J. Endocrinol. Invest. 29: 536-543, 2006

Growth hormone status in morbidly obese subjects and correlation with body composition

S. Savastano[1], C. Di Somma[1], A. Belfiore[2], B. Guida[2], F. Orio Jr[1], F. Rota[1], M.C. Savanelli[1], T. Cascella[1], A. Mentone[1], L. Angrisani[3], G. Lombardi[1], and A. Colao[1]

[1]Division of Endocrinology, Department of Molecular and Clinical Endocrinology and Oncology; [2]Unit of Physiology, Department of Neuroscience, University Federico II, Naples; [3]Department of Surgery, S. Giovanni Bosco of Naples, Naples, Italy

ABSTRACT. Morbidly obese subjects are characterized by multiple endocrine abnormalities and these are paralleled by unfavorable changes in body composition. In obese individuals, either 24-h spontaneous or stimulated GH secretion is impaired without an organic pituitary disease and the severity of the secretory defect is proportional to the degree of obesity. The GHRH+arginine (GHRH+ARG) test is likely to be the overall test of choice in clinical practice to differentiate GH deficiency (GHD) patients. Similarly to other provocative tests, GHRH+ARG is influenced by obesity *per se*. Therefore, a new cut-off limit of peak GH response of 4.2 µg/l in obese subjects has been recently assumed. The aim of the present study was to investigate the reciprocal influence between decreased GH secretion and body composition in a group of 110 morbidly obese subjects, using the new cut-off limit of peak GH response to GHRH+ARG test for these subjects. In our study, GHD was identified in 27.3% of the obese subjects, without gender difference. In GDH obese subjects body mass index (BMI), waist circumference, waist-to-hip ratio (WHR), fat mass (FM), and resistance (R) were higher while reactance (Xc), phase angle, body cell mass (BCM), IGF-I, or IGF-I z-scores were lower than in normal responders ($p<0.001$). In all obese subjects, GH peak levels showed a negative correlation with age, BMI, waist circumference and FM, and a positive correlation with IGF-I. In the stepwise multiple linear regression, waist circumference and FM were the major determinants of GH peak levels and IGF-I. In conclusion, using the new cut-off limit of peak GH response to GHRH+ARG test for obese subjects, about 1/3 morbidly obese subjects were GHD. GHD subjects showed a significantly different body composition compared with normal responders, and the secretory defect was correlated to different anthropometric variables with waist circumference and FM as the major determinants.

(J. Endocrinol. Invest. 29: 536-543, 2006)

INTRODUCTION

Morbidly obese subjects are characterized by multiple endocrine abnormalities and these are paralleled by relevant and unfavorable changes in body composition, ie increased visceral fat, and decreased body free fat mass (FFM) (1-3).

In obese subjects, either 24-h spontaneous GH secretion or stimulated GH release is impaired, including GH secretion in response to all traditional pharmacological stimuli acting on the hypothalamus, such as insulin-induced hypoglycemia or arginine (ARG), and to direct somatotrope stimulation by exogenous GHRH (4-7).

However, it is widely accepted that the GH response to the provocative test is influenced by obesity *per se* (8) and that the GH deficiency (GHD) in obesity may be a functional reversible status (2, 4, 5). Nevertheless, the severity of the secretory defect has been reported to be proportional to the degree of obesity, the entity of this alteration being inversely proportional to the increase in body fat (9). In this context, there is evidence that in adult patients with hypopituitarism, the severity of GHD measured as peak GH after the combined GHRH-ARG test is correlated with the degree of bone loss (10), the abnormality of

Key-words: GH deficiency, IGF-I, body composition, obesity.

Correspondence: S. Savastano, MD, PhD, Department of Molecular and Clinical Endocrinology and Oncology, "Federico II" University of Naples, Via S. Pansini 5, 80131 Naples, Italy.

E-mail: sisavast@unina.it

Accepted February 9, 2006.

lipid profile (11), the severity of cardiac impairment (12) and changes in body composition (13).
The GHRH+ARG is a potent and reproducible test, which is unaffected by gender and aging, and it is likely the overall test of choice in clinical practice. A GH response of 9 µg/l or less with a GHRH+ARG test was diagnostic for severe GHD (14). However, this cut-off limit of peak GH response to GHRH+ARG test in lean subjects is not reliable in obese individuals (8, 15). In fact, the GH response to GHRH+ARG test, similarly to other provocative tests, is influenced by obesity *per se* and a new cut-off limit of peak GH response of 4.2 µg/l in obese subjects has been recently assumed (16).
The aim of this study was to investigate the reciprocal influence between decreased GH secretion and body composition in a group of morbidly obese subjects, investigating the GH secretion with the GHRH+ARG using the new cut-off limit of peak GH response to GHRH+ARG test for obese subjects, and evaluating body composition by conventional bioelectrical impedance analysis (BIA) and impedance vector analysis (BIVA).

MATERIALS AND METHODS

Subjects

This study includes 110 subjects (85 females and 25 males) with clinically significant obesity [body mass index (BMI) 41.6±4.6 kg/m²], aged 32.1±11.9 yr. The subjects were consecutively recruited among over 150 morbidly obese subjects referred to the Endocrinology Unit of the Department of Molecular and Clinical Endocrinology and Oncology, from 2003-2004, and the selection was based on the following criteria: 1) the absence of diabetes mellitus, liver or renal failure, cancer, and acute or chronic inflammatory diseases based on a complete medical examination and laboratory investigations; 2) none of the subjects was chronically treated with any type of medication; 3) the absence of other pituitary secretory deficiencies, specifically: a) diabetes insipidus was ruled out by normal urine volume (<2.5-3 l/24 h) with normal urine osmolality (>300 mmol/kg); b) normal adrenal function was demonstrated by early-morning (at 09:00 h) cortisol concentrations >80 µg/l, 24-h urinary free cortisol levels >30 µg/24-h and normal response of cortisol to low dose ACTH test (1 µg ev); c) the absence of secondary hypothyroidism was demonstrated by normal free T_4 (fT_4) (>8 ng/l) concentrations with normal TSH levels; d) the absence of secondary hypogonadism was demonstrated by: i) in pre-menopausal women with a normal menstrual pattern (ie at least 10 menstrual periods in the previous year, the last <60 days before the 1st examination), normal estradiol levels (>20 pg/ml) with normal FSH and LH levels; ii) in men by normal testosterone levels (>3 µg/l) with normal FSH and LH levels.
Obese subjects were given a standardized interview to obtain information about the duration of obesity, eating patterns, smoking habits and physical exercise. In particular, subjects were also asked to make a daily record of the amount of physical activity (no exercise; ≤2-3 h/week; ≥2-3 h/week).
The duration of obesity was defined as the time interval since significant obesity had occurred. The estimation of dietary intake was assessed by Winfood (Medimatica software medico 1999, Rome, Italy). The daily calorie intake and diet composition were calculated during a personal interview, using a detailed food-frequency questionnaire of 130 foods and beverages (17).
Hormonal investigations were performed during the early follicular phase, 5-7 days after spontaneous menses.
Informed consent was obtained from all subjects in accordance with institutional guidelines, and the study design was made in accordance with the Helsinki II declaration.

Anthropometry

All anthropometric measurements were made with the subjects wearing only underwear without shoes. Standing height was measured to the nearest cm using a wall-mounted stadiometer. Body weight (bw) was determined to the nearest 50 g using a calibrated balance beam scale. BMI was calculated as weight (kg) divided by height squared (m²) and used as an index for obesity. Measurements of the waist circumference were taken at the mid point between umbilicus and xiphoid, and for hip circumference at the widest point around the hips. The waist-to-hip circumference ratio (WHR) was thereafter calculated.

Methods

Serum GH levels were measured by immunoradiometric assay (IRMA) using commercially available kits (HGH-CTK-IRMA, Sorin, Saluggia, Italy). The sensitivity of the assay was 0.2 µg/l. The intra- and interassay coefficients of variations (CV) were 4.5 and 7.9%, respectively. Plasma IGF-I was measured by IRMA after ethanol extraction. The sensitivity of the assay was 0.8 µg/l. The normal IGF-I range in 20-40, 41-60, and over 60-yr-old subjects was 110-494, 100-300, and 78-260 µg/l, respectively. The intra-assay CV were 3.4, 3.0, and 1.5% for low, medium, and high points on the standard curve, respectively. The interassay CV were 8.2, 1.5, and 3.7% for low, medium, and high points on the standard curve, respectively.
The GHRH+ARG was performed according to Ghigo et al. (14): ARG (arginine hydrochloride, Salf, Bergamo, Italy) was administered at a dose of 0.5 g/kg, up to a maximal dose of 30 g, slowly infused from time 0 to 30 min, while GHRH (1-29, Geref, Serono, Rome, Italy) was given at a dose of 1 µg/kg as iv bolus at time 0. Blood samples were taken every 15 min from –15 up to 90 min. In a normal lean population (14-16), the GH response after GHRH+ARG was classified as severe GHD when the GH peak was ≤9 µg/l, partial GHD when the GH peak was 9.1-16.5 µg/l, and normal when the GH peak was ≥16.5 µg/l. However, according to recent findings described by Biller et al. (15) and by Corneli et al. (16), where the GH peak cut-off for differentiating GHD patients and controls is 4.1 and 4.2 µg/l, respectively, in obese subjects and where BMI affects the GH response to the GHRH+ARG test, we classified our obese subjects as severe GHD when the GH peak was ≤4.2 µg/l, and normal responders when the GH peak was higher than this cut-off point. For this reason all of the following data were analyzed according to a 4.2 µg/l cut-off point.

Conventional bioelectrical impedance analysis

Body composition was determined by conventional BIA and by BIVA. Resistance (R) and reactance (Xc) were measured by a single

J. Endocrinol. Invest. 29: 536-543, 2006

investigator with a single-frequency 50 kHz bioelectrical impedance analyzer (BIA 101 RJL, Akern Bioresearch, Firenze, Italy) according to the standard tetrapolar technique, with the subject in supine position and the electrodes placed on the dorsal surface of the right foot and ankle, and right wrist and hand. The body composition was calculated from bioelectrical measurements and anthropometric data by applying the software provided by the manufacturer, which incorporated validated predictive equations for total body water (TBW), fat mass (FM) and FFM, and extra-cellular water (ECW) (18, 19). Soft tissue hydration of individual subjects was evaluated by BIA vector analysis. R and Xc were normalized by the height of subjects (R/H and Xc/H) and the resulting vectors were plotted on a graph reporting the gender-specific 50th, 75th, and 95th tolerance ellipses of similar vectors calculated from a reference healthy population (20). According to the RXc graph method, vectors falling within the reference gender-specific 75th tolerance ellipse indicated normal hydration, short vectors (below the lower pole of the 75th tolerance ellipse) indicated over-hydration and long vectors (above the upper pole of the 75th tolerance ellipse) indicated under-hydration (21). The vector position was also compared with the fat-fluid linear threshold discriminating between short vectors from either edematous or obese subjects falling out of the lower pole of the reference 75% tolerance ellipse, with vectors from obese subjects without edema expected to fall above the fat-fluid threshold and vectors from edematous patients that expected to fall below the fat-fluid threshold (21). The length of the vector was calculated as $|Z|=\sqrt{[(R/H)2+(Xc/H)2]}$ and the phase angle of the vector as the arctan of Xc/R.

Statistical analysis

Values are given as mean±SD. Repeated analysis of variance (ANOVA) measures with the Bonferroni test for multiple comparisons was used for paired data. The Pearson bivariate correlation analysis was used to compute the correlation between variables. The stepwise multiple linear regression was performed to evaluate the relative importance of age and the parameters of body composition on the peak GH after GHRH+ARG and IGF-I. In this analysis, we entered only those variables that had a p value <0.05 in the univariate analysis.

Data were stored and analysed using the SPSS program (Statistical Package for Social Science, release 11.01; SPSS Chicago, IL, USA). p values <0.05 were considered statistically significant.

RESULTS

The dietary intake based on an interview-administered questionnaire and the body composition of the study subjects were reported in Tables 1 and 2, respectively. No subjects stated they took exercise regularly. The soft tissue hydration, according to the RXc graph method, showed that no subject vectors were below the boundary line threshold discriminating between the obese and the oedematous, indicating a normal hydration. All vectors fell in the lower left quadrant, out of the boundary line of 75th tolerance ellipse, as expected in morbidly obese subjects with normal hydration. When subjects were considered as a whole, peak GH levels were 12.2±6.5 µg/l. According to peak GH levels at 4.2 µg/l, GHD was identified in 27.3% of the subjects (Table 2). No differences emerged in dietary intake between GHD obese subjects and normal responders (Table 1). GHD obese subjects showed a significantly higher age compared with normally responding obese subjects (Table 2). However, none of the obese subjects was over the age of 60. In GDH obese subjects BMI, waist and hip circumference, WHR, FM, and R were significantly higher, while Xc, phase angle, body cell mass (BCM), IGF-I, or IGF-I z-scores were lower when compared with normally responding obese subjects (Table 2).

In all of the obese subjects, GH peak levels showed a significant negative correlation with age, BMI and FM, and a positive correlation with IGF-I (Fig. 1, 2). GH peak showed also a negative correlation with waist and hip circumference as well as WHR (r=–0.567, r=–0.285, and r=–0.303, respectively; p<0.001).

Gender difference

According to gender, males showed a dietary intake significantly higher than females (Table 1). No differences were found in the GH peak or GHD prevalence (females: 28.2 *vs* males: 24%, respectively; p=ns) as well as in age, BMI, IGF-I or IGF-I z-scores (Table 3). As found in the normal population, male obese subjects showed significantly increased FFM and TBW compared to females, while FM was significantly lower (Table 3). No differences in waist and hip circumference and WHR were evident between males and females.

Table 1 - *Dietary intake based on interviewer-administered questionnaire in 110 morbidly obese patients according to gender and to GH peak values after GHRH+arginine (ARG) test [GH deficiency (GHD), GH peak values <4.2 µg/l].*

	Females (85)	Males (25)	Normal responders (80)	GHD (30)	p-values
Energy intake, MJ/*die*	11.4±1.6	12.7±0.8*	11.7±1.5	11.7±1.7	p<0.001
Total carbohydrate, % energy	51.9±6.7	49.7±4.5	51.4±6.5	51.3±7.2	ns
Total fat, % energy	32.7±5.5	35.8±4.8*	33.7±5.6	32.7±5.1	p<0.05
Total protein, % energy	17.5±3.3	18.6±3.2	17.1±3.2	18.1±3.4	ns

Table 2 - *Anthropometry, body composition, by bioelectrical impedance analysis (BIA), electrical variables, by bioelectrical impedance vector analysis (BIVA), and endocrine parameters in morbidly obese subjects according to GH response at the GHRH+ARG test.*

	Severe GHD GH <4.2 µg/l	Normal responders GH>4.2 µg/l	*p*-values
No. 110	30	80	
Age (yr)	38.9±13.3	29.6±10.4	p<0.001
BMI (kg/m²)	44.4±3.3	40.5±4.6	p<0.001
Waist (cm)	128±5.8	115±7.8	p<0.001
Hip (cm)	133.7±5.9	129.4±8.3	p=0.1
WHR	0.96±0.3	0.89±0.79	p<0.001
FM (kg)	58.9±5.8	47.7±12.8	p<0.001
FFM (kg)	62.3±12.4	65.3±10.2	ns
R (Ohm)	444.8±58.7	412.6±59.5	p=0.01
Reactance (Ohm)	42.9±7.0	54.3±6.8	p<0.001
Phase angle (°)	6.6±0.6	7.4±0.1	p<0.001
BCM (kg)	33.6±7.2	40.5±9.7	p=0.001
TBW (l)	47.7±11.1	47.1±6.9	ns
GH peak levels (µg/l)	3.6±1.0	15.5±4.2	p<0.001
IGF-I (µg/l)	94.0±28.7	216.1±43.2	p<0.001
IGF-I z-scores	–1.3±0.38	0.01±0.5	p<0.001

BMI: body mass index; WHR: waist-to-hip ratio; FM: fat mass; FFM: free FM; R: resistance; TBW: total body water; BCM: body cell mass.

The same correlations reported previously in all obese subjects were found when the data were analyzed according to gender. In particular, in males, a significant negative correlation was present between GH peak and age (r=–0.409; $p<0.01$), BMI, waist and hip circumference, WHR and FM (r=–0.698, r=–0.888, r=–0.449, r=–0.821, and r=–0.789, respectively; $p<0.001$), while a strong significant positive correlation was present between GH peak and IGF-I (r=0.932; $p<0.001$). In females, apart from the same significant negative correlations between GH peak and age (r=–0.220; $p<0.01$), BMI, FM, waist and hip circumference, (r=–0.358, r=–0.448, r=–0.513, and r=–0.285, respectively; $p<0.001$), and a positive correlation between GH peak and IGF-I (r=0.818; $p<0.001$), a significant positive correlation also emerged with FFM (r=0.291; $p<0.001$). Conversely, there was no significant correlation between GH peak and WHR.

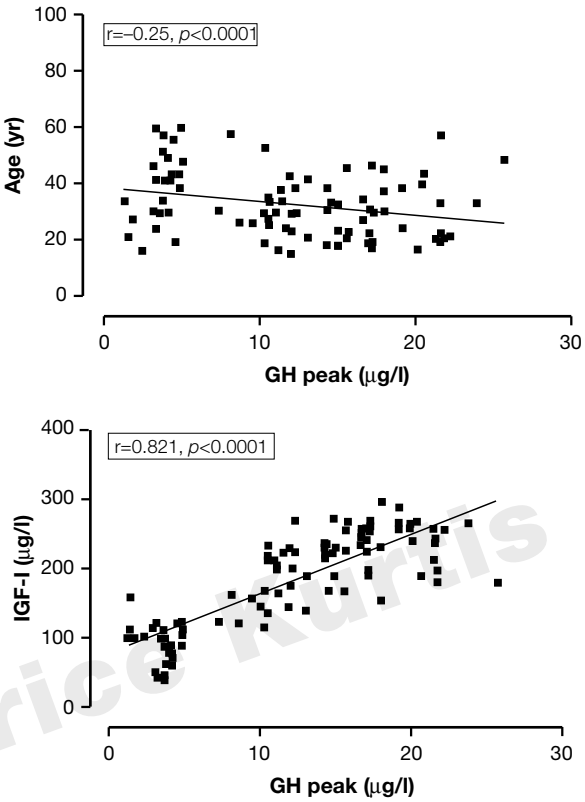

Fig. 1 - *Correlation between peak GH response to the GHRH+arginine (ARG) test and age and IGF-I levels.*

Multiple linear regression analysis study

The results of the stepwise multiple linear regression are shown in Table 4. The stepwise multiple linear regression was performed to evaluate the relative importance of age and parameters of body composition on the GH peak after GHRH+ARG and on IGF-I. Waist circumference and FM were the major determinants of GH peak levels and of IGF-I in all obese subjects (Table 4).

DISCUSSION

The results of this study show that 27.3% of morbidly obese subjects were GHD when tested with the GHRH+ARG test using the recently proposed GH peak cut-off point for obese subjects of 4.2 µg/l. Moreover, GHD obese subjects and normal responder obese subjects represent quite different populations. In fact, all anthropometric variables were different in the two subject groups, and the GH peak correlated with body composition abnormalities evaluated by BIA and BIVA. In particular, as reported previously by our group, the unchanged

J. Endocrinol. Invest. 29: 536-543, 2006

Table 3 - *Anthropometry, body composition, by bioelectrical impendance analysis (BIA), electrical variables, by bioelectrical impendance vector analysis (BIVA), and endocrine parameters in morbidly obese subjects according to gender.*

	Females	Males	*p* values
No. 110	85	25	
Age (yr)	32.7±11.9	30.2±12.3	ns
BMI (kg/m²)	42.0±4.9	40.1±3.0	ns
Waist (cm)	119.9±8.9	116.7±10.1	ns
Hip (cm)	131.5±8.5	128.0±4.9	ns
WHR ratio	0.91±0.79	0.91±0.65	ns
FM (kg)	53.5±11.6	42.9±12.5	*p*<0.001
FFM (kg)	60.3±7.3	78.5±8.9	*p*<0.001
R (Ohm)	423.9±62.6	412.4±54.2	ns
Reactance (Ohm)	51.9±9.2	48.6±4.9	ns
Phase angle (°)	7.2±1.0	7.1±0.8	ns
BCM (kg)	38.1±9.9	40.5±8.2	ns
TBW (l)	44.3±5.2	57.5±8.5	*p*<0.001
GH peak levels (µg/l)	12.5±6.7	11.4±5.5	ns
IGF-I (µg/l)	178.6±66.7	197.0±69.8	ns
IGF-I z-scores	–0.8±0.8	–0.3±0.8	ns

BMI: body mass index; WHR: waist-to-hip ratio; FM: fat mass; FFM: free FM; R: resistance; TBW: total body water; BCM: body cell mass.

length of the impedance vector indicated a normohydration status for all of the subjects in our study group (21, 22). Therefore, it is possible to rule out that subtle variations of the hydration of soft tissues can propagate errors in the prediction of body composition from the reference methods to the predictive equations used in conventional BIA.

It is well-known that altered GH axis in obesity is paralleled by changes in body composition, ie, increased visceral fat, and decreased lean body mass and bone mineral density, closely resembling those reported to occur in organic GHD patients. The insulin tolerance test (ITT) has been considered the gold standard GH stimulation test in the diagnosis of GHD; however, the combined GHRH+ARG test has recently been the most commonly used alternative test to ITT (14, 23-26). In this context, it is widely accepted that the GH response to the provocative test is influenced by obesity *per se* (2, 4-8), and that GHD in obesity may be a functional reversible status.

In fact, recently, BMI has been shown to affect the GH response to the GHRH+ARG test (8, 15, 16). Biller et al. (15), by comparing five different GH stimulation tests for diagnosing GHD in adults, reported a GH peak cut-off point after GHRH+ARG to differentiate GHD patients and controls at 4.1 µg/l. This result was recently confirmed by Corneli et al. (16) in an Italian cohort of lean, overweight and obese subjects, and a cut-off limit of 4.2 µg/l in obese individuals was assumed. In our study group, we confirm that using more restrictive criteria, GHD is present in about 1/3 obese subjects. In this context, it is possible to conclude that the combined GHRH+ARG test with the recently assumed 4.2 µg/l cut-off value is also reliable enough to detect GHD in morbidly obese subjects without evident hypopituitarism; moreover, it can differentiate this

Table 4 - *Results of the stepwise multiple linear regression analysis.*

			β-coefficient	t	*p*-values
Morbidly obese subjects					
	GH peak				
		Waist	–0.30	–3.69	0.000
		FM	–0.27	–2.56	0.012
		BMI	–0.08	1.46	0.146
		Age	–0.18	–1.53	0.130
	GH peak				
		Waist	–0.04	–4.36	0.000
		FM	–0.02	–1.75	0.085
		BMI	–0.03	0.99	0.325
		Age	–0.00	–0.41	0.663

BMI: body mass index; FM: fat mass.

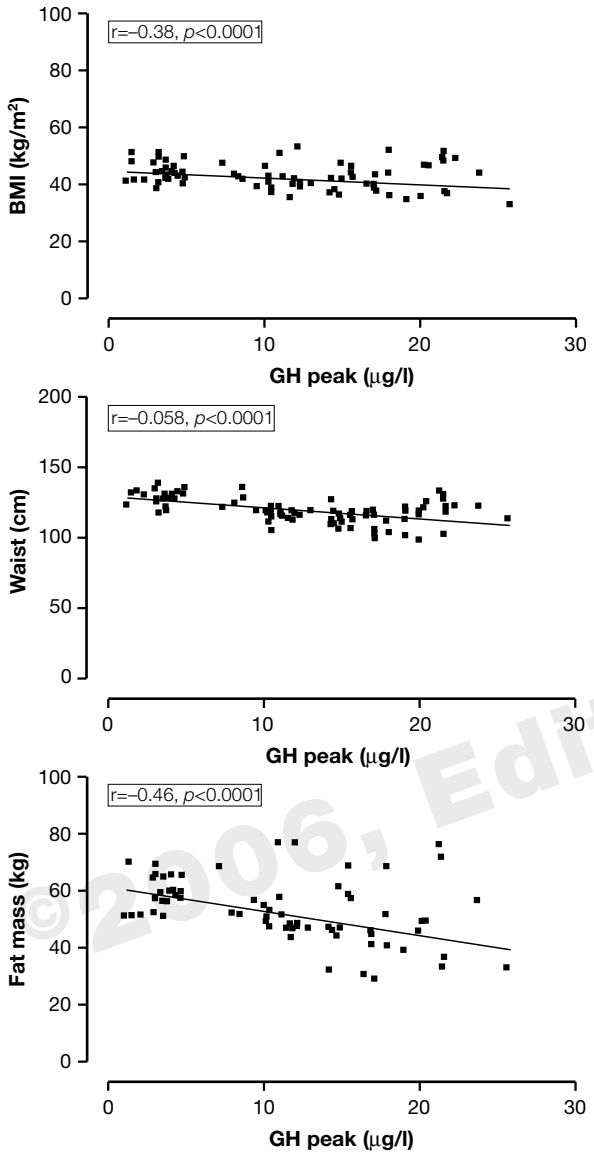

Fig. 2 - *Correlation between peak GH response to the GHRH+arginine (ARG) test and body mass index (BMI), waist circumference and fat mass (FM).*

subgroup from a larger group of morbidly obese subjects where only a variable degree of GH secretory defects may be present as the consequences of their altered metabolic balance, ie free fatty acid metabolism (27-29).

Iranmanesh et al. (30) reported that both GH secretion and clearance in men were proportional to the degree of obesity. Therefore, it was of some interest to investigate in morbidly obese subjects too whether or not a similar relationship was present between the severity of the GH secretory defect evaluated by the GHRH+ARG test and the degree of obesity or, alternatively, with anthropometric differences, such as the abdominal fat distribution. In this contest, we observed that either waist circumference or WHR were significantly higher in GHD obese group than in normal responder obese group, thus suggesting that an increased visceral fat area in GHD could be important in influencing the reduction in stimulated GH secretion. However, the positive correlation between WHR and indices of visceral fat distribution assessed by computerized tomography evidenced in normal weight subjects are less evident in obese subjects. Therefore, WHR cannot be considered as a reliable index of visceral/sc fat distribution in obese individuals, particularly if they are females (31). In our study group, the peak GH levels showed a significant inverse correlation with age, BMI, waist circumference, and FM (32). However, at multiple regression analysis waist circumference and FM were the major determinants of GH peak. In this context, our data are in line with the evidence that in adult patients with hypopituitarism, the severity of GHD measured as peak GH after the combined GHRH+ARG test is correlated with the degree of bone loss, abnormality of lipid profile or severity of cardiac impairment, and changes in body composition (10-13).

The presence of the highly significant effect of FM on GH secretory defect suggests that, similarly to the relevance of FFM in the assessment of levothyroxine dosage in the treatment of thyroid diseases (33), not only BMI but also body composition variables, such as FM, might be employed to calculate the amount of recombinant human GH to be administered.

Apart from BMI and age, the diagnostic capability of different provocative tests in detecting GHD in obese subjects has also been reported to be influenced by many other potentially confounding effects, such as gender, sleep, nutritional status, stress and physical exercise. To investigate the relevance of gender and reduce the influence of different confounding variables, we evaluated the GH secretory response separately in female and male morbidly obese subjects with comparable BMI, age, physical exercise and nutritional status. As expected, male and female obese subjects showed significantly different anthropometric variables, such as FM, FFM and TBW. However, the GH peak or GHD prevalence were the same in both sexes. The lack of the well-known gender influence (34, 35) on GH response might not be surprising, taking into account that both male and female subjects were affected by a severe and long-standing obesity responsible for a deep impairment of the normal GH secretion. The evidence of significant correlation between GH peak

J. Endocrinol. Invest. 29: 536-543, 2006

levels and FFM in females and not in males, suggests some speculations. In particular, body composition in morbidly obese males, with particular regard to FFM, might be influenced by different anabolic mechanisms other than GH, nutrition, or physical exercise. Moreover, unexplored variables, such as androgens, should be taken into account.

In conclusion, we demonstrated that, using the more restrictive cut-off limit of peak GH response to GHRH+ARG test for obese subjects proposed by Biller et al. and Corneli et al. (15, 17), in our study group of morbidly obese subjects 27.3% were GHD. According to this threshold, GHD subjects compared with normal responders showed a significantly different body composition. Moreover, the secretory defect evaluated by the GHRH+ARG test is correlated not only to BMI, but also to different anthropometric variables, and waist circumference and FM were the major determinants.

ACKNOWLEDGMENTS

This study was partially supported by a grant from SERONO Italy.

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