Endocrine
DOI 10.1007/s12020-015-0530-0

ORIGINAL ARTICLE

Severe growth hormone deficiency and empty sella in obesity: a cross-sectional study

Carla Lubrano · Marta Tenuta · Daniela Costantini · Palma Specchia · Giuseppe Barbaro · Sabrina Basciani · Stefania Mariani · Alfredo Pontecorvi · Andrea Lenzi · Lucio Gnessi

Received: 16 December 2014 / Accepted: 10 January 2015

Abstract Obesity is associated with blunted growth hormone (GH) secretion. In some individuals, hypothalamic–pituitary (HP) structural lesions may contribute to GH deficiency (GHD). We explored pituitary morphology in obese patients with suspected GHD and its association with cardiovascular risk factors, body composition, and cardiac morphology. One hundred and eighty-four adults obese patients with symptoms and signs of GHD (147 females and 37 males; mean age 46.31 ± 12.11 years), out of 906 consecutive white obese outpatients, were evaluated. The main measures were anthropometric data, blood pressure, lipid profile, glycemic parameters, pituitary hormones, and insulin-like growth factor-1 values, echocardiography, magnetic resonance imaging (MRI) of the HP region, body composition, and growth hormone-releasing hormone plus arginine test. Seventy patients had GHD (GH peak values <4.2 μg/mL). GHD patients showed significantly higher body mass index and fat mass, lower lumbar bone mineral density, increased left ventricular mass index, and epicardial fat thickness. The MRI of the HP region showed empty sella (ES) in 69 and normal pituitary in one of the 70 GHD patients; the 114 patients with normal GH response had ES ($n = 62$, 54 %), normal pituitary ($n = 37$, 32 %), microadenomas ($n = 10$, 8 %), and other pituitary abnormalities ($n = 5$, 4 %). ES was a significant independent predictor of GH secretory capacity as determined by multiple regression analysis. The close relationship between ES and GH secretory capacity points out to the possibility of the organic nature of GHD in a portion of obese individuals and opens a new scenario with regard to the potential of GH treatment on metabolic consequences of obesity.

Keywords Growth hormone deficiency · Pituitary · Magnetic resonance imaging · Empty sella · Obesity

Introduction

Obesity is a disease not always attributable to caloric imbalance, and various hypotheses are emerging to explain, at least in part, this growing epidemic [1]. The identification of conditions with causative roles in the development and maintenance of obesity and its comorbidities may have important clinical consequences.

Neuroendocrine dysfunctions are frequent in obese patients, and the common assumption is that they are functionally linked to increased adipose tissue with potential for delayed identification and investigation of HP diseases [2].

The HP unit plays a central role in the maintenance of normal weight being directly involved in the control of energy homeostasis [3]. Either insufficiency or excess of anterior pituitary hormones have subtle effects on the accumulation of body fat severity of which depends on the mixture of changes, their degree, and duration. For example, Cushing's disease and excess of prolactin (PRL) may be associated with increased visceral fat; insufficiencies of anterior pituitary hormones affect the accumulation of

C. Lubrano · M. Tenuta · D. Costantini · P. Specchia · G. Barbaro · S. Basciani · S. Mariani · A. Lenzi · L. Gnessi (✉)
Section of Medical Pathophysiology, Food Science and Endocrinology, Department of Experimental Medicine, University of Rome "La Sapienza", Policlinico Umberto I, 00161 Rome, Italy
e-mail: lucio.gnessi@uniroma1.it

A. Pontecorvi
Department of Internal Medicine, Catholic University of the Sacred Hearth, Rome, Italy

Published online: 23 January 2015

adipose tissue [2]. A blunted growth hormone (GH) response is a frequent feature in obese individuals generally considered a functional result of obesity. However, obesity associates with profound changes in the structure of neurons and glia in the hypothalamus [4] and frequently shares with ES, idiopathic intracranial hypertension, and high intracranial pressure, all conditions with some degree of hypopituitarism [5, 6]. Collectively, abnormalities of the HP unit may be either a consequence of obesity or contribute to its development through a persistent organic failure. Therefore, in the obese patients with clinical characteristics of HP disease, an adequate functional and morphological assessment of HP unit is important to improve health outcomes [7].

We evaluated HP MRI findings and cardiometabolic condition in obese individuals with clinical features of GHD. We report evidence that among the obese individuals, the coexistence of signs and symptoms of GHD other than obesity is frequent, and there is a marked association of ES with severe GHD. Furthermore, we found a significant relationship between the impaired GH secretion and the metabolic unhealthy phenotype in obese patients.

Materials and methods

Study design and participants

Nine hundred and six consecutive unselected white obese outpatients [676 females and 230 males; age range 11–64 years, mean ± SD 42.36 ± 13.09 years; BMI, expressed as weight (kg)/height (m^2) ≥30 kg/m^2], referred to our center for a first-level approach to the study of obesity and its comorbidities, were evaluated for a clinical, metabolic, and therapeutic assessment of obesity during the period of 2007–2013. All patients underwent neurological, ophthalmological, and baseline endocrine evaluations. 184 patients (37 males, 147 females, mean age 46.31 ± 12.11 years) with normal GH values and normal-to-low levels of IGF-1 for sex and age, in an appropriate clinical context [8], namely those with signs and symptoms of GHD according to the Endocrine Society consensus guidelines [9], underwent the GHRH plus arginine test (Fig. 1). In particular, patients were selected if presenting IGF1 standard deviation score (SDS) between −1 and −3 and at least one symptom and one sign among these: lumbar T score < −1; lean mass% < 60 %; upper body fat deposition index (UFDI), the ratio between upper body fat (neck, arms, and trunk fat in kg) and lower body fat (legs fat in kg) >1.5; epicardial fat thickness (EFT) >7 mm in females and >8 mm in males; ejection fraction (EF) < 60 %; diastolic left ventricular diameter (DLVD) > 55 mm; systolic left ventricular diameter (SLVD) > 43 mm; LVMI > 100 g/m^2; altered triglycerides (>1.69 mmol/L), or total cholesterol (>5.17 mmol/L) levels. Exclusion criteria were short stature or decreased growth rate issues in childhood, pregnancy, lactation, or drugs known to affect pituitary function.

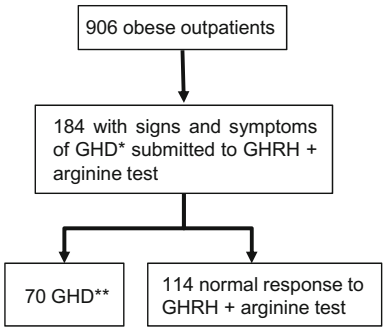

Fig. 1 Study design. *GHD* growth hormone deficiency; * according to (8, 9), ** peak value to GHRH plus arginine test <4.2 μg/L

If adrenocorticotropic hormone (ACTH) deficiency was suspected, insulin tolerance test and cortisol daily curves were performed [9].

No patient was treated with any drug until first line evaluation and stimulation tests were performed.

The study was approved by the biomedical research ethic committee of the University of Rome "La Sapienza." This study is registered with ClinicalTrials.gov, number NCT02092779. All patients provided a written informed consent according to the Declaration of Helsinki.

Clinical measurements

Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. The waist circumference (WC) was measured just above the bony landmark of the iliac crest and expressed in centimeters. Hip circumference was measured around the pelvis at the point of maximal protrusion of the buttocks. Sitting systolic and diastolic blood pressure (SBP–DBP) was measured twice at 5-min intervals, and the average of two measurements was used for analysis.

Laboratory

Blood samples were collected after an overnight fast. Lipid status [total cholesterol (total-C), HDL cholesterol (HDL-C), and triglycerides (TG)] were determined using automated enzymatic method (Dade Behring SPA Milan). LDL cholesterol (LDL-C) was calculated using the Friedwald formula. The glucose determinations were performed using the hexokinase method (Aeroset Abbot Park, IL, USA), insulin was measured by radioimmuno-assay (Bayer

Diagnostics, Milan, Italy). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from Matthews et al. [10]. HbA1c was determined by an automated system (Bio-Rad Laboratories, Hercules, CA, USA). IGF-1 was assayed by an immunoradiometric assay (Diagnostic System Laboratories Inc., Webster, TX, USA). Thyroid-stimulating hormone (TSH) and PRL measurements were performed by chemiluminescence (Abbott Laboratories, Abbott Park, IL, USA). ACTH and GH were measured by radioimmuno-assay (CISbio, Cedex, France; DiaSorin S.p.A., VC, Italy). All samples were assayed in duplicate, with intra-assay and inter-assay mean coefficients of variation of 2 and 4 %, respectively. The GHRH plus arginine test was performed as follows. One microgram per kilogram of body weight of intravenous GHRH (Ghrh Ferring, Ferring S.p.A., Milano, Italy) as a bolus plus 0.5 g/kg of body weight up to a maximum of 30 g of arginine hydrochloride (iv infusion over 30 min) were given, and blood samples were taken at −15, 0, and +30, +45, +60 after stimulation. GH results were read with BMI-dependent cut-off values for diagnosis of adult GHD, as suggested by Corneli et al., in respect of a reference obese Italian population with multiple pituitary hormone deficits [11]: peak value <4.2 μg/L for obese patients. The area under the concentration–time curve (AUC) was calculated by the trapezoidal method.

Magnetic resonance imaging (MRI)

Pituitary gland MRI was performed using a 1.5 T scanner (Signa HDx, General Electric, Milwaukee, WI) with gadolinium contrast enhancement. The mid sagittal T1 image centered at the pituitary stalk was used to measure the central height, maximum length, and cross-sectional area of the gland. All measurements were obtained independently by two experienced physicians (A.P., A.L.) blinded to the clinical diagnosis with the aid of Codonics Software v4.0.1 [12]. Pituitary adenomas were distinguished by craniocaudal diameter taken in coronal sections into MA (smaller than 10 mm) and macroadenoma (larger than 10 mm). Patients with pituitary diameter ≤2 mm and more than 50 % filled with cerebrospinal fluid (CSF) were considered as total ES; patients with pituitary diameter ≥3 mm but ≤7 mm (the mean diameter of normal pituitary gland in adults) and less than 50 % filled with CSF were considered as partial ES [13].

Echocardiography

Participants underwent high-resolution M–B mode transthoracic echocardiography using a 2.5 MHz Probe (Esaote MyLab40, Esaote Europe B.V., The Netherlands). Two-dimensional echocardiography and standard M-mode measurements of left ventricle were performed as described [14, 15]. EF%, LVMI, SLVD, DLVD, and EFT were measured.

Dual-emission X-ray absorptiometry (DXA)

DXA measurement of body composition was performed using a DXA scan (QDR 4500 W, Hologic Inc., Bedford, MA, USA): lean mass, fat mass and bone mass were obtained as percent and as amount of fat (in grams) with a coefficient of variation <1 % for bone density and <1.5 % for fat mass [16]. Delimiters for regional analysis were determined by standard software (Hologic Inc., S/N 47168 VER. 11.2).

Statistical analysis

Data were analyzed by means of STATISTICA software, version 8.0 (Stat Soft, Inc., Tulsa, Oklahoma) and MedCalc Statistical Software version 13.0.2 (MedCalc Software bvba, Ostend, Belgium). Results are expressed as mean ± standard deviation (SD) unless otherwise specified. Differences between groups were analyzed using ANOVA for continuous variables. Linear correlation and multiple linear regression analyses were performed to identify associations between GH AUC and metabolic parameters and to identify the best predictor of GH peak and HOMA-IR. The cut-off threshold for peak GH after GHRH plus arginine was analyzed by receiver operating curve (ROC). For the purpose of ROC analysis, we assumed the patients with ES to be GHD according to our results and other studies [17]. All statistical assessments were considered significant if $p < 0.05$.

Results

The demographic, anthropometric, and clinical characteristics of the 184 patients with at least one symptom and one objective sign possibly related to GHD disease [8, 9] stratified according to the GH peak values after GHRH plus arginine are shown in Table 1. Seventy patients had a peak GH response to GHRH plus arginine lower than 4.2 μg/L (mean ± SD, 2.31 ± 1.25 μg/L) that was compatible with the diagnosis of GHD; all of them showed a complete or partial ES except for one patient who had normal pituitary (NP) according to morphological criteria. 16 out of 69 GHD ES patients (23.18 %) had multiple deficiencies: 15 out of 22 males had central hypogonadism, and two showed also ACTH deficiency; one female had ACTH deficiency. One hundred and fourteen patients [62 ES, 37 NP, ten microadenomas (MA) and five with other pituitary abnormalities (OPA)] had a normal response to GHRH plus

Table 1 Demographic, anthropometric, and clinical characteristics of the patients according to peak GH values after GHRH plus arginine test

	Normal	GHD[a]	*p* value
n	114	70	
ES	62 (54 %)	69 (98.6 %)	<0.001
NP	37 (32 %)	1 (1.4 %)	<0.001
MA	10 (8 %)	0	<0.05
OPA	5 (4 %)	0	ns
Gender (female/male)	99/15	48/22	<0.005
Age (years)	45.33 ± 13.16	47.94 ± 9.96	ns
Height (m)	1.63 ± 0.08	1.65 ± 0.11	ns
Weight (Kg)	100.92 ± 21.64	116.80 ± 31.65	<0.001
BMI (Kg/m^2)	38.02 ± 7.11	42.70 ± 10.16	<0.001
WC (cm)	118.43 ± 16.43	128.90 ± 18.81	<0.001
WHR	0.98 ± 0.09	0.95 ± 0.07	<0.01
HR (beats/min)	69.31 ± 9.86	72.11 ± 9.64	ns
SBP (mmHg)	127.62 ± 16.41	133.05 ± 15.21	<0.05
DBP (mmHg)	80.21 ± 9.98	82.37 ± 9.69	ns
Total-C (mmol/L)	5.15 ± 0.92	5.3 ± 1.07	ns
LDL-C (mmol/L)	3.189 ± 0.86	3.2 ± 0.98	ns
HDL-C (mmol/L)	1.26 ± 0.32	1.2 ± 0.32	ns
TG (mmol/L)	1.52 ± 0.95	1.96 ± 1.31	<0.05
Glucose (mmol/L)	5.31 ± 0.89	5.85 ± 0.98	<0.001
Insulin (pmol/L)	157.17 ± 116.05	207.52 ± 147.10	<0.05
HOMA-IR	5.43 ± 4.20	8.18 ± 6.33	<0.001
HbA1c (%)	5.75 ± 1.05	6.27 ± 1.04	<0.01
HbA1c (mmol/mol)	39 ± 3.15	45 ± 3.12	<0.01
TSH (mIU/L)	1.57 ± 1.28	1.98 ± 1.52	ns
ACTH (pmol/L)	6.28 ± 3.95	7.03 ± 4.24	ns
PRL (pmol/L)	510.43 ± 325.65	488.26 ± 326.95	ns
GH (μg/L)	0.47 ± 0.79	0.22 ± 0.27	<0.01
IGF-1 (nmol/L)	21.38 ± 11.38	17.41 ± 7.00	<0.01
IGF-1 SDS	−1.12 ± 2.06	−1.66 ± 1.76	ns
GH peak (μg/L)	14.45 ± 12.64	2.31 ± 1.25	<0.001
GH AUC (μg/L/h)	435.12 ± 329.92	84.98 ± 49.70	<0.001
EF (%)	66.51 ± 3.41	65.19 ± 4.23	<0.05
LVMI (g/m^2)	108.97 ± 22.73	117.85 ± 19.74	<0.01
SLVD (mm)	30.48 ± 3.37	32.45 ± 3.93	<0.001
DLVD (mm)	49.53 ± 3.92	51.68 ± 4.23	<0.001
EFT (mm)	8.08 ± 1.12	8.49 ± 0.99	<0.05
L2-L4 BMD (g/cm^2)	1.05 ± 0.12	1.01 ± 0.12	<0.05
Hip BMD (g/cm^2)	1.01 ± 0.15	1.03 ± 0.15	ns
Body fat (%)	40.62 ± 6.11	42.52 ± 5.12	<0.05
Body lean (%)	59.38 ± 6.11	57.48 ± 5.12	<0.05
Arms fat (%)	49.15 ± 8.93	47.17 ± 12.40	ns
Legs fat (%)	42.55 ± 7.64	39.80 ± 9.55	<0.05
UFDI	1.89 ± 0.56	2.07 ± 0.54	<0.05
MetS[b]	56 (49 %)	46 (66 %)	<0.05

Values represent mean ± SD unless otherwise indicated

ES empty sella, *MA* microadenoma, *OPA* other pituitary abnormalities, *NP* normal pituitary, *BMI* body mass index, *WC* waist circumference, *WHR* waist to hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *TG* triglycerides, *Total-C* total cholesterol, *HDL-C* high density lipoprotein cholesterol, *HOMA-IR* homeostasis model assessment of insulin resistance, *HbA1c* glycated hemoglobin, *ESR* erythrocyte sedimentation rate, *hs-CRP* high-sensitivity C-reactive protein, *WBC* white blood cells, *TSH* thyroid stimulating hormone, *ACTH* adrenocorticotropic hormone, *PRL* prolactin, *GH* growth hormone, *IGF-1* insulin-like growth factor-1, *IGF-1 SDS* IGF-1 standard deviation score, *EF* ejection fraction, *LVMI* left ventricular mass index, *SLVD* systolic left ventricular diameter, *DLVD* diastolic left ventricular diameter, *EFT* epicardial fat thickness, *BMD* bone mineral density, *UFDI* upper body fat deposition index, *MetS* metabolic syndrome

[a] Peak GH value <4.2 μg/L

[b] Number of patients with MetS, percentage value in parentheses

arginine (14.45 ± 12.64 μg/L, range 4.40–78.5) with high variability. The group of patients with GHD was heavier, with higher WC, SBP, TG, blood glucose, insulin, HOMA-IR, WBC, and HbA1c values compared with normal GHRH plus arginine responders. Waist-to-hip ratio (WHR), basal GH, and IGF-1 were significantly lower in

this group. The echocardiographic parameters related to the left ventricle were significantly altered in the GHD group, and lower EF% and higher EFT were present. Body composition by DXA revealed that in GHD patients, L2–L4 BMD and legs fat % were significantly lower, while the UFDI value was significantly higher compared with normal GHRH responders. Thus, the patients with GHD were heavier but not fatter and showed a particular distribution pattern of the adipose tissue characterized by a greater UFDI. The prevalence of metabolic syndrome (MetS) in the patients with GHD was higher compared with the control group (66.0 vs. 49 %, $p < 0.037$).

Linear correlation analyses to assess the relationships between AUC of GH response to GHRH plus arginine test and MetS diagnostic parameters, insulin and HOMA-IR showed a significant inverse association between preserved GH secretory capacity and all the parameters evaluated with the only exception of HDL-C that showed a significant direct relationship (Table 2).

Table 2 Linear correlation analyses comparing AUC of GH response to GHRH plus arginine test and diagnostic parameters of MetS

	Mean ± SD	Pearson *R*	*p*
AUC (μg/L/h)	301.34 ± 312.61		
WC (cm)	122.42 ± 18.05	−0.39	0.000
SBP (mmHg)	129.62 ± 16.15	−0.19	0.012
DBP (mmHg)	81.00 ± 9.90	−0.18	0.020
HDL-C (mmol/L)	1.13 ± 0.19	0.19	0.020
Triglycerides (mmol/L)	1.66 ± 1.00	−0.24	0.001
Glucose (mmol/L)	5.51 ± 0.96	−0.32	0.000
Insulin (pmol/L)	176.13 ± 130.50	−0.22	0.005
HOMA-IR	6.46 ± 5.25	−0.27	0.000

AUC area under the curve, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high density lipoprotein cholesterol, *HOMA-IR* homeostasis model assessment of insulin resistance

Age- and sex-adjusted multiple regression analyses for the association between GH peak response to GHRH plus arginine test and selected covariates related to body composition and to pituitary morphology possibly involved in the modulation of GH secretion (BMI, WC, UFDI, ES) revealed that ES and UFDI were independent predictors of GH secretory capacity (Table 3A). Age- and sex-adjusted multiple regression analysis for the association of HOMA-IR with BMI, WC, and GH peak values is presented in Table 3B: GH peak was significantly associated with HOMA-IR. Furthermore, the odds ratio for GHD in ES patients was 63.44 (95 % CI 8.53–471.85; $p = 0.0001$).

ROC analysis (Fig. 2) to identify the GH cut-off value after GHRH plus arginine revealed that the cut-off with best pair of values for sensitivity and specificity (80.34 and 91.30 % respectively) was 5.73 μg/L.

Discussion

Adult GHD causes a clinical syndrome characterized by increased fat mass, adverse changes in lipid metabolism, carbohydrate metabolism, and cardiovascular function [18–20]. GH replacement therapy normalizes many of these signs and symptoms, but it is not approved in the absence of an appropriate clinical context, namely structural HP defects [21, 22]. The estimated incidence of adult-onset GHD is between 12 and 19 cases per million of the population [23]. However, the true incidence of adult-onset GHD remains unknown, owing in part to the lack of standardization of diagnostic criteria, and in part because not all patients at risk are routinely assessed for the diagnosis of GHD. Consensus statements indicate only adult patients with structural HP disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies are worth to be considered for evaluation for adult-acquired GHD [8, 9]. Moreover, screening in a clinical setting for GHD in obese patients is generally

Table 3 Multiple linear regression analysis for the association between GH peak (A) and HOMA-IR (B) and selected covariates adjusted for sex and age

Covariates	*β*	SE	*T* (138)	*B*	SE	*p* value
(A) Dependent variable, GH peak						
Intercept			36.81915	10.30003	3.57467	0.000517
BMI (kg/m^2)	−0.083590	0.133891	−0.15673	0.25105	−0.62431	0.533682
WC (cm)	−0.111171	0.133418	−0.08991	0.10790	−0.83326	0.406456
UFDI	−0.194511	0.085731	−3.70997	1.63517	−2.26886	0.025175
ES	0.437956	0.082668	11.97970	2.26126	5.29780	0.000001
(B) Dependent variable, HOMA-IR						
Intercept			0.78472	3.042892	3.877664	0.434033
BMI (kg/m^2)	0.230181	0.144283	1.59534	0.148831	0.093291	0.113046
WC (cm)	0.062239	0.147945	0.42069	0.018510	0.043999	0.674670
GH peak (μg/L)	−0.219659	0.083342	−2.63563	−0.101282	0.038428	0.009412

(A) $R = 0.58162782$, $R^2 = 0.33829092$ adjusted $R^2 = 0.30376697$

(B) $R = 0.45273682$, $R^2 = 0.20497063$ adjusted $R^2 = 0.18069492$

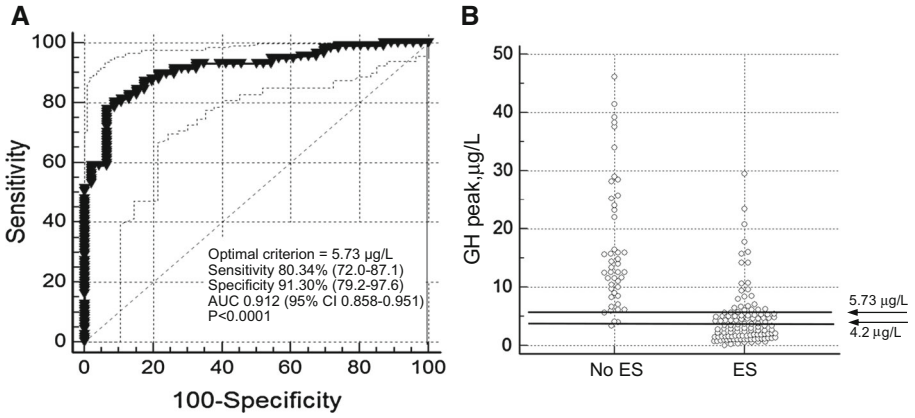

Fig. 2 Sensitivity and specificity of peak serum GH response to the GHRH plus arginine test in the study population. In panel A, ROC analysis that includes all the patients tested revealed an AUC of 0.912 (95 % CI 0.858–0.951); optimal criterion, sensitivity, and specificity with confidence intervals are shown in the box. In panel B, the use of a cut-off value of 5.73 µg/L of GH to minimize the total classification error of GHD had a sensitivity and specificity of 80.34 and 91.30 %, respectively, for ES. The currently accepted cut-off value of 4.2 µg/L is also shown

not accepted, mainly because of the negative influence of abdominal and visceral obesity on the secretion of GH [24].

However, a number of clinical questions still remain unanswered. Is the blunted GH response always functional (namely, correctable with weight reduction) or, in a proportion of obese patients, might GHD be organic? What is the clinical context for the evaluation of GHD in obese individuals? How much does GHD contribute to the cardiometabolic risk factors associated with obesity? Are there potential therapeutic consequences in terms of GH replacement therapies?

We found that among obese individuals with nonspecific signs and symptoms of GHD, ES is frequent, and the majority of them have a biochemically severe GHD, with a strong association between GHD and ES. Moreover, 23.18 % of ES GHD patients show multiple hormonal deficiencies. These data suggest ES as an associated organic cause in a proportion of formerly defined "idiopathic" GHD and open a new scenario on the actual prevalence of organic GHD in obesity. ES is seen in a range between 8 and 35 % of the general population [25]. Incidence and prevalence of hypopituitarism are estimated to be 4.2 per 100,000/years and 45.5 per 100,000, respectively [26]; this means a prevalence of less than 0.05 %. These data are inconsistent with the reduced GH response to GHRH plus arginine found in 39.2–61 % of the patients with primary ES [5, 27], which would predict a much higher prevalence of GHD. Thus, in obesity, ES is under diagnosed, and the expected prevalence of GHD could be underestimated. These findings indicate that complicated obesity may underlie GHD, and the clinical context to search for GHD in obese could be broader than was supposed. A rational consequence, worth being considered further, is that the quite variable improvement of GH secretion after weight loss might not occur when GHD and ES associate. Accordingly, persistence of ES despite a significant weight loss after bariatric surgery has been reported [28], suggesting that in the presence of an organic basis for GHD, weight reduction, although beneficial, could not be curative.

Low endogenous GH secretion in the obese state associates with increased cardiometabolic risk factors [21]. Reduced GH secretion has been correlated with an adverse lipid and lipoprotein profile, increased abdominal adipose tissue mass, higher hs-CRP, and increased prevalence of diabetes [18]. However, since GH levels decline with aging and weight gain, and both elderly and obese individuals have a higher risk of developing cardiometabolic diseases independent of reduced GH [29], it is difficult to determine whether changes in metabolic environment are specifically related to GHD or other concomitant conditions. In line with previous reports [18], we found an inverse association between GH secretory capacity and the essential components of MetS, HbA-1c, and HOMA-IR values. Our findings extend the data available so far in the sense that the main parameter associated with insulin resistance is the GH peak independently from BMI and WC.

In our obese GHD patients, we found reduced lumbar BMD and lean body mass percentage and increased UFDI, a DXA-derived parameter strictly related to EFT that conveys information about the ratio between subcutaneous and visceral fat [17, 30]. All these conditions are known signs of GHD, virtually ascribable to the reduced action of GH on muscle, bone, and fat [21, 31] and offer a possible explanation for the coexistence of sarcopenia and osteopenia in a subset of obese patients [32].

LVMI, SLVD, DLVD, and EFT were significantly increased in our GHD group, suggesting cardiac structural

changes related to the impaired GH secretion capacity, possibly due to the increased intramyocellular fat deposition seen in individuals with blunted GH response [33, 34]. Some studies have disclosed beneficial effects of recombinant human GH treatment in patients with idiopathic dilated cardiomyopathy and ischemic cardiomyopathy [35, 36]; exogenous GH is able to improve significantly cardiac function, with decreases in left ventricular end-diastolic and end-systolic dimensions [37]. Furthermore, EFT was significantly reduced after short-term GH replacement in patients with adult-onset GHD [38]. Our results do not confirm the decrease of cardiac mass seen in other studies involving GHD patients [39, 40], although these data were taken from small populations of normal/overweight patients. The cardiac abnormalities we found might be a typical trait of organic GHD in obesity. Overall, these findings suggest that the GH secretory capacity is a major determinant of cardiac morphology and metabolic phenotype of the obese patients.

Multiple regression analysis, performed to evaluate the influence of different covariates on GH secretion, shows that pituitary morphology and to lesser extent UFDI, but not BMI and WC, are related to GH peak values. These new findings suggest that the presence of ES might be the strongest determinant of reduced GH secretion in obese patients. Although novel, this is not unexpected since brain structural defects [9], including ES syndrome and all the conditions compatible with acquired ES (traumatic brain injury, surgery, irradiation, infarction, inflammatory or infiltrative disorders), are recognized causes of organic GH deficiency. Interestingly, the GH peak response to GHRH plus arginine stimulus, more than BMI and WC, associates with HOMA-IR, suggesting that the GH secretory capacity is the major independent predictor of insulin resistance in the obese patients with symptoms and signs of GHD.

Obesity is the most important confounding factor for the diagnosis of nonfunctional GHD in adults. Nearly half of the patients with acquired HP disease are overweight or obese and normal GH secretory capacity is crucial for cardiometabolic health; thus, a proper GH peak cut-off value is important to identify organic GHD in obese patients. We suggest a cut-off value of 5.73 μg/L GH peak response to GHRH plus arginine for GHD that derives from a ROC analysis based on ES as positive condition for organic GHD [5, 17]. This cut-off differs from the currently accepted 4.2 μg/L GH diagnostic cut-off peak value in obese subjects. Based on the old and new cut-off, respectively 70 (38 %) and 98 (53 %) of the 184 patients with at least one symptom and one objective sign related to GHD were classified as having severe GHD. We think our cut-off value as appropriate, with ES being the covariate most strongly associated with the GH peak, in comparison with WC, BMI, IGF-1, impairment of lipid profile, reduced bone mineral density, and cardiac abnormalities. Furthermore, our cut-off is similar to the 5.5 μg/L value proposed in obese patients aged 26–65 years [41], confirming that testing for GHD should be performed in patients with underlying HP disorders and strengthening the concept that ES should not be considered as merely an incidental finding, rather as a structural condition likely associated with GHD in obesity.

Clinical trials assessing the effects of GH treatment in obese patients showed consistent reductions in adipose tissue mass and in particular visceral depots [18]. Moreover, studies in patients with abdominal obesity demonstrate a marked effect of GH therapy on lipid and glucose homeostasis [18]. Therefore, administration of recombinant human GH has great potential to influence the onset and metabolic consequences of obesity, but the clinical use in obesity remains controversial [18, 21]—although, a recent study conducted on a large population of adult onset GHD patients, demonstrates that, in GH-treated patients, mortality decreases in total and due to malignancy compared with untreated patients, even after adjustment for all possible measured confounders [42].

Conclusions

The coexistence of morphological alterations and signs/symptoms of HP disease is frequent in obese patients. Our data, providing ES as an underlying organic cause for GHD in a portion of obese patients, portend new therapeutic outcomes. Whether GH replacement may improve obesity and the associated cardiometabolic risk factors in obese individuals with GHD and ES needs further studies.

Although the question remains whether ES and GHD are common co-travelers due to obesity and their cooccurrence reflects a causal effect of fat mass on ES pathogenesis and GHD, the high concurrence of ES and severe GHD in obese patients may have important consequences both for clinical screening and therapeutic approach, since the recovery of normal GH secretion because of GHD arising from ES is uncertain and the GH replacement in these patients might be appropriate.

There are some limitations in our study. This was a cross-sectional study, so we could not assess the causal relationship between the covariates evaluated and GHD. Second, the sex structures of the cohort is not balanced, but the interference of this factor with the results is unlikely since all the analytic data were corrected for age and sex.

Acknowledgments This work was supported by a Grant (C26A14M9TR) from the University of Rome "La Sapienza", Progetti di Ateneo.

Conflict of interest The authors declare no conflict of interest.

References

1. C. Lubrano, G. Genovesi, P. Specchia, D. Costantini, S. Mariani et al., Obesity and metabolic comorbidities: environmental diseases? Oxid. Med. Cell. Longev (2013). doi:10.1155/2013/640673
2. J. Weaver, Classical endocrine diseases causing obesity. Front Horm. Res. **36**, 212–228 (2008). doi:10.1159/00001153678
3. G.J. Morton, D.E. Cummings, D.G. Baskin, G.S. Barsh, Schwartz MW central nervous system control of food intake and body weight. Nature **443**, 289–295 (2006)
4. J.P. Thaler, C.X. Yi, E.A. Schur, S.J. Guyenet, B.H. Hwang et al., Obesity is associated with hypothalamic injury in rodents and humans. J. Clin. Invest. **122**, 153–162 (2012). doi:10.1172/JCI59660
5. L. De Marinis, S. Bonadonna, A. Bianchi, G. Maira, Giustina A primary empty sella. J. Clin. Endocrinol. Metab. **90**, 5471–5477 (2005)
6. A. Giustina, G. Aimaretti, M. Bondanelli, F. Buzi, S. Cannavò et al., Primary empty sella: why and when to investigate hypothalamic-pituitary function. J. Endocrinol. Invest. **33**, 343–346 (2010)
7. I.W. Seetho, Wilding JP How to approach endocrine assessment in severe obesity? Clin. Endocrinol. **79**, 163–167 (2013). doi:10.1111/cen.12256
8. K.K. Ho, GH deficiency consensus workshop participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH research society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur. J. Endocrinol. **157**, 695–700 (2007)
9. M.E. Molitch, D.R. Clemmons, S. Malozowski, G.R. Merriam, Vance ML evaluation and treatment of adult growth hormone deficiency: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. **96**, 1587–1609 (2011). doi:10.1210/jc.2011-0179
10. D.R. Matthews, J.P. Hosker, A.S. Rudenski, B.A. Naylor, D.F. Treacher et al., Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia **28**, 412–419 (1985)
11. G. Corneli, C. Di Somma, R. Baldelli, S. Rovere, V. Gasco, The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. Eur. J. Endocrinol. **153**, 257–264 (2005)
12. K.R. Krishnan, P.M. Doraiswamy, S.N. Lurie, G.S. Figiel, M.M. Husain et al., Pituitary size in depression. J. Clin. Endocrinol. Metab. **72**, 256–259 (1991)
13. A.D. Elster, Modern imaging of the pituitary. Radiology **187**, 1–14 (1993)
14. S. Migliaccio, G. Barbaro, R. Fornari, G. Di Lorenzo, M. Celli, C. Lubrano et al., Impairment of diastolic function in adult patients affected by osteogenesis imperfecta clinically asymptomatic for cardiac disease: casuality or casuality? Int. J. Cardiol. **131**, 200–203 (2009)
15. S. Mariani, D. Fiore, G. Barbaro, S. Basciani, M. Saponara et al., Association of epicardial fat thickness with the severity of obstructive sleep apnea in obese patients. Int. J. Cardiol. **167**, 2244–2249 (2013). doi:10.1016/j.ijcard.2012.06.011
16. L. M. Donini, E. Poggiogalle, V. Del Balzo, C. Lubrano, M. Faliva, et al. How to estimate fat mass in overweight and obese subjects. Int. J. Endocrinol. (2013) doi:10.1155/2013/285680
17. M. Maghnie, A. Lindberg, M. Koltowska-Häggström, M.B. Ranke, Magnetic resonance imaging of CNS in 15,043 children with GH deficiency in KIGS (Pfizer International Growth Database). Eur. J. Endocrinol. **168**, 211–217 (2013)
18. A.Y. Kargi, G.R. Merriam, Diagnosis and treatment of growth hormone deficiency in adults. Nat. Rev. Endocrinol. **9**, 335–345 (2013)
19. V.E. Chaves, F.M. Júnior, Bertolini GL The metabolic effects of growth hormone in adipose tissue. Endocrine **44**, 293–302 (2013)
20. C. Di Somma, A. Ciresi, M.C. Amato, S. Savastano, M.C. Savanelli et al., Alteration of the growth hormone axis, visceral fat dysfunction, and early cardiometabolic risk in adults: the role of the visceral adiposity index. Endocrine (2014). doi:10.1007/s12020-014-0471-z
21. K.G. Alberti, P. Zimmet, J. Shaw, The metabolic syndrome–a new worldwide definition. Lancet **366**, 1059–1062 (2005)
22. D.E. Berryman, C.A. Glad, E.O. List, G. Johannsson, The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. Nat. Rev. Endocrinol. **9**, 346–356 (2013)
23. K. Stochholm, C.H. Gravholt, T. Laursen, J.O. Jørgensen, P. Laurberg et al., Incidence of GH deficiency-a nationwide study. Eur. J. Endocrinol. **155**, 61–71 (2006)
24. H. Makimura, T. Stanley, D. Mun, S.M. You, S. Grinspoon, The effects of central adiposity on growth hormone (GH) response to GH-releasing hormone-arginine stimulation testing in men. J. Clin. Endocrinol. Metab. **93**, 4254–4260 (2008)
25. M.R. Sage, P.C. Blumbergs, Primary empty sella turcica: a radiological anatomical correlation. Australas. Radiol. **44**, 341–348 (2000)
26. H.J. Schneider, G. Aimaretti, I. Kreitschmann-Andermahr, G.K. Stalla, E. Ghigo, Hypopituitarism. Lancet **369**, 1461–1470 (2007)
27. M. Gasperi, G. Aimaretti, E. Cecconi, A. Colao, C. Di Somma et al., Impairment of GH secretion in adults with primary empty sella. J. Endocrinol. Invest. **25**, 329–333 (2002)
28. Q.G. D'Alessandris, N. Montano, F. Bianchi, F. Doglietto, E. Fernandez et al., Persistence of primary empty sella syndrome despite obesity surgery: report of two unusual cases. Br. J. Neurosurg. **26**, 875–876 (2012). doi:10.3109/02688697.2012.697215
29. S. Melmed, Idiopathic adult growth hormone deficiency. J. Clin. Endocrinol. Metab. **98**, 2187–2197 (2013)
30. C. Lubrano, M. Saponara, G. Barbaro, P. Specchia, E. Addessi et al., Relationships between body fat distribution, epicardial fat and obstructive sleep apnea in obese patients with and without metabolic syndrome. PLoS ONE **7**, e47059 (2012). doi:10.1371/journal.pone.0047059
31. R.J. Brummer, B.A. Bengtsson, The effects of growth hormone on body composition. Asia Pac. J. Clin. Nutr. **4**, 151–155 (1995)
32. E.A. Greco, R. Fornari, F. Rossi, V. Santiemma, G. Prossomariti et al., Is obesity protective for osteoporosis? Evaluation of bone mineral density in individuals with high body mass index. Int. J. Clin. Pract. **64**, 817–820 (2010)
33. M.A. Bredella, M. Torriani, B.J. Thomas et al., Peak growth hormone-releasing hormone-arginine-stimulated growth hormone is inversely associated with intramyocellular and intrahepatic lipid content in premenopausal women with obesity. J. Clin. Endocrinol. Metab. **94**, 3995–4002 (2009)
34. A.E. Malavazos, G. Di Leo, F. Secchi, E.N. Lupo, G. Dogliotti et al., Relation of echocardiographic epicardial fat thickness and myocardial fat. Am. J. Cardiol. **105**, 1831–1835 (2010). doi:10.1016/j.amjcard.2010.01.368
35. J.G. O'Driscoll, D.J. Green, M. Ireland, D. Kerr, R.I. Larbalestier, Treatment of end-stage cardiac failure with growth hormone. Lancet **349**, 1068 (1997)
36. D.L. Roman, E.R. Bobillo, Reversing idiopathic dilated cardiomyopathy with growth hormone: is this possible? Ann. Intern. Med. **126**, 834 (1997)

37. A. Frustaci, N. Gentiloni, M.A. Russo, Growth hormone in the treatment of dilated cardiomyopathy. N. Engl. J. Med. **335**, 672–673 (1996)
38. E. Ferrante, A.E. Malavazos, C. Giavoli, F. Ermetici, C. Coman et al., Epicardial fat thickness significantly decreases after short-term growth hormone (GH) replacement therapy in adults with GH deficiency. Nutr. Metab. Cardiovasc. Dis. **23**, 459–465 (2013)
39. G. Lombardi, C. Di Somma, L.F. Grasso, M.C. Savanelli, A. Colao et al., The cardiovascular system in growth hormone excess and growth hormone deficiency. J. Endocrinol. Invest. **35**, 1021–1029 (2012). doi:10.3275/8717
40. A. Colao, The GH-IGF-I axis and the cardiovascular system: clinical implications. Clin. Endocrinol. (Oxf) **69**, 347–358 (2008). doi:10.1111/j.1365-2265.2008.03292
41. A. Colao, C. Di Somma, S. Savastano, F. Rota, M.C. Savanelli et al., A reappraisal of diagnosing GH deficiency in adults: role of gender, age, waist circumference, and body mass index. J. Clin. Endocrinol. Metab. **94**, 4414–4422 (2009)
42. K. Stochholm, A. Berglund, S. Juul, C.H. Gravholt, J.S. Christiansen, Socioeconomic factors do not but GH treatment does affect mortality in adult-onset growth hormone deficiency. J. Clin. Endocrinol. Metab. **99**, 4141–4148 (2014)