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The pathophysiological basis of bone tissue alterations associated with eating disorders

DOI 10.1515/hmbci-2016-0006
Received January 18, 2016; accepted February 9, 2016

Abstract: Anorexia nervosa (AN) and obesity are two major eating disorders present nowadays in Western countries. They are both characterized by striking body composition variations and hormonal alterations, which impact on skeletal metabolism, inducing bone tissue modifications and, thus, often cause an increased risk for fractures. AN and obesity are characterized by a severe reduction in fat mass and a high expression of it, respectively, and in both conditions hormones secreted or modulated by body fat content are important determinants of low bone density, impaired bone structure and reduced bone strength. In addition, in both AN and obesity, increased marrow adiposity, which correlates with low bone density, has been observed. This review will discuss the pathophysiological basis of bone alterations associated with AN and obesity, conditions of extreme energy deficiency and excess, respectively.

Keywords: adipose tissue; anorexia; bone; obesity; skeleton.

Introduction

Anorexia nervosa (AN) and obesity are the two major eating disorders, and are both characterized by marked body composition modifications and hormonal alterations which, in turn, influence bone metabolism causing an increased risk for fractures [1–5].

In particular, AN is characterized by a severe reduction in fat mass and obesity by a high expression of it. The importance of body composition alterations is based on observations that suggest several potential mechanisms to explain the complex relationship between adipose tissue and bone: fat has long been viewed as a passive energy reservoir, but after the discovery of leptin and the identification of other adipose tissue-derived hormones and serum mediators [6–8], it has come to be considered an active endocrine organ involved in the modulation of other tissues homeostasis. Adipose tissue, in fact, secretes various inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are believed to have adverse metabolic, skeletal and cardiovascular consequences [9]. Moreover, as IL-6 other fat-derived mediators, which include leptin, adiponectin, and resistin affect human energy homeostasis and are involved in bone metabolism, contributing to the complex relationship between adipose and bone tissue [10]. Finally, fat tissue is one of the major sources of aromatase, an enzyme also expressed in the gonads, which synthesizes estrogens from androgen precursors. Estrogens are steroid hormones, which play a pivotal role in the maintenance of skeletal homeostasis, protecting against osteoporosis by reducing bone resorption and stimulating bone formation [11]. Thus, the pathophysiological role of adipose tissue in skeletal homeostasis lies in the production of several adipokines and hormones, which modulate bone remodeling via their effects on either bone formation or resorption.

As the demonstration that bone cells express several specific hormone receptors, the skeleton has come to be considered an endocrine target organ [12–15], and as recent observations have shown that bone-derived factors, such as osteocalcin and osteopontin (OPN), affect body weight control and glucose homeostasis [16–18], the bone has come to be considered an endocrine organ itself [19]. These considerations suggest a potential role of bone as a player of a potential feedback mechanism between the skeleton and other endocrine organs [19]. Thus, the cross-talk between fat and bone likely constitutes a homoeostatic feedback system in which adipokines and bone-derived molecules represent the link of an active bone-adipose axis.

Finally, adipocytes and osteoblasts originate from a common progenitor, a pluripotential mesenchymal stem cell [20], which has an equal propensity for

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differentiation into adipocytes or osteoblasts (or other lines) under the influence of several cell-derived transcription factors. This process is complex, suggesting significant plasticity and multifaceted mechanism(s) of regulation within different cell lineages, among which are adipocytes and osteoblasts [21, 22]. Several human and animal studies have examined the function of adipocytes in bone marrow. Mesenchymal stem cells isolated from bone marrow in postmenopausal osteoporotic patients express more adipose differentiation markers than those from subjects with normal bone mass [23], and noticeable fatty infiltration in the bone marrow of rats following oophorectomy has been observed, suggesting a pivotal role of estrogens in regulating adipocyte and osteoblast recruitment [24].

This review will discuss the pathophysiological basis of bone alterations associated to AN and obesity, conditions of extreme energy deficiency and excess, respectively.

Anorexia nervosa and bone metabolism: energy homeostasis, hormone, body composition and bone marrow alterations

AN is a psychiatric disorder characterized by high morbidity and mortality, with the highest mortality rates among mental disorders. The 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) has revised the diagnostic criteria for the disease, which now include caloric restriction leading to severe underweight, intense fear of gaining weight and distorted body image (Table 1). Amenorrhea has not been included among the criteria in DSM-V [25].

Table 1: Classification of anorexia nervosa.

Academic purposes has classified AN patients into three different categories: 1. low weight 2. short-term recovered 3. long-term recovered
The American Psychiatric Association has subdivided AN into two distinct categories: 1. Restrictive type (RAN), patients exhibit “restricted food intake without binge eating or purging” 2. Binge-eating/purging type (BPAN), involving both “binge eating/purging episodes during anorexia and bulimia phases”

Modified from Faye WH et al. (1996); DSM-V, 2013.

The lifetime prevalence of AN in the general population is estimated between 0.3% and 0.9% in women, while it is <0.3% in men. AN primarily affects adolescent girls and young women, although it has occasionally been described in pediatric patients as well as in elderly women [26].

In the evolution of AN, energy homeostasis and hormone alterations occur, with most of them likely reflecting an adaptive response to malnutrition in an attempt to retain energy reserves. Patients with AN are characterized by a typical body composition phenotype with an extremely low percentage of body fat, when compared with healthy women with similar body mass index (BMI) [27], that, in association with the hormone adaptive condition, likely induces negative effects on bone metabolism. In fact, subjects affected by AN frequently present bone diseases, which include impairment of linear growth and reduced bone mineral density (BMD), associated with changes in bone turnover and structural and microarchitectural alterations, leading to increased fracture risk, as observed in postmenopausal osteoporosis [28]. In fact AN can significantly lead to impairment of peak bone mass, which plays a pivotal role in skeletal homeostasis (Figure 1).

The mechanisms involved in bone tissue alterations in AN are very complex and not, as yet, fully clarified. For instance, in patients with AN, leptin levels, which reflect energy stores, are very low, while adiponectin, which plays a pivotal role in energy homeostasis and insulin sensitivity, have been found higher than in matched controls [28].

Leptin stimulates the differentiation of stromal cells to osteoblasts, increases proliferation of osteoblasts and inhibits osteoclastogenesis. Moreover, systemic

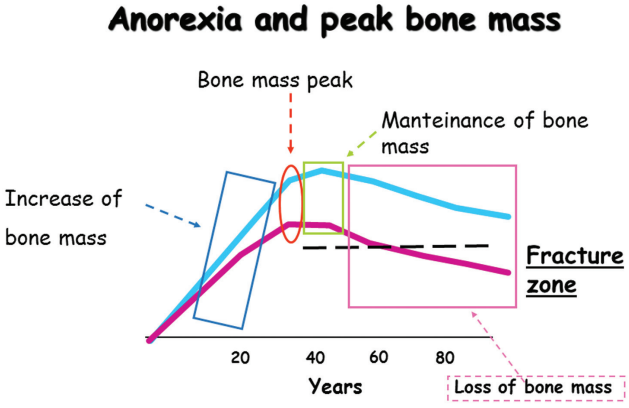

Figure 1: The figure depicts the modification of bone mineral density (BMD) during life.
In particular, peak bone mass is reached within the third decade of life, after which BMD is maintained during adult life. BMD starts to decline after the fifth decade of life.

administration of leptin to adult mice results in reduced bone fragility [28], while leptin-deficient and leptin receptor-deficient mice, despite an obese and hypogonadal phenotype, are characterized by high bone mass due to increased bone formation [28]. Data in humans are contradictory: with regard to leptin's action on bone physiology, either a beneficial role [29, 30], a detrimental one [31, 32], and a central inhibitory or a peripheral stimulatory effect of leptin on bone metabolism have been described. In women with AN, low leptin levels have been correlated with lower lumbar spine and hip BMD [33], as well as with microarchitecture alterations [34].

Interestingly, in vitro studies have demonstrated the expression of both adiponectin and its receptors in osteoblasts, as well as in osteoclasts; in addition, adiponectin affects osteoblastogenesis either positively or negatively, while suppressing osteoclastogenesis [28]. The locally produced adiponectin likely exerts more important effects on bone than circulating adiponectin. Indeed, although data regarding the effects of adiponectin on BMD in humans are largely inconsistent, there is enough evidence to hypothesize a negative correlation between circulating adiponectin levels and BMD [35]. Moreover, a negative association between adiponectin levels and BMD was observed in patients affected by AN [36].

In subjects affected by AN the plasma levels of ghrelin, an orexigenic peptide which also act as growth hormone (GH)-segretagogue and secreted primarily by the oxyntic cells of the stomach, are high when compared to normal controls. Remarkably, the refeeding of these patients does not lead to normality [28]. In addition, patients with AN show high fasting levels of peptide YY (PYY), an anorexigenic, gut-derived peptide secreted in response to food ingestion, which remain elevated even after an increase in body weight. Conversely, fasting levels of gastric inhibitory polypeptide (GIP), secreted from K-cells in the duodenum in response to food ingestion are low as compared to those of healthy controls [28].

Ghrelin, apart from stimulating GH release, modulates osteoblasts activity, increasing their proliferation and differentiation [37, 38]. Further, ghrelin infusion in experimental animal model determines an increase of BMD [38], but ghrelin knockout animal models show normal skeletal metabolism [39]. Healthy adolescent girls show a correlation between ghrelin secretion and BMD independently from body composition, circumstance not observed in adolescent girls with AN [40], suggesting that ghrelin probably does not play a major role in the skeletal status of these patients.

The system of neuropeptide Y (NPY), PYY and Y receptors, is a major regulator of energy homeostasis, and there are growing evidences that it is also important in bone metabolism. In particular Y2 knockout mice (Y2-/-) are characterized by increased cancellous bone volume, with increased trabecular number and thickness as well as neuropeptide Y knockout mice (NPY-/-) [41]. In contrast, NPY over-expression in the arcuate nucleus leads to weight gain and tibial BMC reductions through a decrease in osteoblastic activity [42]. Leptin constitutes an important regulator of NPY activity and low levels of leptin lead to enhanced hypothalamic NPY expression [43].

Finally, GIP enhances osteoblasts function [44], nevertheless no association between GIP levels and BMD values has been observed in subjects with AN [45].

Sex steroid hormones modulate the integrated metabolic interaction among major organs crucial for metabolically demanding activities such as reproduction and metabolic functions. Adipose tissue accumulation is sexually dysmorphic and females have a higher percentage of body fat than males. Adipose tissue distribution is also different, with females accumulating more subcutaneous fat and males accumulating more visceral fat [46]. Sex steroids are required to regulate adipocyte metabolism and they influence the sex-specific remodeling of particular adipose depots, thus strongly influencing body fat distribution and adipocyte differentiation and physiology.

Patients affected by AN show a characteristic body composition phenotype with an extremely low amount of body fat, and female subjects affected by AN typically have amenorrhea, which was a diagnostic criterion for AN until the latest revision of DSM. Amenorrhea in AN patients has a hypothalamic origin and it is due to a regression of the LH secretory pattern to prepubertal or pubertal standards [28]. Leptin is probably the mediator between low energy stores and impaired hypothalamic function, although there is evidence that ghrelin might have an independent impact on LH pulsatility [28]. Hypogonadotropic hypogonadism has also been described in male subjects affected by AN, with both low testosterone levels and relatively low gonadotropin levels [28], and females with AN likewise show low testosterone levels, with dehydroepiandrosterone sulfate (DHEAS) levels either normal or low [28].

It is well known that estrogens play a pivotal role in bone metabolism, improving bone formation and inhibiting bone resorption [47–49]. Indeed, estrogens inhibit receptor activator of nuclear factor kappa-B ligand (RANKL) and stimulate osteoprotegerin (OPG) secretion by osteoblasts [50] and they might also increase bone formation by inhibiting secretion of sclerostin, a transcription factor expressed by osteocytes that otherwise inhibits *wnt* signaling and therefore osteoblastic activity [50]. Postmenopausal osteoporosis is mainly the consequence of an

imbalance between bone formation and resorption with an increase in bone resorption due to the reduction of estrogen levels, and hypogonadism constitutes a major cause of secondary osteoporosis also in young male individuals [51]. Nevertheless, amenorrhea is not the only mechanism of bone loss in AN, in fact women with AN have lower BMD values as well as women with hypothalamic amenorrhea, but with normal BMI, indicating that other factors contribute to bone disease [52]. These factors are represented by androgens, which apart from being aromatized to estrogens, have direct effects on osteoblast differentiation and proliferation [53]. In women with AN, a correlation between androgen (testosterone and DHEAS) levels and BMD, as well as in adolescent boys, has been observed [54, 55].

Hypercortisolemia affects bone metabolism, and both endogenous hypercortisolism, as Cushing syndrome, and the use of oral glucocorticoids have been associated with a significant increase in fracture risk [56, 57]. In fact, cortisol acts directly on osteoblasts and osteocytes, enhancing their apoptosis [58–62], and reduces both osteoblast and osteoclast formation [59]. However, it increases the lifespan of osteoclasts leading to a temporary increase in bone resorption [60]. AN is a condition in which a relative hypercortisolemia exists for an adaptive mechanism to maintain euglycemia in a state of low energy availability [50]. In subjects affected by AN higher cortisol concentrations are associated with lower BMI and fat mass, and are related to an increased frequency of cortisol secretory bursts and a longer cortisol half-life [50]. Weight gain leads to a significant decrease in cortisol burst frequency [50]. Individuals with AN show a negative correlation between hypercortisolemia and bone formation markers, whereas there is no association between cortisol levels and bone formation in healthy controls [61], and 12-h overnight mean serum cortisol levels correlate negatively with lumbar spine and hip BMD [62].

Insulin growth factors I and II (IGF-I and IGF-II) also appear to significantly affect bone metabolism in AN patients. IGF-I enhances bone formation through its action on mature osteoblasts [63] and normal circulating levels of IGF-I are of primary importance for the preservation of cortical bone mass [64]. In subjects with AN low levels of GH binding protein suggest decreased expression of the GH receptor and a state of GH resistance [65]. This is confirmed by the observation of lower levels of IGF-I despite higher concentrations of GH than in controls [66]. Higher GH concentrations are consequent to an increase in secretory burst amplitude and frequency, and higher basal GH secretion [66]. The increase in GH is likely an adaptive response to maintain euglycemia in a state of starvation by increasing availability of gluconeogenic substrates through increased lipolysis. GH concentrations are inversely associated with BMI and fat mass in AN patients, and are likely driven by lower levels of IGF-I and higher levels of ghrelin [66, 67]. Lower IGF-I levels are associated with lower levels of bone formation markers, lower bone density, and impaired bone microarchitecture [34, 68]. Whereas normal-weight girls with higher GH concentrations have higher levels of bone turnover markers, this association is not observed in girls with AN, suggestive of skeletal GH resistance [66]. This is further confirmed by lack of a significant increase in levels of IGF-I and bone turnover markers following administration of supraphysiologic doses of rhGH to adult women with AN over a 3-month period, indicative of hepatic and bone resistance to GH [69]. Instead, the administration of recombinant human IGF-I (rhIGF-I) in replacement doses causes an increase in markers of bone formation in adolescent girls and adult women with AN [70, 71].

Triiodothyronine (T3) acts on osteoblasts regulating their differentiation, proliferation and apoptosis by direct and indirect mechanisms [72–74]. Hypothyroidism is associated with prolonged bone turnover and with increased fracture risk [75–77]. T3 levels are low in patients with AN with a simultaneous increase in reverse T3 levels, while thyroid-stimulating hormone (TSH) usually remains within normal limits, creating a hormonal profile resembling the sick euthyroid syndrome. Thyroxine (T4) may also be decreased, and delayed patterns of TSH response to thyrotropin-releasing hormone (TRH) stimulation have also been described [28]. However, the contribution of thyroid axis alterations to AN bone disease is currently unclear.

BMI and lean mass are independent predictors of bone density in males and females with AN [55, 68, 78]. Although lower fat mass is associated with lower bone density, lean mass is a stronger determinant of bone density measures than fat mass, consistent with mechanical loading having a protective effect on bone. In adult women with AN, weight gain is associated with a preferential increase in bone density at the total hip, whereas menstrual recovery is associated with an increase in bone density at the spine [55]. In adolescent girls with AN, increases in lean body mass during weight recovery predict increases in bone density [79]. Finally, in adolescents with AN, recovery of weight and menses is associated with an improvement in bone accrual rates, although residual deficits persist, concerning for suboptimal peak bone mass acquisition despite recovery [80].

In healthy children and adults, a reciprocal relationship has been described between marrow adiposity and

bone parameters at both axial and appendicular skeleton [81–84]. Misra and colleagues have shown, using magnetic resonance spectroscopy techniques, that adults with AN have increased marrow fat compared to normal-weight controls, and that marrow fat is inversely associated with areal bone density measures [85]. Additionally, preadipocyte factor-1 (Pref-1), a member of the epidermal growth factor-like family of proteins, that reduces differentiation within the osteoblast lineage, is higher in women with AN than controls, and higher Pref-1 levels are associated with higher marrow fat and lower areal BMD [86]. Both marrow fat and Pref-1 levels decrease with recovery from AN [87].

Finally, inducible brown adipose tissue (BAT), or beige fat, seems to have anabolic effects on the skeleton in animal models [88], and positive associations of cold activated BAT with bone density measures in healthy adults and with cross-sectional dimensions on bone in healthy children have also been reported [89, 90]. Women with AN have lower cold-induced BAT than controls [91], likely an adaptive response to reduce cold-induced thermogenesis and energy expenditure, and lower BAT content is associated with lower bone density. In addition, IGF binding protein-2 is an inverse predictor of cold-induced BAT and BMD, possibly subsequent to increased binding to IGF-1, a crucial regulator of brown fat adipogenesis [92].

Obesity and bone metabolism: energy homeostasis, hormone, body composition and bone marrow alterations

Obesity, which is due to an imbalance where energy intake exceeds energy expenditure over a prolonged period, has always been known and recognized as a risk factor for metabolic and cardiovascular diseases [93], and considered a protective factor for bone loss and osteoporosis. In fact postmenopausal women, who often present weight gain and obesity, have an increased risk of developing hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, and some specific types of cancers, have always been considered protected against osteoporosis [11, 93, 94].

Even though body fat and lean mass are correlated with BMD, with obesity apparently exerting protection against bone loss, especially after menopause, during the last decades numerous evidences have described an opposite event, suggesting an inverse relationship between obesity and osteoporosis. In particular, recent studies have shown that an increased abdominal fat tissue could be considered a risk factor for bone loss and osteoporosis [95–97]. Interestingly, in men obesity correlates with hypogonadism, changes in body composition, glucose tolerance alteration, increased cardiovascular risk factors, and osteoporosis [46], strongly suggesting the lack of gender-specific events.

The mechanism whereby increased central adiposity leads to metabolic alterations, cardiovascular morbidity and bone loss has been largely based on the demonstration that adipose tissue secretes a number of cytokines and bioactive compounds, the adipokines.

The adipokines, which include a variety of pro-inflammatory peptides, are involved in many physiological or pathological processes, including inflammation, endothelial damage, atherosclerosis, impaired insulin signaling, hypertension and bone remodeling. Adipokine disregulation is a strong determinant of the low-grade inflammatory state of obesity, which promotes a cascade of metabolic alterations leading to cardiovascular complications, insulin resistance or diabetes mellitus and bone loss [6, 8].

Leptin, the first identified adipose tissue-derived factor, as mentioned above, is an anorexigenic hormone secreted by adipocytes in proportion to body fat content. Leptin levels are typically elevated in obesity, considered a leptin-resistant state [98]. In obese individuals hyperleptinemia has been widely recognized as an independent cardiovascular risk factor associated with hyperinsulimenia and insulin resistance [99] while its effect on bone is complex, as both negative and positive actions have been reported on the skeleton and on BMD, particularly [29–32]. In vivo studies indicate that the effect of leptin might depend on its site and mode of action [100], and it has been proposed that peripheral administration of leptin could increase bone mass by inhibiting bone resorption and increasing bone formation, while it appears to inhibit bone formation through a central nervous system effect [101]. In vitro studies also found that leptin modulates directly bone marrow-derived mesenchimal stem cells (BMSCs) enhancing their differentiation into osteoblasts and inhibiingt their differentiation into adipocytes [102]. Finally, leptin also inhibits the expression of NPY, a hypothalamus-derived peptide, essential for the regulation of food consumption, energy homeostasis, and bone remodeling [41]. In particular, NPY seems to promote osteoblast proliferation and activiy in vitro [103].

Adiponectin exerts a protective role on cardiovascular system and glucose metabolism, and in contrast with leptin, serum adiponectin levels are reduced in obese and diabetic subjects and increase after weight loss [104]. Low

levels of adiponectin are a common feature of obesity and correlate with insulin resistance [105]. Adiponectin levels are inversely related to the circulating levels of C reactive protein (CRP), TNF-α and IL-6, which are, especially the latter two, powerful inhibitors of adiponectin expression and secretion in cultured human adipose cells [106]. Human osteoblasts express adiponectin and its receptors, and in vivo and in vitro studies show that adiponectin increases bone mass by suppressing osteoclastogenesis and activating osteoblastogenesis [107], likely indicating that a rise in adiponectin levels, caused by fat reduction, could have a beneficial effect on BMD.

Resistin is produced by macrophages and visceral adipocytes, it is elevated in obesity, regulates insulin sensitivity in skeletal muscle and liver and is positively associated with insulin resistance and glucose tolerance in both human and animal models [108]. Resistin might also play a role in bone remodeling as it is expressed in mesenchimal stem cells, osteoblasts, and osteoclasts, and appears to increase osteoblast proliferation, cytokine release and osteoclast differentiation [109].

TNF-α is a pro-inflammatory cytokine which plays important regulatory effects on lipid metabolism, adipocyte function, insulin signaling and bone remodeling [110]. Its expression has been shown to correlate with percent body fat and insulin resistance in humans [111], and it was further recognized that inflammatory processes predispose to bone loss, giving rise to speculation that inflammatory cytokines, such as IL-6 and TNF-α, may play critical roles in osteoclast activity [112]. It has also become clear that TNF-α promotes RANKL production by BMSC and mature osteoblasts, reduces OPG production, and upregulates the receptor receptor activator of nuclear factor kappa-B ligand (RANK) on osteoclast precursors, increasing their sensitivity to prevailing RANKL concentrations [113]. Additionally, TNF-α turns out to have another property that is relatively unique among the inflammatory cytokines, it has potent effects on osteoclastogenesis as it not only promotes RANKL production but synergizes with RANKL to amplify osteoclastogenesis, and to intensify osteoclastic resorption by directly modulating RANKL-induced signal transduction pathways [114]. These effects are likely a consequence of the fact that RANKL is a TNF-superfamily member and functions through many of the same pathways induced by TNF-α itself.

IL-6 is a cytokine which has a wide range of actions. It is secreted by several cell types, including fibroblast, endothelial cells and adipocytes, and its plasma levels are significantly up-regulated in human obesity and insulin resistance [115]. As TNF-α IL-6 also is a well-recognized stimulator of osteoclastogenesis and bone resorption. Several data show that IL-6 mRNA is expressed in pre-osteoblasts and osteoblasts [116] and that it stimulates osteoblast proliferation and differentiation by controlling the production of local factor [117]. In addition, IL-6 may play a role in bone formation in conditions of high bone turnover [118].

Although ghrelin, a 28-amino-acid acylated peptide, is mainly secreted by the stomach and it represents the principal endogenous ligand for growth hormone secretagogue receptor (GHS-R) type 1a. Ghrelin, which does not meet the definition of an adipokine as it is not secreted by adipose tissue, is involved in the regulation of glucose metabolism and lipogenesis both directly and through interactions with several adipokines. Ghrelin is known to stimulate the differentiation of pre-adipocytes into adipocytes and antagonize lipolysis, and its levels are inversely correlated with BMI and insulin resistance [119]. Moreover, Ghrelin exerts anti-inflammatory and cardio-protective effects through its inhibitory actions on TNF-α, IL-1, and IL-6, and exerts a protective role on bone metabolism acting both directly and indirectly on bone cells function, inhibiting osteoclastogenic precursors and osteoclastogenic cytokines such as TNF-α, IL-1, and IL-6, and modulating osteoblast differentiation and function, through regulation of the GH-insulin-like growth factor axis [120]. In addition, ghrelin interacts with leptin in modulating bone structure in an age-dependent manner, as recently shown [121].

Adipocytes and osteoblasts originate from a common progenitor, a pluripotential mesenchymal stem cell [20], which has an equal propensity to differentiate into adipocytes or osteoblasts or other lines, such as chondrocytes, fibroblast, and endothelial cells, upon the influence of several cell-derived transcription factors. This process is complex, suggesting significant plasticity and multifaceted mechanism(s) of regulation within different cell lineages, among which are adipocytes and osteoblasts [21, 22].

Transdifferentiation is the irreversible switching of differentiated cells that sometimes occurs during disease [122], and it involves partially differentiated cells (e.g. pre-osteoblasts) that switch to another lineage (e.g. adipocytes) [123]. Recently, a correlation between the osteo-adipogenic transdifferentiation of bone marrow cells and numerous bone metabolism diseases has been established [124]. Obesity increases fat bone marrow content in adult premenopausal women with obesity, and greater vertebral marrow fat has been associated with high fat mass and with lower trabecular bone density [125]. Similarly, in obese men, bone marrow fat is inversely associated with cortical bone parameters [126].

Finally, as the observation that bone cells produce specific bone-derived factors, the skeleton has come to be considered an endocrine organ itself [19]. In fact, emerging evidences point to a critical role for the skeleton in several homeostatic processes including energy balance and adipose metabolism, and the connection between fuel utilization and skeletal remodeling seems to begin in the bone marrow with lineage allocation of mesenchymal stromal cells into adipocytes or osteoblasts.

Mature bone cells secrete factors that modulate insulin sensitivity and glucose metabolism, such as osteocalcin (OCN), an osteoblast-specific protein and a major non-collagenous protein in the extracellular matrix [127]. Karsenty and co-authors demonstrated that uncarboxylated OCN, acting as a pro-hormone, can increase β-cell proliferation, insulin secretion, insulin sensitivity, and adiponectin expression [128]. Thus, osteoblasts may be able to regulate glucose metabolism by modulating the bioactivity of OCN. In addition, more recent studies showed that OCN bioactivity is modulated by enhanced sympathetic tone driven by leptin, which has been shown to suppress insulin secretion by β-cells [129], and other recent studies have demonstrated an inverse correlation between serum OCN and plasma glucose levels, supporting a role for this pathway in humans [130]. Thus, a novel picture has emerged linking glucose metabolism, adipose stores, and skeletal activity.

Since its first description more than 20 years ago, OPN has emerged as an active player in many physiological and pathological processes, including biomineralization, tissue remodeling, and inflammation. As an extracellular matrix protein and proinflammatory cytokine, OPN is thought to facilitate the recruitment of monocytes/macrophages and to mediate cytokine secretion in leukocytes. Modulation of immune cell response by OPN has been associated with various inflammatory diseases and may play a pivotal role in the development of adipose tissue inflammation and insulin resistance [131]. Several studies have described OPN as a critical regulator of adipose tissue inflammation, insulin resistance, and diabetes mellitus. OPN expression is drastically up-regulated by 40- and 80-fold in adipose tissue from diet-induced and genetically obese mice, respectively [132]. OPN expression in adipose tissue as well as circulating OPN levels were substantially elevated in obese, diabetic, and insulin resistant patients compared with lean healthy subjects, and conversely that dietary weight loss significantly decreased OPN concentrations [133–136]. Finally, more recently, simultaneous up-regulation of IL-18 and OPN in peripheral blood mononuclear cells (PBMCs) has been reported in obese individuals as compared to lean subjects. Intriguingly, treatment with a neutralizing IL-18 antibody diminished OPN secretion from PBMCs, indicating that IL-18 regulates OPN expression [137]. These findings point toward a specific pathophysiological role of OPN also in human inflammatory processes linked to obesity-induced adipose inflammation, insulin resistance, type 2 diabetes and its complications.

Conclusions

AN and obesity are the two most important eating disorders, and are characterized by high reduction and increase in body fat content, respectively. In both the disorders the modifications in body composition and the altered hormonal pattern impact skeletal metabolism causing a decline in bone tissue density and quality, often leading to an increased fracture risk.

The importance of body composition changes are based on several observations suggesting potential mechanisms to explain the complex relationship between adipose and bone tissues: 1) adipose tissue, which has long been regarded as a passive energy reservoir, secretes multiple adipose tissue-derived hormones and cytokines involved in energy homeostasis and metabolism regulation; 2) as the demonstration that bone cells secretes specific factors that affect body weight control and glucose homeostasis, fat is considered an endocrine organ itself and a player of an active bone-adipose axis; 3) adipocytes and osteoblasts originate from a common pluripotential mesenchymal stem cell, that has an equal tendency to differentiate into adipocytes or osteoblasts (or other lines) upon the influence of different stimuli on cell-specific transcription factors.

However, the mechanisms by which all these events occur remain, in part, unclear, and further research is necessary to fully characterize the impact of these hormones and cytokines independent of each other and of body compositions.

Funding: Ministero dell'Istruzione, dell'Universitá e della Ricerca, (Grant/Award Number: 'PRIN 2011 052013').

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