty acid receptor 3) and GPR43 (also termed free fatty acid receptor 2). These receptors are expressed in gut, adipose tissue, and the peripheral nervous system (Rosenbaum et al. 2015).

Furthermore, increasing evidence indicate that gut microbial-derived SCFAs (specifically propionate) may affect central appetite regulation. Gut microbiota-produced SCFAs also modulates appetite and energy intake through the stimulation of anorexigenic gut hormone (hormones peptide tyrosine tyrosine (PYY) and glucagon-like peptide (GLP-1) release) (Chambers et al. 2015). A recent study also suggested a direct effect of colonic propionate (independent of PYY and GLP-1), inhibiting reward-based eating behavior via striatal pathways (Byrne et al. 2016).

To sum up, these studies suggest that acetate exerts its actions primarily on energy harvest and basal thermogenesis/fat oxidation, whereas butyrate and propionate have more direct effects on feeding behavior and physical activity.

## Metabolic Endotoxemia

Lipopolysaccharide (LPS) is a component of Gram-negative bacteria cell walls, which is among the most potent and well-studied inducers of inflammation. Gut microbiota-derived LPS leading to metabolic endotoxemia is involved in the onset and progression of inflammation and metabolic diseases (Lassenius et al. 2011). Metabolic endotoxemia is defined as the sufficient LPS concentration in circulation that is necessary to promote a low-level chronic inflammatory state and cause insulin resistance, obesity, and type 2 diabetes (Lassenius et al. 2011; Amar et al. 2011). A high-fat diet contributes to a higher abundance of LPS-containing microbiota as well as plasma LPS levels with consequent systemic inflammation in both man and animal models (Amar et al. 2011). Experimental LPS infusion results in hyperglycemia and hyperinsulinemia (Amar et al. 2011). CD14/TLR-4 knockout mice, resistant to LPS, were also resistant to high-fat diet-induced metabolic diseases, because the triggering of the inflammatory cascade in the liver and in adipose tissue was significantly reduced in these animals, disclosing the role of CD14 to set host's insulin sensitivity in

physiological conditions (Amar et al. 2011). A high-fat diet (HFD) induces adherence and translocation of commensal bacteria from the intestine into the blood and adipose tissue in mice in correlation with increased inflammatory cytokines (Amar et al. 2011). A HFD produces significant changes in the composition of gut microbiota (Parks et al. 2013), which could have a major influence on immune cell function (Maynard et al. 2012). However, considering that inflammation itself may affect intestinal microbiota and barrier integrity is difficult to establish categorically that changes in intestinal microbiota precede and cause inflammation. Regardless, it is likely that changes in intestinal permeability contribute to a vicious cycle that exacerbates obesity-associated inflammation. In humans, circulating LPS has been significantly associated with obesity and insulin resistance (Moreno-Navarrete and Fernández-Real 2014). A high-fat diet results also in increased plasma LPS whereas bariatric surgery- or diet-induced weight loss exerted opposite effects, improving obesity-associated metabolic disturbances in parallel to decreased plasma LPS concentration (Moreno-Navarrete and Fernández-Real 2014).

Lipopolysaccharide binding protein (LBP) is a key circulating mediator of Toll-like receptor (TLR) pathway mainly produced in liver that binds LPS through the interaction with lipid A and enhances the proinflammatory effects of LPS (Moreno-Navarrete and Fernández-Real 2014). LBP gene has been identified as an important candidate for conferring genetic susceptibility to type 2 diabetes on chromosome 20q, and nonsynonymous single nucleotide polymorphism (SNP) in this gene has been associated with atherosclerosis, myocardial infarction, and metabolic syndrome (Eckert et al. 2013). Similar to genetic studies, cross-sectional and longitudinal studies in mice and humans reveal that serum LBP concentrations are strongly increased in association with obesity and insulin resistance (Moreno-Navarrete and Fernández-Real 2014; Tilves et al. 2016; Liu et al. 2014). Interestingly, these associations have been also shown in children (Moreno-Navarrete and Fernández-Real 2014), suggesting that the proinflammatory effect of circulating LBP might be an early contributor on obesity-associated metabolic deterioration. Furthermore, serum LBP concentration is significantly associated with carotid intima media thickness after controlling for the effects of age, gender, BMI, and hsCRP and positively associated with cardiovascular disease (Moreno-Navarrete and Fernández-Real 2014). Two prospective recent studies pointed to LBP as a marker of prediabetes and metabolic syndrome (Tilves et al. 2016; Liu et al. 2014). A recent study in LBP KO mice demonstrated that the depletion of LBP protects against high-fat diet-induced weight gain, increasing systemic energy expenditure, and the browning of white adipose tissue (Gavaldà-Navarro et al. 2016). Strickingly, the same study demonstrated that the depletion of LBP results in insulin resistance (Gavaldà-Navarro et al. 2016), dissociating the relationship between white adipose tissue browning and insulin action.

All these studies show the importance of circulating LBP in the progression of obesity-associated metabolic disturbances and immunologic alterations, hinting at LBP might be a key component in gut microbiota-induced metabolic endotoxemia associated with obesity and insulin resistance.

### Epigenetic Changes

Differences in blood DNA methylation pattern have been shown in a small cohort of eight healthy pregnant women according to the composition of the dominant phyla (Kumar et al. 2014). Mothers were selected on the basis of the relative abundance of the dominant phyla, four exhibited a predominance of the Bacteriodetes and Proteobacteria, whereas *Firmicutes* were predominant in the other four women. Deep sequencing of DNA methylomes revealed a clear association between bacterial abundance and epigenetic profiles. The genes with differentially methylated promoters in the group in which *Firmicutes* was dominant were linked to risk of metabolic disease, predominantly cardiovascular disease and alterations in lipid metabolism, obesity, and the inflammatory response (Kumar et al. 2014). Despite further longitudinal and in-depth studies are required, the link between gut microbiota and epigenetics could represent another way of interaction between microbiota and metabolic disease.

## Diet Interactions with Gut Microbiota

The most important known determinant of gut microbiota is the diet, being its composition and the amount of calories strong modifiers of microbiota (Zhang et al. 2010). Germ-free animals are resistant to high-fat diet-induced obesity and metabolic syndrome (Bäckhed et al. 2007). However, genetically identical germ-free animals respond differently to a high-fat diet (De La Serre et al. 2010). Twins, especially monozygotic (MZ) twins, have been reported to have more similar interindividual fecal microbiota than unrelated people (Turnbaugh et al. 2009). Genetically identical mice fed a fat-enriched carbohydrate-free diet did not develop insulin resistance uniformly. The subgroup of mice that did show a marked change in insulin sensitivity presented a distinct gut microbiota (Serino et al. 2012). Thus, the host genotype affects the development of the gut microbiota and gut bacterial composition. Nevertheless, concordant normal weight MZ twins had more similar bacterial populations than the MZ twins discordant for obesity, again suggesting the importance of the diet in addition to the genetic background (Simoes et al. 2013).

### High-Fat Diets

High-fat diets are associated with substantial changes in composition of the colonic microbiota at the phylum and genus levels, including reductions in intestinal Gram-negative and Gram-positive bacteria such as levels of *bifidobacteria* (Jeffery and O'Toole 2013). These changes result in increased metabolic endotoxemia and insulin resistance (Lassenius et al. 2011; Amar et al. 2011).

### Plant Versus Animal Diets

Rats fed a long-term high fiber diet had higher total bacteria, increased relative abundance of *Bifidobacteria*, and decreased *Firmicutes* compared with rats fed a

high protein diet (Saha and Reimer 2014). Diet modification with increasing protein or fiber content in maternal diet during pregnancy and lactation modifies gut microbiota of dams which may influence in the establishment of gut microbiota in offspring (Hallam et al. 2014).

In humans, a study looking at global bacterial populations in vegans, vegetarians, and control subjects found that vegans had decreased levels of *Bacteroides* spp., *Bifidobacterium* spp., *Escherichia coli*, and *Enterobacteriaceae* spp. compared to control patients, with vegans serving as an intermediate population (Zimmer et al. 2012). In this sense, a diet based on whole grains and prebiotics in humans led to a reduction in phylotypes related to endotoxin-producing opportunistic pathogens like *Enterobacteriaceae* or *Desulfovibrionaceae*, while those related to gut barrier-protecting bacteria of *Bifidobacteriaceae* were increased (Xiao et al. 2014).

A decreased intake of fruits and vegetables is associated with reduced microbial gene richness, suggesting that long-term dietary habits may affect gene richness (Cotillard et al. 2013). Dietary intervention improves low gene richness and clinical phenotypes, but seems to be less efficient for inflammatory variables in individuals with lower gene richness. In weight maintenance phase, the overall tendency was to return to a baseline level suggesting a transient effect of dietary intervention on gut microbiota (Cotillard et al. 2013). The transitory effect of the diet on microbial population has been described. Short-term consumption of diets composed entirely of animal or plant products can rapidly alter microbial community and diversity (David et al. 2014). Nevertheless, only the long-term changes on diet seem to define what type of microbial population is present. Microbiota composition is strongly associated with long-term diet, with *Bacteroides* being associated with diets enriched in animal products and *Prevotella* genus being associated with diets that contained more plant-based foods (Wu et al. 2011). Long-term dietary habits could explain the stability of gut enterotypes over time (Lim et al. 2014). These long-term changes determine the metabolites produced and the potential impact on the health of the host.

Diet interacts strongly with the geographical location of the individual (Yatsunenko et al. 2012). Significant differences in the phylogenetic composition and diversity of fecal microbiota were noted between US residents and those from Malawians and Amerindians (Yatsunenko et al. 2012). These differences could not due only to genetic factors. The environment, the typical Westerns diet in US residents, has also an important role. In this line, gut microbiota of rural children in Burkina Faso who consumed a plant-rich diet was significantly different from microbiota of children from Italy who consumed a low-fiber diet. The African children had lower levels of *Firmicutes* than of *Bacteroidetes* whereas the European children had high levels of *Enterobacteriaceae* (*Shigella* and *Escherichia*) (De Filippo et al. 2010). Gut microbiota from Russian cities resembled those of Western countries, which is presumably associated with increased consumption of meat products and processed food. However, the gut microbiota in rural residents of Russia is distinctly enriched in *Firmicutes* and *Actinobacteria*, which is presumably associated with high consumption of starch-rich bread and natural products (Tyakht et al. 2013). In a study of Mongolian rural and urban population, changes in the

seasonal dietary composition in the rural population have been associated with changes in the composition of gut microbiota populations (Zhang et al. 2014). Long-term dietary intake influences the structure and activity of human intestinal microbiota. These findings imply that the dietary habits formed over a long period may play a key role in the composition of gut microbiota over other variables such as ethnicity, sanitation, and climate.

The microbiota composition is not stable over the whole lifetime of an individual, especially at the extremities of life. Changes of microbiota in elderly may be attributable to diet, with increased sugar/high-fat foods and diseases (Claesson et al. 2012).

The microbiota has probably an active role modulating the response to diet in animals and humans. Early consumption of a high-fiber diet during growth can offer protection from obesity after a high-fat diet (Maurer et al. 2010). The gut microbiota in obese and lean mice has specific characteristics that are transmittable and confers a different response against high fat or vegetable diets (Ridaura et al. 2013). In humans, the microbiota composition and the abundance of several species such as *Firmicutes* can predict the responsiveness to diet in obese individuals which could reveals the potential of microbiota signatures for personalized nutrition (Korpela et al. 2014).

## Exercise Impact on Gut Microbiota

Increasing evidence exist that physical activity can modulate gut microbiota profile. Although a direct causal relationship between exercise and gut microbial composition and function has not been established and is inextricably linked with dietary adjustments, several potential mechanisms by which physical activity and fitness might modify the microbiota have been reported. Abrupt exercise involves the production of multiple metabolites and inflammatory mediators. Prolonged excessive exercise also has deleterious influence on intestinal function due to the redistribution of blood from the splanchnic circulation to actively respiring tissues. Prolonged intestinal hypoperfusion impairs mucosal homeostasis and causes enterocyte injury. These events render the gut mucosa susceptible to endotoxin translocation. By contrast, moderate exercise has been associated with a lesser degree of intestinal permeability, preservation of mucous thickness, and lower rates of bacterial translocation (O'Sullivan et al. 2015).

Several studies in experimental models addressed the relationship between gut microbiota composition and physical exercise. In 2007, Bäckhed et al. suggested the existence of a microbiota-muscle axis that protects mice from obesity (Bäckhed et al. 2007). Consistent with this notion, the bacterial abundance of *Clostridiaceae* and *Bacteroidaeae* families and *Ruminoccocus* genus were found to be negatively associated with blood lactate levels in exercised animals, whereas a positive association was found for *Oscillospira* genus (Petriz et al. 2014). The changes exerted by physical exercise on gut microbiota depend on the physiological state of the individual. Accordingly, forced exercise increased microbiota richness in obese, hypertensive, and normal rats, which were dependent on their physiological state (Petriz

et al. 2014). It has been also observed that exercise induces more effective changes in the microbiota in juvenile rats than in adult rats (Bressa et al. 2017). In addition, it has been described a higher abundance of *R. hominis*, *A. muciniphila*, and *F. prausnitzii* in active women than in their sedentary peers (Bressa et al. 2017). These species have been related to health-promoting effects. Both *R. hominis* and *F. prausnitzii* have a beneficial effect on health as they produce butyrate, which has a positive impact on intestinal health and lipid metabolism, and *F. prausnitzii* also produces metabolites with anti-inflammatory action (Bressa et al. 2017).

More studies in human are necessary due to the difficulty to isolate the effects of exercise against other divergent factors. Exercise and diet often go hand in hand; an active lifestyle is frequently associated with a high consumption of fruits and vegetables, whereas sedentarism is associated with the consumption of high-calorie and fatty foods. Indeed, exercise interventions in human populations have resulted in an improvement in diet habits.

## Antibiotics, Microbiota, and Obesity

Emerging epidemiological studies have disclosed that exposure to antibiotics in early life was associated with increased risk of excess adiposity. It seems that gut microbiota has increased susceptibility to perturbations in the extreme stages of life, particularly during infancy, in which a stable microbial community skills need to be developed (Zeissig and Blumberg 2014). Infants acquire much of their founding microbiota at birth, and these microbial populations subsequently undergo maturation over the next several years. A microbiota with adult-like complexity is developed by 3 years of age, which corresponds to the transition to a diet similar to that of adult individuals and to the development of major components of acquired (adaptive) immunity (Martin et al. 2010).

Approximately 70 years ago, veterinary scientists showed that adding low – subtherapeutic – doses of antibiotics to the food or water of livestock resulted in promotion of growth (Taylor and Gordon 1955). A wide variety of antimicrobial agents has been demonstrated to have these effects regardless of drug class (antibiotic, ionophore, or antiseptic), chemical structure, mode of action, and spectrum of activity (Butaye et al. 2003). Importantly, when animals are exposed to antibiotics early in life, the effects on both growth promotion and feed efficiency are greater than if the exposure occurs later in life (Butaye et al. 2003). The effects associated with age are consistent with the concept of a critical developmental period for shaping host metabolism, with early life being more vulnerable to change than later in life. Antibiotic-mediated promotion of growth is widely practiced by farmers because it is very effective. It is supposed that the use of antibiotics leads to growth promotion by reducing infection. However, the antibiotic-mediated effects on metabolism were also observed in mice that were reared in specific pathogen-free conditions (Cox et al. 2014).

Experiments in animal models have provided direct evidence that supports a link between treatments with low doses of antibiotics with growth promotion (Taylor and

Gordon 1955). Early life is the key period for microbe-mediated programming of host metabolism (Cox et al. 2014). Administration of low doses of penicillin or oxytetracycline has been shown to lead to weight gain in mice, but high doses resulted in weight loss (Cox et al. 2014). Treating mice with subtherapeutic doses of penicillin, vancomycin, and chlortetracycline led to increased fat mass and increased levels of short-chain fatty acids in these animals, suggesting that the altered microbiota had an enhanced metabolism that could drive induction of downstream hepatic genes involved in lipogenesis (Cho et al. 2012).

In humans, a number of epidemiological studies suggest that antibiotic exposure in infancy is associated with a higher body mass index (BMI) (Trasande et al. 2013) as well as an increased risk of overweight and obesity later in childhood (Saari et al. 2015; Azad et al. 2014). Exposure to antibiotics appears to be particularly detrimental during the first 6 months of life (Trasande et al. 2013; Saari et al. 2015). The intestinal microbiota perturbation caused by antibiotic exposure in the perinatal period appears to program the host to an obesity-prone metabolic phenotype, which persists after the antibiotics have been discontinued and the gut microbiota has recovered (Turta and Rautava 2016). Among 11,000 children from the United Kingdom, antibiotic exposure during this time period significantly increased the risk of overweight at 38 months of age (OR 1.22 after adjusting for potential confounding factors; $p = 0.029$). Boys may be more affected by early antibiotic exposure than girls: antibiotic exposure during the first 6 months of life was associated with overweight at the age of 2 years in boys (adjusted OR 1.34 with 95% CI 1.06–1.66) in a cohort study of 12,000 children from Finland (Saari et al. 2015) but the association was not detected in girls (adjusted OR 1.16 with 95% CI 0.87–1.56). Antibiotics administered in the first year of life of Canadian infants increased the likelihood of a child being overweight at 9 years and 12 years of age, as well as having elevated central fatness (Azad et al. 2014). A dose-response relationship pertaining to the number of courses of antibiotics during the first 2 years of life and the risk of childhood obesity was observed in a cohort of more than 64,000 children from the United States (Bailey et al. 2014). These epidemiological studies based on tens of thousands of subjects clearly demonstrate an association between early antibiotic exposure and the development of overweight. However, establishing a causal link between the two is more difficult. In adults, a recent retrospective study using a large population (208,002 diabetic cases vs. 815,576 matched controls) demonstrated a higher adjusted risk for type 2 diabetes among individuals with recurrent exposures to penicillin, cephalosporins, macrolides, and quinolones, but not for exposure to antiviral or antifungal medications (Boursi et al. 2015). Otherwise, in a randomized double-blind placebo-controlled trial that evaluates the effects of short-term antibiotics exposure on insulin sensitivity and energy metabolism demonstrated that vancomycin treatment during 7 days resulted in a significant decrease in microbial diversity and composition and a lower production of SCFAs, but no significant effects was found on peripheral, hepatic, and adipose tissue insulin sensitivity, energy metabolism, and low-grade inflammation neither just after treatment cessation nor at 8 weeks follow-up (Reijnders et al. 2016).

It is well established that other disturbances in perinatal microbial contact may increase the risk of obesity. Colonization of an infant relies on vertical transmission from the mother at the time of delivery; thus, maternal exposure to antibiotics or an altered delivery route could also affect microbiota establishment and consequent effects on weight gain. Antibiotic exposure immediately prepartum, as occurs in more than 30% of US women to prevent Group B *Streptococcus* infection (Verani et al. 2010), could have a direct effect on the vertical transmission of microbiota (which occurs from mother to child during pregnancy or childbirth and after). Infants born by cesarean section (CS) delivery do not acquire the physiological inoculum of colonizing microbes from the birth canal and maternal gut that vaginally born infants receive. Substantial differences in gut microbiota between infants born by CS or through the vaginal route have been reported in early infancy (Dominguez-Bello et al. 2010). In the immediate neonatal period, vaginally delivered newborns are colonized by maternal vaginal lactobacilli whereas maternal skin microbes are detected in the feces of individuals born by CS (Dominguez-Bello et al. 2010). The differences in gut microbiota composition between vaginally and CS delivered children extend until the age of 7 years (Salminen et al. 2004). The clinical significance of this phenomenon is demonstrated by a recent systematic review and meta-analysis of epidemiological studies indicating that the risk of childhood obesity in infants born by CS is 1.34-fold (95% CI 1.18–1.51) as compared to vaginally born subjects even if maternal BMI is taken into consideration as a confounding factor (Kuhle et al. 2015). It should be borne in mind that in most centers prophylactic antibiotics are administered to mothers undergoing CS.According a Cochrane systematic review, antibiotic use before elective CS reduces infectious complications in the mother but its effects on the child are unknown (Smaill and Grivell 2014). It is possible that at least a part of the reported association between CS delivery and the risk of obesity may in fact be mediated by antibiotic exposure.

It is well known that antibiotics are important and potentially life-saving drugs that have considerably reduced the rates of human mortality and morbidity. Short-term side effects are also well known, but not those that occur in the long run. The long-term impact of antibiotics on the intestinal microbiota and the metabolism of the host are still a field to elucidate.

## Novel Therapeutic Targets in Obesity

It will be essential to determine whether an altered gut microbiota precedes the development of obesity and metabolic syndrome and to identify the underlying molecular mechanisms. Increased mechanistic insights of how the microbiota modulates metabolic disease in humans may pave the way for identification of innovative microbiota-based diagnosis and/or therapeutics. Despite initial skepticism, fecal microbiota transplantation was recently demonstrated to be a real therapeutic alternative in some diseases such as *Clostridium difficile* infection, being more effective than the usual treatment with vancomicin (van Nood et al. 2013).

*Akkermansia muciniphila* represents between 1% and 5% of human intestinal microbiota (Plovier et al. 2017). Several studies demonstrated decreased abundance of *A. muciniphila* in obesity and type 2 diabetes, and its recovery in parallel to the improvement of obesity-associated metabolic disturbances in patients with obesity undergoing caloric restriction (Plovier et al. 2017; Le Chatelier et al. 2013). Functionally, the administration of live *A. muciniphila* prevents the development of high-fat diet-induced obesity, insulin resistance, and gut barrier dysfunction in mice (Plovier et al. 2017). Therefore, even though clinical trials in patients with obesity remain to be performed, these studies in mice suggest *A. muciniphila* as a promising target in the management of obesity and related disorders. For the moment, first data in humans suggest that both live and pasteurized *A. muciniphila* are well tolerated in subjects with obesity and appear safe for oral administration in the context of obesity (Plovier et al. 2017).

## Summary

1. Gut microbiota is linked with the onset and development of metabolic disorders such as obesity and type 2 diabetes.
2. The gut microbiota has profound effects on metabolism of several dietary components and produces numerous metabolites that can be detected in the circulation.
3. Intestinal flora can modulate both energy balance and energy stores through the production or the secretion of specific molecules such as short-chain fatty acids.
4. Gut microbiota-derived lipopolysaccharide is the most important known factor involved in the onset and progression of inflammation and metabolic diseases.
5. The microbiota composition is not stable over the whole lifetime of an individual, especially at the extremes of life.
6. The microbiota composition and the abundance of several species such as *Firmicutes* can predict the responsiveness to diet in obese individuals, revealing the potential of microbiota signatures for personalized nutrition.
7. Moderate exercise has been associated with a lesser degree of intestinal permeability, preservation of mucous thickness, and lower rates of bacterial translocation.

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# Eating Disorders

7

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## Contents



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**Abstract**

Three main features define the grouping of eating disorders (ED): (a) a definite and persistent disturbance of eating or eating-related behavior, (b) an altered consumption or absorption of food, and (c) significant impairment of physical health and/or psychosocial functioning. In 2013 DSM-5 revised the diagnostic classification of feeding and eating disorders (FED). Feeding disorders are not related to body weight and shape concerns, while eating disorders usually include abnormal eating habits as well as prominent concerns about body weight and shape. Obesity is not included in the current classifications of mental disorders and is not considered as an eating disorder per se. However, some nonhomeostatic eating patterns may be related to the development and perpetuation of obesity. Furthermore, interactions between obesity and eating disorders (ED) are relevant, and both medical and surgical interventions for obesity require an accurate assessment of eating behavior before, during, and after treatment. This chapter describes the clinical features of the eight DSM-5 diagnostic categories of the FED grouping. Then it looks at binge eating disorder and many other eating patterns that often occur in association with obesity. The impact of DSM-5 on the epidemiology of FED is reviewed. The last section of the chapter talks about some recent practice guidelines for treatment of FED and the role of pharmacologic agents.

**Keywords**

Binge eating disorder · DSM-5 · Feeding and eating disorders · Food addiction · Obesity · Other specified feeding or eating disorders · Pharmacologic agents · Practice guidelines · Psychiatry · Treatment

## A Brief Historical Note

The word *obesity* comes from Latin: *ob*, because of + *esum*, food that has been eaten. Despite this, eating disorders (ED) have traditionally been regarded as psychiatric disorders, completely distinct from obesity.

In 1959 the psychiatrist Albert Stunkard (1922–2014) first described two eating patterns – *night eating* and *binge eating* – often associated with obesity (Stunkard 1959). *Night eating* indicates pressing urges to eat after dinner and/or at night. *Binge eating* means eating large amounts of food in a limited period of time, feeling out of control and unable to limit the type or amount of food eaten.

Almost three decades before, Moshe Wulff (1878–1971), physician and psychoanalyst, had described four cases of "an interesting oral symptom complex and its relationship to addiction" (Wulff 1932). They appear very similar to current clinical pictures of *bulimia nervosa* and/or *binge eating disorder*. According to Wulff's report, all the four women suffered from binge eating, but vomiting was reported only in two cases and overweight/obesity in the other two. Body shame and disgust (in German: *Ekel*) with the body were always present (see Table 1).

**Table 1** Wulff's four cases of binge eating

| Case | Age of onset of binge eating | Disgust with the body | Binge eating | Purging behaviors | Overweight/ obesity |
|---|---|---|---|---|---|
| A | Adolescence | Yes | Yes | – | Yes |
| B | Adolescence | Yes | Yes | Vomiting | – |
| C | After 30 | Yes | Yes | – | Yes |
| D | Adolescence | Yes | Yes | Vomiting | – |

Remarkably, Wulff considered binge eating as an addictive behavior. He put the accent on the relationship of this syndrome to craving (in German: *Sucht*) and anticipated recent studies on addictive eating and food addiction.

In the early 1990s, Robert Spitzer et al. proposed a new diagnostic label – *binge eating disorder* – for individuals with obesity who suffer from recurrent binge eating. They do not regularly engage in the compensatory behaviors observed in bulimia nervosa to avoid weight gain (self-induced vomiting, laxative misuse, fasting, strenuous physical exercise, etc.) (Spitzer et al. 1993).

This symptom cluster presentation was included in Appendix B of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders as a possible new ED diagnostic category (DSM-IV, Criteria sets and axes provided for further study, p. 729) (American Psychiatric Association 1994). In 2013 the DSM-5 formally recognized *binge eating disorder* (BED) as an official new diagnostic category in the group of *feeding and eating disorders* (American Psychiatric Association 2013).

BED has connected the medical area of obesity with the psychiatric field of ED. This bridge has contributed to attracting attention to the biological aspects of eating disorders, to the psycho-social and psychiatric sides of obesity and to the intersections between the two fields. At present, some clinicians and researchers believe that the aforementioned polarization is flawed. They recommend moving toward a model of shared knowledge and collaboration that thinks about obesity and ED as two sides of the same coin (Day et al. 2009; Neumark-Sztainer 2009). Accordingly, some wide-ranging expressions like *nonhomeostatic eating disorders* or *weight-related disorders* have been created. At the same time, in clinical practice, a similar multidimensional team approach to the assessment and treatment has been developed in both fields.

## Should Obesity Be Included Among Eating Disorders?

Eating disorders (ED) are defined by three main features:

- A definite and persistent disturbance of eating or eating-related behavior
- An altered consumption or absorption of food
- Significant impairment of physical health and/or psychosocial functioning.

Both the International Classification of Diseases (ICD) (World Health Organization 2010) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association 2013) regard ED as mental disorders.

As regards obesity, in recent years this condition has been formally proclaimed to be a medical disease by some authoritative bodies, such as the American Association of Clinical Endocrinologists (in 2012) and the American Medical Association (in 2014). However, to identify obesity only on the basis of a BMI or percentage body fat above a given threshold, and to label it a disease per se, leads to many conceptual problems (Heshka and Allison 2001; American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2016).

A recurring question is whether to consider obesity as a mental or behavioral disorder, in particular as an ED characterized by compulsive consumption of food and inability to restrain from eating, despite the desire to do so. As a matter of fact, some nonhomeostatic eating patterns may be related to the development and perpetuation of obesity, but it is unfeasible to set up diagnostic criteria for obesity based on a *definite and persistent disturbance* of eating or eating-related behavior. For that reason, obesity is not included in the current classifications of mental disorders and is not considered as an eating disorder per se.

Obesity appears as a complex phenomenon, while body mass index (BMI) is a single number that combines different biomarkers possibly associated with both disease and health. Furthermore, psychosocial and behavioral variables, such as binge eating, emotional eating, food craving/addiction with their neural correlates, play an essential role in many cases (VanderBroek-Stice et al. 2017). In conclusion, considering obesity as a homogeneous condition appears incorrect, and the term should be used at least in the plural: *obesities* (Bosello et al. 2016).

## Classification of Eating Disorders

ICD (currently in version 10) classifies health disorders and provides diagnostic assistance to promote international comparability in the collection, statistical processing, and presentation of clinical and epidemiological data. DSM (currently in version 5) is designed for the same aims but is limited to mental disorders.

The ICD-10 diagnostic categories for ED are collected in Table 2.

A final version of ICD-11 for approval at the World Health Assembly is expected in 2018. It is very likely that ICD-11 will merge feeding and eating disorders into a single grouping that will include the new categories of *avoidant-restrictive food intake disorder* and *binge eating disorder.*

In 2013 DSM-5 revised the diagnostic classification of ED and introduced a new name for this class: *Feeding and Eating Disorders* (FED).

The whole body of FED involves abnormal feeding or eating behaviors that are not developmentally appropriate or culturally approved and not explained by another health condition. In particular, *feeding disorders* (e.g., pica, rumination disorder,

**Table 2** ICD-10 diagnostic categories for ED (World Health Organization 1992)

| | |
|---|---|
| Anorexia nervosa | F50.0 |
| Atypical anorexia nervosa | F50.1 |
| Bulimia nervosa | F50.2 |
| Atypical bulimia nervosa | F50.3 |
| Overeating associated with other psychological disturbances | F50.4 |
| Vomiting associated with other psychological disturbances | F50.5 |
| Other eating disorders | F50.8 |
| Eating disorder, unspecified | F50.9 |

**Table 3** DSM-5 diagnostic categories for FED (APA 2013)

| |
|---|
| Pica |
| Rumination disorder (RD) |
| Avoidant/restrictive food intake disorder (ARFID) |
| Anorexia nervosa (AN) |
| Bulimia nervosa (BN) |
| Binge eating disorder (BED) |
| Other specified feeding or eating disorders (OSFED) |
| Unspecified feeding or eating disorders (UFED) |

**Table 4** Diagnostic categories for ED in prepubertal age

| |
|---|
| Early onset anorexia nervosa and atypical or subthreshold forms |
| Early onset bulimia nervosa and atypical or subthreshold forms |
| Early onset binge eating disorder |
| Food avoidance emotional disorder |
| Food phobias |
| Functional dysphagia |
| Pervasive refusal |
| Selective eating |

avoidant/restrictive food intake disorder) are not related to body weight and shape concerns, while *eating disorders* (e.g., anorexia nervosa, bulimia nervosa, binge eating disorder) include abnormal eating behavior as well as prominent concerns about body weight and shape.

In comparison with DSM-IV, in DSM-5 the number of diagnostic categories for FED has increased from three to eight (Table 3).

ED symptoms may also appear in childhood and early adolescence. ICD and DSM diagnostic criteria do not classify ED in prepubertal age children. Authors like Bryan Lask and Rachel Bryant-Waugh (2013) have suggested a list of some major clinical pictures for subjects younger than 14 years (Table 4).

## DSM-5 Diagnostic Criteria for FED

*Pica* involves repeated eating of nonedible substances.

*Rumination disorder* (RD) involves voluntary regurgitation of foods which are then re-chewed and re-swallowed or spit out.

The essential feature of the new category *Avoidant/restrictive food intake disorder* (ARFID) is eating an insufficient quantity or variety of food to meet sufficient energy or nutritional requirements for the individual. The avoidance or restraint of food intake leads to significant weight loss or failure to gain weight, or other negative impacts on physical health. On the other hand, there is no clear body image distortion or abnormal preoccupation with body weight/shape.

DSM-5 has broadened the category of *anorexia nervosa* (AN) by dropping the requirement for amenorrhea. The past requirement (absence of at least three menstrual cycles) excluded men, girls who had not started menstruating, women underweight still reporting some spontaneous menstrual activity, and women taking estrogen/progesterone drugs. DSM-5 suggests four severity levels for AN on the basis of BMI: mild $\geq$17, moderate 16–16.99, severe 15–15.99, and extreme $<$15 kg/m$^2$.

There are two subtypes: restricting and binge-eating/purging. Table 5 summarizes DSM-5 diagnostic criteria for AN.

The DSM-5 criteria have broadened the category of *bulimia nervosa* (BN) as well by reducing the frequency of binge eating and compensatory actions from twice weekly to once a week for at least 3 months. DSM-5 indicates four severity levels for BN defined by the weekly frequency of binge eating episodes and inappropriate compensatory behaviors: mild 1–3, moderate 4–7, severe 8–13, and extreme $\geq$14.

There are no subtypes. Table 6 recaps current diagnostic criteria for BN.

**Table 5** Diagnostic criteria for anorexia nervosa

| |
|---|
| Persistent restriction of food intake |
| Significantly low body weight |
| Intense fear of gaining weight |
| Disturbance in the way one's body weight and shape are experienced |
| **Two subtypes** |
| *Restricting type*: weight loss is accomplished through dieting and/or strenuous physical exercise |
| *Binge-eating/purging type*: recurrent episodes of binge eating and purging behaviors |

**Table 6** Diagnostic criteria for bulimia nervosa

| |
|---|
| Recurrent episodes of *binge eating* (overeating + loss of control) |
| Recurrent inappropriate compensatory behavior (self-induced vomiting; misuse of laxatives, enemas, diuretics; fasting; excessive physical exercise) |
| Binge eating and compensatory behaviors occur, on average, at least once a week for 3 months |
| Body weight and shape excessively influence self-evaluation |

**Table 7** Diagnostic criteria for binge eating disorder

| |
|---|
| Recurrent episodes of *binge eating* (overeating + loss of control) |
| Binge eating is not associated with recurrent inappropriate compensatory behavior |
| Binge eating occurs, on average, at least once a week for 3 months |
| There is marked distress regarding binge eating that is often accompanied by negative emotions such as shame, guilt or disgust |

The change with the greatest impact in DSM-5 was the inclusion of *binge eating disorder* (BED) in the FED grouping as a distinct, formal diagnostic category. DSM-5 indicates four severity levels for BED defined by the weekly frequency of binge eating episodes: mild 1–3, moderate 4–7, severe 8–13, and extreme ≥14.

There are no subtypes. Table 7 sums up current diagnostic criteria for BED.

*Unspecified* feeding or eating disorders (UFED) and *Other specified feeding or eating disorders* (OSFED) are two "umbrella-diagnoses."

UFED category is used when there is no sufficient information (e.g., in emergency room settings) to make a formal diagnosis or to describe a cluster of symptoms, but there is a well-grounded suspicion of disordered eating.

Finally, the OSFED category applies to clinical cases in which ED symptoms do not meet all the diagnostic criteria required for an official full-syndrome diagnosis. As a result, OSFED includes:

- *Subthreshold or atypical anorexia nervosa* (e.g., body weight is within a normal range or above)
- *Subthreshold or atypical bulimia nervosa* (e.g., binge eating episodes and compensatory behaviors are less frequent than 12 during the last 3 months)
- *Subthreshold or atypical binge eating disorder* (e.g., binge eating episodes are less frequent than 12 during the last 3 months)

## Binge Eating Disorder (BED) and Obesity

BED is the full-threshold DSM-5 ED most often associated with obesity. Consequently, it requires special attention. The close relationship of BED with obesity has made it a field of study which has deeply involved and connected internal medicine, psychiatry, clinical psychology, and neurophysiology (Cuzzolaro and Vetrone 2009). Neuroimaging studies support the hypothesis of alterations in some neural substrates (e.g., orbitofrontal cortex, frontostriatal areas) with heightened responses to palatable food cues and hypofunctioning during reward and inhibitory processes (Balodis et al. 2015).

An episode of overeating with loss of control is called *binge eating*, a symptom that crosses the entire field of ED and the whole spectrum of body weights. Both observational and experimental studies focused on three possible risk factors for *binge eating*: (a) deficits in emotion regulation processes, (b) extreme dieting, and

**Table 8** Comparison of DSM-5 diagnostic criteria for BN and BED

| Clinical features | DSM-5 bulimia nervosa | DSM-5 binge eating disorder |
|---|---|---|
| *Overweight/obesity* | Not required. It may occur | Not required, but it usually occurs |
| *Regular (on average, at least weekly) binge eating for at least* 3 *months* | Required | Required, with distress regarding binge eating, and at least three out of five descriptors (eating: very rapidly; until feeling uncomfortably full; when not feeling hungry; alone; and/or feeling disgusted after overeating) |
| *Regular (on average, at least weekly) compensatory behaviors:* e.g., *self-induced vomiting, laxatives and/or diuretics misuse, excessive exercise, fasting* | Required | Do not occur or are occasional |
| *Overvaluation of body weight and shape* | Required | Not required, but body image uneasiness usually occurs |
| *Subtypes* | None | None |
| *Remission specifier* | Full remission/partial remission | Full remission/partial remission |
| *Severity specifier* | Frequency of compensatory behaviors (mild 1–3/week; moderate 4–7; severe 8–13; extreme ≥14) | Frequency of binge eating (mild 1–3/week; moderate 4–7; severe 8–13; extreme ≥14) |

(c) body dissatisfaction. In many cases, it remains uncertain which comes first: weight problems, bingeing, or dieting?

The core feature of BED is the presence of frequent and recurrent episodes of binge eating (like BN), but no regular use of inappropriate compensatory weight-loss behaviors (unlike BN). The frequency cut-point for DSM-5 diagnosis of BED is one outburst of binge eating per week for 3 months. As a result, BED is usually associated with obesity. A synoptic table shows together DSM-5 diagnostic criteria for BN and BED (Table 8).

DSM-5 introduced a severity specifier for BED, based on the weekly frequency of binge-eating episodes (1–3, 4–7, 8–13, ≥14). A recent study supported the validity and utility of this specifier. The four severity groups were not statistically different in demographics and BED age-onset, but differed significantly from each other in BMI, eating disorder psychopathology, lifetime and current psychiatric disorder comorbidity, psychosocial impairment, and treatment outcome (Dakanalis et al. 2017).

Overvaluation of body shape/weight in BED probably should be, but is not yet in DSM-5, a diagnostic specifier for BED. A matched study verified that both men and women with BED-obesity suffer from a significantly more negative body image than

persons with non-BED-obesity (Cuzzolaro et al. 2008). As a matter of fact, individuals with BED present greater dissatisfaction and distress about their body appearance than people with non-BED-obesity and may exhibit weight and shape concerns comparable to BN patients and higher than AN patients. An interesting community survey found that body image disparagement could be a severity indicator for BED and able to provide even stronger information than the DSM-5 rating based on binge-eating frequency (Grilo et al. 2015).

In DSM-5, obesity is not a required condition for the diagnosis of BED. Should excess adiposity be included as a criterion for BED in the same way as underweight is a criterion for the diagnosis of AN? This question is still uncertain.

Many studies and systematic reviews support the distinction between BED- and non-BED-obesity on the basis of different variables, also using DSM-5 diagnostic criteria, that are broader than previous DSM-IV provisional criteria.

According to a recent systematic review, BED-obesity is related to increased healthcare utilization and healthcare costs (Agh et al. 2015).

BED is associated with many physical illnesses (Olguin et al. 2017). Strongest associations are with diabetes and cardiovascular diseases (Thornton et al. 2017).

Health-related quality of life (HRQoL) is more damaged, especially mental HRQoL.

Some researchers observed that BED might be even more useful as a marker of psychopathology than as a new distinct diagnostic entity (Stunkard and Allison 2003). In fact, current and lifetime psychiatric comorbidity is much higher in BED-obesity than in non-BED-obesity. Mood and anxiety disorders, substance use disorders, and personality disorders (especially borderline, avoidant, and obsessive-compulsive personality pathology) are very common. In obesity surgery candidates, BED is associated with a high prevalence of mental disorders, beyond the already elevated rate observed in individuals with obesity class III.

However, a question remains: does BED represent a really separate, reliable, and valid diagnostic category? Despite its inclusion in DSM-5 as an autonomous category, BED diagnosis and treatment strategies require further deepening. For example, a distinction between *objective* (loss of control with consumption of an unusually large amount of food) and *subjective* binge eating (loss of control with consumption of a normal or small amount of food) appears problematic. There is evidence that the size of the binge is of much lower diagnostic and clinical value than the experience of being out of control (Mond et al. 2010). The ICD-11 will likely remove that requirement. Longitudinal diagnostic stability is low for all DSM-IV eating disorders (Peterson et al. 2011). Diagnostic crossover is high also when using DSM-5 criteria, particularly in adolescence. BED or purging disorder in early adolescence predicts BN in later adolescence (Allen et al. 2013).

## OSFED and Other Eating Patterns

OSFED subgrouping and other eating patterns that often occur associated with obesity have need of some more words.

## Chewing and Spitting

In chewing and spitting (CS), food is eaten, chewed, not swallowed but spat out. CS, when engaged in at high frequencies, can result in or be associated with medical and psychosocial problems. Different diagnostic criteria have been proposed, for example, at least one CS episode per week in the previous month (Guarda et al. 2004).

## Night Eating

Night eating behavior is frequent among individuals with obesity, particularly among bariatric surgery candidates (Mitchell et al. 2015). *Night eating syndrome* (NES) is not a DSM-5 official diagnosis, but it is included in the OSFED category. In 2010 an international research group proposed a set of provisional diagnostic criteria for NES that are often applied (Table 9) (Allison et al. 2010).

Some authors define *nocturnal eating syndrome* as eating at night after having gone to bed (Cerú-Björk et al. 2001). Morning anorexia is common in NES but is rare among nocturnal eaters. Restless legs syndrome is frequently associated with nocturnal eating. However, a distinction between night eating and nocturnal eating as two different syndromes appears futile.

## Purging Disorder

In 2005 the expression *purging disorder* (PurD) was introduced to give a name to a particular syndrome, which did not fulfill diagnostic criteria for AN binge-eating/purging type nor BN. It is defined as repetitive purging behavior to influence weight or shape in the absence of binge eating among individuals who are not underweight. Table 10 shows the provisional diagnostic criteria (Keel et al. 2005). In DSM-5 PurD

**Table 9** Proposed diagnostic criteria for NES

| |
|---|
| Consumption of at least 25% of daily caloric intake after the evening meal |
| *and/or* Nocturnal awakenings with ingestions at least twice per week |
| Awareness of the eating episodes |
| Distress or impairment in functioning |
| The above criteria must be met for a minimum duration of 3 months |

**Table 10** Proposed diagnostic criteria for PurD

| |
|---|
| Recurrent purging behavior (self-induced vomiting; misuse of laxatives, enemas, diuretics)<br>Purging occurs at least once a week for 3 months |
| The purging is not associated with objectively large binge episodes |
| Self-evaluation unduly influenced by body shape or weight and/or intense fear of gaining weight or becoming fat |
| The purging does not occur during the course of anorexia nervosa or bulimia nervosa |

is not listed as a discrete diagnosis, but named as part of OSFED. However, it is not less severe than full-threshold ED. A recent study, with a median follow-up of about 9 years, reported a standardized mortality rate of 3.90, nearly twofold higher than the mortality reported for BN (Koch et al. 2014).

## Eating Disorders Postobesity Surgery

An increasing number of cases of disordered eating – e.g., inappropriate restraint of food intake and/or self-induced vomiting due to a morbid fear of regaining weight – have been reported after weight loss surgery. The emergence of classical ED (AN or BN) occurs rarely, but significant eating problems and purging behaviors with important clinical implications are far more widespread (Marino et al. 2012).

Many persons with obesity, mainly females, feel very dissatisfied with their physical appearance, and the relationship with their body image does not always improve after weight loss surgery. In a recent survey, postbariatric patients looking for surgical body contouring showed great body image disparagement and, in some cases, fulfilled diagnostic criteria for *body dysmorphic disorder* (Pavan et al. 2017).

In 2004 Adriano Segal et al. proposed a set of ten diagnostic criteria for a new ED that they named *Post-Surgical Eating Avoidance Disorder* (PSEAD) (Segal et al. 2004). However, at present no official taxonomy exists to classify such eating problems that should be included in the OSFED subgrouping.

## Grazing

Grazing is an insidious eating pattern, often associated with obesity and weight regain. Grazing (picking, nibbling) may be defined "as an eating behavior characterized by the repetitive eating . . . of small/modest amounts of food in an unplanned manner" (Conceição et al. 2014, p. 973). Two subtypes – compulsive and non-compulsive grazing – can be distinguished from loss of control, that is, a feature of the compulsive form. Grazing is frequently associated with AN, BN, BED-, and non-BED-obesity. It is a significant predictor of weight regain after weight loss treatments and bariatric surgery (Parker and Brennan 2015).

## Emotional Eating

Many individuals report eating after negative (e.g., sad mood) and/or positive emotions (e.g., joy feeling). High emotional eaters eat significantly more after negative emotions than after positive emotions. *Emotional eating* seems to be positively associated with general and eating psychopathology, binge eating, pressure to be thin and muscular from peers, and negatively related to mindfulness and body image flexibility (Thompson et al. 2017).

## Muscle Dysmorphia

In DSM-5 *muscle dysmorphia* is classified as a form of *body dysmorphic disorder* (BDD). A person with this disorder is preoccupied with concerns that his/her body build is too small and insufficiently muscular.

Individuals with this problem are often preoccupied also with other body areas. They have high rates of substance use disorders and suicidality.

Other unhealthy behaviors are usually present: compulsive physical exercise, abuse of anabolic steroids, excessive diet concerns, and unbalanced food choice aimed at increasing muscular mass and decreasing fat mass.

Muscle dysmorphia is currently conceptualized as a form of BDD (the ancient dysmorphophobia), but it does have similarities to the ED, as reflected by its previous names *reverse anorexia nervosa* or *bigorexia*.

## Orthorexia Nervosa

In 1997, in the *Yoga Journal*, the US physician Steven Bratman coined the term "orthorexia" and called "health food junkies" some individuals led to dangerous consequences by dietary rules intended to promote health. Orthorexia nervosa (ON) is an expression modeled on *anorexia nervosa* to indicate a possible new eating disorder.

ON is not recognized as an official psychiatric diagnosis and is not mentioned in DSM-5 as an autonomous ED. In 2016 Dunn and Bratman proposed two main diagnostic criteria for ON that are summarized in Table 11 (Dunn and Bratman 2016).

## Food Craving/Addiction

*Selective food craving* is defined as an intense desire to consume a particular food or a specific food class that is hard to resist (e.g., chocolate, fats, carbohydrates).

Some authors have highlighted that carbohydrate consumption increases serotonin release, a neurotransmitter involved in such functions as mood control and sleep onset. Many persons learn to overeat foods rich in carbohydrates to feel better (Wurtman and Wurtman 1995, #25447).

The term *food addiction* appeared in 1956 in an article on the features of addictive eating and drinking. Randolph defined this expression as " . . . a specific adaptation to one or more regularly consumed foods to which a person is highly sensitive, produces a common pattern of symptoms descriptively similar to those of other addictive processes" (Randolph 1956, p. 198).

**Table 11** Proposed diagnostic criteria for ON

| | |
|---|---|
| Obsessive focus on dietary practices believed to promote optimum health (*healthy eating*) | *For example, inflexible dietary rules, recurrent and persistent preoccupations related to food, compulsive behaviors* |
| Consequent clinically significant impairment | *For example, consequent medical complications and/or significant distress and/or impairment in important areas of functioning* |

Fifty years after, the phenomenon has become a focus of interest for many researchers, and the neurobiological overlap between addiction and some forms of obesity has received a growing deal of attention. It is recognized as falling within the spectrum of ED, particularly in patients with BN, BED, and/or co-occurring addictive disorders and obesity (Wiss and Brewerton 2017).

An underlying hypothesis is that some foods act in the brain through similar mechanisms as substances of abuse. Randolph's article indicated coffee, corn, eggs, milk, potatoes, and wheat. At present highly palatable and energy-dense foods – above all foods rich in sugar, fat and salt – are considered to be potentially addictive. Accordingly, food and beverage industries are often accused of studying and producing *addictive foods* to boost sales.

The substantial reinforcing effects of both food and drugs are mediated by rapid dopamine increases in the brain reward circuitries that, in vulnerable individuals, can override the brain's homeostatic control mechanisms. Some functional magnetic resonance imaging studies examined the neural correlates of addictive-like eating behavior. Persons with high scores at the Yale Food Addiction Scale (YFAS) showed comparable patterns of neural activation as substance dependence: reduced activation of inhibitory regions (e.g., lateral orbitofrontal cortex) in response to food intake (receipt), and elevated activation in reward circuitry (e.g., dorsolateral prefrontal cortex and caudate) in response to food cues (anticipated receipt) (Gearhardt et al. 2011).

However, the notion of food addiction remains controversial and the scientific debate on this subject is still in its embryonic stage. In particular, the expression seems to merge two different taxonomic concepts: substance-based addiction (such as heroin addiction) and behavioral addiction (such as gambling) (Hebebrand et al. 2014).

## Binge Drinking

The term *binge drinking* (BD) refers to patterns of heavy episodic alcohol consumption (Rolland and Naassila 2017). Many reports define BD as the pattern of drinking that brings a person's blood alcohol concentration (BAC) to a level $\geq$0.08%. Adults usually reach this BAC with the consumption of five (males) or four (women) alcoholic drinks in a 2-h period. Youth weigh less than adults and are likely to reach a BAC $\geq$0.08% with fewer drinks.

Due to its episodic nature, BD does not fulfill the criteria for alcohol dependence. However, BD is a common problem and many adolescents report this harmful behavior. The teen brain is developing and more vulnerable to alcohol-induced damage and cognitive impairment.

## Drunkorexia

The practice refers to a combination of alcohol use and diet-related behaviors. In many countries, a growing number of adolescents and young adults intentionally do not eat and then go on to drink alcohol in excess.

The main features of *drunkorexia* are: (a) recurrent episodes of heavy alcohol consumption (binge drinking) and (b) inappropriate compensatory behaviors aimed to avoid weight gain (e.g., self-induced vomiting, fasting, misuse of laxatives and diuretics, extreme physical exercise).

Some findings suggest that young people with *drunkorexia* may be at risk for development of both ED and substance use disorders (Hunt and Forbush 2016).

## Taxonomy and Nosology

Three final thoughts about classification and diagnosis of disordered eating behaviors may be useful.

Firstly, many eating patterns cross the whole spectrum of body weights and may be present in the entire field of ED (Fig. 1).

Secondly, DSM is a cross-sectional, descriptive, categorical classification system. In a longitudinal and transdiagnostic perspective, it is essential to highlight that:

- There are obvious transitions from OSFED and subthreshold ED to full-threshold ED and vice versa
- Many individuals with BN had a previous history of AN
- Cross-over from BED to BN is high in adolescence (Allen et al. 2013).

Thirdly, taxonomies – such as DSM and ICD – are overarching systems of classification that are a prerequisite for diagnosis. They separate diseases and disorders on the basis of natural boundaries (e.g., infectious diseases) or expert consensus

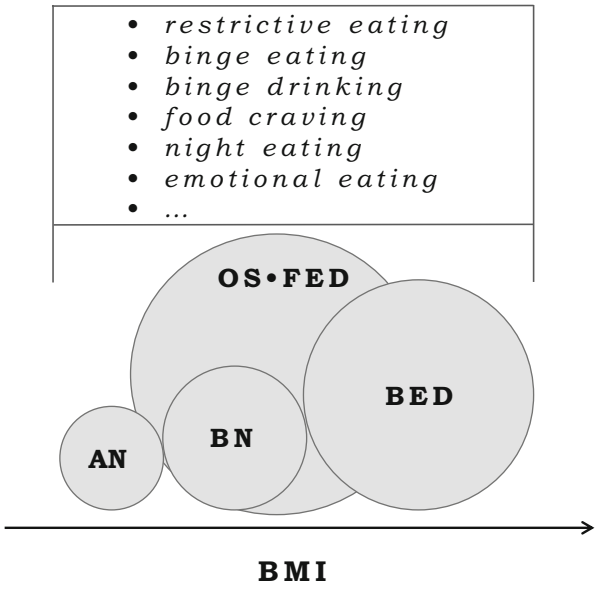


**Fig. 1** Cross-diagnostic eating patterns

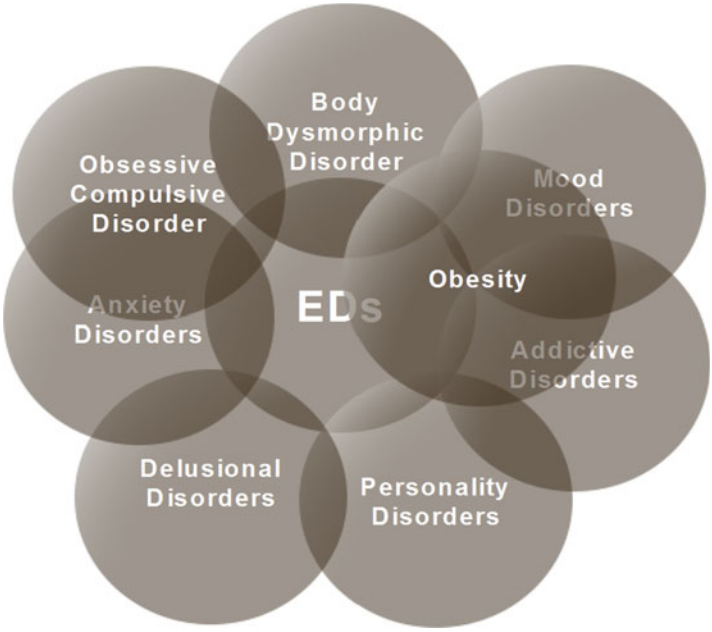


**Fig. 2** Links of eating disorders (EDs) with other diagnostic categories

(e.g., ED and the majority of mental disorders). On the other hand, nosology explores the linkages among different diagnostic categories, within a taxonomy. ED present significant links with many other pathological conditions: they may co-occur, occur sequentially, and share clinical features and risk factors (Fig. 2).

## Impact of DSM-5 on the Epidemiology of FED

With DSM-IV classification of ED, at least half the cases seen in clinical practice were relegated to the residual category *Eating disorder not otherwise specified* (EDNOS). Therefore, DSM-5 has broadened diagnostic criteria for AN, BN, and BED.

In a survey of 3043 adolescents (1254 boys and 1789 girls, mean age 14.19 $\pm$ 1.61), the researchers used DSM-IV and DSM-5 criteria for comparison (Flament et al. 2015). The one-point prevalence of full-threshold ED increased from 1.8% (DSM-IV) to 3.7% (DSM-5), and the one-point prevalence of subthreshold ED decreased from 5.1% (DSM-IV) to 3.4% (DSM-5) (Fig. 3).

A nationwide Finnish study of 2825 women (mean age 24) explored the impact of DSM-5 changes on the prevalence and prognosis of AN (Mustelin et al. 2016).

The authors observed a 64% increase in the lifetime prevalence of AN from 2.2% (DSM-IV) to 3.6% (DSM-5) with increased diagnostic heterogeneity. The new cases (subthreshold AN for DSM-IV, but full-threshold AN for DSM-5) had:

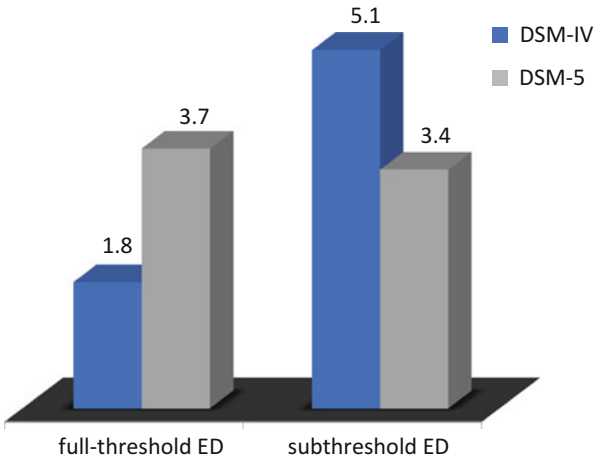


**Fig. 3** Eating disorders prevalence: DSM-IV versus DSM-5

- A later age of onset
- A higher minimum BMI
- A shorter duration of illness
- A more benign course of illness
- A higher 5-year probability of recovery

As regards the prevalence of all DSM-5 ED, an Australian prospective population study followed 1383 adolescents (49% males) from 14 to 20 years of age (Allen et al. 2013). The authors found that at age 20, the 1-month prevalence for any DSM-5 ED was 15% in females (most BN or BED) and 3% in males (mostly OSFED) (Fig. 4). Female-male ratio was 5:1. Diagnostic stability was little for all ED, and transition from BED to BN was especially high.

It is well known that a great proportion of bariatric surgery candidates report disordered eating habits that are usually associated with other mental health problems.

James Mitchell et al. investigated, with a multicenter study, ED prevalence in a large sample of 2266 patients with obesity (women 78.6%; median age 46 years; median BMI 45.9 kg/m$^2$), before weight loss surgery (Mitchell et al. 2015). Almost half of them reported a sense of lack of control over eating, and 1 out of 5 satisfied diagnostic criteria for full-threshold ED (BED 16% or BN 2%). NES was even more frequent than BED (Fig. 5).

## Links Between Obesity and ED

Obesity and ED may co-occur or occur sequentially.

Several studies on onset and outcome predictors of AN, BN, and BED have highlighted the importance of so-called *weight suppression* (the difference between highest past weight and current weight). On the other hand, *dieting* and *weight suppression* may be risk factors for future increases in adiposity.

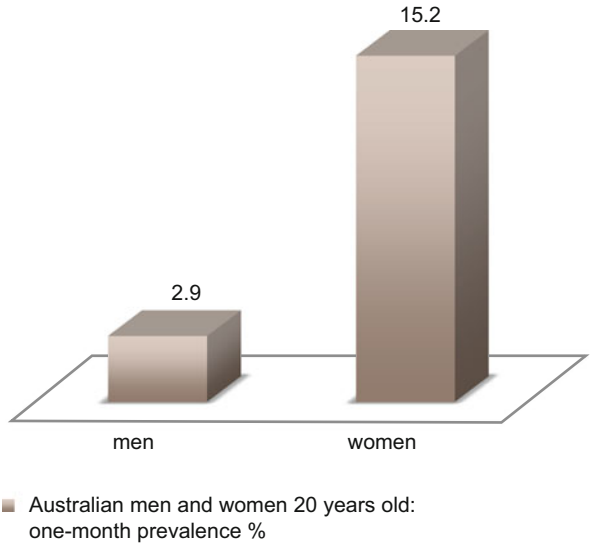


**Fig. 4** Prevalence for any DSM-5 ED at age 20

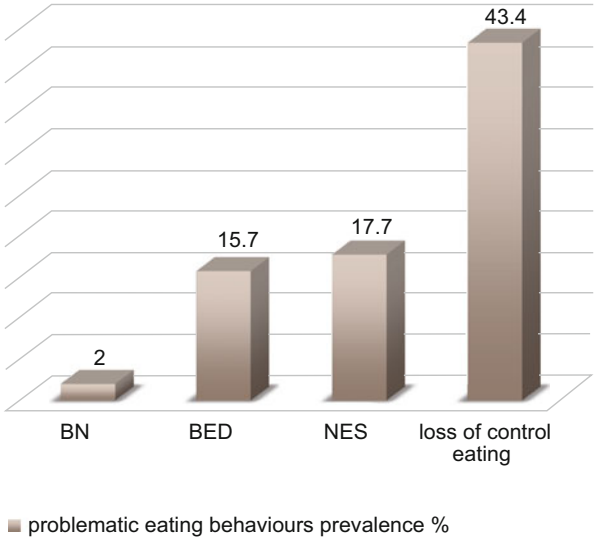


**Fig. 5** Prevalence of eating disordered behaviors in obesity surgery candidates

As regards BN, child overweight/obesity is a risk factor for this disorder. Besides, genetic predisposition to obesity was found in individuals with BN (Hebebrand et al. 2002), and increasing numbers of individuals with BN are also obese (Mitchell et al. 2015).

Childhood-onset obesity is associated with an actual history of ED at a later age (Cena et al. 2017). In particular it should be stressed that adolescents with a history of overweight/obesity represent a considerable portion of patients with restrictive

ED. They may have a poorer prognosis for the ED as they take longer to be identified and treated (Lebow et al. 2015).

Severe weight loss (>10 kg in 1 year) in adolescents is not healthy, regardless of whether the end-weight is in theory within a healthy range. In this field, the so-called *atypical anorexia nervosa not underweight* represents a serious problem.

During the last few years, the Royal Children's Hospital in Melbourne, Australia, has reported a new phenomenon. There has been a more than fivefold increase in the percentage of adolescents who have been admitted and have received the diagnostic label *EDNOS-Wt* (eating disorder not otherwise specified who do not meet the weight criteria for AN) (Sawyer et al. 2016). According to DSM-5, the diagnosis would be *OSFED, atypical anorexia nervosa*. Those adolescents did not meet the diagnostic criteria for AN because, when admitted, they were normal weight or overweight/obese. Nevertheless, they experienced the same medical complications (e.g., severe bradycardia, orthostatic instability) of weight loss, and showed similar cognitive and psychological profiles to adolescents with full-threshold AN. Also, their Eating Disorder Examination (Fairburn et al. 2008) scores showed more severe concerns related to eating and body image in comparison with AN patients, probably because their weight was still much higher than the desired weight. Compared with the AN patients, more adolescents with atypical AN (71% vs. 12%) were overweight or obese before the onset of the disorder. They had lost more weight (17.6 kg vs. 11.0 kg) over a longer period (13.3 vs. 10.2 months).

The interesting findings reported above show that atypical AN may be as severe as AN full syndrome and reinforce the need for alertness about extreme weight loss in adolescence, regardless of end-BMI.

A recent clinical report addresses the interaction between obesity prevention and ED in teenagers (Golden et al. 2016). It provides pediatricians with evidence-informed tools to: (a) identify behaviors that predispose to both obesity and ED and (b) focus on a healthy lifestyle rather than on weight through appropriate prevention messages.

## Practice Guidelines for Treatment of FED

First, it should be noted that most patients with ED do not enter the mental health care system and do not receive specific treatments. Recent data based on a meta-analysis suggest that only about 1 in 3 cases of AN and 1 in 13 cases of BN enter the mental health care system (Smink et al. 2012) (Fig. 6). Improving access to services is needed as a general principle of care.

In the last decades, many national scientific associations have published or updated clinical practice guidelines for evidence-based treatment of ED.

The Royal Australian and New Zealand College of Psychiatrists guidelines are among the most recent. This document was the first based on DSM-5 (Hay et al. 2014). In December 2016, in the United Kingdom, the National Institute for Health and Care Excellence (NICE), published online a draft short version, of the NICE guidance "Eating disorders: recognition and treatment" (National Institute for Health

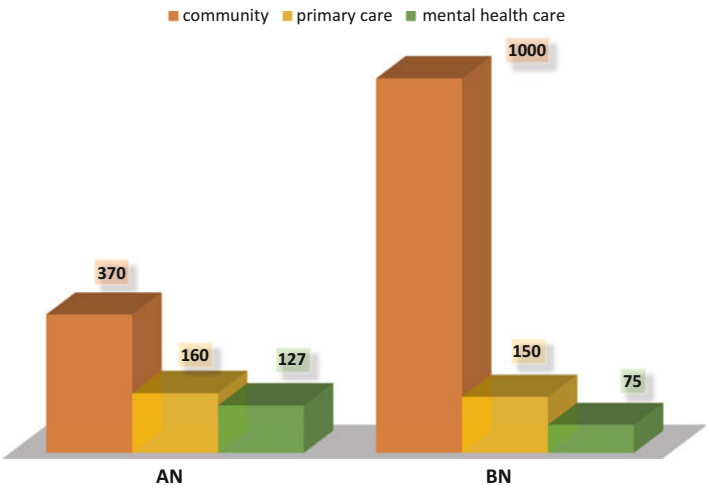


**Fig. 6** One-year prevalence of AN and BN at different levels of care

and Care Excellence 2016) for consultation. The expected publication date of the final version is May 2017.

In a majority of instances, feeding and eating disorders are long-term diseases. Cross-over from one syndrome to another (e.g., from AN to BN, from BED to BN) and weight instability are common. These conditions require a multidimensional and multiprofessional team approach for assessment and treatment.

Professionals working with people suffering from an ED should be trained and skilled, particularly in working with multidisciplinary teams.

According to clinical data, the most appropriate places for treatment for any given patient may be: (a) outpatient clinic, (b) partial hospitalization program, (c) residential rehabilitation center, and (d) general hospital inpatient unit.

In determining the initial level of care, or a change to a different level, it is essential to consider together accurately: (a) age, (b) gender, (c) the overall physical condition, (d) medical complications, (e) disabilities, (f) motivation for treatment, (g) psychiatric comorbidity, (h) suicide risk, (i) nonsuicidal self-injurious behaviors, (j) alcohol or substance misuse, (k) personality, (l) family dysfunctions and resources, (m) social support, and (n) available services.

Assessment and treatment of medical complications and dietary counseling are part of a multidisciplinary approach. Psychological interventions are the cornerstone. Many treatments have been explored in ED and have proved to produce significant results: ED-focused cognitive-behavioral therapy ED-focused psychodynamic therapy, ED-focused single- or multi-family therapy, etc. For people with an OSFED, the treatments for the ED it most closely resembles are indicated. Mindfulness-based interventions can be helpful for grazing (Levine and Koepp 2011).

There is little evidence on behavioral and psychological treatments for people with BED, but these techniques are considered first-line interventions. They include

binge-eating-focused guided self-help programs, individual and group binge-eating-focused cognitive behavioral therapy, individual and group interpersonal psychotherapy, and dialectical behavior therapy. Psychological treatments for binge eating have a very limited effect on body weight and, as a general rule, weight loss should be a posttherapy target.

Pharmacotherapy should not be offered as the sole treatment for ED. It may be an adjunctive treatment when patients have limited response to psychotherapy alone, or they present other psychiatric symptoms such as mood or anxiety disorders. When prescribing drugs for ED patients, the physician should take into account nutritional status, medical complications, and compensatory behaviors that may have an impact both on the effectiveness and the side effects of the medications.

No medication has been officially approved for AN.

High dose fluoxetine (60 mg/day) has been approved for BN.

As regards BED symptoms, during the last three decades, many different classes of drugs have been investigated by open-label studies and randomized controlled trials (RCT). Many medications have significant effects on binge-eating frequency and/or body weight (Cuzzolaro 2016; McElroy 2017) (Table 12).

However, at present, only one medication has been approved, in the United States, for adults with moderate to severe BED: lisdexamfetamine – a central nervous system stimulant prodrug of the amphetamine class – that is also used in

**Table 12** A list of drugs explored for BED treatment

| Class | Drug | Binge eating | Weight loss |
|---|---|---|---|
| Tricyclic antidepressants | imipramine | * | |
| | desipramine | * | |
| Selective serotonin reuptake inhibitors | citalopram | * | * |
| | S-citalopram | * | * |
| | fluoxetine | * | * |
| | fluvoxamine | * | * |
| | sertraline | * | * |
| Serotonin and/or norepinephrine reuptake inhibitors | atomoxetine | * | * |
| | venlafaxine | * | * |
| | duloxetine | * | * |
| Antiobesity drugs | orlistat | | * |
| Antiepileptics | topiramate | * | * |
| | zonisamide | * | * |
| | lamotrigine | | ? |
| Other drugs | baclofen | * | |
| | sodium oxybate | * | * |
| | acamprosate | ? | ? |
| | lisdexamfetamine | * | * |

* Significant reduction in comparison with placebo

the treatment of children with attention deficit hyperactivity disorder, ADHD (Fornaro et al. 2016; McElroy 2017). The other drugs remain off-label treatments.

Limited evidence suggests that some drugs (e.g., SSRI, melatonergic medications, topiramate), light therapy, and psychological interventions may be useful to treat NES.

Among biological therapies, deep brain stimulation, repetitive transcranial magnetic stimulation, and prefrontal cortex transcranial direct current stimulation are recently being studied in ED. Research in this field is still in its early stages. A thorough knowledge of the neurobiological relationships among eating behavior, reward systems, and affect regulation systems is still defective.

On a final note, to monitor the effectiveness of pharmacological and psychological treatments for ED, outcome measures should include the specific symptoms, the medical and psychiatric comorbidities, the person's general level of functioning, and the health-related quality of life.

## Summary

Eating disorders (ED) have traditionally been regarded as mental disorders, completely separate from obesity. This polarization is flawed, and the development of models that synthesize and share knowledge is recommended.

In 2013, the DSM-5 revised the diagnostic classification of ED and introduced a new name for this class, and feeding and eating disorders (FED). Three main features define the grouping of FED: (a) a definite and persistent disturbance of eating or eating-related behavior, (b) an altered consumption or absorption of food, and (c) significant impairment of physical health and/or psychosocial functioning.

In DSM-5 the number of diagnostic categories for FED has increased from three to eight: pica, rumination disorder, avoidant/restrictive food intake disorder, anorexia nervosa, binge eating disorder, bulimia nervosa, other specified feeding or eating disorders, and unspecified feeding or eating disorders. Furthermore, this classification DSM-5 has broadened diagnostic criteria for AN, BN, and BED with an important impact on the epidemiology and the clinical characteristics of FED.

The DSM-5 formally recognized the *binge eating disorder* (BED) as an official new diagnostic category that has further connected the medical area of obesity with the psychiatric field of ED. As well as BED, many other eating patterns often occur associated with obesity such as night eating, emotional eating, grazing, eating disorders post-obesity surgery, food craving/addiction. Consequently, both medical and surgical interventions for obesity require an accurate assessment of eating behavior and possible psychiatric comorbidity before, during, and after treatment.

FED are usually long-term diseases and need a multidimensional and multiprofessional team approach for assessment and treatment. Drugs should not be offered as the sole intervention for ED but may be an adjunctive treatment when patients have limited response to psychotherapy alone, or they present other psychiatric symptoms.

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# Clinical Assessment of the Patient with Overweight or Obesity

8

James D. Crane and Barbara M. McGowan

## Contents



**Abstract**

There is a global pandemic of obesity. Now widely recognized as a disease in its own right, obesity is capable of adversely affecting the function of all organ systems and worsening the course of many coexisting morbidities. While the ability to carry out a basic clinical assessment of obesity is increasingly necessary for healthcare professionals in all fields, the comprehensive assessment of obesity requires multidisciplinary expertise, including that of obesity physicians, dieticians, psychologists and/or psychiatrists, and bariatric/metabolic surgeons. This assessment must consider potential drivers of obesity, the effect of obesity on an individual's physical and mental health, physical function, and the impact of obesity on other aspects of their wellbeing including their family, social, and economic lives.

**Keywords**

Obesity · Clinical assessment · Multidisciplinary team working · Comorbidities · Severity scores

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## Introduction

The epidemic of overweight and obesity has spread from advanced economies into the developed world, and in 2014, there were an estimated 1.9 billion adults globally who were overweight, of whom 600 million were obese (WHO 2016). Obesity is an established risk factor for, or is associated with, a multitude of other conditions including hypertension, coronary vascular disease, type 2 diabetes, stroke, and cancers to name but a few of the most important. It has been estimated that in 2010, overweight and obesity caused 3.4 million deaths and was responsible for loss of around 100 million disability-adjusted life years globally (Lim et al. 2012). The costs of treating obesity and its sequelae are huge. For the UK, the Foresight Report, commissioned in 2007, estimated that by 2050 the total direct and indirect economic cost of obesity could reach £50 billion per annum in 2007 pounds (Foresight 2007). People with obesity use primary care and acute care services more frequently than those of normal weight (Guallar-Castillón et al. 2002); healthcare workers of all types will encounter obesity with growing frequency over the coming decades. The clinical assessment of obesity will become a routine and increasingly important healthcare activity and should be directed toward both an understanding of the cause for a person's obesity and a search for any present or impending sequelae. This chapter will provide an overview of the comprehensive obesity assessment, some of which is possible in primary care with the remainder usually requiring a referral to a specialist multidisciplinary team.

## The Clinical Assessment of Obesity

### Overview of the Clinical Assessment of Obesity

While, on a practical level, obesity is usually rather crudely defined by a person's body mass index (BMI) (BMI = weight (kg) ÷ height ($m^2$)), most of the negative health effects of obesity can be attributed to an elevation of fat mass (the most common cause for an increased BMI). The extent to which increased fat causes or influences the numerous and varied diseases associated with obesity is dependent on many things: the underlying cause for its increase, its anatomical location, its distribution between the different types of adipose tissue, its overspill into ectopic (nonadipose) sites, and its interaction with other aspects of the patient's prevailing medical and social circumstances. Obesity may be "simple," i.e., the result of normal adaptive or maladaptive physiological processes faced with a sustained surfeit of energy, or it may be secondary to a pathological process. The location of excess fat at different body sites and in different adipose types is influenced heavily by genes, both through their determination of the intrinsic properties of adipose cells and of the cell signaling molecules that regulate adipose tissue. This is most obviously evident in the marked differences in male and female fat distribution. Fat depots vary markedly in their association with metabolic disease, with upper-body (principally abdominal) fat being more "unhealthy" than lower body (gluteal or femoral) fat

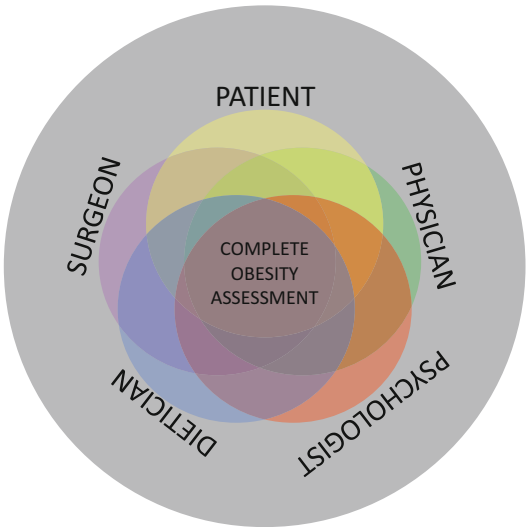


**Fig. 1** The multidisciplinary assessment of the patient with obesity. The *gray circle* represents the context in which the assessment is made: the patient's health, economic, social, and family circumstances. The *colored circles* represent the unique expertise of each member of the multidisciplinary team, with the complete obesity assessment requiring the input of all of these

(Lee et al. 2013). Recent research has suggested that individuals may have a genetically determined upper limit to their capacity to store fat in "healthy" sites, and as such have different thresholds above which excess fat is stored in metabolically unhealthy or ectopic sites (Lotta et al. 2017). Once present in ectopic sites, there may also be a person-specific threshold for fat to cause tissue or organ dysfunction (Taylor and Holman 2015). Increased body weight can impact on health independent of the pathophysiology of adiposity, for example by exacerbating pain from joint disease or physically compressing the airways to cause obstructive sleep apnea. In addition, individuals with obesity continue to be subject to discrimination in various forms in many modern societies with a knock-on effect on quality of life and psychological or psychiatric ill health. Thus, a complete assessment of obesity must investigate all these aspects to provide a proper description of its severity and requires the expertise of multiple healthcare disciplines including physicians, surgeons, dieticians, and psychologists. Importantly, it also requires self-reflection and honest testament from the patient themselves (Fig. 1).

## History, Examination, and Screening Investigations

### Clues to Etiology

Taking a careful weight history can reveal many clues as to the cause of an individual's weight gain. While the exact causes of the current obesity epidemic continue to be elucidated and debated, it is widely accepted to be driven largely by a surfeit of readily available, high energy food for a population leading ever more sedentary lives yet who remain evolutionarily adapted to survive in an environment of relative food scarcity. Notwithstanding this, under ordinary circumstances food intake is regulated by long-term neurohumoral homeostatic mechanisms, principally

involving signaling of overall energy stores from leptin and insulin, that over time equilibrate energy intake with energy expenditure to maintain a body weight set point. In some individuals, these homeostatic mechanisms result in a stable bodyweight above the healthy weight range, while in others they fail to hold body weight and progressive weight gain ensues (Vistisen et al. 2014). This may be the result of specific impairments: for example, obesity has been linked to resistance to leptin (Frederich et al. 1995), exemplified by the relative lack of potency of leptin as a pharmacotherapy to successfully reduce weight in patients with obesity (other than those with leptin deficiency) (Heymsfield et al. 1999). Superimposed on the homeostatic control of food intake are the so-called "hedonic" influences involving higher cortical and limbic pathways (concerned with the reward value of eating certain foods), and short-term neurohumoral signaling patterns controlling meal onset and conclusion (satiety). It is hypothesized that, at times, hedonic drivers overcome the metabolic homeostatic mechanisms and drive excessive energy intake (Yu et al. 2015). Exploring the circumstances surrounding periods of accelerated weight gain, or indeed weight loss (outside concerted efforts to lose weight), can often elucidate important contributory factors. The activity of hedonic pathways is influenced by, among other things, emotional stress. Indeed, it is commonplace for obese patients to describe periods of accelerated weight gain coinciding with stressful life events or as part of coping mechanisms for psychological or psychiatric illnesses, e.g., depression, in which case addressing the underlying cause is essential to the successful treatment of their obesity. Energy intake may be driven by other factors external to these control mechanisms. For example, alcoholic drinks are rarely consumed for their nutritional value, yet often contain a considerable amount of energy and may be drunk due to dependency or social imperatives leading to periods of significant excesses of energy intake. Another frequently encountered scenario is weight gain following cessation of high levels of physical activity, for example in an ex-elite athlete or when someone loses a very physical job. In such cases, habits around the timing, frequency, or size of meals may alter the neurobiological control of initiation of feeding, meal cessation (satiety), or interval between meals (Asher and Sassone-Corsi 2015), which subsequently fails to revert to normal as energy expenditure falls.

Obesity resulting from secondary pathology may also give rise to abrupt weight increase. Although almost always accompanied by other discernible symptoms or signs, the high-profile of body image and negative connotations of obesity often lead to weight gain being the presenting complaint. Thyroid hormone receptor activity is a key modulator of resting energy expenditure through its regulation of futile substrate cycles and uncoupling of oxidative respiration from ATP synthesis (Vaitkus et al. 2015). Hypothyroidism may induce weight gain from a stable baseline or accelerate the course of ongoing weight increase. Cushing's syndrome (glucocorticoid excess) has a complex effect on adipose tissue (Fardet and Fève 2014), initiating first the liberation of free fatty acids from adipose stores, followed by a regionally specific hypertrophic and hyperplastic effect on central adipose tissue. In combination with its catabolic effect on muscle mass and appetite stimulating effects in the hypothalamus (Spencer and Tilbrook 2011), chronic overexposure to

glucocorticoids causes a characteristic central adiposity with wasting of limb tissues. A similar pattern may also be seen with partial lipodystrophy syndromes. Lesions of the hypothalamus leading to dysregulation of energy balance and obesity may result from head injury, vascular, or neoplastic conditions and lead to abrupt increase in weight coincident with the onset of the lesion.

Work from the Genetics of Obesity Study at Cambridge University (www.goos.org.uk), and elsewhere, has identified specific monogenic causes of obesity sharing the characteristic of very early onset of excessive weight gain. With increasing prevalence of obesity in children, the discriminatory power of the presence of an early-onset of obesity will diminish. However, when combined with a careful family history revealing a pattern suggestive of Mendelian inheritance, a monogenic cause should be considered. In the case of leptin deficiency, hyperphagia and obesity can be completely ameliorated by administration of replacement hormone (Farooqi et al. 2002), transforming prognosis for these individuals.

Obesity is a prominent feature of other genetic syndromes, most prominently Bardet-Biedl and Prader-Willi syndromes. Bardet-Biedl, characterized by obesity, retinitis pigmentosa, polydactyly, renal anomalies, urogenital tract defects, and learning difficulties, is an autosomal recessive condition of cilia dysfunction and may cause obesity due to defective trafficking of the leptin receptor (Guo and Rahmouni 2011). Prader-Willi is an autosomal dominant syndrome usually due to sporadic chromosomal events leading to deletion or loss of function of a region on the long arm of chromosome 15, 15q11-13. Sufferers are typically short in stature with learning difficulties, behavioral problems, hypotonia, hypogonadism, and abnormalities of sleep. Feeding difficulties related to hypotonia result in initial failure-to-thrive, but this is followed by pronounced hyperphagia and obesity. The underlying molecular mechanisms linking Prader-Willi to obesity remain unclear but are likely to be polyfactorial (Khan et al. 2016). Other genetic syndromes linked to obesity have been characterized but are extremely rare. Nevertheless, genetic investigations are warranted when obesity is of early onset and accompanied by other congenital or developmental anomalies.

**Summary**

General factors to consider in the obesity history:

- Age of onset of excess weight
- Where onset as a young child, the presence of other traits suggestive of genetic syndromes
- Family history of obesity and its pattern, especially if severe obesity is dichotomously present with normal weight
- Pattern of weight gain, noting periods of acceleration or weight loss and their relation to health or life events
- Intake of alcohol or other highly calorific liquids
- Success and failure of previous attempts at losing weight

## Identification of Sequelae and Important Comorbidities

**Cardiovascular disease**. The prevalence of hypertension (usually defined as systolic BP >140 mmHg and/or diastolic BP >90 mmHg) may be up to 75% in obese people, compared to approximately 25% of the population as a whole. Diagnosis in obese patients may be confounded by a lack of availability of appropriately sized sphygmomanometry cuffs and the absence of a prior diagnosis should not be relied upon as an indicator of normotension. Both due to the high prevalence of hypertension and its role as a prominent risk factor for cardiovascular death, improvement in blood pressure is a key health goal for patients with concomitant obesity and hypertension; its identification is an important priority in the obesity clinic. It is widely accepted that 24 h ambulatory blood pressure monitoring outperforms clinic measurements in predicting cardiovascular events and this is the preferred diagnostic test in most guidelines.

Obesity is strongly associated with atherosclerotic disease, both independently and through sequelae such as dyslipidemia and diabetes. Some patients with obesity attribute even quite marked exercise-induced chest or limb pain as being simply due to their weight and may not volunteer the presence of these symptoms without direct questioning. The presence of significant coronary arterial disease may have important implications for both short-term health and potential treatment options for obesity, in particular bariatric surgery and anesthetic risk, and should be characterized as fully as possible.

Even in the absence of significant ischemic heart disease, obesity is associated with a specific cardiomyopathy. The etiology is multifactorial and due to the effects of volume overload from a hyperdynamic circulation, the metabolic effects of excess fat deposition in the heart ("lipotoxicity") and the bioenergetic effects of insulin resistance and a switch to exclusive fatty acid metabolism (Abel et al. 2008). Comorbidities, including diabetes, hypertension, and obstructive sleep apnea, have additional deleterious effects on the myocardium. Hypertrophy, which may be eccentric or concentric, and fibrosis result in ventricular dysfunction that is often predominantly diastolic in the early stages. Breathlessness on exertion, orthopnea, and paroxysmal nocturnal dyspnea are all commonly encountered symptoms that raise suspicion of cardiomyopathy. Technical limitations of readily available investigations often lead to challenges in accurately characterizing the heart's function. While fluid retention and the presence of subcutaneous edema of the lower limbs may be due to heart failure, it may also be due to other factors such as the activation of the renin-angiotensin-aldosterone system associated with obesity that leads to salt and water retention, the increase in hydrostatic pressure of the lower limb venous system due to compression of the abdomino-pelvic vessels, or through dysfunction of the lymphatic system (linked to obesity through unknown mechanisms). A raised jugular venous pulsation/pressure may be difficult to see but when present usually indicates pulmonary arterial hypertension that may be due to congestive cardiac failure or cor pulmonale due to the chronic hypoxia of obstructive sleep apnea and obesity hypoventilation. Valvular disease, somewhat counterintuitively, may be *less* frequent in obese people (Singh et al. 1999).

A quantified estimate of the 10-year risk for cardiovascular and cerebrovascular events can be made using risk engines, such as QRISK-2 (Hippisley-Cox et al. 2008), developed and validated against datasets of the general primary care population in the UK and which, in contrast to other risk engines such as those derived from the Framingham and UKPDS datasets, includes BMI as a variable.

**Summary**
Basic cardiovascular assessment should include:

- Enquiry after personal history of exercise induced pain of the chest or limb
- Family history of hypertension or vascular disease
- Smoking and alcohol history
- History of exertional breathlessness, orthopnea, or paroxysmal nocturnal dyspnoea
- Examination of the cardiovascular system
- Electrocardiography
- Echocardiography, nuclear medicine perfusion scan or other cardiac imaging if symptoms are present
- FBC, creatinine, electrolytes, B-type natriuretic peptide (be aware that false negatives are more frequent in obesity), urinalysis for protein

**Metabolic disease**. The obesity epidemic advances hand-in-hand with that of type 2 diabetes, with insulin resistance increasing directly as a function of BMI. However, the degree of insulin resistance for a given level of adiposity is subject to much inter-individual variability. Fat is stored in several adipose tissue depots which are functionally distinct (Fig. 2) and site of fat deposition is highly influential. Central fat accumulation in the "android" pattern results in greater insulin resistance than peripheral fat accumulation in the "gynecoid" pattern (these common terms are used advisedly as body fat distribution does not always split neatly along gender lines). These patterns are easily identifiable visually and are evaluated by the waist-to-hip circumference ratio (as defined by the World Health Organization: the waist is taken to be the point midway between the apex of the iliac crest and the lower limit of the ribcage, and the hip is taken to be the maximum circumference around the buttocks with the tape parallel to the floor). More important, but invisible on examination, are interindividual differences in liver and pancreatic ectopic fat accumulation and their impact on insulin sensitivity and beta cell function, respectively. Gross steatosis of the liver may result in detectable hepatomegaly, with or without tenderness, if significant inflammation (steatohepatitis) is present. Diabetes is often present without symptoms (or without symptoms having been recognized) for a prolonged period of time prior to diagnosis. Symptoms should be enquired after, including those of hyperosmolarity (polyuria, nocturia, polydipsia, intermittent visual acuity deficit), frequent bacterial

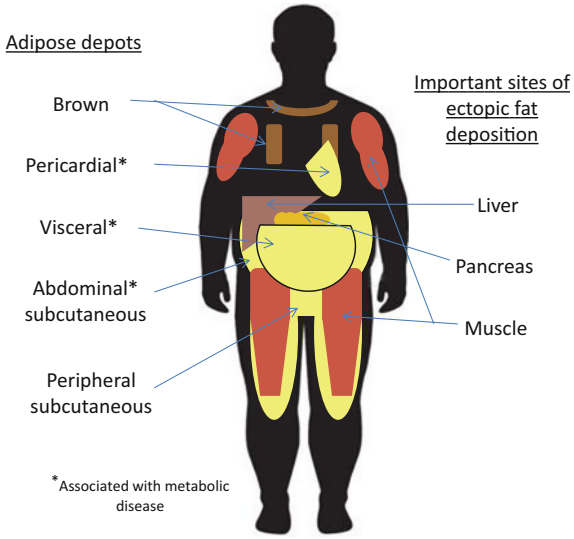


**Fig. 2** Location of fat depots and sites of ectopic fat deposition. White adipose tissue exists in functionally distinct depots. Abdominal subcutaneous, visceral (omental, mesenteric, retroperitoneal, and perinephric) and pericardial fat are associated with an increased risk of metabolic and vascular disease. Brown fat tissue is found around the neck and mediastinum. Lipid may also deposit ectopically in nonadipose tissue with adverse biochemical and metabolic effects. Important sites of ectopic fat deposition include skeletal muscle and liver (causing insulin resistance) and the pancreas (causing islet dysfunction)

or fungal infections of the genitourinary tract or skin, or weight loss that is significant or out of keeping with a patient's efforts. Glycated hemoglobin (HbA1c) remains the best available measure of diabetes control, with the risk of vascular complications increasing in line with HbA1c (Stratton et al. 2000). With standardization of laboratory measurement of HbA1c, diagnosis of diabetes (and "prediabetes") is now approved without the need for formal oral glucose tolerance testing (WHO 2011). An initial assessment of the "severity" of diabetes in essence equates to the measurement of glycemia (using HbA1c) and identification of microvascular complications (retinal photography, estimation of glomerular filtration rate, screening for albuminuria, and foot examination) and macrovascular complications (identification of cardiovascular or stroke disease through history and examination and electrocardiography). More sophisticated investigations of diabetes complications can be guided by initial findings. In those with poor glycemic control and retinopathy for whom aggressive weight loss interventions are being considered, sequential retinal photographs should be planned during and after intervention due to the likelihood of rapid correction of HbA1c and the possibility that this may lead to worsening of retinopathy (Thomas et al. 2014). When established neuropathy is present, podiatry

surveillance may be necessary as increased mobility and altered biomechanics following large weight loss may increase the risk of new pressure ulcers or Charcot foot (Murchison et al. 2014).

Obesity, insulin resistance, and hyperlipidemia/dyslipidemia are intimately linked. Energy excess leads to obesity and adiposity, adiposity results in saturation and dysfunction of adipose depots, impaired lipid storage leads to elevated circulating free fatty acids and triglycerides resulting in ectopic lipid deposition, ectopic fat in the liver and pancreas impairs insulin activity, reduced hepatic insulin signaling leads to altered hepatic lipoprotein synthesis and impairs clearance of atherogenic apolipoprotein B100-containing particles (VLDL, IDL, LDL), strongly increasing cardiovascular risk. Hyperlipidemia itself is largely asymptomatic and detectable signs on examination relatively uncommon; corneal arcus may be present. A basic lipid profile including total cholesterol, HDL-cholesterol, and triglyceride concentrations enables a QRISK-2 calculation and assessment of pancreatitis risk (triglyceride >1000 mg/dl (11.2 mmol/L) (Berglund et al. 2012).

**Summary**

Basic metabolic assessment should include:

- Waist circumference and waist-to-hip ratio
- In the absence of previous diabetes diagnosis:
  - Enquiry after symptoms of hyperglycemia
  - Fasting glucose and HbA1c
- In the presence of a previous diabetes diagnosis:
  - Family history of type 2 diabetes
  - HbA1c and review of home blood glucose monitoring (if available)
  - Foot examination
  - Urinalysis for protein and urine sample for albumin:creatinine ratio
  - Enquiry after adherence to retinal screening, outcomes from this and fundoscopy if not-adherent
  - Screening questions for contraindications to metformin, SGLT-2 inhibitors and GLP-1 agonists (since these agents may be preferred for the purposes of facilitating weight loss)
- Examination for stigmata of familial hyperlipidemia syndromes
- Lipid profile (total and HDL-cholesterol and triglyceride as a minimum)

**Reproductive Health**. Obesity is associated with impairments of both male and female reproductive health. In men, aromatase, present in adipose tissue, is responsible for the aromatization of the A-ring of testosterone, converting it to estradiol. Since estradiol is equally as able to suppress the hypothalamo-pituitary-gonadal axis through negative feedback as testosterone, leutinizing hormone (LH) is not

upregulated to restore testosterone levels resulting in symptoms of hypogonadism which include erectile dysfunction, loss of libido, gynecomastia, testicular and penile atrophy, reduced muscle bulk, neurocognitive symptoms, and infertility. Hypogonadism may be found in up to 60% of men presenting for bariatric surgery (Calderón et al. 2014). Erectile dysfunction is commonly the trigger for seeking medical attention for hypogonadism, but may also be caused by many of the other consequences of obesity, for example vascular disease, medications, or depression. Medical practitioners may be misled by low *total* testosterone levels in obese patients and diagnose hypogonadism, missing alternative etiologies. Two-thirds of testosterone circulates tightly bound to sex hormone binding globulin (SHBG) (and much of the rest weakly bound to albumin) rendering it unavailable for biological activity but nonetheless detectable on a total testosterone assay. Reductions in SHBG thus reduce the total testosterone concentration but have little impact on free testosterone (or bioavailable testosterone – free + albumin-bound testosterone). As such, total testosterone is unreliable in obese patients for whom free (or bioavailable) testosterone should be measured instead. Obesity also adversely impacts spermatogenesis in men resulting in both reduced sperm count and motility (Hammoud et al. 2008) and an assessment of male fertility is also warranted.

In women, the predominant impact of obesity on reproductive health is through its association with polycystic ovarian syndrome (PCOS). Although the precise pathophysiology of PCOS is incompletely understood, hyperinsulinism driven by adiposity and insulin resistance is thought to be of primary importance. Hyperinsulinism is associated with increased pituitary LH, and the combination of the two results in increased androgen production by the ovary. This is exacerbated by suppressed hepatic SHBG and results in the clinical features of PCOS that may be present in up to three quarters of obese women of child-bearing age. These include: oligomenorrhea (menstrual cycle of >35 days), anovulatory amenorrhea, infertility, acne, male-pattern alopecia, and hirsutism. Diagnosis is confirmed by the Rotterdam Criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004): presence of 2 out of 3 of oligo/anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovaries (on ultrasound), with exclusion of other etiologies (for example Cushing's syndrome, congenital adrenal hyperplasia and androgen-secreting tumors). Elevated LH, while not formally part of the diagnostic criteria, is usually present.

Overall, obesity is associated with reduced fecundity even in women without ovulatory disruption (Gesink-Law et al. 2007) and also with reduced success of assisted conception (Shah et al. 2011). As a result, access to assisted conception is often restricted for obese women. For example, in the United Kingdom, although national guidelines fall short of excluding obese women from in-vitro fertilization, funding bodies typically insist on a BMI <30 kg/m$^2$. Due to the central importance placed on fertility by many patients, the identification of fertility as a motivation for

weight loss and knowledge of local rules for access to fertility interventions is an important part of the clinical assessment of obese female patients and will affect treatment decisions and timescales.

**Summary**
Basic reproductive health assessment should include:

- In men:
  - Enquiry after symptoms of low libido and erectile dysfunction
  - Enquiry after desire for fertility
  - Systemic examination for signs of hypogonadism (loss of body hair, gynecomastia, loss of muscle bulk)
  - Genital examination (pubic hair, phallus length, testicular size, and consistency)
  - Testosterone, LH/FSH, SHBG, LFT, blood to be taken in early morning (at of before 9 am)
  - Semen analysis if evidence of hypogonadism and fertility is desired
- In women:
  - Obstetric history
  - Menstrual history
  - Examination for signs of androgen excess (facial/body hair, male pattern balding, acne)
  - If PCOS/androgen excess suspected: testosterone, LH/FSH, SHBG, transvaginal ultrasound

**Gastrointestinal disease**. Gastroesophageal reflux disease has a clear association with obesity (Jacobson et al. 2006). Increased abdominal pressure predisposes to hiatus hernia and lower-esophageal sphincter dysfunction, which may be further impaired by metabolic changes including elevation of estrogen. Obesity is also associated with the development of Barrett's esophagus and esophageal adenocarcinoma (Singh et al. 2013). Presence of upper gastrointestinal (UGI) pathology may influence choice of intervention for obesity: history of inflammatory disease is a contraindication to intragastric balloon insertion and endoluminal liners (e.g., Endobarrier™). Bariatric surgery has been variously reported to improve or worsen symptoms of reflux, which may influence surgical decisions on the choice of, or contraindication to, the surgical procedure (Mion and Dargent 2014). Symptoms of UGI pathology include retrosternal burning pain (particularly associated with food), dysphagia, odynophagia, acid brash, nocturnal wheeze, laryngitis, and pharyngitis, particularly in the morning. Dysphagia may be due to obesity-associated dysmotility or strictures of the esophagus, either inflammatory or neoplastic.

Obesity, in particular central obesity, is a potent risk factor for cholesterol gallstone disease. Gallstone cholecystitis is the likely reason for obesity being linked to an increased risk of gallbladder cancer. Cholecystitis can be detected through the presence of symptoms, principally right-upper quadrant pain that may radiate to the right shoulder tip and is exacerbated by fat intake, which may be accompanied by a positive Murphy's sign on examination. Symptoms may be acute and accompanied by vomiting and fever, or milder and chronic, but are absent altogether in the majority of cases. Choledocholithiasis may result in a history of intermittent jaundice or of gallstone pancreatitis. Rapid weight loss, for example through very low calorie diets or bariatric surgery, predisposes to gallstone formation lending importance to the detection of gallstone disease prior to such interventions. Cholesterol gallstones are radiolucent and rarely seen on plain x-ray, while computed tomography is only 80% sensitive. Ultrasound is highly sensitive and is the investigation of choice.

The presence of nonalcoholic fatty liver disease (NAFLD) is almost universal in patients with morbid obesity and is instrumental in driving insulin resistance. In a proportion of cases it is accompanied by steatohepatitis (NASH), probably driven by the accumulation of toxic lipid intermediates in the hepatocyte (Caligiuri et al. 2016), which is associated with progression to cirrhosis in up to a third of cases. In one meta-analysis, NASH was found in over one-third of patients undergoing bariatric surgery (Machado et al. 2006). NAFLD and NASH may be detectable by clinically apparent hepatomegaly which may or may not be tender. If cirrhosis is present, the signs of portal hypertension may be found including ascites, splenomegaly, and distended abdominal veins. Other signs of liver failure include spider naevi, Dupuytren's contracture, palmar erythema, and jaundice. NASH-related cirrhosis is becoming an increasingly common indication for liver transplant. Although the impact of obesity on graft and patient survival is variable across studies (Perez-Protto et al. 2013; La Mattina et al. 2012) and may not actually be that deleterious, obesity often features as a relative contraindication in transplant criteria (Varma et al. 2011) and obese patients can face a longer wait on the transplant list (Segev et al. 2008). Significant weight loss, for example after bariatric surgery (Lasailly et al. 2015), is a highly effective treatment for NAFLD and NASH. The early detection of NASH is thus of great importance. Transaminases are often normal, although NAFLD is characteristically associated with elevation of alanine aminotransferase (ALT) before aspartate aminotransferase (AST) with an AST:ALT ratio of $<0.8$ (in contrast to alcoholic liver disease). Gamma glutamyl transferase (GGT) is often also raised. Noninvasive attempts to differentiate steatohepatitis from simple steatosis have been sought to avoid the need for liver biopsy. At the most basic level, further AST rise resulting in an AST:ALT ratio of $>0.8$ is associated with the presence of cirrhotic scarring (fibrosis). More complex scoring systems, such as the FIB-4 index (Sterling et al. 2006), may be helpful. Conventional imaging is generally unable to differentiate the two. Ultrasonographic transient elastography scores correlate with the presence of fibrosis, but the technique is subject to technical

challenges in obese patients. Biopsy is usually necessary if confirmation of cirrhosis is required.

**Summary**
Basic gastrointestinal assessment should include:

- Alcohol history
- Enquiry after symptoms of reflux, inflammation, ulceration, or strictures of the UGI tract
- Enquiry after right-upper quadrant symptoms associated with gallbladder pathology or hepatitis
- Examination of gastrointestinal system
- FBC, ALT, AST, gamma GT, ALP, bilirubin, electrolytes
- UGI endoscopy if symptoms present
- Liver ultrasound

**Respiratory disease**. Respiratory symptoms, such as exertional dyspnoea, are highly prevalent in obese people and are often due to the impact of obesity on normal cardiorespiratory physiology rather than any underlying respiratory disease. The increased oxygen requirement of a high body mass, reduced chest wall compliance, and an increased work of breathing lead to higher respiratory muscle oxygen demand. However, a number of respiratory pathologies are specifically linked to obesity, most notably obstructive sleep apnea and obesity hypoventilation syndrome.

Obstructive sleep apnea (OSA) refers to the repetitive occlusion of the upper airways due to loss of dilatory muscle tone during normal rapid eye movement (REM) sleep paralysis, resulting in apnea, hypoxia, and arousal. Suggestive symptoms include snoring, excessive daytime sleepiness (resulting from inadequate REM sleep), and morning headache of uncertain pathogenesis. These may be accompanied by neurocognitive and/or mood disturbances. Validated risk scores which predict the presence of OSA have been developed and include the Epworth Sleepiness Scale (Johns 1991) and the STOP-BANG (Chung et al. 2008) score. Diagnosis is confirmed during observed sleep through polysomnography, or alternatively through sleep oximetry which may be carried out in the patient's home. It is based on the frequency of recorded hypopnea (reduction in ventilation of at least 50% resulting in a fall in oxygen saturation by 4% or more) and apneas (cessation of breathing for >10 s). The number of episodes per hour of sleep is termed the Apnea-Hypopnea index (AHI). Mild OSA is defined as an AHI of 5–15, moderate 15–30, and severe >30. AHI increases exponentially with BMI (Newman et al. 2005), and subsequent poor sleep may contribute to increased appetite and weight gain (Spiegel et al. 2004), locking patients into a vicious cycle of increasing weight and worsening OSA. The presence of OSA is associated with

an increased risk of cardiovascular events and the development of pulmonary arterial hypertension. Early weight loss intervention is central to reducing the severity. For patients with OSA undergoing bariatric surgery, anesthetic and analgesic drugs may further reduce tone in the dilatory muscles of the upper airway, impair the arousal response to hypoxemia and reduce ventilatory drive, increasing the likelihood of respiratory failure in the perioperative period. Preoperative diagnosis with initiation and optimization of nonsurgical management (continuous positive airway pressure) is likely to reduce the risk of complications at the time of surgery.

A separate condition, but one that often coexists with OSA (particularly at the severe end of the OSA spectrum) is obesity hypoventilation syndrome (OHS). The restrictive effect of excess body tissue mass on ventilation necessitates a response from the respiratory centers of the central nervous system to increase minute-ventilation and maintain a normal partial pressure of carbon dioxide ($pCO_2$). In patients who develop OHS, this response is impaired, resulting in hypoventilation and hypercapnia (raised $pCO_2$). Hypercapnia may cause an increase in somnolence and cognitive impairment ("$CO_2$ narcosis"), flushing (due to $CO_2$-induced vasodilatation), muscle twitches/myoclonus, and palpitations. Hypoventilation also worsens hypoxia and thus pulmonary hypertension leading to more severe dyspnea and higher right heart pressures. Physical signs include plethora, subcutaneous edema, asterixis ("$CO_2$ retention flap"), right ventricular heave, split S2 with a loud pulmonary component, heart murmurs (initially the early diastolic murmur of pulmonary regurgitation, resulting in progressive volume overload, right ventricular dilatation, and then the pansystolic murmur of tricuspid regurgitation), and elevated JVP (initially with a prominent A-wave, then, when tricuspid regurgitation develops, a giant V-wave). Diagnosis is confirmed by the presence of daytime hypercapnia on arterial blood gas analysis and treatment is with weight loss and noninvasive ventilation (either by continuous or bilevel positive airway pressure, with or without supplemental oxygen).

Asthma is diagnosed with higher frequency in the obese population, although BMI does not appear to be clearly associated with either an increase in airway hyper-responsiveness or airway inflammation (Zammit et al. 2010). The symptoms may instead be due to the physical effect of increased abdominal pressure and chest wall tissue mass on lung compliance, lung volumes, and airway caliber and demonstrates the capacity of obesity to worsen lung function in the presence of any underlying lung pathology. As such, identification of pulmonary disease represents an indication for more urgent efforts at weight loss in the obese patient. The possible exception is in the case of end-stage obstructive airways disease in which elevated BMI may confer a survival advantage (Schols et al. 1998), an example of the obesity paradox – the counterintuitive association of obesity with a survival advantage in certain conditions that also include congestive cardiac failure, malignancy, and critical illness.

**Summary**
Basic respiratory assessment should include:

- Enquiry after symptoms of breathlessness and the circumstances of these
- Enquiry after symptoms of snoring or daytime sleepiness
- Enquiry after symptoms of $CO_2$ retention
- Questionnaire-based screen for OSA (e.g., Epworth or STOP-BANG questionnaire)
- Examination of respiratory and cardiovascular systems
- Arterial blood gas if OHS suspected
- Spirometry
- Polysomnography or overnight sleep oximetry if screening questionnaire for OSA high or if considering surgical intervention for weight

**Musculoskeletal disease**. Obesity has been consistently shown to be a strong risk factor for osteoarthritis (OA). For example, in the Framingham Study, the relative risk for the presence of osteoarthritis in women of the highest weight quintile was 2.07 compared to those of the lowest three quintiles (Felson et al. 1988). Obesity results in biomechanical strain through the joints of the lower limbs, hastening cartilage loss. Metabolic and systemic inflammatory changes in obesity have also been implicated: obesity increases the risk of small joint osteoarthritis as well as that of large joints (Yusuf et al. 2010). Obesity makes lower limb joint arthroplasty technically more challenging and results in more rapid wearing of joint prostheses, both of which contribute to poorer outcomes from arthroplasty in obese patients. BMI-based eligibility criteria for elective joint replacement surgery are becoming commonplace (The Royal College of Surgeons of England 2016). Weight loss results in improvement of symptoms of native joint osteoarthritis and more successful arthroplasty, leading to disabling osteoarthritis being a common indication for bariatric surgery. Obesity may also be a risk factor for the development of inflammatory arthritis (George and Baker 2016) which, due to widespread awareness of the strength of obesity as a risk factor for osteoarthritis, may be misdiagnosed as OA. Synovial inflammation is the predominant feature of inflammatory arthritides and is much less important (though often still present) in osteoarthritis. Its major symptom, painful joint stiffness after a period of disuse (e.g., in the morning), is thus much more pronounced and lasts for longer (an hour or more) in inflammatory arthritides than in OA (usually less than half an hour). Pain on use of the joint is more pronounced in OA.

Low back pain is amongst the commonest chronic symptoms in the general population and is even more prevalent in obese patients (Shiri et al. 2010). Pain may be related to pathology of the bony structures of the spine such as degenerative disc disease or spinal stenosis, or to that of the surrounding soft tissues. Nerve root

impingement in the exit foramina of the spine by intervertebral disc herniation may result in sciatica, the symptom of burning, or electric shock-like pain in the legs, and is reproducible on examination on a straight-leg-raise test. The etiology of low back pain is not always clear even after extensive investigation and imaging is best guided by orthopedic specialists. The clinical approach is usually conservative with exercise and chronic pain management.

Clinical assessment of orthopedic conditions in obese patients should be geared toward accurate diagnosis and an attempt to quantify its impact on function and quality of life to allow for goal-orientated interventions with shared decision-making by obesity and orthopedic or rheumatology teams and the patient, allowing for realistic predictions of the impact of bariatric or orthopedic surgical interventions on the morbidity associated with musculoskeletal disease.

**Summary**

Basic musculoskeletal assessment should include:

- Enquiry after symptoms of inflammatory and degenerative joint disease
- Medication history, especially steroid use as a potential driver of weight gain
- Determination of the extent of associated functional limitation
- Determination of any BMI or obesity-related barriers to accessing treatment

**Neoplastic disease**. Obesity has been estimated to account for up to 20% of cancer deaths (Calle et al. 2003), while significant and sustained weight loss is protective against cancer mortality (Sjöström et al. 2007); See ▶ Chap. 1, Epidemiology of Obesity). The authors of the second report on Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective by the World Cancer Research Fund and American Institute for Cancer Research (World Cancer Research Fund/American Institute for Cancer Research 2007) concluded that there exists convincing evidence to link adiposity to cancer of the esophagus (adenocarcinoma), pancreas, colorectum, breast (in post-menopausal women), endometrium, and kidney, as well as a probable link to gallbladder cancer. The symptom of recent and significant weight loss, common to all advanced malignancies, is not rare in the obesity clinic due to ongoing attempts to lose weight. However, weight loss that is surprising for the patient or seems excessive for the degree of effort should prompt further investigation.

The cardinal symptom of esophageal cancer is dysphagia, though odynophagia or retrosternal pain may also be present. A high index of suspicion is warranted for patients with a history of severe reflux or Barrett's esophagus and diagnosis is usually by endoscopy.

Pancreatic cancer is most often diagnosed late with the onset of painless obstructive jaundice (for tumors of the pancreatic head) or epigastric pain that may radiate to the back and be relieved by sitting forward (for tumors of the body and tail). Obstruction of the pancreatic duct may result in acute pancreatitis and destruction of the pancreatic parenchyma may result in new onset diabetes mellitus with insulin deficiency at diagnosis.

Colorectal cancer may present with unexplained iron deficiency anemia, change of bowel habit or rectal bleeding. Approximately half are rectal and palpable on digital examination.

Following public awareness campaigns, many women are used to performing self-examination of the breasts and may be able to report and locate any lumps they have noticed. Other symptoms include nipple discharge that may be blood stained, new nipple inversion, or skin changes. Breast cancer screening is routine from age 50 in the UK and attendance should be checked. Breast examination should be performed for those aged over 50 who have not attended screening and breast lumps are best investigated in a dedicated clinic, usually with ultrasound-guided fine-needle aspiration or biopsy of suspicious nodules.

Endometrial cancer is rare before the age of 45 years and the usual presentation is with postmenopausal bleeding which should prompt referral for transvaginal ultrasound and/or uteroscopy for diagnosis.

Renal cell cancer can present with painless hematuria, loin pain, or palpation of an asymptomatic abdominal mass. Unilateral left varicocele is a textbook but uncommon presentation.

In any obese patient with malignancy, caution should be employed before pursuing aggressive weight loss interventions due to the possibility of a survival advantage in obese patients. Studies have found a survival benefit for patients with overweight or obesity in several tumor types and including disseminated malignancies (Tsang et al. 2016), although the validity of this finding has been questioned (Lennon et al. 2016).

**Summary**

Basic cancer assessment should include:

- In women approaching menopause or postmenopausal:
  - Breast examination (unless they are up to date with an effective screening program)
  - Enquiry after symptoms of intermenstrual or postmenopausal PV bleeding
- Enquiry after symptoms of dysphagia
- Enquiry after a change of bowel habit
- Abdominal examination for epigastric or right-upper quadrant masses
- Urinalysis for blood

**Neurological disease**. Obesity is convincingly linked to the syndrome of idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri and previously known as benign intracranial hypertension, a name which fell out of favor due to the small but appreciable incidence of blindness in patients with IIH of approximately 2% per annum (Best et al. 2013). Ninety percent occurs in obese women of childbearing age and incidence in this population is approximately 20 per

100000 per annum. Patients report symptoms of high-pressure headache (worse in the mornings, on Valsalva maneuver or lying flat) and/or with visual symptoms including diplopia and blurred vision. Reduced visual acuity, a VIth nerve palsy, and papilledema (causing an enlarged blind spot) may be present on examination. Brain imaging may show subtle changes including an empty sella turcica (which may or may not result in hypopituitarism) and stenosis of the transverse cerebral venous sinus. Diagnosis is made on lumbar puncture in the lateral position with an opening pressure of $>25 cmH_2O$ and cerebrospinal fluid of normal composition. Weight loss of 5–10% of total body weight is effective at reducing intracranial pressure, symptoms, and papilledema (Wong et al. 2007). While waiting for this, pharmaceutical treatment is with carbonic anhydrase inhibitors (acetozolomide) or occasionally high-dose steroids if there are concerns about imminent visual loss. Therapeutic lumbar puncture to lower CSF pressure can be effective and CSF-shunting surgical procedures are required when other treatments have failed. Bariatric surgery-induced weight loss has been shown to be a highly effective treatment for the reduction of headache and papilledema (Manfield et al. 2017).

In sufferers of migraine headache, obesity has been linked to increased severity and frequency of episodes, perhaps through effects on inflammatory mediators and/or neurotransmitter disturbances, though whether migraine prevalence increases with BMI is uncertain (Ornello et al. 2015; Bond et al. 2011). Few data exist on the impact of weight loss on migraine, although one study in a pediatric population suggests that weight loss may reduce the frequency of migraine attacks (Hershey et al. 2009).

**Summary**
Basic neurological assessment should include

- Enquiry after symptoms of high pressure headache (particularly in younger, female patients)
- If headaches present, fundoscopy to assess for papilledema
- Enquiry after symptoms of nerve entrapment syndromes, particularly carpal tunnel syndrome, and any functional limitation associated with these
- Neurological examination

**Psychiatric**. In addition to the impact on physical health, obesity is also linked to psychiatric ill health. Depression and anxiety disorders are more prevalent in obese people, although typically studies have found this to be only a modestly strong association (Scott et al. 2008) which is greater in females than males. There is a high prevalence of obesity among people with psychotic disorders such as schizophrenia (Ventriglio et al. 2015), which is likely to be mediated through the impact of psychosis on lifestyle and the appetite stimulating effect of antipsychotic medication. Interestingly, there appears to be an inverse correlation between BMI and suicide risk in the general population (Bjørngaard et al. 2015) and a possible link between bariatric surgery and an increased suicide risk postoperatively (Tindle et al. 2010).

Overall, major psychiatric disorders are relatively common in obese patients and must be fully assessed and addressed prior to embarking on bariatric surgery or other radical weight loss interventions.

For a small minority of patients, their obesity is primarily driven by the presence of a definable disorder of over eating, most notably binge eating disorder (BED), bulimia nervosa (BN), and night eating syndrome (NES), although prevalence may be significantly higher in patients presenting for interventions like bariatric surgery (Niego et al. 2007). In the fifth revision of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the key diagnostic criterion for both BED and BN is the combination of the recurrent eating of excessive amounts of food within a discrete time-frame with a sense of a lack of control over eating during the episode. BN is characterized by attempts to compensate for overeating and avoid weight gain (e.g., vomiting or excessive exercise), which may be successful or unsuccessful (and thus potentially leading to obesity). BED is characterized by feelings of distress regarding the binges, rapid eating, eating when not hungry or when feeling uncomfortably full, and eating in secret due to embarrassment. NES involves recurrent episodes of awakening from sleep to eat or excessive food consumption after the evening meal in a manner that is not consistent with a diagnosis of BED. Patients often find it difficult to discuss eating disorders in face-to-face consultation and questionnaire-based screening tools may be more revealing in the first instance, followed by more specific enquiry based on the patient's answers. Intervention for eating disorders is predominantly with psychological interventions such as cognitive behavioral therapy. Interestingly, some studies have shown very high response rates to placebo and also to weight loss programs that do not consider eating disorders (Stunkard and Allison 2003). Spontaneous remission is also common.

**Summary**

Basic psychiatric assessment should include:

- Assessment by a dietician, psychologist, or psychiatrist with expertise in eating disorders
- Screening for depression and anxiety (for example, by using a questionnaire such as the depression module from the PHQ questionnaire (Spitzer et al. 1999) (PHQ-9), or the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983))
- In patients with a history of psychotic illness, a full medication history with attempts to map it to weight changes
- In patients with suicidal ideation, assessment of safety by a psychiatrist prior to interventions such as bariatric surgery

**Quantifying obesity severity – scoring systems**. Obesity is a multifactorial, multifaceted, and complex disease and as such defining the severity of a patient's obesity is not straightforward. Nonetheless, attributing a severity rating to a

patient's obesity is useful to assess the urgency for intervention and follow its success over time. In the simplest terms, obesity is defined and then staged according to BMI in the World Health Organization classification: 25.0–29.9 kg/$m^2$ = overweight, 30.0–34.9 = class I obesity, 35.0–39.9 = class II obesity, and 40.0 or higher = class III obesity. This has the advantage of being easy to calculate, requiring few data and being translatable between populations. However, it ignores body composition such that even those with very little adiposity but high muscle mass may be classified as obese and does not allow for any description of comorbid status. To address these and other deficiencies, more sophisticated scoring systems have been developed.

Aylwin and Al-Zaman published The King's Obesity Staging Criteria in 2008 (Aylwin and Al-Zaman 2008). The impact of obesity is considered with respect to distinct domains of health and well-being with each domain staged according to defined criteria, from stage 0 (normal health), through stage 1 (at risk of disease) and stage 2 (established disease) to stage 3 (advanced disease). An updated version of the criteria (Whyte et al. 2014) is reproduced in Table 1. Serial scoring allows clinicians to assess the impact of interventions and has been used to show the benefit of bariatric surgery across all domains (Neff et al. 2014).

Sharma and Kushner introduced The Edmonton Clinical Staging System in 2009 (Sharma and Kushner 2009), which stages obesity according to the presence of comorbidity and limitations on function, from stage 0 with no impact, to stage 4 with potentially end-stage disease or severely disabling limitation on function. The full-staging criteria are reproduced in Table 2, with the suggested management from the original publication for patients at each stage. Edmonton stage has been shown to predict mortality in obese people. In one study, when applied to data from the National Health and Human Nutrition Surveys (NHANES) III, an Edmonton stage of 2 was associated with a mortality hazard ratio of 1.57 and a stage of 3 with a hazard ratio of 2.69 when compared to stages 0 and 1 (Padwal et al. 2011).

## Summary

Whether or not obesity constitutes a disease continues to be debated, but there is no doubt that it is a major risk factor, and in many instances the primary risk factor, for a number of the biggest health issues in the modern world. These affect every body system and have a knock-on effect beyond the purely medical to the detriment of health-related quality of life, economic activity, and social inclusion. A holistic assessment of obesity must therefore cover all these aspects of health and well-being to enable an effective management strategy to be planned. Careful clinical history taking and examination can suggest the likely etiology of an individual's obesity. In some cases it is related to remediable external factors such as poor food choices, excess alcohol consumption, or appetite-stimulating medications, or to remediable internal factors such as eating disorders or Cushing's syndrome. More often than not, it is due to largely nonmodifiable

**Table 1** Modified King's Obesity Staging Criteria (Whyte MB, Velusamy S, Aylwin SJ. Disease severity and staging of obesity: a rational approach to patient selection. Curr Atheroscler Rep. 2014;16(11):456, reproduced with permission)

| | Stage 0 | Stage 1 | Stage 2 | Stage 3 |
|---|---|---|---|---|
| A – **A**irway | **Normal**<br>No snoring<br>Neck circumference <43 cm<br>Epworth score <10 | **Mild sleep apnea**<br>Snoring<br>Epworth score ≥10<br>AHI <15/h<br>Neck circumference >43 cm<br>Mild asthma | **Requires CPAP**<br>Witnessed apnea<br>AHI ≥15/h<br>Uses CPAP (controlled)<br>Severe asthma | **Cor pulmonale**<br>Obesity hypoventilation syndrome<br>Uncontrolled OSA |
| B – **B**ody Mass Index | **<35 kg/m$^2$** | **35–50 kg/m$^2$** | **50–60 kg/m$^2$** | **>60 kg/m$^2$** |
| C – **C**ardiovascular Risk | **<10%**<br>CVD risk <10% over 10 years | **10–20%**<br>CVD risk 10–20% over 10 years<br>T2DM | **Heart disease**<br>Stable IHD<br>CCF NYHA class I–II<br>>20% CVD risk over 10 years | **Heart failure**<br>Severe angina<br>CCF NYHA III–IV |
| D – **D**iabetes | **Normal**<br>Fasting or random glucose <5.7 mmol/L<br>Normal HbA1c | **Impaired fasting glycemia**<br>Impaired fasting glucose<br>Impaired glucose tolerance<br>Previous gestational diabetes | **Type 2 diabetes**<br>Diet, insulin or oral hypoglycemic agent controlled<br>HbA1c <9% | **Uncontrolled type 2 diabetes**<br>HbA1c ≥9%<br>Advanced microvascular disease |
| E – **E**conomic Complications | **Normal**<br>Obesity has no financial impact | **Financial impact**<br>Increased travel costs<br>Increased clothes costs | **Workplace disadvantage**<br>Earnings limited by obesity<br>Receiving benefits due to obesity | **Unemployed**<br>Unemployed due to obesity<br>Financial effect on third party (e.g., carer required to reduce income) |
| F – **F**unction | **Normal**<br>No limitation | **Mildly impaired**<br>Manages 1 flight of stairs<br>Limitation on recreation | **Moderately impaired**<br>Can manage <1 flight of stairs<br>Third party assistance for ADLs or for dependents<br>Limitation on work | **Severely impaired**<br>Housebound<br>Wheelchair user<br>Registered disabled |

(*continued*)

**Table 1** (continued)

| | Stage 0 | Stage 1 | Stage 2 | Stage 3 |
|---|---|---|---|---|
| G – **G**onadal and Reproductive Health | **Normal**<br>Normal sexual and reproductive function<br>Celibate (not seeking a physical relationship) | **PCOS/ erectile dysfunction**<br>PCOS<br>Low testosterone (men)<br>Impaired sexual function/ erectile dysfunction | **Subfertility**<br>Subfertility or unable to access IVF<br>Marital/ relationship breakdown due to obesity<br>Cessation of all sexual activity | |
| H – Mental **H**ealth Status | **Normal**<br>Good mental and physical wellbeing | **Low mood**<br>Low mood or poor QoL | **Mild-moderate depression**<br>Takes treatment for depression | **Severe depression**<br>Suicidal ideation<br>Active self-harm<br>Unmanaged substance misuse |
| I – Body **I**mage and Eating Behavior | **Normal**<br>Minimal or no concern<br>Normal eating pattern | **Does not like looking in mirror**<br>Comfort eating<br>Inappropriate eating cues<br>Mild body image dysphoria | **Avoids social interaction or mirrors**<br>Severe body image dysphoria<br>Controlled eating disorder | **Eating disorder**<br>Active eating disorder<br>Social phobia |
| J – Gastro-esophageal **J**unction | **Normal**<br>No symptoms of GORD | **GORD**<br>GORD controlled on standard PPI therapy | **Esophagitis**<br>Esophagitis on OGD within last 12 months<br>Severe GORD symptoms<br>Requires high-dose PPI | **Barrett's esophagus** |
| K – **K**idney | **Normal** | **Proteinuria** | **GFR <60 ml/ min** | **GFR <30 ml/min** |
| L – **L**iver | **Normal** | **Raised LFT/ NAFLD on ultrasound** | **NASH** | **Liver failure** |



**Abbreviations:** *AHI*, apnea/hypopnea index; *CVD*, coronary vascular disease; *T2DM*, type 2 diabetes; *IHD*, ischemic heart disease; *CCF*, congestive cardiac failure; *NYHA*, New York Heart Association; *ADL*, activity of daily living; *IVF*, in vitro fertilization; *GORD*, gastroesophageal reflux disease; *PPI*, proton pump inhibitor; *OGD*, oesophagogastroduodenoscopy; *CPAP*, continuous positive airway pressure; *BMI*, body mass index; *PCOS*, polycystic ovary syndrome; *QoL*, quality of life; *GFR*, glomerular filtration rate; *LFT*, liver function test; *NAFLD*, nonalcoholic fatty liver disease; *NASH*, nonalcoholic steatohepatitis

**Table 2** The Edmonton Clinical Staging System (Sharma AM, Kushner RF. A proposed clinical staging system for obesity. Int J Obes (Lond). 2009;33(3):289–95, reproduced with permission)

| Stage | Description | Management |
|---|---|---|
| 0 | No apparent obesity-related risk factors (e.g., blood pressure, serum lipids, fasting glucose, etc., within normal range), no physical symptoms, no psychopathology, no functional limitations, and/or impairment of well being | Identification of factors contributing to increased body weight. Counseling to prevent further weight gain through lifestyle measures including healthy eating and increased physical activity |
| 1 | Presence of obesity-related subclinical risk factors (e.g., borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.), mild physical symptoms (e.g., dyspnea on moderate exertion, occasional aches and pains, fatigue, etc.), mild psychopathology, mild functional limitations, and/or mild impairment of well being | Investigation for other (non-weight related) contributors to risk factors. More intense lifestyle interventions, including diet and exercise to prevent further weight gain. Monitoring of risk factors and health status |
| 2 | Presence of established obesity-related chronic disease (e.g., hypertension, type 2 diabetes, sleep apnea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder, etc.), moderate limitations in activities of daily living, and/or well being | Initiation of obesity treatments including considerations of all behavioral, pharmacological, and surgical treatment options. Close monitoring and management of comorbidities as indicated |
| 3 | Established end-organ damage such as myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis, significant psychopathology, significant functional limitations, and/or impairment of well being | More intensive obesity treatment including consideration of all behavioral, pharmacological, and surgical treatment options. Aggressive management of comorbidities as indicated |
| 4 | Severe (potentially end-stage) disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations, and/or severe impairment of well being | Aggressive obesity management as deemed feasible. Palliative measures including pain management, occupational therapy, and psychosocial support |

influences on the balance between appetite and food intake on the one hand, and energy expenditure on the other. Imaging, laboratory tests, and other clinical investigations are necessary to screen for complications that are not easily detectable through history and examination. Proper assessment requires the skills of multiple disciplines including physicians, surgeons, psychiatrists, psychologists, and dieticians. A service structured to facilitate the effective multidisciplinary team working of these healthcare professions with the engagement of the patient and patient-support groups is essential to optimize the management of obesity in a patient-centered, individualized manner.

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# Obesity and NAFLD

9

Paul Cordero, Jiawei Li, and Jude A. Oben

## Contents



**Abstract**

Obesity is currently considered the main health challenge of the twenty-first century. It is a chronic pro-inflammatory disease which systemically affects normal physiology and metabolism, causing multiple associated diseases such as cardiovascular disease, diabetes, nonalcoholic fatty liver disease (NAFLD), and several types of cancer, among others. The main contributors for NAFLD development and progression include high concentrations of diet and adipose tissue-derived free fatty acids and pro-inflammatory adipocytokines. These fatty

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acids are released from adipocytes and/or from dietary intake and are delivered to the liver. The fatty acids in the hepatocytes can then be oxidized by the mitochondria or converted into triglycerides for intracellular accumulation. With elevated mitochondrial oxidation levels, there is an overproduction of reactive oxygen species and other species that mediate hepatic injury, inflammation, and apoptosis. In order to manage obesity and NAFLD, nutritionally based body weight management is the principal modifiable risk factor. Thus, dietary interventions for body weight loss should be the main therapeutic approach, although pharmacotherapy and, in some specific situation, surgical or bariatric endoscopic interventions may be necessary.

**Keywords**
Obesity · Nonalcoholic fatty liver disease · Metabolic syndrome · Nonalcoholic steatohepatitis · Intra-abdominal fat · Fatty liver · Insulin resistance · Fatty acids · Steatosis

## Obesity

Obesity is defined as a disproportionate body weight for height with an excessive accumulation of adipose tissue that is usually accompanied by mild, chronic, systemic inflammation (Gonzalez-Muniesa et al. 2017). Although obesity is stated as a body mass index (BMI) greater than 30 Kg/m$^2$, this value should be interpreted with caution, since the BMI is an indirect measure of adiposity. Other anthropometric measurements and alternative indices based on skinfold thickness, trunk measurements (waist and hip circumferences), and limb measurements (arm and calf circumferences) may better characterize the extent of obesity and adipose tissue-associated health risk (Madden and Smith 2016). This excess visceral fat accumulation is associated with increased risk of cardiovascular events, insulin resistance, nonalcoholic fatty liver disease (NAFLD), some types of cancer, and other adverse pathological conditions (Gonzalez-Muniesa et al. 2017).

## Human Evolution and Obesity

Human physiology and metabolism are consequences of evolutionary adaptation to the environment during thousands of years. Nutrient metabolism and optimization were one of the main pressures for human survival. Therefore, the genetic background has been adapted against these stresses, improving metabolic energy expenditure and saving the extra energy supply for potential future resource-deficient environments (Chakravarthy and Booth 2004; Neel et al. 1998). However, during the last century and, more precisely, the last decades, the availability of energy-dense food in the Western society parallel a decrease in energy expenditure due to a sedentary lifestyle, generating an energy imbalance. As a consequence, the initial advantageous evolutionary adaptation is currently beginning to associate with

obesity and its related diseases, increasing all causes of morbidity and mortality (Abdelaal et al. 2017; Gallicchio et al. 2009).

The energy surplus gets stored in the adipose tissue. The specialized cells of this tissue, the adipocytes, secrete a number of bioactive compounds called adipokines (e.g., leptin, adiponectin, visfatin, and apelin), which are implicated in appetite regulation, inflammatory processes, energy expenditure, and metabolism (Gonzalez-Muniesa et al. 2017; Haslam and James 2005). Furthermore, infiltrated macrophages in adipose tissue by monocyte chemoattractant protein-1 (MCP-1) stimulation also secreted pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which suppress the synthesis of adiponectin, with this circumstance being also associated with other obesity comorbidities (Testelmans et al. 2013; Walker et al. 2014), covering a wide range of diseases such as type 2 diabetes, cardiovascular diseases (e.g., hypertension, cardiovascular and cerebrovascular stroke), NAFLD, psychological problems, gallbladder disease, or osteoarthritis (Haslam and James 2005). Furthermore, obesity has also been associated with different types of cancer, suggesting it being a major risk factor for hepatocellular carcinoma (HCC) development (Yang et al. 2017).

The evaluation of the crude genetic effect in obesity-related energy imbalance varies among different studies. This is because of the possible interaction with other factors such as dietary profile, lifestyle patterns, or epigenetic background (Asghari et al. 2017; Cordero et al. 2015a; Rankinen et al. 2006).

The epigenetics studies how the changes around the DNA sequence, without altering the nucleotide sequence, could affect gene expression (Bird 2007). This means that although having a specific genetic sequence, there are implicated mechanisms in its transcription (and later translation to bioactive proteins) which may modulate the impact of the genetic background. While the modification of the genetic background may take many generations, adaptive and regulatory changes in the epigenetic profiles can occur quicker. Furthermore, epigenetic profiles are currently being managed as prognostic biomarkers for intervention, succeeding against obesity or as therapeutic targets for gene expression regulation control (Milagro et al. 2011; Uriarte et al. 2013). For example, it has been shown that the methylation levels of TNF-α and leptin in subcutaneous adipose tissue are associated with a better response to a low caloric diet intake (Cordero et al. 2011a). These marks can also be transmitted to the descendants as they are more prone to be altered during perinatal periods affecting subsequent generations (Cordero et al. 2015a).

Obesity is a chronic disease and its prevalence has increased in all different populations at all ages. According to different lifetime periods, obesity had a crucial importance during periconceptual time frames. During this critical development window, an adverse pro-obesogenic in utero environment is associated with placental circulatory problems, early pregnancy loss, stillbirth, premature birth, maternal gestational diabetes, higher offspring body weight at birth, or fetal malformations (Poston et al. 2016). However, maternal excessive fat mass accumulation does not only exert direct effects on the fetuses during pregnancy. Novel human and animal studies have linked maternal obesity with the development of obesity and associated

diseases, including NAFLD, throughout different lifetime periods of offspring (Catalano and Shankar 2017; Cordero et al. 2015b; Mouralidarane et al. 2015). Taking advantage of this malleability as therapeutic window, there have been studies on the supplementation with epigenetically active micronutrients during pregnancy and their possible effect in the prevention of obesity-related comorbidities in the offspring (Cordero et al. 2014; Waterland et al. 2008).

### Therapeutic Approaches

Besides the non-modifiable personal characteristic such as the genetic background, some mechanisms involved in obesity development are modifiable, such as epigenetics. However, the exact modulatory pathways are still unclear and the primary treatment against obesity is focused in dietary and lifestyle intervention. While varied hypocaloric diets may be prescribed for body weight loss, personalized diets assisted by a nutritionist in order to educate the patients on better dietary habits are beneficial (DiMaria-Ghalili et al. 2016; Jortberg et al. 2015). Furthermore, improving the success of these interventions, these diets should take into account current scientific knowledge on specific individual genetic (and epigenetic) background, as well as potential gene-nutrient interactions (Goni et al. 2014). Other dietary-based treatments also include the synergistic use of pharmacological drugs to decrease the absorption of nutrients or increase satiety. Furthermore, besides facilitating the successful body weight loss, some of these drugs are also beneficial for glucose homeostasis and lipid profile management (Apovian and Aronne 2015; Carter et al. 2012; Jensen et al. 2014).

Further options in obesity intervention after diet and/or pharmacological approach include the implementation of an intragastric balloon, which occupies a volume in the stomach and increases satiety by a volumetric mechanism (Laing et al. 2017). These endoscopically implanted devices have demonstrated safety and effectiveness, and its use is rapidly increasing in developed countries. If this treatment fails, there is the possibility of bariatric surgery, which is further discussed in other chapter of this book.

## Obesity-Induced Liver Disease (Nonalcoholic Fatty Liver Disease, NAFLD)

Hepatic steatosis or fatty liver is defined by intra-hepatocyte lipid vesicular accumulation. If this hepatic fat accumulation in NAFLD leads to inflammation and hepatocellular injury, it can lead to a more severe stage of NAFLD named nonalcoholic steatohepatitis (NASH). While NAFLD encompasses the whole spectrum of the disease, NASH is defined as the presence of primary hepatic steatosis and inflammation with hepatocellular injury, which can progress to fibrosis, cirrhosis, and HCC (Moore 2010; Neuschwander-Tetri 2017) (Fig. 1). It has been estimated that, in Western countries, there is a prevalence of 20–30% of NAFLD in the general

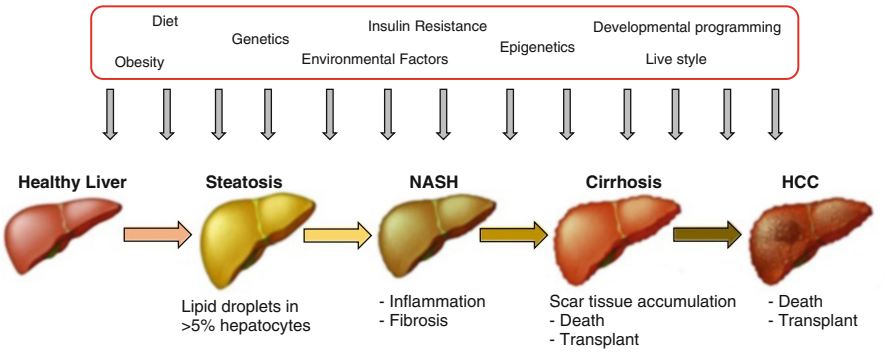


**Fig. 1** The NAFLD spectrum and development

population and up to 2–5% of people present some form of NASH. Furthermore, the evolution of this liver disease to cirrhosis or hepatocarcinoma is up to 1–2% persons (Satapathy and Sanyal 2015). Thus, the economic burden is huge, and it is estimated to be more than 100 billion dollars per year in the USA and 35 billion burden combining Italy, Germany, the UK, and France (Younossi et al. 2016a). Although initial liver fat accumulation is not directly or strongly associated with mortality risk, more advanced NAFLD stages, including fibrosis, increase all-causes mortality risk (Dulai et al. 2017). Indeed, a retrospective study in Europe, America, and Asia over 30 years reported that fibrosis state is the feature associated with increased liver-associated diseases, hepatic transplantation, and mortality rates (Angulo et al. 2015). A long-term clinical and histological follow-up study of biopsy-proven NAFLD patients found that survival among these individuals was lower than that of the matched reference population (Ekstedt et al. 2006). In this cohort the 41% of NAFLD patients showed progression in their stage of fibrosis, which was associated with increased overall mortality but primarily as a result of cardiovascular disease or other extrahepatic malignancies and, to a lesser extent, liver-related causes (Ekstedt et al. 2006).

NAFLD is closely associated with obesity, insulin resistance, hypertension, large waist circumference, hypertriglyceridemia, kidney disease, and hypercholesterolemia and therefore has been defined as the liver manifestation of the metabolic syndrome (Adams et al. 2017). Both excessive body weight and visceral adiposity are the main risk factors for NAFLD. In a recent meta-analysis including 85 studies and more than 8.5 million patients across 22 countries, Younossi et al. estimated that the obesity prevalence among NASH patients was 80% in North America, 89% in Europe, and 95% in Oceania. Although these rates were lower for NAFLD, the authors identified an association between the year of study publication and an increase in NAFLD prevalence being consistent with increasing prevalence of obesity, which fuels metabolic diseases and NAFLD (Younossi et al. 2016b). Due to the current rise of obesity prevalence in children, it is becoming apparent that NAFLD is now the most common cause of liver disease in childhood. Furthermore, in children, NAFLD is also a risk factor for extrahepatic diseases such as insulin

resistance or type 2 diabetes, cardiovascular diseases, and sleep disorders, among others (Selvakumar et al. 2017).

Besides obesity, other risk factors are implicated in NAFLD development. Age is directly proportional with NAFLD prevalence, and, curiously, NAFLD progression is faster in older patients (Bertolotti et al. 2014). There is higher NAFLD prevalence in males, probably due to a protective effect of estrogens in obesity as well as difference in adipose tissue accumulation patterns between sexes (Yang et al. 2014). Furthermore, although several studies reveal the ethnic background as an independent risk factor for development and progression of NAFLD, it is not clear if other factors, such as socioeconomic status, may be a confounding factor in these studies (Kalia and Gaglio 2016). Maybe the differences in the genetic background according to the ethnic origin may better explain these differences in these kinds of studies.

## Pathogenic Origins of NAFLD

The pathogenesis of NAFLD is poorly understood. While obesity and insulin resistance are thought to be crucial in the development of NAFLD, the excess fat deposition within the liver is also thought to arise from a wide variety of insults. The combination of these insults, such as an alteration on lipid uptake, synthesis, degradation, and/or secretion, leads to hepatosteatosis (Neuschwander-Tetri 2017; Adams et al. 2017; Milic et al. 2014). Current dietary consumption profiles exceed the recommendations for simple sugars and fat intakes. When the load of energy exceeds the lipid storage capacity in the adipose tissue, this fat has to be stored in other tissues which traditionally do not have storage function. Moreover, the abnormal adipocyte hypertrophy due to accumulation of energy surplus is associated with the release of adipocytokines and cytokines with pro-inflammatory effects. The excess of dietary glucose and fructose uptakes also activates the de novo lipogenesis pathway for the synthesis of fatty acids in hepatocytes.

The association between fat accumulation and hepatic injury, until recently, was explained using the two-hit hypothesis. This hypothesis proposed that obesity-related increased supply of free fatty acids (FFA), and enhanced de novo lipogenesis, led to hepatic fat accumulation, and, subsequently, the liver became sensitized to a second pro-inflammatory hit of oxidative stress, cytokines, and endoplasmic reticulum (ER) mediated stress (Day and James 1998). Nowadays, it is considered that multiple hits induce adipokine secretion, ER and oxidative stress at the cellular level that subsequently induce hepatic steatosis, inflammation, and fibrosis (Takaki et al. 2013). These inputs include impaired FFA oxidation mediated by hyperinsulinemia and mitochondrial damage, reduced export of triglycerides (TG) as very low-density lipoproteins (VLDLs), and increased esterification of FFAs to TGs (Moore 2010). Thus, lipolysis increases the concentration of FFAs, which are removed from the circulation by hepatocytes. The mitochondrial beta-oxidation pathway consequently becomes saturated, leading to accumulation of TG in the liver as well as an increase of reactive oxygen species (ROS)

(Spahis et al. 2017). ROS can stimulate the release of pro-inflammatory cytokines such as TNF-α, IL-6, and the pro-fibrogenic cytokine transforming growth factor beta (TGF-β). TNF-α and TGF-β induce caspase activation and therefore hepatocyte cell death via apoptosis. TNF-α also impairs redox reactions of the electron transport chain further promoting ROS production (Neuschwander-Tetri 2017). Furthermore, in obesity, adipocytes are another source of the immunomodulatory cytokine TNF-α, which has also been implicated in molecular mechanisms influencing insulin resistance (Lin et al. 2015).

Besides dietary and visceral adipose tissue enlargement, there is also a genetic component in the susceptibility of NAFLD and its progression. For example, polymorphisms in patatin-like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily 2 (TM6SF2), and membrane-bound O-acyltransferase domain containing 7 (MBOAT7) genes have been linked with the degree of hepatic fat accumulation and liver fibrosis (Krawczyk et al. 2017; Petaja and Yki-Jarvinen 2016). Furthermore, polymorphisms of adipokines such as omentin-1 and resistin, both synthesized by the adipose tissue, are considered as genetic risk factors for NAFLD development (Kohan et al. 2016).

Finally, emerging data support that the intestinal microbiome contributes to NAFLD development and progression. The alteration of the normal intestinal bacteria composition can trigger to intestinal inflammation and gut barrier damage, enhancing the microbiome metabolites access to the liver, which increase hepatic inflammation and injury (Brandl and Schnabl 2017; Doulberis et al. 2017). Current evidence also suggest a crosstalk between gut hormones such as glucagon-like peptide-1 (GLP1) and ghrelin and intestinal gut microbiota, which may point to new approaches for improving the understanding of NAFLD and obesity pathogenesis and treatment (Koukias et al. 2017).

## Diagnosis of NAFLD

Initially, NAFLD may present as an asymptomatic disease; therefore, it is important to target main groups at risk for early detection and treatment during initial states of the disease. Therefore, obese individuals with diabetes and metabolic syndrome should be screened early. Different, easy-to-apply indices for NAFLD diagnostic have been described based on anthropometric characteristics such as body weight, height, or waist circumference. These indices are simple and accessible and are an adequate first screening approach (Motamed et al. 2016a, b).

Some plasma biomarkers for NAFLD diagnosis have shown promising results, although they also have specific weaknesses as individual markers for diagnosis and staging of NAFLD. Therefore, a more efficient approach may be the combination of different serum biomarkers, including hepatic injury markers (alanine transaminase, aspartate transaminase), inflammatory markers (platelets, C-reactive protein, ferritin, malondialdehyde, pentraxin 3, adiponectin, leptin, fibroblast growth factor 21, TNF-α, IL-6, MCP-1), or structural markers (CK-18, hyaluronic acid, collagen 7-s) (Neuschwander-Tetri 2017; Dietrich and Hellerbrand 2014;

Hadizadeh et al. 2017). For example, the NAFLD fibrosis score combines age, hyperglycemia, BMI, platelet count, albumin, and AST/ALT ratio (Angulo et al. 2007) to determine the presence of fibrosis; meanwhile BARD score allows the identification of patients without significant fibrosis (negative predictive level of 96%) by using BMI, AST/ALT ratio, and diabetes score (Harrison et al. 2008). Thus, patients with a positive BARD score are 17 times more likely to have advanced fibrosis than those without a positive score. The enhanced liver fibrosis (ELF) test includes the combination of plasma levels of hyaluronic acid, aminoterminal peptide of procollagen III (P3NP), and tissue inhibitor metalloproteinase I (Timp1) adjusted by the age of the patients (Lichtinghagen et al. 2013). While the potential of these scores is enormous, their clinical utility remains presently unclear. The current National Institute for Clinical Excellence (NICE) guidelines essentially uses the ELF score as a determinant of severe fibrosis (https://pathways.nice.org.uk/pathways/non-alcoholic-fatty-liver-disease#path=view%3A/pathways/non-alcoholic-fatty-liver-disease/non-alcoholic-fatty-liver-disease-overview.xml&content=view-index).

However, due to the current lack of sensitivity and specificity of routine laboratory biochemical analyses, imaging techniques are considered as useful diagnostic tools because of its general availability and economic cost. Imaging techniques such as magnetic resonance imaging (MRI), ultrasound, or computer tomography (CT) can diagnose some NAFLD stages, but they are not able to detect more advanced stages of this disease as NASH. For this discrimination, it requires a biopsy (Lapadat et al. 2017). Thus, the combination of imaging techniques, plasma biomarkers, and other scoring systems is a promising noninvasive tool for the early diagnosis in NAFLD patients. However, the current diagnostic "gold standard" for accurately describing NAFLD and its various stages remains a liver biopsy. The NAFLD activity score (NAS) is a biopsy-based semiquantitative scoring system developed by Kleiner et al. (Kleiner et al. 2005) for the grading and staging of histological lesions. It is based on four main sub-scores for steatosis grade, lobular inflammation, and ballooning injury as described in Table 1. From these parameters, histological classification of steato-steatosis is already diagnostic of NAFLD (Kleiner et al. 2005). Fibrosis is scored as F0, F1, F2, F3, and F4 corresponding to absent, mild, moderate, severe, and cirrhosis.

In order to homogenize the current diagnosis approach to NAFLD, the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO) have stablished a European guideline, whose flow chart is represented in Fig. 2 (European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O 2016). In summary, after the initial presence of any of the main metabolic risk factors (obesity and other metabolic syndrome-related features), a steatotic biomarkers assessment and plasma liver transaminases measurement should be carried out. Depending on the results, if there is no steatosis, there should be a follow-up of 3–5 years before a new assessment, but in the presence of steatosis, there should be an assessment of fibrosis. If there is a positive fibrosis assessment and in case if any of the hepatic transaminases is elevated (independently of the presence of liver steatosis), the

**Table 1** NAFLD activity score

| | Score |
|---|---|
| **Steatosis degree (% hepatocytes with lipid droplets)** | |
| <5% | 0 |
| 5–33% | 1 |
| >33–66% | 2 |
| >66% | 3 |
| **Lobular inflammation (inflammatory loci per 200× field)** | |
| No foci | 0 |
| <2 | 1 |
| 2–4 | 2 |
| >4 | 3 |
| **Hepatocyte ballooning** | |
| None | 0 |
| Few balloon cells | 1 |
| Many cells/prominent ballooning | 2 |

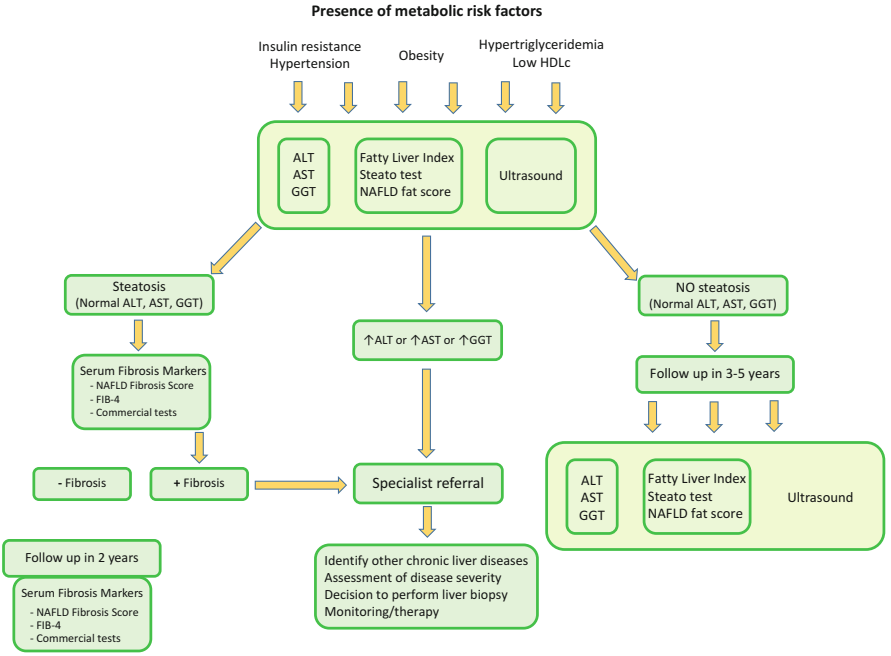


**Fig. 2** Diagnostic flow chart to assess NAFLD severity by the EASL-EASD-EASO Clinical Practice Guidelines (2016)

patient should be referred to a specialist in order to receive the most adequate diagnosis, therapy, and monitoring (European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O 2016).

## Therapeutic Approaches to NAFLD

The initial elective treatment for the vast majority of NAFLD patients should be focused on achieving body weight reduction. The American Association for the Study of the Liver (AASLD) recommends a loss of at least 3% to 5% of the initial body weight through a hypocaloric diet for liver fat content reduction, describing a weight loss up to 10% as the minimum for finding an improvement in liver necroinflammatory features (Chalasani et al. 2012). A recent study including a 6-month dietary intervention on NAFLD patients based on Mediterranean diet showed a decrease on the prevalence of advanced steatosis from 93% to 48% of the patients. Furthermore, there was a significant improvement on AST, ALT, GTT, total cholesterol, HDLc, or insulin sensitivity, among other plasma biochemical markers (Gelli et al. 2017). This dietary-based body weight loss should be used in parallel to a personalized physical exercise routine in order to be more beneficial in NAFLD patients (Chalasani et al. 2012).

While hypocaloric interventions are the gold treatment for NAFLD improvement, there are an increasing number of nutritional-based treatments focused on a molecular-based intervention against the increase of ROS, with dietary supplements including vitamin E, vitamin D, coenzyme Q, polyphenols (berberine, resveratrol, silymarin), polyunsaturated fatty acids, or prebiotics (Spahis et al. 2017). There are also an increasing number of studies linking vitamins with NAFLD, particularly vitamins A, $B_3$, $B_{12}$, D, and E, in which supplementation has been demonstrated as a promising therapeutic option in the treatment of NAFLD (Li et al. 2016). From these, the most promising vitamin currently tested for NAFLD treatment is vitamin E, which is a tocopherol with high antioxidant activity and therefore prevents the overproduction of ROS. Thus, the AASLD recommended the use of vitamin E at daily dose of 800 IU/day as the first-line pharmacotherapy in nondiabetic adults with biopsy-proven NASH (Chalasani et al. 2012). The use of other micronutrient supplements in rodent models for the prevention of diet-induced NAFLD development has been also demonstrated. Thus, the supplementation with one-carbon metabolism-related compounds such as vitamin $B_{12}$, folic acid, choline, and betaine showed an epigenetic regulation of hepatic lipid metabolism-related genes parallel to a protection against obesogenic diet-induced hepatic fat accumulation (Cordero et al. 2011b; Cordero et al. 2013a, b).

There are no approved drugs for NASH treatment. However, different studies have described potential pharmacotherapeutic approaches for NAFLD. For example, in a murine experimental model of pro-atherogenic-induced NAFLD, the combination of leucine, sildenafil, and metformin increased hepatic fatty acid oxidation and reduced the diet-induced increases of ALT, TGF-β, PAI-1, IL-1β, TNF-α, and collagen expression, as well as reversed hepatocyte ballooning and TG accumulation (Bruckbauer et al. 2016). It has also been described that the combination of different antidiabetic drugs (empagliflozin and linagliptin) synergistically ameliorates a high-fat diet-induced murine NASH model decreasing pro-fibrogenic markers and fatty acid synthesis (Jojima et al. 2016). Moreover, the antihypertensive drug angiotensin II blockers may be used against liver fibrosis. These antihypertensive drugs may also

be beneficial against NAFLD-related cardiovascular disease. It has been shown that there is an epigenetic regulation, based on the methylation of the angiotensin II receptors in NAFLD patients (Asada et al. 2016). However, there is controversy associated with the theory of targeting renin-angiotensin system pathway for fibrotic stages of NAFLD. A murine study using losartan demonstrated its potential effect as antifibrotic treatment in NASH stages of NAFLD (Yoshiji et al. 2009). Yet, recently, it has been suggested that it is the dietary intervention rather than the use of losartan which reversed nonalcoholic steatohepatitis in a mouse model of obesity and insulin resistance (Verbeek et al. 2017). Finally, a recent phase 2 trial of the long-acting glucagon-like peptide-1 analogue, liraglutide, with NASH patients demonstrated that this compound is safe, is well tolerated, and led to histological resolution of features of nonalcoholic steatohepatitis (Armstrong et al. 2016). Nine (39%) of 23 patients who received liraglutide and underwent end-of-treatment liver biopsy had resolution of definite nonalcoholic steatohepatitis compared with two (9%) of 22 such patients in the placebo group. Two (9%) of 23 patients in the liraglutide group versus eight (36%) of 22 patients in the placebo group had progression of fibrosis. The effect of liraglutide may be due to a decrease in energy intake, as it has been demonstrated that the use of the same doses of this drug improved body weight management (Wilding et al. 2016). Interestingly, as regards mechanism of action, it has been also described that liraglutide improves the liver sinusoidal milieu in cirrhosis (de Mesquita et al. 2017). Thus, these positive but not yet completely defined effects warrant extensive, longer-term studies.

Bariatric surgery widely exceeds any other treatment available today, against obesity and associated comorbidities such as insulin resistance, cardiovascular risk, or NAFLD, among others, by improving body weight reduction and loss of the excess visceral adipose tissue (Aguilar-Olivos et al. 2016; Kini et al. 2007). Therefore, this procedure is recommended for patients with a BMI of 40 $kg/m^2$ or higher and in those with at least a BMI of 35 $kg/m^2$ but including other obesity comorbidities. However, besides the overwhelming economic cost, bariatric surgery is only feasible for a minority of patients due to the inherent of surgery: some patient don't want surgery and others are not medically fit to undergo general anesthetic. Besides the physiological improvement, molecular biomarkers of inflammation, and oxidative stress such as TNF-α, superoxide dismutase, malondialdehyde, MCP1, or C-reactive protein were also ameliorated (Poitou et al. 2015; Schmatz et al. 2017). As mentioned, the main caution of this therapeutic approach is the need of a long-time postoperative follow-up carried out by a team of multidisciplinary health professionals (DiMaria-Ghalili et al. 2016; Jortberg et al. 2015).

## Conclusions

NAFLD is been defined as the hepatic manifestation of the metabolic syndrome, which is mainly caused by obesity. NAFLD has become a major global health challenge because of its rapid rise in prevalence, yet difficulties in accurate diagnosis and lack of approved pharmacological therapies provide a challenge. Indeed, the

majority of NAFLD patients are clinically asymptomatic, and there are currently no noninvasive methods for assessing the degree of NAFLD. Most NAFLD situations may be reverted through body weight loss, with nutrition being the principal modifiable risk factor. Therefore, it is necessary to invoke diagnostic tools, preventive measures, and combined interventions to curb the obesity and NAFLD epidemic.

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# Obesity and Type 2 Diabetes

# 10

Sviatlana Zhyzhneuskaya and Roy Taylor

## Contents



This chapter separately describes the pathophysiology of type 2 diabetes and that of obesity. The relationship between these two conditions is then discussed, together with practical issues of clinical management.

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**Abstract**

This chapter separately describes the pathophysiology of type 2 diabetes and that of obesity, and identifies the relationship between these states. The important concept of long-term reversibility of type 2 diabetes is discussed along with the beta-cell dedifferentiation, which explains the insulin secretory defect.

Obesity brings about distinct pathophysiological changes as a consequence of individuals' pattern of food intake and levels of activity. The practical issue of clinical management is considered with particular reference to the weight management goals for type 2 diabetes.

Following therapeutic weight loss in both conditions, long-term avoidance of weight regain is vital and is optimally achieved by a combination of ongoing food energy restriction and daily physical activity.

**Keywords**

Type 2 Diabetes · Pathophysiology · Twin Cycle Hypothesis · De novo lipogenesis · Obesity · Whitehall II study · Hepatic insulin resistance · Long term reversibility of type 2 Diabetes · Counterpoint study · Counterbalance study · Beta-Cell Dedifferentiation · Beta-Cell reduction · Impairment of insulin secretion · Beta-Cell exhaustion · Desensitization of Beta-Cell · Endoplasmic reticulum (ER) stress · Deposition of amyloid · Muscle insulin resistance · Liver insulin resistance · Intracellular insulin action · Elevation of non-esterified-fatty-acids (NEFA) · Insulin resistance and mitochondrial function · IRS-2 phosphorylation · Physical inactivity · Visceral fat · Ectopic fat · Subcutaneous adipose tissue · Personal fat threshold (PFT) hypothesis · Management of body weight · Diabetes in Remission Clinical Trial (DiRECT) · Type 2 Diabetes dietary management · Dietary management for weight loss · United Kingdom Prospective Diabetes Study (UKPDS) · The Look AHEAD study (Action for Health in Diabetes Study) · Avoidance of weight regain approaches · Exercise · Bariatric Surgery

## The Nature of Type 2 Diabetes

### Pathophysiology

Over the last two decades, failure of control of liver glucose production as the primary cause of hyperglycemia in type 2 diabetes has gradually became clear (Singhal et al. 2002; Taylor et al. 1996a; Basu et al. 2005; Firth et al. 1986). This underlies both fasting and postprandial homeostasis. Insulin sensitivity of the liver is central to normal control of this process (Ravikumar et al. 2008), and in turn, this is directly regulated by the extent of liver fat accumulation. The relevance of the rising liver enzymes prior to onset of type 2 diabetes can now be fully understood (Sattar et al. 2007). The increasing alanine aminotransferase

reflected the increased liver fat levels. Insight into the potential rapid restoration of normal fasting plasma glucose levels came from the observation that weight loss secondary to gastric banding was the major factor in post-surgical remission of type 2 diabetes (Dixon et al. 2008). The major driver of this was not the method but the degree of weight loss (Dixon et al. 2008). The concept that incretins, postprandial hormones, played a role in post-bariatric surgery normalization of fasting plasma glucose (Guidone et al. 2006) was unlikely on theoretical grounds and has since been shown to be not relevant (Lingvay et al. 2013; Steven et al. 2016a). Pories originally reported that restriction of food intake identical to that enforced after bariatric surgery would normalize blood glucose control (Pories et al. 1995). The observation that this occurs within 7 days of commencing food restriction (Guidone et al. 2006; Henry et al. 1986) set in place the final piece of information for the Twin Cycle Hypothesis to be postulated (Taylor 2008). The hypothesis allows a simplified understanding of type 2 diabetes and is shown diagrammatically in Fig. 1.

The postulates of the Twin Cycle Hypothesis were tested in the Counterpoint study using a very low calorie diet (600 kcal/day for 8 weeks) (Lim et al. 2011a). Within 7 days of withdrawing metformin and initiating negative energy balance, liver fat content had decreased by 30% and liver insulin sensitivity had normalized as had normal fasting plasma glucose. Over 8 weeks, pancreas fat levels decreased and first-phase insulin response increased to within the nondiabetic control range. The degree of muscle insulin resistance did not change significantly after return to normal glucose control.

Further prospective observations supporting the Twin Cycle Hypothesis were obtained from the Whitehall II study. The 13-year trajectories of fasting and postload blood glucose, insulin sensitivity and insulin secretion leading to the diagnosis of diabetes in a large, middle-age, metabolically healthy population clearly show the relatively rapid beta cell decrease in function over the 18 months prior to diagnosis (Fig. 2). Among subjects who developed diabetes, the levels of fasting and postload glucose and insulin secretion 13 years before the diagnosis were higher and insulin sensitivity was lower than those among the group that remained normoglycemic. In the incident diabetes cases, slow linear increases in fasting and postload glucose were followed by a rapid increase prior to diabetes diagnosis (Tabak et al. 2009).

The prognostic value of detecting raised intrahepatic fat levels for development of type 2 diabetes is well established, and normal levels make diabetes unlikely over the following 7 years (Shibata et al. 2007). Reflecting this, elevated ALT was found to be a risk factor for developing type 2 diabetes, independent of obesity, body fat distribution, plasma glucose, lipid, AST, bilirubin concentrations, and family history (Ohlson et al. 1988). In a study of abnormal LFTs and their relationship to clinical findings in 175 unselected diabetic outpatients, the type 2 diabetic patients more frequently had elevated ALT (22% vs. 5.3%) and GGT (23.7% vs. 10.5%) levels than those with type 1 diabetes (Salmela et al. 1984).

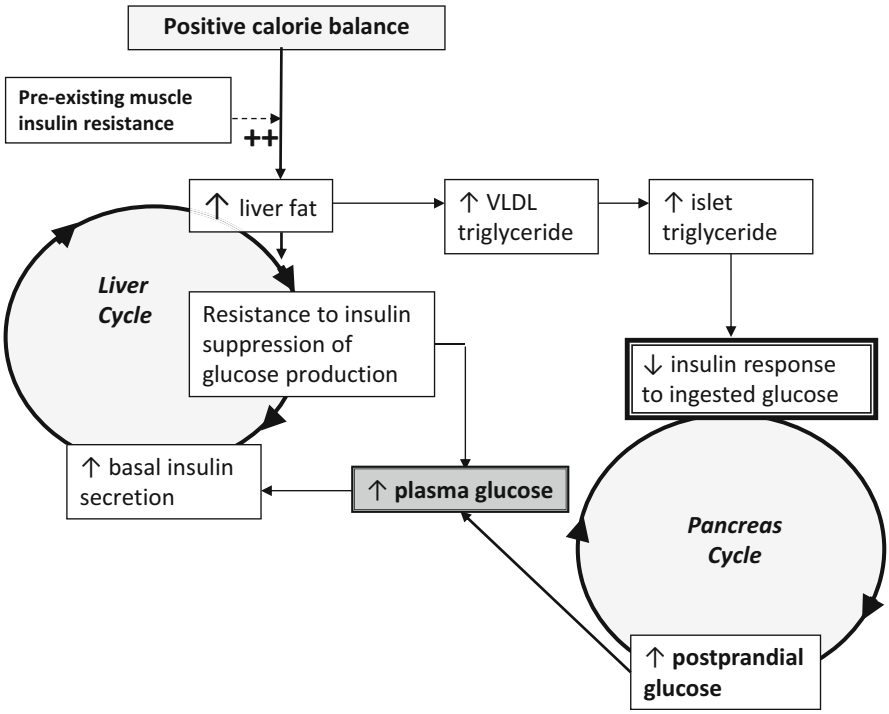


**Fig. 1** The Twin Cycle Hypothesis. During long-term intake of more calories than are expended each day particularly when there is relative insulin resistance in muscle blocking glycogen synthesis, any excess carbohydrate must undergo de novo lipogenesis. This only can occur in the liver and particularly promotes local fat accumulation. Because insulin stimulates de novo lipogenesis, pre-existing insulin resistance and consequent higher plasma insulin levels (determined by family or lifestyle factors) will lead to more rapid accumulation of liver fat. In turn, the increased liver fat will cause relative resistance to insulin suppression of hepatic glucose production. Over many years, a modest increase in fasting plasma glucose level will stimulate increased basal insulin secretion rates to maintain euglycemia. The additional hyperinsulinemia will further increase the conversion of excess calories to liver fat. This process is further stimulated by elevated plasma glucose levels (Adiels et al. 2006). A cycle of hyperinsulinemia and blunted suppression of hepatic glucose production becomes established. Fatty liver leads to increased export of VLDL triacylglycerol (Adiels et al. 2006) which will increase fat delivery to all tissues, including the islets. Excess fatty acid availability in the pancreatic islet would be expected to impair the acute insulin secretion in response to ingested food (Lalloyer et al. 2006; Lee et al. 1994), and at an individual level of fatty acid exposure, postprandial hyperglycaemia will occur. The hyperglycaemia will further increase insulin secretion rates, with consequent enhancement of hepatic lipogenesis, spinning the liver cycle faster and driving the pancreas cycle. Eventually, the fatty acid and glucose inhibitory effects on the islets reach a trigger level that leads to a relatively sudden onset of clinical diabetes (Taylor 2013). Importantly, the hypothesis predicted that the cycles could be reversed, with reversal of type 2 diabetes to normal plasma glucose control (Modified from Taylor (2008) and reproduced with permission from Taylor (2013)

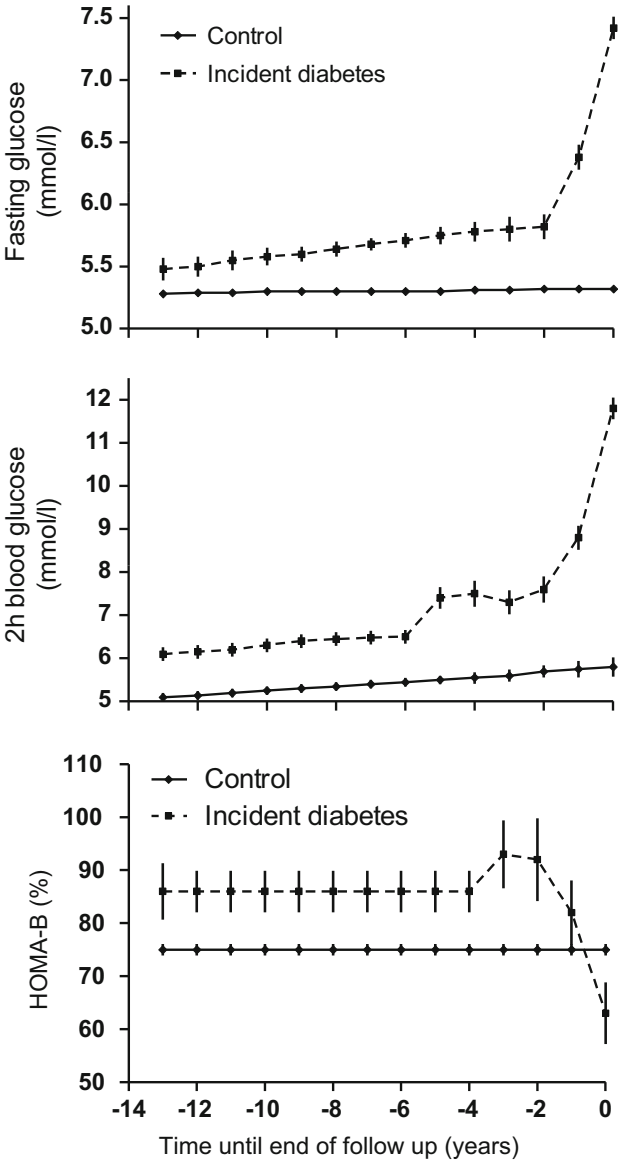


**Fig. 2** Change in fasting plasma glucose (upper panel), 2 h post OGTT plasma glucose (middle panel) and HOMA-S insulin secretion during the 16 year follow-up in the Whitehall II study. Of the 6538 people, 505 developed diabetes. Time 0 was taken as diagnosis of diabetes or as end of follow-up for those remaining normoglycemia (Redrawn with permission from Tabak et al. 2009)

## Long Term Reversibility of Type 2 Diabetes

After weight loss of more than 10% of initial body weight, type 2 diabetes of short duration reverses to normoglycemia in most individuals (Lim et al. 2011a; Steven et al. 2013; Steven and Taylor 2015). The underlying correction of excessive levels of fat in liver and pancreas persists providing that weight regain is avoided (Steven et al. 2016b). Several studies have reported normoglycemia over several years. The Look AHEAD study achieved an average of 8.6% weight loss at 1 year, but the range of weight loss was sufficient to achieve reversal of type 2 diabetes in 11.5% of participants (Gregg et al. 2012). After 4 years, the average weight loss from baseline had declined to 4.7%, but this average includes some with considerable weight loss and a substantial number (7.3%) had remission of diabetes (fasting glucose $<$7.0 mmol/l and HbA1c $<$6.5%). The degree of weight loss in predicting remission was notable, with those achieving weight loss of $>$6.5% having a remission rate of 16.4% at 1 year. Several smaller studies or case reports have demonstrated long-term return of blood glucose control to nondiabetic levels off all oral hypoglycemic agents (Steven et al. 2013; Paisey et al. 2002; Peters et al. 2015).

To evaluate whether longer-term return to nondiabetic blood glucose levels was accompanied by persistent normalization of liver and pancreas fat levels, a group of people who had reversed their type 2 diabetes by energy restriction were followed up for 6 months. The Counterbalance (Counteracting Beta-cell failure by Long-term Action to Normalize Calorie intake) study established that during weight stability, all abnormalities of liver and pancreas function remained reversed (Steven et al. 2016b). The major changes are summarized in Fig. 3. It was notable that the continued remission was independent of BMI, and the implications of this are discussed below.

## Beta-Cell Dedifferentiation

The United Kingdom Prospective Diabetes Study (UKPDS) famously demonstrated an impairment of insulin secretion and a reduction of β-cell by 50% at the time of diagnosis of overt Type 2 Diabetes. It also showed that this progression of β-cell failure was not able to be modified by any of the current available blood glucose lowering treatment (Holman 2006). The Belfast Diet Study to evaluate the effects of intensive dietary management of newly diagnosed diabetes also showed the steady, progressive rise in FPG associated with a progressive fall in β-cell function during the first 10 years after the diagnosis during diet treatment alone (Levy et al. 1998). For both studies, beta-cell function data were modelled from fasting plasma glucose and insulin observations, permitting an overall estimate in the fasting state.

The earliest defect of insulin secretion in type 2 diabetes is a loss of first-phase insulin secretion in response to intravenous glucose (Vaag 1999). It had been accepted for many years that this was irreversible and could not be restored to a useful degree by any pharmacological treatment. However, the Counterpoint study showed in 2011 that this defect is entirely reversible in the first few years of

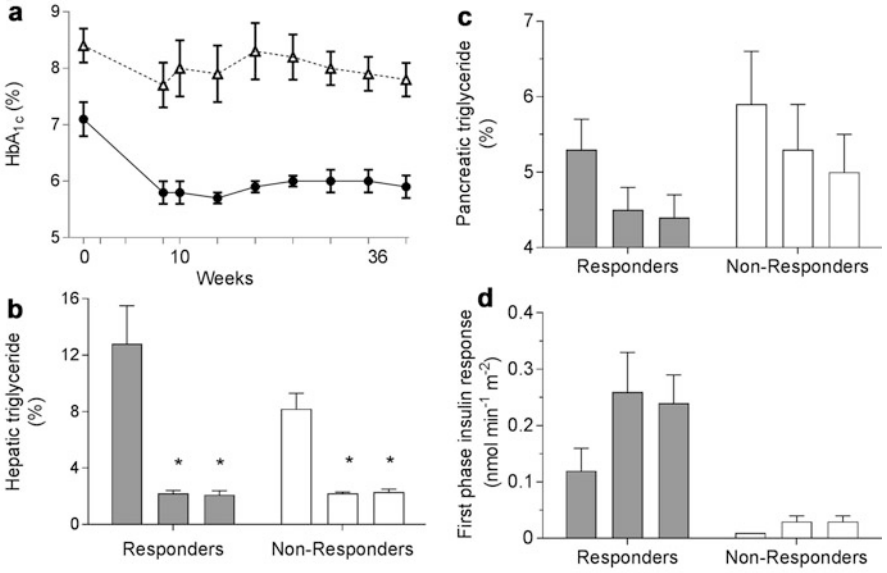


**Fig. 3** The Counterbalance study. Individuals with type 2 diabetes of up to 23 years duration followed a very low calorie diet (~700 kcal/day) and lost approximately 15 kg in weight. Those with shorter duration of diabetes typically responded by achieving non-diabetic fasting plasma glucose (<7.0 mmol/l). After a stepwise transition back to normal eating they were reviewed at monthly intervals. Average weight remained steady for 6 months. Panel A: change in fasting plasma glucose in Responders (closed symbols) and Nonresponders (open symbols). Panel B: similar and sustained decrease in liver fat content in both groups despite ongoing overweight or obesity. Panel C: fall to low levels of pancreas fat in the Responders and in Nonresponders only to levels similar to baseline Responder levels. Panel D: first phase insulin response was higher in Responders at baseline and increased to normal levels, whereas the grossly deficient baseline level in Nonresponders did not change (Figure adapted with permissions from Steven et al. (2016b) and previously published as Taylor and Barnes (2017)

diagnosis of type 2 diabetes if the fat-induced stress on the beta cell was removed (Lim et al. 2011a).

Historically, several different hypotheses have been proposed in order to attempt to explain the development of beta-cell dysfunction in type 2 Diabetes. Firstly, beta-cell exhaustion due to the increased secretory demand was thought to arise from insulin resistance (DeFronzo et al. 1992). Long continued hyperinsulinemia due to obesity related insulin resistance is entirely compatible with long-term normal glucose tolerance (Kahn 2001). Also, the longitudinal data from the Pima Indians points out that beta-cell function is enhanced in apparently healthy subjects as insulin resistance progresses (Weyer et al. 1999).

Secondly, desensitization of the beta-cell due to the elevation of the glucose levels or "glucose toxicity" has also been proposed (Yki-Jarvinen 1992; Robertson et al. 1994). UKPDS data suggest that in the early stages of diabetes, glucose is unlikely to be a critical factor determining the beta-cell dysfunction progression based on

observation that the disease progressed or worsened despite the "normalization" of glucose levels and continuation of the therapy (UKPDS 1998, 1999).

Thirdly, the deposition of amyloid (Kahn et al. 1999; Opie 1901) and apoptosis as a result of the deranged metabolic state (Efanova et al. 1998; Shimabukuro et al. 1998) have been implicated in a reduction of beta-cell mass. The deposition of amyloid in the islets has been reported in a high proportion with type 2 diabetes (Westermark and Wilander 1978; Rocken et al. 1992; Johnson et al. 1989). The islet amyloid polypeptide (IAPP) is a protein component of fibrils that are forming the amyloid deposits (Westermark et al. 1987; Cooper et al. 1987). IAPP is getting produced in the islet cells and released together with insulin (Kahn et al. 1990). When islet amyloid increases in the monkey, the glucose tolerance gets worse (Howard 1986). The reduction of the beta-cell mass seems to be associated with significant islet amyloidosis (Howard and Van Bueren 1986; de Koning et al. 1993). Amyloid fibrils have been shown to be cytotoxic to the beta-cells in vitro resulting in death by apoptosis (Lorenzo et al. 1994; Janson et al. 1999). Wang et al. have studied islet amyloidosis by computerized fluorescent microscopy in transgenic mice bearing the amyloidogenic human IAPP gene and developing typical islet amyloid (Wang et al. 2001). However, type 2 diabetes occurs without accumulation of amyloid, and it appears unlikely to be the cause of decreased beta-cell function in type 2 diabetes.

Fourthly, endoplasmic reticulum (ER) stress response, an adaptive mechanism used to align ER functional capacity and demand, occurs in obesity and type 2 diabetes and in the beta-cell; prolonged ER stress has been suggested to impair the synthesis of insulin (Cnop et al. 2012). Data obtained in animal models of diabetes have suggested that the changes in lipid metabolism could contribute to the development of beta-cell dysfunction (Unger 1995). Also, a high-energy diet, associated with a high fat intake, may contribute to the decrease in beta-cell function (Tsunehara et al. 1990). These observations were nicely brought together by the studies of Anne Clark and others. When fatty acid concentrations are elevated in vitro, lipid synthesis and storage within the beta-cell is favored and chronic exposure of the beta-cell to fatty acid excess directly impairs glucose-stimulated insulin secretion (Elks 1993; Lalloyer et al. 2006; Zhou and Grill 1994). Long-term exposure to increased levels of fatty acids in vitro directly results in beta-cell stress and dysfunction (Pinnick et al. 2010). Exposure of the INS1 beta-cell line to oleic acid brings about storage in intracytoplasmic vacuoles, whereas the saturated fatty acid palmitate induces expansion of the endoplasmic reticulum producing dramatic "splits" or widening in the endoplasmic reticulum (Pinnick et al. 2010). This is associated with markers of endoplasmic reticulum stress, typically increased in human beta-cells from individuals with type 2 diabetes (Laybutt et al. 2007; Marchetti et al. 2007). The exposure to a more physiological mixture of saturated and unsaturated fatty acids decreases insulin secretion, and removal of fatty acid from the medium allows return of insulin secretion over 24 hours (Pinnick et al. 2010). This observation lays the basis for understanding the in vivo reversal of type 2 diabetes and restoration of the non-diabetic first-phase insulin response (Lim et al. 2011a; Steven et al. 2016b). Human

islets cells are known to take up fatty acids avidly, and incubation in 0.33 mmol/l palmitate brings about both a large increase in islet triglyceride content and major impairment of function (Lalloyer et al. 2006). Once hyperglycemia occurs, the additional stress of elevated glucose is likely to compound the metabolic insult (Poitout et al. 2010).

Autopsy studies of patients with type 2 diabetes have reported reduced β-cell mass, and this has long been accepted as the reason for decreased insulin secretory function (Westermark and Wilander 1978; Butler et al. 2003; Saito et al. 1979; Kloppel et al. 1985). However, in such histological studies, the apparent progressive reduction in β-cells in type 2 diabetes was judged by decreased insulin immunostaining. Such assessments were based on insulin secretory function rather than definitively identified beta-cells. Very recently, the loss of beta-cell function in type 2 diabetes was shown to be explained by beta-cell dedifferentiation rather than beta-cell death (Brereton et al. 2014; Spijker et al. 2015; Talchai et al. 2012; Wang et al. 2014; White et al. 2013). Chronic positive energy balance may result in reduced expression of beta-cell transcription factors such as Pdx1, Nkx6.1, and MafA (Brereton et al. 2014; Spijker et al. 2015; Talchai et al. 2012). This leads to the loss of end-differentiated genes including insulin and induction of dismissed genes like lactate dehydrogenase and hexokinase (Weir et al. 2013). Accili et al. proposed that enhanced FoxO1 nuclear translocation is able to maintain the activation of some of beta-cell transcription factors like MafA which preserves glucose oxidation and suppresses fatty acid oxidation resulting in limitation of mitochondrial stress. FoxO1 can initiate a compensatory response that leads to preservation of beta-cell function under metabolic stress.

Lineage tracing studies in mice with beta-cell specific deletion of FoxO1 exposed to metabolic stressors including ageing and multiple pregnancies demonstrated that loss of beta-cell mass was not due to death but rather due to dedifferentiation (Talchai et al. 2012). Loss of insulin staining was encountered together with induction of genes not normally expressed in adult beta-cells including mesenchymal marker vimentin and pancreatic progenitor marker neurogenin 3.

A further change in the stressed, dedifferentiated beta cell is highly relevant metabolically. Following loss of beta-cell specific transcription factors as a result of chronic hyperglycemia, glucagon production by beta cells becomes switched on (Brereton et al. 2014; Marroqui et al. 2015). Following reversal of type 2 diabetes in vivo, a fall to normal of fasting plasma glucagon levels occurs at the same time as return of normal beta-cell function (Steven et al. 2015).

Genetic predisposition plays a part in determining individual susceptibility to type 2 diabetes (Groop and Lyssenko 2008; Ahlqvist et al. 2011). It is likely that genetic factors underlie the susceptibility of the beta-cell to fat-related metabolic stress. Genome-wide association scans and candidate gene approaches have identified approximately 40 genes so far those have been linked with type 2 diabetes and a similar number, but mostly different, with obesity (Hayes et al. 2007; Rampersaud et al. 2007). The majority of type 2 diabetes genes have been associated with impairment of β-cell function. It is estimated that the genes identified already can predict only 15% of type 2 diabetes (Bogardus 2009).

## Pathophysiological Effects of Obesity

### Insulin Resistance in Muscle

Studies using the euglycemic hyperinsulinemic clamp technique have dominated opinion in this field. The term "clamp" refers to the maintenance of constant blood glucose level in by a variable infusion of glucose to balance the biological effect of constant hyperinsulinemia. The amount of glucose required is an index of the sensitivity to insulin – or conversely, resistance to insulin.

Both the euglycemic insulin clamp and limb catheterization studies have demonstrated insulin resistance in skeletal muscle as a feature of obesity (Bogardus et al. 1985; Kelley et al. 1999). At the high insulin concentrations induced, skeletal muscle may account for 70–90% of total body disposal of intravenously delivered glucose (DeFronzo et al. 1985; Yki-Jarvinen et al. 1987). Under these conditions, the liver and the gut (DeFronzo et al. 1981) and adipose tissue (Marin et al. 1987) account only for a very small proportion of glucose uptake. This information was gathered on lean subjects, and in obesity adipose tissue will account for a higher proportion of glucose uptake. Although muscle insulin resistance measured by this method has been illuminating, it does not reflect glucose disposal after a meal. In nonobese subjects, 30% of meal derived glucose is present in muscle at peak glycogen concentration 5 h after a meal (Taylor et al. 1993). This must be borne in mind when considering the clinical relevance of reported insulin resistance in muscle.

Nonetheless, whole body insulin resistance mainly reflects muscle insulin resistance is notably associated with excess fat accumulation and has been shown to be the earliest feature predicting onset of type 2 diabetes (Petersen et al. 2007).

#### Mechanisms: Pathway of Intracellular Insulin Action

The cause of muscle insulin resistance has been intensively researched, and as a consequence, the molecular action of insulin has been defined. In order to cause a biological effect, insulin must first to bind to specific cell surface receptors which lead to tyrosine phosphorylation of IRS-1 mediating the effect of insulin on glucose metabolism (Taniguchi et al. 2006; DeFronzo 2010; White et al. 1988). This is followed by the activation of a cascade of phosphorylation-dephosphorylation reactions. IRS-1 activates PI-3 kinase (Sun et al. 1992), which catalyses 3′ phosphorylation of PI, PI-4 phosphate, and PI-4,5 diphosphate, and augments glucose transport and glycogen synthase (Ruderman et al. 1990; Brady et al. 1997; Dent et al. 1990). Exhaustive searches for genetic links of signaling defects to obesity and type 2 diabetes have been notably unsuccessful.

Because muscle is the early pre-diabetic site of insulin resistance (Ferrannini et al. 1999; Cline et al. 1999; Kahn 1994) and is widely regarded as accounting for of the largest proportion of insulin stimulated glucose uptake, the muscle-specific insulin receptor knockout mice (MIRKO) were created with the expectation that they would be particularly susceptible to type 2 diabetes. In this mouse model, there is almost complete ablation of insulin receptor expression in all skeletal muscles (Bruning et al. 1998). It was a surprise that the MIRKO mice were able to maintaining normal

blood glucose levels up to at least 20 months of age (Bruning et al. 1998). In response to insulin, the glucose uptake into muscles was severely decreased, but it was normal in response to exercise (Wojtaszewski et al. 1999). However, the insulin stimulated glucose transport in adipose tissue was increased by approximately threefold in MIRKO mice (Kahn 2003). In man, Savage et al. have identified a PPP1R3A FS variant, which encodes a truncated protein that is mistargeted within the cell and decreases muscle glycogen synthesis activity. It increases phosphorylase activity resulting in the decrease of muscle glycogen content in humans. Even though this abolished postprandial uptake of ingested glucose and storage as muscle glycogen, no postprandial hyperglycemia necessarily occurs (Savage et al. 2008). This mutation is present in approximately 1 in 70 UK whites which increases the potential relevance of that finding (Savage et al. 2008). Again like the MIRKO mouse studies, this indicates that lack of insulin responsiveness of muscle does not necessarily cause type 2 diabetes. Other susceptibility factor(s) are clearly necessary in addition.

### Mechanisms: Substrate Level Control of Measured Insulin Sensitivity

The deleterious effect of fat accumulation on glucose metabolism was described by Unger as "lipotoxicity" (Unger 2003). Studies on elevation of nonesterified-fatty-acids (NEFA) resulted in severe muscle and liver insulin resistance (Kashyap et al. 2004; Richardson et al. 2005; Dresner et al. 1999; Johnson et al. 1992). These studies also reproduced the core defects of type 2, with additional inhibition of insulin secretion in those susceptible to type 2 diabetes (Kashyap et al. 2003). It was demonstrated by the magnetic resonance spectroscopic studies that the organ specific insulin resistance was closely associated with intramyocellular and intrahepatic fat accumulation (Mayerson et al. 2002; Belfort et al. 2006; Miyazaki et al. 2002; Bajaj et al. 2003). Increased levels of intracellular intermediates of triacylglycerol and NEFA metabolism (fatty acyl CoA, diacylglycerol, ceramides) impair insulin signaling and multiple intracellular steps of glucose metabolism and cause the observed severe insulin resistance (Kashyap et al. 2004; Belfort et al. 2005; Griffin et al. 1999). As intramyocellular levels of triacylglycerol increase, insulin resistance in muscle tends to increase (Greco et al. 2002), and this gives a very direct insight into the relationship between obesity and muscle insulin resistance. However, it is relevant to note that sustained return to a nondiabetic state in humans is routinely achieved with no appreciable change in the level of muscle insulin resistance (Lim et al. 2011a).

### Other Postulated Mechanisms

Insulin resistance in skeletal muscle is associated with mitochondrial function (Petersen et al. 2004). Although this was considered initially as a possible cause of type 2 diabetes, it is now clear that the changes in ATP production are secondary to the metabolic state. No defect is present in early type 2 diabetes but becomes apparent when plasma glucose is over 8 mmol/l (Schrauwen-Hinderling et al. 2007). Observed rates of mitochondrial ATP production can be modified by

increasing or decreasing plasma fatty acid concentration (Brehm et al. 2006; Lim et al. 2011b). Additionally, the onset of insulin stimulation of mitochondrial ATP synthesis is slow, gradually increasing over 2 h and distinct from the acute onset of insulin effect (Lim et al. 2010). Mitochondrial defects cannot be primary in the etiology of common type 2 diabetes (Taylor 2012).

## Insulin Resistance in Liver

Hepatic insulin resistance has long been recognized to be associated with obesity (Basu et al. 2005). Fasting hepatic glucose output is raised in both obesity and further in type 2 diabetes (Singhal et al. 2002) compared with lean subjects (Taylor et al. 1996b). Post-prandial suppression of hepatic glucose output is inadequate in both conditions (Singhal et al. 2002; Taylor et al. 1996b). Unlike muscle insulin resistance, it relates closely to liver fat content and is entirely reversible (Ravikumar et al. 2008; Lim et al. 2011a). Obesity is strongly associated with fat accumulation in the liver at all ages, from early childhood to adulthood (Bedogni et al. 2005). This is a dose relationship between the degree to which children are overweight and the presence of fatty liver as demonstrated by an autopsy study (Schwimmer et al. 2006). In adolescence, 30% of obese individuals have fatty liver (Perseghin et al. 2006) and the extent of liver fat accumulation is inversely proportional to habitual daily physical activity, both in type 2 diabetes and normal glucose tolerance (Perseghin et al. 2007).

Net storage of liver fat can only occur when daily energy intake exceeds expenditure. It has to be the results of excess uptake of fatty acids, as overspill from adipose tissue, relative inhibition of lipid oxidation or de novo lipogenesis. The latter is important as individuals with muscle insulin resistance cannot store ingested glucose as muscle glycogen, and the body has only one pathway to permit safe storage of the ingested energy – synthesis of triglyceride from glucose. Overfeeding with sucrose for 3 weeks has been shown to cause a 30% increase in liver fat content (Sevastianova et al. 2012). The associated metabolic stress on hepatocytes brought about a 30% rise in serum ALT. Both liver fat and serum ALT fell to normal during a subsequent hypocaloric period. The link between fat accumulation and raised ALT is important as a general indicator of metabolic stress of the hepatocyte. Superimposed upon positive calorie balance, the extent of portal vein hyperinsulinemia will determine how rapidly conversion of excess sugars to fatty acid occurs in the liver as the pathway of de novo lipogenesis is not subject to insulin resistance. In groups of both obese and nonobese subjects, those with higher plasma insulin levels have markedly increased rates of hepatic de novo lipogenesis (Schwarz et al. 2003; Rabol et al. 2011; Petersen et al. 2012).

IRS-2 phosphorylation mediates the Insulin action in liver (Fig. 4) (DeFronzo 2010). Inside the hepatocyte, fatty acids could appear as a result of de novo lipogenesis, uptake of nonesterified fatty acid and LDL, or lipolysis of intracellular triacylglycerol (Taylor 2013). The lower ability to oxidize fat within the hepatocyte might be one of the factors for the accumulation of the liver fat (Belfort et al. 2006).

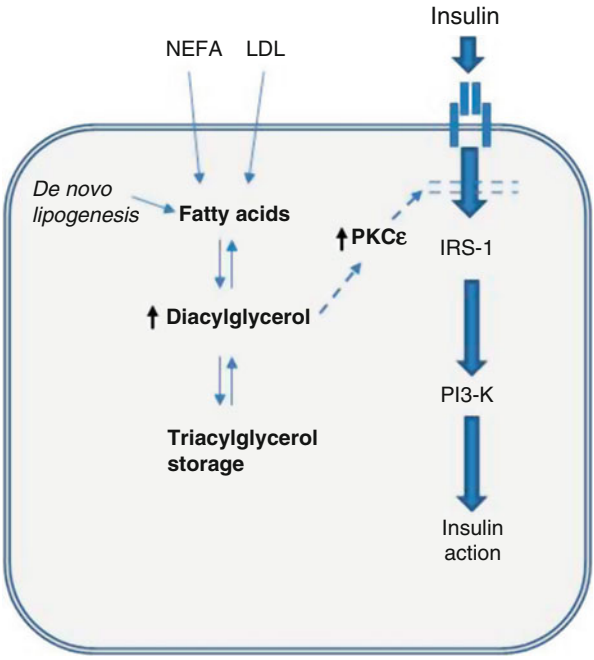


**Fig. 4** Mechanisms of inhibition of insulin action within the hepatocyte. Excess fatty acids and diacylglycerol can directly inhibit critical steps in the pathway of intracellular insulin action in respect of control of hepatic glucose output (Reproduced with permission from Taylor (2013)

Diacylglycerol excess has a deleterious effect on the activation of protein kinase C epsilon type which inhibits the signaling pathway from the insulin receptor to insulin receptor substrate 1 (IRS-1) (Samuel et al. 2010) – the first post receptor step in intracellular insulin action. When there is a chronic excess of energy intake with food, a raised level of diacylglycerol inside the cell prevents the normal action of insulin, and therefore the production of glucose by the liver gets out of control (Taylor 2013). The excess fatty acids stimulate the ceramide synthesis by esterification with sphingosine and the ceramides in turn cause the sequestration of Akt2 and activation of gluconeogenic enzymes (Taylor 2013).

Insulin resistance in skeletal muscle ensures facilitation of conversion of energy from carbohydrate into the hepatic de novo lipogenesis with increased production of VLDL-triglyceride (Petersen et al. 2007). The data from this study also demonstrated that skeletal muscle insulin resistance develops before hepatic insulin resistance, and that the increased triglyceride synthesis by the liver after meals in insulin resistant people will predispose them to nonalcoholic fatty liver disease (NAFLD).

## Inactivity

Relatively low levels of physical activity contribute to the positive energy balance over many years as obesity develops, and obesity itself completes the vicious circle by decreasing the ability to undertake physical activity. The increase in inactivity rates among the population is a growing problem especially in the economically rich countries.

Physical inactivity is associated with increased insulin resistance (Sigal et al. 2004). The evidence from the Finnish Diabetes Prevention Study demonstrates that weight loss and maintenance of this through the diet and physical activity reduces the incidence of type 2 diabetes by more than a half (Tuomilehto et al. 2001). Lifestyle interventions combining limitation of quantity of food with increased daily physical activity are the mainstay of programs to manage body weight (Sigal et al. 2004). Men with low physical activity levels and type 2 diabetes have much higher mortality rates compared with their fitter counterparts (Wei et al. 2000).

### Increased Visceral and Ectopic Fat

Subcutaneous adipose tissue permits the safe storage of chemical energy. The evolutionary role of visceral adipose tissue is less certain, but it provides a readily mobilizable energy depot which will deliver directly to the liver. Excess visceral fat is associated with both obesity and insulin resistance (Ritchie and Connell 2007; Fox et al. 2007). It has been also linked with increased in-hospital mortality (Tsujinaka et al. 2008) and ischemic heart disease (Mathieu et al. 2008). Although visceral fat secretes leptin, adiponectin, resistin, interleukin-6, and tumor necrosis factor, each of these appears to play a modulatory role in metabolic control which is minor compared both with the primary hormones such as insulin and substrate effects on insulin sensitivity. In practice, the major significance of visceral fat is to permit ready clinical assessment of how excessive fat stores have become by the simple measurement of waist circumference. If the visceral stores are prominent, it is likely that fat will be building up in ectopic sites.

The most evident ectopic fat store is within the liver. The prevalence of NAFLD in the US adults was observed to be 46%, with progression to steatohepatitis in 12.2% (Williams et al. 2011). The extent of fat build up in the liver tends to reflect increasing adiposity. Some ethnic groups, and especially Hispanics in USA, are particularly prone to NAFLD (Williams et al. 2011). The higher prevalence in men might relate to differing sex-steroid metabolism (Browning et al. 2004) or simply greater capacity of subcutaneous fat stores in women.

Accumulation of ectopic fat in other sites has been less studied. In obesity, storage at sites such as pericardial and intramyocardial fat tends to be increased (Gaborit et al. 2012). Whether or not obesity per se is associated with increased intra-pancreatic fat content is less certain as most large studies have used methodology likely to report visceral fat contamination due to the irregular shape of the pancreas (Al-Mrabeh et al. 2017).

## Relationship Between Type 2 Diabetes and Obesity

Type 2 diabetes is often regarded as a disease related to obesity. However, the majority (72%) of people with BMI over 40 kg/m$^2$ have no diabetes (Gregg et al. 2007). Conversely, half of all newly diagnosed people with diabetes are not

obese (Logue et al. 2013). The relationship between body weight and type 2 diabetes is nicely illustrated by data from the Nurses' Health Study. This showed that there is a fourfold increase in T2DM prevalence for women of BMI 23–25 compared with those of BMI less than 22 kg/m$^2$ (FB et al. 2001). The implications of this striking observation have not been widely appreciated. As would be expected, the study also confirmed the exponential relationship between type 2 diabetes and rising BMI such that the most obese category had a 37-fold increased prevalence. It is clear that obesity per se is permissive but not sufficient to cause type 2 diabetes.

The distribution of BMI for the 5102 people with newly diagnosed type 2 diabetes recruited into the United Kingdom Prospective Diabetes Study (UKPDS) is shown in Fig. 5 (UK Prospective Diabetes Study (UKPDS) 1991). The distribution is unimodal with a slight skew to the right. It demonstrates that only a minority of the newly diagnosed have a BMI greater than 35 kg/m$^2$ and 36% of the subjects had a BMI less than 25 kg/m$^2$. This distribution is right-shifted from that during the time of recruitment for UKPDS (between 1977 and 1991) when 64% of the adult UK population had a BMI less than 25 kg/m$^2$ (Rosenbaum et al. 1985). From today's perspective, it is remarkable that so many people with newly diagnosed type 2 diabetes had normal BMIs. Indeed, careful reviews in that era concluded that obesity did not have a major influence on type 2 diabetes (Jarrett et al. 1979; Taylor 1989; Leslie and Pyke 1985). Given that the risk of type 2 diabetes rises steeply at higher BMI's and that higher BMI's are now more prevalent, it is not surprising that the association between obesity and T2DM is much more evident today.

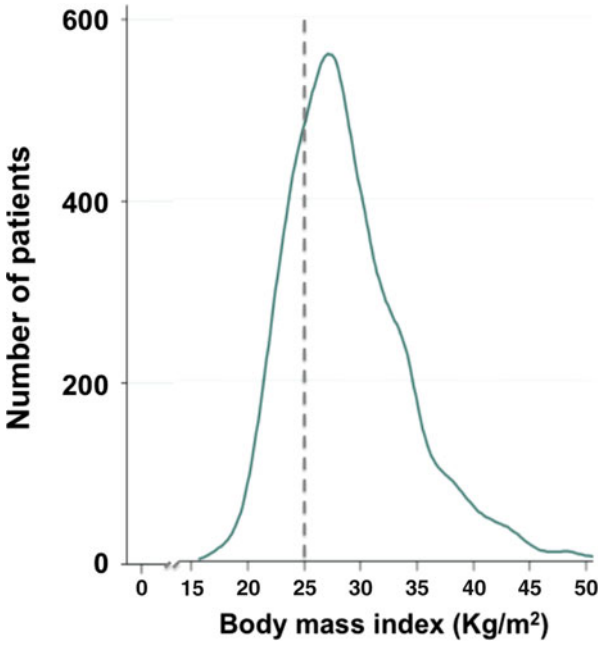


**Fig. 5** BMI distribution in the entire cohort of the UK Prospective Diabetes Study. The newly diagnosed people with type 2 diabetes were recruited between 1977 and 1991. It is striking that 36% had a BMI less than 25 kg/m$^2$ (Reproduced with permission from Taylor and Holman (2015)

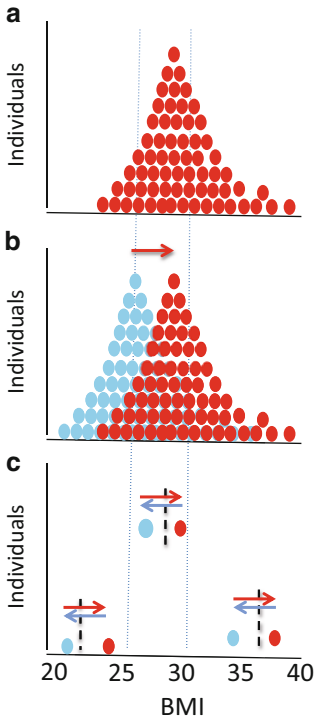


**Fig. 6** The Personal Fat Threshold versus population distributions. Panel A shows a representative frequency distribution of BMI for a group of individuals with type 2 diabetes, not as a smooth curve but as individuals (T2DM). Panel B shows the frequency distribution of BMIs in blue for the individuals depicted in Fig. 2a before they gained weight. The red frequency distribution, when diabetes had developed, is right shifted (red arrow) and usually interpreted as indicating a higher prevalence of obesity in a population with type 2 diabetes. However, the arbitrary cut off points of the BMI scale do not apply to individuals. Panel C shows three illustrative individuals from Panel A, demonstrating their relative positions within the population BMI distribution. One is obese, one overweight and one normal weight. Weight loss of 15 kg in each case resulted in return to normal glucose tolerance although their classification by the population measure of BMI did not change. Each individual has a personal fat threshold (dotted line) above which excess fat is stored within liver and pancreas. This individual susceptibility has no relationship to categories of BMI, despite the higher probability of diabetes being precipitated in the obese range. For each individual, moving to the right of their personal fat threshold triggers T2DM (red arrows), and moving to the left of the line restores normal glucose tolerance (blue arrows) (Reproduced with permission from Taylor and Holman 2015)

These observations have been explained by the Personal Fat Threshold (PFT) hypothesis which focuses upon the individual rather than the populations mean (Taylor and Holman 2015). This is explained diagrammatically in Fig. 6. When an individual exceeds their personal fat threshold, they become likely to develop type 2 diabetes, and it is clear that the hypothesized PFT is independent of BMI. The majority of obese individuals are splendidly equipped to store very large quantities

of fat in a metabolically safe fashion in subcutaneous adipose tissue. But some apparently slim individuals have a low capacity in this depot, and ectopic fat builds up at low BMI's. As an extreme example, in generalized lipodystrophy and effective absence of subcutaneous fat, gross fatty liver disease occurs, and diabetes is common (Reitman et al. 2000). Depending upon the genetically determined susceptibility of the beta-cell to exhibit endoplasmic reticulum stress and consequent beta-cell de-differentiation, diabetes may or may not occur (Talchai et al. 2012; Lee et al. 1994; White et al. 2016). Prolonged Intralipid® infusion in people predisposed to develop type 2 diabetes is known to severely impair beta-cell function (Storgaard et al. 2003). If a person with recent onset type 2 diabetes loses the excess weight, going down below his or her PFT makes likely a return to normal glucose control and reversal of diabetes (Lim et al. 2011a; Steven et al. 2016b; Taylor and Holman 2015). Moderate calorie restriction achieving weight reduction by approximately 8 kg is accompanied by reversal of hepatic steatosis and hepatic insulin resistance leading to a normalization of basal rates of hepatic glucose production and improvement in fasting plasma glucose (Ravikumar et al. 2008; Petersen et al. 2005). The Counterpoint study employed a very low-calorie diet in recently diagnosed people with type 2 diabetes and demonstrated reduction of liver fat by 30% within the 7 days and normalization of fasting plasma glucose (Lim et al. 2011a). Continuation of the weight loss brings about decrease in pancreatic fat and return of glucose stimulated insulin secretion in type 2 diabetes (Lim et al. 2011a; Steven et al. 2016b; Taylor and Holman 2015).

Appreciation of the individual susceptibility to type 2 diabetes appears to be determined both by the relative inability to store fat safely in subcutaneous tissues at any given BMI and by the relative susceptibility of beta-cells to de-differentiate in the presence of excess intrapancreatic fat. This allows understanding of the phenomenon that type 2 diabetes can occur at any BMI reflecting a degree of weight gain excessive for the individual. It also allows understanding that weight loss resulting in a BMI above 30 kg/m$^2$ can achieve metabolic normality.

## Management of Body Weight in Type 2 Diabetes

### Goals

The twin goals of management of body weight in type 2 diabetes are achievement of weight loss and, very importantly, long-term avoidance of weight regain. Wing and Hill proposed criteria for successful weight loss and maintenance: Loss at least 10% of their body weight and weight stability for at least 1 year (Wing and Hill 2001). Six key strategies were proposed based on the data from the National Weight Control Registry: high level of physical activity, low energy, and low-fat diet, eating breakfast, self-monitoring weight on the regular basis, keeping the consistent eating pattern, and catching "slips" before they turn into lager weight regain (Wing and Phelan 2005). However, application of cross-sectional data introduces confounders,

and care is required in interpreting such data. In particular, different strategies are required to achieve weight loss, and to achieve long-term weight stability.

How much weight loss is sufficient to lose diabetes and put it into the long-term remission? This question had been raised in the Counterpoint study where participants have lost on average 15 kg of weight during 8 weeks of VLCD (800 kcal) and the majority reversed type 2 diabetes (Lim et al. 2011c). Reversal of diabetes was not observed with weight loss of less than 8 kg.

Currently the Diabetes in Remission Clinical Trial (DiRECT) is underway in UK Primary Care (Leslie et al. 2016). This trial uses the low-energy liquid diet to achieve substantial weight loss in subjects with early type 2 diabetes (< 6 years duration). A distinct subsequent long-term phase uses limitation of overall food intake and increased daily physical activity together with regular contact with health care professional. The co-primary endpoints are the reduction of weight at 1 year 15 kg or more and the reversal of type 2 diabetes with HBA1C <48 mmol/mol at 1 year. This study has a longitudinal follow up of subjects for total of 2 years. It will help to determine the success of a defined period of weight loss followed by a sustained support program for long-term weight maintenance (The first year results now published showed that almost 9 out of 10 people (86%) who lost 15 kg or more put their Type 2 diabetes into remission. Lean et al. Lancet. 2018;391(10120):541–51. https://doi.org/10.1016/S0140-6736(17)33102-1).

## Reported Dietary Weight Loss Interventions in Type 2 Diabetes

Dietary management for the people with type 2 diabetes has been evolving over many decades. It differs from primary prevention advice to be applied to populations at risk in that there is a potent motivator for people who have been diagnosed – to escape from diabetes entirely and avoid the risk of blindness, amputation, and premature death.

In UKPDS, the response to the diet was reported in the 3044 newly diagnosed who had fasting plasma glucose of 12.1 ± 3.7 mmol/l and weight of 130 ± 26% ideal body weight (UKPDS Group 1990). Initial body weight did not determine the glycemic response to weight loss, as could be predicted from the Personal Fat Threshold hypothesis (Taylor and Holman 2015). In this study, 16% of the group reached a normal FPG less than 6 mmol/l after 3 months, reflecting variable motivation to achieve a large reduction in energy intake and meaningful weight loss (UKPDS Group 1990). The Belfast Diet Study showed that treatment with diet alone for the first 10 years after the diagnosis of type 2 diabetes is associated with progressive rise in FPG, but this study concentrated on composition of food rather than quantity (Levy et al. 1998).

The longest randomized controlled study to date of an intensive lifestyle intervention for weight management is Look AHEAD (Action for Health in Diabetes Study). This study showed that over 8 years overweight or obese people with type 2 diabetes lost 4.7% of initial body weight in the intensive lifestyle intervention group (versus 2.1% in usual care group) (LookAhead 2014). 26.9% of the intervention group lost >10% of initial body weight by the end of a trial. The degree of weight

loss in predicting remission was notable, with those achieving weight loss of >6.5% having a remission rate of 16.4% at 1 year. However, these results appeared less impressive than may have been desired in view of the intensive and expensive nature of the intervention. There was an emphasis on exercise in LookAhead, and this may have been counterproductive (see below).

Very low energy diets rapidly improve plasma glucose control. The old extremely low energy diets (330 Cal/day) brought about weight loss of 10.5 ± 0.4 kg with improvement in fasting plasma glucose (Henry et al. 1985). Using a modern 600kcal/day liquid formula diet, superior average weight loss (15.2 kg) has been reported, with complete normalization of plasma glucose within 7 days (Lim et al. 2011c). Although it has been assumed that rapid weight loss is always followed by weight regain, this concept developed in the absence of appropriate continuing support programs. Ongoing weight stability following rapid weight loss and a careful step-wise reintroduction of normal foodstuffs has been shown to be achievable (Steven et al. 2016b).

## Approaches to Long-Term Avoidance of Weight Regain

The principal dietary interventions for long-term use which are supported by evidence will be considered: low-fat diet, restricted carbohydrate diet, Mediterranean diet, and intermittent energy restriction.

A low-fat diet (<30% total energy from fat) has long been widely advised. The idea became popularized by an epidemiological association between different countries of high fat intake with cardiovascular death (Keys 1953). Such associations from cross-sectional studies have repeatedly been shown not represent cause and effect (Feinman et al. 2015), but the belief in a low fat diet for health is very widespread and reflected in current guidelines for type 2 diabetes. A head-to-head comparison of low-fat diet with an energy-restricted diet showed no significant difference in weight loss (Jeffery et al. 1995), whereas combination of the low-fat plus low-energy diet versus low-fat diet alone (Schlundt et al. 1993; Pascale et al. 1995).

Moderate carbohydrate restriction is simple to implement, particularly in the context of family eating. Low-carbohydrate diets continue to arouse strong feelings, possibly as a backlash against more extreme carbohydrate avoidance diets (Feinman et al. 2015; Spiro and Stanner 2016). A restricted carbohydrate diet brings about an increase in the proportion of calories from fat, conflicting with long-held beliefs about the risks of higher-fat diets. However, the practical outcome has been shown to be beneficial for both weight management and improvement in cardiovascular risk factors (Bazzano et al. 2014). The macronutrient composition of diet, for equivalent weight loss, does not affect liver fat content or any other aspect of fat distribution (de Souza et al. 2012). These points have been incorporated into evidence-based nutrition guidelines (Dyson et al. 2011).

The Mediterranean diet consistently has been reported to be advantageous in terms of weight control and cardiovascular health (Estruch et al. 2016; Garcia-Fernandez et al. 2014; Martinez-Gonzalez and Martin-Calvo 2016), with a

decreased diabetes incidence independent of weight (Salas-Salvado et al. 2011). A combination of Mediterranean with carbohydrate restriction may be beneficial (Esposito et al. 2014).

Time-limited approaches to eating (such as alternate day or intermittent fasting) appear to be very suitable for some individuals as an alternative to daily calorie restriction. This is as effective as calorie restriction for weight loss and maintenance for up to 12 months (Davis et al. 2016). The proportion of people losing more than 5% in weight has been reported to be higher with intermittent energy reduction (60–65%) compared to daily energy restriction (37%) (Harvie et al. 2013). For ongoing avoidance of weight regain, 1 day of energy restriction per week was found to be successful. Using the 5:2 approach in type 2 diabetes achieves comparable reductions in weight and HbA1c to calorie restriction with no adverse effects on exercise levels or appetite (Carter et al. 2016; Harvie and Howell 2016). Longer-term weight maintenance outcomes are currently lacking.

Omission of breakfast runs counter to beliefs about this meal, although the latter mainly derived from cross-sectional studies, often with a potential commercial bias (Brown et al. 2013). Clearly the approach of not eating before noon suits some people and not others. Prospective study suggests a major energy advantage of this pattern of eating with no disbenefit in terms of eating more later in the day (Clayton et al. 2016; Kealey 2016).

Over recent years, guidelines have moved away from enforcing any particular macronutrient composition to acknowledging that there is no "one best diet" for every individual with diabetes (Dyson et al. 2011). In practice, long-term energy intake can be minimized by using an approach suited to the individual. Taken together, these studies illustrate important points. Clear separation of a limited duration weight-loss phase followed by a weight-maintenance phase of both calorie limitation and increased physical activity may be a more successful approach (Steven et al. 2016b). Confirmation of this in a large population is currently being sought (Leslie et al. 2016). The nature of support and advice about eating during long-term weight maintenance clearly deserves close study.

## Exercise

The energy expenditure achieved by the amount of exercise feasible for overweight, older people is modest and easily cancelled out by a snack. To maximize weight loss, the initial approach must recognize the dangers of compensatory eating brought about by any sudden increase in exercise (Finlayson et al. 2009; Hopkins et al. 2014; King et al. 2012). This increase in energy intake, partly conscious and partly subconscious is counterproductive and underlies the common observation that exercise in overweight people does not result in weight loss. The impact of compensatory overeating varies between individuals (Hopkins et al. 2014) but can be entirely avoided. Studies focused on decreased energy intake with no additional exercise achieve ~15% weight loss in 8 weeks. In contrast, the intensive exercise advised in LookAhead, only achieved a maximum weight loss of 8.5% despite

dietary input (LookAhead 2014). This matter must be seen as distinct from the extremely important role of increased physical activity in achieving long-term weight control (Wing and Phelan 2005).

A sustained increase in physical activity is without doubt vital for the long-term avoidance of weight regain and is the single most solid outcome of research across the weight-maintenance field (Pronk and Wing 1994; Kayman et al. 1990). A combination of diet and exercise achieves better weight loss compared with diet alone after 20 weeks of treatment (8.3 kg vs. 5.6 kg respectively) and in 1 year (7.9 vs. 3.8 kg) (Wing 1989). It is possible that the effect of increasing daily physical activity on food limitation is greater in men (Wood et al. 1991).

## Bariatric Surgery

For individuals who are not able to achieve weight loss by overall restriction of energy intake, bariatric surgery is an effective option. The overall effects of surgery – including involuntary restriction of food intake, rapid weight loss, post-prandial hypoglycemia, risk of surgical complications – must be discussed with the individual and spouse/partner. Randomized studies comparing outcomes are not informative, as individuals most suited to surgery are not the same people as those most suited to an effective dietary approach. The multicenter Swedish Obese Subjects study (SOS) is important as an observational nonrandomized study comparing different types of bariatric surgeries with medical weight loss treatment (Sjostrom et al. 2004). The remission was three times greater and the risk of type 2 diabetes development was more than three times lower for the bariatric surgery group at 10 years of follow up (Sjostrom et al. 2004).

Bariatric surgery is very successful in achieving sustained major weight loss (Dixon et al. 2008; Buchwald et al. 2009). Indeed, it is the only successful weight loss intervention which can be done by doctors to patients irrespective of the degree of motivation to lose weight. The nature of the operation is important only in the degree of energy restriction enforced, as illustrated by the lesser effect of gastric banding or the equivalent effects of gastric sleeve surgery compared with Roux-en-Y gastric bypass (Dixon et al. 2008; Schauer et al. 2012). Any procedure which results in rapid food entry into the ileum will bring about a greatly increased GLP-1 response after, and many studies have drawn attention to the association with metabolic changes (Guidone et al. 2006; Jorgensen et al. 2012; Laferrere et al. 2007). However, such studies do not indicate any causal relationship and matched feeding studies demonstrate very precisely that identical metabolic changes in type 2 diabetes are achieved by pair feeding studies (Lingvay et al. 2013). Detailed examination of the metabolic changes demonstrates no detectable effect of the GLP-1 spike itself (Steven et al. 2016c; Isbell et al. 2010a; Jimenez et al. 2013). These observations solely concern the early metabolic response to bariatric surgery and other potential effects of the enhanced postprandial GLP-1 response, such as on appetite in the long term, remain to be definitively established.

Other effects of bariatric surgery include changes in bile acid handling and in the gut microbiota, and the consequences of these await precise evaluation. The re-

routing of nutrients after bariatric surgery may affect enterohepatic recirculation of bile acids with potential effects upon glucose metabolism (Pournaras et al. 2012). Obesity alters the gut microbiota, and conversely distinct changes occur after successful treatment by bariatric surgery (Palleja et al. 2016; Zhang et al. 2009). Other hypotheses concerning the metabolic effects of bariatric surgery have been postulated, based largely upon rodent studies. The foregut hypothesis that exclusion of nutrients from the proximal small bowel is unlikely to be relevant to humans, given the striking similarity between the metabolic effects of sleeve gastrectomy and Roux-en-Y gastric bypass for any given degree of weight loss (Schauer et al. 2014). The hindgut hypotheses of incretin production effect is effectively ruled out by the observations on paired feeding studies and other direct human observations (Lingvay et al. 2013; Steven et al. 2015; Isbell et al. 2010b).

Weight loss achieved by bariatric surgery decreases mortality in diabetes by up to 92% (Adams et al. 2007). On the basis of all the evidence to date, The International Diabetes Organization have issued a treatment algorithm for bariatric surgery for type 2 diabetes, supporting use in people with BMI 35–39.9 kg/m$^2$ when hyperglycemia is inadequately controlled by lifestyle and optimal medical therapy and in those with BMI $\geq$ 40 kg/m$^2$ (Rubino et al. 2016). Nonetheless, it should be considered whether an individual has exhausted the available dietary methods of weight loss shown to be effective before referring for surgery.

## Conclusions

The recent advances in understanding of type 2 diabetes have allowed clarification of the interaction between the effects of accumulating stores of excess fat. Currently in the UK, around half of people newly presenting with type 2 diabetes are obese, setting in perspective the relationship between the two conditions. As the BMI distribution of the population shifts further to the right, continued increase in prevalence of type 2 diabetes can be predicted. At the individual level, personal action to decrease body weight can return a person from the state of having type 2 diabetes to normal metabolic control. The sustained reversal of type 2 diabetes may or may not be associated with decrease of BMI below 30 kg/m$^2$.

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# Obesity, Hypertension, and Dyslipidemia

11

Vasilios Kotsis, Christina Antza, Giannis Doundoulakis, and Stella Stabouli

## Contents



**Abstract**

Hypertension and dyslipidemia are closely related with obesity. Obesity releases nonesterified fatty acids into the circulation, increasing fasting plasma triglycerides, reducing high-density lipoprotein cholesterol, and inducing a shift to a pro-atherogenic composition (small, dense) of low-density lipoproteins. Obesity activates the sympathetic nervous system, increases sodium and water reabsorption, and increases the production of angiotensin II factors that determine hypertension shift in obese people.

**Keywords**

Obesity · Hypertension

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| Abbreviations | |
|---|---|
| 24 h ABPM | 24 hour ambulatory blood pressure monitoring |
| Ang | Angiotensin; RAS: Rennin–Ang system |
| BMI | Body Mass Index |
| BP | Blood pressure |
| FFAs | Free fatty acids |
| HDL | High-density lipoprotein |
| IDL | Intermediate density lipoproteins |
| LDL | Low-density lipoprotein |
| MAG | Monoacylglycerol |
| MetS | Metabolic syndrome |
| NAFLD | Non-alcoholic fatty liver disease |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| PLs | Phospholipids |
| SNS | Sympathetic nervous system |
| TAG | Triacylglycerol |
| TG | Triglycerides |
| VLDL | Very low density lipoproteins |

## Introduction

The prevalence of obesity doubled between 1980 and 2008, affecting not only high but also middle- and low-income countries. Obesity and modern life style includes a shift from the labor and agricultural work to sedentary jobs and the lack of physical exercise with increase in caloric intake as prepared out of house food typically includes more sugar and trans lipids compared to home meals. Children and adolescents watch more TV and exercise less as outside physically active play has been replaced with video games.

Obesity is associated with hypertension, type II diabetes mellitus, heart failure, dyslipidemia, chronic kidney disease, and cancer (Mancia et al. 2013; Kotsis et al. 2005; Nagarajan et al. 2016). According to the World Health Organization (WHO) 44% of the prevalence of diabetes, 23% of the prevalence of ischemic heart disease, and 7–41% of certain types of cancer are attributable to obesity. Metabolic syndrome (MetS) includes abdominal obesity, high blood pressure, elevated plasma glucose levels (insulin resistance and type II diabetes mellitus), high serum triglycerides, and low high-density lipoprotein (HDL) levels. The exact definition of the metabolic syndrome differs between various organizations, but its importance and relationship to type 2 diabetes is evident. Obesity is often accompanied by obstructive sleep apnea syndrome (Bibbins-Domingo et al. 2017) and nonalcoholic fatty liver disease (NAFLD) that are considered as additional risk factors for cardiovascular disease (Kalia and Gaglio 2016). Abdominal obesity is associated with reduced insulin-mediated glucose muscle uptake causing hyperinsulinemia and insulin resistance that linked to increased cardiovascular risk factors. The cardiometabolic syndrome is very

important since heart attacks and strokes are the major causes of the high mortality rates in type 2 diabetic patients, and the need for prevention is increased in such patients. Thus, obesity has evolved from a social problem to a severe health problem.

The relationship between obesity and hypertension is well established both in children and adults in different populations and ethnic groups (Kotsis et al. 2005; Stabouli et al. 2005; Bramlage et al. 2004; Baik et al. 2000). Normal weight was reported in 58.1% of true normotensive subjects (confirmed both with office and 24 h ABMP), while obesity was found in 43.7% of the true hypertensive subjects. In patients followed up by primary care physicians, the prevalence of hypertension was increased from 34.3% in the normal weight population to 74.1% in the obesity population (Bramlage et al. 2004). Cardiovascular disease mortality among men aged <65 years increased linearly with greater body mass index (Baik et al. 2000).

Obesity is associated with impaired lipid metabolism. Insulin resistance and lipolysis induce free fatty acid (FFA) release that increase fasting plasma triglycerides (TG), and decrease high-density lipoprotein (HDL) cholesterol and shift low-density lipoproteins (LDL) to a more proatherogenic composition (small, dense LDL) (Franssen et al. 2011). According to the latest guidelines of European Society of Cardiology/European Society of Atherosclerosis, the target of lipid metabolism is focused on LDL. Patients having low to moderate risk should have LDL levels below 115 mg/dl, in high-risk patients LDL target is below 100 mg/dl, and in very high-risk patients the target is below 70 mg/dl (Catapano et al. 2016). Despite that LDL quantity is the main target in patients with hyperlipidemia, the residual risk from increased TG and low HDL and LDL quality should not be underestimated especially in obese subjects.

## Obesity-Induced Hypertension

Sympathetic nervous system, renal mechanisms, inflammation, and hormones such as leptin, insulin, corticosteroids, and the renin-aldosterone angiotensin system seem to have a key role in obesity-induced hypertension (Kotsis et al. 2010). The interaction of these mechanisms with behavioral aspects such as salt and potassium intake, and physical exercise plays an important role in obesity-induced hypertension.

Electronic medical records from children and adolescents in the USA examined data from a population of 117,618 children and adolescents aged 6–17 years with measured height, weight, and blood pressure. The proportion of children with normal blood pressure fell, while those with prehypertension or hypertension increased as BMI percentage increased above the obesity threshold, suggesting that obesity early in life is associated with increased BP. Severe obese children compared to moderately obese children have a threefold increased risk of hypertension (Lo et al. 2014). Data from the Framingham Heart Study, a population-based prospective cohort study, confirm the increased prevalence of hypertension in obese subjects. Participants from the Offspring and Third Generation studies were analyzed

and the prevalence of hypertension was increased from 11.5% in normal weight subjects to 22.8% in overweight and 37.6% in the obese group. The prevalence of hypertension increased significantly with increasing BMI category (Molenaar et al. 2008).

## Mechanisms of Obesity-Induced Hypertension

The sympathetic nervous system (SNS) seems to be activated in obesity. High-energy intake increases norepinephrine turnover in peripheral tissues, raises resting plasma norepinephrine concentrations, and amplifies the rise of plasma norepinephrine in response to stimuli such as upright posture. Peripheral α1- and β-adrenergic receptors also found to be stimulated contributing to the elevated sympathetic activity. Pharmaceutical blockade of α and β adrenergic system reduced blood pressure levels in obese animal models and human studies (Landsberg and Krieger 1989).

Increased levels of circulating FFAs in obese populations enhance vascular α-adrenergic sensitivity and increase α-adrenergic tone. Lysophospholipids and FFAs inhibit Na+, K + −ATPase, and the sodium pump, raising vascular smooth muscle tone and resistance. Na/K-ATPase is binding with lysophospholipids and FFAs, the epidermal growth factor receptor is activated and reactive oxygen species are increasingly produced (Stepniakowski et al. 1995).

Increased sodium and water excretion through pressure natriuresis and diuresis is the first renal mechanism in the development of hypertension in obese people. If excretion exceeds intake, extracellular-fluid volume decreases reducing venous return and cardiac output. Renal blood flow consequently decreases, and the kidney retains salt and water until arterial pressure returns to normal. During the early stages of obesity, before loss of nephron function secondary to glomerular injury, primary sodium retention occurs because of an increase in renal tubular reabsorption. Extracellular-fluid volume is expanded because of volume overload. Sympathetic activation appears to mediate at least part of the obesity-induced sodium retention and hypertension since adrenergic blockade or renal denervation markedly attenuates these changes. Recent observations suggest that leptin actions in the hypothalamus may link excess weight gain with increased sympathetic activity (Hall et al. 2000). High fat diet in conscious dogs increases rennin activity, while fat restriction has the opposite effects. Under normal conditions, RAS represents a regulatory mechanism, which prevents extreme variations in arterial pressure (especially very low values) that may reduce organ perfusion, while high salt intake reduces the production of Ang II (Hall 1997).

Adipose tissue has important paracrine physiology. Adipose tissue-derived angiotensinogen may enter the circulation having systematic actions or may have local actions at the perivascular adipose tissue. Renin, Ang II, angiotensinogen, and Ang II receptors are found in abundance in adipose mass suggesting that a local tissue Ang system is settled at adipocyte level. The tissue RAS and the circulating RAS are in a state of constant interaction. Angiotensinogen locally produced is taken

up by the cells that Ang II receptors are over expressed. Angiotensinogen production leads to elevation of BP through the actions of Ang II, which induce systematic vasoconstriction, direct sodium and water retention, and increased aldosterone production (Campbell 1987). Studies in patients under sodium restriction, which activates the RAS system, provided evidence for a presynaptic potentiating effect of Ang II on sympathetic neurotransmission (Taddei et al. 1995).

The renal effects of obesity include both structural and functional adaptations, such as increased glomerular filtration rate, increased renal blood flow, and renal hypertrophy. Patients with obesity have increased filtration fraction with a role for afferent arteriolar dilation in the mediation of the increased trans-capillary hydraulic pressure gradient. Elevation in GFR may be mediated in part by increased protein consumption and increased tissue blood flow need. Weight gain has been associated with an expanded renal medullary interstitium in humans and in animal models of obesity. Physical compression of both kidneys is generated from the accumulation of adipose tissue around the organs, a fact that demonstrates the vital role of visceral obesity in the development of renal disease. Deposition of extracellular matrix throughout the renal medulla is expanded, and the tissue surrounding the ducts of Bellini at the vascular pole tends to prolapse. Lipids and proteoglycans compress the renal parenchyma toward the pole of the kidney resulting in the formation of round-shaped, enlarged kidneys in obese subjects (Dwyer et al. 2000). The primary histologic features are relatively few lesions of focal segmental glomerulosclerosis, profound glomerular enlargement due to glomerular hyalinosis and fibrosis, as well as lipid accumulation in the glomeruli and adhesion to Bowman's capsule. Despite the observed high incidence of glomerulomegaly, glomerular changes in obesity-induced renal injury are incomparable with those of diabetic nephropathy, mainly because of the lower severity of changes in the mesangial space. Other causes of renal injury, apart from high-fat intake, could possibly include overexpression of Ang II with a consequent increase in proliferative factors such as transforming growth factor-b and plasminogen activator inhibitor, high protein diet, as well as hyperinsulinemia (Kambham et al. 2001). Mechanisms of obesity-induced hypertension are summarized in Fig. 1.

## Hormones Related to the Obesity-Induced Hypertension

Obesity and insulin resistance are two well-connected conditions. Normally, insulin exhibits a sodium-retaining effect through its direct action on the renal tubules. A potential enhancement of sodium retention because of acute hyperinsulinemia could increase blood pressure in obese patients, but in chronic hyperinsulinemia this mechanism has no significant effect on blood pressure regulation. Insulin is also reported to acutely increase SNS activity and norepinephrine levels in both normotensive and hypertensive subjects, but the main action of insulin is peripheral vasodilation that is mediated by a β-adrenergic mechanism (Anderson et al. 1992; Hall 1993).

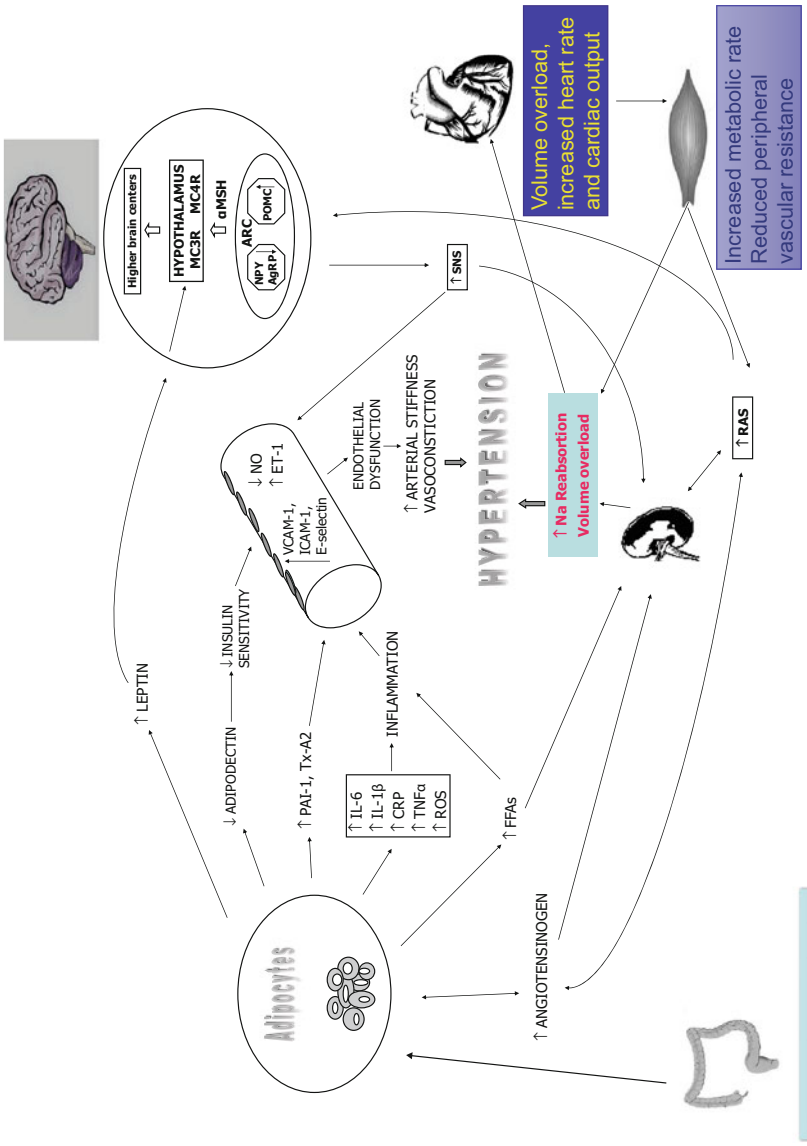


**Fig. 1** Mechanisms of obesity-induced hypertension (Modified from Kotsis et al. 2010)

Leptin is a peptide hormone secreted from adipose tissue that activates the sympathetic nervous system in animal models. Leptin plays a physiological role in thermogenesis, energy expenditure, and by decreasing food consumption. Leptin is bound to its short-form receptors and transported across the blood–brain barrier to the arcuate nucleus to modulate appetite controlling feedback mechanisms of neuropeptides. Studies in animals and humans with leptin deficiency show high incidence of obesity but absence of hypertension. Leptin deficiency in the $Lep^{ob/ob}$ mouse leads to early-onset of obesity, hypercorticosteronemia, hyperglycemia, hyperinsulinemia, and hypothyroidism (Schubring et al. 1999). Besides the high body weight, $Lep^{ob/ob}$ mice are hypotensive (Mark et al. 1999). Leptin deficiency in human is also associated with similar metabolic abnormalities but normal blood pressure (O'Rahilly 2009), whereas increased leptin levels have been reported in essential hypertension (Agata et al. 1997). Obesity without hypertension is a characteristic of the melanocortin 4 receptor (MC4-R) null mouse. The MC4-R deficiency in mouse is related to obesity, hyperglycemia, hyperinsulinemia, and hypometabolism. Despite obesity MC4-R-deficient mice are not hypertensive (Sutton et al. 2006).

In obese humans selective resistance of leptin actions has been reported, and despite high leptin levels there is no reduction in food intake or increase in energy expenditure, while the SNS stimulation is still present (Correia et al. 2002). Neuropeptide Y is a neurotransmitter, expressed in the hypothalamic arcuate nucleus at high rates during fasting. Its orexigenic action is combined with reduction in thermogenesis and downregulation of the sympathetic neurons. Normally, its expression is suppressed by high leptin levels. In the leptin-resistant state, neuropeptide Y should rather be considered overexpressed acting as a vasoconstrictor and could have a role in the obesity-related hypertension (Lundberg et al. 1987). Glucocorticoids increase food intake, reduce energy expenditure, and promote insulin resistance, fat accumulation, and hypertension. Obese rodent models of obesity, which are characterized by hypercorticosteronemia, restore their lower body weight after adrenalectomy that is regained with glucocorticoid replacement treatment (Saruta 1996). Obese individuals have increased adipose levels of 11b–hydroxysteroid dehydrogenase-1,72,73, an enzyme that regenerates active cortisol from the inactive 11-keto forms. The aP2-HSD1 mice overexpress the enzyme in fat cells and develop obesity, insulin resistance, dyslipidemia, and hypertension. These mice have increased sensitivity to dietary salt and increased plasma levels of angiotensinogen, Ang II, and aldosterone (Masuzaki et al. 2003). These reports suggest that a local activation of glucocorticoid production in the adipose tissue induce an activation of the RAS, which mediates a salt-sensitive form of hypertension in obesity.

Finally, there are people with obesity who are protected from hypertension. Ethnicity plays a role in the development of obesity-induced hypertension. The Pima Indians of Arizona have the highest reported prevalence of obesity in the world, but a relatively low prevalence of hypertension and atherosclerotic disease (Saad et al. 1990). The lack of increase in muscle sympathetic nervous activity (MSNA) with increasing adiposity and insulinemia in Pima Indians may explain, in part, why this population has a low tendency for hypertension, despite the high prevalence of obesity.

## Obesity-Induced Dyslipidemia

Conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention, NHANES III was designed to provide USA national representative data estimating the prevalence of major diseases. Approximately 63% of men and 55% of women aged 25 years or older in the US population were overweight or obese and 21% of men and 27% of women were obese suggesting that 1 to 4 US citizens were obese between 1990 and 2000. High blood pressure was the most common overweight- and obesity-related health condition and its prevalence showed a strong increase with increasing weight status category. In obese subjects the prevalence of hypertension was more than 40% and followed closely by high cholesterol levels with a prevalence of more than 35% in both gender, while the prevalence of diabetes was lower around 10–15% depending on the gender and the severity of obesity. Among younger men and women cholesterol levels of overweight and obese were elevated compared with the normal weight group, but there was no evidence of a gradient increase with weight status category, as seen in hypertension status, suggesting that severe obese did not have the highest lipid levels. Among older subjects, cholesterol levels were significantly increased only in overweight individuals (Must et al. 1999). In women using linear trend analysis, changes in BMI from normal weight to overweight categories of BMI was associated with higher TG levels and lower HDL levels independently of their menopausal status. Overweight in premenopausal women was found to be associated with 18 mg/dL higher total cholesterol levels, 26 mg/dL higher non-HDL levels, and 17 mg/dL higher LDL levels compared to normal weight women (Denke et al. 1994). In young men BMI increase from normal weight to overweight was associated with increased total cholesterol levels by 23 mg/dL, non-HDL levels by 27 mg/dL, and LDL levels by 23 mg/dL. For middle-aged and older men, the same change in BMI was associated with smaller but still significant differences in triglycerides and HDL cholesterol levels, whereas the LDL cholesterol levels were unchanged (Denke et al. 1993). The typical dyslipidemia of obesity consists of increased TG and FFA, decreased HDL, and normal or slightly increased LDL, with increased small dense LDL. The concentrations of plasma apolipoprotein B are also often increased, partly due to the hepatic overproduction of apo B containing lipoproteins.

## Lipoprotein Metabolism

Dietary fats consist of triacylglycerol (TAG) (90–95% of the total energy derived from dietary fat), phospholipids (PLs), sterols (mainly cholesterol, β-sitosterol), and fat-soluble vitamins. Although β-sitosterol accounts for 25% of dietary sterols, it is not absorbed by humans under physiological conditions (Iqbal and Hussain 2009). The digestion of lipids begins in the oral cavity through exposure

to lingual lipases and continues in the stomach through the effects of both lingual and gastric enzymes. TAG is digested primarily by pancreatic lipase in the upper segment of the jejunum. The activity of pancreatic lipase on the sn-1 and sn-3 positions of the TAG molecule results in the release of 2-monoacylglycerol (2-MAG) and free fatty acids (FFAs), which are uptake by the enterocytes via passive diffusion and specific transporters. Further hydrolysis of 2-MAG (by pancreatic lipase) results in the formation of glycerol and FFAs (Pan and Hussain 2012). The specific cholesterol transporter Niemann-Pick C1 Like 1 protein (NPC1L1) is responsible for taking up the cholesterol by the enterocytes (Davis et al. 2004). MAG and free fatty acids are first converted to diacylglycerol (DAG) by acyl coenzyme A monoacylglycerol acyltransferase (MGAT) enzymes. DAG is then converted to TAG by acyl coenzyme A diacylglycerol acyltransferases 1 and 2 (DGAT1 and DGAT2). TAG is also synthesized from glucose by the glycerol-3-phosphate pathway. In this pathway, three isoforms of phosphatidic acid phosphohydrolase (PAPase, also known as lipins 1–3) hydrolyze the phosphate to form DAG, which finally synthesizes TAG as in the MAG pathway (Takeuchi and Reue 2009).

Cholesterol-esters and TG are packed together with phospholipids and apolipoprotein (apo) B48 to form chylomicrons, which are gradually converted into chylomicrons remnants and are delivered into the liver. The liver synthesizes TG-rich lipoproteins called very low-density lipoproteins (VLDL). Apo B100 is the structural protein of VLDL, which is secreted by the liver and transports intermediate density lipoproteins (IDL) and LDL (Klop et al. 2012). Chylomicrons and VLDL change form during lipolysis to produce chylomicron remnants and dense LDL, respectively. Chylomicron remnants are uptaken again by the liver and LDL is primarily uptaken by the liver via the LDL receptor. The LDL receptor is regulated by the proprotein convertase subtilisin/kexin type 9 (PCSK9). When PCSK9 is bound to the LDL receptor, then the LDL receptor is destroyed due to degradation. In contrast, when PCSK9 is absent LDL receptor is recycled back to the surface of the hepatocytes (Lambert et al. 2012).

The small intestine plays a role for the cholesterol uptake and delivery in the circulation. Intestinal apolipoprotein A-1 acceptor molecule (ABC1A1), which is synthesized from enterocytes and hepatocytes, seems to be responsible for the intestinal cholesterol mobilization and HDL formation and constitutes the main form of HDL. HDL promotes the uptake of cholesterol from peripheral tissues and returns cholesterol to the liver. The cholesterol within HDL is changed into cholesterol-esters by HDL-associated lecithin-cholesterol acyltransferase (LCAT), while cholesterylester transfer protein (CETP) and phospholipid transfer protein (PLTP) are responsible for the same procedure for the HDL particles in the circulation. At this stage, HDL requires TG from TG-rich lipoproteins in exchange for cholesterol-esters as a direct consequence of the CETP action. In the liver, hepatic lipase hydrolyses HDL-associated TG and also phospholipids induce the formation of smaller HDL particles, which can contribute again to the reverse cholesterol transport (Klop et al. 2012).

## Obesity and Lipoproteins

Obesity is the result of excessive energy intake and low energy expenditure. Adipose tissue is now recognized as an important secretory organ releasing into the circulation many peptides that affect metabolism. Increased adipose tissue mass increase FFA into the circulation. FFA release from adipose tissue is suppressed by insulin in both lean and obese individuals, but in obesity the process is insulin resistant. FFA release per unit fat mass is less in subjects with obesity than in those who are lean. However, because of the increased fat mass, total FFA delivery to the circulation is increased in obesity. Despite high plasma insulin concentrations in response to a standard meal, obese subjects fail to suppress FFA release from adipose tissue. Increased availability of fatty acids will decrease glucose utilization in muscle and stimulate hepatic glucose production. Elevated FFA also increases pancreatic β-cell accumulation of lipids which may be a part of the link between obesity, insulin resistance, and development of type 2 diabetes. Adipose tissue is an important site for the disposal of dietary triacylglycerol in the postprandial period. Obesity is typically characterized by increased postprandial lipemia, reflecting at least in part prolonged circulation of dietary fatty acids. These fatty acids will be removed by several tissues, including skeletal muscle, pancreas, and liver instead of adipose tissue. In obesity, adipose tissue overloaded with TAG has reduced buffering capacity for lipid storage in adipocytes. Fat cells fail in their normal role to protect other tissues from the daily influx of dietary fatty acids (Frayn 2001; Pan et al. 1997; Byrne et al. 1991). Lipolysis of TG-rich lipoproteins is impaired in obesity by reduced mRNA expression levels of LPL in adipose tissue (Clemente-Postigo et al. 2011), reductions in LPL activity in skeletal muscle, and competition for lipolysis between VLDL and chylomicrons. The increased synthesis of VLDL in the liver can inhibit lipolysis of chylomicrons, which promotes hypertriglyceridemia (Klop et al. 2012).

The free VLDL particles undergo enzymatic exchanges with other lipoprotein particles such as HDL and LDL, via cholesterylester transfer protein (CETP). Once these TG-rich lipoprotein particles are exposed to various lipases, then the HDL particles become smaller and undergo metabolism and excretion by the kidney, resulting in decreased HDL levels. In the presence of hypertriglyceridemia, the cholesterol-ester content of LDL decreases, whereas the TG content of LDL increases by the activity of CETP. The increased TG content within the LDL is hydrolyzed by hepatic lipase, which leads to the formation of small, dense LDL particles. Small dense LDL are relatively slowly metabolized with a 5-day circulating time, which promotes its atherogenicity. The VLDL particles undergo also lipolysis, resulting in VLDL remnants and consequently formation of small, dense LDL particles (Klop et al. 2013). Lipoprotein obesity-induced dyslipidemia mechanisms are shown in Fig. 2.

Inflammation has a special role in obesity-induced dyslipidemia. Macrophage, TNF-α, IL-6, IL-1, and serum amyloid A (SAA) may promote dyslipidemia (Gutierrez et al. 2009). The presence of macrophages in adipose tissue increases in obesity. Obese people have higher macrophage infiltration into adipose tissue compared to thin people, and this is correlated with higher TGs and lower HDL

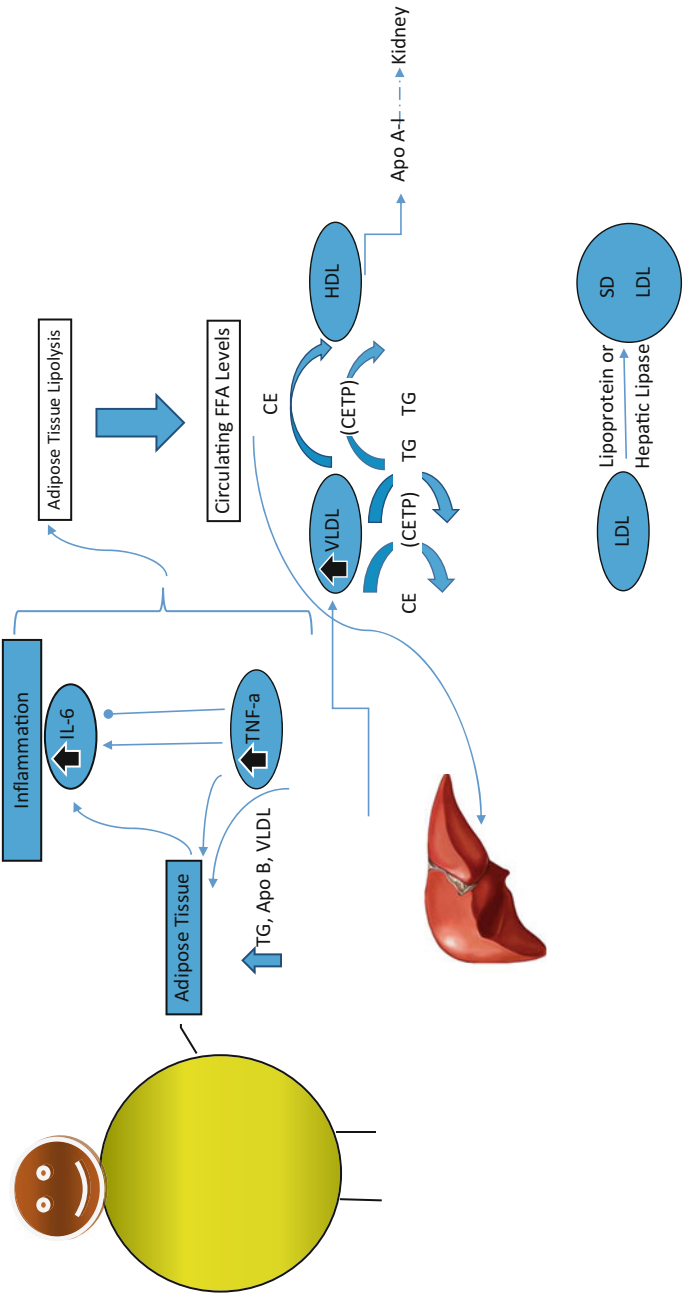


**Fig. 2** Obesity and lipoprotein metabolism

(Huber et al. 2008). A macrophage-specific marker (*CD68*), most found in subcutaneous adipose tissue, is also positively correlated with plasma-free fatty acid as well as LDL and negatively correlated with HDL levels (Huber et al. 2008). TNF-α was found positively correlated with hypertriglyceridemia and VLDL not only in animals but also in humans (Mohrschladt et al. 2000). After increasing TNF-α levels in the circulation of hamsters TG-rich particles increased, while increased serine phosphorylation of insulin receptor substrate-1 and elevated apo B48 production may further increase plasma TGs and exacerbate dyslipidemia (Qin et al. 2008). IL-6 is also associated with hypertriglyceridemia and negatively with serum HDL-cholesterol levels (Jonkers et al. 2002). The administration of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1, also reduces expression of Apo A1 in hepatic cells and plasma. Apo A1 is responsible for HDL structure and low concentrations of apoA1 are independent predictors for the presence and severity of cardiovascular disease (Hardardottir et al. 1994). IL-10 has different actions; increased IL-10 levels are associated with increased plasma triglyceride levels, but decreased total cholesterol and LDL levels (van Exel et al. 2002). SAA an acute-phase protein that is produced in the liver, in adipose tissue, intestinal epithelial cells, and macrophages is an apolipoprotein that can replace apolipoprotein A1 (apoA1) as the major HDL apolipoprotein and found increased in subcutaneous white adipose tissue of obese patients. The role of SAA protein in regulating gene expression related to lipid metabolism shows increased inflammatory cytokine gene expression (IL-6 and TNF-a) and glycerol release indicating increased lipolysis by decreasing the expression of perilipin, a lipid droplet–protective protein, which would then allow an increase in hormone-sensitive lipase activity (O'Brien and Chait 2006; Poitou et al. 2005; Chen et al. 2008).

Adiponectin has the opposite effect on dyslipidemia compared to TNF-a, IL6, and IL-1, and its increase is correlated with increased HDL levels and decreased triglycerides and LDL levels. Adiponectin acts directly to lipoprotein lipase, enhancing VLDL clearance and reducing plasma triglyceride levels. Adiponectin activates 5triphosphate-activated protein kinase (AMPK) in the liver, an action that marks the beginning of a sequence of reactions. AMPK inhibits acetyl coenzyme A carboxylase (ACC), and this coenzyme decreases the concentration of malonyl CoA, which is finally responsible for the increase of free fatty acids (Yamauchi et al. 2002). Moreover, its action is based on mRNA expression and secretion of apo A1, suggesting that adiponectin might increase HDL in the liver (Oku et al. 2007).

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# Obesity and Obstructive Sleep Apnea Syndrome

12

Ian W. Seetho and John P. H. Wilding

## Contents



**Abstract**

Obstructive sleep apnea (OSA) is a common condition that forms part of the spectrum of sleep disordered breathing (SDB). It may affect between 6 and 17% of all adults, but the risk rises with increasing body weight and it is very common in people with obesity. OSA causes symptoms of daytime sleepiness which can be disabling for patients, and this is currently the main criterion used to determine if treatment should be offered. Although obesity itself is associated with hypertension, hyperlipidaemia and dysglycaemia, emerging evidence shows that those

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with sleep apnoea are more likely to have all of these abnormalities at any given weight, and subsequently have a higher risk of developing cardiovascular disease. OSA is particularly common in people with type 2 diabetes, affecting at least a quarter of patients, and is associated with a higher risk of developing microvascular complications such as retinopathy. The main treatment used for OSA is continuous positive airway pressure ventilation (CPAP), and this has been shown to reduce daytime sleepiness and lower blood pressure, but no prospective randomised controlled trials have shown reduction in CV risk or improvement in diabetes. Weight loss is also an effective treatment, and some patients can stop CPAP treatment after bariatric surgery.

**Keywords**
Sleep Apnea · Obesity · Sleep disordered breathing · Type 2 diabetes · Cardiovascular disease

**Abbreviations**

| | |
|---|---|
| AHI | Apnea-hypopnea index |
| BMI | Body mass index |
| CPAP | Continuous positive airway pressure |
| HDL | High-density lipoprotein |
| LDL | Low-density lipoprotein |
| OSA | Obstructive sleep apnea |
| SDB | Sleep-disordered breathing |

## Introduction

Sleep-disordered breathing (SDB) is characterized by a spectrum of altered sleep homeostasis that ranges from simple snoring to obstructive sleep apnea with excessive daytime somnolence. SDB is associated with hypertension, cardiovascular disease, type 2 diabetes, and metabolic impairment (Nieto et al. 2009). There is also evidence linking disrupted sleep patterns to other adverse health consequences such as neurocognitive deficits, impaired quality of life, and an increased risk of accidents (Beebe et al. 2003). While there are different forms of SDB, the majority of research studies have focused on OSA and its complications and the potential interactions with obesity, diabetes, metabolic syndrome, and its components.

In England, there was a marked rise in the proportion of adults with obesity between 1993 and 2013 from 13.2% to 26% among males and from 16.4% to 23.8% among females (Health and Social Care Information Centre 2015). By 2050, 60% of males and 50% of females will be obese if current trends continue, with NHS costs attributable to obesity expected to double to £10 billion and wider costs to society estimated to reach £49.9 billion per year (Foresight 2007).

Obesity is defined as an excess accumulation of body fat and is classified according to the body mass index (BMI), that is, calculated as weight(kg)/ height $(m)^2$. According to the World Health Organization classification, adults with a body

mass index (BMI) of 25 to 30 kg/m$^2$ are classed as "overweight," and those with a BMI of 30 kg/m$^2$ or more may be referred to as having obesity. Those with a BMI with a body mass index (BMI) of 40 kg/m$^2$ or more may be referred to as having severe (previously termed "morbid") obesity. It should be noted that the threshold values may differ among populations (WHO Expert Consultation 2004), with Asian populations in particular having lower BMI cutoffs. It is recognized that the regional distribution of body fat, such as abdominal and visceral adiposity, may also be important in determining metabolic and cardiovascular health risks in obesity (Tchernof and Despres 2013).

## Obstructive Sleep Apnea

OSA is a common condition with prevalence in the adult population ranging from 6% to 17% and may be as high as 49% in older persons (AHI > 15 events per hour of sleep) (Senaratna et al. 2017).

The major risk factors of OSA are obesity, gender, and increasing age (Malhotra and White 2002). Cross-sectional estimates that up to 40% of patients with OSA will also have type 2 diabetes (Meslier et al. 2003), and the prevalence of OSA may be up to 23% in patients who are known to have type 2 diabetes (West et al. 2006). Prevalence estimates of OSA in severe obesity have been reported to be between 40% and 90% (Schwartz et al. 2008).

In OSA, repeated apneas or hypopneas occur during sleep with subsequent daytime hypersomnolence (Young et al. 1993). These episodes are characterized by recurrent episodes of upper airway obstruction and changes in intrathoracic pressure that result in recurrent periodic oxygen desaturations, with frequent sleep arousals and fragmented sleep (Young et al. 1993; Tasali and Ip 2008). An apnea is defined as the complete cessation of airflow for at least 10 seconds. A hypopnea is defined as a reduction in airflow that is followed by an arousal from sleep or a decrease in oxyhemoglobin saturation (Punjabi 2008) (Table 1).

The presence of OSA may be assessed by formal polysomnography studies with the number of apneas and hypopneas per hour during sleep, termed the apnea-

**Table 1** Clinical features of OSA

| |
|---|
| Excessive somnolence |
| Loud snoring |
| Concerned partner who has witnessed apneic episodes |
| Choking symptoms while waking up |
| Loss of concentration |
| Unrefreshed sleep |
| Other symptoms that may be reported |
| Nocturia |
| Reduced libido |
| Nocturnal sweating |

**Table 2** AHI for diagnosis and classification of OSA (Flemons et al. 1999)

| Diagnosis | Events per hour |
|---|---|
| Normal | <5 |
| Mild OSA | 5–15 |
| Moderate OSA | 15–30 |
| Severe OSA | >30 |

*AHI* apnea-hypopnea index, *OSA* obstructive sleep apnea

hypopnea index (AHI) classifying the severity of OSA. The AHI measures the frequency of reduction in airflow associated with collapse or narrowing of the airways (Caples et al. 2005). This index classifies the severity of OSA based on the number of obstructive breathing episodes per hour during sleep; mild AHI, 5 to 15 events per hour; moderate OSA, 15 to 30 events per hour; and severe OSA >30 events per hour (Flemons et al. 1999) (Table 2).

Besides the AHI, the frequency of oxygen desaturation episodes and severity of somnolence symptoms are also used (Flemons et al. 2003). Although the diagnosis of OSA can be made when the AHI is >5 events/h. in a patient with excessive daytime sleepiness, it is also important to distinguish the severity of daytime somnolence symptoms as patients with mild OSA (AHI 5–15 events/h) may not always require treatment if there are no sleepiness symptoms with only minor impairment of daily functioning. Patients with moderate and severe OSA (AHI > 15 events/h) who have a history of daytime sleepiness with impaired social and occupational function should be offered treatment (National Institute for Health and Care Excellence 2008; Parati et al. 2013).

## Associations and Complications of OSA

OSA is associated with a clustering of clinical cardio-metabolic manifestations. There is evidence linking OSA to the metabolic syndrome that comprises obesity, insulin resistance, hypertension, and dyslipidemia (Coughlin et al. 2004). It is also well documented that OSA affects cardiovascular risk. In the Wisconsin Sleep Cohort Study and the Sleep Heart Health Study, it was found that there was a relationship between OSA and hypertension (Nieto et al. 2000; Young et al. 1997). People with OSA have an increased risk of developing atherosclerosis (Kylintireas et al. 2012), with increased arterial stiffness (Doonan et al. 2011), leading to coronary artery disease (Peker et al. 2006), cerebrovascular disease (Yaggi et al. 2005), cardiac arrhythmias (Hoffstein and Mateika 1994; Mehra et al. 2006), and heart failure (Gottlieb et al. 2010). OSA poses important perioperative risks for obese individuals who are particularly vulnerable during anesthesia and sedation and are at an increased risk of developing postoperative respiratory and cardiopulmonary complications (Chung and Elsaid 2009; Liao et al. 2009).

The reduction in time spent sleeping that is typical of OSA may have profound effects on glucose regulation, insulin resistance, appetite, and energy balance (Knutson et al. 2007). OSA may induce fatigue and with increasing daytime

somnolence, contributing to reduced physical activity and a decrease in energy expenditure that may contribute to weight gain, insulin resistance, and further worsening of OSA.

Understanding the potential influence of OSA on the components of the metabolic syndrome and the mechanisms by which such interactions may contribute to metabolic dysregulation is important because such knowledge may define appropriate targets and lead to more precisely administered preventive actions in addressing health outcomes such as cardiovascular disease, obesity, and type 2 diabetes.

## Compromised Metabolism

### OSA, Insulin Resistance, and Type 2 Diabetes

OSA severity is correlated with the degree of perturbation in glucose homeostasis, an effect that is independent of obesity (Tasali et al. 2008; Shaw et al. 2008). The prevalence of OSA in type 2 diabetes has been reported with different rates in several population-based studies that are not directly comparable due to differences in populations studied and how OSA was assessed. This has been found to range from 18% of patients in primary care based on an assessment of electronic records (Heffner et al. 2012) and 23% in a mixed primary and secondary care population of patients with type 2 diabetes who had overnight oximetry testing (West et al. 2006) to as high as 86% in the Sleep AHEAD (Action for Health in Diabetes) Study cohort comprising obese subjects with type 2 diabetes who were investigated with polysomnography (Foster et al. 2009).

There is substantial evidence for the association between OSA, insulin resistance, and type 2 diabetes. OSA is independently associated with alterations in glucose metabolism and an increased risk of type 2 diabetes (Tasali et al. 2008; Shaw et al. 2008). Sleep-disordered breathing as assessed by AHI was observed to be independently correlated with insulin resistance; this association was seen in both obese and nonobese subjects (Ip et al. 2002). Punjabi et al. (2002) found that sleep-disordered breathing, based on the AHI, was associated with glucose intolerance and insulin resistance in mildly obese men without diabetes or cardiopulmonary disease and that increasing AHI was associated with worsening insulin resistance independent of obesity (Punjabi et al. 2002). The Sleep Heart Health Study showed that OSA was associated with impaired glucose tolerance and insulin resistance (Punjabi et al. 2004), and in the Wisconsin Sleep Study cohort, there was an association between OSA and type 2 diabetes (Reichmuth et al. 2005). Botros et al. (2009) found that OSA increased the risk of type 2 diabetes in a cohort of 544 patients referred for evaluation of SDB after adjusting for age, gender, ethnicity, blood glucose, body mass index, and weight change (Botros et al. 2009). Tamura et al. (2012) observed that OSA-induced hypoxia was associated with increases in glycated hemoglobin regardless of glucose tolerance status (Tamura et al. 2012). In a longitudinal study, men without diabetes were followed up for a mean of 11 years, and it was demonstrated that OSA was independently related to the development of insulin resistance

(Lindberg et al. 2012). In a cross-sectional analysis in the European Sleep Apnoea Cohort (ESADA) Study, the prevalence of type 2 diabetes and poorer glycemic control was observed to be associated with increasing severity of OSA assessed by the ODI (Kent et al. 2014). Another study that retrospectively analyzed health data in a cohort of people with OSA found that the initial severity of OSA was associated with subsequent risk of developing type 2 diabetes (Kendzerska et al. 2014). It should be noted that these studies have been based on observational data that can only suggest an association and not causality. Vgontzas et al. (2000) evaluated obese males with symptomatic sleep apnea with age- and BMI-matched controls and found mean fasting blood glucose and insulin levels were higher in OSA than in obese controls suggesting that sleep-disordered breathing is an independent risk factor for hyperinsulinemia (Vgontzas et al. 2000). Conversely, two studies did not find an independent association between OSA and insulin resistance (Onat et al. 2007; Gruber et al. 2006). In summary, despite mixed findings in relation to the link between OSA and insulin resistance, there is nevertheless evidence that suggests a role for increased insulin resistance as a potential intermediary mechanism that may influence cardio-metabolic risk.

Several potential mechanisms could explain the pathophysiological links between OSA and impaired glucose metabolism (Fig. 1). These mechanisms are interacting and potentially synergistic, and therefore all pathways shown in Fig. 1 are equally important. These include intermittent hypoxia and sleep fragmentation that may alter sympathetic activity (Somers et al. 1995), effects on endocrine (Meston et al. 2003) and hypothalamic-pituitary-adrenal axes (Vgontzas et al. 2007), oxidative stress and inflammatory responses (Lavie 2009), and changes in adipokines that may alter glucose metabolism (Drager et al. 2010c; Punjabi and Polotsky 2005).

## OSA and Metabolic Syndrome

One of the major implications of the global rise in obesity has been an associated rise in the prevalence of the metabolic syndrome (Zimmet et al. 2001). The metabolic syndrome, also known as the insulin resistance syndrome, or "syndrome X" (Reaven 1988) has been variably defined based on clustering of abnormalities of factors including insulin resistance, dyslipidemia (low HDL cholesterol and raised triglycerides), hyperglycemia, and blood pressure (Eckel et al. 2005), with the most recent definition of the syndrome requiring central adiposity as a key feature (Alberti et al. 2009).

There is also evidence that OSA is associated with the metabolic syndrome, independently of adiposity (Coughlin et al. 2004; Nieto et al. 2009). The term "syndrome Z" reflects the close interaction between OSA and cardiovascular disease risk (Wilcox et al. 1998). In a study of 529 newly diagnosed OSA patients who had polysomnography, metabolic syndrome based on the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III definition occurred in about half of the patients; prevalence rates of metabolic syndrome in OSA have previously been reported to be between 23% and 87% using this definition (Bonsignore et al. 2012a).

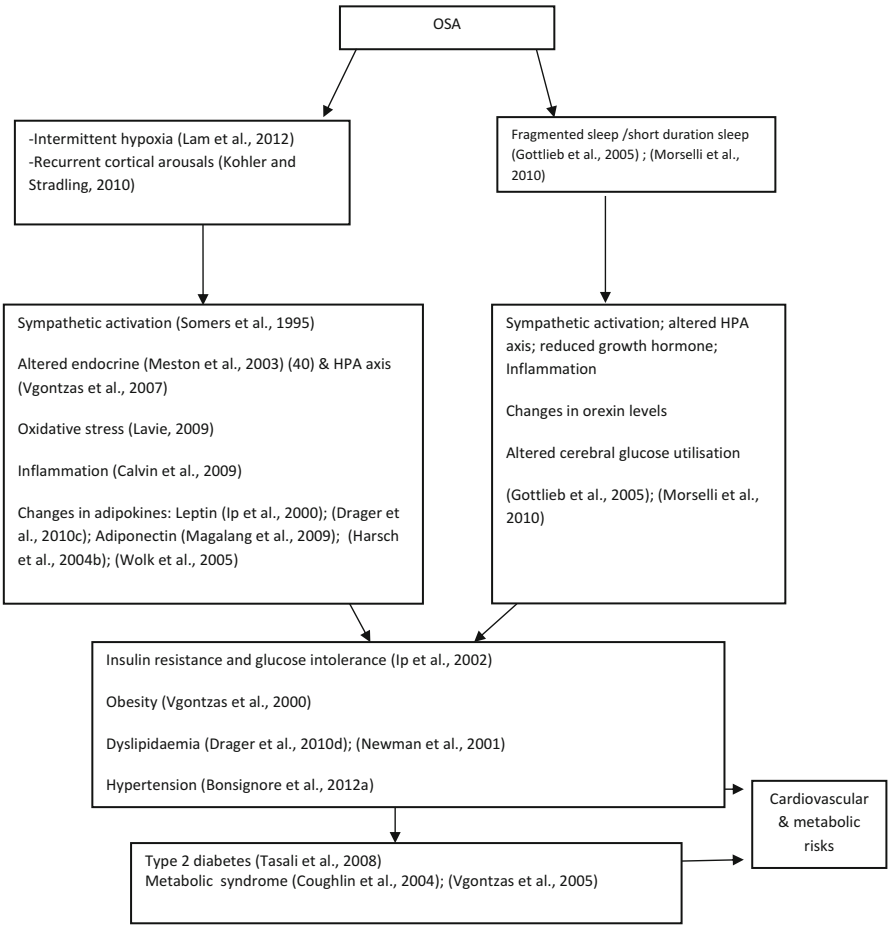


**Fig. 1** Interacting pathophysiological pathways in OSA and impaired metabolism including type 2 diabetes and metabolic syndrome. These pathways are interacting and potentially synergistic, and therefore all the mechanisms shown are equally important. Selected references are in parentheses

The association between OSA and the metabolic syndrome may influence cardiometabolic dysregulation (Lam et al. 2012). OSA patients are more likely to have abnormalities in components characterizing the metabolic syndrome, and conversely, there may be a higher prevalence of OSA in patients with metabolic syndrome (Basoglu et al. 2011).

Many studies have demonstrated relationships between OSA and metabolic syndrome. In patients well matched for total adiposity, it was found that OSA was independently associated with metabolic syndrome components including increased blood pressure, higher fasting insulin, and dyslipidemia and increased insulin resistance (higher HOMA values) (Coughlin et al. 2004). In another study, this association was found to be independent of obesity mainly from increased

triglyceride and glucose but not insulin resistance (Gruber et al. 2006). In a study of patients with OSA from China, there was a fivefold risk of having metabolic syndrome that was associated with waist circumference, diastolic blood pressure, and fasting glucose (Lam et al. 2006). Such effects may be independent of obesity: the severity of OSA as measured by the AHI was found to be a strong predictor of metabolic syndrome parameters that included hypertension, dyslipidemia, and hyperglycemia (Kono et al. 2007). Another study demonstrated that nonobese OSA subjects had metabolic abnormalities associated with dyslipidemia and hypertension (Lin et al. 2012). Thus, the coexistence of metabolic syndrome and OSA may have detrimental effects on cardiovascular risk and glycemia. The extent to which OSA has direct effects on components of the metabolic syndrome was found to be dependent on the severity of OSA (Kono et al. 2007) and was correlated with insulin resistance and inflammatory markers (Peled et al. 2007). It is conceivable that OSA itself may represent a complex marker of adverse metabolic and cardiovascular factors. OSA may simply be a marker for upper body obesity, as most of the studies did not measure this directly; however those studies that controlled for total body fat and fat distribution, for example, using bioimpedance (Coughlin et al. 2004), computed tomography (Kono et al. 2007), or waist-hip ratio (Basoglu et al. 2011), still show a striking excess of metabolic syndrome in OSA patients. It seems unlikely that small residual differences in body composition explain the entire clinical picture; furthermore there are a number of plausible biological mechanisms that link OSA itself to components of the metabolic syndrome.

### Obesity

In OSA, many factors may contribute to the effects on metabolism. People with OSA had greater visceral adiposity compared with BMI-matched obese controls, and there was a strong association between visceral obesity and OSA (Vgontzas et al. 2000). Intra-abdominal and visceral adiposity has been closely associated with insulin resistance with increased lipolysis and fatty acid availability (Bjorntorp 1991), as well as dyslipidemia, hypertension, and hyperglycemia (Kono et al. 2007).

OSA may perpetuate the cycle of obesity by inducing fatigue and tiredness; the symptoms of somnolence from sleep fragmentation might have the effect of discouraging physical activity in these patients. Conversely, obesity is associated with mechanical effects that may predispose to upper airway obstruction and OSA. The factors causing upper airway obstruction in obesity are only partly understood (Schwartz et al. 2008). Suggested mechanisms include increased collapsibility of pharyngeal structures during air movements, altered chest wall dynamics, and respiratory muscle compliance and function (Schwartz et al. 2008). The adiposity in the neck leads to increased neck circumference, with pharyngeal airway narrowing and enlargement of tissue in the upper airways such as the lateral pharyngeal wall and posterior tongue. Lung volumes are also reduced due to the effects of central obesity in recumbency that may decrease

tracheal traction forces and pharyngeal wall tension (Isono 2012). Upper airway collapsibility is increased, and lung volumes may be decreased (Schwartz et al. 2008). Other reported mechanisms include neuromechanical changes such as adipokines and inflammatory cytokines that may modulate upper airway patency (Punjabi 2008) and ventilatory stability (Fogel et al. 2004; Schwartz et al. 2008).

## OSA and Cardiovascular Disease

With disruption of the normal sleep architecture, the association of OSA with metabolic syndrome, obesity, and type 2 diabetes may increase the risk of cardiovascular disease. Indeed there is evidence suggesting that OSA may contribute or potentially exacerbate cardiovascular disease (Peker et al. 2006; Marin et al. 2005). Studies have shown an association between OSA with hypertension, coronary disease, stroke, atrial fibrillation, and heart failure (Monahan and Redline 2011). Potential mechanisms include the effects of intermittent hypoxia, recurrent arousals, and intrathoracic pressure changes, leading to sympathetic activation, inflammation, and oxidative stress that may increase the risk of hypertension (Kohler and Stradling 2010). Impaired cardiac contractility and negative intrathoracic pressure may increase left ventricular afterload, decrease preload, and stroke volume (Bradley and Floras 2009). Additionally, OSA is also linked with atherosclerosis (Drager et al. 2010a). Therefore, OSA may have potentially serious consequences if discovered later on in the course of the disease. Several studies have suggested that continuous positive airway pressure (CPAP) treatment can attenuate the cardiovascular effects of OSA although large-scale randomized controlled trials are still needed (Bradley and Floras 2009). Furthermore, long-term adverse cardiovascular events are lower in patients with severe OSA who are treated with CPAP (Marin et al. 2012).

### Hypertension

It is known that OSA has an adverse effect on blood pressure and OSA patients have an increased risk of hypertension, independent of obesity and age (Peppard et al. 2000b; Lavie et al. 2000). Furthermore, untreated patients with proven OSA have been found to have an increased risk of hypertension (Marin et al. 2012). This may be attributable to increased sympathetic activity, with chemoreflex activation, oxidative stress, systemic inflammation, and endothelial dysfunction from repeated arousals and intermittent hypoxia (Kapa et al. 2008; Pedrosa et al. 2011). There may be a role for vasoactive hormones such as renin-angiotensin-aldosterone system activation in OSA-related hypertension with evidence of increased angiotensin II and aldosterone levels in OSA although this remains to be clarified (Moller et al. 2003; Pedrosa et al. 2011). Additionally, the effects of reduced slow wave sleep on vascular function in OSA may affect cardiorespiratory function by increasing sympathetic activation and pressor responses (Monahan and Redline 2011). There is evidence that suggests that CPAP treatment may have BP-lowering effects in

patients with severe OSA by reducing renin-angiotensin system activity (Fava et al. 2014; Nicholl et al. 2014).

### Dyslipidemia

In patients with metabolic syndrome, it was observed that patients with OSA had higher triglycerides, cholesterol, LDL, and cholesterol/HDL and triglycerides/HDL ratios; furthermore OSA severity (AHI) was independently associated with increased triglycerides and cholesterol/HDL ratio (Drager et al. 2010d). In the Sleep Heart Health Study, alterations in lipid profiles were found in relation to the respiratory disturbance index (RDI) in different subject groups. For example, high-density lipoprotein (HDL) cholesterol levels were inversely related to the RDI in women and in men less than age 65 years; triglyceride levels were associated with the level of RDI only in younger men and women. Total cholesterol level did not vary across quartiles of RDI, although there was a trend toward higher cholesterol in those with higher RDI in the men less than age 65 years (Newman et al. 2001). Another study of OSA patients observed a significant association between the AHI and HDL cholesterol that was independent of age, gender, BMI, diabetes, and lipid-lowering medication; at 6 months, there were improvements in lipid levels with CPAP therapy (Borgel et al. 2006).

The link between severity of OSA and lipid metabolism is not fully understood and may involve activation of the inflammatory cascade (Alam et al. 2007) and intermittent hypoxia (Drager et al. 2010b). Several murine studies have provided evidence for potential mechanisms. Chronic intermittent hypoxia may induce dyslipidemia through increased triglyceride and phospholipid synthesis (Li et al. 2005b), and may lead to upregulation of expression of pathways involved in lipid synthesis (Li et al. 2005a). Impaired clearance of triglyceride-rich lipoproteins and inactivation of lipoprotein lipase and upregulation of lipoprotein lipase inhibition may contribute to hyperlipidemia fasting levels of plasma triglycerides and very low-density lipoprotein cholesterol (Drager et al. 2012, 2013). With animal models of intermittent hypoxia, there may be more control over variables such as diet, genotypes, oxygen profile, obesity, and sleep fragmentation (Jun and Polotsky 2009). The protocols may however vary in frequency, intermittent hypoxia cycle length, and severity of the hypoxic stimulus (Drager et al. 2010c). Levels of intermittent hypoxia may be more severe than that seen in OSA. Furthermore, intermittent hypoxia causes hypoxemia with hyperventilation and hypocapnia rather than hypercapnia that occurs with airway obstruction (Jun and Polotsky 2009). These factors may potentially affect gene expression and may limit generalizability of these findings.

Animal studies of intermittent hypoxia have demonstrated glucose intolerance and insulin resistance in lean mice with acute intermittent hypoxia (Iiyori et al. 2007) and in obese mice exposed to chronic intermittent hypoxia for 12 weeks (Polotsky et al. 2003). Human volunteers exposed to acute sustained hypoxia for 30 min (Oltmanns et al. 2004) and acute intermittent hypoxia simulating moderate OSA for 5 h (Louis and Punjabi 2009) also demonstrated impaired glucose tolerance.

### Autonomic Function

Several studies have found autonomic abnormalities in OSA that are attenuated with continuous positive airway pressure (CPAP) therapy (Somers et al. 1995; Imadojemu et al. 2007). During sleep in OSA, intermittent hypoxia and recurrent arousals stimulate sympathetic responses by mechanisms that include chemoreflex and baroreflex changes, vasoconstrictor effects of nocturnal endothelin release, and endothelial dysfunction (Narkiewicz and Somers 2003; Kohler and Stradling 2010). Sympathetic activation increases hepatic glycogenolysis and gluconeogenesis (Punjabi and Polotsky 2005). The stimulation of lipolysis increases circulating free fatty acid metabolites that inhibit insulin signaling and reduce insulin-mediated glucose uptake, contributing to insulin resistance (Delarue and Magnan 2007).

### Hypothalamic-Pituitary-Adrenal Axis

Activation of the HPA axis may provide a further mechanistic link between OSA and diabetes. There is evidence for potential OSA effects on the HPA axis as several studies have reported enhanced cortisol secretion in OSA (Lanfranco et al. 2010). Increased cortisol levels may contribute to hyperglycemia by reducing insulin secretion and glycogen synthesis and increasing gluconeogenesis (Rosmond 2003). It should be noted that an increased cortisol secretion in OSA has not been consistently reported in the literature (Lanfranco et al. 2010). For example, Dadoun et al. (2007) found no association in cortisol profiles and OSA in obese men (Dadoun et al. 2007). This may reflect an interaction between OSA and the HPA axis that may involve different mechanisms. Alterations in HPA axis activity may potentially be induced by intermittent hypoxia or by altered neural control of corticotroph function (Drager et al. 2010c; Lanfranco et al. 2010). Obese patients with OSA were found to have an increased adrenocorticotrophic hormone (ACTH) response to corticotrophin-releasing hormone (CRH) compared with obese controls (Lanfranco et al. 2004). Additionally, sleep deprivation has been associated with increased HPA axis activity that can potentially affect insulin resistance and may also predispose to obesity and metabolic syndrome (Spiegel et al. 1999; Buckley and Schatzberg 2005).

Several studies have examined the effects of OSA treatment on the HPA axis. The results have been mixed in terms of effects of CPAP treatment on cortisol production. Meston et al. (2003) found no relation between cortisol and OSA severity and no measurable response to nasal CPAP treatment (Meston et al. 2003). Vgontzas et al. (2007) demonstrated that OSA in obese men is associated with increased nocturnal cortisol levels, compared with controls, that were corrected after the use of CPAP for 3 months (Vgontzas et al. 2007). Consistent with this, another study found that 3 months of CPAP therapy decreased evening salivary cortisol concentrations in severe OSA patients (Schmoller et al. 2009).

### Oxidative Stress and Activation of Inflammatory Pathways

Repeated episodes of intermittent hypoxia and reoxygenation in OSA may cause oxidative stress with increased production of reactive oxygen species that may

contribute to altered glucose homeostasis. The formation of reactive oxygen species may impair pancreatic beta cell function and insulin secretion (Punjabi and Polotsky 2005). This may be due to increased pancreatic beta cell proliferation and apoptosis with mitochondrial oxidative stress (Xu et al. 2009). Hypoxia-inducible factor-1 is upregulated in many tissues during hypoxia and modulates the expression of proteins that mediate adaptive responses to hypoxia some of which may influence glucose metabolism (Lavie 2003, 2009; Punjabi and Polotsky 2005).

Additionally, reactive oxygen species formation may have an important role in activating inflammatory responses and have been implicated in the upregulation of transcription factors nuclear factor-κB (NF-κB), and activator protein 1 with increased expression of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-8 (Calvin et al. 2009). TNF-α and IL-6 are increased in patients with OSA (Vgontzas et al. 2000), and there is evidence that these cytokines may have a role in insulin resistance (Alam et al. 2007). Expression of TNF-α and plasma IL-6 is higher in subjects with insulin resistance (Kern et al. 2001). TNF-α may downregulate genes required for normal insulin action and the peroxisome proliferator-activated receptor-γ (an insulin-sensitizing nuclear receptor) and may have direct effects on insulin signaling and induction of elevated free fatty acids via stimulation of lipolysis (Moller 2000). IL-6 levels have been found to be correlated with insulin resistance in adipose tissue (Bastard et al. 2002).

### Changes in Adipokine Profiles

There is evidence that OSA may be associated with altered adipokine levels. The adipokines leptin and adiponectin are hormones produced mainly by adipocytes that have a range of effects on physiological processes. The main function of leptin is its role in regulation of appetite and energy regulation, but it also influences glucose regulation (Ceddia et al. 2002). Adiponectin has roles in fat distribution, inflammation, and insulin sensitivity (Trujillo and Scherer 2005). It acts as an insulin-sensitizing hormone, and low levels are found in type 2 diabetes (Harsch et al. 2004b). One study found elevated serum leptin levels in OSA that are reduced following CPAP treatment (Ip et al. 2000), consistent with the observation that intermittent hypoxia increases leptin expression and inhibits insulin secretion (Drager et al. 2010c). However other studies on leptin levels and OSA have shown no effect independent of adiposity (Lui and Ip 2010). Insulin resistance is associated with low levels of adiponectin (Magalang et al. 2009), although the mechanism remains unclear; intermittent hypoxia has been proposed as a putative mechanism so adiponectin concentrations have been studied in OSA, with equivocal findings (Harsch et al. 2004b; Wolk et al. 2005).

### Sleep Duration/Fragmented Sleep

Shortened sleep duration from fragmented sleep may be associated with altered glucose regulation and insulin resistance (Morselli et al. 2010; Spiegel et al. 2009). Short sleep duration is associated impaired glucose regulation and an increased prevalence of diabetes (Gottlieb et al. 2005). Potential mechanisms underlying this

effect may include sympathetic activity which may impair glucose regulation via lipolysis, alterations in the hypothalamic-pituitary-adrenal axis, reduced growth hormone secretion, appetite changes, and inflammatory responses that may influence glucose and insulin homeostasis. Other mechanisms include upregulation of orexin neurons and altered cerebral glucose metabolism (Gottlieb et al. 2005; Morselli et al. 2010).

### Diabetes Complications

A number of studies have shown that OSA may be associated with increased risk of the complications of diabetes, independently of glucose control. These studies were not randomized controlled trials and were based on observational findings at a point in time from the populations examined. It may be possible that control group comparisons were difficult given the nature of the complications necessitating treatment. West et al. (2010) showed that in men with type 2 diabetes, the presence of OSA is associated with diabetic retinopathy (West et al. 2010). Mason et al. (2012) found a high prevalence of SDB in patients with type 2 diabetes and diabetic macular edema, although no relationship was observed between the severity of SDB as defined by ODI and macular edema (Mason et al. 2012). Proposed mechanisms that may influence retinal damage include increases in blood pressure and sympathetic activation, oxygen desaturation causing retinal hypoxia with production of vascular growth factors, and autonomic dysregulation (Mason et al. 2012). Tahrani et al. (2012) reported an association between OSA and peripheral neuropathy in patients with type 2 diabetes and proposed increased oxidative stress and microvascular changes as potential mechanisms (Tahrani et al. 2012).

In relation to diabetes nephropathy, a prospective study to evaluate the OSA and microalbuminuria found no correlation between urinary albumin excretion and OSA in a cohort with type 2 diabetes although this may have been due to the small study sample size (Buyukaydin et al. 2012). In another study of Japanese subjects, nocturnal intermittent hypoxia was found to be associated with microalbuminuria in females with type 2 diabetes (Furukawa et al. 2013).

In summary, there is evidence to suggest that OSA may be associated with an increased risk of complications in people with diabetes. The evidence has so far been from observational studies; randomized controlled trials (e.g., of CPAP) to show a reduction in complications would have to be long term and difficult to conduct because it would be unethical to withhold treatment from symptomatic patients with OSA.

## Possible Treatments

### Treatment of OSA

The different modalities for the treatment of OSA are presented in the table below (Table 3).

**Table 3** Different modalities for treating OSA

| |
|---|
| CPAP |
| Weight loss (lifestyle and bariatric surgery interventions) |
| Oral devices |
| Surgery (upper airway) |
| Possible others (pharmacotherapy; positional therapy; novel methods such as upper airway muscle training and stimulation; transnasal insufflation; oral pressure therapy) |

## Treatment: CPAP

CPAP treatment abolishes repetitive upper airway obstruction during sleep by splinting the airway open to facilitate airflow to reduce daytime sleepiness and improve health status and quality of life (Ballester et al. 1999; Jenkinson et al. 1999). It is the treatment of choice in patients with moderate-severe OSA(National Institute for Health and Care Excellence 2008). It is also recommended in mild OSA if symptoms are severe enough to affect quality of life or daily activities and if lifestyle or other treatments have been unsuccessful (National Institute for Health and Care Excellence 2008). CPAP intervention studies have allowed the study of the potential effects of OSA treatment and whether specific effects in patients can be modified and provided important insights on the relation between SDB and altered metabolism. OSA therapy may be a potential avenue for addressing cardio-metabolic risk given the role of OSA in glycemic and metabolic dysregulation.

### Diabetes

Studies have explored the influence of continuous positive airway pressure (CPAP) therapy on glucose homeostasis have thus far yielded mixed findings (Surani and Subramanian 2012; Hecht et al. 2011; Iftikhar and Blankfield 2012). Harsch et al. (2004a) reported that there was improved insulin sensitivity in patients without diabetes at 2 days and at 3 months of CPAP treatment (Harsch et al. 2004a), but these subjects were nonobese, limiting the generalizability of this finding. Although Dawson et al. (2008) found no significant change in HbA1c levels after an average of 41 days of CPAP treatment, it was noted that nocturnal glucose levels were decreased with CPAP therapy and therefore a potential effect on glycemia (Dawson et al. 2008). In an observational study by Babu et al. (2005), there were lower fasting and postprandial glucose levels following 3 months of CPAP, with improved glycemic control in patients with glycated hemoglobin (HBA1c) $> 7\%$ (Babu et al. 2005). Nevertheless, these studies were limited by an absence of a placebo treatment group.

Several randomized controlled trials have been performed (Table 4). It was demonstrated that nasal CPAP treatment of OSA for 1 week improved insulin sensitivity in males without diabetes, and this improvement appeared to be maintained after 12 weeks of treatment in those with moderate obesity (Lam et al. 2010). Another study by Weinstock et al. (2012) found that CPAP did not aid a reversion to normal glucose tolerance in subjects with impaired glucose tolerance. However, there was suggestion of improved insulin sensitivity in those patients with

**Table 4** Therapeutic versus sham CPAP studies in glucose control and insulin resistance

| Study | Population | Parameters | CPAP regimen | Findings |
|---|---|---|---|---|
| West et al. (2007) | 42 men with type 2 diabetes and newly diagnosed OSA (>10 oxygen desaturation of >4% per hour) randomized | Glycemic control and insulin resistance (insulin resistance was assessed by both HOMA and euglycemic-hyperinsulinemic clamp); lipid profile, adiponectin, hsCRP | Randomized to therapeutic (n = 20) or placebo CPAP (n = 22) for 3 months | CPAP did not affect glycemic control or insulin resistance |
| Comondore et al. (2009) | Subjects with AHI > 15 (13 patients completed protocol) | Cardiovascular measures (urinary microalbumin, catecholamines, blood pressure, homeostasis model for insulin resistance score, and endothelial function resistance score) | Randomized to either CPAP or no therapy for 4 weeks followed by washout for 4 weeks and then a crossover to the other intervention | Although insulin resistance (HOMA) decreased with CPAP, the difference was not significant. Likewise, the other cardiovascular measures did not show significant improvements |
| Lam et al. (2010) | 61 men randomized with moderate-severe OSA (AHI > 15) | Effects of nasal CPAP treatment of OSA on insulin sensitivity in male subjects without diabetes mellitus | Randomized to therapeutic nasal CPAP (n = 31) or sham CPAP (n = 30) (n = 29 completed 12 weeks therapeutic CPAP, n = 30 completed 1 week of sham CPAP) | Therapeutic nasal CPAP treatment for 1 week improved insulin sensitivity in obese men (BMI > 25) without diabetes, and the improvement was maintained after 12 weeks of treatment |
| Weinstock et al. (2012) | 50 subjects with OSA (AHI > 15) and impaired glucose tolerance | Normalization of the mean 2 hour OGTT; a secondary outcome was improvement in the Insulin sensitivity index | Randomized to 8 weeks of CPAP or sham CPAP; patients crossed over to other therapy after a 1-month washout | CPAP did not normalize impaired glucose regulation Insulin sensitivity improved in subjects with severe OSA (AHI ≥ 30) |
| Hoyos et al. (2012) | 65 men randomized with AHI > 20 & ODI >15 (46 completed protocol) | Visceral abdominal and liver fat, insulin sensitivity | Real or sham CPAP for 12 weeks; at the end of the 12-week blinded period, all participants had real CPAP for an additional 12 weeks | No group differences at 12 weeks At 24 weeks, insulin sensitivity was improved but not visceral abdominal or liver fat |

severe OSA (AHI > 30) (Weinstock et al. 2012). However, West et al. (2007) reported that CPAP treatment compared with sham CPAP treatment in men with OSA and type 2 diabetes improved Epworth Sleepiness Scale (ESS) scores, but did not improve glycemic control or insulin resistance (West et al. 2007).

Individual heterogeneity in terms of glycemic responses to CPAP suggests most of these studies were probably underpowered to show significant effects on glycemic control and that the encouraging results seen in uncontrolled observational studies are in general not confirmed in randomized controlled trials. It is possible that for individuals with impaired glucose tolerance, other approaches such as intensive lifestyle intervention may be more effective in preventing progression to type 2 diabetes (Pepin et al. 2012; Gillies et al. 2007; Tuomilehto 2009).

Nevertheless, a recent observational study of OSA patients with type 2 diabetes assessed clinical outcomes and cost-effectiveness of CPAP treatment compared with nontreatment. It was found that CPAP use was associated with significantly lower blood pressure, improved glycemic control, and was more cost-effective compared with patients who were not treated with CPAP (Guest et al. 2014). However, this study had limitations because patients were not randomized to the treatments received, by the use of observational data and reliance on clinical outcome findings that were based on clinical entries in patient records. Therefore, no cause-and-effect inferences regarding CPAP treatment and these outcomes can be made.

## Metabolic Syndrome

In order to understand CPAP treatment effects on cardio-metabolic profiles, studies have examined the effect of CPAP on the metabolic syndrome components as endpoints. Randomized controlled trials have evaluated the metabolic syndrome by comparing therapeutic and sham CPAP (Table 5).

A meta-analysis of randomized trials found that there were favorable effects of CPAP treatment in terms of improving blood pressure responses (Haentjens et al. 2007). In terms of the effects on lipid profiles, there have been mixed results from different studies although the current evidence suggests that CPAP treatment may decrease total and LDL cholesterol (Bonsignore et al. 2012b). Previous work by Coughlin et al. (2007), a randomized crossover trial with sham CPAP as control, did not show any differences in lipids (Coughlin et al. 2007). In other controlled trials, Comondore et al. (2009) randomized subjects to 4 weeks of CPAP or no therapy, with crossover after washout for 4 weeks; although no significant differences in lipid levels were found, there appeared to be reduced triglyceride levels (Comondore et al. 2009). Robinson et al. (2004) randomized patients to either 1-month therapeutic or sub-therapeutic CPAP and found a trend toward a decrease in total cholesterol after CPAP (Robinson et al. 2004). One randomized crossover trial with 2 months of therapeutic and sham CPAP showed that treatment with CPAP improved postprandial triglyceride and total cholesterol levels (Phillips et al. 2011).

An interventional controlled study in males without diabetes did not find a significant change in weight, body fat, insulin resistance, or lipid profiles with

**Table 5** Therapeutic versus sham CPAP studies in metabolic syndrome

| Study | Population | Parameters | CPAP regimen | Findings |
|---|---|---|---|---|
| Coughlin et al. (2007) | Randomized controlled trial 35 OSA subjects randomized (34 completed protocol) | Metabolic syndrome (using NCEP AT III), blood pressure, glucose, lipids, insulin resistance, | Each group received 6 weeks of therapeutic or sham CPAP and then treatment crossover for further 6 weeks | Significant decreases in systolic and diastolic blood pressure. No change in glucose, lipids, insulin resistance, or the proportion of patients with metabolic syndrome |
| Hoyos et al. (2013) | Analysis of results from a randomized controlled trial 65 men with OSA randomized (46 completed protocol) | Effect on metabolic syndrome (using international consensus guidelines and NCEP ATPIII criteria) (analysis of results from Hoyos et al. 2012) | Real or sham CPAP for 12 weeks | 12 weeks of CPAP therapy did not affect numbers of patients with metabolic syndrome |

6 weeks of CPAP treatment as opposed to sham CPAP therapy (Coughlin et al. 2007). Nevertheless, there were improvements in blood pressure control following CPAP intervention (Coughlin et al. 2007). A controlled study by Hoyos et al. (2012) evaluated 12 weeks of therapeutic versus sham CPAP on visceral adiposity and insulin sensitivity in males without diabetes and found that there was no significant effect of CPAP on either parameter (Hoyos et al. 2012).

In a further analysis, it was noted that the 12 weeks of CPAP therapy did not have a significant effect on the number of subjects with metabolic syndrome (Hoyos et al. 2013). Another placebo-controlled study by Kritikou et al. (2014) compared 2 months of therapeutic and sham CPAP in nonobese subjects and found no significant difference in metabolic markers including IL-6, tumor necrosis factor, leptin, adiponectin, and highly sensitive C-reactive protein. CPAP treatment was not sufficient to alter these factors in this study although it was noted that the short duration of therapy may have limited metabolic alterations (Kritikou et al. 2014). A recent meta-analysis of CPAP trials suggests that CPAP therapy may actually lead to weight gain that could potentially negate any direct effects of treatment on other components of the metabolic syndrome (Drager et al. 2015). Taken together, the results of studies suggest that CPAP in isolation may not be sufficient for OSA patients with the metabolic syndrome, although there is reasonably consistent evidence for a beneficial effect on blood pressure. It has been proposed that there may be a role for a multifaceted approach for these individuals in order to manage their cardio-metabolic risk (Pepin et al. 2012). Thus it is envisaged that measures to promote proper sleep hygiene and weight loss may be important.

## Treatment: Weight Loss

It is clear that the promotion of weight loss activities and lifestyle changes has the potential to improve glucose regulation. There is also evidence that supports the role of weight loss in the treatment of OSA (Veasey et al. 2006) (Table 6).

In the Wisconsin Sleep Cohort Study, subjects were prospectively observed for change in AHI and the development of SDB with weight change; weight control

**Table 6** Selected studies relating to weight loss with lifestyle and bariatric surgery in OSA

| **Lifestyle interventions** | | | |
|---|---|---|---|
| **Study** | **Population** | **Study protocol** | **Key findings** |
| Peppard et al. (2000a) | 690 randomly selected employed Wisconsin residents | Prospective study of change in AHI and odds of developing moderate-severe SDB with respect to change in weight | Relation between weight gain and increased SDB severity. Weight loss was associated with reduced SDB severity and likelihood of developing SDB |
| Kuna et al. (2013) | 264 obese adults with type 2 diabetes and OSA | Randomized to either intensive lifestyle intervention with a behavioral weight loss program (controlled diet, physical activity) or diabetes support and education (3 group sessions annually) over 4 years | Intensive lifestyle intervention produced greater reductions in weight and AHI over 4 years than diabetes support and education. Effects on AHI persisted at 4 years, despite an almost 50% weight regain |
| Tuomilehto et al. (2009) | 72 patients (BMI 28–40) with mild OSA completed the protocol | Randomized to either very low-calorie diet (VLCD) program with supervised lifestyle modification or routine lifestyle counseling for 1 year | VLCD combined with active lifestyle counseling effectively reduced body weight and a significant reduction in AHI compared with the control group |
| Tuomilehto et al. (2013) | Follow-up study to Tuomilehto et al. (2009). 57 patients completed the follow-up over 4 years | Assessment of long-term efficacy of lifestyle intervention during 4-year follow-up in OSA subjects who participated in the initial 1-year randomized intervention trial (see Tuomilehto 2009) | Intervention achieved reduction in the incidence of progression of the OSA compared with the control group. The improvement in OSA that was sustained even 4 years after the active intervention |
| Kline et al. (2011) | 43 sedentary and overweight/obese adults with OSA AHI $\geq$ 15 | Randomized to intensive exercise training or low-intensity stretching regimen | Compared with stretching, exercise resulted in a significant reduction in AHI and ODI despite nonsignificant changes in body weight |

(*continued*)

**Table 6** (continued)

| | | | |
|---|---|---|---|
| Kajaste et al. (2004) | 31 obese male symptomatic OSA patients (ODI > 10) | All subjects had active weight reduction based on the cognitive-behavioral approach (CBT) (24 months) and a very low-calorie diet (6 weeks) and were randomly selected to have either nasal CPAP or without CPAP for the initial 6 months | Weight loss and improvement of OSA was achieved by the CBT weight loss program. CPAP in the initial phase of the weight reduction program did not result in significantly greater weight loss |
| Thomasouli et al. (2013) | Systematic review and meta-analysis of 12 randomized controlled trials with lifestyle interventions in adults with OSA. Diet and diet plus CPAP therapy were compared in three studies (n = 261), and intensive lifestyle programs and routine care were compared in six studies (n = 483) | To evaluate the impact of diet, exercise, and lifestyle modification programs on indices of obesity and OSA parameters | Intensive lifestyle management can significantly reduce obesity and OSA severity Lifestyle modification combined with CPAP may confer additional benefits in OSA |
| Chirinos et al. (2014) | 181 obese patients, moderate-severe OSA and CRP > 1 mg/l. 136 completed the study. Intention to treat analysis for 146 subjects | Randomized parallel group 24-week trial that compared the effects of CPAP, weight loss, or both in adults with obesity. (Weight loss interventions included weekly counseling, unsupervised exercise, and cognitive-behavioral therapy) | Weight loss with CPAP therapy had an incremental effect in reducing insulin resistance and serum triglyceride levels, compared with CPAP alone. Additionally, combined treatment may result in a larger reduction in blood pressure than either treatment alone |
| **Metabolic-bariatric surgery** | | | |
| **Study** | **Population** | **Parameters studied** | **Key findings** |
| Dixon et al. (2012) | 60 obese patients (BMI 35–55), recently diagnosed with OSA AHI ≥ 20 | Randomized to a conventional weight loss program (regular consultations with dietitian and physician, with use of very low-calorie diets) or to laparoscopic adjustable gastric banding | Bariatric surgery produced greater weight loss but did not result in a statistically greater reduction in AHI compared with conventional weight loss therapy |
| Buchwald et al. (2004) | Systematic review and meta-analysis of 136 fully extracted studies (total 22,094 patients) | Systematic review and meta-analysis to determine the impact of bariatric surgery on weight loss, diabetes, hyperlipidemia, hypertension, and OSA | Bariatric surgery produced effective weight loss in morbidly obese individuals with beneficial effects in the majority in terms of diabetes, hyperlipidemia, hypertension, and OSA |

was associated with decreased AHI and a reduced likelihood of OSA (Peppard et al. 2000a). These findings are supported by evidence from randomized controlled trials. In the Sleep AHEAD Study, obese subjects with type 2 diabetes and OSA were either randomized to a program of intensive lifestyle intervention comprising behavioral weight loss and physical activity or to diabetes support and education. It was found that the intensive lifestyle intervention reduced weight and AHI over 4 years more than diabetes support and education alone (Kuna et al. 2013). Other randomized trials investigating various lifestyle modifications such as very low-calorie diets combined with active lifestyle counseling (Tuomilehto et al. 2009), intensive exercise training (Kline et al. 2011), cognitive-behavioral weight loss, and very low-calorie diet (Kajaste et al. 2004) showed improved OSA severity with these interventions. These effects of lifestyle measures in OSA may potentially be sustained over time (Tuomilehto et al. 2013; Kuna et al. 2013). In a randomized parallel group trial that compared the effects of CPAP, weight loss, or both treatments for 24 weeks in adults with obesity, combination therapy with weight loss and CPAP had a beneficial effect in reducing insulin resistance, serum triglyceride levels, and blood pressure (Chirinos et al. 2014). Pharmacotherapy for obesity may also show benefit for some patients. The SCALE sleep apnea study randomized patients with moderate to severe sleep apnea to lifestyle treatment alone or to lifestyle treatment plus the GLP1 receptor agonist liraglutide 3 mg by daily injection for 32 weeks. Patients treated with liraglutide lost more weight (5.7 vs. 1.6 kg) and had a greater improvement in AHI (from a baseline of 40 events per hour; 12.2 reduction with liraglutide versus 6.1 with lifestyle alone (Blackman et al. 2016).

For patients who are unable to lose sufficient weight by lifestyle interventions alone, pharmacotherapy may be useful adjunct therapy. The influence of weight loss with the use of medications such as Glucagon-like peptide-1 (GLP-1) agonists in type 2 diabetes may potentially influence OSA. GLP-1 is an incretin that is released by intestinal L-cells in response to nutrient ingestion, which enhances glucose-stimulated insulin release by pancreatic beta cells and acts on satiety pathways to reduce food intake. The SCALE sleep apnea trial was a randomized double-blind placebo-controlled trial that investigated the effects of a 3 mg daily injection of the GLP-1 agonist liraglutide, combined with lifestyle intervention in obese and overweight subjects with moderate to severe OSA who were intolerant of or declined CPAP treatment compared with lifestyle intervention alone. Patients treated with liraglutide lost more weight (5.7 vs. 1.6 kg) and had a greater improvement in AHI (from a baseline of 40 events per hour; 12.2 reduction with liraglutide versus 6.1 with lifestyle alone) (Blackman et al. 2016).

## Treatment: Oral Appliances

Dental or mandibular advancement devices (MADs) have a role in the treatment of OSA and are worn during sleep, holding the lower jaw forward in order to prevent retroglossal collapse (Malhotra and White 2002). The American College of

Physicians has recommended MADs for patients who are unable to tolerate CPAP but who prefer the MAD (Qaseem et al. 2013). In studies that compared MAD with no treatment and sham oral devices, the MAD was found to improve OSA in terms of signs and symptoms, AHI score, arousal index score, and minimum oxygen saturation (Qaseem et al. 2013). In studies that compared MAD with CPAP, CPAP was found to be more effective for improving OSA including AHI and arousal index scores and minimum oxygen saturation (Qaseem et al. 2013). The potential side effects of MAD use include tooth pain, temporal mandibular junction discomfort, dry mouth, excessive salivation, and, in the long term, potentially altered bite with teeth movement (Young and Collop 2014).

### Treatment: Upper Airway Surgery

Various upper airway surgical procedures may be performed for OSA including uvulopalatopharyngoplasty (UPPP) in which redundant soft palate tissue is resected. Other procedures include laser-assisted palatal procedures and radiofrequency ablation techniques (Malhotra and White 2002). However, at present, there is insufficient evidence to conclusively demonstrate that upper airway surgical interventions are more effective than CPAP or MADs because of the heterogeneity in surgical procedures and outcomes that have been evaluated (Young and Collop 2014). Furthermore, surgical procedures may have attendant risks; with insufficient evidence to show benefits of this approach to OSA, it is not recommended as initial treatment (Qaseem et al. 2013). It has been suggested that these procedures may potentially be beneficial for alleviating snoring symptoms for patients whose main complaint is snoring but with minimal or no apnea on formal testing (Malhotra and White 2002).

## Other Possible Treatments

The use of pharmacological agents has been explored as a possible treatment modality for OSA (Qaseem et al. 2013). Positional therapy involves the use of assistive devices to avoid the supine position during sleep, for example, a vibrating device when the supine position is assumed, in order to reduce the frequency and severity of obstructive events when supine (Young and Collop 2014). At present, there is insufficient evidence in the literature to support the use of pharmacological or positional therapy as treatment for OSA (Qaseem et al. 2013). Other novel methods that have been described that require further research include upper airway muscle training to increase upper airway muscle tone and other methods such as transnasal insufflation to deliver continuous high-flow humidified air through an open nasal cannula and oral pressure therapy which involves the application of a vacuum to the mouth, pulling the soft palate forward to stabilize the tongue for improved airway patency (Young and Collop 2014).

## Conclusions

In recent years, our understanding of the potential ramifications of having OSA in obesity has greatly improved. It is clear that OSA has important long-term effects on metabolism in obese individuals. We are still at a stage of hypothesizing how specific mechanisms are involved in the pathogenesis of metabolic responses. In people with obesity and metabolic syndrome, the consequences of having OSA may potentially be ameliorated by different treatment methods. Crucially, the current literature justifies further investigation of OSA in obesity as a potential driver of metabolic abnormalities and as a target for treatment.

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# Impact of Obesity on Cardiovascular Disease

13

Lyn D. Ferguson and Naveed Sattar

## Contents



**Abstract**

Obesity is associated with increased risk of cardiovascular disease (CVD), heart failure, diabetes, cancer, and ultimately all-cause mortality. Obesity is causally related to dyslipidemia, hypertension, and diabetes, all strong CVD risk factors, and so causally related to CVD risk. In fact, a substantial part of the risk imparted by obesity on CVD outcomes operates via traditional risk factors. Obese men are almost twice as likely and women almost two and half times as likely to develop hypertension. Obese individuals are around 50% more likely to have a stroke and have around 6–12 times higher risks of developing type 2 diabetes compared to those with a normal BMI.

Obesity is also linked to greater risk for development of heart failure. Yet, there appears to be an obesity paradox in established heart failure such that the risk of death is lower in overweight and mildly obese individuals than in those with

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normal weight. Such observations are likely partially driven by reverse causality whereby disease-specific issues drive weight loss rather than higher weight per se being protective.

While obesity is most commonly defined by BMI, the importance of body fat distribution and markers such as waist circumference, waist: hip ratio, visceral and ectopic fat volumes are becoming better appreciated. The concept of harmful fat distribution is therefore topical and recent evidence suggest those who can store more fat subcutaneously (and so delay their ectopic depot expansions until much heavier) have lesser diabetes and cardiovascular risks. This paradigm may also largely explain men's greater risks for both chronic conditions at similar BMI's to women.

Trials of weight loss add strong support for causal links between adiposity and CVD; for example, the best evidence suggests that losing around 1 kg reduces SBP by around 1 mmHg. Weight loss also improves lipid profiles with reduced total cholesterol, LDL-cholesterol, and in particular triglyceride levels. Weight loss of around 5 kg reduces the risk of obese individuals progressing to impaired glucose tolerance and type 2 diabetes. In those with type 2 diabetes, 5 to $<10\%$ intentional weight loss is associated with 3.5 times increased odds of obtaining a 0.5% reduction in HbA1c. Not surprisingly, substantial weight loss has been associated with significantly lower mortality from several causes.

This chapter will show how the best epidemiological evidence, using methods to lessen the impact of reverse causality, supports strong graded links between adiposity and CVD. It will also examine and explain the apparent obesity paradox of heart failure. The chapter will then describe the effect on CVD outcomes of robust lifestyle and surgical intervention studies and trials. Finally, we will also explain how genetics data have helped support causal associations between increasing BMI and CVD, including understanding better the causal links between regional adiposity and CVD.

In conclusion, several lines of evidence, including observational, trial, and genetic, collectively support causal links between obesity, cardiovascular morbidity and mortality, and all-cause mortality.

**Keywords**
Obesity · Cardiovascular disease · Heart failure · Obesity paradox · Weight reduction · Bariatric surgery · Regional adiposity · Ectopic fat

## Obesity: Definitions, Epidemiology, Measures, and Associations with All-Cause Mortality

The World Health Organization (WHO) estimates $>1.9$ billion adults are overweight worldwide, of whom 600 million are obese (World Health Organisation 2016). A recent pooled analysis of 1698 population-based measurement studies with 19.2 million participants across 186 countries showed the global age-standardized mean BMI increased from 21.7 kg/m$^2$ in 1975 to 24.2 kg/m$^2$ in 2014 in men and from

22.1 kg/m$^2$ in 1975 to 24.4 kg/m$^2$ in 2014 in women. The age-standardized prevalence of obesity has increased from 3.2% in 1975 to 10.8% in 2014 in men and from 6.4% to 14.9% in women. 2.3% of the world's men and 5% of women were severely obese with a BMI $\geq$35 kg/m$^2$. It is projected by 2025, the global obesity prevalence will be 18% in men and surpass 21% in women; severe obesity will surpass 6% in men and 9% in women (NCD Risk Factor Collaboration 2016).

Obesity is classically defined according to body mass index, calculated by dividing the person's weight in kilograms by the square of their height in meters. Normal BMI is defined as 18.5–24.9 kg/m$^2$; overweight, a BMI of 25–29.9 kg/m$^2$; and obesity, a BMI $\geq$ 30 kg/m$^2$. Obesity can be further classified according to severity: obesity grade I: BMI 30–34.9; grade II: BMI 35–39.9; and grade III: BMI $\geq$40 kg/m$^2$ (World Health Organization 2000). However, these thresholds were largely based on White European populations. Consequently, the WHO recommend defining overweight as a BMI >23 kg/m$^2$ and obese as a BMI >27.5 kg/m$^2$ in Asian populations (World Health Organization Expert Consultation 2004) and the IDF recommend a cut-off waist circumference of 80 cm for Asian women and 90 cm for Asian men (International Diabetes Federation 2006). Analysis of UK Biobank data of around 500,000 individuals confirmed the need for lower BMI cut-offs in nonwhite individuals to reflect the higher diabetes prevalence in these groups. A white participant with a BMI of 30 kg/m$^2$ has the equivalent diabetes prevalence as a South Asian individual with a BMI of 22.0 kg/m$^2$, a black individual with a BMI of 26.0 kg/m$^2$, a Chinese woman with a BMI of 24.0 kg/m$^2$, and Chinese man with a BMI of 26.0 kg/m$^2$ (Ntuk et al. 2014).

Since BMI does not account for adipose distribution and may underestimate cardiovascular risk for certain populations, there are numerous alternative measures of adiposity including waist circumference and waist-to-hip ratio. "Central" obesity is commonly defined as waist circumference >102 cm in men and >88 cm in women, or waist-to-hip ratio > 1.0 in men and >0.85 in women (World Health Organization 2000). Again, these cut-offs vary by ethnicity. Among women, a waist circumference of 88 cm in the white subgroup equated to the following: South Asians, 70 cm; black, 79 cm; and Chinese, 74 cm. Among men, a waist circumference of 102 cm equated to 79, 88, and 88 cm for South Asian, Black, and Chinese participants, respectively (Ntuk et al. 2014).

Obesity has major health implications as it is associated with increased risk of cardiovascular disease (CVD), diabetes mellitus, cancer, and ultimately all-cause mortality (World Health Organisation 2011; The Global BMI Mortality Collaboration 2016). In a large meta-analysis of 239 prospective studies across four continents, the Global BMI Mortality Collaboration investigated the association between BMI and all-cause mortality. Relative to BMI in the healthy range (20–25 kg/m$^2$), all-cause mortality increased throughout the overweight and obese ranges. Those with grade 1 obesity (BMI: 30.0– < 35.0 kg/m$^2$) were 45% as likely to die than those with normal BMI (22·5–<25·0 kg/m$^2$), while those with grade 2 obesity (BMI: 35·0–<40·0 kg/m$^2$) were almost twice as likely to die (HR 1.94). Those with grade 3 obesity (BMI: 40·0–<60·0 kg/m$^2$) had the highest all-cause mortality with a hazard ratio (HR) 2.76 (The Global BMI Mortality Collaboration 2016). Mortality increased

log-linearly with increasing BMI >25 kg/m$^2$ across all four continents. This increase was steepest in the young (HR 1.52 aged 35–49 years vs. 1.21 aged 70–89 years for every 5 kg/m$^2$ units higher BMI) and in men (HR 1.51 in men vs. 1.3 in women) (Fig. 1). While attempting to minimize reverse causality through analysis of never-smokers without previous disease surviving at least 5 years, the authors admit full past medical history data was not always available. It is possible that the less pronounced association between increasing BMI and all-cause mortality with age may be due to unidentified chronic illness or subclinical disease. In other words, the stronger associations of BMI with mortality outcomes in the young may be due to less reverse causality.

This chapter also noted men had higher risks for dying at similar elevated BMIs to women. This more pronounced increased mortality in men chimes with previous reports that men at equivalent BMIs have increased ectopic fat, for example, liver fat, leading to greater insulin resistance and type 2 diabetes prevalence (Sattar 2013). Unfortunately, this meta-analysis did not include other measures of adiposity to assess fat distribution between subcutaneous, visceral, and ectopic compartments. Interestingly, all-cause mortality showed a U-shaped association with BMI with increased mortality at lower BMIs below the normal range, although once again this U-shape was far less pronounced in the younger group likely due to less reverse causality at this age.

## Obesity, CVD Morbidity, and Mortality

Individuals with class I obesity (BMI 30 to <35 kg/m$^2$) have a 75% higher risk of CVD death compared to those with a BMI of 22.5 to <25 kg/m$^2$. This risk appeared to be higher with more severe obesity to over 2.5 fold with grade II obesity (BMI 35 to <40 kg/m$^2$) and a fourfold higher risk in those with grade III obesity (BMI >40 kg/m$^2$). Although less pronounced, those who are overweight are also at an 11–35% higher risk of CVD death. Overall, for every 5 units increase in BMI in those with a BMI >25 kg/m$^2$, the risk of dying from CVD increased 49% (The Global BMI Mortality Collaboration 2016).

Stroke mortality is also higher as BMI increases, with a 42% higher risk for every 5 units increase in BMI. This increase was greatest in Europe (52%), followed by East Asia (50%) and Australia (49%), but failed to reach statistical significance in South Asia. On ascending obesity categories, those with grade I obesity had an overall 49% higher risk of death from stroke and those with grade III obesity an over threefold higher risk. In contrast to CVD, overall there was no statistically significant higher stroke risk in those who were mildly overweight (BMI: 25–27.5), except in East Asia. With a BMI of 27.5 to <30 kg/m$^2$, stroke risk increased by 23%, with most of this driven by a 51% increased stroke mortality risk in East Asia (The Global BMI Mortality Collaboration 2016).

Interestingly, the risk of CVD and stroke mortality was also higher in those who were underweight, with a 33% higher CVD mortality risk and 38% higher stroke mortality risk in those with a BMI of 15 to <18.5 kg/m$^2$. This is despite excluding

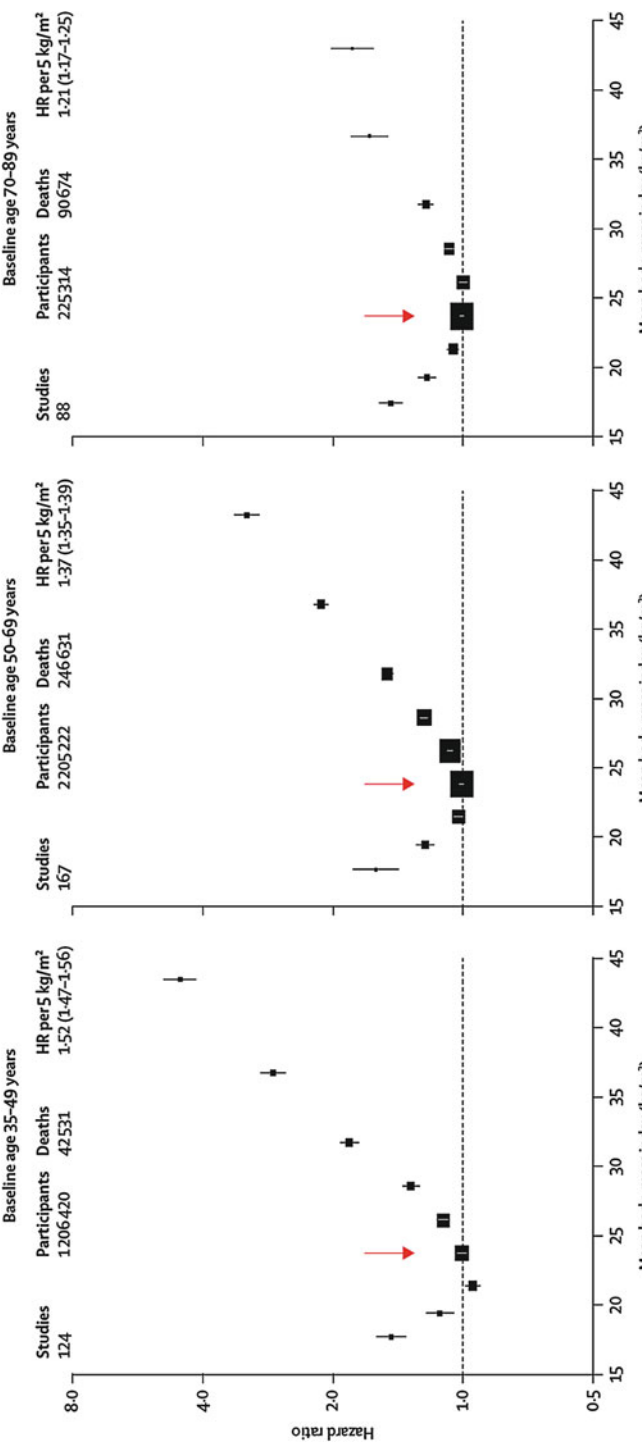


**Fig. 1** Association of BMI with all-cause mortality by age category. Mortality increases log-linearly with increasing BMI >25 kg/m$^2$. This increase is steepest in the young. HR 1.52 aged 35–49 years versus 1.21 aged 70–89 years for every 5 kg/m$^2$ units higher BMI. The *red arrow* shows the reference category BMI 22·5–<25·0 kg/m$^2$ (The Global BMI Mortality Collaboration 2016)

those with known preexisting chronic disease, the first 5 years of follow-up, and restricting to never-smokers. However, the authors acknowledge not all participants had full data available on coexisting chronic diseases. It is likely some participants had subclinical disease and thus reverse causality likely operated despite several methodological advances included in this study.

Obesity is clearly a CVD risk factor; however, there is debate as to whether this is an independent risk factor per se or whether it is its close association with other risk factors that drives increased risk, namely type 2 diabetes, hypertension, and dyslipidemia. In a meta-analysis by Guh et al., they found a strong association between obesity and type 2 diabetes. The pooled incident rate ratio (IRR) of type 2 diabetes in overweight men was 2.4 and obese men 6.74, while the IRR of diabetes in overweight women was 3.92 and obese women 12.41. Being overweight or obese also increased the likelihood of developing hypertension. The pooled IRR of hypertension in overweight men was 1.28 and for obese men 1.84. The corresponding figures for females were 1.65 and 2.42. The association of obesity with diabetes and hypertension appeared stronger in women (Guh et al. 2009).

In an earlier study, the National Health and Nutrition Examination Survey III, there was a strong association between increasing BMI, hypertension, and dyslipidemia with increased total cholesterol, total cholesterol:HDL-cholesterol ratio, and decreased HDL-cholesterol. Obese men had an average 9 mmHg higher systolic blood pressure (SBP) and obese women an 11 mm Hg higher SBP compared with those with a BMI $<25$ kg/m$^2$. Mean serum total cholesterol levels were also higher with increasing BMI. Total cholesterol was a mean 18 mg/dL higher in obese men and 22 mg/dL higher in obese women compared to those with a BMI $<25$ kg/m$^2$. Mean HDL-cholesterol levels were lower in both sexes by around 10 mg/dL as BMI increased from $<25$ to $>30$ kg/m$^2$. These relationships were seen across ethnicity and most ages, with the highest relative risk among younger individuals, despite increased prevalence of obesity, hypertension, and lipid abnormalities with increasing age (Brown et al. 2000).

The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration undertook a pooled analysis of 97 prospective cohorts with 1.8 million participants to investigate to what extent the potential causal association of BMI on CHD and stroke were due to adiposity per se versus the associated metabolic risk factors: i.e., higher blood pressure (BP), cholesterol, and glucose. They found for every 5 kg/m$^2$ higher BMI, the risk of CHD increased 27% and that of stroke 18% after adjusting for confounding factors. After additional adjustment for BP, cholesterol, and glucose, this risk fell to 15% for CHD and 4% for stroke. The authors suggested that 46% of excess CHD risk from increased BMI and 76% excess risk for stroke were explained by these three metabolic risk factors. Similar findings were seen between Asian and Western cohorts (North America, Western Europe, Australia, and New Zealand). On individual risk factor analysis, BP was the most important, explaining 31% of excess CHD risk and 65% excess stroke risk (The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration 2014). This is not unexpected as blood pressure is a known risk factor for both, especially stroke.

Compared with those with normal weight, being overweight was associated with a 26% increased CHD risk and 13% increased stroke risk. This was even more apparent in those with a BMI $\geq$30 kg/m$^2$, where obesity was associated with a 69% increased risk of CHD and 47% increased risk of stroke. This was seen across both Asian and Western cohorts. 50% of this excess CHD risk in the overweight and 44% in those classified as obese was explained collectively by BP, cholesterol, and blood glucose. These factors were even more prominent in stroke, with 98% of excess stroke risk in those overweight and 69% of those with obesity explained by all three metabolic risk factors. Consequently, strategies targeted at lowering blood pressure, cholesterol, and glucose in the overweight and obese could half the excess risk of CHD and cut excess stroke risk by 75%. However, even after accounting for these risk factors, increased BMI is still associated with increased risk, which can only be tackled through effective weight loss (The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration 2014).

The Emerging Risk Factors Collaboration similarly investigated the association of BMI plus additional adiposity measures including waist circumference and waist-to-hip ratio with risk of first-onset CVD. Further, they determined whether the addition of such measures, either alone or in combination, enhanced CVD risk prediction. Analysis of 58 prospective studies including 221,934 people in 17 countries revealed in those with a BMI $\geq$ 20 kg/m$^2$, for every 1SD (4·56 kg/m$^2$) higher BMI, there was a 23% increased CVD risk. Similar risk was found for a 1SD (12.6 cm) higher waist circumference (27%), and for a 1SD (0·083) higher waist-to-hip ratio (25%), after adjustment for age, sex, and smoking status. Following additional adjustment for systolic blood pressure (SBP), history of diabetes, and total and HDL cholesterol, these risks dropped to 7% with BMI, 10% with waist circumference, and 12% with waist-to-hip ratio. Importantly, on including BMI, waist circumference, or waist-to-hip ratio either individually or together in risk prediction models, this did not improve 10 year CVD risk prediction when conventional risk factors including SBP, diabetes history, and lipid levels were included. The authors argue this does not mean ignoring adiposity markers but rather understanding obesity is a key risk factor for high blood pressure, lipids, and blood glucose, all of which must be targeted to reduce CVD risk. Increased adiposity appears to be a common risk factor for both CVD and stroke (each SD increase in adiposity measure is associated with a 20–25% increased risk of stroke), highlighting the importance of tackling obesity to reduce both heart disease and stroke. Finally, the authors counteract previous claims that waist-to-hip ratio should be the baseline adiposity measure, showing similar risk levels between this and BMI, and that BMI has the best reproducibility. One study limitation was the majority of participants were of European descent (Emerging Risk Factors Collaboration et al. 2011).

Consequently, there is variation in CVD recommendations as to whether to include BMI or other adiposity measures in risk calculators which already incorporate many classic metabolic risk factors. The WHO and the US National Heart, Lung, and Blood Institute recommend assessment of both BMI and waist circumference in those with a BMI of 25–34.9 kg/m$^2$ (World Health Organization 2000;

National Institutes of Health 1998). NICE recommends formal CVD risk assessment through the QRISK2–2016 CVD risk calculator which incorporates BMI, as does the JBS3 calculator which is based on QRISK2. However, the ASSIGN risk calculator used in Scotland, as well as many other CVD risk scores, e.g., Framingham and SCORE, do not include adiposity measures.

Thus, there seems to be equipoise on whether or not to include BMI or another measure in CVD risk scoring. Certainly, where lipids are not available, as in low-income countries, researchers have shown that addition of BMI does add considerable value to risk prediction. The biggest single study testing the value of BMI is QRISK2. This prospective open cohort study collected routine general practice data on various cardiovascular risk factors, including BMI, in 2.3million patients aged 35–74, of whom there were 140,000 cardiovascular events. They generated a risk-prediction model, QRISK2, to predict an individual's risk of cardiovascular disease in the next 10 years. The results showed that for every 5 unit increase in BMI, the risk of CVD was higher by 8% in women and 9% in men independent of other risk factors although there is an age interaction (captured in the risk score) so that with increasing age, BMI associations with outcomes were lower (Hippisley-Cox et al. 2008). BMI is therefore included in the QRISK2 risk calculator recommended by NICE.

## Heart Failure and the Obesity Paradox

Obesity is associated with double the risk of developing heart failure. Yet, higher BMIs appear to be associated with a survival "advantage" in those with already established disease, the so-called obesity paradox of heart failure (Oreopoulos et al. 2008).

Early studies by Kenchaiah et al. investigated the relationship between BMI and heart failure incidence among 5881 participants in the Framingham Heart Study (mean age, 55 years; 54% women). After adjusting for established risk factors, for every 1 kg/m$^2$ higher BMI, there was a 5% higher risk of heart failure in men and 7% higher risk in women. Obesity was associated with double the risk of heart failure compared to normal BMI (18.5–24.9), with a hazard ratio (HR) in women of 2.12 and HR 1.9 for men. Heart failure risk increased across BMI categories, with a HR of 1.46 for women and 1.37 in men per increase in BMI category from normal (18.5–24.9) to overweight (25.0–29.9) to obese ($\geq$30.0 kg/m$^2$). There appeared to be no threshold effect (Kenchaiah et al. 2002).

Why does obesity translate into increased heart failure risk? Obesity is associated with numerous well-established heart failure risk factors: hypertension, coronary artery disease, renal disease, diabetes, and obstructive sleep apnea. However, less appreciated is the effect of obesity on cardiac hemodynamics, left ventricular (LV) structure and function, as beautifully outlined by Lavie et al. As body weight increases (including fat-free mass), circulating volume increases, increasing LV stroke volume and cardiac output. This leads to RV hypertrophy, enlargement, and RV heart failure, as well as LV enlargement, increased LV wall stress, LV hypertrophy, and LV systolic

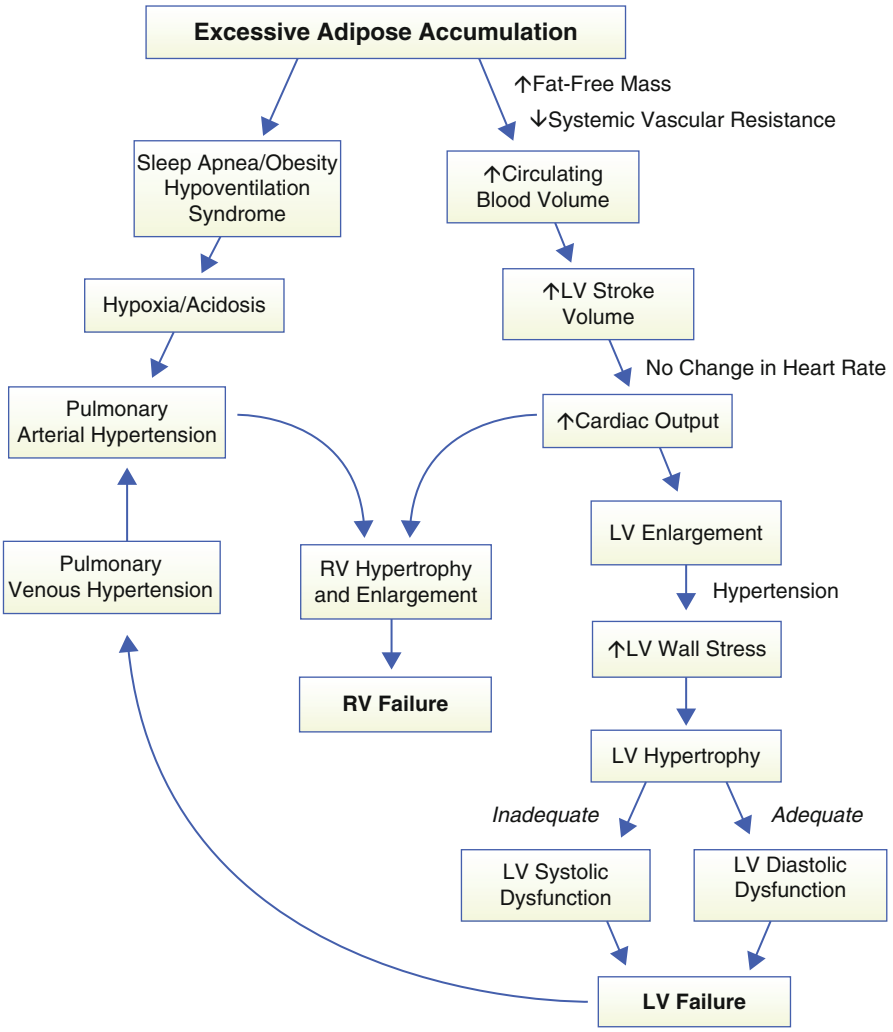


**Fig. 2** Pathophysiology of heart failure in obesity. As body weight increases (including fat-free mass), circulating volume increases, increasing left ventricular (LV) stroke volume and cardiac output. This leads to LV enlargement, increased LV wall stress, LV hypertrophy, and LV systolic or diastolic dysfunction, leading to LV failure, which in turn can contribute to RV failure (Lavie et al. 2013)

or diastolic dysfunction, leading to LV failure. This in turn can cause pulmonary venous hypertension, pulmonary arterial hypertension, and RV failure (Fig. 2). Around 50% of obese individuals have hypertension, with cumulative effects on LV morphology. Hypertension is associated with concentric left ventricular hypertrophy (LVH). When chronic and combined with obesity, a mixed eccentric-concentric LVH occurs, which is now thought to be a form of concentric LVH (Lavie et al. 2013). Thus, many routes can lead from obesity to heart failure.

However, once individuals have heart failure, there appears to exists a paradox whereby being overweight or obese is apparently "protective" compared to being normal weight. This was first reported by Horwich et al. who showed obesity was not associated with increased mortality in heart failure, with higher BMI an independent predictor of improved survival at 2 years, but not 5 years. However, the study consisted only of those with advanced heart failure awaiting transplant (Horwich et al. 2001). Cachexia, associated with poor prognosis, can occur in later stages of heart failure and is characterized by weight loss. It is possible obese patients were not as ill as those with lower BMIs, with survival benefit due to obese patients being at an earlier stage of disease, hence no survival advantage by 5 years. Those who were overweight or obese also used more ACE inhibitors, which are known to improve heart failure prognosis.

Lavie et al. examined the association of obesity with clinical outcomes in those with milder heart failure (New York Heart Association (NYHA) class I to III) using various body composition markers. For every 1% absolute higher percent body fat, this was associated with a $>$ 13% lower risk of major clinical events. However, this study was small (209 patients) with only 28 events and retrospective (Lavie et al. 2003).

A meta-analysis of nine observational trials (total n = 28,209) showed those with chronic heart failure (CHF) who were overweight or obese had lower all-cause and cardiovascular mortality than those without elevated BMI (Oreopoulos et al. 2008). Three of these studies grouped underweight and normal weight individuals together, potentially biasing favorable results to those with higher BMIs; however, their findings were similar even after excluding these studies. There were also biases in patient characteristics, with obese patients being younger, less often smokers, less myocardial infarctions, better ejection fractions, and greater use of beta-blockers but also more comorbidities, e.g., diabetes and hypertension. However, even after adjusting for these factors, the authors argue there was still an apparent "protective" effect of being overweight or obese with CHF. It should be noted these studies were observational and there have been no randomized controlled trials (RCTs) that examined mortality outcomes after intentional weight loss in obese patients with heart failure. While many researchers have tried to look at various ways to explain this paradox, they have been unable to rule out bias and confounding. Thus, randomized trials of weight loss are needed before one can definitively determine whether being obese is genuinely protective in heart failure, or otherwise. For now, researchers should refrain from stating obesity per se is a "protective" factor in patients with heart failure.

## Weight Reduction Including the Role of Bariatric Surgery on Cardiovascular Risk Reduction

Intentional weight loss has numerous cardiovascular benefits. Losing around 5 kg has been associated with improved lipid profiles with reduced total cholesterol, LDL-cholesterol, and triglycerides (Poobalan et al. 2004), as well as reduced systolic

blood pressure by around 4.4 mmHg (Neter et al. 2003). Weight loss has also been associated with a reduced risk of obese individuals progressing to impaired glucose tolerance and type 2 diabetes. Consequently, lifestyle interventions aimed at a 5–10% (approximately 5–10 kg) weight loss in those with a BMI of 25-35 kg/m$^2$ are recommended to reduce the risk of cardiovascular and metabolic diseases (Scottish Intercollegiate Guidelines Network 2010). In reality, however, individuals attending a lifestyle weight management program lose around 3% body weight (National Institute for Health and Care Excellence 2014).

Weight management programs can provide an effective combination of dietary advice, physical activity, and behavioral therapy. In a comparison of five studies, median weight loss for the combined interventions was 4.6 kg versus 0.48 kg for diet alone (National Institute for Health and Clinical Excellence (NICE) 2006). In the Look AHEAD (Action For Health in Diabetes) study, Wing et al. investigated the effects of an intensive lifestyle intervention versus usual care in improving cardiovascular risk factors in 5145 overweight and obese patients with type 2 diabetes. The intensive lifestyle intervention consisted of reduced calorie intake of 1200–1800 kcal/day depending on baseline body weight and increased physical activity up to 175 min/week of moderate intensity activities with the aim of losing 10% body weight. They found modest weight loss of 5 to $<$10% was associated with improved glycemic control, lipid profiles (HDL-cholesterol and triglycerides but not LDL-cholesterol) and blood pressure at 1 year, with even greater benefits from further weight loss (Wing et al. 2011).

In a follow-up study, Wing et al. investigated the longer-term effects of intensive lifestyle interventions on CVD risk factors over 4 years by comparing those who maintained various degrees of weight loss versus those who regained weight. They found those who had significant weight loss of 8–20% at 1 year and kept this off at year 4 maintained improvements in systolic blood pressure, lipid profiles (triglycerides, HDL-C), and HbA1c. There were improvements in several of these CVD risk factors even in those who regained some weight (Wing et al. 2016). After a median follow-up of 9.6 years, the intervention group lost more weight than control group (6% vs. 3.5%, respectively) and again benefits in CVD risk factors were seen. However, intensive lifestyle interventions did not reduce cardiovascular morbidity and mortality (HR 0.95, 95% confidence interval 0.83–1.09) (The Look AHEAD Research Group 2013). It may be that greater weight reductions are required to reduce cardiovascular events. The control group also used more statins compared to the intervention group. Notably, given the aforementioned mechanisms of cardiovascular risk driven by obesity via lipids, hypertension, and diabetes, patients in Look AHEAD had generally excellent blood pressure, lipid levels, and glycemic control at baseline. Moreover, most were women and few were smokers so in many ways, Look AHEAD participants had low CVD risks levels even before interventions to lose weight were put in place, making it much harder to show meaningful CVD benefits with significant weight loss.

In those with a BMI $\geq$40 kg/m$^2$ or $\geq$35 kg/m$^2$ with comorbidities, bariatric surgery can be considered as this can result in numerous cardiovascular benefits as well as reduced all-cause mortality (Jensen et al. 2014). The Swedish Obesity Study

was a prospective controlled study of 4047 obese individuals followed over an average of 10.9 years. Two thousand and ten individuals underwent bariatric surgery, while 2037 matched controls received standard treatment. There were dramatic and sustained improvements in weight loss after 10 years, with weight loss stabilized at 25% after gastric bypass, 16% after vertical-banded gastroplasty, and 14% after banding, compared to an average weight change of $<\pm 2\%$ in the control group. Importantly, overall mortality was lower in the bariatric surgery group with a hazard ratio (HR) of 0.76 in the surgery group compared to the control group receiving conventional treatment (95% confidence interval (CI) 0.59–0.99). This lower mortality was clear even after adjusting for sex, age, and additional risk factors (HR 0.71, 95% CI 0.54–0.92) (Sjöström et al. 2007). Due to ethical and pragmatic reasons, this study was not randomized. However, there were no significant interactions between study group and the covariables of sex, presence or absence of diabetes, BMI, age, and previous cardiovascular events. Comparison of baseline characteristics showed no statistically significant difference in history of pre-existing diabetes, previous MI, stroke, cancer, or lipid-lowering therapy between groups.

In a subsequent study of Swedish Obese Subjects, Carlsson et al. showed bariatric surgery was more efficient than usual care in preventing type 2 diabetes in obese individuals. Using a similar, prospectively matched cohort of 1658 patients who underwent bariatric surgery and 1771 obese matched controls, the incidence rates of type 2 diabetes were 28.4 cases per 1000 person-years in the control group and 6.8 cases per 1000 person-years in the surgery group. After multivariable adjustments, the HR for incidence of diabetes was 0.17 in the bariatric surgery group compared to obese matched controls. This was despite the fact that those in the intervention group had higher body weights and more risk factors than the control group (Carlsson et al. 2012).

The association of bariatric surgery, weight loss, and cardiovascular events including myocardial infarction and stroke were analyzed as secondary outcomes (Sjöström et al. 2012). There were fewer cardiovascular deaths in the bariatric surgery group (28 out of 2010 patients) compared to the control group (49 out of 2037 patients), adjusted hazard ratio 0.47. Bariatric surgery was also associated with fewer fatal or nonfatal myocardial infarctions and stroke (199 incident cardiovascular events among 2010 patients in bariatric surgery group versus 234 events among 2037 patients in the control group). Interestingly, there was no interaction between BMI and treatment with regards to cardiovascular events, indicating that among the obese, higher baseline BMI is not necessarily associated with a greater health benefit of bariatric surgery.

Adams and colleagues have reported similar lower mortality rates after bariatric surgery. In a retrospective cohort study, all-cause and cause-specific mortality rates were compared in 7925 surgical patients and 7925 severely obese control subjects matched for age, sex, and BMI. During a mean follow-up of 7 years, adjusted all-cause mortality was lower by 40% in the gastric bypass group compared to the control group (37.6 vs. 57.1 deaths per 10,000 person-years). Coronary artery disease-related deaths were lower by 56% (2.6 vs. 5.9 per 10,000person-years), diabetes-related deaths were lower by 92% (0.4 vs. 3.4 per 10,000 person-years), and

cancer deaths lower by 60% (5.5 vs. 13.3 per 10,000 person-years) (Adams et al. 2007).

In a large systematic review and meta-analysis including 29,208 bariatric surgery patients and 166,200 nonsurgical controls, the results suggested a greater than 50% lower mortality risk among the surgery group compared to nonsurgical controls (OR 0.48, 95% CI 0.35–0.64, $I^2 = 86\%$). Bariatric surgery was also associated with a 46% lower risk of composite cardiovascular adverse events (OR 0.54, 95% CI 0.41–0.70, $I^2 = 58\%$), 54% lower risk of myocardial infarction (OR 0.46, 95% CI 0.30–0.69, $I^2 = 79\%$), and 51% lower risk of stroke (OR 0.49, 95% CI 0.32–0.75, $I^2 = 59\%$) (Kwok et al. 2014). However, there was significant heterogeneity between the 14 studies analyzed as part of this meta-analysis, and a modest risk of bias could not be discounted in most studies, in line with their observational nature.

Finally, a recent randomized controlled trial compared bariatric surgery versus intensive medical therapy for optimal type 2 diabetes management (Schauer et al. 2017). One hundred and fifty patients with type 2 diabetes and a BMI ranging from 27 to 43 kg/m$^2$ were randomly allocated to either intensive medical therapy alone or intensive medical therapy in addition to Roux-en-Y gastric bypass or sleeve gastrectomy. After 5 years of follow up, 14 of the 49 patients (29%) in the gastric bypass group achieved the primary outcome of a HbA1c level $\leq$ 6.0%, compared to 11 out of 47 (23%) in the sleeve gastrectomy group, versus 2 of 38 patients (5%) in the medical therapy only group. Those who underwent bariatric surgery had greater reductions in mean HbA1c compared to those on medical therapy only (2.1% versus 0.3% reduction $p = 0.003$), greater weight loss, less use of insulin, lower triglyceride, higher HDL-cholesterol levels, and improved quality of life after 5 years. There was only one late reoperation in the bariatric surgery group; mild anemia was noted more often in the surgical group. Unfortunately, the study was not powered to examine differences in cardiovascular morbidity and mortality, and larger trials are needed to address these.

## What Can Genetic Studies Tell Us About the Impact of Obesity on CVD?

Observational studies have shown an association between obesity and cardiovascular disease. However, they cannot prove causality and are subject to confounding, that is, another variable aside from the exposure of interest contributing to the outcome, and reverse causality, where those with the outcome may be more prone to the exposure. Randomized controlled trials, if well conducted, overcome these issues; however, such trials are not always possible or feasible due to time, ethical, or cost constraints. By using Genome Wide Association Studies (GWAS), a number of Single Nucleotide Polymorphisms (SNPs) in numerous genes associated with BMI have been identified. Using these SNPs, investigators can use Mendelian Randomization to attempt to prove a causal association between increased BMI and adverse cardiovascular outcome. This work, if done well and with SNPs that are pure for the exposure of interest, function as a natural randomized controlled trial (Burgess et

al. 2012). The genetic variant is the proxy for the risk factor, that is, the "intervention" group. This is assigned to an individual randomly at conception and thus individuals born with multiple BMI raising genes will have lifelong higher BMI compared to individuals with few or none of these genes.

Nordestgaard et al. used this Mendelian Randomization approach to test a causal association between BMI and ischemic heart disease (IHD). They measured BMI and genotyped 75,627 Danish individuals for three SNPs: FTO(rs9939609), MC4R (rs17782313), and TMEM18(rs6548238). There were 11,056 IHD events. The odds ratio (OR) for BMI and IHD were compared between observational studies and combined allele scores. For every 4 $kg/m^2$ higher BMI, observational studies reported a 26% higher risk of IHD (OR 1.26), whereas an instrumental variable analysis using the allele score suggested a 52% higher IHD risk (OR 1.52) (Nordestgaard et al. 2012). In terms of risk factors, an earlier study by the same group investigated the causal link between BMI and blood pressure with rs9939609 (FTO) and rs17782313 (MC4R) genotypes as surrogates for BMI. Accounting for antihypertensive use and adjusting for numerous variables including age, sex, height, and sociobehavioral variables, for every 10% increase in BMI, they found a 3.85 mmHg increase in systolic blood pressure and 1.79 mmHg increase in diastolic blood pressure, confirming observational associations (Timpson et al. 2009).

A separate Mendelian Randomization analysis by Holmes et al. investigated the causal role of BMI with cardiometabolic disease in 34,538 European-descent individuals (6073 CHD, 3813 stroke cases, and 4407 type 2 diabetes cases). They used a genetic score consisting of 14 BMI-associated SNPs and confirmed causal effects of BMI on type 2 diabetes, systolic blood pressure, HDL-cholesterol, fasting glucose, fasting insulin, and IL-6. However, they did not prove causality for BMI and CHD or stroke, although the analysis may have been underpowered (Holmes et al. 2014).

Hagg et al. confirmed for the first time a causal relationship between BMI and ischemic stroke, with a HR of 1.83 per SD increase in BMI, using a 32 SNP genetic score. They also found a causal role for increased BMI and heart failure (HR 1.93 per SD increase in BMI). However, their initial findings did not show a causal association of BMI with CHD (HR 1.13 per SD increase in BMI, 95% confidence interval 0.7–1.84, $p = 0.62$) (Hägg et al. 2015).

Overall, genetic studies add some further support for a causal link between obesity, several CVD risk factors and CVD outcomes, and heart failure, although further studies are needed.

## Regional Adiposity and Cardiometabolic Disease

It is increasingly recognized that differences in body fat distribution may play an important role in cardiometabolic disease. In particular, increased central obesity has been associated with increased cardiometabolic risk and has been proposed to be a more sensitive marker of risk than BMI. Indeed, a large systematic review of 15,923 subjects with baseline CAD showed a direct relationship between higher waist circumference and WHR (central obesity markers) with higher mortality, with those

in the highest central obesity tertile 70% more likely to die compared to the lowest tertile. However, in the same study BMI was inversely associated with mortality (Coutinho et al. 2011). This has led some to question if the "obesity paradox" is actually the "obesity paradox of BMI" in those with established CAD (Després 2011).

However, waist circumference should still be interpreted in relation to the individual's BMI. It is influenced not only by increased visceral fat but also from increased abdominal subcutaneous fat (Després 2012). Modern imaging techniques, from basic ultrasound to multidetector CT to the gold standard MRI, have allowed us to more accurately assess and quantify subcutaneous and visceral fat volume, as well as ectopic fat volume in the liver, skeletal muscle, pancreas, and heart through $^{1}H$ Magnetic Resonance Spectroscopy (Britton and Fox 2011).

The ectopic fat hypothesis suggests that as one consumes excess calories/reduces energy expenditure, subcutaneous adipose tissue (SAT) stores become overwhelmed and excess fat "spills over" more rapidly into visceral and ectopic sites including the liver, skeletal muscle, heart, vasculature, and possibly also the pancreas (Fig. 3). These "ectopic" fat stores are not classically associated with substantial tissue fat

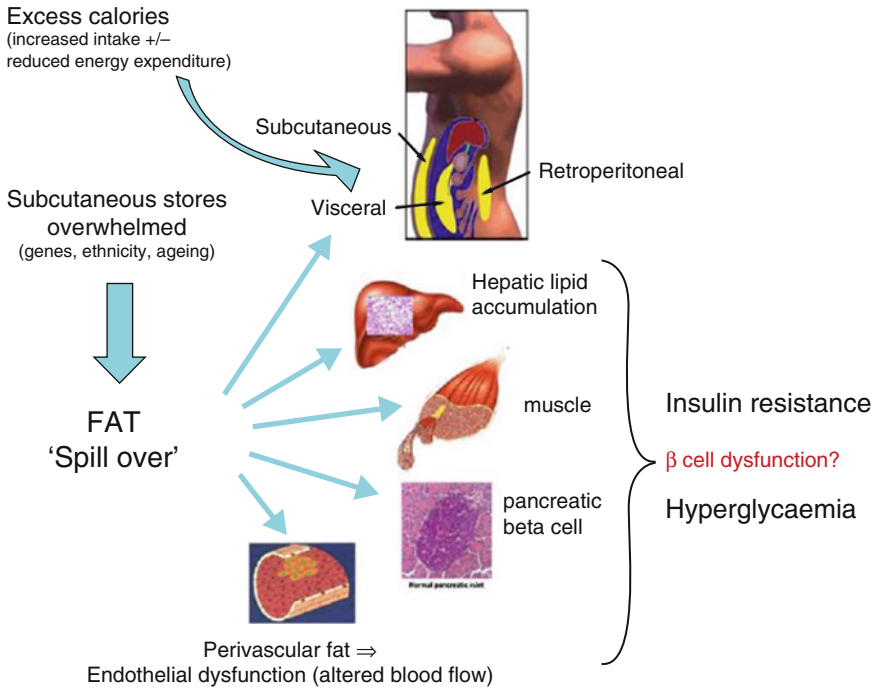


**Fig. 3** Ectopic fat hypothesis. The ectopic fat hypothesis suggests that as one consumes excess calories/reduces energy expenditure, subcutaneous adipose tissue (SAT) stores become overwhelmed and excess fat "spills over" more rapidly into visceral and ectopic sites including the liver, skeletal muscle, heart, vasculature, and possibly also the pancreas. Certain risk factors such as male sex, ageing, ethnicity, e.g., South Asian origin, and genetics may predispose to more rapid exhaustion of subcutaneous stores into visceral and ectopic stores (Sattar and Gill 2014).

storage. When free fatty acids are normally deposited in SAT, there is adipocyte hyperplasia. However, when the SAT becomes dysfunctional, the adipocytes hypertrophy and this has been associated with the development of type 2 diabetes (Weyer et al. 2000). Numerous factors including male sex, certain ethnic groups, e.g., South Asians, increasing age, and lifestyle factors, e.g., smoking, may predispose individuals to more rapid filling of visceral and ectopic fat stores at a given BMI but more work is also needed here to expand this body of work (Sattar and Gill 2014; Britton and Fox 2011).

Rather than being causal per se, visceral fat may serve as a marker of more "dangerous" ectopic fat. Rossi et al. (2011) showed a strong correlation between visceral fat volume and liver lipid content and pancreatic lipid content. Nonalcoholic fatty liver disease (NAFLD) is associated with obesity and type 2 diabetes. Excess intrahepatic fat may arise from hyperinsulinemia working in conjunction with excess energy intake to drive de novo lipogenesis in the liver (Stefan et al. 2008). Fatty liver in turn renders the liver more insulin resistant through numerous proposed cellular mechanisms, including through increased hepatic diacylglycerol (DAG). Hepatic gluconeogenesis in such cases is poorly suppressed and so the liver can continue to make glucose when not normally needed resulting in hyperglycemia and type 2 diabetes (Sattar and Gill 2014).

Men have more visceral fat at a given BMI than women which may partially explain the higher prevalence of type 2 diabetes in men compared to women, although other fat depots were not measured in this study (Nordström et al. 2016). There are also ethnic differences in adipose tissue distribution. For example, some studies suggest South Asians are less able to store fat in "safer" superficial subcutaneous adipose stores and fat more easily "spills over" into deeper subcutaneous and visceral fat compartments as well as ectopically into the liver. There may also be differences in subcutaneous abdominal adipocyte morphology between South Asians and Europeans (Sattar and Gill 2014). This may in part account for the observation that South Asian individuals develop type 2 diabetes at lower BMIs than their white European counterparts (Ntuk et al. 2014). However, we await longitudinal studies to gain a better insight into prospective changes in adipose tissue distribution and morphology in response to weight changes.

Ectopic circulatory fat can also accumulate with increased hepatic production of very low density lipoprotein cholesterol (VLDL-C) and increased serum triglyceride levels (Sattar and Gill 2014). It is thought excess ectopic pancreatic fat may also contribute to development of type 2 diabetes through impaired β-cell function (Lim et al. 2011), which is reversible with weight loss.

But does greater central or ectopic fat translate into higher risk for cardiovascular disease? Ding et al. undertook a case-cohort study in 998 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) study and 147 MESA participants who developed incident coronary heart disease, to investigate whether pericardial fat volume assessed by cardiac CT predicted incident CHD. They found that a 1 SD increase in pericardial fat was associated with a 33% higher risk of CHD (relative hazard 1.33) in unadjusted analyses. After adjusting for age, sex, ethnicity, BMI, and other CVD risk factors, this association remained significant, although the

confidence interval was broadened (relative hazard 1.26, 95% confidence interval 1.01–1.59). The association did not statistically differ between sexes. After adjustment, those in the highest pericardial fat quartile had over twice the risk of CHD (relative hazard 2.09) relative to those in the lowest quartile (Ding et al. 2009).

Ectopic fat accumulation in the renal sinus may potentially affect renal function through compressing the renal artery and vein (Britton and Fox 2011). Using the Framingham Heart Study, Foster et al. investigated the association of renal sinus fat with CKD and hypertension. Renal sinus fat area was assessed using CT in 2923 individuals. Around 30% of participants had "fatty kidney," defined using sex-specific cut points of $\geq$0.710 $cm^2$ in men and $\geq$0.445 $cm^2$ in women. Those with increased renal sinus fat were over twice as likely to have hypertension (OR 2.12, 95% CI 1.75–2.56, $p < 0.0001$); this persisted, although was attenuated, after adjusting for BMI (OR 1.49, 95% CI 1.22–1.83, $p < 0.0001$) or VAT (OR 1.24, 95% CI 1.00–1.53, $p = 0.049$). The odds of CKD were also doubled in those with "fatty kidney" (OR 2.30, 95% CI 1.28–4.14, $p = 0.005$). This was only noted with CKD defined by cystatin C and was not significant after multivariable adjustment with creatinine defined eGFR. Cystatin C is produced by adipose tissue and so the prevalence of CKD with this marker may be overestimated in the obese. However, there is still a significant association between CKD estimated from cystatin C and fatty kidney even after adjusting for BMI or abdominal VAT (OR 1.86) (Foster et al. 2011).

Preliminary genetic data has shown 11 "favorable adiposity" variants associated with lower risk of type 2 diabetes, hypertension, and heart disease. These "favorable adiposity" alleles are associated with increased subcutaneous–to–visceral adipose tissue ratio, decreased insulin levels, and higher adipose storage capacity. Using UK Biobank data from over 160,000 participants and data from five other studies, the 50% of participants with the most favorable adiposity alleles had higher BMIs and body fat percentage compared to those with the least number of alleles, yet also had reduced risk of type 2 diabetes, hypertension, heart disease, and lower blood pressures. The key suggestion from these data is that it is not simply an increased BMI which can increase disease risk but rather how and where the excess body fat is stored (Yaghootkar et al. 2016).

Future prospective large-scale studies are now needed to provide sufficient power to associate various ectopic fat depots with adverse cardiovascular outcomes. It is hoped this will be provided through analysis of 100,000 MRI scans of body fat distribution undertaken on UK Biobank participants in the coming years.

## Summary

In conclusion, several lines of evidence, including observational, trial, and genetic, collectively support causal links between obesity, cardiovascular morbidity and mortality, and all-cause mortality (Table 1). For prediction, while measures of obesity have clear importance to diabetes risk scores, their inclusion in CVD risk prediction are less frequent, mainly due to far more modest associations and especially once other downstream risk factors (lipids, BP, and diabetes) are included.

**Table 1** Types of evidence linking obesity to CVD

| Type of evidence | Findings |
|---|---|
| Observational/ epidemiological | Epidemiological studies show a clear association between obesity and CVD, particularly when efforts to limit reverse causality are put in place. For every 5 units increase in BMI in those with a BMI >25 kg/ $m^2$, the risk of dying from CVD was 49% higher (The Global BMI Mortality Collaboration 2016). Obesity is also associated with an increased risk of developing heart failure |
| Risk factor associations | Obesity is causally related to dyslipidemia, hypertension, and in particular type 2 diabetes. Most of the CVD risk imparted by obesity may operate via traditional risk factors |
| Genetic | Mendelian randomization studies are consistent with causal links between BMI raising genes and CHD risk as well as with causal links to type 2 diabetes, systolic blood pressure, high triglyceride, and low HDL-cholesterol (Holmes et al. 2014) |
| Interventions | Intensive lifestyle interventions designed to lose 5–10% of body weight have been associated with improved glycemic control, lipid profiles, and blood pressure in obese individuals with type 2 diabetes (Wing et al. 2011). In approximate terms, a 1 kg weight loss yields a 1 mmHg reduction in SBP. Bariatric surgery has been associated with lower all-cause mortality (adjusted HR 0.71) (Sjöström et al. 2007), lower incidence of type 2 diabetes (HR 0.17) (Carlsson et al. 2012), fewer cardiovascular deaths (adjusted HR 0.47), and fewer myocardial infarctions, and stroke (Sjöström et al. 2012). Risk factor changes with bariatric surgery were confirmed in a recent randomized trial of patients with type 2 diabetes (Schauer et al. 2017) |

While numerous studies have identified an apparent obesity paradox in those with heart failure and to a lesser extent in those with existing CVD, these findings are observational and may be subject to reverse causality. Prospective randomized controlled trials of intentional weight loss in obese heart failure patients are needed to properly address the question of whether intentional weight loss in this group is detrimental or not. Finally, more recent evidence, both imaging and novel genetic findings, support differential causal associations between tissue specific fat depositions and cardiometabolic outcomes. Indeed, individuals able to better expand subcutaneous fat stores appear at lower cardiometabolic risks at a given BMI than those less able to do so. The ramifications of current findings to clinical practice and public health agendas are clear – overweight or obese individuals need to be supported to help lose weight or lessen weight gain to reduce their risks of numerous diseases including adverse CVD outcomes.

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# Obesity in Children and Adolescents

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## Contents



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**Abstract**

This chapter reviews the definitions, prevalence, etiology, comorbidities, prevention, and treatment of childhood obesity. Obesity in childhood and adolescents is highly prevalent with the rates of severe obesity, in particular, increasing considerably. Biological contributors, principally in the form of genetic risk which is susceptible to expression in the context of an obesogenic environment, account for the primary etiology of childhood obesity. Critical periods in child development, including gestation and early infancy, early childhood, and adolescence, are especially vulnerable to various factors that may increase the likelihood of later obesity. Comorbidities associated with childhood obesity are similar to those seen in adults: hypertension, dyslipidemia, insulin resistance, nonalcoholic fatty liver disease, obstructive sleep apnea, and psychosocial distress. Treatment to date relies mostly on lifestyle modification therapy despite the fact that outcomes in the real-world clinical setting remain dismal, particularly for adolescents with severe obesity. As the field of pediatric obesity management continues to mature, pharmacotherapy may prove to be a helpful adjunctive treatment and access to bariatric surgery for eligible adolescents may increase as evidence of its safety and effectiveness continues to accumulate.

**Keywords**

Childhood obesity · Adolescent obesity · Definitions · Prevalence · Etiology · Comorbidities · Treatment · Prevention

## Introduction

Obesity in childhood has reached epidemic proportions, although it is not as widespread as obesity in adults. This chapter will highlight the definitions, prevalence, etiology, comorbidities, prevention, and treatment aspects of obesity in children and adolescents. Unless otherwise specified, "youth" in this chapter is referring to children and adolescents.

## Definitions

Obesity in children and adolescents is defined using body-mass index (BMI) percentiles for a given age and sex. In 2000, the United States Centers for Disease Control and Prevention (CDC) developed normative reference growth charts for children at every half-year from age 2 years to 20 years (Ogden et al. 2002). Using these growth charts, youth are classified into four categories: under-weight

(BMI-percentile <5th), normal-weight (BMI-percentile ≥5th to <85th), overweight (BMI-percentile ≥85th to <95th), and obese (BMI-percentile ≥95th). However, due to the inability of the 2000 CDC growth charts to accurately define and display BMI-percentiles >97th, growth charts have been adapted in order to define more severe obesity values (Gulati et al. 2012). Obesity in youth can therefore be divided into three distinct categories: class 1 obesity (BMI-percentile ≥95th – < 1.2 times 95th percentile; or BMI ≥30 kg/m$^2$), class 2 obesity (BMI ≥1.2 times 95th percentile – <1.4 times 95th percentile; or BMI ≥35 kg/m$^2$), and class 3 obesity (BMI ≥1.4 times 95th percentile; or BMI ≥40 kg/m$^2$). The term "severe obesity" includes class 2 and 3 obesity. For infants and toddlers under 2 years of age, overweight is characterized as weight-for-recumbent length ≥95th percentile.

The World Health Organization (WHO) established similar metrics that encompass not only youth above the age of 2 years but also 0–24 months. These metrics were originally designed to identify under- and malnutrition but have now been applied to obesity categorization. WHO guidelines utilize z-scores instead of percentiles, and accordingly, for children 5–19 years of age, overweight is defined as BMI above 1 standard deviation (+1 z-score) and obesity is defined as 2 standard deviations (+2 z-score) above the WHO Growth Reference median.

To address the arbitrariness of the centile (i.e., 85th and 95th) approach and to provide relevance to an international population, the International Obesity Task Force developed definitions of childhood overweight and obesity that are based on six nationally representative datasets. These cutoffs for age (2–18 years) and sex are defined to pass through a BMI of 25 and 30 kg/m$^2$, respectively, at age 18 to correspond with the well-established adult cutoffs (Cole et al. 2000). See Table 1 for summary.

In the clinical setting, BMI is used to determine obesity status and as a means of risk stratification in children and adolescents. Despite its widespread application as a surrogate measure of adiposity, BMI is derived from the ratio of weight and height without accounting for the magnitude of body fatness or different distributions of fat or fat-free mass. The normal growth and maturation of youth as they transition from

**Table 1** Definitions of obesity according to organization

| Organization (reference population) | Definition | |
|---|---|---|
| World Health Organization (WHO Child Growth Standards) | Birth – <5 years | Overweight: Weight-for-height > +2 SD<br>Obese: Weight-for-height > +3 SD |
| | 5–19 years | Overweight: BMI-for-age > +1 SD<br>Obese: BMI-for-age > +2 SD |
| US Centers for Disease Control and Prevention (CDC growth chart) | 2–18 years | Overweight: BMI-for-age-and-sex ≥85th – <95th percentile<br>Obese: BMI-for-age-and-sex ≥95th percentile |
| International Obesity Task Force (multinational data set) | 2–18 years | Overweight: Age-and-sex specific centile that corresponds to BMI of 25 at age 18<br>Obese: Age-and-sex specific centile that corresponds to BMI of 30 at age 18 |

childhood through puberty and into young adulthood skews the relationship between BMI and adiposity, a phenomenon that is not fully addressed by BMI percentiles. Due to this, BMI as a means of classifying adiposity on the individual level can be flawed and lead to misclassification. As expected, very few (<5%) normal-weight children present with excess adiposity; conversely, almost all children with class 2 and 3 obesity present with excess adiposity. However, among children with overweight and class 1 obesity, there is substantial discordance between BMI and dual energy x-ray absorptiometry (DXA)-derived excess adiposity, which can lead to misclassification. These findings are consistent across sexes and racial/ethnic groups (Ryder et al. 2016). As such, caution should be taken in assigning a diagnosis of obesity to youth in these BMI ranges.

## Epidemiology

The global prevalence of overweight and obesity in youth has risen substantially since the 1970s (Swinburn et al. 2011). Although this upward trend has appeared to level off since the mid-2000s, the overall prevalence of obesity subcategories (i.e., severe obesity) continues to rise (Skinner et al. 2016). According to the 2013–2014 National Health and Nutrition Examination Survey, the prevalence of class 1 obesity in the United States for 2–19 year olds was estimated to be 17.4%. This estimate has remained consistent since 2003–2004. For class 2 obesity, the prevalence has risen from 4.0% in 1999–2000 to 6.3% in 2013–2104, with class 3 obesity rising from 0.9% to 2.4% over this same time period (Skinner et al. 2016).

The prevalence of obesity increases with age, with class 1 obesity estimates of 9.2% for 2–5 year olds, 17.9% for 6–11 year olds, and 20.9% of 12–19 year olds. Similar patterns have been reported for youth with class 2 and class 3 obesity. Further, there is a trend towards a younger onset of obesity which has the potential consequence of more cumulative exposure (Lee et al. 2010). The prevalence of overweight and obesity does not seem to vary by sex, although differences have been reported among various racial and ethnic groups in the United States. Notably, obesity prevalence is lowest among Whites and highest among Blacks and Hispanics. These same racial/ethnic differences are present in overweight, class 1 and class 2 obesity, but not in class 3 obesity (Skinner et al. 2016). These data are consistent between sexes and show similar trends with age, with older youth having higher obesity prevalence rates in all racial/ethnic groups.

Unfortunately, obesity tracks strongly from childhood into adulthood. Data from the Bogalusa Heart Study have shown that overweight youth have a 47–64% chance of developing class 1 obesity in adulthood. This "canalization" of obesity to adulthood increases as the degree of obesity in childhood increases. That is, among 12 year olds with BMI 95th–98th percentile, 84% develop class 1 obesity in adulthood. Among 12 year olds with BMI >99th percentile, 100% develop class 1 obesity, 88% develop class 2 obesity, and 65% develop class 3 obesity in adulthood. This underscores the need for early prevention strategies and the need for robust treatment of pediatric obesity.

## Etiology

As in adults, obesity in children and adolescents is the quintessential multifactorial, chronic disease. Specifically, there are multiple biological, psychological, and social determinants of, or contributors to, excess adiposity. In addition to the additive effects of these contributors, there are also interactive and multiplicative effects of these influences (Katzmarzyk et al. 2014). Bioecological Systems Theory is a useful framework for organizing the numerous determinants of childhood obesity by depicting individual child-level factors at the center, which include, for example, genetic predisposition, prenatal environment, and child temperament, surrounded by progressively more distant influences such as the family and community. It is important to also recognize that there are critical periods of time in a child's development that are especially vulnerable to insult or influence which in turn may increase the odds of developing obesity. These critical periods include gestation/early infancy, adiposity rebound of early childhood, and adolescence. Adiposity typically increases from birth to one year of age, after which it decreases to a nadir around age 5–7 years. From there, adiposity increases again to adolescence, which is characterized by a rapid increase in adipocyte size and number. Being large for gestational age, rapid weight gain during infancy, and early adiposity rebound each increase the risk for the development of obesity. Further, adipocyte number, which is generally determined by the end of adolescence, is another important risk factor of adult obesity.

## Genetics

One of the primary determinants of obesity is heritability, though the exact contribution is a matter of debate. Twin-twin and nontwin sibling studies suggest that 40–70% of the individual variability in common obesity is due to genetics (Manco and Dallapiccola 2012). The correlation coefficient for monozygotic twin pairs has been reported to be 0.74, dizygotic twin pairs at 0.32, and siblings at 0.24 (Maes et al. 1997). Despite this high degree of correlation, the majority of the causative genes have yet to be identified. From genome-wide association studies, it appears that common obesity results from the additive effects of multiple single nucleotide polymorphisms that each have small contributions. To date, 127 novel loci have been linked with common obesity (Singh et al. 2017).

Unlike the genetics of obesity in adulthood, the genetic influence on obesity in childhood changes with age. For example, polymorphisms in the FTO gene, one of the genes most robustly associated with obesity, varies with age in that there is no association between FTO variants and birth weight, but the association emerges by the first weeks of life and persists through childhood and into adolescence (Manco and Dallapiccola 2012). It has been hypothesized that the prenatal environment may temper the expression of the FTO gene.

In children with *severe, early-onset* obesity, approximately 7% may have genetic mutations or chromosomal abnormalities (Farooqi and O'Rahilly 2008). Monogenic

obesity arises from a mutation in a single gene and most commonly stems from aberrations in the leptin-melanocortin pathway. For normal energy regulation, leptin, secreted by adipose tissue, relays information about energy stores to the hypothalamus. Specifically, leptin stimulates the pro-opiomelanocortin/cocaine and amphetamine-related transcript (POMC/CART) neurons in the arcuate nucleus of the hypothalamus. POMC, via prohormone convertase 1 (PC1), is cleaved into adrenocorticotropic hormone (ACTH) and alpha-melanocyte stimulating hormone (α-MSH), the latter of which stimulates the melanocyte-4 receptor (MC4R) to decrease appetite. Mutations in the genes for leptin (LEP), leptin receptor (LEPR), PC1, POMC, and most commonly, MC4R are associated with early-onset (in first year of life) severe obesity. Additional clinical features are dependent on the specific mutation. For instance, leptin, in addition to inhibiting food intake, also controls reproductive functions and puberty and is involved in T-cell immune response mechanisms. Accordingly, LEP and LEPR mutations are associated not only with severe early-onset obesity but also pubertal delay from hypogonadotropic hypogonadism and poor immunity (Singh et al. 2017). PC1 mutation is associated with early-onset severe obesity and postprandial hypoglycemia, hypogonadism, and hypocortisolemia (Singh et al. 2017). An abnormally high proinsulin level instead of insulin may aid in this diagnosis as PC1 mutation limits the ability to process prohormones into functional proteins. Deficiency in POMC has the added features of pale skin and red hair (due to the lack of α-MSH which regulates melanin synthesis) and adrenal insufficiency from lack of ACTH. MC4R mutations are associated with accelerated linear growth and disproportionate hyperinsulinemia (Farooqi and O'Rahilly 2006). Mutation in the transcription factor, SIM 1 (single-minded 1), has also been implicated in early-onset severe obesity with hyperphagia and increased linear growth. SIM 1 mutation is believed to be associated with a decrease in periventricular MC4R mRNA (Zegers et al. 2014). Finally, mutations in brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin-related kinase B (TrkB), which have a key role in the central regulation of the energy balance, have also been associated with early-onset severe obesity (Waterhouse and Xu 2013).

In contrast to monogenic obesity, syndromic obesity typically has its onset after the first year of life and is usually associated with developmental delay and anomalies of major organs. Examples include Prader-Willi syndrome (PWS), Bardet-Biedl syndrome (BBS), Cohen, Alstrom, Albright's hereditary osteodystrophy, Beckwith-Wiedemann, and Carpenter syndromes.

PWS is due to the loss of function of the long arm of paternally derived chromosome 15 and occurs in 1 in 10,000–25,000 births. PWS is characterized by an early phase (birth to 9 months) of hypotonia, poor feeding, and failure to thrive followed by a later phase of hyperphagia and development of obesity, growth delay, hypogonadism, and learning and behavioral challenges (Khan et al. 2016). Phenotypic characteristics may include short stature, small hands and feet, characteristic facial features including almond shaped eyes, and often scoliosis and strabismus (Cassidy et al. 2012). A key finding in individuals with PWS is notably high ghrelin levels in the fasting and postprandial states compared to normal controls which contributes to the hyperphagia and obesity. Other hormones are also implicated,

such as thyroid and growth hormone (Khan et al. 2016). Finally, hypotonia also contributes considerably to the decreased energy expenditure. Treatment of PWS with growth hormone during childhood may have beneficial effects on growth, body weight and composition, and exercise capacity.

BBS is a pleiotropic autosomal recessive disorder that includes the following cardinal features: obesity, retinitis pigmentosa, postaxial polydactyly, renal anomalies, learning disabilities, and urogenital track abnormalities. The prevalence is 1 in 125,000–160,000 in the general population and to date, 15 genes have been identified which account for this syndrome. It is believed that these genes encode for ciliary function which in turn play a role in leptin receptor trafficking across cell membranes (Guo and Rahmouni 2011). The defect in leptin activity leads to obesity. Alstrom syndrome is another autosomal recessive ciliopathy but much more rare than BBS, with a prevalence of less than 1 in every 1,000,000. Compared to BBS, children with Alstrom are more likely to have sensorineural hearing loss and have a higher incidence of type 2 diabetes mellitus.

Furthermore, many other syndromes that are not primarily associated with obesity often display obesity as a phenotype. These include, for example, Down syndrome, Turner syndrome, and Fragile X.

## Prenatal Contributors

The prenatal environment is another contributor to the development of childhood obesity. Research suggests that stimuli or insults during gestation may alter gene expression via epigenetic changes. Prenatal exposure to maternal obesity (whether at conception or excess weight gain during pregnancy) and gestational diabetes, for example, are strong predictors of large for gestational age (LGA) infants. It is hypothesized that these infants are more likely to have hyperglycemia which in turn increases insulin production and subsequent increase in adiposity during childhood. Infants born small for gestational age (SGA), as from maternal smoking, preeclampsia, or maternal under nutrition, is another predictor of childhood obesity, though the association is not as robust as for infants born with LGA. It is theorized that the undernourished fetus adapts to the poor prenatal environment but then experiences a mismatch in energy utilization and supply when born into the postnatal environment of nutrient abundance. Among SGA infants, those who experience rapid catch-up growth seem to be most at risk for later obesity (Campbell 2016).

## Endocrine Factors

Endocrine causes are rare, accounting for less than 1% of childhood obesity. As a group, these conditions are typically associated with poor linear growth and/or short stature. Cushing's syndrome, for example, is characterized by growth failure in the presence of persistent weight gain. Clinical features additionally include moon facies, hirsutism, acne, and wide, violaceous striae. Most cases of Cushing's

syndrome are iatrogenic though rarely it can arise from pituitary or adrenal tumors. Growth hormone deficiency is associated with growth deceleration and abdominal accumulation of fat. Bone age and puberty are also delayed, though not always. Hypothyroidism alone does not cause severe obesity in childhood though it can be associated with lesser forms of obesity. As such, clinical guidelines do not support the routine screening of youth with obesity for hypothyroidism.

## Hypothalamic Obesity

Although most obesity is related to aberrations in energy-sensing signals at the level of the hypothalamus, hypothalamic obesity generally refers to obesity due to damage to this area of the brain as from brain tumor, inflammation, trauma, radiation, or aneurysm. Hypothalamic obesity has been identified in 30–50% of children who had surgical resection of brain tumors, particularly craniopharyngiomas and astrocytomas. In contrast to common obesity, hypothalamic obesity is characterized by several unique endocrine differences. For instance, children with hypothalamic obesity tend to have more severe forms of leptin resistance, corrected for BMI, than those with common obesity. Further, where peripheral insulin resistance drives β-cell compensatory hypersecretion of insulin in common obesity, abnormal neural regulation of β-cells is characteristic of hypothalamic obesity. There is a suggestion that this increased insulin secretion without insulin resistance in hypothalamic obesity is a causative contributor to extra growth. Finally, some studies suggest that hypothalamic obesity is also associated with decreased sympathetic tone which in turn may decrease metabolic rate. The phenotype of hypothalamic obesity is extreme hyperphagia, often manifesting as food-seeking behavior or foraging, and often chronic fatigue. Importantly, hypothalamic obesity is typically resistant to the usual calorie restriction and exercise therapy that is the mainstay of common obesity treatment. Several medications have been examined as possible candidates for the treatment of hypothalamic obesity in children, all with only modest effect in very small samples. These medications include: stimulants such as dextroamphetamine, the somatostatin analogue, octreotide, which blocks insulin secretion, and the glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide (Kim and Choi 2013). Roux-en-Y gastric bypass surgery may have some potential as an effective treatment but long-term studies are lacking (Bretault et al. 2013; Weismann et al. 2013).

## Dietary Factors

Despite the obvious assumption that youth with obesity must be consuming excess calories over energy requirements, the research to support this is limited. Some reports paradoxically suggest that youth with obesity have lower energy intake. This may be related to limitations of measurement and also to the variable contribution that the type of nutrient rather than quantity of nutrient may play in the development of obesity. However, for youth, the role of dietary composition in the development of

obesity is not well understood. For instance, it is suggested that dietary fats may play a role in the development of childhood obesity but evidence thus far does not support a specific recommendation regarding quantity and/or quality of fat needed to prevent childhood obesity. Further, data on protein intake is inconsistent and does not allow for firm conclusions. Regarding beverages, the contribution of sugar sweetened drinks to obesity is not clear, although they do contribute to extra energy intake. Fruit juice intake, on the other hand, is *not* predictive of obesity in several longitudinal studies. Eating breakfast and eating family meals are other dietary behaviors which have been variably identified as protective against the development of childhood obesity, but again the evidence is not uniformly consistent (Agostoni et al. 2011).

For infants, much research has identified breast feeding as another protector against childhood obesity, yet these results are also not consistent. Proposed mechanisms that may account for the protective effect are that formula-fed infants, compared to breast-fed infants, may rely more heavily on external cues to cease eating rather than their own internal cues of satiety and formula-fed infants consume more protein than breast-fed infants. Although there has been some research assessing the relative contribution of different macronutrients in infants' diets to the development of childhood obesity, the results are limited. There is scant evidence that high-protein diets in infancy may contribute to obesity but insufficient evidence to suggest that carbohydrate or fat content is a factor. Early introduction of solids (before age 3–5 months, depending on the study) is a more robust risk factor for the development of childhood obesity and much less so is delayed transition from bottle to a sippy cup. A few studies suggest that tea and coffee consumption at age 2 years contributes to severe obesity but there are no prospective studies that examine the effect of juice or sugar sweetened beverage consumption during first 1000 days as a risk factor.

## Physical Activity

Physical activity and sedentary behaviors have also been studied as potential contributors to childhood obesity. Although data on the causal direction of physical inactivity and obesity in youth is inconsistent, most studies suggest that children with obesity are less active than their lean counterparts, have poorer movement skills, and prefer sedentary activities. While the WHO and other health-related nongovernment organizations recommend that children engage in at least 60 minutes of moderate to vigorous physical activity daily, many do not, particularly adolescents. Sedentary behaviors such as television viewing, playing video games, or with computers and phones may be taking the place of physical activity. Some studies have identified a dose-response relationship between the hours spent watching TV and the prevalence of obesity in children. The relationship between video game or computer use and obesity is less consistent and may be related to the placement of food advertisements in these domains and/or whether or not the games involve movement, as in exergames (Schmidt et al. 2012).

The relative contribution of excess energy intake versus decreased energy expenditure in the development of childhood obesity is a matter of debate. Some longitudinal studies support that excess energy intake is the primary driver of childhood obesity while others support that decreased energy expenditure in the primary driver. Yet others are inconclusive (Bleich et al. 2011).

## Sleep

Poor sleep, including decreased quality and/or quantity, is also associated with obesity. Studies supporting this correlation are particularly strong for children, in contrast to infants and adolescents. For adults, aberrations in leptin and ghrelin have been implicated as one of the potential causal mechanisms between poor sleep and obesity. However, little data supporting this exists for children. Poor sleep, at least in adolescents, has also been associated with poor diet quality, and a small study in children identified that short sleep duration and poor sleep quality were associated with emotional eating and eating in response to external cues, respectively. These studies suggest that eating behaviors may additionally contribute to the relationship between obesity and sleep (Miller et al. 2015).

## Psychosocial Contributors

As in adults, psychosocial factors in youth, including mental illness and stress, may not only be a consequence of obesity but also contribute to the development of obesity. Indeed, the relationship between mental illness and obesity is bidirectional. It is important to recognize, however, that although the prevalence of depression, for example, is not higher among youth with obesity in the general population, it is higher among youth with obesity who seek weight management care. This may be true for anxiety as well, though the evidence is weaker. Several mechanisms by which mental illness contributes to obesity have been proposed. For example, mental illness, often associated with inflammation, can lead to activation of the hypothalamic-pituitary-adrenal axis which in turn increases cortisol production and subsequent fat deposition. Additionally, mental illness is often accompanied by poor eating, limited physical activity, and sleep disturbances, all of which may lead to obesity.

Curiously, there is also a modest association between attention-deficit/hyperactivity disorder (ADHD) and obesity in youth. It is hypothesized that the deficient inhibitory control seen in children with ADHD could lead to overconsumption when not hungry. Further, strong delay aversion (manifesting as impulsivity) could favor the tendency to eat easy and convenient, calorie dense processed foods instead of preparing a meal. Finally, deficits in attention or executive function could cause difficulty in adhering to regular eating patterns that support a healthy weight. The "reward deficiency syndrome" has been alternatively described to account for the relationship between ADHD and obesity. This is referring to relatively low levels of

dopamine activity in attentional areas and brain reward pathways which result in an attempt to compensate by using reinforcing behaviors such as eating (Cortese et al. 2008).

Recently, research has focused on the role of child temperament and parenting style on the development of childhood obesity. For instance, research suggests that infants and young children with "negative temperaments" who react quickly and strongly to stimuli and are difficult to soothe are susceptible to weight gain. Proposed mechanisms include that (1) these infants are more likely to be fed in an attempt to soothe them, and (2) these infants are prone to later difficulties with self-regulation such as limiting the consumption of highly palatable foods. Regarding parenting style, some evidence suggests that both permissive and authoritarian (strict disciplinarians) parents (but authoritarian more than permissive) are more likely to raise children with obesity compared to authoritative parents who rely on positive reinforcement and limited punishment (Anzman-Frasca et al. 2012). Additionally, the quality of the parent-child relationship or "goodness of fit" between the parents' and child's style may also influence these associations between child temperament, parenting style, and childhood obesity.

### Environmental Contributors

Many of the environmental determinants of obesity, such as food insecurity, close proximity to fast food restaurants and convenience stores (often replete with high calorie foods), and food deserts, are not unique to the pediatric population. Other environmental exposures that have been implicated as contributors to childhood obesity include the early use of broad spectrum antibiotics and the use of obesogenic psychotropic medications, such as atypical antipsychotic drugs.

## Comorbidities

### Cardiovascular Comorbidities

Youth with obesity suffer from many of the same risk factors and comorbidities as adults with obesity including hypertension, dyslipidemia (most commonly exhibited as high levels of triglycerides and low levels of HDL-cholesterol), and elevated levels of inflammation (e.g., C-reactive protein) and oxidative stress (e.g., oxidized LDL-cholesterol). The prevalence estimates of prehypertension (often defined as systolic and/or diastolic blood pressure $\geq$ 90th to $<$95th percentile) and hypertension (often defined as systolic and/or diastolic blood pressure $\geq$ 95th percentile) among children and adolescents with overweight or obesity are approximately 20% and 5%, respectively (Yang et al. 2016). In contrast, estimates are much lower in the overall pediatric population: prehypertension 10% and hypertension 1.5% (Xi et al. 2016). Similarly, the prevalence of dyslipidemia (defined as high total cholesterol, low HDL-cholesterol, or high non-HDL cholesterol) is approximately 18% in youth

with overweight and 39% in youth with obesity vs. only 15% in youth with normal weight (Kit et al. 2015). Early signs of subclinical cardiovascular disease are also commonly found in youth with obesity such as endothelial dysfunction (a precursor of atherosclerosis), arterial stiffening, and thickening of the carotid arteries. Not all studies have been consistent in these findings, especially in youth with moderate obesity or overweight, and novel cardiovascular biomarkers are needed to improve risk stratification. Nevertheless, the emergence of these types of vascular problems early in life sets the stage for increased risk of myocardial infarction and/or stroke later in life. Cardiovascular disease should be viewed as a chronic condition that evolves over many decades, the foundations of which are laid during childhood. Therefore, when cardiovascular risk factors and vascular problems surface within the first two decades of life, particularly in the context of excess adiposity, they should be taken seriously and treated with appropriately intensive interventions.

## Metabolic and Endocrine Comorbidities

Children and adolescents with obesity are also at risk of developing many chronic metabolic and endocrine-related diseases such as type 2 diabetes mellitus, metabolic syndrome, and polycystic ovary syndrome (PCOS), and may additionally experience either accelerated or delayed pubertal development.

Insulin resistance, along with central adiposity, increases the risk of type 2 diabetes, a disease that is predicted to afflict approximately one out of three children born today at some point in their lifetime. Type 2 diabetes, while still relatively uncommon in childhood, affects approximately 20,000 children and adolescents in the United States and is projected to affect nearly four million children globally by the year 2025 (Lobstein and Jackson-Leach 2016). Obesity predisposes to type 2 diabetes primarily through the worsening of insulin resistance, which can often lead to the development of hyperglycemia and/or impaired glucose tolerance (i.e., prediabetes). Data from adult trials have demonstrated that the onset of type 2 diabetes can be delayed and/or prevented altogether with intensive lifestyle counseling or in response to treatment with certain medications such as metformin, orlistat, thiazolidinediones, or GLP-1 receptor agonists. Considering the debilitating nature of type 2 diabetes and the strain it places on the healthcare system, it seems prudent to aggressively treat obesity and metabolic dysfunction starting early in life with the explicit goal of delaying or preventing its development in later in adulthood.

Metabolic syndrome is a clustering of five factors including increased waist circumference (central adiposity), high blood pressure, elevated fasting blood glucose, low HDL-cholesterol, and hypertriglyceridemia. Although a formal definition of metabolic syndrome exists for adults, there is currently no consensus for youth. Reasons for this lack of clarity on the definition of metabolic syndrome in the pediatric population include the instability of cardiometabolic risk factors during pubertal development, lack of hard clinical outcomes demonstrating that the presence of metabolic syndrome in childhood increases later risk in adulthood, limitations of a dichotomous designation despite the continuous nature of the relevant risk

factors, and an incomplete understanding of the underlying pathophysiology of the syndrome. Despite uncertainty, it is thought that excess abdominal obesity and insulin resistance may be requisite and unifying features of the metabolic syndrome (i.e., central to its pathology). Yet, contrary to the evidence base in adults, pediatric data are mixed as to whether the measurement of waist circumference adds meaningful information to risk stratification beyond that of BMI alone.

Polycystic ovary syndrome is another endocrine-related condition associated with obesity and insulin resistance. It is characterized by elevated androgen levels, irregular menses, and excess body hair. First line treatment for PCOS often includes weight loss and exercise, with metformin sometimes used to target insulin resistance. Like many conditions, PCOS most commonly affects those with a genetic predisposition to the syndrome and currently it is unclear whether obesity precedes its development or instead is a consequence of the physiological sequelae. However, treatment of the underlying obesity and insulin resistance remains the mainstay of clinical management.

## Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is an umbrella term used to classify a range of liver disorders related to excess fat. The earliest stage is hepatic steatosis, which is characterized by the deposition of lipid droplets within >5% of hepatocytes. Unchecked, NAFLD can progress into more severe forms of liver disease, including nonalcoholic steatohepatitis (NASH). NASH is distinguished from simple steatosis by the presence of hepatocyte injury (hepatocyte ballooning and cell death), inflammation within cells, and/or collagen deposition (fibrosis). NASH can progress further to cirrhosis and hepatocellular carcinoma, which eventually can lead to liver transplantation or death (Feldstein et al. 2009). The overall prevalence of NAFLD is estimated to be 13% in youth aged 2–19 years old (Schwimmer et al. 2006). Yet, among youth with obesity, the prevalence of NAFLD ranges from 30 to 90% (Schwimmer 2016). This wide heterogeneity in prevalence rates is likely due to a number factors including genetic predisposition (Santoro et al. 2012), differences in measurement techniques and subsequent clinical diagnosis (Schwimmer et al. 2014), and racial/ethnic disparities (Nobili et al. 2015). Further, the prevalence also increases with degree of adiposity, with 60–80% of youth with severe obesity presenting with biopsy-proven NAFLD (Xanthakos et al. 2006, 2015). Among youth with severe obesity and NAFLD, approximately 20% have NASH. Fibrosis is a less common feature in pediatric NAFLD, which is consistent with the chronic nature of this disease – one that develops over a period of decades.

Despite the high prevalence and seriousness of NAFLD, effective treatment strategies in youth have yet to be identified. Lifestyle modification therapy (i.e., diet, physical activity, and behavioral modification) is the cornerstone of pediatric NAFLD and obesity treatment. However, even under intensive inpatient treatment conditions, lifestyle modification as a monotherapy often fails to sustainably reverse

NAFLD in youth (Koot et al. 2016). Pharmacotherapy options such as metformin and vitamin E have shown to be no more effective than placebo or lifestyle modification therapy in children with NAFLD (Lavine et al. 2011; Nobili et al. 2008). Cysteamine bitartrate, an adiponectin multimer, has shown only modest improvements in biomarkers of NAFLD without histological improvements in youth with NAFLD (Dohil et al. 2012; Schwimmer 2015). Bariatric surgery has shown promise as a treatment approach in adults (Mummadi et al. 2008) but remains controversial as a NAFLD treatment for the pediatric population (Xanthakos and Schwimmer 2015). However, there is evidence that the laparoscopic sleeve gastrectomy procedure can reverse liver biopsy features of NASH in 90% of cases among youth with severe obesity and NAFLD (Manco et al. 2017). Nevertheless, even if bariatric surgery is proven effective and safe in the long-term, the overall impact will likely be low, given the limited accessibility and relatively low uptake of this treatment. Moreover, surgery is not indicated in youth with milder forms of obesity or younger children and since NAFLD occurs across the entire BMI-spectrum and is not exclusive to youth with severe obesity (Schwimmer et al. 2006), alternative scalable treatment strategies are needed.

## Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing and is characterized by frequent partial or full obstruction of the upper airway which can result in accompanying hypoxia and poor sleep quality. The gold standard for the diagnosis of OSA is the polysomnogram. Obstructive apneas and hypopneas per hour (AHI) during sleep define the severity: AHI 1–5 per hour is mild OSA; AHI 6–10 per hour is moderate OSA; and AHI >10 per hour is severe OSA. While data are not entirely consistent, on the whole, OSA seems to be more prevalent among youth with obesity than their normal weight peers. Further, although there are some reports linking untreated OSA in youth with obesity and derangements in cardiovascular, metabolic, inflammatory, and neurocognitive measures, these studies are limited. Treatment options include adenotonsillectomy, which is curative in less than 50% of youth with accompanying obesity, and positive airway pressure which is limited by poor compliance. Bariatric surgery has shown some promise as an effective treatment in small studies.

## Musculoskeletal Comorbidities

Obesity in youth is associated with a higher prevalence of musculoskeletal pain, fractures, and injuries. Obesity-related orthopedic conditions that are unique to the pediatric population include slipped capital femoral epiphysis (SCFE) and Blount's disease. SCFE, which by definition is seen before growth plate closure, occurs when the femoral head either acutely or chronically slips posteriorly and inferiorly off the femoral shaft because of sheer force. Increased body mass and hip abduction

generally seen in youth with obesity are contributors to SCFE. The typical presentation is a limp and/or pain in the groin, thigh, or knee. Surgical treatment in indicated. Blount's disease is a skeletal disorder causing a varus deformity of the tibia. This is a developmental condition caused by excess stress on the medial tibial condyle and manifests as bowed legs. Treatment includes bracing and sometimes corrective orthopedic surgery.

## Psychological Comorbidities

Overall, mental health issues appear to be more common among youth with obesity compared to their normal-weight counterparts. Based on a large United States National Health Survey, children with obesity were 1.1–1.2 times more likely to have poor mental health (Tevie and Shaya 2015). However, studies examining the relationship between specific psychiatric disorders, whether internalizing (e.g., depression and anxiety) or externalizing (e.g., oppositional defiance disorder) and obesity in youth are mixed.

Generally, community-based samples of youth with obesity do not differ from their normal weight peers with respect to internalizing disorders. However, obesity treatment-seeking youth tend to have higher rates of anxiety and depression. Some studies suggest 30–50% of youth seeking weight management treatment have depression, and one third have anxiety (Latzer and Stein 2013). The degree of obesity and other variables such as bullying have been identified as mediators between the depression-obesity relationships. For instance, it appears that as children become adolescents and move to adulthood, there are increased rates of both depression and anxiety with increasing weight. Further, increased rates of suicidal ideation and self-injurious behavior have been found in adolescents with obesity compared to their normal weight peers, though there is no difference in the rate of completed suicide (Small and Aplasca 2016).

Another area that has received much attention is the relationship between attention-deficit/hyperactivity disorder (ADHD) and obesity. Research suggests that the prevalence of obesity in youth with ADHD is higher than in those without ADHD. However, youth with ADHD who are prescribed stimulant medication have lower rates of obesity than their non-ADHD peers. More general externalizing behaviors (e.g., disobedience, aggression) have also been associated with overweight/obesity in childhood (Rankin et al. 2016). For both internalizing and externalizing concerns, it is often unclear if the symptoms are contributors to or a result of obesity.

Youth with obesity are also more likely to report extreme dieting behaviors, including the use of laxatives, diet pills, and self-induced vomiting, and there is an increased lifetime prevalence of bulimia nervosa for treatment seeking youth with obesity (Rankin et al. 2016). Although not necessarily endorsing full binge eating disorder (BED) criteria, 20–40% of adolescents and adults with severe obesity endorse binge-eating symptoms. Further, emerging evidence suggests that approximately 5% of younger children (i.e., 6–10 years old) may meet full criteria for BED (Latzer and Stein 2013).

Decreased self-esteem has also been associated with obesity in several studies, particularly as children age. Youth with obesity report higher body dissatisfaction than their normal-weight peers. The relationship between increasing weight and decreasing self-esteem is not necessarily linear; several other factors have been found to influence or attenuate the relationship, for example gender, race, or country of residence. However, worldwide, and regardless of age and gender, bullying has been found to contribute to decreased self-esteem for children with obesity (Latzer and Stein 2013).

Children with overweight and obesity are at much greater risk for being bullied than their normal-weight peers, with some estimates suggesting the rate is 4–8 times higher (Rankin et al. 2016). Bullying comes from many perpetrators, including peers, educators, parents, and health care providers, and excess weight is the most common reason individuals are bullied. As noted previously, studies also show that children who are bullied are more likely to have decreased self-esteem and increased internalizing and externalizing problems. Furthermore, youth with obesity who are bullied about their weight are more likely to avoid school and have lower school performance (Puhl and King 2013).

Finally, health-related quality of life (HRQoL) is found to be lower for those with obesity, and this tends to become more pronounced as children get older. Compared to healthy children, those with severe obesity report decreased HRQoL across all domains (i.e., physical, social, emotional, and school functioning) and are over five times more likely to have impaired overall HRQoL. Strikingly, children with severe obesity report similar HRQoL to children diagnosed with cancer, a group previously thought to have the lowest QoL scores compared to peers with or without other medical conditions (Schwimmer et al. 2003).

## Cancer

Obesity in adulthood has been associated with the development of at least 13 cancers (Lauby-Secretan et al. 2016), and both the degree and duration of obesity further potentiate these risks (Arnold et al. 2016; Renehan et al. 2008). Presently, the causal link between obesity and cancer is not completely understood. There have been multiple mechanisms proposed to explain the underlying biology, including: (1) chronic systemic inflammation, driven by proinflammatory monocytes/macrophages and cytokines that populate the adipose tissue (Germano et al. 2008), (2) increased circulating proangiogenic factors, required for adipose tissue expansion (Sica et al. 2008), and (3) enhanced production of sex hormones, particularly estrogen and its metabolites, due to excess adiposity (Ladikou and Kassi 2017). Although these mechanisms and their interactions have been documented in adults with obesity and cancer, their presence and significance within a pediatric population has yet to be established.

The cumulative lifetime burden of obesity has been shown to contribute to and exacerbate future cancer risk (Arnold et al. 2016). Recently, associations between obesity in childhood and adult-onset cancers have been established (Lauby-Secretan

et al. 2016). It should be noted that these studies are limited and more research is needed to provide a causal link. However, from a prevention perspective, treating obesity may be a means of reducing future cancer risk or improving cancer treatment outcomes, especially since adults with obesity have inferior cancer outcomes for certain tumor types (Lohmann et al. 2016). Limited studies in pediatric hematologic malignancies have also shown inferior survival, increased relapse, and increased treatment-related mortality among pediatric patients with obesity (Orgel et al. 2014).

### Mortality

Providing evidence of a link between childhood obesity and adult mortality is a challenging undertaking. Epidemiological studies take decades of time and millions of children followed over their entire lifespan in order to adequately assess whether associations exist. Despite these challenges, there are a limited number of studies that have attempted to examine whether obesity in childhood leads to early mortality from all-causes, cardiovascular disease, and type 2 diabetes. For example, in Israel where all adolescents undergo a medical evaluation at age 17 years in anticipation of mandatory military service, large amounts of data have been collected since 1967 which has allowed for examination of mortality outcomes on over two million adolescents (Twig et al. 2016a, b). Key findings from studies using these data include that adolescents with obesity were more likely to have died from coronary heart disease, stroke, sudden death, and all causes combined later in adulthood when compared to adolescents whose BMI was 5th to 24th percentile at age 17; the risk of death for total cardiovascular causes was more than 3.5 times higher. Importantly, the increased risk of cardiovascular disease mortality in adulthood was not exclusive to adolescents with obesity; the increased risk was present among overweight youth and even youth at the 75th–84th BMI percentile (Twig et al. 2016b). Similarly, there was a trend of increased mortality from type 2 diabetes in adolescents with obesity (Twig et al. 2016a). Smaller studies in groups of American Indians have shown that obesity in childhood is associated with premature death and death from all-causes in adulthood (Franks et al. 2010). While these studies are not definitive and it is difficult to determine causality, they suggest that obesity in childhood increases the risk of premature death from chronic diseases.

## Individual/Patient-Level Prevention and Intervention

### Settings and Targets of Prevention and Intervention Strategies

The first step in the prevention and intervention of obesity is identification of the problem. The primary care clinic with the schedule of frequent visits during childhood is the ideal setting for obesity screening. The American Academy of Pediatrics (AAP) and other US national guidelines recommend universal annual assessments of children's BMI starting at age 2 years using the CDC normative BMI percentiles to

diagnose overweight or obesity. For children under 2 years of age, it is recommended that health practitioners use the WHO charts to identify obesity when the sex-specific weight-for-recumbent length is ≥97th percentile. Strong evidence suggests that treating obesity early in childhood, specifically during the preschool years (ages 2–5 years old), offers the best chance of achieving positive outcomes. Conversely, later identification and intervention during the adolescent years is associated, on average, with relatively poor outcomes in terms of adiposity/BMI reduction. Therefore, primary care providers (PCPs) are well-positioned to spot early signs of trouble in relation to BMI trajectories in younger children and point the family in the right direction to receive the help they need. Further, the PCP is appropriately positioned to identify signs and symptoms which would suggest a diagnosis of common obesity versus monogenic-, syndromic-, or endocrine-related obesity. These may include early-onset severe obesity with hyperphagia, developmental delay, poor linear growth, and hypogonadism. Additionally, youth with obesity should be routinely and regularly screened for comorbid conditions including diabetes, hypertension, dyslipidemia, NAFLD, PCOS, obstructive sleep apnea, musculoskeletal pain, mental illness/stress, and bullying.

Current standards for PCPs include preventative guidance for all children and adolescents, irrespective of BMI, regarding diet and physical activity, with both the individual and family as agents of change (Barlow 2007). Recommendations include structured and balanced meals, moderate to vigorous physical activity and limited screen time. PCPs are to recommend zero sugar-sweetened beverages and to suggest whole fruit over fruit juice. Various groups have developed campaigns and slogans to assist with these recommendations (e.g., 5–2–1–0 for 5 fruits/vegetables, 2 hours or less of screen time, 1 hour of physical activity, and 0 sugar-sweetened beverages daily). In 2011, the United States Department of Agriculture (USDA) began using MyPlate, rather than the MyPyramid, for an easy resource to develop healthy meals. MyPlate is a visual of a plate, sectioned into quadrants, with a cup attached. The quadrants each represent a food group: protein, grain, fruit, and vegetable, and the cup represents dairy. This visual is meant to guide appropriately balanced meals.

For the child with overweight or obesity, the AAP recommends a staged approach to intervention (Barlow 2007). If a child is overweight with risk factors or obese, they move to the Stage 1 which includes the same preventative messages delivered by the PCP for normal weight youth but at more frequent intervals and with the goal of BMI reduction. If BMI does not improve after 3–6 months, it is recommended that the patient be moved to Stage 2, wherein monthly visits are recommended. Stage 2 interventions include a more structured approach such as meal planning with a dietician, screen time reduction to ≤1 hour per day, structured and supervised physical activity, self-monitoring of behavior changes, and planned reinforcement for behavior changes. Patients who do not decrease their BMI in Stage 2 should be referred to structured multidisciplinary weight management programs (Stage 3), which are typically beyond the PCP office, and may include specialized diets and/or pharmacotherapy. Stage 4 includes tertiary care multidisciplinary programs for childhood obesity and may include pharmacotherapy, device therapy, and/or bariatric surgery for eligible patients.

In spite of the guidelines suggesting a staged approach to the treatment of childhood obesity, studies that have evaluated the effectiveness of primary care-based obesity interventions have generally demonstrated lackluster results. This should not come as a surprise given the recalcitrant nature of obesity, demanding intensive and comprehensive treatment, and the types of constraints on time and resources faced by many PCPs in the clinical setting. Tertiary care programs specializing in weight management are much better equipped to appropriately manage youth with obesity. Many of these programs offer comprehensive services with a multidisciplinary team that often includes a bariatrician, registered dietician, behavioral psychologist, and physical therapist/exercise physiologist. In some of the more advanced programs, treatments range from standard lifestyle modification therapy to low-calorie diet plans, pharmacotherapy, and bariatric surgery. Owing to the complexity of obesity and its strong biological underpinnings, many children and adolescents will require the comprehensive and intensive treatment approaches often found exclusively in tertiary care programs. Another intensive treatment modality that may have some utility is immersion therapy in which the child lives in a therapeutic environment (e.g., special camps or hospital setting) for an extended duration of time. The immersion programs which also include cognitive behavioral therapy have better long-term outcomes than those that do not (Kelly and Kirschenbaum 2011).

In addition to the setting in which obesity interventions are delivered, the *target* of the intervention (i.e., the youth alone, the parent alone, or the youth and parent together) has been examined as a variable which may predict success. Parents are often involved in the intervention for pediatric patients and the data are clear that parent involvement is critical for younger children. From a practical standpoint, parents make food decisions and purchases for the family. Further, children mimic the eating behaviors and food preferences of their parents. As such, parent modeling of healthy behaviors is an important aspect of intervention and research suggests that increased parent involvement in the treatment of obesity for young children predicts greater weight loss (Jansen et al. 2011). Additionally, some have found that treating only parents without children present for the intervention results in significant weight change for younger children. For adolescents, the data are not as clear. Adolescence is a time of increased independence from parents and time spent with peers. However, as it relates to healthy eating in particular, it is important to consider that parents continue to do most of the food purchasing. Additionally, teenagers eat about five meals per week with their families. Earlier research evaluating parent involvement in adolescent obesity treatment suggested that there were no differences when parents were or were not involved in the intervention. More recently, researchers identified that parent self-monitoring by way of food logs and parent weight loss were most predictive of adolescent weight loss; parent self-report of pressuring their children to eat at baseline was associated with less weight loss in adolescents (Sato et al. 2011). In all, it is clear that parental influence on youth does affect weight loss, though the strength and pattern of these relationships changes with age.

At present, there are no accepted metrics that define successful BMI reduction for youth with obesity. For many children and adolescents with obesity, achieving normal weight with nonsurgical means is not a practical goal. Therefore, with further research, it will be important to identify thresholds of BMI reduction associated with meaningful improvements in risk factors and comorbidities to guide decisions about treatment type and intensity. Some evidence suggests that a BMI z-score reduction of at least 0.25 may be clinically meaningful, whereas other data suggest a higher threshold of reduction is required – 0.5 BMI z-score units. However, it stands to reason that the thresholds of meaningful BMI reduction may vary by obesity severity. For example, a child with severe obesity may need to lose more weight than a child with moderate obesity to achieve clinically meaningful improvements in cardiometabolic risk factors.

## Lifestyle Modification Therapy

As for adults, comprehensive lifestyle modification therapy for youth generally consists of dietary-, physical activity-, and behavioral counseling, all of which should ideally address various aspects of caloric intake and energy expenditure. A general principal is to focus on small, concrete changes that the patient and family can reasonably apply to their daily lives. Examples include reducing or eliminating sugar-sweetened beverage consumption, adding fruits and vegetables to the menu, cutting back on fast food meals, reducing portion sizes, and incorporating more physical activity into daily routines. Given the advantages of self-monitoring on behavior change, food logging and/or activity monitoring are often recommended. Treatment programs also typically work with patients and families to predict and problem-solve for more challenging times, for example, how to manage holidays or relapse, and often in tertiary care programs, a mental health provider will use cognitive-behavior therapy approaches such as teaching coping skills or cognitive restructuring for other individually relevant topics (e.g., emotional eating) with the patients and/or their parents.

Most evidence suggests that better outcomes are achieved when lifestyle modification therapy is introduced early in childhood before the onset of severe obesity. In contrast, lifestyle modification therapy used alone is generally ineffective when deployed in adolescents with severe obesity. A comprehensive review of the literature for the United States Preventative Services Task Force recently demonstrated that lifestyle modification counseling involving 26 hours of contact over 6 months was associated with meaningful reductions in BMI (defined as BMI z-score reduction of 0.25 units) among children and adolescents. The report also concluded that 52 hours of contact over 12 months was associated with a greater degree of BMI reduction. Despite these findings, it should be noted that 26+ hours of in-person contact is impractical for many families and that attrition rates are high in pediatric weight management programs. As motivation wanes over time, adherence to healthy lifestyle habits also wanes, and further, in response to weight loss, the body initiates

a cascade of countervailing forces making compliance to lifestyle recommendations even that much more difficult. Therefore, in the real-world clinical setting, where there are no incentives for attending visits like there may be for research studies, lifestyle counseling alone is often insufficient to elicit clinically meaningful and durable BMI reductions in most youth with obesity, yet should serve as the backbone of treatment. Early identification (perhaps within weeks of treatment initiation) of those who are most likely to be unsuccessful with lifestyle modification therapy alone and preemptive escalation of therapy will likely be the key to improving outcomes.

## Pharmacotherapy

Since obesity is largely biologically driven, it stands to reason that treatments that target the underlying pathophysiology of excess adiposity, such as medications, may enhance outcomes (Mead et al. 2016). However, the two most well-studied medications in children and adolescents, orlistat and metformin, are only modestly effective. Orlistat, a lipase inhibitor, is the only FDA-approved obesity medication for adolescents ages 12 and older. The degree of BMI reduction with orlistat treatment is relatively small (less than 3%) and gastrointestinal side effects hamper its widespread use. Metformin, a biguanide, is not FDA-approved for an obesity indication in youth but is sometimes prescribed to treat insulin resistance in the context of obesity. Pediatric clinical trials have demonstrated modest BMI reduction (approximately 3%) with metformin treatment in adolescents without diabetes accompanied by a side effect profile characterized by mild-moderate gastrointestinal discomfort (Park et al. 2009). Other less well-studied medications, including exenatide and topiramate, have demonstrated similarly modest weight loss but reasonably good safety profiles. Phentermine is sometimes used in an "off-label" fashion to treat obesity in adolescents yet no randomized clinical trials (at least in the modern era) have been performed in the pediatric population.

One of the challenges currently facing the field of pediatric obesity medicine is determining appropriate indications for the use of pharmacotherapy in youth with obesity. All medications have risks and these need to be carefully balanced against the prospect of benefit while acknowledging the known perils of persistent obesity. As more studies are performed in the pediatric population, clarity should begin to emerge regarding proper indications for the use of obesity medications. It will be imperative to identify medications with strong long-term efficacy and acceptable safety profiles considering treatment may be (and probably should be) life-long given the chronic nature of this disease. Medications should be used as tools along with comprehensive lifestyle modification therapy. Pharmacotherapy used in the absence of behavior change is likely to be ineffective. Although the field of pediatric obesity pharmacotherapy is in its infancy, a number of new obesity medications have been recently approved by the FDA for adult use, offering hope that clinical trials in children and adolescence will soon commence.

## Bariatric Surgery

Bariatric surgery is typically reserved for adolescents with severe obesity and significant obesity-associated comorbidities. Current guidelines suggest bariatric surgery can be considered for adolescents with a BMI $\geq$35 kg/m$^2$ with serious comorbidities such as type 2 diabetes, steatohepatitis, pseudotumor cerebri, and/or sleep apnea, or for adolescents with BMI $\geq$40 kg/m$^2$ with less severe comorbidities. Guidelines also recommend that the adolescent candidate should have achieved Tanner IV or V pubertal development and completed at least 95% of expected linear growth to be eligible for surgery. In addition, candidates should have a strong understanding of the lifestyle changes required after surgery, demonstrate mature decision-making ability, and have evidence of strong social support. The most commonly performed surgeries for adolescent obesity are currently Roux-en-Y gastric bypass (RYGB) and the vertical sleeve gastrectomy (VSG). The adjustable gastric band has fallen out of favor and is seldom used owing to its inferior weight-loss efficacy compared to RYGB and VSG and concerns regarding band slippage and other side effects. While bariatric surgery is a highly effective obesity treatment for most adolescents with severe obesity, with studies reporting approximately 30% average BMI reduction at 1–2 years, the procedures are irreversible, life-altering, and are associated with long-terms risks such as micronutrient deficiencies. Moreover, little is known about long-term durability and risks, and as such, decision-making about bariatric surgery in adolescents has been controversial (Doyle et al. 2014). These factors likely explain the low uptake of bariatric surgery, which is on the order of 1000 procedures per year in the United States despite the fact that 3–4 million adolescents meet the BMI indications for bariatric surgery. Even as the evidence base of long-term outcomes matures, bariatric surgery will likely remain a low volume treatment owing to its extreme nature and irreversibility.

## Device Therapy

Although yet to be tested in the pediatric population, obesity device therapy holds promise as an effective and safe treatment modality for children and adolescents. The intragastric balloon occupies stomach volume and thereby reduces hunger and enhances satiety. Adult trials have reported 5–10% weight loss with 6 months of treatment. One small pediatric trial reported a BMI reduction in the range of 8–10% with approximately 18 weeks of treatment. Vagal nerve blockade or VBLOC is another promising device therapy for obesity through its ability to reduce food intake. One adult trial reported mean weight loss of approximately 8% with 2 years of treatment. No pediatric trials of VBLOC have been conducted to date. Although the degree of weight loss with device therapy appears to be modest-moderate, the relative safety and reversibility of these treatments make them potentially attractive for the pediatric population.

## Population-Based Prevention and Intervention

The primary setting for population-based prevention programs has been within the school. However, these programs generally show only very small mean BMI reductions, with age affecting findings. Programs that target only school-age children show modest BMI reductions but those that focus exclusively on teenagers do not. Other factors that are associated with increased effectiveness of school-based programs include (1) addressing multiple components, e.g., eating, physical activity, attitudinal changes, and environmental modifications, (2) parental involvement, and (3) longer duration, especially those lasting at least a year. Although schools are a primary setting for prevention programs, other important venues include the home, childcare centers, primary care clinics, and the broader community; research supports that outcomes are better for those programs that involve more than one setting.

With the dramatic increase in the prevalence of childhood obesity world-wide, prevention strategies at the national level have taken shape. For example, in the United States, there have been several legislative and regulatory changes, as well as voluntary agreements with public and private organizations to improve the weight status of youth. These have come largely as a result of the White House Task Force on Childhood Obesity and its Let's Move! initiative. An example of passed legislation is the new nutrition standards for public schools including standards for foods that compete (i.e., a la carte) with the government subsidized school lunch. Private groups have encouraged the development of hospitals earning the distinction of being "Baby Friendly," which use breastfeeding as the default feeding approach for newborns.

Other countries have also worked on the national level to provide education and modify environments to promote healthy lifestyles. For example, Brazil has initiatives to promote: breastfeeding and decrease high-fat and sugar consumption in the first year of life; school policies that promote healthy food practices and restrict the availability of high-fat, -sugar, and -salt foods in the school; and marketing regulations that restrict products advertised to families of infants and young children. Further, given the high-sodium diets in Brazil, the Brazilian ministry has been working with the food industry to gradually reduce sodium in processed foods (Silva et al. 2013).

Another notable large-scale community intervention is EPODE, Ensemble Prévenons l'Obésité Des Enfants (Together, Let's Prevent Childhood Obesity), which started in 2004 in France with ten pilot communities and has expanded since then to over 500 communities in six countries. This intervention fosters healthier lifestyles by employing stakeholders at multiple levels, including a central level comprised of ministries and health groups, for example, and a local level consisting of, for instance, health professionals, families, and teachers (Borys et al. 2012).

Overall, the effect sizes of these preventative interventions across settings are small, on the order of 0.25 $kg/m^2$ BMI reduction or −0.05 z-score change (Wang et al. 2015). The small improvements from preventative efforts are up against the high and increasing rates of obesity in recent decades. Many areas need further

research, for example, identification of specific approaches for subgroups (e.g., adolescents) and strategies for nonschool settings. Given the multiple contributors to obesity, it is not reasonable to expect any one intervention to accomplish the feat of changing the course of pediatric obesity.

## Summary

Childhood obesity has reached epidemic proportions, including a particularly concerning increase in the prevalence of youth with severe obesity in recent years. This multifactorial chronic disease with biological, psychological, social, and environmental determinants is often recalcitrant to lifestyle modification therapy, the cornerstone of treatment. Research which addresses early prevention, for example, during gestation, and mitigation of modifiable determinants such as poverty's chronic stress, food insecurity, marketing of processed foods, and limitations in physical activity in schools, are necessary for reversing the trends in childhood obesity. At the same time, further research is needed for the development of deliberate, comprehensive interventions delivered at key times during a child's development for the millions of youth who are already affected.

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# Exercise in the Treatment of Obesity

# 15

R. Drew Sayer and James O. Hill

## Contents



**Abstract**

Increasing physical activity through structured aerobic exercise should be a cornerstone of behavioral weight loss programs. Recently, numerous scientific and popular media pieces have discounted the role of exercise for weight loss, which may discourage those trying to lose weight from exercising. However, existing data clearly demonstrate that exercise – either alone or when combined with dietary energy restriction – promotes clinically meaningful weight loss in the

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majority of people and may be especially important for maintaining weight loss for the long-term. Therefore, the purpose of this chapter is to critically evaluate the role of exercise for weight loss and weight loss maintenance. Topics covered in this chapter include: a discussion of the direct and indirect influences of exercise on energy balance; a review of the impact of exercise on body weight during each stage of obesity treatment; recommendations for incorporating exercise into obesity treatment programs; the role of exercise in the prevention of weight gain; and a discussion of the challenges of making lasting changes in health behaviors.

**Keywords**
Exercise · Weight loss · Weight loss maintenance · Energy balance · Metabolic regulation

## Introduction

Treating obesity requires two stages – getting the weight off and keeping it from returning. The intent of this chapter is to provide evidence-based recommendations for incorporating exercise into each stage of obesity treatment. It is far too common to see messages in the media discouraging those trying to lose weight from exercising. For example, a recent article on vox.com was titled "Public confusion about exercise – why you shouldn't exercise to lose weight, explained with 60+ studies" (Belluz and Zarracina 2017). The public messaging that exercise is unimportant for obesity treatment is surprising and reflects an underappreciation of how exercise affects the regulation of energy balance, which is the foundation for understanding and treating obesity. It also reflects inattention to decades of exercise science research.

This chapter has been divided into five parts. In part 1, the framework of energy balance is used to predict how exercise, alone or in combination with energy restriction, could impact energy balance and body weight during each stage of obesity treatment. In part 2, research on exercise and obesity treatment is summarized. Rather than providing an extensive review of individual research studies, scientific evidence for this section was based upon reviews, meta-analyses, and key randomized studies. Results will be discussed as consistent or inconsistent with expected results based on the regulation of energy balance. The existence and importance of individual differences in response to exercise will also be discussed. In part 3, recommendations for incorporating exercise into weight management programs will be provided. The role of exercise in prevention of weight gain will be briefly discussed in part 4. Finally, part 5 provides a discussion of the critical and difficult challenge of permanently changing health behaviors such as exercising regularly. Of note, physical activity includes planned exercise and movement throughout the day not part of planned exercise. Because increasing planned exercise is the most relevant form of physical activity for the purpose of managing body weight, exercise (rather than physical activity) will primarily be used throughout the chapter.

## Part 1: How Exercise Impacts the Regulation of Energy Balance

The regulation of energy balance provides a useful foundation for understanding factors that can impact body weight. Reviews of energy balance regulation are available (Hill et al. 2012; Hill 2006). Figure 1 illustrates the major components of energy balance, with each being influenced by a variety of genetic, environmental, and psychosocial factors. Energy balance is often presented as an overly simplistic model of "Calories In versus Calories Out," but the regulation of energy balance is incredibly complex and involves a multitude of interacting biological systems. The Foresight Report from the UK provides a great description of the multiple systems that can impact the components of energy balance, and thus body weight (Butland et al. 2007). Any factor that affects body weight must work through energy balance. It is critical to appreciate that the components of energy balance are interactive, and a change in any one component can cause changes in the others. Body energy stores (and body weight) remain stable if the amount and composition of energy intake matches the amount and composition of energy expenditure. Perturbations to this system (e.g., changes in diet or physical activity) may or may not lead to changes in body energy stores, depending on the magnitude of the perturbation and the compensation that occurs in other components. For example, compensatory changes in energy expenditure, energy stores, and metabolic regulation occur in response to energy reduction and weight loss (Hill et al. 2012; Hill 2006; Sumithran et al. 2011; Steig et al. 2011). The result is that – on any given weight loss intervention – some people lose a lot of weight, some lose a little weight, some lose no weight, and some gain weight. This is illustrated in Fig. 2, which shows individual amounts of weight loss in response to a low fat or a low carbohydrate diet from a previously published clinical trial (Foster et al. 2003). This individual variability is a result of the interplay among components of energy balance – and if each could be measured accurately – changes in body weight during weight loss interventions would likely be completely explained.

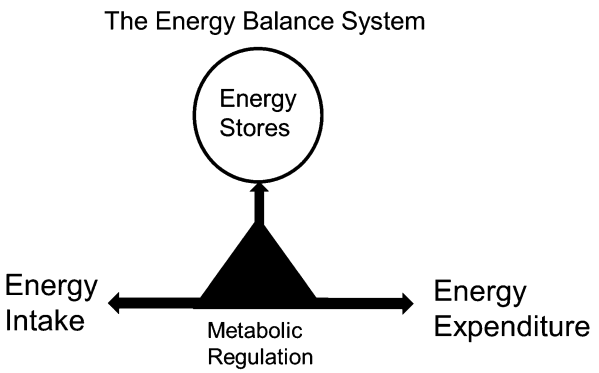


**Fig. 1** Major components of energy balance: energy intake, energy expenditure, energy stores, and metabolic regulation

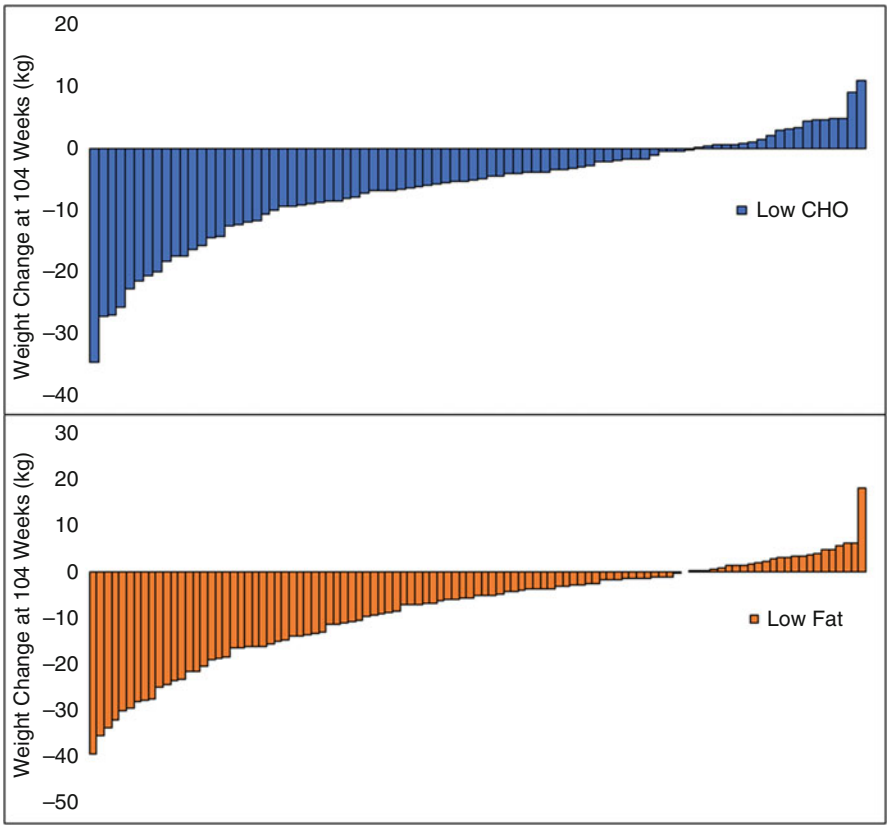


**Fig. 2** Individual amounts of weight loss in a study comparing low-fat and low-carbohydrate diets for treatment of obesity (Foster et al. 2003). Each bar is a single subject. The top graphs shows individual weight loss on the low carbohydrate diet and the lower graph shows individual weight loss on the low fat diet

## Metabolic Regulation

Metabolic regulation is an important and often underappreciated component of energy balance that explains how energy intake can be partitioned into body stores (e.g., adipose tissue, glycogen, or muscle) or oxidized for energetic needs (energy expenditure). The term metabolic regulation is used in this chapter to refer to the regulation of a variety of metabolic processes including: sensitivity to hormones such as insulin, leptin, and ghrelin; capacity for substrate oxidation, sensitivity, and time-course in matching substrate oxidation to substrate availability; energy storage and extraction from muscle, adipose tissue, and liver; and ability to match appetite and energy intake to energy expenditure (Rynders et al. 2017; Goodpaster and Sparks 2017; Freese et al. 2017; van Ommen et al. 2014). The concept of differences in metabolic regulation gets directly at the "is a calorie a calorie" argument,

frequently highlighted in the popular media. From an energy balance framework, a calorie has the same energy regardless of its source. However, the fate of that calorie can vary depending on its source (fat, carbohydrate, protein) and an individual's state of metabolic regulation. For example, during periods of positive energy balance, both the composition of the consumed energy (e.g., fat vs. carbohydrate) and differences in metabolic regulation can determine how much of the excess energy is stored versus oxidized in the body. A great deal of research in this area has focused on metabolic flexibility, which is defined as the ability to adapt substrate oxidation to fuel availability (Rynders et al. 2017; Goodpaster and Sparks 2017), and which may be critical in body weight regulation. Differences in many aspects of metabolic regulation, such as metabolic flexibility, are often best revealed during perturbations to energy balance. These, in turn, can affect the way in which other components of energy balance respond and can impact the body weight at which the system re-equilibrates. It has been proposed that metabolic inflexibility is a driver of obesity (Freese et al. 2017), perhaps through a tendency for excess energy to be stored versus oxidized.

Substantial evidence suggests that a lack of exercise is associated with poor metabolic regulation and that regular exercise is associated with optimal metabolic regulation. This is certainly true with regard to metabolic inflexibility, where physical inactivity promotes metabolic inflexibility and exercise training increases metabolic flexibility (Rynders et al. 2017; Goodpaster and Sparks 2017). In metabolically flexible people, skeletal muscle, adipose tissue, and the liver work in concert to facilitate rapid metabolic shifts in substrate oxidation depending on fuel availability (Rynders et al. 2017; Goodpaster and Sparks 2017). For example, increased lipolysis during fasting is matched with increased fat oxidation by skeletal muscle in metabolically flexible individuals. After meals, lipolysis is quickly inhibited and skeletal muscle metabolism switches rapidly to oxidation of glucose. These shifts are blunted in inactive and obese individuals resulting in metabolic inflexibility. During the day, metabolically flexible individuals have a higher total fat oxidation than metabolically inflexible individuals. Regular exercise also optimizes appetite regulation (Blundell et al. 2015). Recognizing that most body organs and systems may be involved in optimal metabolic regulation, it has been suggested that the term phenotypic flexibility may be used to quantify metabolic regulation (van Ommen et al. 2014). Various perturbations to energy balance (e.g., diet and exercise challenges) are being used to identify metabolic (or phenotypic) flexibility, but these are not readily available for use in obesity treatment programs (van Ommen et al. 2014).

### Impact of Exercise Without Food Restriction

The energy balance framework can be used to examine what might happen when overweight/obese people increase exercise, either with or without changes in diet. Exercise alone is often dismissed as not producing weight loss (Belluz and Zarracina 2017). From an energy balance framework, increases in exercise in overweight/obese individuals should lead to more energy expended that is directly proportional to the amount of exercise performed. This should produce a negative energy balance

that is determined by the amount of increased energy expenditure from exercise minus any compensation that occurs in other energy balance components. For example, energy intake and/or sedentary time could increase after exercise, which would reduce the extent of negative energy balance and impact weight loss. The degree of compensation could vary from none or very little to total compensation or even overcompensation. Thus, from an energy balance perspective, increasing exercise could result in substantial weight loss, a little weight loss, no weight loss, or even weight gain. The critical question becomes how much compensation occurs and why it occurs in some individuals to a greater or lesser extent than others. Fortunately, this question has been addressed by many research studies that will be discussed in section "Research on Weight Loss during Exercise-Only Interventions Supervised Exercise".

Exercise is often compared to energy intake restriction as a method of producing weight loss. While both strategies produce an amount of negative energy expenditure determined by the amount of exercise or food restriction minus compensation by other aspects of energy balance, there are important differences in how each is achieved. The time and effort required to achieve a given amount of negative energy balance is much different for exercise than for energy intake restriction. Large amounts of negative energy balance can be achieved quickly though restricting energy intake, but the same degree of negative energy balance produced by exercise would take much longer. For example, reducing energy intake by 500 kcal/day is seen as a modest intervention and can be achieved quickly and relatively easily. It generally produces slow, gradual weight loss of ~1 pound/week. The same amount of negative energy balance produced by exercise would require 1–1.5 h of moderate-vigorous intensity exercise, a difficult achievement for an overweight, sedentary individual.

### Impact of Combining Exercise with Food Restriction

As concluded above, most people who are overweight or obese find that food restriction is the most feasible way to lose weight. An important question is whether there is an additional benefit of adding exercise to food restriction during weight loss. From an energy balance point of view, this would depend on the amount of exercise performed and the compensation seen in other components of energy balance. Again, unless there is total compensation, some additional weight loss should be produced by adding exercise to energy intake restriction during the weight loss phase of obesity treatment.

Exercise performed during active weight loss should also improve metabolic regulation. This would be seen as improved metabolic (or phenotypic) flexibility, leading to more favorable fat oxidation and a greater loss of body fat. However, increased metabolic flexibility might be more important for weight loss maintenance than for weight loss. In rodent models (Steig et al. 2011), exercise has been shown to counter some of the metabolic changes that occur in response to weight loss and facilitate weight regain. In humans, exercise improves appetite regulation which may help people better adhere to the diet prescription (Blundell et al. 2015; Blundell 2017).

Exercise also improves many aspects of mental health that may contribute to better adherence to both diet and exercise prescriptions during weight loss. These positive impacts include better self-efficacy, improved mood, better management of depression and anxiety (Bize et al. 2007; Paluska and Schwenk 2000), and enhanced executive function skills (Erickson and Kramer 2009).

In summary, from an energy balance perspective, adding exercise to energy restriction should result in greater weight loss than with energy restriction alone unless compensation for the increased exercise from other energy balance components is complete. There should be significant individual differences in how much additional weight loss is seen that depend on the amount of exercise performed and the extent of compensation.

### Exercise for Weight Loss Maintenance

The challenges are different for the active weight loss and weight loss maintenance phases of obesity treatment. Negative energy balance will produce weight loss in accordance with the extent of the imbalance, but no specific threshold of negative energy balance must be achieved to lose weight. The active weight loss phase of obesity treatment (energy restriction) is also time-limited (usually 6 months or less). Conversely, weight loss maintenance is characterized by a need to exactly match energy intake and energy expenditure and to maintain that balance permanently. The situation is further complicated by the fact that many physiological changes occur with weight loss that tend to promote weight regain. These include reductions in energy expenditure due to declines in resting metabolic rate, the thermic effect of food, and the energy cost of movement (Hill et al. 2012; Hill 2006), decreases in fat oxidative capacity, changes in hormones associated with appetite (Sumithran et al. 2011), and increases in efficiency of storage of excess energy (Steig et al. 2011). Maintaining weight loss requires constantly "pushing back" against these physiological changes. Regular exercise has been shown to counteract many of these compensatory adaptations in response to weight loss, which may help improve long-term weight loss maintenance.

## Filling the Energy Gap

Total daily energy expenditure is reduced after weight loss due to reductions in resting metabolic rate, the thermic effect of food, and the energy cost of physical activity (Hill et al. 2012; Hill 2006). At this lower level of energy expenditure, energy intake must be accordingly reduced in order to maintain energy balance. This reduction in energy requirements makes it easier to overeat, and the metabolic adaptations to weight loss facilitate efficient storage of excess energy as body fat. Hill et al. (Hill 2006; Hill et al. 2009) coined the term "energy gap" to describe the difference between energy requirements before and after weight loss. The energy gap can be used conceptually to determine the degree of behavioral change required to maintain weight loss (Fig. 3, top). Some crude estimates of the minimum size of the energy gap were presented by Hill et al. (Hill 2006) based on measures of energy

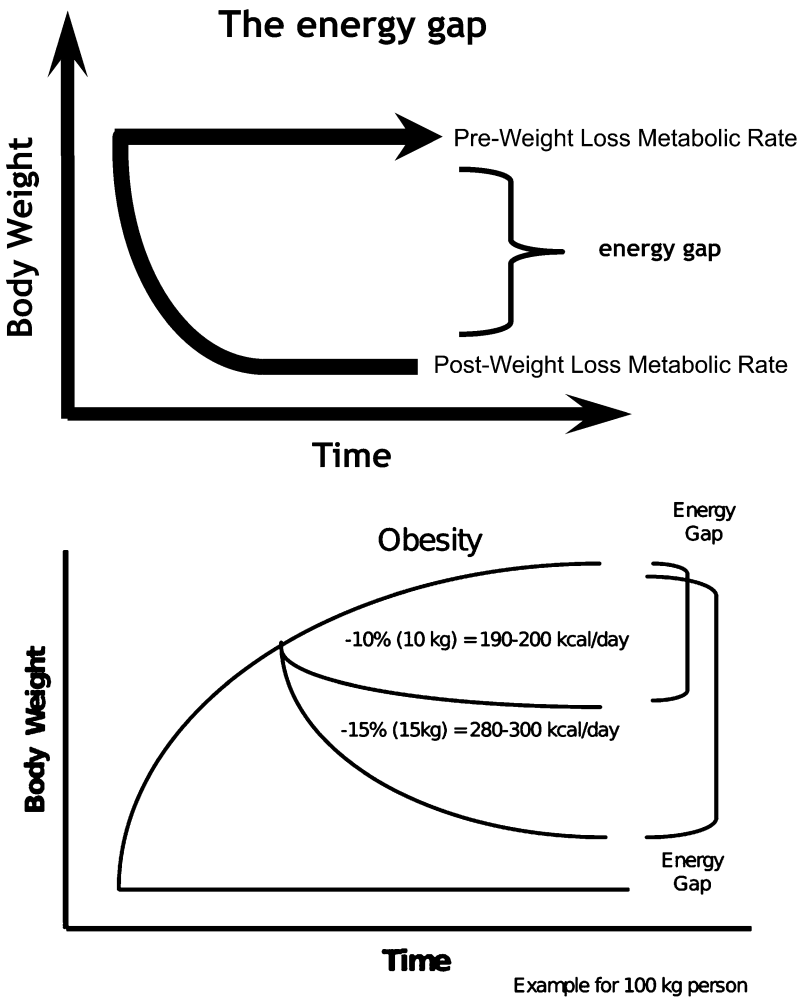


**Fig. 3** Illustration of the concept of energy gap (top). The lower panel provides some rough estimates of the size of the energy gap

expenditure before and after weight loss as determined from whole room calorimetry (Fig. 3, bottom). The size of the energy gap increases with amount of weight loss. The minimum energy gap for a 10% weight loss in a 100 kg person would be about 180–200 kcal/day and would be 280–300 for a 15% weight loss. These are just estimates, and because subjects were more inactive in the calorimeter than in real life, likely underestimate the energy gap. While there will certainly be some individual variability in the size of the energy gap, it is clear that substantial behavior change is required to maintain weight loss. It is important to note that the energy gap must be filled permanently since energy requirements will not, on their own, return to pretreatment levels.

The energy gap could be filled with some combination of energy intake restriction or increased energy expenditure (e.g., exercise). Using energy intake restriction alone to maintain a reduced body weight is extremely difficult because weight loss also produces metabolic changes including increased hunger, decreased fat oxidation, and increased capacity to rapidly store excess energy. It is not possible for most people to maintain the necessary amount of energy intake restriction over long periods of time in the face of strong biological drives to eat and regain body weight. The principal reliance on reducing energy intake to maintain weight loss is likely a primary driver of the poor success of behavioral weight loss programs.

Alternatively, all or part of the energy gap can be filled with physical activity in the form of purposeful exercise. From an energy balance point of view, increasing energy expenditure with exercise to fill the energy gap should allow people to eat an amount of energy that is not dramatically less than they were eating before weight loss. In fact, completely filling the energy gap by increasing energy expenditure would theoretically allow people to maintain their weight loss while eating the same amount of energy after weight loss as before. For practical purposes, filling the energy gap created by substantial weight loss would require amounts of exercise significantly higher than currently recommended for the general public in most countries. It is, therefore, likely that most people wishing to lose weight (especially weight loss $\geq$10%) and keep it off permanently will need to combine exercise with modest restrictions in energy intake.

While conscious food restriction is difficult to maintain over time, changes in food choices can lead to reduction in energy intake without conscious efforts to restriction. For example, reducing energy density and portion sizes have both been shown to lead to reductions in voluntary intake (Rolls 2017). This strategy will likely fill only a small part of the energy gap, but does not lead to increased hunger, and can be used to reduce the amount of exercise needed. Higher protein diets have also been suggested to increase satiety and improve long-term weight loss (Leidy et al. 2015). Combining exercise with a diet with reduced energy density, smaller portion sizes, and a higher protein content represents a prudent strategy for preventing weight regain following significant weight loss although data from long-term randomized trials are needed to support this recommendation.

## Improving Metabolic Regulation

We have previously discussed the ways in which exercise improves metabolic regulation. Having optimal metabolic regulation should be particularly important for weight loss maintenance. Being metabolically flexible results in an improved capacity for fat oxidation and helps direct consumed energy toward oxidation rather than storage in adipose tissue. Regular exercise may also facilitate coupling of energy intake and energy expenditure. In a classic study published in 1956 (Mayer et al. 1956), Jean Mayer and colleagues presented a J-shaped curve that described the relationship between energy intake and energy expenditure among male mill workers in West Bengal. The authors suggested that energy intake and energy

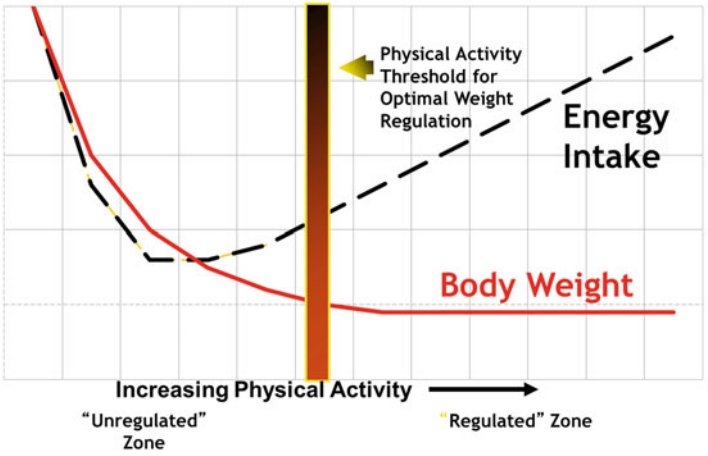


**Fig. 4** Illustration of the concept of how regular physical activity may increase the coupling between energy expenditure and energy intake. Individuals below the theoretical physical activity threshold are in an unregulated zone where energy intake is high despite low levels of physical activity. Above the regulated zone, energy intake is tightly coupled to energy expenditure. (Modified from the work of Jean Mayer Rolls 2017)

expenditure are coupled at higher rates of energetic flux but they become uncoupled with a more sedentary lifestyle resulting in higher energy intake despite lower energy expenditure. Others have suggested there may be a threshold of physical activity above which energy intake is optimally coupled to energy expenditure. Increasing exercise to a level that crosses this threshold should provide an advantage in weight loss maintenance. Figure 4 is a modification of Mayer's J-shaped curve that illustrates this concept and shows how energy balance regulation may be different in physical active versus sedentary individuals. In fact, increased metabolic flexibility may be part of the mechanism by which individuals show accurate coupling between energy intake and expenditure. Overall, an enhanced metabolic regulation facilitated by exercise should provide an advantage in "pushing back" against the biological mechanisms that promote weight regain.

The mental health benefits of exercise that were discussed in section "Impact of Combining Exercise with Food Restriction" also apply during weight loss maintenance and could facilitate adherence to diet and exercise goals.

In summary, the benefits of exercise on energy balance regulation during weight loss maintenance include:

1. A more sustainable way of filling the energy gap, requiring less caloric restriction and greater likelihood of achieving a diet that can be maintaining over the long-term
2. Better metabolic regulation, which leads to increased metabolic (or phenotypic) flexibility, better appetite regulation, and an advantage in oxidizing rather than storing more excess energy

3. Increased sense of self-efficacy, facilitation of executive function skills, better management of depression and anxiety, and enhanced mood

## Part 2: Summary of Clinical Research Evaluating the Impact of Exercise on Weight Loss and Weight Loss Maintenance

The purpose of this section is to summarize the research regarding the impact of exercise, either alone or combined with restriction of energy intake, on obesity treatment. We rely on the multiple reviews and meta-analyses that have been published in this area, with an intent to relate the best evidence to the theoretical predications from our understanding of the regulation of energy balance. Three broad themes are apparent in the literature that will be addressed in this section; (1) Exercise-only interventions produce weight loss (and fat loss) in overweight/obese subjects. This is seen both in studies using supervised and unsupervised exercise. Both the amount of exercise performed and the resulting amount of weight loss are variable among subjects in both types of studies. (2) The combination of exercise and energy intake restriction produces more weight loss and more favorable changes in body composition than diet-only or exercise-only interventions. (3) Exercise may be especially important for preventing weight regain following clinically meaningful weight loss, but large amounts of exercise may be needed.

### Research on Weight Loss During Exercise-Only Interventions

#### Supervised Exercise

Exercise alone produces weight loss in most overweight/obese individuals. Several laboratories have studied the impact of supervised exercise on body weight in overweight/obese individuals (King et al. 2008; Herrmann et al. 2015; Lee et al. 2005). Unsupervised exercise suffers from lack of knowledge about the magnitude of the intervention, making the interpretation of outcomes difficult. The results from studies using supervised, verified exercise are more consistent. When individuals who are overweight or obese increase exercise, there is some degree of compensation, but overall body weight is reduced in the majority of subjects. This has been demonstrated by King et al. (2008) who reported that when they engaged in supervised exercise, the majority of overweight/obese subjects lost weight and the few who did not compesated for the increase in energy expenditure by increasing energy intake. Many of those who did not lose weight actually lost body fat. The average weight loss was very similar to that predicted from amount of exercise performed, but there was wide individual variability in response, even though the amount of exercise performed was similar in all participants. Similar results have been reported from the Donnelly (Herrmann et al. 2015) and Ross Laboratories (Lee et al. 2005). Lee et al. (2005) from the Ross Laboratory, in a series of elegant studies, demonstrated that the same degree of negative energy balance produced by verified food restriction or verified exercise,

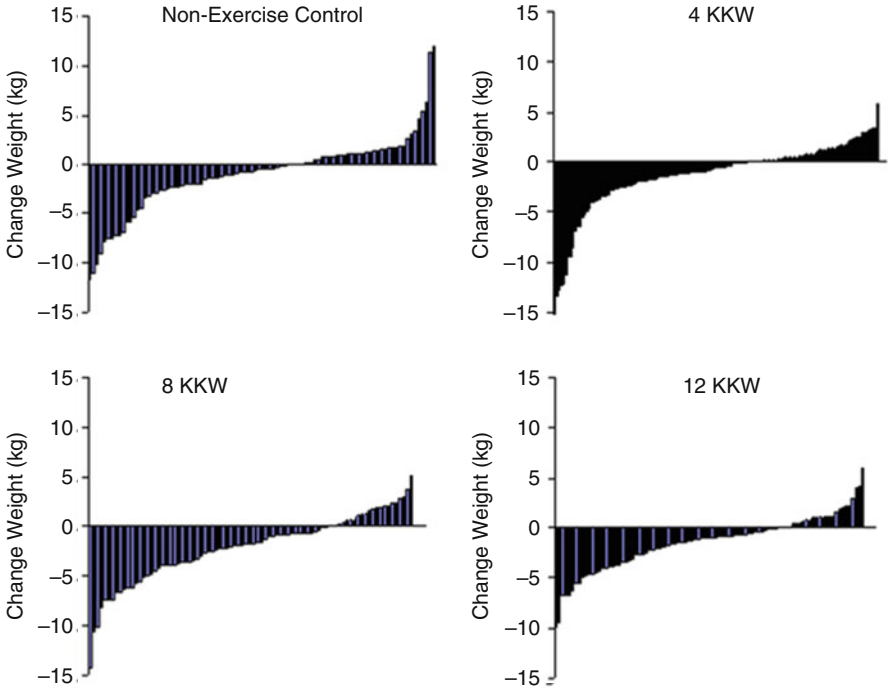


**Fig. 5** Data from Church et al. (2009) show individual data for change in weight with a supervised exercise program. Each bar is a single subject. Subjects were randomized to either a nonexercise control condition or to one of three levels of exercise

led to the same degree of weight loss. This suggests that the amount of compensation for a given amount of negative energy balance was not different for food restriction or exercise.

Reliance on average weight loss masks the substantial within-treatment variability that is ubiquitous among weight loss trials, especially exercise-only interventions. A typical example of this phenomenon is shown in Fig. 5, from research by Church and colleagues in 2009 (Church et al. 2009). Average weight loss was modest after 6 months of supervised exercise for the low (~72 min/week) and moderate (~136 min/week) duration exercise groups, but average weight loss closely matched predicted weight loss based on exercise energy expenditure (low: 1.4 kg actual vs. 1.0 kg predicted weight loss, moderate: 2.1 kg actual vs. 2.0 predicted). On the other hand, weight loss in the high duration exercise group (~194 min/week) was significantly less than predicted (1.5 kg actual vs. 2.7 kg predicted), which indicates that – on average – participants assigned to the high duration exercise group partially compensated for the increase in exercise energy expenditure by eating more and/or reducing non-exercise energy expenditure. Whether changes in total energy intake or diet composition are dependent on exercise dose is an important research question and deserves more research attention.

The distribution of weight loss for each study group presented in Fig. 5 clearly demonstrates that average results fail to tell the full story of exercise-induced weight loss. Approximately one-third of participants lost more weight than predicted, which indicates a complete lack of compensation or even a spontaneous reduction in energy intake and/or increase in nonexercise energy expenditure. Another one-third lost near the predicted amount of weight based on exercise energy expenditure (no metabolic or behavioral compensation) and the last one-third lost no weight or gained weight (complete or overcompensation) after 6 months of supervised exercise with >99% documented adherence to the exercise intervention in all exercise groups. These results indicate that the majority of people initiating an exercise-only weight loss program can expect to lose weight at a rate that would be predicted from exercise energy expenditure and that some individuals may lose even more weight than predicted by spontaneously reducing energy intake and/or increasing nonexercise energy expenditure. It is also clear that some individuals are unlikely to lose any weight (and may even gain weight) during exercise-only interventions. Therefore, identifying which individuals are most likely to succeed or fail to achieve clinically meaningful weight loss by exercise is a critical need in the field of obesity science and treatment.

The identification of responders and nonresponders to exercise-only weight loss interventions is an area of intense investigation. The best available evidence suggests that acute exercise and long-term exercise training induce profound and variable alterations in energy balance that impact the amount of weight loss in response to exercise interventions. Further, sex differences in response to exercise-only interventions have been described with men potentially being more likely to lose weight during exercise-only interventions compared to women, but this finding is not consistent in the literature. During a 10-month supervised exercise aerobic exercise intervention, Donnelly and colleagues (Herrmann et al. 2015) found that ~55% of participants (equal proportions of men and women) lost >5% body weight and were categorized as responders. Men – but not women – who responded to the exercise intervention demonstrated many important differences at baseline and in response to the intervention that explain differences in body weight changes. At baseline, male responders had lower fat-free mass and lower total daily energy expenditure compared to nonresponders. In response to the intervention, responders increased total daily energy expenditure by ~400 kcal (consistent with the exercise prescription) while nonresponders did not increase total daily energy expenditure. Male responders also tended to increase nonexercise energy expenditure during the intervention, while nonresponders demonstrated a trend toward decreased nonexercise energy expenditure. Importantly, the decrease in nonexercise energy expenditure among male nonresponders was roughly equivalent to the increase in exercise energy expenditure, which suggests that nonresponders compensated for the exercise by being more sedentary throughout the day. As regards energy intake, neither responders nor nonresponders significantly changed energy intake during the 10-month intervention but energy intake was higher among nonresponders at every time point compared to responders. Interestingly, no observed differences in energy expenditure or intake between female responders and nonresponders could

account for the differences in body weight change (i.e., both responders and non-responders increased total daily energy expenditure with no change in energy intake).

The J-shaped relationship between energy intake and energy expenditure that was proposed by Mayer et al. (1956) was recently confirmed in a systematic review of 28 studies (14 cross-sectional and 14 exercise training interventions) (Beaulieu et al. 2016). In a series of rigorous clinical studies, Blundell, King, and colleagues have greatly contributed to the understanding of how acute exercise and long-term exercise training impact appetite and energy intake to explain the observed variability in weight loss achieved via exercise-only interventions. Their results have been described in a number of excellent reviews to which the reader is referred for additional reading on the topic (Blundell et al. 2015; Blundell 2017). Briefly, exercise training can result in increased feelings of fasting-state hunger, which stimulates increased energy intake to reduce or eliminate the energy deficit caused by exercise. However, this response is highly variable and may be offset by enhanced meal-induced satiety (greater feelings of fullness after meal consumption) with exercise training. The relative extent to which these responses are present is a major determinant of exercise-induced weight loss. Responders are characterized by either no change or a decrease in fasting hunger after exercise training compared to nonresponders who more commonly report increased feelings of hunger and increased energy intake.

### Unsupervised Exercise

Many research studies have evaluated the impact of unsupervised exercise on body weight. These studies have been summarized in reviews and meta-analyses (Thorogood et al. 2011; Franz et al. 2007; Chin et al. 2016). Overall, there is clear evidence that increasing exercise, without any energy intake restriction, leads to some weight loss in most overweight/obese individuals. Chin et al. (2016) evaluated the results of available reviews and meta-analyses and additional key studies, and concluded that exercise without any diet intervention results in 2–3% weight loss in overweight/obese subjects. The amounts of exercise recommended, the amount actually performed, and the resulting weight loss were all highly variable. There is a great need for better controlled studies, using supervised exercise to evaluate the relationship between amount of exercise performed and amount of weight loss.

### Weight Loss During Exercise-Only Interventions: Summary

To summarize, results from well-conducted randomized clinical trials and meta-analyses clearly show that exercise-only interventions produce weight loss. Average weight loss in exercise-only interventions using supervised exercise support the theoretical predictions based on our understanding of the regulation of energy balance (increased exercise produces negative energy balance). However, the amount of weight loss in response to exercise-only interventions (with both supervised and unsupervised exercise) is highly variable with responses ranging from much greater than predicted weight loss to weight gain. Baseline and exercise

training-induced differences in total daily energy expenditure, hunger, and compensatory energy intake are principal drivers of weight loss during exercise-only interventions, but these responses are better described among men compared to women. Results of unsupervised exercise-only interventions should show even greater between-subjects variability in weight loss since there will also be differences in amount of exercise actually performed. While it is clear that exercise alone can produce weight loss, exercise-only interventions, in the amounts commonly performed, are unlikely to meet the goals and expectations of most individuals pursuing weight loss.

## Research on Weight Loss During Combined Exercise and Dietary Restriction

Results from strong randomized clinical trials and meta-analyses (Franz et al. 2007; Chin et al. 2016; Wu et al. 2009; Swift et al. 2014) have consistently shown that weight loss interventions that combine exercise and energy intake restriction produce more weight (and fat) loss than those using either exercise or energy intake restriction alone. Summarizing across many studies using different amounts of exercise, Chin et al. (2016) estimated that adding exercise to energy intake restriction produces an additional 2–4 kg of weight loss, which supports current obesity treatment guidelines to utilize *comprehensive lifestyle programs* that include an energy-restricted diet and increased exercise for weight loss (Jensen et al. 2014). Combined exercise and energy intake restriction interventions also produce substantial individual variability as described previously in this chapter. Future obesity research should focus on identifying individuals who are most likely to succeed on each particular weight loss strategy (or combination of strategies) in order to develop individualized obesity treatment programs to maximize their effectiveness.

Few research weight loss studies actually measure how much exercise was done, and rarely even attempt to measure the degree of compensation in increased energy intake and decreased physical activity in response to exercise. It is inappropriate to expect that the amount of weight loss expected can be predicted from the amount of exercise recommended considering the variability in compensatory responses to the exercise program. There is a great need for highly controlled research studies evaluating the combination of exercise and energy intake restriction on body weight that involve accurate measurement of both energy expenditure and energy intake. Such interventions would also afford the opportunity to investigate biological factors (i.e., compensatory reductions in non-exercise energy expenditure) that drive individual variability in weight loss. However, these interventions are incredibly expensive and difficult to conduct for more than a few weeks. There is currently very little research to allow for the determination of how the amount of exercise added to energy intake restriction affects weight loss. Based on the regulation of energy balance, more exercise should produce greater energy expenditure and more weight loss in most people.

### Weight Loss During Combined Exercise and Dietary Restriction: Summary

The data are overwhelmingly consistent that more weight loss is achieved when exercise is included with energy intake restriction during the weight loss phase of obesity treatment. It is thus surprising than anyone is providing messages to the public that exercise is not effective for weight loss. Overall, existing research supports our theoretical predications based on our understanding of the regulation of energy balance. Both energy restriction and energy expenditure (exercise) contribute to negative energy balance and the combination produces greater negative energy balance than either alone. The individual differences in amount of weight lost are due to individual differences in compensation both for energy restriction and increased exercise. Overall, more people should lose more weight when they add exercise to energy intake restriction during the active phase of obesity treatment.

## Research on Exercise and Weight Loss Maintenance

There are surprisingly very few carefully controlled studies of the impact of exercise during weight loss maintenance. Because weight loss maintenance is different from weight loss, it is important to understand the impact of exercise alone versus exercise plus energy restriction versus exercise plus modifications in diet composition or energy density. There is insufficient information in the literature to evaluate these questions.

The available reviews of exercise for weight loss maintenance conclude that weight loss maintenance is better when individuals engage in exercise compared to when they do not (Simpson et al. 2011; Hunter et al. 2010). All of these reviews note the lack of high quality data in this area. There is wide variation in the amount of exercise recommended, the dietary recommendations, and the definition of successful weight loss maintenance. From the existing research, it is impossible to provide accurate guidance for the optimum pattern of exercise and the optimum interaction of exercise and diet during weight loss maintenance. Chin et al. (2016) in a review of this topic concluded that the weight of the available data supports recommendations to include exercise as part of a weight loss maintenance program. While they also suggest that the amounts of exercise required to have a significant impact on weight loss maintenance may be greater than the 150 min/week recommended to the general public, they provide no specific recommendation.

As previously discussed, exercise during weight loss maintenance would be expected to improve metabolic regulation, enhancing resistance to weight gain. While it has been shown that increased exercise enhances metabolic flexibility (Sumithran et al. 2011; Steig et al. 2011) and improves appetite regulation (Blundell et al. 2015; Blundell 2017), to our knowledge there are no studies that have evaluated enhanced metabolic regulation as a predictor of successful weight loss maintenance.

While there are numerous studies comparing diet composition during weight loss maintenance and numerous studies examining exercise during weight loss maintenance, there are surprisingly few studies examining the interaction of the two. For example, are low fat or low carbohydrate diets equally effective in active and

sedentary individuals (i.e., metabolically flexible vs. metabolically inflexible) during weight loss maintenance? Several recent publications suggest that weight loss on different diets depends on the pretreatment glucose and insulin status of the subjects (Astrup and Hjorth 2017). If this is the case, exercise, which alters glycemic status, might be expected to interact with diet composition in producing weight loss.

### Exercise and Weight Loss Maintenance: Summary

From a regulation of energy balance framework, increasing exercise should be a critical factor for weight loss maintenance. The available data certainly support exercise as a factor facilitating weight loss maintenance, but unfortunately there is insufficient research to determine how critical exercise is for weight loss maintenance. There is especially a lack of studies using levels of exercise that would fill or mostly fill the energy gap.

The concept of the energy gap provides a useful way to begin to evaluate the importance of exercise. Energy intake restriction alone would not be expected to be a successful weight loss maintenance strategy given the difficulty of managing increased hunger over long periods of time. The best evidence for this is that energy intake restriction has been used for decades as the major strategy for weight loss maintenance, with very poor long-term success (Mann et al. 2007). Obesity rates continue to rise despite the plethora of obesity treatment programs focused on restricting energy intake (Hales et al. 2017). There is great need for carefully controlled research to evaluate the impact of different degrees of exercise combined with different types of dietary recommendation for weight loss maintenance. For example, the combination of very high levels of exercise combined with reductions in the energy density of the diet may provide a good and testable strategy for weight loss maintenance.

### The Impact of Increasing Exercise May Vary with Differences in Metabolic Regulation

This review has been focused on the impact of exercise in overweight/obese individuals. Based on the theoretical framework first proposed by Mayer (Mayer et al. 1956), the impact of physical activity on energy balance should be different in those above versus those below a theoretical threshold of physical activity. In physically active, nonobese individuals, increases in exercise would not be expected to produce major changes in body weight, because of accurate coupling of energy intake to energy expenditure.

## Part 3: Recommendations for Incorporating Exercise into Weight Management Programs

### How Much Exercise Should Be Recommended?

The first Physical Activity Guidelines for Americans were developed in 2008 and recommend 150 min/week of moderate intensity exercise per week or 75 min/week of intense exercise (2008 Physical Activity 2008) for general health benefits.

The Physical Activity Guidelines for Americans recommend 300 min/week of moderate intensity exercise or 150 min/week of vigorous intensity exercise for even greater health benefits, including weight loss. Guidelines from the American College of Sports Medicine are similar with the suggestion that ~300 min/week of exercise may be needed for weight management (Donnelly et al. 2009). We have not exhaustively reviewed guidelines from individual countries but most are aimed at overall health and recommend 30 min/day for 5–7 days/week for adults, with no specific recommendations for obesity treatment. Some countries appear to be increasing recommended amounts of exercise for the general public. Australian exercise guidelines recommend that adults accumulate 150–300 min (2 ½– 5 h) of moderate intensity exercise or 75–150 min (1 ¼–2 ½ h) of vigorous intensity exercise, or an equivalent combination of both moderate and vigorous activities, each week (Brown et al. 2012). Japan recommends 60 min/day for all adults (Kanosue et al. 2015). Exercise guidelines specifically for obesity treatment are not widely available.

There is substantial evidence that exercise levels of at least 150 min/week of moderate intensity exercise (or 75 min/week of high intensity exercise) would improve overall health (2008 Physical Activity 2008), but these levels are not likely to be sufficient to have a big impact on amount of weight loss or on successful weight loss maintenance. Such amounts of exercise would not fill very much of the energy gap that would be seen with even moderate amounts of weight loss. For example, following the exercise guidelines of 150 min/week of moderate intensity exercise would produce a negative energy balance of approximately 525–1050 kcal/week compared with 3500 produced by 500 kcal/day of energy intake restriction. The amount of additional weight loss expected (given some compensation) is minimal. Additionally, this amount of exercise would fill only a small part of the energy gap that would be produced by weight loss of 10% or more. Given that some compensation would be expected, following the current exercise guidelines of most countries would not be expected to produce very much more weight loss than food restriction alone and would not be expected to contribute significantly to successful weight loss maintenance.

While there is growing evidence that 150 min/week of exercise is insufficient for obesity treatment, there is insufficient research to provide specific recommendations. Ostendorf et al. (2018) demonstrated with objectively measured physical activity that successful reduced-obese individuals engaged in more physical activity than weight matched never-overweight subjects. The reasons that high levels of physical activity may be required for obesity treatment is not clear, but could related to the need to counter the previously discussed physiological changes that occur with weight loss and which promote weight regain.

There is a great need for research to better identify goals for exercise in obesity treatment. However, we can make estimations from some available data and from our understanding of the regulation of energy balance. Jakicic et al. (Jakicic and Otto 2005) have studied how amount and intensity of exercise impact weight loss maintenance. Overall, they concluded that higher doses of exercise are associated with greater success in maintaining weight loss. They suggest that it may take

60 min/day or more moderate intensity exercise to prevent weight regain. This estimation is supported from research from the National Weight Control Registry (NWCR), a registry of successfully weight loss maintainers. In this group of approximately 10,000 participants, the average weight loss is about 30 kg and the average amount of exercise performed is about 60 min/day (Catenacci and Wyatt 2007). A substantial number of NWCR participants report even more amounts of exercise. Interestingly, only about 9% of NWCR participants report not engaging in regular exercise.

The concept of the energy gap can also be used to estimate how much exercise might be needed to maintain weight loss. In section "Exercise for Weight Loss Maintenance" above, estimates of the energy gap were provided using measures of energy expenditure before and after weight loss as determined from whole room calorimetry to provide some estimates for the minimum size of the energy gap (Fig. 3, bottom). The energy gap for a 10% weight loss in a 100 kg person would be about 180–200 kcal/day and would be 280–300 for a 15% weight loss. However, keep in mind that these values were obtained in a whole room calorimeter where movement is far more limited than in usual life. It is likely that these represent a minimal energy gap and that the actual energy gap is greater. However, using these values, and assuming moderate intensity exercise involves expending 3.5–7 kcal/min, it would take 200–400 min/week of exercise to maintain a 10% weight loss and 300–600 min/week of exercise to maintain a weight loss of 15%. All of these values are greater than those recommended in most countries. Mathematical models can likely be used to better determine the size of the energy gap (Dawson et al. 2014).

With minimal evidence in support, a recommendation of 60 min/day of moderate intensity exercise for weight loss maintenance seems a reasonable starting goal for obesity treatment programs. It must be recognized that there will be wide individual variation in the amount of exercise required for weight loss maintenance, with some people needing more and some less. Overall, the more weight lost, the more exercise that will be required to increase likelihood of weight loss maintenance success. Helping participants achieve 60 min/day of exercise at the end of active weight loss should increase the amount of weight loss, minimize loss of lean body mass. It would then allow small modification of this amount based on success in maintaining weight loss. It is important to note that these recommendations are based largely on observational and retrospective studies and well-controlled and adequately powered randomized trials are needed to make firm conclusions regarding the amount of exercise required for long-term weight management.

## How to Use Exercise During Weight Loss

The data strongly support that high levels of exercise produce more weight loss and help maintain that weight loss to a greater extent than food restriction alone. Providing exercise goals for all participants in weight management programs is recommended. It is reasonable to aim for 60 min/day by the end of active treatment (usually <6 months). It is recommended to start low and gradually increase exercise

goals. For very overweight participants, walking is a great way to begin to increase exercise and goals can be as low as 10–15 min/day. It may be useful to have a structured system for how rapidly to increase exercise.

The optimum frequency and duration of exercise during weight loss and weight loss maintenance is not clear. The U.S. physical activity guidelines (2008 Physical Activity 2008) provide good advice for starting an exercise program and for combining bouts of exercise during the day to meet physical activity goals. If the goal is to accumulate 60 min/day of moderate intensity exercise, this can be accumulated through multiple bouts of intentional exercise combined with increase movement in daily life. It is also not clear whether getting 60 min/day of exercise every day is important or whether 420 min/week could be obtained during 5 or 6 days/week.

If participants can reach a goal of 60 min/day or 420 min/week of exercise by the end of active weight loss, their chances of maintaining weight loss will be increased. In transitioning from active weight loss to weight loss maintenance, it will likely be necessary to make adjustments to the amount of exercise required. For some individuals, this will likely result in the need for less exercise and for others more exercise. It is important to stress here that the energy gap is not likely going to be reduced significantly over time, so the method used to fill the energy gap should be one that can be maintained permanently. This means that a failure to maintain high levels of exercise would be a risk factor for weight regain. Similarly, if the energy gap is filled with energy intake restriction, this would need to be maintained permanently.

There are a variety of exercise monitors available that allow participants to monitor how much physical activity they do. These devices used in isolation appear to be minimally effective in producing weight loss, but can be important when used as a part of a weight management program that helps participants set reasonable goals and help them find ways to achieve these goals. The devices vary from inexpensive pedometers to more expensive devices that monitor movement in more complex ways (accelerometers) (Clark et al. 2017). Most smart watches and smart phones now are capable of tracking physical activity.

## Which Kinds of Exercise Should Be Recommended?

Overall, research in this area suggests that aerobic or endurance exercise should be the primary type of exercise recommended for obesity treatment. The specific exercise mode (walking/running, cycling, rowing, etc.) is not important as long as the duration and intensity is sufficient to induce a significant energy deficit. As discussed, 150 min/week of moderate intensity aerobic activity (such as brisk walking) or 75 min/week of vigorous intensity aerobic activity (such as jogging) may be effective for the primary prevention of weight gain but is unlikely to produce clinically meaningful weight loss or help with the prevention of weight regain after significant weight loss. A recommendation of 60 min/day or 420 min/week of moderate intensity exercise is a reasonable (yet ambitious) goal for obesity

treatment. However, so far, no upper limit of exercise for health benefits has been identified and the benefits increase with higher levels of exercise.

Most obesity research and treatment programs focus on aerobic or endurance exercise for weight management because resistance training is unlikely to induce a large enough energy deficit to produce clinically meaningful weight loss. Resistance exercise may increase energy expenditure through hypertrophy of skeletal muscles, but this effect is also likely to be small in the overall picture of body weight regulation. Resistance exercise training does help to preserve the loss of lean mass during weight loss, especially when combined with a higher protein diet (>25% of total energy intake from protein). For this reason, 2 or more days/week of resistance training that involves all major muscle groups is recommended during weight loss and weight loss maintenance in addition to aerobic exercise and dietary restriction.

## Part 4: Exercise in the Prevention of Weight Gain

While the focus of this chapter is on obesity treatment, there is an extensive literature on exercise and weight gain prevention. See Church (2014) for a review of this topic. From an energy balance point of view, prevention should be more achievable than treatment of obesity. This is because the process of becoming overweight or obese and inactive leads to declines in metabolic flexibility (poor metabolic regulation) that completes a vicious circle of helping maintain the overweight/obese state. Second, the energy gap for prevention of weight gain is much lower than the energy gap for weight loss maintenance (Hill et al. 2003). There is incomplete understanding of the precipitating factors that lead to weight gain in individuals or populations. It is likely, however, that a decrease in exercise is an important factor contributing to weight gain and obesity.

## Part 5: Adherence to Exercise: The Science of Behavior Change

In treating obesity, attention must be given both to what behaviors would work if they were performed and to how to help people achieve such behavior changes over the long term. The available data strongly support high levels of exercise for obesity treatment, but currently our ability to produce and maintain such levels is poor (Bryan et al. 2017). Our inability to help overweight/obese individuals achieve and sustain changes in health behaviors is one of the greatest challenges we face in obesity treatment.

Our inability to increase exercise in the population is not likely due to lack of information. There is no shortage of exercise prescriptions, exercise facilities, and books with specific plans for increasing exercise and physical fitness. Yet, getting overweight/obese individuals to make exercise a part of their usual day has been difficult (Bryan et al. 2017). This is not surprising, as behavior changes meant to increase physical activity are opposed by our biology and our environment. There is a strong biological attraction to sedentary activities and the modern environment has

largely engineered physical activity out of our lives (Hill et al. 2003). We cannot yet fundamentally change our biology, and we are unlikely to quickly transform the current environment into one which consistently promotes physical activity. Consequently, our field must focus on promoting self-regulatory skills to help people make better choices over the long-term in the current environment (Michie et al. 2009). Making and sustaining changes in health behaviors that oppose our biology and our environment will require strong internal motivation. Currently, we have not had great success in identifying how to develop such motivation.

Most behavior change processes rely heavily on executive function, which includes many basic cognitive processes including attention, memory, and cognitive inhibition). These processes have been shown to be enhanced by exercise (Erickson and Kramer 2009). However, executive function is energetically costly and may not be sufficient to maintain behavior changes. We need to identify other potential psychological/behavioral targets for behavior change, particularly ones that can impact sustainability of behavior change. This may require a better understanding of internal motivation for behavior change. Our research group recently developed a new theory of behavior change (the Maintain IT model) (Caldwell et al. 2018) that identifies centered identity as addressing internal motivation for change, making it a potentially important target for behavioral change programs. This involves helping individuals better understand how the lifestyle they want to achieve (e.g., increased exercise) may align with their life values and purpose.

It may be helpful to help participants in obesity treatment programs to understand that increasing exercise will impact their metabolism. A large percentage of people who come to weight management program believe that their metabolism is somehow "broken." In fact, this is partially true in that most have poor metabolic regulation reflected by metabolic inflexibility and poor appetite control. Helping obesity treatment program participants understand that increasing exercise can correct their metabolism might be a good incentive.

Permanently modifying both diet and exercise is difficult, and our field has had little long-term success in permanently changing either (Bryan et al. 2017). There is a great need to identify and test new behavioral/psychological targets (mechanisms) that can be modified to increase adherence to exercise recommendations. While it is important to continue to identify factors than can impact obesity treatment, without a better ability to permanently change health behaviors, we will not be able to put what we learn into practice.

## Conclusion

It is irresponsible not to include goals for increasing exercise into obesity treatment programs. Most overweight/obese individuals who engage in exercise along with food restriction during the weight loss phase of obesity treatment will lose more weight than those who do not. Further, engaging in exercise during weight loss maintenance greatly increases the chances of success in avoiding weight regain. Levels of exercise that enhance successful obesity treatment are significantly higher

than levels recommended to the general public, and currently we do not have a great ability to produce and maintain these levels.

While there are no rigorous scientific data to prescribe specific exercise doses for obesity treatment, including exercise in the intervention improves the chances of success in achieving and maintaining weight loss. Based on a review of the available research, establishing a goal of having subjects achieving 60 min/day of moderate intensity exercise seems prudent. This amount may need to be modified (up or down) during weight loss maintenance, and may need to be tailored to each individual based on initial responsiveness to the intervention. It is important to increase exercise gradually to meet this goal. There is an urgent need for carefully controlled research studies that contribute to a science base sufficient to allow development of specific exercise guidelines for obesity treatment.

It is important to recognize that there will be substantial variation in the response to exercise both during active weight loss and weight loss maintenance. Some individuals will respond much more than others. However, even in those who lose minimal amounts of additional weight, exercise will help improve body composition.

Regular exercise impacts energy intake and expenditure, but one of its most powerful impact on body weight regulation is through enhancing metabolic regulation. As more research emerges in this area, it is becoming clear that those engage in regular exercise have an advantage in avoiding weight gain or regain. There are sufficient data to conclude that the state of physical inactivity is the abnormal state and one that predisposes to weight gain.

While the data clearly show the importance of exercise in obesity treatment, our ability to initiate and sustain increases in exercise is extremely poor. There is a desperate need for a better understanding of factors that can impact the initiation and maintenance of exercise in overweight/obese individuals. These factors may include the physical and social environment, a better understanding of behavioral phenotypes, and a better understanding of motivation for behavior change. In particular, it appears to be important to help participants in obesity treatment programs to understand why exercise is important. Many such participants believe that their "slow" metabolism contributes to their obesity. While they do not have a lower than expected energy expenditure, they are likely metabolically inflexible, a situation that can be totally or partially "fixed" by regular exercise.

In conclusion, it is time to stop confusing the public by saying that exercise is not effective for managing body weight and to start getting serious about how to produce permanent increases in exercise.

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# Psychological Approaches in the Treatment of Obesity

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## Contents



**Abstract**

There are a wide range of psychological approaches for addressing issues of obesity from population level to individually responsive interventions; this chapter focuses on clinically based interventions. However, regardless of the type of

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intervention, a psychological perspective helps us to acknowledge and address the context in which a person experiences their weight, including bias and stigma which has considerable impact on physical and emotional wellbeing. Difficulties with weight do not occur in isolation but are a result of a complex interaction between physiological, psychological and social factors but too often this is over-simplified and results in a narrow focus on behaviour change. This chapter begins with consideration of the role that weight and food can have for individuals in order to understand why changing eating habits is challenging. It also highlights a range and combination of therapeutic models which have been found to be useful in working with obesity.

**Keywords**
Obesity · Psychological stress · Cognitive behavioral therapy · Compassion focused therapy · Mindfulness

Trying to find effective solutions for obesity has been the focus of research for decades. Most people who lose weight regain about one third of it within 1 year, typically returning to baseline within 3–5 years (Castelnuovo et al. 2011). Despite the power of bariatric surgery for weight loss, there are people who continue to struggle with and regain their weight, which leads us to ask "what are we missing?" In answering this question, we have to recognize that we are not looking for a one-dimensional intervention; but instead we need to develop a better understanding of obesity as an interaction between physiological, psychological, social, environmental, and political factors. This was recognized in the Foresight report (McPherson et al. 2007). Visually mapping the complexity has been helpful to target the potential for multilevel interventions, but it has also made the treatment of obesity feel overwhelming, and so single-dimension interventions are continuing to be considered.

Outcomes of psychological interventions for obesity will be discussed later in this chapter, but if only weight as an outcome is considered, psychological interventions, on their own, do not yield clinically significant results. In developing psychological interventions, research has focused less on how they can work in combination with other elements (e.g., surgery, dietetics, etc.) for the longer term. Part of the reason for this may also link to the difficulty in researching multicomponent interventions for a population that is significantly more heterogenous than the umbrella term "obesity" leads us to understand.

The most significant contribution psychology therefore has to offer in the treatment of obesity is to increase our understanding of the range of psychosocial factors that contribute to the development and maintenance so that they can be considered within the context of a person's genetics, physiology, environment, and system.

This chapter will present psychosocial themes for obesity to help to understand the range of diverse issues linked to its causes and maintenance. Psychological interventions and their evidence base will then be discussed.

## Weight Stigma

Misconceptions about obesity are prevalent throughout all societies where obesity is viewed as negative. Believing that weight is within an individual's control and can be easily modified leads to the assumption that obesity represents character deficits (Akabas et al. 2012) such as greed and laziness. It is these inaccurate beliefs that form the basis of weight stigma and prejudice. People living with obesity are far more likely to experience discrimination linked to their weight than their non-obese peers (Carr and Friedman 2005) with reports of discrimination increasing as BMI increases (Puhl et al. 2008). It is found within the media, employment, healthcare settings, education, and interpersonal relationships (Puhl and Heuer 2009). People living with obesity are held more responsible for their condition than people with eating disorders or depression with a lack of self-discipline being attributed to the development of obesity and binge eating disorder (Daria and Latner 2013). Lacking in perceived social support for those living with obesity can negatively impact on well-being and psychological adjustment as social support is commonly cited as having a protective effect on distress (Cohen et al. 2000).

The messages healthcare professionals convey to their patients about obesity, if experienced as stigmatizing, have the potential to undermine the relationship with the clinician (Malterud and Ulriksen 2011). Among healthcare professionals, addressing weight problems can be oversimplified and seen as a matter of personal effort (Brownell et al. 2005; Puhl and Heuer 2009; Sabin et al. 2012). This lack of understanding about the complexity of obesity can lead healthcare professionals to blame the individual (Kirk et al. 2014), but there are also practical difficulties such as lack of time in consultations, inadequate referral sources, and lack of expertise which can lead healthcare professionals to feel they have let their patients down (Kirk et al. 2014). People living with obesity are left feeling berated and disrespected by their health provider, upset by comments about their weight, and worried that they will not be taken seriously and, consequently, reluctant to address weight concerns (Bertakis and Azari 2005; Brown 2006). This also has the potential to make decision-making for engagement more difficult for a person with obesity (Brown and Thompson 2007).

Limited beliefs in a patient's ability to make lifestyle change and feeling ill-equipped to offer support are reasons cited by healthcare professionals who dislike treating people with obesity (Foster et al. 2003). Not having a range of treatment options to prescribe can also lead clinicians to struggle, prefering another diagnosed condition for which they can more confidently offer treatment (e.g., diabetes, sleep apnea) (Kirk et al. 2014). The level of experience and training does not seem to make a difference with weight discrimination reported from clinicians in training (Swift et al. 2013) through to qualified practitioners (Phelan et al. 2015).

Cyclic obesity and weight-based stigma (COBWEBS) has been described as a stressor and forms a positive feedback loop (Tomiyama 2014). Stigma is a negative emotional experience which prompts biochemical, physiological, cognitive, and behavioral changes which impact on eating behavior leading to further weight gain and increased exposure to weight stigma. This process becomes a vicious cycle.

In 2015 a national survey in Britain of social attitudes toward obesity was conducted (Ormston and Curtice 2015). This sought to explore beliefs that the British population had about the cause, responsibility, and identification of obesity. While it referenced weight stigma, the design of the questionnaire inadvertently reinforced stigmatizing views of obesity by only offering participants options that fit with the "eat less and move more" belief (three options related to food and three options related to exercise). Of 2179 people, 91% indicated that obesity was caused by "fast food," and 82% felt it was due to a sedentary lifestyle. It missed an opportunity to extend ideas that increased weight can have a wider range of causes and that weight stigma can have a significant impact on the emotional and physical well-being of a person living with obesity.

Rather than encouraging weight loss (Ogden and Clementi 2010), weight stigma is associated with a number of negative consequences which significantly impact on the ability to negotiate change, including:

- Increasing the risk of maladaptive eating patterns and eating disorder symptoms (Benas and Gibb 2008)
- Increasing the risk of binge eating (Ashmore et al. 2008)
- Increasing calorie intake while decreasing the perception of control of food (Major et al. 2014)
- Negatively impacting on mood with higher levels of depression reported and lower self-esteem (Gatineaum and Dent 2011)
- Interfering with people's ability to engage in physical activity, with poor body image and anxiety about discrimination compounding exercise avoidance (Gatineaum and Dent 2011)
- Decreasing both physical- and mental health-related quality of life (over and above age, BMI, and medical comorbidity) (Latner et al. 2013)
- Interfering with the relationship between a patient and their healthcare provider (Malterud and Ulriksen 2011)
- Negatively impacting on ambivalence for engaging in treatment of weight issues (Brown and McClimens 2012)
- Negatively impacting on treatment outcomes for obesity (Wott and Carels 2010)

Weight stigma can be directed toward people living with obesity, but it can also be turned inward and directed at the self, leading to the development of internalized weight stigma. This internalization creates negative, self-destructive, and critical thoughts (Almeida et al. 2011).

## Motivation

Probably the most talked about aspect for those involved in weight management treatment is motivation: "are 'they' motivated to change?" But this overused question taps into an extremely complex area. There is a suggestion that health professionals simply advising patients to lose weight can increase motivation (Jackson

et al. 2013), but what does that actually mean? Pietrabissa et al. (2012) usefully highlighted that motivation for change is not synonymous with motivation for participating in an intervention, suggesting that there are increased adherence difficulties for people who have been urged by others to engage in an intervention. Self-determination theory (Deci and Ryan 2000) highlights the importance of autonomy; people will differ in their reasons for engaging, as well as the level of autonomy they have within those reasons. So, for example, if a person feels they have autonomous motivation for food choice, they gain satisfaction and pleasure from the behavior; it is congruent with their values and goals related to their self-system (e.g., "It is important that I manage my diabetes and so eating breakfast helps me to regulate my blood sugar"). When a person has more controlling motivation for a behavior, they perform that behavior because of self-imposed pressures such as guilt or anxiety (Ryan and Connell 1989) or they want to achieve a reward or avoid a punishment (e.g., "banning" a takeaway to avoid feeling ashamed for not eating healthily). By focusing on autonomously motivated behaviors either as a result of an intervention or self-directed, greater regulation of eating and weight management has been noted (Pelletier et al. 2004) along with maintenance of these changes over time (Guertin et al. 2015).

Understanding both the motivation to lose weight and ambivalence about whether the suggested changes are possible needs to be balanced with whether the costs outweigh the perceived benefits (McEvoy and Nathan 2007). Exploring self-beliefs and self-efficacy are the central tenets of most psychologically based therapeutic approaches in the treatment of obesity to address motivation and ambivalence.

## The Meaning of Food

The meaning of food needs to be considered within a historical context. The influence of significant societal events such as war and subsequent economic hardship leaves a legacy of cultural narrative around the way food is approached. Within the UK there are successive generations who have been influenced by the rationing (directly and indirectly) of food during World War II; clients in therapy talk about their parents and grandparents discouraging food waste. An awareness of famine in the world compounds this message encouraging us to "eat everything on our plate." The focus on finishing food is often cited by people who are struggling to regulate their consumption and who feel disconnected from their cues to satiety. By not being allowed to "leave the table" until food is finished, children are inadvertently taught to disregard their physical signals of satiety which makes following weight management advice, years later, difficult to do.

Parents, peers, and significant others play a fundamental role in our eating habits (Markey 2014) from what we are given to eat to the meaning that food has emotionally. The idea of food only in survival terms ("food as fuel") ignores the many functions and their meanings: food can express love and care, can be used to celebrate family events and to exert power and control, and is a powerful way of satisfying our hedonic needs.

## Food as Means of Emotional Coping

The phrase "comfort eating" is very widely used, but unfortunately it has narrowed our understanding of the function and meaning that food has on an emotional level. Food can be associated with comforting or soothing memories (such as a food cooked by an important family member), but when we regularly use food to manage emotion and struggle with our weight, it is rarely experienced as comforting. The term "emotional eating" more helpfully recognizes that our eating can be triggered by a range of emotions and serve many different functions, e.g., to calm, reward, assuage sadness or guilt, or distract from feelings of frustration or isolation (Marks 2015).

When, how, and if we eat can be a powerful way of influencing not only our own emotions but also the emotions of those around us. Our response to food as a baby is one of the first ways we are able to influence others, and it continues to be a means of exerting control throughout our life. We can learn to garner approval or positive affirmation or pacify others by eating the food they provide for us. We can learn to demonstrate our defiance and rebellion by refusing food, and we can learn to eat secretly if we feel unable to openly exert control or influence.

Hemmingson (2014) proposed that socioeconomic disadvantage is fundamentally linked to weight gain through psychological and emotional distress of all within the family. The associated stress can lead to parental frustrations and relationship discord. However, if we expand this model, we can more usefully acknowledge the impact on the development of resilience when a child lacks support, has unacknowledged and/or unmet emotional needs, and a general lack of insecurity, regardless of the family's socioeconomic situation. Childhood emotional abuse predicts emotional eating in adulthood (Moulton et al. 2015). Depression, post-traumatic stress disorder (PTSD) symptoms, negative affect, and emotional dysregulation have been found to be associated with increased emotional eating (Michopoulos et al. 2015). Resilience, which among other definitions can be described as a process to harness resources in order to sustain well-being (Southwick et al. 2014), mitigates against low self-esteem and self-worth, negative self-belief and emotions, powerlessness, depression, anxiety, insecurity, and a heightened sensitivity to stress. Hemmingson (2014) suggests that these inner disturbances eventually cause an emotional overload, triggering a range of weight gain-inducing effects including maladaptive coping strategies (e.g., emotional eating), chronic stress, appetite upregulation, low-grade inflammation, and possibly reduced basal metabolism. The combination of these changes over time cause further weight gain and the development of obesity; therefore tackling the emotional root causes of weight gain could potentially improve both treatment and prevention outcomes.

The development of food as a means of coping can also occur later in life as a result of life changes, for example, having children; the different demands required on a person can lead to the forgetting of self and instead focusing on the care of others. When we fail to acknowledge our own emotional need, we do not have time or we do not feel worthy of the time needed, food can become a powerful way of anaesthetizing emotions consciously or unconsciously and can become

increasingly more powerful with the frequency of use. Women may be more susceptible to emotional disinhibition of eating (LeBlanc et al. 2015).

There is evidence of the physiological impact of the prospect of particular foods on our mood (Tang et al. 2012) and the impact of food on blood glucose and the associated lift in energy and mood (Lustman and Clouse 2005). However, there is perhaps an over-attribution of the effect of particular foods, for example, a belief that chocolate will make a person feel better. Evidence suggests that it is the passage of time, in other words waiting for feelings to pass or circumstances to change, not food consumption, that may be responsible for improvements in mood (Wagner et al. 2014).

## The Meaning of Weight

Messages about food and weight are culturally bound and change over time. Perceptions of beauty have moved from increased weight representing fertility, wealth, and social standing to using the term obesity to represent negative health outcomes. A greater understanding about the impact weight has on a variety of health conditions has led to the notion of a "healthy weight" and considerable anxiety about increasing levels of obesity.

A smaller body size is now desirable in western cultures with fashion and media skewing this further from a "healthy weight" into criticisms of the use of underweight imagery and models, along with digital technology creating unrealistic ideals of beauty. The combination of health and media discourses emphasizing the importance of weight, an increased availability of food, and high levels of stress have led to a thriving diet industry and high levels of body dissatisfaction and obesity.

### Weight as a Means of Emotional Coping

Our body becomes one of the ways we can relate to the world and to others around us. We can achieve approval or attract interest if we have a culturally desired body shape, but we can also use our body to hide: from others' interest, to avoid demands and to ease pressure from the expectations of others.

The link between weight and trauma is increasingly being recognized as of central importance for people who have long-standing problems with their weight. Experiencing PTSD symptoms is associated with increased risk of becoming overweight or obese, and PTSD symptom onset alters BMI trajectories over time (Kubzansky et al. 2014; Pagoto et al. 2012). PTSD may influence weight gain both through biological and behavioral mechanisms which may operate simultaneously (Kubzabsky et al. 2014). PTSD is associated with physical inactivity (Chwastiak et al. 2011), increased consumption of unhealthy foods and beverages (Hirth et al. 2011), and generally dysregulated food intake related to dependence on activation of the brain reward system (Adam and Epel 2007). In addition, dysregulated neuroendocrine function, including enhanced negative feedback

sensitivity of the glucocorticoid receptors, blunted cortisol levels, and exaggerated catecholamine responses to trauma-related stimuli, has been found in adults diagnosed as having PTSD (Vanitallie 2002). Recent work has suggested that neuropeptide Y is a likely mediator between PTSD and metabolic imbalances owing to high levels of exposure to sympathetic activation (Perkonigg et al. 2009).

The prevalence of childhood sexual abuse has been found to be higher among people who live with obesity (Thomas et al. 2008; Aaron and Hughes 2007) and nearly 22% of people within specialist weight management programs (Gabert et al. 2013). It is important therefore to consider the function that increased body weight can serve. Examples frequently heard in clinic are "if I lose weight I become more visible," or "if I lose weight I may get unwanted attention from others." These are important to explore because they help to understand the sometimes difficult to articulate ambivalence about weight reduction.

The relationship between body dissatisfaction, negative affect, overconsumption, and weight gain has been described by Marks (2015) as the "circle of discontent," suggesting that reciprocal causal relationships exist between negative affect and the consumption of high-density food and drinks. Negative public perceptions of large body size lead to individuals' dissatisfaction with their own body size. The high levels of negative affect associated with body dissatisfaction may be damped by emotional support and exacerbated by inadequate or inappropriate social network involvement (Cohen 2004). Focusing on understanding these relationships are suggested to be important targets for obesity interventions (Markey et al. 2016).

## Weight and Emotional Well-Being

### Mental Health

There is a complex bidirectional relationship between mental health and obesity. As already described, food can be used as a means of managing affect which, if done consistently over a period of time, will lead to weight gain and potential obesity (Goldschmidt et al. 2014). This is compounded by the impact of some psychiatric medication which increases appetite (Schwartz et al. 2004). Equally, many people who live with obesity and who have experienced the stress of internal or external weight stigma can develop mental health problems (Ratcliffe and Ellison 2015).

The relationship between mental health and obesity varies depending on the subset of population being considered. In a meta review by Magallares and Pais-Ribeiro (2014), it was found that women with obesity report less mental health difficulties than women without obesity but that men with obesity report more mental health problems than men without obesity. Changes in the mental health well-being of people begin to vary when the type of weight loss intervention is considered, with people who are seeking weight loss treatment showing increased rates of depression and bipolar disorders (McElroy et al. 2004). The highest rates of distress and mental health prevalence are found within those who are seeking bariatric surgery: a meta-analysis of studies focusing on pre-bariatric surgery mental

health found that in a population of over 65,000, 95% had depression preoperatively (Dawes et al. 2016).

There are two main mechanisms which explain the relationship between obesity and depression in terms of physical processes:

1. Latrogenic mechanisms, for example, the suppression of satiety, increase of calorie-dense food consumption, and a reduction in physical activity, are noted with some antidepressant, mood stabilizing, and antipsychotic medications (Fava et al. 2000).
2. Metabolic-neurochemical processes in which the release of serotonin, a neurochemical linked to both the control of mood and satiety, is impaired due to insulin resistance (Caballero et al. 1988; Palacios et al. 2017).

### Stress

Psychosocial stress including both perceived stress and stressful life events is positively associated with weight gain but not weight loss (Harding et al. 2014). The neurobiology of stress overlaps significantly with that of appetite and energy regulation (Sinha and Jastreboff 2013). Stress induces secretion of glucocorticoids, which increase motivation for food and insulin. This promotes food intake and obesity. Eating pleasurable food then reduces the physiological stress response which reinforces this association (Dallman 2010), and so similarly, stress has a bidirectional relationship with obesity.

## The Impact of Disturbed Eating Patterns and Eating Disorders on Obesity

### The Experience of Dieting

People living with obesity are likely to have tried to lose weight on multiple occasions, particularly those seeking specialist treatment. For some people being able to lose any weight feels impossible, while for others they will be very successful at weight loss, but maintenance is problematic. While there is an established body of literature that highlights the physiological mechanisms leading to weight gain after a period of dieting (e.g., Sumithran and Proietto 2013), there are also compelling reasons for weight regain from a psychological perspective.

Restraint theory (Herman and Polivy 1975) predicts that extreme cognitive restraint (e.g., setting limits about which foods are allowed or banned and considered good or bad) is likely to make an individual more responsive to external cues such as the smell of food or internal cues such as emotions. If diet rules are rigidly applied, any deviation can feel like a "failure" (Coelho do Vale et al. 2016). Thus eating a "forbidden" hedonic food which is not part of the diet plan can be overemphasized; a lapse can escalate into a collapse followed by an abandonment of the diet.

Frequently people state that they will "get back to it tomorrow" or "start again on Monday" and so lapsing becomes part of the culture of dieting. Goal pursuit theory suggests that in order to successfully achieve a goal, behaviors which are not aligned with it should be avoided (e.g., Achtziger et al. 2008), but in the case of food choice, the process of denial and self-control increases the preoccupation with particular foods (Ogden 2003), frequently lead to "irresistible urges" and cravings that are difficult to restrain (Coelho do Vale et al. 2016).

Repeated experiences of being "on" and "off" a diet will have a negative impact on an individual's self-efficacy while increasing the experience of shame and frustration (Green et al. 2009). Years of dieting and weight cycling will increasingly erode a person's belief that change is possible. This frustration and perceived helplessness in turn increases the use of food to manage these difficult emotions resulting in a dilemma of how to reduce intake in order to lose weight without activating unhelpful psychological responses. It can also lead to a state of vigilance where anxiety and/or monitoring about food choice is never far away (Green et al. 2009) even when not following a diet "I shouldn't really have this but. . .."

## Binge Eating

Eating disorders, particularly binge eating disorder, are associated with increased rates of obesity (Hudson et al. 2007), a heightened risk of developing future metabolic problems (Hudson et al. 2010), a high prevalence of comorbid psychiatric disorders, and elevated suicide risk (Welch et al. 2016). Compared to obesity alone, people who live with obesity and binge eating have lower levels of health satisfaction, higher rates of major medical disorders (Bulik et al. 2002), and a more severe psychopathological profile (Fandiño et al. 2010).

Binge eating is defined as the consumption of larger than usual amounts of food within a relatively short period of time. It is characterized by a sense of loss of control over eating without the subsequent purging found with bulimia nervosa, and so of all the eating disorders, it is most frequently associated with obesity. Lifetime prevalence of obesity by eating disorder has been found to be 4.6% for anorexia nervosa, 21.1% for eating disorders not otherwise specified, 33.2% for bulimia nervosa, and 87.8% for binge eating disorder (Villarejo et al. 2012).

There are a number of different psychological theories that attempt to explain the trigger for binge episodes:

- The affect regulation model proposes that an increase in negative emotions triggers binge episodes; binge eating therefore functions to alleviate negative affect by using food to soothe and distract (Hawkins and Clement 1984).
- Escape theory (Heatherton and Baumeister 1991) proposes that when a person feels overwhelmed by higher level, abstract thinking (particularly when thoughts are critical) binge eating helps to escape by narrowing cognitive attention, instead of focusing on the more immediate environment (Baumeister 1990). However, unlike the affect regulation model, the escape theory suggests that emotional

distress increases after the completion of a binge, when self-awareness returns. This is supported by anecdotal clinical experience as the negative emotional and cognitive experiences following a binge frequently increase the risk of future binges.

- Expectancy theory adds that binges are maintained by a person's beliefs about the effects of binge eating (e.g., "it takes my mind off. . .," "it makes me feel better") which develop through learning and repetition (Hohlstein et al. 1998). This is useful to consider because it is the expectations of the consequences of binge eating rather than the actual consequences that will maintain this behavior.

All three theories predict that binge eating is triggered by negative affect but that binge eating does not reduce negative emotions beyond the episode of eating, reinforcing that we overestimate the impact food has on the management of emotion (Wagner et al. 2014).

It is only in the most recent version of the *Diagnostic and Statistical Manual of Mental Disorders* (APA 2013) that binge eating disorder was recognized as an eating disorder in its own right. While it is more widely talked about now, media representation of severe obesity often uses stereotypical images (Gollust et al. 2012) of people binge eating, and so there can be confusion between the two. This can lead to one of the two problematic assumptions: (1) everyone with severe obesity binge eats and/or (2) assessment for binge eating disorder is ignored.

People who binge eat and who live with obesity often miss meals which make managing cravings extremely difficult. Masheb and Grilo (2006) found that more than half of a group of people with obesity and binge eating disorder missed breakfast, but those who did eat regularly weighed less. There is extensive literature around the psychosocial causes and maintenance of binge eating behavior but relatively less which describes the physiological triggers. It is useful therefore to note a review by Mathes et al. (2009) in which animal literature was considered to understand the neurobiological basis of binge eating.

## Psychological Interventions

Having described some of the main psychosocial factors influencing the development, maintenance, and experience of living with obesity, a starting point for intervention is to decide on the focus. Psychological interventions, while not yielding the same magnitude of weight reductions that bariatric surgery does, are still of central importance in supporting people who live with obesity. Interventions which are able to address the multiple issues involved with obesity, such as affect management, habit change, ambivalence, stigma, eating disorder, and mental health, can provide the most useful interventions. Obesity treatment should be individually tailored, and realistic goals should be clearly set at the outset (Pietrabissa et al. 2012); these goals may not always be connected to weight loss but instead may, as a precursor, address some of the barriers to change.

## Targeting Behaviors

Weight loss is not a behavior. While this is often stated, it is worth repeating because it reminds us to consider the multiple behaviors needed for changes to weight, and it helps us to steer clear of the "eat less, move more" discourse. Most weight management services reinforce and are commissioned on the basis of weight loss as a central outcome. This is also frequently the patient's preoccupation. However, supporting the person to set behavioral goals at the outset helps to more clearly understand which aspects of change are presenting difficulties.

People have the potential to play an active role in the regulation of their eating behaviors, e.g., regular eating, planning daily or weekly meals, and preparing shopping lists (Otis and Pelletier 2008), and so an assessment of the barriers and ambivalence around setting these goals is essential. Being realistic about goals is important: setting goals that are too rigid (e.g., an inflexible eating plan) has the potential to trigger activation of "failure" narratives. Feeling that a person has "failed" with their diet can lead to a reduction in self-efficacy, lower mood, and an increase of stress, shame, and helplessness. These negative experiences are often paradoxically managed by using emotional eating strategies to distract or soothe. Including some a priori "if-then" implementation intentions can therefore help people close the gap between setting goals and actually attaining them (Gollwitzer and Sheeran 2009). If flexibility is built into a long-term plan, people are able to bolster their self-regulatory ability, to maintain or even increase motivation to persist (Coelho do Vale et al. 2016), and to feel less anxious about "suddenly" losing control of their eating. Having a flexible plan is likely to enhance goal-adherence and therefore goal attainment (Coelho do Vale et al. 2016) and is associated with better weight maintenance (Westenhoefer 2001).

More clearly targeted behaviors and associated-self efficacy can improve maintenance of an eating plan. For example, focusing on increasing confidence to manage temptations is more likely to result in weight loss than global self-efficacy and motivation (Armitage et al. 2014).

Behavioral treatments focusing on restrictive eating and weight loss are in general successful in the short-term but are not very effective in maintaining weight loss in the long term. Maintaining cognitive control for prolonged periods is difficult and may be undermined by physiological responses to weight loss (Sumithran and Proietto 2013). Typically, people regain weight within 5 years (Wilson and Brownell 2002). In a thoughtful study by Kirk et al. (2014), people living with obesity spoke of the complexities they experienced when trying to lose weight; when there was no clear reason for their unsuccessful weight loss, they blamed themselves for failing.

## Cognitive Behavioral Therapy

Perhaps the most extensively used psychological model, applied to a wide range of physical and mental health conditions, is cognitive behavioral therapy (CBT). It is frequently used in approaches to obesity (Cassin and Atwood 2017). It is an

approach that connects the experience of thoughts, feelings, physical sensations, and behavior into a framework that helps people to cope more effectively (Turnball 1996). Part of the appeal of the model is that it is versatile and can be adapted to different modalities (face-to-face individual and group, telephone, text, computerized, self-help reading material), and a range of health professionals can use elements of the model depending on their level of training.

CBT for weight loss has been found to result in an average weight reduction of 9% over a 3-year period with the majority of people regaining weight (Cooper et al. 2010). However the value of using CBT is greater for reducing attrition from weight loss programs (Tagliabue et al., 2015) and preventing relapse (Werrij et al. 2009) than weight loss alone. CBT has been found to be helpful in reducing episodes of binge eating (Grilo et al. 2011), but in studies with relatively short-term follow-up (e.g., 12 months), no weight loss is evident (Grilo et al. 2011).

The way we think and feel about food choices and weight are profoundly important (Nauta et al. 2000), and so using CBT to explore cognitive distortions and thinking errors can highlight extremely useful issues which may otherwise present as barriers and/or sabotage of change. CBT programs that are not focused on weight loss, discourage becoming overly focused on calorie restriction and aim instead to promote "healthy eating," to improve participants' well-being and to encourage physical activity (Rapoport et al. 2000).

## Motivational Interviewing

Motivational interviewing (MI) is another psychological intervention used by many different types of healthcare professionals and for a range of conditions. Originally designed for working with addictions, the transtheoretical model of change (DiClemente and Prochaska 1998) proposed that change is a process rather than a discrete event and that by understanding where in the process of change a person is, tools within the model of MI can help to explore and resolve ambivalence about change, support self-efficacy, and enhance intrinsic motivation. Resolution of ambivalence frees the person to consider alternatives (Miller and Rose 2015).

The effectiveness of MI for weight loss is limited; while having some impact, the degree of weight loss is minimal (Armstrong et al. 2011; Barnes and Ivezaj 2015). It has been found to be a useful adjunct when combined with other interventions for weight management, physical activity, and diet (Tuah et al. 2011). Carels et al. (2007) found adding a component of motivational interviewing for people who were struggling to meet behavioral treatment goals resulted in increased weight loss and greater engagement in exercise than a matched group who did not receive MI.

## Dialectical Behavior Therapy

Dialectical behavior therapy (DBT) was originally designed to support people with borderline personality disorder (Linehan 1993) and later was developed to treat

eating disorders (Agras et al. 2000). The DBT model suggests that emotional eating can be viewed as providing temporary relief from negative or overwhelming affect by numbing, soothing, and avoiding (Blocher-McCabe et al. 2004).

Research into the use of DBT has more frequently been focused on eating disorders than weight management. However, it has value in working with people who live with obesity and who frequently use emotional eating as a coping strategy but do not meet the diagnostic criteria for eating disorders (Glisenti and Strodl 2012). Self-regulation skills are emphasized which include an ability to tolerate uncomfortable states (e.g., negative emotions, cravings) and a reduction of pleasure (e.g., choosing to exercise rather than watching TV). There is an established link between emotional regulation and depression on eating behavior (Michopoulous et al. 2015), and so, despite expectations, the passage of time rather than food is more responsible for an improvement in mood (Wagner et al. 2014). DBT strategies which focus on distress tolerance and emotional regulation are therefore important to build in advance of addressing cognitive strategies.

Further research is needed (Glisenti and Strodl 2012), but results from pilot studies suggest that DBT can be delivered effectively in a group format and can support weight stabilization, reduce eating psychopathology, and has low attrition rates (Roosen et al. 2012; Peat et al. 2014; Mushquash and McMahan 2015).

## Compassion Focused

Compassion-focused therapy (CFT) considers that if we have high levels of shame and self-criticism it is very difficult to be self-supporting or self-reassuring (Mayhew and Gilbert 2008). Negative judgment and self-criticism are very often observed in people living with obesity, resulting from their experience of weight stigma and also from repeatedly being unable to lose weight or prevent weight regain (Burk-Braxton 1996). Feeling guilty or ashamed about weight can prompt disengaging coping responses, such as avoidance, negative self-talk, crying, and isolating oneself. These responses are likely to prevent active coping styles which may be more helpful for weight loss, such as problem-solving, confronting, and seeking social support (Conradt et al. 2009). Self-compassion, however, allows for an acknowledgment of mistakes and shortcomings, enabling the individual to consider changing unhelpful behaviors and attempt new goals, rather than berating themselves for previous failures (Neff and Vonk 2009). Self-soothing, which is an aspect of compassion-based interventions, enables a less critical attitude toward oneself, distracting away from critical, uncompassionate, and judgmental self-talk which is often associated with dieting (Mantzios and Wilson 2015).

Research into the use of CFT interventions for weight management is in its relative infancy, and so there is limited evidence for its use. It is however beginning to be recognized for its utility in developing strategies to buffer against the negative impact of external and internalized weight stigma (Hilbert et al. 2015). Self-compassion is highlighted as a useful avenue to explore both for obesity and body dissatisfaction (Marks 2015).

## Mindfulness

Mindfulness is defined as the ability to attend, in a nonjudgmental way, to one's own physical and mental problems during ordinary, everyday tasks (Epstein 1999). There has been a great deal of interest in the application of mindfulness to eating behavior. Intuitively it has good face validity for its benefit for interrupting automatic and unconscious eating behaviors which can lead to weight increase.

Mindfulness programs have been designed for general well-being, for targeted difficulties, e.g., depression (Gu et al. 2015), or to target specific behaviors. Targeting behaviors is the most interesting area to date for the potential benefits when applied to eating. By learning to pay attention to the present moment rather than being distracted by thoughts concerned with the past or future, there is a greater opportunity to notice physiological responses to hunger and satiety. It is a very useful approach to develop greater self-regulation, noticing cravings without acting on them, therefore enabling weight loss (Mantzios and Wilson 2015a). A reduction in binge eating has also been noted (Godfrey et al. 2015). Specific programs have been designed such as the Mindfulness-Based Eating Awareness Training (MB-EAT, Kristeller and Wolever. 2010). MB-EAT appears to have value as an intervention for binge eating and warrants further investigation as an approach to weight loss.

## The Way Forward

Combining psychological theory with knowledge of physiological processes is fundamental to developing a more comprehensive approach to obesity. Central to this is clearly listening to the perspective of people with obesity, respecting their lived experience, and appreciating the relationships between mental health and obesity (Kirk et al. 2014). A collaboration of psychological, physiological, and social understanding has the potential to shift the health discourse about the personal controllability of obesity into a less stigmatizing health culture.

While psychological interventions for complex obesity have a limited effect size for weight loss alone, consideration of psychological factors are of central importance to weight loss maintenance (Pietrabissa et al. 2012) by addressing the way in which food, weight, and emotional well-being interact with our social systems. Food and weight have many meanings and functions for people; therefore increasing our understanding in a compassionate and nonjudgmental way through research and clinical practice will enable the building of alternative strategies to meet the emotional and physical needs instead of the panacea that food has become.

Currently we refer to obesity as if it is one condition which is measured by BMI. This creates the problem of trying to develop interventions for "obesity" because we are assuming heterogeneity. Rarely do we use the term "underweight" as a target for intervention, instead we treat low immune systems or amenorrhea or assess for osteoporosis or anorexia or food avoidance. Yet reducing obesity is the focus of intervention for people with increased weight which is perhaps a reflection of weight stigma within healthcare. Instead, by defining the physical, emotional, and behaviors

problems: diabetes, hypertension, emotional eating, depression, irregular eating, limited protein, etc., we can more clearly consider interventions that would be helpful. This requires a comprehensive and sensitive assessment rather than the assumption that obesity is the problem. The work in developing staging systems for obesity (e.g., Sharma and Kushna 2009) has begun to challenge automatic assumptions between weight and health and more clearly offers areas to target intervention. Noticing the language change from "being obese" to "having obesity or "living with obesity" enables us to recognize obesity as a condition rather than a descriptor of a whole person. It is these fundamental shifts that will begin to change the way we offer support for people who struggle with and live with obesity.

Psychological interventions are most usefully applied when models are combined. Examples of useful elements include:

- Motivational Interviewing to frame and explore ambivalence
- CBT to understand repeated cycles of behavior and to recognize points to apply alternative strategies
- mindfulness to attend in the moment to eating behaviors that have become unconscious and automatic
- DBT to develop greater emotional regulation and distress tolerance.

These interventions need to be held within a compassion-focused framework which acknowledges and addresses the critical judgment, internalized external weight stigma, and supports maintenance of change even if it does not always go according to plan.

Our challenge is how to meaningfully conduct research which not only captures the diversity of obesity but is also able to reflect the complexities of multicomponent interventions.

## Key Points

1. Weight stigma is a significant factor which influences the health and well-being of people living with obesity as well as negatively impacting on weight.
2. Weight loss is not a behavior. It is multidimensional which requires and enables multiple targets for intervention.
3. If weight is the only target of an intervention, we miss a wide range of issues that compound the habits associated with eating and weight and that impact on physical and emotional health and well-being.
4. Both weight and food have meaning and function that if explored help us to understand ambivalence.
5. "Emotional eating" is a more appropriate term to describe the way food is used to manage affect rather than "comfort eating."
6. Psychological interventions work best when multiple models are integrated with physiological understanding. Adopting a biopsychosocial approach is essential when working with people who live with obesity.

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# Surgical Approaches in the Treatment of Obesity

17

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**Abstract**

Bariatric-metabolic surgery is the most effective treatment option for clinically severe obesity that offers significant and durable weight loss. In this chapter, we examine the evidence for the common bariatric surgical procedures. We explore the mechanisms of action of surgery on weight loss and glycemic control, including changes in key hormones related to energy balance and glucose homeostasis. We discuss the role of the endocrinologist in helping decide the appropriate patients for bariatric-metabolic surgery and addressing non-surgical aspects of perioperative care, most notably nutritional and metabolic support. The acute post-surgical and longer-term nutritional and metabolic complications of surgery as well as recommendations for post-operative lifestyle, nutritional and comorbidity follow-up are also reviewed.

**Keywords**

Bariatric surgery · Metabolic surgery · Weight loss · Obesity

## Chapter Objectives

At the end of the chapter, the reader should be able to:

1. Discuss the common bariatric surgical procedures and understand the mechanisms of action.
2. Discuss the evidence for the use of bariatric-metabolic surgery.
3. Understand the mechanisms of weight loss and improvement in obesity-related complications following bariatric-metabolic surgery.
4. Identify and select appropriate patients for bariatric-metabolic surgery.
5. Discuss the appropriate preoperative work-up prior to surgery.
6. Recognize acute and long-term complications after surgery.
7. Appreciate the long-term lifestyle, nutritional and comorbidity follow-up required after bariatric-metabolic surgery.
8. Discuss future directions in surgical approaches to treat obesity, including the use of medical devices.

## Introduction

Obesity is a serious chronic disease that is associated with significant morbidity and mortality. Obesity leads to metabolic and mechanical complications including type 2 diabetes (T2DM), hypertension, hyperlipidemia, nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, obstructive sleep apnea, osteoarthritis, and certain cancers. The social, psychological, and economic impact of obesity is also well recognized.

Lifestyle interventions focusing on healthy diet and exercise remain the foundation of obesity management, as they are for other chronic conditions such as T2DM, hypertension, and coronary artery disease. Improvement in obesity-related medical conditions is observed with moderate sustained total body weight loss (TBWL) of 5–10%, which may be achieved with lifestyle interventions (Jensen et al. 2014). However, for the majority, such modest weight loss achieved is usually difficult to sustain in the long-term. This is due to physiological neuro-hormonal changes following weight loss that drive food-seeking behavior to increase energy intake while simultaneously reducing energy expenditure and together these physiological adaptations provide ideal conditions for weight regain and obesity relapse (Sumithran et al. 2011).

Bariatric-metabolic surgery is the most effective treatment option for clinically severe obesity that offers significant and durable weight loss. Surgical alteration of the gastrointestinal (GI) anatomy leads to sustained change in central regulation of energy balance and metabolism. The resulting weight loss provides broad ranging benefits including reduced mortality (especially from cardiovascular disease, diabetes, and cancer), improvement in obesity-related health outcomes, and better quality of life (Mechanick et al. 2013).

## Common Types of Bariatric-Metabolic Surgical Procedures

The three most common bariatric-metabolic procedures performed worldwide are sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), and adjustable gastric band (AGB) (Fig. 1).

### Adjustable Gastric Banding

The AGB involves laparoscopic placement of an adjustable silicone band around the proximal stomach just below the gastro-esophageal junction. The band is filled with an isotonic solution (e.g., 0.9% sodium chloride), and the amount of fluid can be adjusted via a subcutaneous reservoir fixed to the anterior rectus sheath. In recent years, the use of AGB has decreased compared with other bariatric surgical procedures such as RYGB or SG. Optimal band adjustment is vital for long-term success with the AGB and can be achieved by aiming for the "green zone" (Fig. 2) in adjusting the band (Dixon et al. 2012).

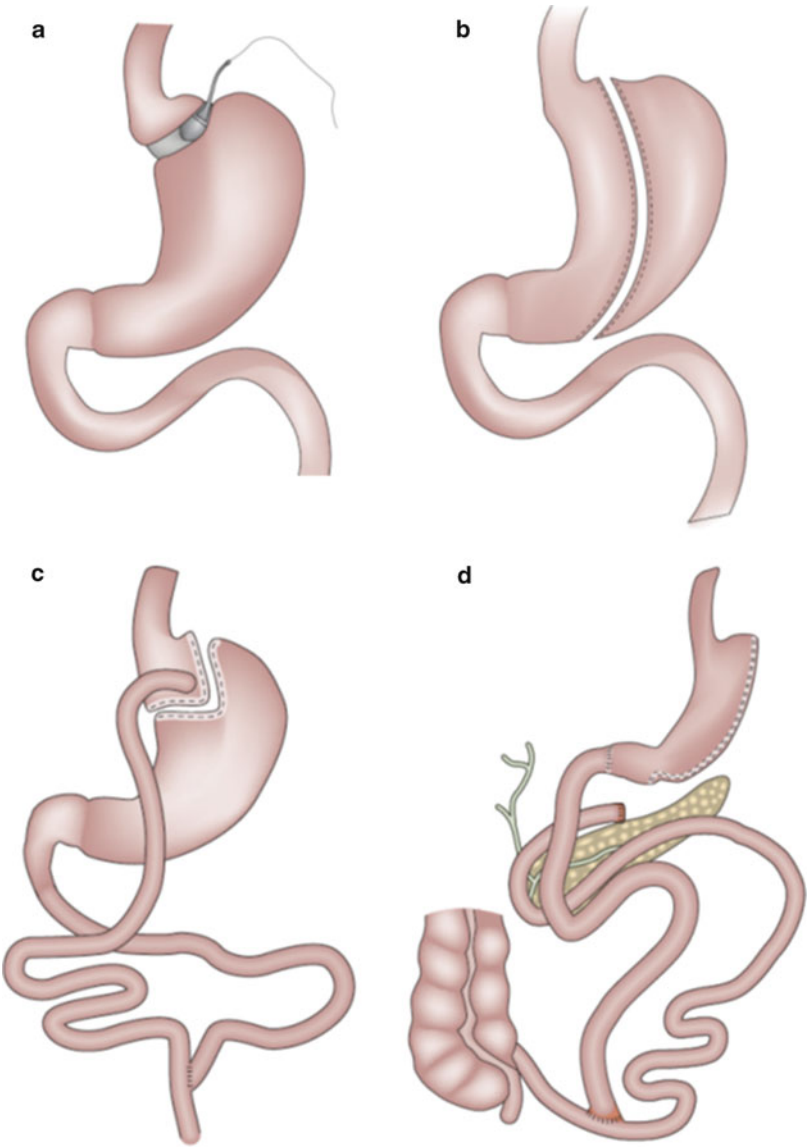


**Fig. 1** The four established bariatric-metabolic procedures (Dixon et al. 2011a). (**a**) Adjustable gastric band, (**b**) Sleeve gastrectomy, (**c**) Roux-en-Y gastric bypass, and (**d**) Biliopancreatic diversion with duodenal switch

## Sleeve Gastrectomy

The SG was initially devised as the first part of a two-stage procedure involving biliopancreatic diversion with duodenal switch (BPD-DS). The rationale for the two-step approach was that the weight loss due to SG would reduce morbidity and mortality

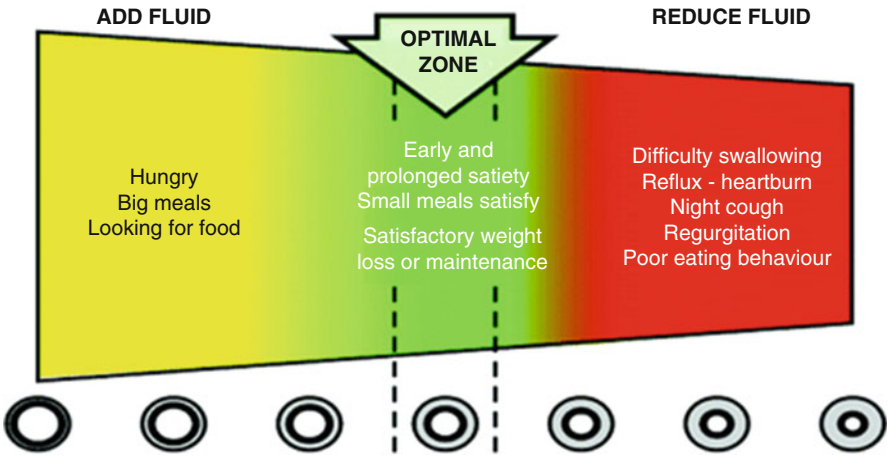


**Fig. 2** Green zone for optimal band adjustment

of the more technically demanding BPD-DS procedure, especially in the super-super obese individuals (BMI >60 kg/m$^2$). However, it was observed that significant weight loss was achieved following SG, which has now cemented its position as a stand-alone procedure to treat clinically severe obesity. Indeed, the SG has now become the most commonly performed bariatric procedure in the US and worldwide.

The SG procedure involves removing the greater portion of the fundus and body of the stomach, creating a long, tubular gastric pouch, or sleeve. Gastric volume is reduced by 80% following the procedure, which leads to changes in various gut hormones and helps to reduce food intake.

## Roux-en-Y Gastric Bypass

RYGB is still considered the "standard" bariatric surgical procedure that consists of two parts: gastric volume reduction and proximal alimentary diversion. First, a small gastric pouch of about 15 ml is created, thereby reducing gastric volume. This pouch is then anastomosed to the jejunum, hence diverting nutrients from the distal stomach, duodenum, and proximal jejunum.

## Biliopancreatic Diversion – Duodenal Switch (BPD-DS)

As mentioned, the BPD-DS has two components. The first part is similar to the SG, whereby a vertical gastrectomy is performed to create a tubular gastric pouch, with reduction in gastric volume. The distal ileum is then divided and anastomosed to the duodenum, in a Roux-en-Y configuration. A second anastomosis of the ileoileostomy is created approximately 75–150 cm proximal to the ileocecal valve. These anastomoses cause ingested nutrients to effectively bypass about 50% of the

small intestine, leading to significant malabsorption of protein and fat, as well as certain micronutrients and vitamins.

The BPD-DS provides the largest amount of weight loss and improved glycemic control in patients with severe obesity and T2DM, compared with RYGB, SG, or AGB. However, the downsides include increased acute postsurgical complications such as leaks and obstruction and long-term complications such as nutritional deficiencies. Hence, its use is limited and BPD-DS comprises <1% of all bariatric operations in the US (Ponce et al. 2016).

## Evidence for the Use of Bariatric-Metabolic Surgery

Bariatric-metabolic surgery leads to significant long-term weight loss which translates to numerous health benefits including reduced mortality especially from cardiovascular disease and cancer, improvement in obesity-related diseases, and improved physical functioning and emotional well-being (Mechanick et al. 2013).

### Weight Loss

The Swedish Obese Subjects (SOS) study is the longest and largest prospective study on bariatric-metabolic surgery, which indicated that weight loss of 20–32% maximally achieved at 1 to 2 years after surgery, was sustained at 18% even after 20 years (Sjostrom 2013). Several randomized controlled trials (RCTs) comparing bariatric-metabolic surgery versus intensive medical therapy for T2DM over a period of 12–60 months have shown that the weight loss achieved varies with the different procedures; BPD has the highest total body percentage weight loss (TBWL) (31%), followed by RYGB (25–28%), SG (21%), and AGB (15%) (Nguyen and Varela 2017). Weight loss seen after AGB is slow and gradual, whereas rapid weight loss can be expected with SG, RYGB, and BPD. Weight loss observed in the medical therapy arms range from 4–8%, which was similar to the results from the LOOK AHEAD trial examining intensive lifestyle intervention in individuals with overweight/obesity and T2DM (Look 2014).

### Mortality Benefit

The sustained weight loss over the long-term following bariatric-metabolic surgery has led to improved overall survival, with cardiovascular and cancer mortality approximately halved after surgery, when compared to matched nonsurgical cohort (Pontiroli and Morabito 2011; Kwok et al. 2014).

## Data for Improvement in Diabetes and Comorbidities

Marked weight loss from bariatric-metabolic surgery leads to corresponding improvements in insulin sensitivity and glycemia, obesity-related dyslipidemia,

inflammatory markers, NAFLD, obstructive sleep apnea (OSA), and ovulatory function and fertility in women with polycystic ovary syndrome. In patients with T2DM, significant improvements in glycemic control are observed in the majority of cases, even to the point of remission of diabetes (stable nondiabetic glycemia of all diabetes medications) (Rubino et al. 2016). RCTs have shown that treatment of obesity and T2DM with bariatric-metabolic surgery is superior to medical therapy in controlling hyperglycemia and cardiovascular risk factors over the medium term (Mingrone et al. 2015; Schauer et al. 2017).

Similar to the weight loss data, the rate of T2DM improvement or remission varies depending on the type of procedure, with BPD-DS being the most effective, followed by RYGB, SG, and AGB. A recent report from the SOS study showed that bariatric-metabolic surgery was associated with reduced risk of microvascular complications over a median follow-up period of 19 years (Carlsson et al. 2017) implicating that improvement in glycemia and other cardiovascular risk markers translate to reduced hard end-points over the longer term.

Apart from T2DM, other obesity-related complications also improve following bariatric-metabolic surgery. A systematic review and meta-analysis have shown that cardiovascular risks factors such as hyperlipidemia, hypertension, and sleep apnea improved in $\geq$70%, 78.5%, and 83.6% of patients who had surgery, respectively (Buchwald et al. 2004). These improvements were maintained with fewer medications required to treat T2DM, hypertension, and hyperlipidemia, compared to nonsurgical controls.

### Improvement in Quality of Life

It has been estimated that obesity has greater negative impact on quality of life than 20 years of aging, an impact that persists even after accounting for demographics, health habits, medical conditions, and depression (Dixon 2010). Quality of life is an important outcome measure for evaluating the efficacy of an intervention for obesity. Numerous studies using quality-of-life questionnaires have consistently shown substantial improvement in health-related quality of life following weight loss from bariatric-metabolic surgery (Dixon 2010; Schauer et al. 2017).

## Mechanisms of Weight Loss Following Bariatric-Metabolic Surgery

The major reason for success with bariatric-metabolic surgery is its ability to alter energy balance and circumvent the body's compensatory physiological responses to weight loss. The sustained weight loss following bariatric-metabolic surgery provides an opportunity to better understand the role of integrated GI physiology in the regulation of energy balance. The body weight regulates at a lower "set-point" following surgery, and a feeling of satiety is created following a small intake of

food. This allows continued weight loss, which is maintained once the body reaches a new set-point.

How surgery modifies these homeostatic mechanisms is still incompletely understood, but there have been several postulations put forth. Earlier constructs based on anatomic "restrictive" and "malabsorptive" concepts do not fit well with more recent clinical observations. There is no significant delay in transit of food within the foregut nor any significant malabsorption of macronutrients observed with major surgical procedures performed such as AGB, SG, or RYGB. Similarly, varying the gastric pouch in RYGB from 10 ml to 30 ml or varying the length of Roux limb from 75 cm to 150 cm does not increase long-term weight loss or improve outcomes.

Bariatric-metabolic surgery leads to changes in key hormones, especially gut hormones, which are related to energy balance and weight loss. Changes in these hormones following the common surgical procedures are shown in Table 1. Ghrelin is the only gut hormone that stimulates appetite. Circulating levels of ghrelin surge before meals and are suppressed by food ingestion, thus implicating the important role of ghrelin in meal initiation and short-term feeding control. Ghrelin levels increase following AGB, as expected for the degree of weight loss but are reduced in SG, due to removal of the gastric fundus, and is variable following RYGB. The role of ghrelin in long-term energy homeostasis and in the action of bariatric-metabolic surgery is still uncertain.

Apart from ghrelin, several other gut hormones have anorexic effects and provide lasting satiety, limiting food intake, and promoting weight loss. One hormone that has a potential important role in the action of bariatric-metabolic surgery is glucagon-like peptide 1 (GLP-1). GLP-1 is secreted from the neuroendocrine L cells in the intestinal mucosa, in response to nutrient stimulation after a meal. GLP-1 has numerous modes of action including stimulation of beta cells to produce insulin, delay of gastric emptying, and suppression of appetite. Indeed, the GLP-1 receptor

**Table 1** Summary of changes in key hormones related to energy balance and weight for the established surgical procedures and for intentional dietary weight loss (Sweeney and Morton 2014; Dixon et al. 2015)

| | AGB | SG | RYGB | BPD | Diet |
|---|---|---|---|---|---|
| Leptin | ↓ | ↓ | ↓ | ↓ | ↓ |
| Insulin | ↓ | ↓ | ↓ | ↓ | ↓ |
| Adiponectin | ↑ | ↑ | ↑ | ↑ | ↑ |
| Glucagon | ↔ | ? | ↑ | ? | ↓ |
| Ghrelin | ↑↔ | ↓ | ↓↔↑ | ↓ | ↑ |
| GLP-1 | ↔ | ↑ | ↑ | ? | ↔ |
| PYY | ? | ↑ | ↑ | ↑ | ↔ |

↑ and ↓indicate a substantial number of studies indicate an increase or decrease, respectively
↔ indicates a substantial number of studies find no change
? indicates that there are too few data to provide reliable trends
For some procedures, there are a number of quality studies that show different results for the change in ghrelin following surgery.
There was insufficient data on GIP, CCK, amylin, and PPP to include these in the table.

agonist, liraglutide, has been approved by the USFDA to treat obesity. GLP-1 levels rise following SG, RYGB, and BPD, probably as a result of expedited transit of nutrients to the distal intestine.

Peptide YY (PYY) is another peptide hormone that is produced by the L cells of the gut. PYY levels rise in proportion to calories ingested following a meal and likely affect central appetite control and gut motility. As with GLP-1, PYY levels are also elevated after RYGB and, to a lesser extent, SG. The diminished acute weight loss effects of gastric bypass in PYY knock-out mice suggests that PYY has a key role in mediating early weight loss in bariatric-metabolic surgery (Chandarana et al. 2011).

Vagal afferent receptors in the upper GI tract send signals to the brain in response to gastric distension and nutrient type. All effective bariatric procedures have a gastric component, which affects the gastric mechanosensitive stretch and motility receptors. The role of these afferents in energy homeostasis is exemplified by studies of the AGB. It is thought that food moving through the gastric band area activates vagal sensory afferents embedded in the gastric muscle of the cardia and generates satiation. Given that the AGB does not directly influence GI hormone concentrations or gastric emptying, it is clear that these mechanical changes to the stomach have a significant impact on long-term energy balance.

Bariatric procedures such as SG and RYGB, but not AGB, lead to changes in plasma bile acid (BA) levels. BA are synthesized in the liver, stored in the gallbladder, and then secreted into the duodenum after ingestion of a meal. The BA are then mostly reabsorbed in the terminal ileum, with a small amount excreted in the feces. These BA act on farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 5 (TGR5) and affect glucose, lipid, and energy metabolism. FXR, a bile acid regulator, may influence hepatic glucose handling by inhibiting gluconeogenesis, improving insulin secretion and sensitivity and stimulating glycogen synthesis. BA activation of TGR5 may stimulate GLP-1 secretion from the L cells, leading to improved weight loss. However, as yet, there is no direct evidence for a causal relationship between BA and improved metabolic control after RYGB.

The human gut microbiome performs important functions including nutrient extraction, prevention of pathogenic colonization, and immunomodulation. In obesity and T2DM, gut microbiome composition is altered and diversity is reduced. This diversity is restored after weight loss following bariatric-metabolic surgery. The potential causal relationship between gut microbiome and metabolic control is supported by evidence that fecal transposition from obese mice to gnotobiotic mice can transmit the abnormal phenotype (Ridaura et al. 2013). In addition, the transfer of fecal microbiodata from patients who had RYGB or vertical banded gastroplasty to germ-free mice resulted in reduced body fat accumulation in recipient mice (Tremaroli et al. 2015). Put together, the evidence suggests that bariatric-metabolic surgery causes specific changes to gut microbiome, which affect weight and metabolic control. At present, it is still unclear whether these changes are specific to the surgical procedure or due to diet-induced weight loss, and whether there are weight-independent therapeutic effects of gut microbiome changes on glycemic control.

## Mechanisms of Improved Glycemic Control: Is It All Due to Weight Loss?

In recent years, there has been intense focus on the potential weight-independent benefits of bariatric-metabolic surgery, particularly in the treatment of T2DM. The notion that T2DM can be treated successfully with surgery with little or no weight loss is indeed attractive, but the evidence supporting this is conflicting. One key feature that supports the notion of therapeutic weight-independent metabolic effects of surgery is the observation in two RCTs that different surgical procedures yielded different T2DM remission rates, at relatively similar amounts of weight loss. RYGB leads to higher DM remission as compared with SG (Schauer et al. 2014), and BPD produces better DM remission rates than RYGB (Mingrone et al. 2015), an observation that is disproportionate to the differences in weight loss seen.

There are a number of hypotheses on the potential mechanisms to explain the beneficial weight loss-independent effects on glycemic control that are seen with some bariatric-metabolic procedures. The main focus is on the improvement in insulin sensitivity after surgery and the potential role of GLP-1 as a mediator of diabetes improvement.

Insulin resistance is the hallmark feature of T2DM, and hyperglycemia ensues when the body is unable to produce enough insulin to overcome the insulin resistance. The improvement in insulin resistance seen after bariatric-metabolic surgery is due to two major factors. Acute caloric restriction following RYGB leads to decreased hepatic glycogen stores and glucose production rate and improvement in hepatic insulin sensitivity. This probably accounts for the early improvement in insulin sensitivity seen after surgery, before any significant weight loss has occurred. Subsequently, postoperative weight loss further improves insulin sensitivity in liver, adipose tissue, and skeletal muscle. There are no differences in improvements in insulin sensitivity with RYGB, AGB, or even control subjects, as long as they are matched for calorie intake and weight loss (Chondronikola et al. 2016). On the other hand, BPD appears to have unique effects on insulin sensitivity, with rapid near-normalization of insulin sensitivity early after surgery (Chondronikola et al. 2016; Mingrone and Cummings 2016).

The "incretin" effect is a well-known phenomenon whereby oral glucose elicits a greater insulin secretion response compared with intravenous glucose, at identical plasma glucose levels. The hormones responsible for this effect are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Bariatric procedures such as RYGB and SG cause five- to tenfold increases in postprandial GLP-1 secretion, leading to speculation that GLP-1 underlies the metabolic improvement following surgery. However, the role of GLP-1 has been recently challenged. Animal knockout studies have shown that mice lacking GLP-1 receptors responded similarly to controls after SG (Wilson-Perez et al. 2013). Likewise, studies using GLP-1 receptor antagonist exendin (9–39) demonstrated that by blocking GLP-1 action after SG or RYGB, there is diminished insulin secretion but the impact on glucose tolerance is limited (Jimenez et al. 2013, 2014). In one study, GLP-1 responses to meal stimuli were also almost identical regardless of glycemic status (DM remission,

nonremission, or relapse) at 2 years after SG (Jimenez et al. 2014), suggesting that GLP-1 is not the key determinant in glycemic improvement in T2DM patients after bariatric-metabolic surgery. This was in contrast to other studies, which have suggested that raised GLP-1 remains a major factor for the marked improvement of glucose tolerance after surgery (Jorgensen et al. 2013; Shah et al. 2014). Hence, the contribution of GLP-1 to the glycemic benefits seen after bariatric-metabolic surgery is still not entirely certain. It may be that elevated GLP-1 levels are important in the early glycemic improvement seen after surgery but of diminishing relevance over time as other factors such as beta-cell function and peripheral insulin sensitivity come into play (Madsbad and Holst 2014).

There are other factors that contribute to improved glucose homeostasis, though it is controversial whether these are beyond weight-loss effects. Intestinal insulin resistance seen in obesity is ameliorated after RYGB, with normalization in insulin-stimulated jejunal glucose uptake after surgery (Makinen et al. 2015). This observation correlated with improvement in whole body insulin sensitivity, though it is unclear if the effect is due to weight loss or the UGI tract bypass per se. Brown adipose tissue (BAT) also has a potential role in glucose homeostasis as BAT activation increases glucose uptake and improves whole-body insulin sensitivity (Chondronikola et al. 2016). BAT activity is increased following weight loss, regardless of whether it is induced by caloric restriction alone, AGB, or RYGB. It remains unclear whether RYGB stimulates BAT activity in addition to that observed in diet restriction alone, given that RYGB also leads to increased BA and GLP-1, which in turn, can increase BAT metabolic activity and cause browning of white adipose tissue (Chondronikola et al. 2016).

Bariatric-metabolic surgery may well offer some weight-independent metabolic benefits, in particular with improvement in glycemic control. However, given the strong association between post-operative weight loss and diabetes remission/improvement, and that the most important factor for diabetes relapse is weight regain, weight loss remains the major contributor to the metabolic benefits observed after surgery. The effects of weight loss and acute caloric restriction on glucose and energy physiology are profound and far-reaching, and it would be challenging to discern the exact contribution of bariatric-metabolic surgery over and above these factors.

## Indication for Bariatric-Metabolic Surgery

The most widely referenced indications for bariatric-metabolic surgery are now historic and date back to the NIH Consensus Statement in 1991 (NIH Conference 1991). Primarily based on BMI and presence of obesity-related complications, individuals that could benefit from surgery include those with BMI $> 40$ kg/m$^2$ or BMI $> 35$ kg/m$^2$ with one or more obesity-related complications.

Given the mounting evidence of improvement in glycemic control in patients with severe obesity and T2DM who have had bariatric-metabolic surgery, major international diabetes organizations have now proposed bariatric-metabolic surgery

to be an established treatment option in the algorithm to manage T2DM (Rubino et al. 2016). Surgery is ***recommended*** for all individuals with T2DM and BMI $\geq$ 40 kg/m$^2$, or those with BMI 35–40 kg/m$^2$ with inadequate glycemic control despite lifestyle and optimal medical therapy. In addition, surgery may be ***considered*** in those with BMI between 30–35 kg/m$^2$ and uncontrolled hyperglycemia despite optimal medical therapy (Rubino et al. 2016). However, the evidence in this lower-BMI cohort is limited, and long-term data demonstrating net benefit is still lacking.

There are few absolute contraindications to surgery; they include contraindications to general anesthesia, serious blood or autoimmune disorders, active drug or alcohol abuse, and severe, untreated psychiatric illness. Patients with limited life expectancy due to cardiopulmonary or other end-organ failure or metastatic/inoperable malignancy are also not suitable for surgery.

As with any operation, the potential benefits of surgery must outweigh the perioperative and long-term risks of surgery. Bariatric-metabolic surgery is strongly recommended and should be prioritized for individuals who suffer from super obesity (BMI >50 kg/m$^2$) or class III obesity (BMI >40 kg/m$^2$) with serious complications that would respond to weight loss. Surgery is also suitable for younger patients, who are likely to develop complications of obesity and subsequent reduced quality of life over time without active intervention. On the other hand, increasing age is a risk factor for postoperative complications and mortality. Caution is advised if the patient is over 65 years of age.

## Procedure Selection: Choice of Procedure

The choice of surgical procedure is guided by the individual's characteristics, aims of therapy, available surgical expertise, and informed patient choice. RYGB provides more weight loss than SG or AGB and may be appropriate for individuals with very high BMI. AGB has lower perioperative risk and reduced early complications compared to RYGB, but higher rate of reoperation for inadequate weight loss (Tice et al. 2008), and thus may be suitable for older individuals where the extent of weight loss and nutritional risks can be controlled, or for those at lower BMI ranges. Apart from the BPD (which is less commonly performed due to concerns surrounding malabsorption), RYGB provides the greatest rate of diabetes remission, a consideration for T2DM patients. The presence of gastroesophageal reflux disease (GERD) may also be another determining factor: RYGB and AGB usually improve GERD symptoms whereas SG may exacerbate GERD. Finally, good quality postoperative care is crucial to the success of the AGB, as regular adjustments to the band are often necessary to maintain optimal function. The decision for AGB should take into account the availability of an appropriate aftercare program. A large English RCT (the By-Band-Sleeve study) is ongoing to evaluate the comparative effectiveness and cost-effectiveness of the three most commonly performed bariatric surgical procedures (AGB, RYGB, and SG) in

severe and complex obesity (Rogers et al. 2014), and results of the study, when available, could further guide procedure selection.

## Predictors of Weight Loss and Metabolic Benefits

One of the holy grails of bariatric medicine is the preoperative identification of individuals that would do well (or for that matter badly) following bariatric-metabolic surgery. Successful outcomes following surgery seem largely dependent on inherent physiological-biological factors, rather than psychological and environmental factors. The performance of bariatric-metabolic surgery may not be as strongly influenced by patient compliance but rather driven by the physiological and hormonal changes that occur following surgery. Hence, it is damaging and unfair to blame the patient for lack of effort with regard to diet and exercise when weight loss is less than expected.

The search continues in isolating the factors that can predict weight loss outcomes following surgery. Preoperative weight loss has been touted as an indicator of "intrinsic motivation" that may guide postoperative weight loss. However, many of the studies were retrospective; uncontrolled studies and a systematic review has shown that the relationship between preoperative weight loss with weight change postoperatively is tenuous at best (Livhits et al. 2012).

Given that biology appears to play the central role in determining successful weight loss following surgery, there is substantial interest in the investigation of genetic factors that may predict individual responses to bariatric-metabolic surgery. However, the correlation between genotype and treatment outcome is still unclear, made more complex with the influence of epigenetics and the environment. At present, potential genetic markers or biomarkers of weight loss following bariatric-metabolic surgery have been limited.

As with any form of weight-loss intervention (or indeed most medical interventions), the distribution of outcomes following bariatric-metabolic surgery follow a normal distribution with a broad standard deviation, and variance is poorly explained. Therefore, there is a wide range of weight loss results that can be classed as "normal" and yet disappointing. This is common in managing a chronic disease.

Meanwhile, the striking metabolic benefits that bariatric-metabolic surgery could offer has spurred intense interest in the potential factors that can influence diabetes outcomes after surgery, and if surgery could potentially be employed primarily as a "metabolic" procedure in nonobese individuals with T2DM. It is worthwhile to note that the pathophysiology of diabetes is the integral factor that determines the degree of metabolic improvement after surgery. The two main determinants of glucose homeostasis are insulin resistance and insulin secretion. In individuals with obesity, insulin resistance usually predominates whereas those with normal weight may have a greater element of insulin secretory defect. Given that insulin resistance generally decreases proportionately to the amount of weight loss (Nannipieri et al. 2011; Ikramuddin et al. 2014), the efficacy of surgery in generating both weight loss and

glycemic control appears attenuated in normal to overweight individuals with T2DM compared with those who are obese (Dixon et al. 2013; Lee et al. 2015).

On the other hand, the improvement in insulin sensitivity and reduced demand on islet cells following weight loss may be insufficient if pancreatic beta-cell dysfunction is the main pathophysiologic driver for hyperglycemia. Approximately 50% of beta-cell function is already lost even at diagnosis of T2DM, with continuing decline in beta-cell function over time (Holman 1998). Hence, individuals with shorter duration of T2DM would be expected to have higher insulin secretory capacity and higher probability of achieving diabetes remission after surgery. Similarly, other factors that reflect better beta-cell function such as better baseline glycemic control, non-insulin requiring, higher c-peptide levels are positively correlated with likelihood of diabetes remission. Given the above, there are compelling reasons for consideration of bariatric-metabolic surgery, early in the diagnosis of T2DM, before the onset of significant diabetic complications or beta cell exhaustion. Indeed, the UK NICE guidelines have recommended that surgery should be prioritized and expedited for those with recent-onset T2DM (within 10 years of diagnosis) (Welbourn et al. 2016).

## Preoperative Assessment and Preparation

Once a decision has been made for bariatric-metabolic surgery, a series of detailed assessments should be organized. Pre-operative assessment involves identification and optimization of obesity-related complications, with the aim to improve perioperative safety and outcomes after surgery.

T2DM is a well-recognized complication of obesity and a major focus of bariatric-metabolic surgery. In the absence of history of T2DM, routine screening for DM using established methods (fasting glucose, 75 g oral glucose tolerance tests or glycated hemoglobin) is recommended and would detect presence of undiagnosed DM. For those with preexisting T2DM, serum c-peptide levels may be useful as a surrogate for beta-cell reserve and aid in assessment of the likelihood of diabetes remission following surgery.

Perhaps surprisingly, nutritional deficiencies are often observed in clinically severe obesity, which is masked by ample energy excess. Up to 80% of bariatric-metabolic surgery candidates have micronutrient deficiencies preoperatively, with common deficiencies being iron, vitamin $B_{12}$, folate, and vitamin D. Appropriate nutritional assessment allows deficiencies to be detected and corrected prior to surgery.

An essential element of preoperative assessment of any surgical patient involves evaluation of the patient's cardiorespiratory status and cardiac risk. After a focused cardiac history and physical examination, an electrocardiogram (ECG) is often obtained routinely. Referral to a cardiologist for more extensive evaluation would be appropriate for patients with preexisting cardiac disease, high cardiovascular risk, or abnormal ECG. OSA is extremely common in the cohort of patients with clinically severe obesity, with some estimates indicating prevalence of OSA as high as 88%. Untreated OSA may develop pulmonary hypertension and are at risk

of cardiac arrhythmias as a result of chronic nocturnal hypoxemia. Patients should be screened for symptomatic OSA using the STOP-BANG questionnaire and if at risk, an overnight polysomnography arranged. These can now be readily performed at home. Continuous positive airway pressure (CPAP) therapy is the mainstay of treatment for moderate to severe OSA, and if used, a period of stabilization is recommended before surgery to allow for adaptation to the device.

Prior to surgery, thorough assessment of the patients' psychosocial situation and their ability to incorporate nutritional and lifestyle changes should be conducted. Unrealistic expectations or incorrect beliefs on what the procedure can achieve must be rectified. Depression, anxiety, binge eating disorder, and other psychiatric disorders are prevalent in individuals considering bariatric-metabolic surgery, and further evaluation by psychologist or psychiatrist recommended if psychiatric illness is suspected.

As part of the preoperative preparation, it is common to institute very low energy diets (VLED) with the aim of achieving weight loss prior to surgery. Preoperative weight loss can preferentially reduce liver volume and visceral adiposity (Colles et al. 2006), which may ease technical aspects of surgery and lead to improved short-term outcomes (Tarnoff et al. 2008). In T2DM, preoperative weight loss with medical nutrition therapy can also improve glycemic control. The VLED, which consists of meal replacements providing $\leq$800 kcal/day, is usually started at least 2 weeks prior to surgery. During VLED, patients with T2DM are recommended to self-monitor their capillary blood glucose regularly, especially if they are on insulin or insulin secretagogues. Reductions in insulin doses are often necessary whilst on VLED, in order to prevent hypoglycemia.

## Risks and Complications of Bariatric-Metabolic Surgery

Bariatric-metabolic surgery is generally regarded as safe, with low morbidity and mortality that is comparable to elective laparoscopic cholecystectomy. Meta-analysis of observational studies has shown that the AGB had the lowest perioperative and postoperative mortality rates (0.07% and 0.21%), followed by SG (0.29% and 0.34%), and then RYGB (0.38% and 0.72%) (Chang et al. 2014). The converse is true for reoperation rates. RCT data have suggested that RYGB has the lowest reoperation rate (3%), followed by SG (9%), and AGB (12%) (Chang et al. 2014). However, the complexity and risks of reoperations are greater with the more complex procedures.

### Surgical and GI Complications

Surgical complications can be general, such as can occur after any surgical procedure, or specific to the type of procedure performed. The procedure-specific complications and "red flag" symptoms that should prompt referral to the bariatric surgical team are shown in Table 2.

**Table 2** "Red flag" symptoms and procedure-specific complications of AGB, SG, and RYGB

| Type of procedure | "Red flag" symptoms | Potential causes to rule out |
|---|---|---|
| **AGB** | Inability to achieve lasting satiety/ inadequate weight loss despite optimal band adjustment | Erosion, leaks in the band system (usually tubing or port), unbuckled band, and proximal gastric pouch dilatation |
| | Intractable reflux symptoms<br>Persistent cough, pneumonia<br>Dysphagia with solids and liquids | Over-filled band<br>Proximal gastric pouch enlargement |
| | Abdominal pain, low-grade fever, port site infections | Band erosion (early or late) |
| **SG** | Fever, tachypnea, tachycardia, abdominal pain | Staple-line leak (early) |
| | Intractable reflux symptoms | GERD and hiatal hernia |
| | Dysphagia, vomiting | Stricture/stenosis (early or late) |
| **RYGB** | Dysphagia, nausea, vomiting | Gastrojejunal strictures (early or late) |
| | Abdominal pain | Leak over anastomotic junction (early)<br>Internal hernias (late), marginal ulcer |
| | Iron-deficiency anemia | Inadequate supplementation, marginal ulcers |
| | "Dumping syndrome" early and late | Hypoglycemia syndromes |

Hemorrhage is a general early complication that occurs in up to 4% of cases, though rates vary depending on operative experience and complexity of cases. Enteric leaks are another early complication that can be difficult to manage and can potentially cause severe peritonitis, sepsis, and multiorgan failure. Leakage can occur at any of the anastomotic junctions or staple lines in RYGB, SG, or BPD, most commonly at the gastrojejunostomy junction with RYGB, and high on the staple line with SG. There is no anastomosis with the AGB, and perforation of the gastroesophageal junction is an uncommon complication with incidence of $<0.5\%$ (Neff et al. 2013).

Regurgitation is common after surgery and is often due to eating too much or too quickly. However, more serious complications such as stricture, stoma stenosis, or herniation must be excluded with relevant clinical and radiological evaluations. Gastrojejunal strictures can occur after RYGB in about 10% of individuals, with typical symptoms of dysphagia and vomiting (Neff et al. 2013). Diarrhea is reported in up to 40% after RYGB with an unclear etiology (Neff et al. 2013). Treatment involves dietary modification and antidiarrheal medications.

Late complications (occurring $>30$ days after surgery) include marginal ulcers, internal hernias, strictures, small bowel obstruction, and gastrogastric fistula. Internal hernias with the reported frequency of 0.4–5.5% in RYGB and up to 38% in BPD have the potential to cause bowel obstruction. Late complications that can arise from AGB include proximal gastric enlargement, erosion, or migration of band and leaks of the band system. High rates of these complications that require reoperation, as well as variability in weight loss and lack of appropriate after-care program has contributed to the decline in popularity of AGB in Europe and US.

The rapid emptying of gastric contents after RYGB, or less commonly SG, can lead to postprandial symptoms, a phenomenon known as dumping syndrome. Symptoms of dumping syndrome are varied and can include diarrhea, nausea, bloating, facial flushing, palpitations, hypotension, and syncope after meals rich in simple carbohydrates. These vasomotor symptoms typically occur within 1 h after eating and are classified as "early" dumping symptoms. "Late" dumping symptoms can include sweating, palpitations hunger, tremors, confusion, and syncope and are thought to be usually due to exaggerated incretin response leading to hypoglycemia, though the definitive cause is yet to be identified. Treatment of dumping syndrome involves dietary modification by avoiding concentrated simple sugars and aiming for small regular meals consisting of protein and complex carbohydrates with low glycemic index. Occasionally, pharmacotherapy with acarbose may be needed. Rarely, endogenous hyperinsulinism due to nesidioblastosis or insulinoma have been reported after surgery (Service et al. 2005), so if symptoms are unresponsive to dietary modification or if there are atypical symptoms, then full workup for hypoglycemia to evaluate for endogenous hyperinsulinism is warranted.

## Long-Term Nutritional Complications

Another major concern after bariatric-metabolic surgery relate to nutritional deficiencies, which depend on the type of surgery performed (common nutritional concerns for each procedure shown in Table 3). More aggressive surgical procedures which promote greater weight loss would also incur higher risk of nutritional deficiencies, with their attendant long-term complications. Short common channels in procedures such as BPD and duodenal switch lead to more malabsorption, due to reduced opportunity for mixture of bile and pancreatic secretions with small intestinal chyme before nutrient absorption (Bal et al. 2012). The concern surrounding malabsorption and malnutrition is the major reason BPD is not widely performed.

**Table 3** Common nutritional concerns for each procedure (Dixon et al. 2011a)

| | AGB | SG | RYGB | BPD / BPD-DS |
|---|---|---|---|---|
| **Iron** | + | +++ | +++ | +++ |
| **Thiamine** | + | ++ | + | + |
| **Vitamin $B_{12}$** | + | ++ | +++ | ++ |
| **Folate** | ++ | ++ | ++ | ++ |
| **Calcium** | + | ++ | ++ | +++ |
| **Vitamin D** | + | + | ++ | +++ |
| **Protein** | + | + | + | ++ |
| **Fat soluble vitamins and essential fatty acids** | + | + | + | +++ |

+ Recommended daily intake (allowance) or standard multivitamin preparation likely sufficient
++ Significant risk of deficiency or increased requirements. Specific supplementation is appropriate especially in higher risk groups
+++ High risk of deficiency. Careful monitoring is recommended. Supplementation well in excess of daily requirements may be necessary to prevent deficiency

Although the standard RYGB does not produce significant malabsorption of macronutrients, long-term vitamin or mineral deficiencies can occur due to gastroduodenal exclusion, major sites of micronutrient preparation and absorption.

The recommended daily protein intake postoperatively is 60–120 g, (Heber et al. 2010; Mechanick et al. 2013) to enhance healing, maintain adequate protein stores, and stem the loss of lean body mass. Protein malnutrition remains a concern after bariatric-metabolic surgery, especially BPD and some forms of gastric bypass, with patients often requiring high-quality protein foods and protein supplements to achieve adequate protein intake. Signs of protein deficiency include edema, loss of lean muscle mass, and hair loss, as well as biochemical findings of anemia and hypoalbuminemia. In severe protein malnutrition, which is not responsive to oral protein supplementation, parenteral nutrition or naso-jejunal feeding may be considered.

Multiple studies have reported on the prevalence of nutritional deficiencies after bariatric-metabolic surgery. However, these results have to be taken in context with the preoperative nutritional status as well as nutritional stores of the individual nutrients. A large study which examined 318 patients at 1 year after RYGB showed various micronutrient deficiencies; vitamin A (11%), vitamin C (34.6%), vitamin D (7%), thiamine (18.3%), riboflavin (13.6%), vitamin B6 (17.6%), and vitamin $B_{12}$ (3.6%) (Clements et al. 2006). Chronic micronutrient deficiencies have detrimental long-term consequences, including nutritional anemias, metabolic bone disease, and neurological complications.

## Nutritional Anemias

A meta-analysis in 2015 have shown that prevalence of anemia nearly doubled in the 12 months after RYGB (Weng et al. 2015). Serum ferritin levels, an indicator of iron stores were lower at 6 months after surgery and continued to decline at 24 and 36 months. Reasons for iron deficiency include changes in dietary composition with reduced meat and dairy intake; hypochlorhydria, which decreases bioavailability of dietary iron; and bypass of the stomach, duodenum and proximal jejunum, where physiological iron absorption takes place. Iron deficiency anemia presents as microcytic, hypochromic anemia and symptoms include fatigue, weakness, pallor, anorexia, depression, light-headedness, hair loss, and koilonychia. Oral iron supplementation (ferrous sulfate, fumarate, or gluconate) may be needed to prevent iron deficiency after surgery, especially in menstruating women (Mechanick et al. 2013). Vitamin C can increase iron absorption and help with resistant iron deficiency (Mechanick et al. 2013). Intravenous iron infusions may be preferable to oral administration in severe iron deficiency, as it replenishes iron stores quicker and is usually better tolerated than large doses of oral iron replacement.

Vitamin $B_{12}$ deficiency is common after RYGB and can occur following SG, due to impaired stomach acidity and intrinsic factor secretion, which facilitate $B_{12}$ absorption. $B_{12}$ deficiency is usually not seen in the short-term due to hepatic and renal stores that can last for up to 3 years. The prevalence of $B_{12}$ deficiency is 3.6% at 12 months after RYGB but rises to 61.8% at $\geq$5 years after RYGB (Bal et al. 2012). Manifestations of $B_{12}$ deficiency include macrocytic anemia, leucopenia, glossitis, thrombocytopenia, paresthesia, and irreversible neuropathies. Both $B_{12}$ and folate are required for

maturation of the erythrocyte and deficiencies in either nutrient can lead to macrocytic anemia. Folate deficiency has also been associated with neural tube defects and cardiovascular disease. Treatment of $B_{12}$-deficiency involves $B_{12}$ replacement, orally or intranasally, with parenteral (intramuscular or subcutaneous) supplementation if adequate $B_{12}$ levels cannot be maintained (Mechanick et al. 2013). Folate deficiency can be treated with 1–5 mg of oral folate daily (Bal et al. 2012). Women who are planning pregnancy should also take 1 mg of folic acid daily as a routine supplement to reduce risks of neural tube defects in the fetus (Bal et al. 2012).

### Metabolic Bone Disease

Clinically severe obesity is associated with impaired bone health due to abnormalities in mineral metabolism such as vitamin D deficiency and secondary hyperparathyroidism (Rousseau et al. 2016). T2DM (which closely tracks obesity) may also adversely impact bone health due to factors including effects of hyperglycemia, adipokines, and antidiabetic medications.

The detrimental effect on bone is compounded following bariatric-metabolic surgery, due to various factors including decreased calcium and vitamin D intake and absorption as a result of surgically induced anatomical changes, change in hormonal and metabolic milieu, and weight loss with consequent skeletal unloading and loss of lean body mass (Yu 2014). Initial concerns about skeletal health following bariatric-metabolic surgery involve observations of sequelae of severe calcium and vitamin D deficiencies such as osteomalacia, osteoporosis, and brown tumors that were seen after earlier bariatric-metabolic procedures. These complications have declined with more aggressive vitamin and mineral supplementation and a shift towards less malabsorptive procedures. However, despite calcium and vitamin D supplementation, longitudinal studies have still shown marked bone loss and increase in bone turnover markers after bariatric metabolic surgery (Yu 2014).

There are challenges in obtaining accurate bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA) scans in severely obese patients and during weight loss. Technical issues include unpredictable impact of soft tissue artifact on DXA, increasing precision errors with increasing BMI and changing fat-lean tissue ratios in the region of interest. Despite these limitations, markedly increased bone resorption markers and quantitative computed tomography measurements of BMD support the data on bone loss after bariatric-metabolic surgery (Yu 2014).

Several population-based cohort studies have examined the effect of bariatric-metabolic surgery on fracture rates (Nakamura et al. 2014; Rousseau et al. 2016; Yu et al. 2017). Most studies showed higher fracture risk with RYGB, though one study showed no increased fracture risk over 2.2 years in a cohort predominantly consisted of AGB patients (Lalmohamed et al. 2012). A recent study suggested a positive relationship between risk of fracture and degree of obesity; highest in the group undergoing bariatric-metabolic surgery, followed by obese controls, and lowest in nonobese controls (Rousseau et al. 2016). In the study, fracture incidence increased after surgery and was site specific, changing from a pattern associated with obesity to a pattern typical of osteoporosis (Rousseau et al. 2016). Another recent study

estimated that RYGB is associated with a 43% increased risk of nonvertebral fracture compared with AGB, with risk increasing >2 years after surgery (Yu et al. 2017).

Given the adverse effect of bariatric-metabolic surgery on bone health, vigilance against nutritional deficiencies and ongoing bone loss is imperative. Despite limitations of DXA scans, they remain the most practical and accessible method of measuring BMD and are recommended at baseline and subsequently every 1–2 years after surgery until BMD stabilizes (Mechanick et al. 2013). Adequate calcium and vitamin D supplementation is also important to maintain sufficiency and avoidance of secondary hyperparathyroidism (Mechanick et al. 2013).

## Neurologic Complications

The estimated incidence of neurologic complications following bariatric-metabolic surgery can be as high as 5%, with the majority being consequences of vitamin (most commonly thiamine and vitamin $B_{12}$) or mineral (most commonly copper) deficiency. Risk factors for development of neuropathy include rate and amount of weight loss, prolonged gastrointestinal symptoms such as vomiting or diarrhea, lack of vitamin or mineral supplementation, low serum albumin and transferrin (as a marker of poor nutritional status), postoperative surgical complications requiring hospitalization, and nonattendance at nutrition clinic after surgery (Ba and Siddiqi 2010).

Perhaps the most feared neurologic complication is Wernicke's encephalopathy, a manifestation of thiamine deficiency that can lead to permanent neurologic disability. Being a water-soluble vitamin, the body has limited thiamine stores and deficiencies can occur within days to weeks after surgery. The classical triad of Wernicke's encephalopathy includes ataxia, ophthalmoplegia, and confusion, though not all features are seen in most patients. Intractable vomiting, though, is a common theme amongst patients who develop this complication, and prophylactic thiamine replacement should be considered in these patients. In post bariatric-surgery patients, polyradiculopathy mimicking Guillain-Barre syndrome can also be seen in thiamine deficiency (Becker et al. 2012). The diagnosis of thiamine deficiency can be confirmed by measuring red blood cell transketolase activity, a thiamine-dependent enzyme, but if suspected treatment should not be delayed pending the result. Treatment includes at least 250–500 mg of intravenous thiamine daily for 3–5 days and supportive care while avoiding intravenous dextrose (Mechanick et al. 2013). Refractory thiamine deficiency should raise the suspicion of small intestinal bacterial overgrowth.

Neurologic presentations of $B_{12}$ deficiency include peripheral neuropathies, depression, paresthesia, spastic paralysis, decreased reflexes, and loss of proprioception. All patients should receive $B_{12}$ supplementation after bariatric-metabolic surgery, although complications can take months to years to develop, by which time both patients and clinicians may be lax about supplementation.

Copper deficiency can occur more than 10 years after RYGB, and is likely due to reduced absorption due to bypass of the stomach and duodenum. It can also result from excessive zinc supplementation, which can interfere with copper absorption. The clinical features and neuroimaging findings closely resemble $B_{12}$ deficiency, with neurologic syndrome of myeloneuropathy-like disorder with spastic gait and

sensory ataxia. Treatment of copper deficiency involves intravenous copper 2–4 mg daily for 6 days (Mechanick et al. 2013), but neurologic complications may not be fully reversible even after replacement.

## Sarcopenia

Lean mass is integral to long-term maintenance of metabolic rate, core body temperature, skeletal integrity, muscle strength, functional capacities, and loss of lean mass is a major factor that contributes to disability in obesity. The combination of low lean mass and high fat mass, known as sarcopenic obesity, works synergistically to adversely impact on numerous health outcomes including hypertension, arterial stiffness, NAFLD, insulin resistance, functional capacity, and activities of daily living.

Presence of sarcopenia does not seem to adversely influence bariatric surgical outcomes after RYGB or SG (Mastino et al. 2016). Sarcopenic patients had similar operative risks, complication rates, and improvement in comorbidities, compared to their nonsarcopenic counterparts. However, management goals for sarcopenic obesity have to focus on maintenance or accretion of lean mass during the period of weight loss, in order to maintain muscle strength and function. This can be achieved with regular aerobic and resistance exercises following surgery. Indeed, several studies incorporating exercise program in postbariatric surgery patients have shown numerous benefits of exercise including improvement in muscle strength, lean mass, aerobic fitness, mobility, coordination, and postprandial blood glucose levels (Shah et al. 2011; Campanha-Versiani et al. 2017; Coleman et al. 2017).

## Prevention of Long-Term Complications

Adherence to post-operative clinical follow-up and nutritional monitoring and supplementation is key to reduce the risks of long-term complications after surgery. Nutritional screening allows for early detection and treatment of deficiencies, although costs do add up over the long-term. Algorithms have been developed to optimize cost-effectiveness of the nutrient panel by reducing the extensiveness of testing without sacrificing detection of clinically relevant deficiencies (Bazuin et al. 2017).

Patients are usually aware of the need for supplementation in the early post-operative period. However, they may believe that it is no longer necessary when their eating habits have stabilized or healthy weight achieved. Some may find the frequency or costs of taking pills in the long-term hard to sustain. An ongoing educational process is needed to remind patients that the nutritional complications of bariatric-metabolic surgery can occur even years to decades after the surgery and on the importance of long-term supplementation and follow-up.

The level of nutritional supplementation should depend on the type of surgical procedure performed, though literature is scant on the micronutrient requirements after bariatric-metabolic surgery. The Endocrine Society recommends that individuals who have had bariatric-metabolic surgery should receive one to two

multivitamins with minerals daily (including at least 1200 mg of elemental calcium and 1000 U of vitamin D3 per day) (Heber et al. 2010). However, procedures with significant malabsorptive component such as extended gastric bypass surgery or BPD-DS would likely require more supplementation.

## Psychological Impact of Bariatric-Metabolic Surgery

Bariatric-metabolic surgery can have profound psychological impact on patients due to variety of reasons including large amounts of weight loss achieved, changes in gut-brain hormone signaling pathways, changes in alcohol absorption and metabolism and psychosocial adaptation to post-surgical lifestyle. Consistent evidence have shown overall improvement in psychopathology, self-esteem, body image, and mental quality of life after bariatric-metabolic surgery, with decrease in depressive symptoms and psychiatric medication use (Yen et al. 2014). There is also a tendency for better cognitive function, with improvement in memory, attention, and executive function (Yen et al. 2014).

Despite overall benefit postoperatively, there remains a sizeable minority of patients who either report temporary mental health benefits only or no psychological improvement at all (Kubik et al. 2013). One potential explanation could be that preoperative patient beliefs that life will dramatically change after bariatric-metabolic surgery may have detrimental effect on psychological health, if these expectations are not met. Presurgical problems that were previously attributed to obesity, but subsequently persist after surgery, may also disappoint.

Similarly, risks of self-harm among bariatric-metabolic surgery patients warrant attention. A recent large cohort study suggests that the risks of self-harm emergencies are higher after surgery than before surgery, with those with a history of mental health issues and living in rural areas particularly vulnerable (Bhatti et al. 2016). Unlike other psychopathologies that improve after bariatric-metabolic surgery, suicide risk remains high and requires long-term monitoring. The reasons for this are still unclear but it is possible that alteration of ghrelin signaling pathways may have a role (Dixon 2016). Evidence suggests that ghrelin may have important central effects beyond energy homeostasis, including learning, memory, reward, motivation, stress responses, anxiety, and depression (Andrews 2011).

Maladaptive and disordered eating behaviors are increasingly recognized after bariatric-metabolic surgery. Some examples include routinely choosing foods with liquid consistencies such as soups and shakes over solid foods, which allow for more volume to be ingested, intentional vomiting or regurgitation after meals, and grazing on food throughout the day. A detailed food diary or dietary history may highlight the presence of an abnormal eating pattern. If persistent, maladaptive eating patterns could lead to weight regain and increase risks of nutritional deficiencies and dental disease. These concerns highlight the importance of adequate support for patients' mental health and psychosocial needs and for access to a clinical psychologist when appropriate (Welbourn et al. 2016).

## Future Directions

### Medical Devices

The success of bariatric-metabolic surgery in delivering significant and durable weight loss indicates that manipulation of the GI tract holds the key in modifying the central regulation of energy balance. There is great interest in the development and use of medical devices targeting the GI tract as a form of less-invasive therapy that could bridge the safety-efficacy gap between lifestyle interventions and bariatric-metabolic surgery (Lee and Dixon 2017). Apart from the AGB, three other types of devices have been approved by USFDA over the past 2 years to treat obesity, including intragastric balloons, vagal nerve neuromodulation, and gastric emptying systems.

There has been decades-long experience with the use of intragastric balloons to treat obesity. It is indicated in individuals with BMI 30–40 kg/m$^2$ for 6-month period of therapy, with TBWL ranging from 6.6–10.2%. The vagal nerve blocking system involves surgical placement of neuromodulator device with electrodes connected to infra diaphragmatic vagal nerve trunks that electrical stimuli to intermittently block vagal nerve signals, with TBWL of 9.2% reported at 1 year. The gastric emptying system involves endoscopic placement of a gastrostomy tube, which allows patients to aspirate gastric contents and ingested food, with reported TBWL of 12.1% at 1 year.

### Endoluminal and Novel Surgical Techniques

The quest for better surgical procedures continues to evolve and aims to address certain limitations and complexities of current surgical techniques. These include single anastomosis gastric bypass, single anastomosis duodenal switch, and gastric plication. The adoption of laparoscopic techniques in performing the various bariatric surgical procedures today has also greatly reduced the mortality and complication risks of surgery. There is a drive towards even less invasive approaches, with the use of endoscopic platforms to pursue the goal of incisionless surgery. Endoluminal gastric plication can be performed with suturing and stapling devices. These devices allow gastric partitioning to reduce the size of the gastric pouch, mimicking bariatric surgical plication. Early data involving small numbers of patients showed promising TBWL of 15–19% over 6–12 month period (Dargent 2016). These techniques remain investigational in nature and require sufficient good quality short- and long-term data through vigorous studies before they can be accepted as established therapies.

## Summary

In patients with severe obesity, bariatric-metabolic surgery provides large and sustained weight loss, which is otherwise difficult to achieve due to the homeostatic feedback control of energy balance. Manipulation of the gut has provided effective solutions, although our understanding of the mechanisms involved is still

incomplete. With increasing knowledge of the gut-brain interactions concerning weight and energy homeostasis, we have tremendous opportunity to develop more targeted and less invasive therapies.

The long-term weight loss following bariatric-metabolic surgery also translates to improvement and remission of obesity-related complications (especially T2DM), better quality of life and survival. Guidelines pertaining bariatric-metabolic surgery are evolving with the emerging evidence. Indications for surgery may broaden in the future, and BMI cut-offs may be lowered such as for those with BMI $< 35$ kg/m$^2$ with T2DM or other metabolic disease. However, surgery is clearly not appropriate for all individuals with severe obesity, and careful multidisciplinary assessments are needed to ensure suitability prior to recommending surgery. As with any other procedure, bariatric-metabolic surgery is not without its complications and long-term follow-up and nutritional supplementation is crucial for safe and successful outcomes.

## Cross-References

► Roles of Gut Hormones in the Regulation of Food Intake and Body Weight
► The Microbiota and Energy Balance

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# Medications Indicated for Chronic Weight Management

18

Donna H. Ryan and Sarah R. Yockey

## Contents



**Abstract**

This chapter reviews the medications currently available for chronic weight management in the USA and some other countries and, for those five medications, discusses mechanism of action, efficacy data, and safety profiles. The chapter also discusses principles of prescribing and best practices for managing patients with medications indicated for weight management. Four of the newer agents (lorcaserin, liraglutide 3.0 mg, naltrexone SR/ bupropion SR, and phentermine/topiramate ER) all act primarily in the central nervous system. They regulate appetite and reduce food intake to help patients better adhere to a dietary

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plan. Orlistat acts peripherally to block absorption of 30% of ingested fat and reinforces adherence to a low-fat diet, thus reducing energy intake. These five newer medications are intended for long-term use to help patients not only lose more weight than with lifestyle changes alone, but also to maintain hard-won weight losses. Best practices in chronic disease prevention and management currently require physicians to help patients manage weight as a pathway to health improvement and those patients who struggle with weight and would derive health benefits from weight loss are candidates for medications. A current trend is to intervene earlier with these medications, especially with patients at higher health risk. The available medications have differing profiles in safety, efficacy, and tolerability. No one medication is right for every patient and the patient's profile must be matched to the medication profile. Thus, providers caring for patients with obesity-associated risk and diseases should be knowledgeable on how to prescribe for chronic weight management. Finally, if patients have success with a medication and lifestyle change to produce weight loss, the medication should be continued to maintain weight loss. Since weight regain is an issue when medications are stopped, restarting medications is also appropriate.

**Keywords**
Obesity pharmacotherapy · Weight management · Liraglutide · Phentermine · Phentermine/Topiramate ER · Naltrexone SR/Bupropion SR · Lorcaserin · Orlistat

## Introduction and Overview

The rising rates of obesity were first observed in the United States in the late 1980s (Flegal et al. 1998) and the problem is now observed in more than 30 countries, making this a global epidemic (Ng et al. 2014). Related to the problem of increasing obesity prevalence are increasing rates, observed globally, of type 2 diabetes and other obesity-associated disease, creating an enormous global health burden, which no country has been successful in reversing (Ng et al. 2014). The pathophysiology that drives weight gain in susceptible individuals and makes weight loss and weight loss maintenance difficult are barriers to large scale efforts at weight loss (Heymsfield and Wadden 2017). This has stimulated efforts to find safe and effective medications to be used with diet and exercise to achieve and sustain weight loss, thus ameliorating the noncommunicable disease burden, the leading cause of mortality world-wide in the twenty-first century.

However, one must recognize that beginning in the mid-twentieth century, sympathomimetic and serotoninergic (fenfluramine) drugs were primarily developed, trialed, and indicated for short-term use. Medications intended for both achieving and sustaining weight loss have only recently come on the scene, beginning with orlistat in 1999 and followed by four newer ones approved since 2012 (lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide 3 mg) (Apovian et al. 2015a). Four sympathomimetic drugs (phentermine, diethylpropion,

benzphetamine, and phendimetrazine) approved more than 50 years ago are still available in the USA and some other countries (Apovian et al. 2015a). These sympathomimetic drugs are labeled by regulatory agencies for short-term use (generally interpreted as up to 3 months) and this is sometimes enforced by medical licensing authorities (Apovian et al. 2015a). However, obesity is a chronic disease and the modern approach would be to utilize a chronic disease management approach for persons with obesity, including prescribing for the long-term (Apovian et al. 2015a). In addition, the cardiostimulatory properties of these drugs and their abuse potential, albeit small, make them less attractive for managing obesity. They should not be used in patients with a history of cardiovascular disease (Apovian et al. 2015a). Thus, this chapter will limit discussion to the five medications available (in some, but not all, countries) for long-term use.

Medicating for obesity management has an unfortunate past that has made regulators and modern prescribers cautious (Bray 2008). Thyroid extract, dinitrophenol, and amphetamine, used in the first half of the twentieth century, were dangerous. Then, even more recently, drugs for weight management (that received regulatory approvals) turned out to have unacceptable toxicity (ephedra, fenfluramine, dexfenfluramine, rimonabant, and sibutramine) (Bray 2008). These past mistakes must serve as learning opportunities. Regulatory authorities (Guidance for industry developing products for weight management 2007; Committee for Medicinal Products for Human Use (CHMP) 2016) have been cautious in guidance for evaluating newer medications, now requiring carefully executed, large studies to demonstrate safety and efficacy, with documentation of effects on adverse events and even mood at every visit. Further, since 2012, there have been cardiovascular outcome trials undertaken (either premarketing or postmarketing) to affirm that these medications have no increased cardiovascular risk when given to high-risk populations (Tran and Thomas 2012). It appears that the safeguards are in place to allow us to finally enter an era of rational evaluation and regulation of new medications. The rationale and justification for these medications is to help achieve more weight loss that can be achieved with lifestyle intervention alone, thus benefitting the health of patients who need to lose weight for health reasons. With knowledge and confidence of safety and efficacy, we can at last have confidence in the medications available with a chronic weight management indication.

## Comments on Interpreting Studies of Weight Loss

In this chapter, we will discuss weight loss efficacy of the medication approved for chronic weight management. In studies submitted for approval of these medications, a background lifestyle intervention is provided and patients are randomized to medication or placebo. There is no clinically significant placebo effect for weight loss. However, lifestyle intervention produces weight loss and the amount of weight loss is related to the intensity of techniques used to change diet and physical activity. Therefore, weight loss in the placebo-treated patients reflects the intensity of the lifestyle intervention and weight loss in medication treated participants reflects

lifestyle change plus the effect of the medication. Another consideration is that there is always variation in weight loss response when any weight loss treatment is imposed. Thus, medication efficacy must be evaluated not only by mean weight loss, but also by the proportion of patients who achieve clinically meaningful weight loss, generally ≥5% or ≥10% loss from baseline. This variation in weight loss response also clarifies that not all patients respond to a given medication. There is currently no way to predict response in advance. With regularity, 20% or more of patients who take any of the weight loss drugs will not achieve meaningful weight loss of 5% or more. The weight loss that is observed in these studies shows a pattern of rapid reduction in body weight (loss of 0.5–1% per week, on average) for the first 3 months and then slowing over the next 3–4 months, followed by stabilization of weight. This reduced body weight observed after 6–7 months of treatment with medications and/or lifestyle can be considered a new "settling point" and does not mean that the treatment is not working. As will be seen in some of the studies discussed herein, when the treatment (medication or lifestyle program) is stopped, then weight regain is observed. With all the medications approved for chronic weight management, patients are more likely to succeed with weight loss maintenance if medications are continued.

The medications currently approved for by the US FDA for chronic weight management of patients with obesity are shown in Table 1. In this table, we describe as a measure of efficacy the proportion of patients who achieve different categories of weight loss (≥5%, ≥10%) with either lifestyle + medication or lifestyle + placebo. We provide further evidence to support weight loss efficacy in the text by discussing mean weight loss. Table 1 also summarizes mechanism of action, dosing, and common side effects and safety issues.

## Orlistat, Marketed as XENICAL or Alli™ in Many Countries

Orlistat is a potent and selective inhibitor of pancreatic lipase that reduces intestinal absorption of fat. Orlistat is the most widely available of the medications discussed in this chapter. It is available nearly world-wide by prescription in 120 mg pills as XENICAL (or over-the-counter at 60 mg dose as Alli) and is taken three times a day before meals.

**Efficacy of Orlistat.** A 2011 systematic review of orlistat evaluated 23 randomized clinical trials using orlistat and lifestyle intervention compared to lifestyle intervention alone in patients with uncomplicated obesity and patients with obesity and diabetes (Leblanc et al. 2011). This meta-analysis showed that those receiving orlistat plus intensive behaviorally based intervention "lost 5 to 10 kg (11 to 22 pounds), average, 8% of baseline weight, compared with 3 to 6 kg in the placebo groups." Table 1 describes categorical (proportion achieving 5% or more or 10% or more) weight loss at 1 year in five studies with orlistat (XENICAL).

Orlistat has data supporting use up to 4 years (Torgerson et al. 2004). In a 4-year double-blind, randomized, placebo-controlled trial (XENDOS Study) of a lifestyle intervention with or without orlistat 120 mg three times daily in 3304 overweight

**Table 1** Medications approved in the USA and some other countries: Mechanism of action, dosing, efficacy (range in proportion of treated individuals who achieve >5% and >10% during phase 3 clinical trials), common side effects, and safety issues. Information from product labels, except where noted

| Drug, generic name,<br>• Dose<br>• Route of administration | Mechanism of action | ≥5% weight loss efficacy at 1 year | ≥10% weight loss efficacy | Common side effects (Bray and Greenway 2007) | Contraindications and warnings (Bray and Greenway 2007) |
|---|---|---|---|---|---|
| Orlistat<br>• 120 mg tid, before mealsOr<br>• 60 mg tid before meals<br>• Oral | Pancreatic lipase inhibitor; blocks absorption of dietary fat | In five studies,<br>Orlistat = 35.5–54.8%<br>Versus<br>Placebo = 16–27.4% | In five studies,<br>Orlistat = 16.4–25.8%<br>Versus<br>Placebo = 3.8–9.9% | • Steatorrhea<br>• Oily spotting<br>• Flatulence with discharge<br>• Fecal urgency<br>• Oily evacuation<br>• Increased defecation<br>• Fecal incontinence | • Contraindicated in pregnancy<br>• Warning: ↑cyclosporine exposure<br>• Liver failure (rare)<br>• Requires coadministration of multiple vitamin<br>• Increased risk of gall bladder disease<br>• Increased urine oxalate; monitor renal function |
| Lorcaserin<br>• 10 mg bid<br>Or | 5-$HT_{2C}$ serotonin agonist with little affinity for other serotonergic receptors; reduces food intake | In two studies combined,<br>Lorcaserin = 47.1%;<br>Versus<br>Placebo = 22.6% | In two studies combined,<br>Lorcaserin = 22.4%;<br>Versus<br>Placebo = 8.7% | • Headache<br>• Dizziness<br>• Nausea<br>• Dry mouth | • Contraindicated in pregnancy<br>• Use with caution with SSRI, SNRI, MAOIs, St |

(*continued*)

**Table 1** (continued)

| | | | | | |
|---|---|---|---|---|---|
| • 20 mg qd<br>• Oral | | Difference from placebo = 24.5% | Difference from placebo = 13.8% | • Fatigue<br>• Constipation | John's wort, Triptans, bupropion, dextromethorphan |
| Phentermine/ Topiramate ER (Phen/TPM)<br>• 7.5 mg/46 mg qd<br>• 15 mg/92 mg qd, indicated as rescue<br>• Oral, once daily dosing (requires titration) | Sympathomimetic Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism); reduces food intake | In two studies, Phen/ TPM (3 doses) = 45–70%; Versus Placebo = 17–21% Difference from placebo = 27.6–49.4% | In two studies, Phen/ TPM (3 doses) = 19–48%; Versus Placebo = 7% Difference from placebo = 11.4–40.3% | • Insomnia<br>• Dry mouth<br>• Constipation<br>• Paresthesias<br>• Dizziness<br>• Dysgeusia | • Contraindicated in pregnancy<br>• Fetal toxicity; monthly pregnancy test suggested<br>• Contraindicated with hyperthyroidism, glaucoma<br>• Do not use with MAOIs or sympathomimetic amines<br>• Acute myopia (rare) |
| Naltrexone SR/ bupropion SR (NB)<br>• 32 mg/ 360 mg<br>• Oral; bid dosing (requires titration) | Opioid receptor antagonist and Dopamine and noradrenaline reuptake inhibitor; reduces food intake | In three studies, NB = 44.2–62.3%; Versus Placebo = 17–43% Difference from placebo = 14–25% | In three studies, NB = 15–35%; Versus Placebo = 5–21% Difference from placebo = 10–14% | • Nausea<br>• Constipation<br>• Headache<br>• Vomiting<br>• Dizziness | • Boxed warning: Suicide risk in depression<br>• Contraindicated in pregnancy<br>• Contraindicated in seizure disorders, uncontrolled hypertension, glaucoma<br>• Do not use with opioids, MAOIs<br>• Hepatotoxicity (rare) |

| | | | | | |
|---|---|---|---|---|---|
| Liraglutide<br>• 3.0 mg<br>• Injection; once daily dosing (requires titration) | GLP-1 receptor agonist; reduces food intake | In two studies, Liraglutide = 62% (O'Neil et al. 2012) and 49% (Saxenda® n.d.a); Versus Placebo = 34.4%(O'Niel et al. 2012) and 16.4% (Saxenda® n.d.a) Difference from placebo = 32.6% (Fidler et al. 2011) and 22.6% (O'Neil et al. 2012) | In two studies, Liraglutide = 22.4% (Saxenda® n.d.a) and 33.9%(O'Neil et al. 2012); Versus Placebo = 5.5% (Saxenda® n.d.a) and 15.4% (O'Neil et al. 2012) Difference from placebo = 16.9% (O'Neil et al. 2012) and 18.5% (Fidler et al. 2011) | • Nausea<br>• Vomiting<br>• Diarrhea<br>• Constipation<br>• Headache<br>• Dyspepsia<br>• Fatigue<br>• Dizziness<br>• Abdominal pain | • Boxed warning: Thyroid C cell tumors in rodents<br>• Contraindicated with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia<br>• Pancreatitis<br>• Hypoglycemia in diabetes<br>• Increased risk of gall bladder disease |

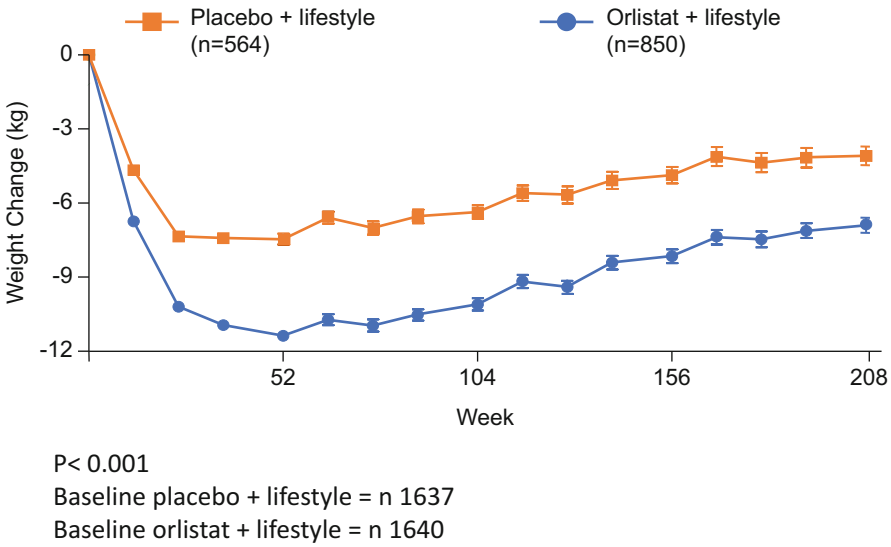



**Fig. 1** Xendos Study (Torgerson et al. 2004): Change in body weight (kg) are depicted as mean and SEM over 4 years (208 weeks) for patients receiving lifestyle intervention and randomly assigned to placebo or orlistat. Statistical analysis is by last observation carried forward (LOCF). Weight loss and maintenance is superior with orlistat when added to lifestyle intervention

patients, 21% of whom had impaired glucose tolerance, mean weight loss at 1 year was 11% with orlistat compared to 6% in the placebo-treated group (Torgerson et al. 2004). As illustrated in Fig. 1, there was a subsequent weight regain, but the orlistat-treated patients remained 6.9% below baseline at 3 years, compared with 4.1% for those receiving placebo. For those with impaired glucose tolerance in this study, there was a reduction of 37% in the progression to type 2 diabetes with lifestyle intervention plus orlistat compared to lifestyle intervention plus placebo (Torgerson et al. 2004).

Orlistat (XENICAL) is the only medication currently approved for weight management for adolescents with obesity. In 539 adolescents who received 120 mg three times per day of orlistat, on average, BMI decreased by 0.55 kg/m$^2$ in the drug-treated group compared to an increase of +0.31 kg/m$^2$ in the placebo-treated group (Chanoine et al. 2005)

Adherence to orlistat use falls off rapidly after initial prescription. In a Canadian study, the use of orlistat among 16,968 people initially started on this drug had fallen to 6% by 1 year and to only 2% by 2 years (Padwal et al. 2007). This may relate to the drug's tolerability profile, discussed below.

**Safety Profile of Orlistat**. Orlistat is not absorbed from the GI track to any significant degree, and its side effects relate to blockade of triglyceride digestion in the intestine (Bray and Greenway 2007) If orlistat is taken with a high fat meal or snack, then the effects of unabsorbed fat – steatorrhea – are likely to occur. The reporting of these events has been questioned. In a comparison of published reports

against the side effects noted on case report forms (Schroll et al. 2016), only 3–33% of the total number of adverse events reported by the investigators were noted in the publications due to the presence of *post hoc* filters. Therefore, counseling patients about gastrointestinal side effects is important, so that patients can stick to lower fat foods. It may also be helpful to take psyllium along with orlistat to minimize gastrointestinal side effects (Cavaliere et al. 2001). Because orlistat can cause small but significant decreases in fat-soluble vitamins some patients may need vitamin supplementation given at bedtime, particularly if it is continued long-term (XENICAL). Orlistat does not seem to affect the absorption of other drugs, except cyclosporine, where exposure is increased (XENICAL). Rare cases of severe liver injury have been reported with patients taking orlistat; however, a causal relationship has not been established (XENICAL). Orlistat has also been associated with calcium oxalate renal stones (XENICAL).

## Lorcaserin, Marketed as Belviq® in the USA and Other Countries

Lorcaserin selectively targets the serotonin 2c receptors to reduce food intake (Halford et al. 2007), but it has low affinity for the serotonin-2b receptors on heart valves. Lorcaserin was called Lorqueess during development and is marketed as Belviq® in the USA and other countries (e.g., Mexico, Canada, Brazil, Australia, and others). It is prescribed at 10 mg twice daily or in a new 20 mg once daily formulation (Belviq® Prescribing Information) (Belviq). It was not approved for use in the EU and the application withdrawn pending additional data on its potential risks and benefits (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002597/wapp/Initial_authorisation/human_wapp_000165.jsp&mid=WC0b01ac058001d128).

**Efficacy of Lorcaserin.** Three clinical studies provided evidence for approval of lorcaserin (Smith et al. 2010; Fidler et al. 2011; O'Neil et al. 2012). Two of these studies called BLOOM (Smith et al. 2010) and BLOSSOM (Fidler et al. 2011) enrolled volunteers who had a BMI $\geq$27 kg/m$^2$ with one comorbidity. The third study called BLOOM DM (O'Neil et al. 2012) enrolled patients with diabetes and a hemoglobin A1C between 7–10% and a BMI of 27–45 kg/m$^2$. In these studies, all patients, including the placebo group, received counseling in diet and physical activity. In BLOOM, mean weight loss $\pm$SE at 1 year was 5.81 $\pm$ 0.16% with lorcaserin 10 mg twice daily, as compared with 2.16 $\pm$ 0.14% for placebo ($P < 0.001$) (Smith et al. 2010). In BLOSSOM, mean weight loss (95% confidence interval) at 1 year with lorcaserin BID was 5.8% (5.5–6.2%), compared with 2.8% (2.5–3.2%) for placebo (Smith et al. 2010). Average weight loss was slightly less in BLOOM DM (O'Neil et al. 2012). Least square mean ($\pm$ SEM) weight loss at 1 year in that study was 4.5 $\pm$ 0.35% with lorcaserin BID and versus 1.5 $\pm$ 0.36% with placebo ($P < 0.001$). However, as with all drugs, these mean values hide considerable individual variability in weight loss. Refer to Table 1 for a description of categorical (proportion achieving 5% and 10%) weight loss with lorcaserin. The weight loss with lorcaserin compared to placebo was associated with improvements

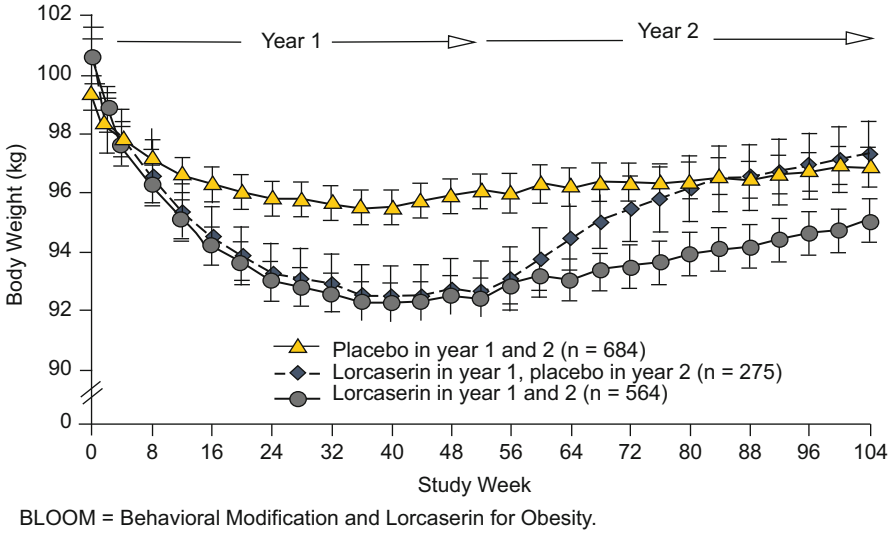



**Fig. 2** BLOOM Study (Smith et al. 2010): Body weight over years 1 and 2 with lifestyle intervention and randomization to lorcaserin or placebo for 1 year. At the end of year 1, patients taking lorcaserin were randomly assigned to placebo or lorcaserin and those on placebo continued for another year. At the end of the second year, weight regain is demonstrated for those who receive placebo. The mean body weight at each study visit is shown, according to study group, during years 1 and 2 among only those patients who continued the study past year 1. Bars indicate standard errors

in cardiovascular risk factors in these studies and particularly improvements in glycemic measures. In the BLOOM-DM study HbA1c decreased 0.9 ± 0.06% with lorcaserin BID, compared to 0.4 ± 0.06% with placebo ($P < 0.001$) and fasting glucose decreased 27.4 ± 2.5 mg/dl compared to a decrease of 11.9 ± 2.5 mg/dl for placebo ($P < 0.001$) (O'Neil et al. 2012).

Figure 2 illustrates long-term use of lorcaserin and what happens when patients stop this drug. At the start of year 2 in BLOOM, patients receiving lorcaserin BID were re-randomized to continue drug or to placebo (Smith et al. 2010). Patients on placebo continued placebo. As can be shown in Fig. 2, among the patients who received lorcaserin 10 mg BID during year 1 and who continued, mean weight was lower than those who changed to placebo. And for those who had weight loss of 5% or more at 1 year, that loss was maintained in more patients who continued to receive lorcaserin during year 2 (67.9%) than in patients who received placebo during year 2 (50.3%, $P < 0.001$) (Smith et al. 2010).

**Safety Profile of Lorcaserin.** Lorcaserin was scrutinized for potential effects on heart valves during Phase III studies where echocardiograms were done on more than 5200 subjects (Cavaliere et al. 2001). There was no statistically significant increase in relative risk of FDA-defined valvulopathy which was 1.16 (95% confidence interval, 0.81–1.67) compared to placebo, and not statistically significant (Cavaliere et al. 2001). There is thus no need for routine echocardiography in patients prescribed lorcaserin. Lorcaserin, as with all medications with an indication

for weight management, is contraindicated in pregnancy. The drug should be used with extreme caution with selective serotonin reuptake inhibitors (SSRIs) or with monoamine oxidase inhibitors (MAOIs), because of the potential risk of serotonin syndrome (Cavaliere et al. 2001).

Lorcaserin is well tolerated. The most common adverse events in phase 3 studies were headache, nausea, dizziness, fatigue, dry mouth, and constipation which were mild and resolved quickly. In lorcaserin and placebo, respective rates of adverse events were for headache 16.8% versus 10.1%, nausea 8.3% versus 5.3%, dizziness 8.5% versus 3.8%, fatigue 7.2% versus 3.6%, dry mouth 5.3% versus 2.3%, and constipation 5.8% versus 3.9% (Cavaliere et al. 2001). In clinical trials of $\geq$1 year duration, 8.6% and 6.7% of individuals in lorcaserin and placebo groups, respectively, discontinued treatment due to adverse events (Cavaliere et al. 2001).

In summary, the best aspects of lorcaserin seems to be in its safety and tolerability. On average, weight loss is less than with other approved agents, but individual patients may respond very well to the drug. An issue is the hypothetical risk of serotonin syndrome and because the background use of SSRI antidepressants is high in patients with obesity, physicians should only prescribe lorcaserin with extreme caution in patients taking SSRIs or serotoninergic agents (Cavaliere et al. 2001).

## Liraglutide 3.0 mg, Marketed as Saxenda® in the USA, EU, and Other Countries

Liraglutide is a GLP-1 agonist that has a 97% homology to GLP-1 (Saxenda® n.d.a). The molecule has 97% homology with native GLP-1 and the changes extend the circulating half-life from 1–2 min to 13 h (Saxenda® n.d.a). Liraglutide reduces body weight through reduction of food intake.(Saxenda® n.d.a). Liraglutide is approved for treatment of type 2 diabetes at a dose of up to 1.8 mg and is marketed as Victoza® (Victoza). The indication for chronic weight management is for liraglutide 3.0 mg, which is marketed in the United States and the European Union as Saxenda™. Liraglutide is given once daily by injection. A dose escalation is required to minimize side effects, beginning at 0.6 mg and increasing by 0.6 mg weekly to the recommended dose of 3.0 mg daily (Saxenda® n.d.a).

**Efficacy of Liraglutide.** Three 56-week studies with liraglutide 3.0 mg form the basis for regulatory approval by the FDA (Pi-Sunyer et al. 2015; Wadden et al. 2013; Davies et al. 2015). One of those studies had an extended follow-up to determine the effect on emergence of type 2 diabetes in at-risk persons (Le Roux et al. 2016). In a large multicenter phase III trial called SCALE (Pi-Sunyer et al. 2015), 3731 patients without diabetes were instructed in a 500 kcal/d deficit diet and lifestyle recommendations and were treated in a ratio of 2:1 with liraglutide 3.0 mg/d (after dose titration) or with placebo. Liraglutide reduced body weight in those who completed 56 weeks by an average of 8.4 kg compared to 2.8 kg on average in the placebo-treated group (Pi-Sunyer et al. 2015). Weight loss of >5% was achieved by 62.3% of those receiving liraglutide but only 34.4% in those with placebo (Pi-Sunyer et al. 2015). The corresponding numbers losing >10% were 33.9% for those on liraglutide

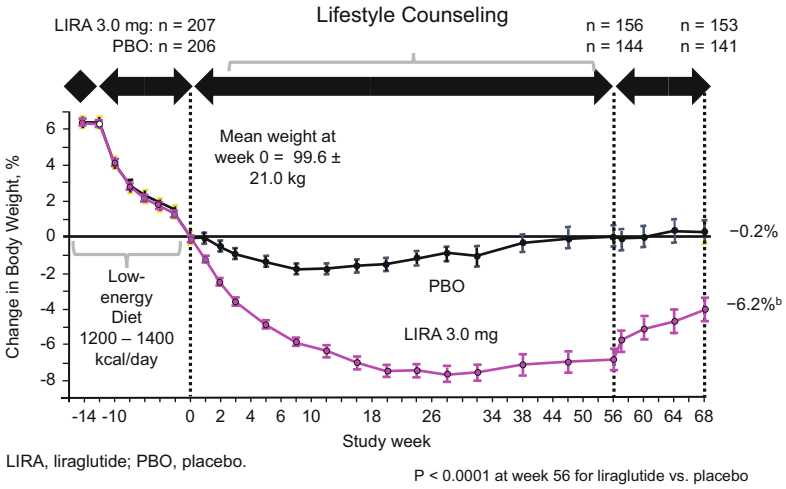



**Fig. 3** SCALE Maintenance Study (Wadden et al. 2013): Percent change in body weight over an initial period of highly structured low calorie diet (1200–1400 kcal per day) is depicted from week 0 to −14. Participants who lost at least 5% received continued lifestyle counseling and were randomized to placebo or Liraglutide 3.0 mg. Percent change in body weight is depicted over 56 weeks for each treatment and then after treatment stopped at week 56, participants returned for 4 follow-up visits through week 68. Note that after initial weight loss on diet alone, participants receiving lifestyle counseling and placebo maintained weight loss. Those on liraglutide 3.0 mg lost additional weight. After medication was stopped, weight regain is observed

3.0 mg and 15.4% for those assigned to placebo (Pi-Sunyer et al. 2015). SCALE has been followed out to 3 years to determine the effect on diabetes prevention (Le Roux et al. 2016) At 160 weeks, 26 of 1472 individuals in the liraglutide 3.0 mg/d treatment group (2%) and 46 of 738 (6%) taking placebo were diagnosed with diabetes while on treatment. The time to onset of diabetes diagnosis with liraglutide 3.0 mg/d was 2.7 times longer than with placebo ($p < 0.0001$) (Le Roux et al. 2016).

Another trial, called SCALE Maintenance, had a unique design where weight loss of at least 5% was induced with a low-energy diet before patients were randomized to lifestyle counseling and either placebo or 3.0 mg/d (after titration) liraglutide (Wadden et al. 2013). This study is illustrated in Fig. 3. Weight loss on the highly structured low-calorie diet given for up to 12 weeks was approximately 6% on average. After randomization, those receiving liraglutide 3.0 mg had additional loss of mean 6.2% (SD 7.3) and for placebo only 0.2% (SD 7.0). The percentage losing 5% and 10% of body weight was more than twice as high in the liraglutide treated patients, compared to placebo, as depicted in Table 1.

The SCALE Diabetes trial (Davies et al. 2015) illustrates not only the weight loss effect of liraglutide 3.0 mg, but also delineates the drug's effect on glycemia. In this study, patients with type 2 diabetes received a lifestyle intervention and were randomized to liraglutide 3.0 mg, liraglutide 1.8 mg, or placebo. At week 56, mean weight losses from baseline were, respectively, 6.0%, 4.7%, and 2.0% (Davies et al. 2015). Exploratory comparisons of liraglutide 3.0 mg versus 1.8 mg in this

study showed that while weight loss differences were clinically and statistically superior for liraglutide 3.0 mg, the effect on glycemia, while statistically significant, was small (−0.19%) (Davies et al. 2015).

Liraglutide has also been studied in patients with obstructive sleep apnea who could not tolerate conventional treatment with continuous positive airway pressure. In that study (Blackman et al. 2016), the primary endpoint was reduction in apnea-hypopnea events per hour. There was a significant reduction in mean events when a lifestyle intervention was given with liraglutide 3.0 mg versus placebo (−12.2 vs. −6.1 events per hour). In these patients, there were also improvements in body weight, systolic blood pressure, and Hemoglobin $A_{1c}$ (Blackman et al. 2016).

**Safety Profile of Liraglutide:** As with other drugs in the GLP-1 receptor agonist class, liraglutide is contraindicated in people with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN2) (Saxenda® n.d.a). As with all medications for weight management, it is contraindicated in pregnancy (Saxenda® n.d.a). Liraglutide should not be studied in patients with a history of pancreatitis and should be discontinued if acute pancreatitis develops (Saxenda® n.d.a). Its safety when combined with other drugs for weight management has not been established. This drug is given by injection, and nausea was one of its most troublesome side effects, occurring in 39.3% of those on liraglutide compared to 13.8% in the placebo-treated group (Saxenda® n.d.a). Diarrhea, constipation, vomiting, dyspepsia, and abdominal pain also occurred in more than 5% of those treated with liraglutide (Saxenda® n.d.a). Mean serum calcitonin was statistically significantly higher in the liraglutide group, but did not require further follow-up and calcitonin monitoring is not required (Saxenda® n.d.a). Hypoglycemia was only a problem in patients also taking sulfonylureas (Saxenda® n.d.a). Blood pressure was significantly reduced, but pulse rate increased by an average of 2.5 beats/min (Saxenda® n.d.a). An increase of >10 beats/min was seen in 34% of the liraglutide-treated group compared with 19% in the placebo-treated group (Saxenda® n.d.a). There were no changes in serum lipids. Liraglutide should be used with caution in patients with renal impairment (Saxenda® n.d.a). If weight loss doesn't exceed 4% by 16 weeks the drug should be discontinued (Saxenda® n.d.a).

Liraglutide has been approved at a lower dose of 1.8 mg/d for the treatment of diabetes and has a different trade name (Victoza) (O'Neil et al. 2012). The indications for these two doses are distinct – if patients with and without diabetes are undertaking a weight loss effort, liraglutide 3.0 mg may be indicated, but if the primary goal is management of glycemia in patients with diabetes, then liraglutide 1.8 mg is indicated. A cardiovascular outcome trial with liraglutide 1.8 mg/d has been completed (Marso et al. 2016). The end-point was a combined index of major cardiovascular events which was reduced significantly in the patients receiving liraglutide, indicating clinical superiority for reduced CVD over the placebo-treated group (Marso et al. 2016). The FDA did not require a cardiovascular outcome trial with liraglutide at the 3.0 mg dose, because of significant overlap in exposure levels among the 1.8 mg and 3.0 mg dose populations (Saxenda n.d.b). A second cardiovascular outcome trial with a long-acting successor molecule, semaglutide, which

consists of modifications to GLP-1, also showed clinical superiority compared to placebo in reductions in cardiovascular outcomes (Marso et al. 2016).

## Phentermine/Topiramate Extended Release (ER) Marketed as Qsymia™ in the USA

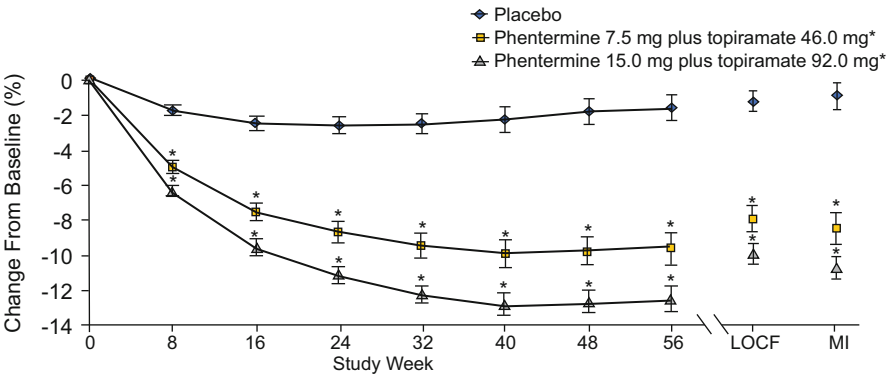
The combination of phentermine and topiramate as an extended release (ER) form (PHEN/TPM ER) is approved for chronic weight management the USA. It is not approved in the EU due to unresolved concerns on cardiovascular and psychiatric safety (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002350/WC500144300.pdf). Phentermine acts to reduce appetite through increasing norepinephrine in the hypothalamus; topiramate may reduce appetite through its effect on GABA receptors (Qsymia). The combination contains lower doses of phentermine (3.75–15 mg) than are usually prescribed when phentermine is used a single agent. The dose of topiramate in the combination is between 23 mg and 92 mg (Qsymia), and is also lower than when topiramate is typically used for migraine prophylaxis or to control seizures.

**Efficacy of Phentermine/Topiramate ER**. Two clinical studies (Allison et al. 2012; Gadde et al. 2011) provided efficacy and safety data for approval of this medication (FDA 2012). The first trial, called EQUIP (Allison et al. 2012) enrolled subjects $\leq$70 years of age with BMI $\geq$35 kg/m$^2$ with controlled blood pressure ($\leq$140/90 mmHg using 0–2 antihypertensive medications), fasting blood glucose $\leq$110 mg/dL, and triglycerides $\leq$200 mg/dL using 0 or 1 lipid lowering medication. EQUIP randomized participants to placebo or PHEN/TPM doses of 3.75/23, and 15/92 mg and achieved mean weight loss of 1.6%, 5.1%, and 10.9% of baseline body weight (Allison et al. 2012).

The other study called CONQUER (Gadde et al. 2011), enrolled adults $\leq$70 years of age with BMI between 27 and $\leq$45 kg/m$^2$, except that patients with type 2 diabetes, had no lower BMI limit. The patients in the CONQUER study had two or more of the following comorbidities: hypertension, hypertriglyceridemia, dysglycemia (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes), or an elevated waist circumference ($\geq$40 inches for men or $\geq$35 inches for women). At 56 weeks, body weight loss was least-squares mean 1.2% (95% CI 1.8–0.7) for placebo, 7.8% (CI 8.5–7.1; $p < 0{\cdot}0001$) for those on PHEN/TPM at the 7.5/43 mg dose, and 10.2 kg (95% CI 10.4–9.3; $p < 0{\cdot}0001$) for PHEN/TPM at the 15/92 mg dose (Gadde et al. 2011). The CONQUER study results are depicted in Fig. 4.

The patient population in the EQUIP and CONQUER studies represents those with higher risk profiles from the consequences of excess weight. A titration period of 2 weeks is required for PHEN/TPM ER, starting at 3.75/23 mg dosage. This combination medication produces mean weight losses approaching 10% which is larger than observed in clinical trials with single drugs (Colman et al. 2012).

The SEQUEL study (Garvey et al. 2012) was a second-year extension of the CONQUER study keeping those patients who participated on their initial treatment




| Patients | Placebo | Mid | Full |
|---|---|---|---|
| Completers (% of randomized) | 557 (57%) | 338 (69%) | 625 (64%) |

*Weight change for either dose vs placebo, P <.0001.

**Fig. 4** CONQUER Study (Gadde et al. 2011): Percent change in body weight over 56 weeks with lifestyle intervention and randomization to placebo or phenterminen 7.5 mg/ topiramate 46 mg or phentermine 15 mg/topiramate 92 mg. The mean body weight for each study group is shown for the study completers across 56 weeks. The mean weight loss of last observation carried forward (LOCF) and multiple imputation(MI) data anlaysis is shown at week 56. Bars indicate standard errors

assignment (SEQUEL) (Fig. 2, Panel D). Patients completing 2 years at the dose of 7.5 mg/46 mg maintained a mean weight loss of 9.3% below baseline and those on the top dose maintained a mean 10.7% weight loss from baseline (Garvey et al. 2012).

Improvements in blood pressure, glycemic measures, HDL cholesterol and triglycerides occurred with both the recommended and the top doses of the medication in these trials (Qsymia). Improvements in risk factors were related to the amount of weight loss (Allison et al. 2012; Gadde et al. 2011). In patients with sleep apnea this combination reduced the severity of symptoms (Garvey et al. 2012).

**Safety Profile of Phentermine/Topiramate ER.** The most commonly observed side effects in these clinical trials were paresthesia, dizziness, dysgeusia (altered taste), insomnia, constipation, and dry mouth (Qsymia). These side effects are related to the constituents of PHEN/TPM ER or, in the case of constipation, to weight loss per se. Phentermine causes insomnia and dry mouth, usually early in treatment, which then resolves. Topiramate is a carbonic anhydrase inhibitor that is associated with altered taste for carbonated beverages and tingling in fingers, toes, and perioral areas and may lead to mild metabolic acidosis.

Safety concerns are seen in several areas. This drug is contraindicated in pregnancy, as are all weight loss medications, but the topiramate constituent requires special precautions in women of childbearing potential (Qsymia). If a patient becomes pregnant while taking PHEN/TPM ER, treatment should be stopped immediately (Qsymia). Topiramate is associated with oral clefts if used during early pregnancy and PHEN/TPM ER is thus US pregnancy Category X (Qsymia).

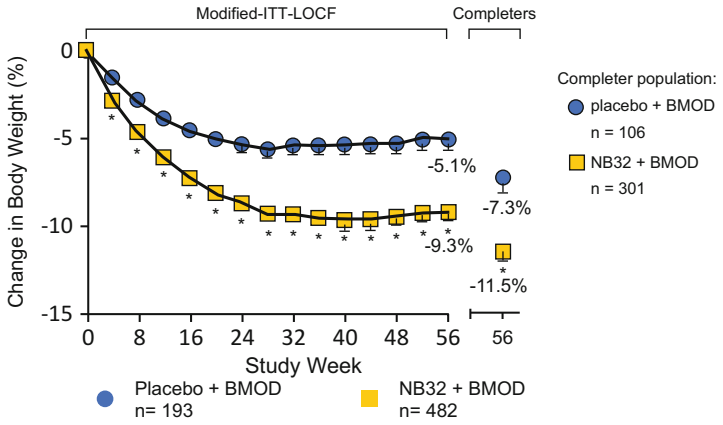
Because of the risk of oral clefts, a negative pregnancy test before treatment and monthly thereafter and use of effective contraception are required (Qsymia). Glaucoma is a rare side effect of topiramate, and the drug is contraindicated in glaucoma (Qsymia). PHEN/TPM ER is also contraindicated in hyperthyroidism and within 14 days of treatment with monoamine oxidase inhibitors (MAOIs) and in patients with hypersensitivity to any of the ingredients in the medication (Qsymia). Other potential issues include risk of kidney stones (associated with topiramate) and increased heart rate in patients susceptible to phentermine (Qsymia).

## Naltrexone SR/Bupropion SR, Marketed as Contrave® in the USA and Mysimba™ in Europe

Bupropion has been long approved in the USA as a single agent for depression and for smoking cessation. Naltrexone is an opioid receptor antagonist that has approval for use as a single agent for addiction to opioids or alcohol. It has minimal effect on weight loss on its own. Bupropion stimulates the POMC neuron which releases α-MSH and β-endorphin in the hypothalamus which stimulates feeding (Greenway et al. 2009). This effect on β-endorphin is blocked by naltrexone thus allowing the inhibitory effects of α-melanocyte stimulating hormone (α-MSH) to reduce food intake by acting on the melanocortin-4 receptor system (Greenway et al. 2009).

**Efficacy of Naltrexone/Bupropion**. Three studies with this combination provided the basis for its approval (Contrave). In the COR I study (Contrave Obesity Research I) (Greenway et al. 2010) there were three treatment arms: placebo, NB 32/360 (32 mg of naltrexone and 360 mg of sustained release bupropion), and NB 16/360 (16 mg of naltrexone and 360 mg of sustained release bupropion). Using the primary analysis population in COR-I, the Least Squares (LS) mean percentage weight loss (SE) at 56 weeks was −1.3% (0.3) for the placebo, −5.0% (0.3) for Naltrexone/Bupropion-16/360 (NB 16/360) ($P < 0.0001$ vs. placebo), and −6.1% (0.3) for NB 32/360 ($P < 0.0001$ vs. placebo) (Greenway et al. 2010). The NB16/360 and NB32/360 treatment arms had improvements in waist circumference, fasting glucose, fasting insulin, homeostasis assessment model of insulin resistance (HOMA-IR), HDL cholesterol, CRP and Impact of Weight on Quality of Life - Lite (IWQOL-Lite) (Kolotkin et al. 2001) scores, when compared to placebo (Greenway et al. 2010).

In COR -BM (Contrave Obesity Research-Behavior Modification) (Wadden et al., 2011), participants were randomly assigned in a 1:3 ratio to either placebo (P) given with a behavior modification program (BMOD) or naltrexone sustained release 32 mg plus bupropion sustained release 360 mg (NB32/360) plus BMOD. The behavior modification program consisted of 28 group sessions, each of 90 minutes' duration. The weight loss in COR BMOD was excellent for both the placebo and active treatment groups. At 56 weeks, mean weight loss in the P + BMOD group was 5.1 + 0.6% and for the NB 32/360 + BMOD group it was 9.3 + 0.4% (P < 0.001 vs. placebo +BMOD) (Wadden et al. 2011). There were significantly greater improvements in waist circumference, insulin, HOMA IR, HDL




*P <.001, for NB32 + BMOD vs placebo + BMOD.

COR/BMOD = Contrave Obesity Research/Behavioral Modification; ITT = intent to treat; LOCF = last observation carried forward.

**Fig. 5** COR/BMOD Study (Wadden et al. 2011): Percent change in body weight over 56 weeks with intensive behavioral modification lifestyle intervention (BMOD) and randomized assignment to placebo or naltrexone 32 mg/ bupropion 360 mg (NB32). The mean body weight for each study group is shown for the Modified-ITT-LOCF population across 56 weeks. The mean weight loss of completers is shown at week 56

cholesterol, and triglycerides (Wadden et al. 2011). As for quality of life measurement, the scores on the IWQOL-Lite questionnaire improved significantly more in the group on active drug treatment than placebo (Wadden et al. 2011). Weight loss in the COR-BM Study is depicted in Fig. 5.

In COR II (Contrave Obesity Research II) (Apovian et al. 2013), participants were randomized 2:1 to combined naltrexone sustained-release (SR) (32 mg/day) plus bupropion SR (360 mg/day) (NB32) or placebo for up to 56 weeks. Significantly greater weight loss was observed with NB32 versus placebo at week 56 (−6.4% vs. −1.2%) ($P < 0.001$) (Kolotkin et al. 2001). The weight loss was accompanied by improvements in cardiometabolic risk markers, weight-related quality of life, and a measure of control of eating (Apovian et al. 2013).

Finally, in patients with type 2 diabetes (Hollander et al. 2013), use of the combination resulted in significantly greater weight reduction compared to placebo (5.0% vs. 1.8%; $P < 0.001$) and significantly greater reduction in HbA1c (−0.6 vs. −0.1%; $P < 0.001$) (Hollander et al. 2013). There was also improvement in triglycerides and HDL cholesterol compared with placebo (Hollander et al. 2013).

**Safety and Tolerability Profile of Naltrexone/Bupropion.** The chief tolerability issue with this medication is nausea, associated with the naltrexone component, which occurs on initiating the drug or escalating its dose (Contrave). While relatively common (about 30% of participants in the phase III studies) it accounted for <7% of drop outs (Contrave). A dose escalation period of 4 weeks is used to minimize this

side effect (Contrave). Other potential issues are concomitant use of SSRIs or MAOIs (Contrave).

The decline in blood pressure is not as great as one would expect from the weight loss in the Phase III trials of naltrexone/bupropion [COR I (Greenway et al. 2010) and COR BMOD trials (Wadden et al. 2011). Because bupropion increases pulse and both bupropion and naltrexone increase blood pressure, the FDA required a pre-marketing study of the combination drug with assessment of cardiovascular outcomes. An interim analysis was done of this trial and even though it showed no increase in cardiovascular event rate, a second cardiovascular outcome trial has been initiated (Nissen et al. 2016).

## Comparison of Medications Approved for Chronic Weight Management

There are no head-to-head comparisons of these medications. However, there is an analysis (Khera et al. 2016) of 28 randomized clinical trials of weight loss medications included trials with Orlistat (N = 17), Lorcaserin (N = 3), Liraglutide (N = 4), Naltrexone/Bupropion (N = 4), and Phentermine/Topiramate (N = 2). The inclusion criteria and background lifestyle interventions differed across studies, so results must be interpreted with caution. Attrition rates were 30–45% across these trials. All five agents were associated with significantly greater weight loss at 1 year than placebo. Across all studies, weight loss of >5% was seen in 23% of the patients treated with placebo and a weight loss of >5% was seen in 44% of those treated with orlistat, in 49% with lorcaserin, in 63% with liraglutide, in 55% with naltrexone/bupropion, and in 75% of those treated with phentermine/topiramate. The highest odds ratio for treatment-related discontinuation of the trial was seen with liraglutide and naltrexone/bupropion (Khera et al. 2016).

## Best Practices in Prescribing Medications Approved for Weight Management

With four new medications, which work through appetite regulation (lorcaserin, naltrexone/bupropion, phentermine/topiramate, and liraglutide), and an older medication (orlistat) which blocks fat absorption and promotes adherence to a low-fat diet, health care providers have new tools that can be used for the long-term to help patients with obesity adhere to a dietary plan and maintain weight loss. However, few of the patients who meet the labeled indications for prescription of medications approved for chronic weight management are receiving these as part of medically directed weight management effort. There are indeed barriers to prescribing that make the current regular use of these medications largely the purview of obesity medicine specialists (>2000 US physicians certified by the American Board of Obesity Medicine and a smaller number in Europe) and bariatric endocrinologists, i.e., endocrinologists who address weight for all their patients. Embedding lifestyle

intervention counseling, an integral part of weight management with or without medications can be challenging to primary care providers. Nevertheless, the following principles can guide *all* practitioners, when weight management is integral to better health management. We adopt the current evidence-based guidelines (Apovian et al. 2015b; Jensen et al. 2014; National Institute for Health and Clinical Excellence: Guidance 2014) and professional society guidances (Garvey et al. 2016a, b) in endorsing these best practices, as noted below.

- Who needs medications? Patients who struggle to achieve weight goals, meet label indications (BMI >30 kg/m$^2$ or >27 kg/m$^2$ with comorbidity), and who need to lose weight for health reasons, such as osteoarthritis, prediabetes, fatty liver, or other conditions are targeted for medications in the 2013 Obesity Guidelines (Jensen et al. 2014) and the Endocrine Clinical Practice Guideline on Obesity Pharmacotherapy (Apovian et al. 2015b). Both the 2013 Obesity Guidelines and the 2006 NICE Guidelines (National Institute for Health and Clinical Excellence: Guidance 2014) recommend medications only after unsuccessful weight loss with lifestyle alone. However, a new approach is taking this a step further, the AACE/ACE Guidelines from 2016 (Garvey et al. 2016a, b) indicate *initial* pharmacotherapy added to lifestyle intervention is appropriate if patients present with one or more severe comorbidities and would benefit from weight loss of 10% or more. Those guidelines don't require a trial of lifestyle therapy with failure before medications can be prescribed. Clearly, health care providers should feel some urgency in helping patients achieve health goals through weight loss, especially when comorbidities are compromising health.
- How should a medication be chosen? The Endocrine Society guideline (Apovian et al. 2015b) indicates that the medications should be used according to the label indications, with attention to contraindications and warnings. The patients profile should be matched to the medication profile; exclude medications from consideration if they are contraindicated or associated with serious warnings. There are other rational concepts to support choice. If patients have trouble with appetite, then one of the medications that influence appetite should be chosen, such as lorcaserin, liraglutide, naltrexone/bupropion, phentermine/topiramate. Also, one should consider dual benefits: orlistat can enforce a low-fat diet and lower plasma LDL cholesterol. Liraglutide 3.0 mg can lower glycemic indices and is associated with reduction in cardiovascular events in addition to affecting appetite and body weight.
- How should the lifestyle component be delivered? The 2013 Obesity Guideline (Jensen et al. 2014) recommends that patients who need to lose weight and to improve health should have access to a comprehensive lifestyle *program* (diet, physical activity, and behavioral intervention) for 6 months or longer and indicate that the gold standard is on site, high intensity (>14 sessions in 6 months) comprehensive intervention delivered in group or individual sessions by a trained interventionist and persisting for a year or more. This is often impractical in primary care practices. Thus, other approaches may be used when patients can't access the gold standard though the amount of weight loss on average may be

less. Thus, referral to community or commercial programs or online programs are acceptable ways to deliver the lifestyle intervention that is the foundation to using medications in a weight loss/maintenance effort.

- How should medication efficacy for weight loss be judged? The best predictor of long-term weight loss is initial weight loss. If patients lose 4–5% of their body weight in 12–16 weeks at the recommended dose of a drug, a good long-term response is likely. If not, the medication is not working and should be stopped. Every medication approved for chronic weight management comes with stopping rules in the label, and we recommend following them.
- How often should patients be followed? According to the Endocrine Guidelines (Apovian et al. 2015b), after prescription, providers should follow patients monthly for the first 3 months and then every 3 months thereafter.
- How long should medications be used? Long-term use of medications is recommended to promote weight loss maintenance, but this may be used intermittently (Apovian et al. 2015b).
- What is the role of off-label prescribing for weight management? The Endocrine guideline (Apovian et al. 2015b) gives a best practice recommendation that providers not prescribe off-label uses of medications approved for other conditions for the sole purpose of producing weight loss. However, weight centric (having weight as the central focus for change) prescribing for chronic disease management is recommended (Apovian et al. 2015b).

## Summary and Conclusions

At long last there are medications currently available for chronic weight management in the USA and some other countries. It is entirely appropriate for health care providers to incorporate these medications into treatment plans, considering the biologic basis of resistance to weight loss and promotion of weight gain that patients with obesity face. Four of the newer agents (lorcaserin, liraglutide 3.0 mg, naltrexone SR/bupropion SR, and phentermine/topiramate ER) all act primarily in the central nervous system. They regulate appetite and reduce food intake to help patients better adhere to a dietary plan. Orlistat acts peripherally to block absorption of 30% of ingested fat and reinforces adherence to a low-fat diet, thus reducing energy intake. These five newer medications are intended for long-term use to help patients not only lose more weight than with lifestyle changes alone, but also to maintain hard-won weight losses.

Best practices in chronic disease prevention and management currently require physicians to help patients manage weight as a pathway to health improvement and those patients who struggle with weight and would derive health benefits from weight loss are candidates for medications. Current guidance is to intervene earlier with these medications, especially with patients at higher health risk. The available medications have differing profiles in safety, efficacy, and tolerability. No one medication is right for every patient and the patient's profile must be matched to the medication profile.

There are many unresolved issues in how to best incorporate these drugs into our treatment armamentarium. Can they be combined for treatment in the same way we combine drugs to manage other chronic diseases? Can we better predict response to medications, to personalize an approach to prescribing? Can we better understand weight regain and perhaps use different agents for weight loss and prevention of regain? It is an exciting time for drug discovery and for better understanding how to use these new agents.

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# An Integrated View of Treatment Options Available for Obesity

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## Contents



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**Abstract**

Controversy surrounded the decision to recognize obesity as a disease, but scientific advances have provided irrefutable logic to this effect. Several professional and scientific organizations now recognize obesity as a disease. The reason for the reluctance was due to our incomplete understanding of physiology and long-held views that obesity should not be medicalized. To do so would detract from the personal responsibility of the population to control their own body weight. Although the latter view is still popular among some in the medical community and lay public, the movement to recognize obesity as a disease has enabled the subsequent step to naturally follow, that is, obesity is a disease that requires treatment. The question then arises: what is the best model of care to treat obesity? Furthermore, what would be the benefit of an integrated obesity care pathway?

**Keywords**

Primary care · Obesity · Lifestyle · Medical education · Weight Management · Clinician

## Why Obesity Should Be Treated Within an Integrated Care Pathway?

### Obesity Is a Disease that Requires Treatment

Controversy surrounded the decision to recognize obesity as a disease, but scientific advances have provided irrefutable logic to this effect. Several professional and scientific organizations now recognize obesity as a disease. The reason for the reluctance was due to our incomplete understanding of physiology and long-held views that obesity should not be medicalized. To do so would detract from the personal responsibility of the population to control their own body weight. Although the latter view is still popular among some in the medical community and lay public, the movement to recognize obesity as a disease has enabled the subsequent step to naturally follow, that is, obesity is a disease that requires treatment. The question then arises: what is the best model of care to treat obesity? Furthermore, what would be the benefit of an integrated obesity care pathway?

### Obesity Treatment Has Been Fragmented and Delivered Relatively Poor Outcomes

The evidence base for obesity care was insufficient for a long time resulting in fragmentation of delivery of care. Moreover, this led to poor outcomes for patients who suffered from obesity. To compound the matter, patients who did not respond to the favorite treatment of a practitioner were often blamed for their lack of weight loss. This vicious cycle also meant that patients blamed themselves thinking that

their inability to lose weight and maintain weight loss was their fault. Even when clinical services offered more than one potential treatment, many patients found that they didn't respond to any of these treatments. Naturally, they discontinued attending the service. These high dropout rates from clinical care pathways made it very difficult to evaluate outcomes, and hence many services remained fragmented.

### The Disease and Its Treatment Were Poorly Understood

Initially, obesity was not recognized as a disease but rather considered as a consequence of gluttony or sloth – two of the mortal sins as depicted by Dante (2017). It therefore followed that, as sins were willful acts, the solution must relate to the patient's own willpower. Treatments were focused on improving the willpower of patients or supporting those who were perceived to have poor willpower. It was thought all that was needed was to "educate" people with obesity and allow them to effectively heal themselves. The benefits of structured behavior programs or patient support systems were not always achieved because the logic of the approach was that if motivated patients could be identified and helped to make the correct choices those patients would find it relatively straightforward to lose weight and maintain weight loss. For those patients who were not able to lose a significant amount of weight, or even more commonly would regain the weight that they have lost, healthcare professionals would view them as somehow morally inferior. This was because the health messages were easy to understand and often delivered to a very high standard.

## What Should Be Achieved by an Integrated Care Pathway for Obesity?

### Set Point

Body fat is now understood to be regulated by a biological set point. This is not surprising as many other similarly important biological parameters have a well-controlled set point. For example, fluid balance is regulated by the subcortical areas of the brain. If a person with intact physiological control has excess fluid, they will reduce the fluid volume by excreting it as urine. Equally, if a subject is dehydrated and consumes fluid they will store it to allow the body to return to euvolemia. Drinking one extra liter of water per day for an entire year above euvolemia does not lead to 365 kg additional weight. The converse is also true in case of hypovolemia, a subject will become thirsty and search out for water.

We now understand that body fat is regulated in a similar way. In case of food intake above the requirements of a subject with normal weight, weight gain will occur but only up to a specific point where energy expenditure is increased to balance the excess food intake. In subjects who are prone to obesity, a reduction in

food intake will result in a reduction in energy expenditure, increased hunger, and storage of any energy that is consumed in an attempt to return the body weight to its set point. The insight from this understanding is that if integrated care for obesity does not reduce the set point for body fat then weight regain is almost inevitable. The question remains how to effectively deliver integrated care for obesity that can reduce the set point for body fat and maintain it in the long-term at a reduced level.

## Which Organ to Treat?

In other diseases where the organ responsible for the disease has been unclear, effective treatments remained challenging until a breakthrough came that explained which organ was responsible for the bulk of the disease. Integrated obesity care in the past focused on adipocytes as the organ of interest and obesity was defined in terms of the signs of the disease, i.e., the fat mass or body mass index. In addition, obesity treatment is often compounded by complications of the disease such as type 2 diabetes, sleep aponea, or functional impairments, which require treatments to organs such as the pancreas, lungs, and muscle. This often resulted in the integrated care models of obesity becoming experts in treating the complications of obesity and simply accepting the fact that reducing and maintaining reduced body fat was far less successful.

Hypertension had similar challenges in the 1960s when it was commonly referred to as essential hypertension because the organ responsible for the disease was still unknown. Today, we know that the majority of genes responsible for hypertension point to the kidney; we also understand the renin-angiotensin-aldosterone system (RAAS) hormone system that regulates blood pressure and fluid balance (Carey and Siragy 2003). We now have effective medication which can attenuate the defects in the RAAS to such an extent that we can now control the disease. The lifestyle changes, medications, and even surgical treatments for hypertension have resulted in a set point shift which allows the subject to maintain the new homeostasis.

## Which Defect Within the Organ to Treat?

The majority of the genes associated with obesity point to the central nervous system (Herrera and Lindgren 2010). The fat mass set point also appears to be centrally controlled with the neuroanatomical areas of the hypothalamus, nucleus tractus solitarius, and area postrema often being identified as key brain regions that integrate signals from the periphery and the higher centers to allow fat mass homeostasis. Where previous efforts have focused on the cortical areas of the brain the scientific evidence that the subcortical areas are in fact critical for set point regulation is now overwhelming. Integrated obesity care may thus have to focus on the subcortical areas of the brain as the organ system of most interest if the set point for body fat needs to be lowered for long term weight loss maintenance.

### Which Symptoms to Address?

The clinical "signs" of obesity are easy to observe as it relates to the body mass index and adipocyte burden of the subject. The "symptoms" of obesity are, however, less often discussed. The clinical history of patients with obesity often reveals an excess in hunger, especially in pediatric populations where parents often report their children are "hungry all the time." In adult clinics, patients more often report that instead of feeling hungry, their problem is that when they start eating it takes a large number of calories to make them feel satisfied. The two most common symptoms of obesity that relate to the disease itself and not only its complications are (1) excess hunger and (2) reduce satiation. The target for integrated obesity care should thus not only be on reducing the signs or even the complications of obesity, but should also reduce the symptoms of obesity. Successful integrated treatments for obesity share all the characteristics that in those who lost a significant amount of weight and were able to maintain the weight loss for a prolonged period, all felt less hungry and more satiated after a meal.

### Targeting Morbid Obesity or Obese Morbidity?

Integrated obesity care should be able to reduce the body fat set point but should also be able to address the multiple complications of obesity. These complications appear at different body mass indexes in different people and also occur in a large number of combinations with each other. An important part of the assessment of patients with obesity is to understand which other organs are diseased as a complication of obesity. Decisions are also needed as to how best to address these complications as to not increase the body fat set point, but also to get these complications under control. The goal is to reduce overall mortality.

## How?

### Multidisciplinary Care Model

There is a worldwide consensus that integrated care for obesity should be delivered by a multidisciplinary team of physicians, surgeons, dieticians, exercise specialists, psychologists/psychiatrists, and nurses. The evidence base, however, lacks as to how this team should be made up and how it should function. A common mistake within multidisciplinary obesity teams is that the roles of the various members of the team are poorly defined, leading to duplication of functions or at worst to internal contradiction. The effectiveness of these multidisciplinary teams can also be hampered if the philosophical approach is different between team members, especially if they have fundamental differences as to how to approach integrated obesity care.

## Model of Integrated Care

Multidisciplinary working became commonplace for the delivery of surgery as a treatment for obesity. The demand for multidisciplinary working was not because such a care model provided better weight loss but was rather instigated in an attempt to reduce the number of complications of surgery. The teams evolved into systems that tried to identify which patients should be considered for surgery, or to identify those where surgery was contraindicated. Other disciplines of medicine, such as transplantation, has a similar models of integrated care where patients entering into the system and clinicians working in the system have the express wish for the patient to end up having surgery. The obesity version of this model often resulted in a reduced number of patients being referred for care, and thus limiting the penetrance of the treatment. A similar situation existed in centers where only diet or only medication was offered, also resulting in a very low penetrance of the treatments.

An alternative model of integrated care is used in cancer centers. Here patients enter into the system and are assessed and treated by a multidisciplinary team. The ultimate treatment modality is, however, not predetermined prior to entry, but rather the members of the multidisciplinary team all contribute to decision making, resulting in a more personalized approach to get the right treatment to the right person at the right time. Such an approach in an integrated obesity care model may have value now that we have more effective diet, exercise, medication, and surgical approaches. Patients may not have to try the treatments in series but rather end up with the treatment that is best for them at that specific time. Such a model also facilitates patients being able to move between treatment modalities if the initial treatment was not successful. Thus, the team's success is not defined by the initial outcome of the first treatment but rather on the team's ability to adapt to treatment successes and failures of each patient.

## Diagnostics

A major limitation for integrated obesity care to be delivered in a model similar to cancer care is the lack of diagnostics that can identify the etiology of the obesity and determine treatment response. Integrated care systems can only implement decision algorithms if these algorithms have good sensitivity and specificity to diagnose the etiological factors that are amenable to treatment. Thus far the misunderstanding of the disease has often resulted in diagnostic approaches being focused on understanding the motivation of the patient and their readiness for change. These concepts are infrequently considered in other diseases that have biological set points such as hypertension therapies or during the treatment of familial hypercholesterolemia. Neither are these considered diagnostically valuable during cancer care.

Genetic testing can be used in certain setting and although very helpful to identify a specific genetic mutation, very few treatments have been shown to be particularly helpful in these monogenetic disorders. Questionnaires have been tried, but reporting bias and variation of response meant that the value of these approaches

as diagnostic tools have been low. Biomarkers have been hypothesized to hold value but none have thus far been shown to have good sensitivity or specificity as diagnostic tools.

## Predicting Treatment Response

Another major limitation is our current inability to predict weight loss outcomes of specific treatments. The variation of outcomes is significant for all treatments of obesity even when delivered in an integrated care model. This uncertainty reduces the penetrance of the treatments and also the referral of patients to integrated obesity care systems. Referring clinicians perceive that the risks are the highest for those treatments that are the most effective such as surgery or medication, but if they cannot quantify the chances of the patient to respond then the perceived risk may outweigh the benefit for the individual that is a "nonresponder." Patients and referring practitioners may be prepared to accept these risks if they knew a patient was likely to have a good outcome. Initially, the level of motivation was thought to determine the outcome, but this has now been shown to have no predictive value during the treatment with intensive lifestyle changes, medications, and surgery. Rather the biological response within 12 weeks of lifestyle and medication and the weight loss at 6–12 months after surgery appears to be more predictive of longer term outcomes. Initial weight loss response is a helpful indicator but not many of our integrated obesity care models have evolved to identify "early responders" and "early nonresponders." This step may help to determine follow-up treatments or changes in approaches that may help the patient.

## Multiple Mechanisms of Treatments

The development of treatment strategies that address different mechanisms of body fat set point reduction has impacted positively on enabling integrated obesity care. In systems where only one medication for obesity exists, it is much harder to offer patients alternatives, especially if that specific medication was not successful. Surgical treatments for obesity have benefitted from having multiple mechanisms by which it could reduce the body fat set point, but even after the most successful surgical procedures there are still patients that regain bodyweight and as such other modalities of treatment that can address alternative mechanisms may be required.

## Changing Approach if Treatment Does Not Work

One of the hardest thing for an integrated care model of obesity to cope with is the failure of the treatment to instigate weight loss in a patient. Equally hard is weight regain after a successful treatment. The tradition in integrated care for diabetes has been to work through an algorithm of care but when one medication stops working to

add on another medication rather than to stop the failing medication and replace it with an alternative. The diet, exercise, and medical treatment of obesity appears to have a large number of patients who respond to the intervention and have more than 10% weight loss, but there are equal if not larger number of patients who don't lose any weight. The concept of responders and nonresponders are now more frequently recognized. It is now becoming clear that those patients that don't lose significant amounts of weight still suffer the same side effects of the interventions. Thus, current best practice within an integrated obesity care model is to discontinue treatments that don't work to protect patients that won't benefit from side effects. These decisions can often be made within 12 weeks of the intervention reaching full intensity.

## Difference Between Motivation and Compliance

There are subtle differences between the motivation of patients and their compliance. Often in obesity services, patients are examined to determine their motivation. This is almost in an attempt to determine whether the patient deserves the treatment. This practice evolved from interventions such as surgery or medication being expensive and not widely available, but also because practitioners thought that if patients are more motivated they may have a better chance of having successful weight loss and weight loss maintenance. Very little evidence exists that the weight loss of patients classified as motivated are any different after intensive lifestyle changes, medication, or surgery when compared with patients that attained lower scores on those scale attempting to measure motivation.

Compliance, on the other hand, is whether a patient will continue with the treatment in the way it has been prescribed. Clearly, patients that have a better biological effect and who physiologically respond to treatment may be more willing to be compliant. However, there are a number of patients who are motivated to start a treatment, do have a biological response, but find compliance with the treatment difficult. These patients lose the benefits of the treatment as soon as they discontinue the interventions. Other patients are by nature more compliant, and even if they had lower levels of motivation for the treatment but have a good biological response and continue to adhere to the treatment schedule then they will continue to be very successful. This type of patient is also at risk if they continue to be compliant with the medication but do not have a biological response as they will then accrue all the side effects without the benefits. Finally, we know that animals that are exposed to obesity treatments continuously have a range of outcomes. The motivation to lose weight is, however, not different in those animals that lose the most weight compared to those that lose the least weight.

## Treatment Targets

A hotly debated topic within multidisciplinary teams that provide integrated obesity care is what the primary outcome of the care should be. Usually, the patients want to

be thin and happy and therefore the treatments are advertised as delivering thinness and happiness. However, a more realistic outcome of all obesity treatments should be aimed at improving health and functionality. The amount of weight loss that needs to be achieved to improve overall health depends on the disease that is being treated. For example, to improve the complication of obesity such as glycemic control in type 2 diabetes as little as 5% weight loss makes a significant difference (Espeland 2007), while other complications such as sleep apnea may require in excess of 10–15% weight loss to reduce the apnea hypopnea index below the threshold to require CPAP treatment (Peppard et al. 2000).

It would, however, be a missed opportunity if an integrated obesity care system does not consider patient wishes and expectations. Often patients are told to be grateful for 5% weight loss because of the potential benefits, while many patients with obesity say they cannot see an obvious difference with 5% weight loss and it doesn't meet their expectations. Some experts have now suggested that weight loss in excess of 15% should be considered as the target.

## Conclusion

### Multidisciplinary Care with Discrete Functions

The current consensus is that a multidisciplinary care is an optimal way to deliver an integrated obesity pathway. Further optimization of the multidisciplinary care model is required to allow each member of the multidisciplinary team to have discrete functions, and thus deliver complementary care that remains patient focused. Only when the healthcare professionals are able to work together without duplicating each other's role will the care be optimized.

### Cancer Model

The model which is being used to deliver cancer care may have many aspects which could benefit integrated obesity care. The cancer care model also is often agnostic as regards which treatment is best, but rather aims to deliver personalized care trying to get the right treatment to the right patient at the right time. The cancer care model also tolerates multiple different treatments and even combination approaches – all in an attempt to control the disease and keep it in remission for as long as possible. This may suit integrated obesity care much better.

### Improved Diagnostics

The availability of better diagnostic tools such as molecular diagnostics revolutionized cancer care and patients could suddenly be streamed into different pathways

which allowed for more sophisticated treatment approaches that delivered better prognoses. These breakthroughs are still awaited in obesity care.

## Predictors of Response

Most therapies that may be used in an integrated obesity pathway are used without the ability of the clinician to predict a response. Instead, a trial of therapy approach is often used with the response after 3 months often predicting long-term outcomes. Thus, different treatments are being tried and changes are made every 3 months if the patient didn't lose at least 5% of their body weight. This is a very reasonable approach, but with more treatments becoming available, this approach can only succeed in an integrated obesity care pathway.

## Making Decisions to Change Treatments Quicker

Traditionally, treatments that were started were not stopped even if the patient had a weak response or failed over time to respond. The approach was to keep the failed treatment going while adding another treatment. This meant that the patient was exposed to the risks of the treatment without getting many of the benefits. The current consensus is for treatments that fail to make patients less hungry and or more satisfied after a smaller meal to be stopped and changed to an alternative. This may often mean that the treatment approach is escalated from diet and exercise to medication to surgical approaches. The key is not to blame the patient if they didn't respond to the treatment but rather to recognize it early and to move on.

In conclusion, integrated obesity care pathways are more likely to succeed if obesity is recognized as a complex and chronic brain disease which has an enormous impact on individuals, healthcare systems, and societies. We are, however, on the brink of significant breakthroughs which will enable us to use better tools to help our patients. The question is whether we can establish the optimal integrated obesity care pathway to ensure that these tools are used to maximize benefits and minimize risk.

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