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Prevalence of the metabolic syndrome in moderately-severely obese subjects with and without growth hormone deficiency

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ABSTRACT. ***Background and aim:*** **There is a considerable heterogeneity in metabolic phenotype among equally obese subjects. Impaired GH secretion is frequent in obese patients, with GH secretion reduced up to levels that are comparable to those found in adult patients with organic GH deficiency (GHD). Low GH status exerts detrimental effects on metabolic abnormalities in organic GHD patients. The aim of this observational, retrospective study was to investigate the prevalence of the metabolic syndrome (MetS) in moderately-severely obese subjects who met criteria for GDH (GHD) and in those with normal GH status (GH sufficient: GHS).** ***Methods and results:*** **One-hundred and ninety-five moderately-severely obese individuals partecipated, 149 women and 46 males [body mass index (BMI) 43.0±4.4 kg/m^2 aged 34.3±11.8 yr] . Main outcome measures were: GH peak after GHRH plus arginine test, IGF-I, MetS parameters according to National Cholesterol Education Program criteria. Fifty-five subjects (27.3%) were GHD (49 females and 6 males). The prevalence of MetS parameters was 70.9% in GHD subgroup *vs* 52.9% in GHS (χ^2=5.281; *p*=0.02) and the likelihood of MetS was highest in GHD subgroup (odds ratio: 2.174; 95% confidence interval 1.113 to 4.248). At the multiple regression analysis either GH peak or IGF-I were the major determinants of waist circumference (β=–0.380, t=-6.110 and β=–0.326, t=–4.704, respectively; *p*<0.001), while age and IGF-I were the major determinants of MetS (β=0.255, t= 3.342, and β=–0.282, t=–3.270; *p*=0.02, respectively).** ***Conclusions:*** **Among moderately-severely obese individuals the prevalence of the MetS was higher in GHD than in GHS subjects. Thus, in obese subjects, GH status investigation might be considered in the clinical evaluation of their metabolic risk profile.**

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INTRODUCTION

There is increasing recognition that the disease risks associated with obesity might be not uniform with a considerable heterogeneity in metabolic phenotype among equally obese subjects (1-4). Visceral obesity is a central feature of metabolic syndrome (MetS) (5). Although currently lacking a universal definition of the diagnostic criteria, MetS is very common in the general population (6, 7). In particular, in north-eastern Italy MetS prevalence ranged from 17.5% to 33.5% according to different diagnostic criteria (8). Apart from the most commonly reported obesity-related co-morbidities (9, 10) obesity is also associated with multiple endocrine perturbations (11, 12). The combined endocrine abnormalities exert profound effects on adipose tissue metabolism and distribution (1, 11, 13-15). In recent years evidence has accumulated that obese subjects have functional GH deficiency (GHD) based on standard criteria used in hypopituitarism (16-21), generally reversible after sustained weight loss (22, 23). Indeed, GH secretion is reduced up to levels that are comparable to those found in adult patients with organic GHD (24), with both central and peripheral factors, such as free fatty acid, accounting for GH secretion abnormalities (14, 17-20). Although it is debatable whether low GH status is a consequence, or a cause, of obesity, a reverse relationships has been also reported to occur since low levels of GH contributed to central obesity and related metabolic abnormalities because of the absence of potent lipolytic GH actions (18-20). Both GH and IGF-I have major anabolic and lipolytic actions on muscle and adipose tissue, respectively (25, 26). The detrimental effects of alterations in the GH/IGF-I axis on the cardiovascular system has been extensively demonstrated in GHD (27, 28), as well as the improvement in several metabolic abnormalities and body composition after GH treatment in GHD patients (29-31). Finally, GH treatment has been proved to exert favorable effects in reducing the adverse metabolic consequence of obesity (32) or visceral obesity in both men and women (33, 34). We previously reported that 27.3% of a population of 110 severely obese subjects exhibited a low GH/IGF-I status associated with significantly higher fat mass (FM) and waist circumference, and lower fat free mass (FFM) than obese subjects with normal GH secretion (35). Taking into account the detrimental effects of low GH status in metabolic abnormalities in GHD patients, the aim of the present study was to investigate the possible maladaptive role of the functional GHD in obesity by comparing the prevalence of the MetS in moderately-severely obese subjects who met criteria for GHD with their counterpart with normal GH status [GH sufficient (GHS)].

SUBJECTS AND METHODS

Inclusion criteria

For the purpose of this study the inclusion criteria were:
- moderate-severe obesity;
- age between 18-65 yr to limit the influence of age on GH/IGF-I axis;

Key-words: GH deficiency, metabolic syndrome, moderate-severe obesity; .

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- absence of diabetes mellitus, liver or renal failure, cancer, and acute or chronic inflammatory diseases based on a complete medical examination and laboratory investigations;
- absence of any type of medication;
- absence of any other pituitary deficiency (36).

Patients

The study population included 195 consecutive moderately-severely obese individuals, 149 women (76.4%) and 46 men (23.6%), referred to our Department from January 1st, 2005 to December 31st, 2007 to participate in a weight loss program and/or for evaluation as bariatric surgery candidates. Mean body mass index (BMI) and age were 43.1±4.5 kg/m^2 (range 35.5-57) and 34.3±11.8 yr (range 18-65), respectively.

Study design

This is a retrospective study planned in a cohort of obese individuals to investigate the influence of GH and/or IGF-I secretory status on MetS prevalence. All patients gave their written informed consent to the study, which had been approved by the Ethics Committee of the University "Federico II" of Naples School of Medicine, Italy. The study design was made in accordance with the Helsinki II Declaration for study on human experimentations.

Main outcome measures

Main outcome measures were MetS parameters, according to the modified National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria (37), GH peak after GHRH plus arginine test (GHRH+ARG), IGF-I.

Study protocol

1. GH status was the major criteria of the study. Thus, obese individuals were divided into GHS and GHD subgroups according to GH peak after GHRH+ARG test, and IGF-I levels were determined.
2. To relate the metabolic parameters to the GH status, we analyzed how many subjects in 2 subgroups suffered from MetS categorizing the subjects by the modified NCEP ATP III, according to the following schema: any 3 of the following: fasting plasma glucose (FPG) ≥100 mg/dl; waist circumference ≥102 cm (men), 88 cm (women); triglycerides ≥150 mg/dl; HDL cholesterol <40 mg/dl (men), <50 mg/dl (women); blood pressure 130/85 mmHg (or treated hypertension) (37). The percentage of subjects with each parameters of the MetS were calculated.
3. Obesity-related anthropometric measurements made with the patients wearing only underwear without shoes. Standing height was measured to the nearest cm using a wall-mounted stadiometer. Body weight was determined to the nearest 50 g using a calibrated balance beam scale. BMI was calculated as weight (kg) divided by height squared (m^2) and used as an index for obesity. Measurements of the waist circumference were taken at the mid-point between umbilicus and xiphoid. The ideal body weight (IBW) was calculated according to the Lorenz's formula: IBW= [height (cm) – 100] – [height (cm) – 150)/2].
4. In pre-menopausal women, data were obtained during the early follicular phase, 5-7 days after spontaneous menses. Fasting glucose, serum insulin, total triglycerides, LDL- and HDL-cholesterol were measured. Fasting blood glucose was determined with an enzymatic test using glucose-oxidase. Type 2 diabetes was defined as a fasting blood glucose level ≥126 mg/dl confirmed in two separate determinations (38). Serum insulin was measured by a solid-phase chemiluminescent enzyme immunoassay using commercially available kits (Immunolite Diagnostic Products Co, Los Angeles, CA, USA), the upper limit of normal range is 15.6 µU/ml. The oral glucose tolerance test (OGTT) was performed using 75 g dextrose. Blood samples were obtained at 0, 30, 60, 90, and 120 min for plasma glucose and insulin measurements. The normal glycemic response to the OGTT was defined according with the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (38). Homeostatic model of assessment (HOMA) index was calculated according to Matthews et al. (39). Lipid status was determined using enzymatic diagnostic kits from Boehringer Mannheim (cholesterol oxidase phenol 4-aminoantipyrine peroxidase and glycerol phosphate oxidase-p-aminophenazone). The GH-IGF-I axis evaluated by measuring the GH peak after GHRH+ARG and assay of circulating IGF-I. The GHRH+ARG was performed according to Ghigo et al. (40): 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] (Serono, Rome, Italy) was given at a dose of 1 mg/kg as iv bolus at time 0. Blood samples were taken every 15 min from –15 up to 90 min. In obese patients, the GH response after ARG+GHRH was classified as follows: GHD when the GH peak is ≤4.2 µg/l and GHS when GH peak >4.2 µg/l (21). Serum GH levels (1 mg/l=45.4 pmol/l) were measured by immunoradiometric assay (IRMA) using commercially available kits (HGH-CTK-IRMA, Sorin, Saluggia, Italy). The sensitivity of the assay was 0.02 mg/l. The inter- and intra-assay variation coefficients (CV) were 2.9-4.5% and 2.4-4.0%, respectively. Serum IGF-I levels was measured by IRMA after ethanol extraction using Diagnostic System Laboratories Inc. (Webster, Texas, USA). The sensitivity of the assay was 0.8 µg/l; the normal range in 20-40 and 41-60 was 110-494 and 100-300 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 inter-assay CV were 8.2, 1.5, and 3.7% for low, medium, and high points on the standard curve, respectively. Since IGF-I levels are related to age, to analyze the relationships between IGF-I levels and the other variables we calculated the SD score (SDS) of IGF-I levels according to age (zSDS). To this aim, we calculated the mean and SD of IGF-I levels in adults (21-40 yr) and middle-aged (41-65 yr) women and men (41). IGF-I levels were classified as deficient (IGFD) when the SDS from the mean was <–2 for age and gender and sufficient when the SDS ranged from >–2 to 2 (28).

Statistical analysis

Values are given as mean±SD. The variables were tested for normal distribution using the Kolmogorow Smirnov test. Variables not normally distributed have been logarithmically transformed as log. Student's t test was used to analyze differences in MetS parameters between the GHS and GHD groups. Differences in MetS parameters between the two study groups were also analyzed using analysis of variance with the Bonferroni *post-hoc* test after adjusting for age and BMI. Pearson's χ^2 test was used to analyze the association between MetS prevalence and GH status (GHS and GHD). The presence of independent and significant associations between parameters of MetS (fasting blood

glucose, waist circumference, triglycerides, HDL-cholesterol, mean systolic blood pressure, mean diastolic blood pressure) and GH status (GHS and GHD) in the study groups were analyzed using multiple logistic regression and odd ratio (OR) and 95% confidence interval (CI) were computed. GH status was considered the independent variable, parameters of MetS were dependent variables. Using waist circumference as dependent variable, a multiple linear regression analysis was performed with the enter selection methods to evaluate the relative importance of GH peak after ARG+GHRH and IGF-I, age and BMI. Using MetS as dependent variable, a second multiple linear regression analysis was performed with the enter selection method to evaluate the relative importance of age, anthropometric variables, and GH status. In this analysis, we entered only those variables that had a *p*-value <0.01 in the univariate analysis. *p*-values <0.05 were considered statistically significant. Data were stored and analyzed using the SPSS program (Statistical Package for Social Science, release 13.0; SPSS Chicago, IL, USA).

RESULTS

One-hundred and forty subjects (71.7%) were GHS (100 females and 40 males) and 55 subjects (27.3%) were GHD (49 females and 6 males). The GHS and GHD study subgroups then were sorted according to BMI as follows: out of 55 moderately obese subjects (BMI≥35; 28.2%), 47 (85.5%) were GHS and 8 (14.5%) GHD ($p<0.001$); out of 118 severely obese subjects (BMI≥40; 60.5%), 79 (66.9%) were GHS and 39 (33.1%) GHD ($p<0.001$); out of 22 super obese subjects (BMI≥50; 11.3%), 14 (63.6%) were GHS and 8 (36.4%) GHD ($p=0.411$). IGFD (42 subjects) was found in 76.3% GHD subjects.

Table 1 reports the results of the metabolic status of the 2 groups. BMI and waist circumference were significantly higher for the GHD *vs* GHS subgroup. Among metabolic parameters fasting glucose, HOMA, and diastolic blood pressure values were significantly higher for GHD *vs* GHS subgroup. Type 2 diabetes mellitus was diagnosed in 12 (8.3%) GHS subjects (5 patients with fasting blood glucose >126 mg/dl in two determinations and 7 patients after OGTT) and 11 (20%) GHD subjects (3 patients with fasting blood glucose >126 mg/dl in two determinations and 8 patients after OGTT). An impaired glucose tolerance was evidenced in 18 (12.5%) GHS subjects and 6 (10.9%) GHD subjects. The prevalence of MetS parameters and MetS in GHS and GHD subgroups was reported in Figure 1. In particular, 70.9% GHD subgroup *vs* 52.9% GHS meet the criteria for MetS ($\chi^2=5.281$; $p=0.02$) and the likelihood of MetS was highest in GHD subgroup (OR: 2.174; 95% CI 1.113 to 4.248). In all patients, age and BMI were related to waist circumference ($r=0.314$; $p<0.01$, and $r=0.182$; $p<0.05$), while anthropometric (BMI, excess of body weight, and waist circumference) and metabolic parameters (plasma lipids FPG and blood pressure) correlated significantly with GH peak and IGF-I (Table 2), with the waist circumference showing the highest correlation after adjusting for age and BMI (GH peak r=–0.415 and –0.535 in male and female, respectively; IGF-I r=–0.482 and –0.475 in male and female, respectively; $p<0.001$), while GH status maintained a significant correlation with MetS also after adjusting for waist circumference ($r=0.146$; $p=0.047$). At the multiple regression analysis, either GH peak or IGF-I were the major determinants of waist circumference (β=–0.380, t=–6.110 and β=–0.326, t=–4.704, respectively; $p<0.001$), while age and IGF-I were the major determinants of MetS (β=0.255, t=3.342, and β=–0.282, t=–3.270; $p=0.02$, respectively).

Table 1 - *Obesity-related anthropometric measurements and metabolic components of the moderately-severely obese subjects divided according to GH status*

No.	GHS 140	GHD 55	*p*
Age (yr)	33.8±12.4	35.6±10.7	0.356
BMI (kg/m²)	42.7±4.5	44.3±4.3	0.025
Excess body weight (%)	88.3±23.1	94.6±23.1	0.101
Waist circumference (cm; males)	113.2±6.8	122.8±11.6	0.005
Waist circumference (cm; females)	114.9±8.7	128.7±6	<0.001
Triglycerides (mg/dl)	162.7±73	168 ±64	0.641
Total cholesterol (mg/dl)	198.5±42	191±46	0.249
LDL-cholesterol (mg/dl)	114.4±39.5	110±43.4	0.509
HDL-cholesterol (mg/dl; males)	54±12.1	51.1±20.7	0.621
HDL-cholesterol (mg/dl; females)	50.3±12.1	47.5±11.7	0.789
Fasting plasma glucose (mg/dl)	90.7±18	98.0±28.5	0.033
2-h glucose (mg/dl)	134.0±46.8	139.0±64.0	0.595
Insulin (μU/ml)	16.7±9	18.8±13.1	0.212
HOMA index	3.8±2.3	4.9±5.3	0.035
IGF-I (μg/l)	206.9±64.2	75.7±21.8	<0.001
Systolic blood pressure (mmHg)	132±15.8	136.8 ±16.3	0.059
Diastolic blood pressure (mmHg)	81.6±11.4	87.3±11.7	0.002

GHS: GH sufficient; GHD: GH deficiency. According to the GH response after arginine+GHRH, GHD was diagnosed when the GH peak is ≤4.2 μg/l. BMI: body mass index; HOMA: homeostasis modell assessment.

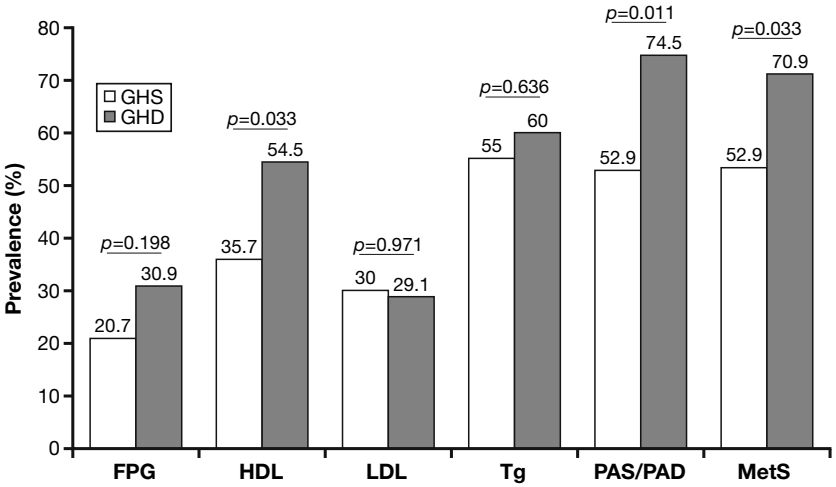

Fig. 1 - *The prevalence of metabolic syndrome (MetS) components and MetS in GH-sufficient (GHS) and GH-deficient (GHD) subgroups. FPG: fasting plasma glucose >100 mg/dl; HDL: HDL-cholesterol <40 and <50 mg/dl in males and females, respectively; LDL: LDL-cholesterol >130mg/dl; Tg: triglycerides >150 mg/dl; SBP/DBP: systolic blood pressure/diastolic blood pressure >130/85.*

DISCUSSION

The purpose of this study was to examine the relationship between the MetS prevalence and GH status in a cohort of moderately-severely obese individuals. Our data demonstrate that when moderately-severely obese subjects are sorted according to GH status, among obese individuals who met criteria for GHD the prevalence of the MetS was significantly higher than that of GHS subjects. It is noteworthy that the prevalence of moderately obese subjects is significantly higher in GHD subgroup, whereas the prevalence of severely and super-obese subjects was similar in GHD and GHS subgroups, confirming that BMI *per se* is not a major determinant of MetS prevalence. In particular, among MetS variables only low HDL-cholesterol and high blood pressure were more prevalent in GHD than in GHS subgroups, while higher than normal waist circumference values were evident in both subgroups. To exclude also any age-related decline in GH and IGF-I secretion, GH status was investigated using a test like GHRH+ARG testing that has been proved to be unaffected by age and gender (40), and IGF-I values were calculated as SDS IGF-I. Furthermore, there were no differences in age between the 2 groups. It is well known that a low GH status deteriorates the metabolic risk profile in GHD patients (27-31, 42) and that obesity and that abdominal/visceral adiposity were also the central finding in both the MetS and untreated GHD in adults with hypopituitarism (14, 43). Moreover, GH treatment has been proved to be effective in obese and/or abdominally obese subjects in reducing visceral adiposity (32-34).

Obesity might be considered as a heterogeneous disor-

Table 2 - *Correlations between obesity-related anthropometric measurements and metabolic components with GH peak and IGF-I in the moderately-severely obese group.*

	GH peak	*p*	IGF-I	*p*
Age (yr)	–0.165	0.021	–0.455	<0.001
BMI (kg/m²)	–0.135	0.061	–0.205	0.004
Excess body weight	–0.111	0.124	–0.237	0.001
Waist circumference (cm; male)	–0.526	<0.001	–0.625	<0.001
Waist circumference (cm; female)	–0.553	<0.001	–0.527	<0.001
Triglycerides (mg/dl)	–0.057	0.428	–0.211	0.003
Total cholesterol (mg/dl)	0.024	0.744	–0.339	<0.001
LDL-cholesterol (mg/dl)	–0.008	0.907	–0.403	0.327
HDL-cholesterol (mg/dl; male)	0.192	0.202	0.148	<0.014
HDL-cholesterol (mg/dl; females)	0.132	0.108	0.428	<0.001
Fasting plasma glucose (mg/dl)	–0.092	0.201	–0.242	0.001
2-h glucose (mg/dl)	–0.047	0.568	0.033	0.686
Insulin (μU/ml)	–0.159	0.026	–0.012	0.868
HOMA index	–0.160	0.025	–0.089	0.218
Systolic blood pressure (mmHg)	–0.234	0.004	–0.452	<0.001
Diastolic blood pressure (mmHg)	–0.266	0.001	–0.454	<0.001

GH peak, GH response after arginine+GHRH; BMI: body mass index; HOMA: homeostasis model assessement.

der endowed with a large number of health problems, both independently or in association with other diseases (1-4, 9-10). However, the metabolic risk associated with obesity might vary widely and a new metabolically normal subset of the obese has been recently described (1-4). Apart from the central role of body size phenotypes (4, 44), a number of study (45-48) have examined the metabolic status of subjects with varying stages of obesity. However, the evaluation of metabolic risk according to severity of obesity is still debatable and still unknown factors have been suggested to occur (47). Finally, it has been also suggested that MetS and not obesity per se might be predictive of the future cardiovascular risk in obesity (48).

Multiple endocrine abnormalities are reported to occur in obesity (11, 12). Some of these abnormalities are considered to be consequences of obesity. In particular, the complex and interrelated mechanisms involved in the low GH state in human obesity are not yet completely understood. However, although the reduction in GH secretion in obesity seemed to be not an absolute or permanent defect, it is well known that the GH/IGF-I axis in obese subjects is altered at different levels, by both central and peripheral factors (14, 16-19).

It is however conceivable that, on turn, endocrine perturbations might act as contributing and amplifying factors to the different metabolic risk profile in obese individuals (11, 12, 14-19). Thus, a number of obesity-related metabolic alteration might also be determined as consequences of the endocrine abnormalities. In this context, a hypothetical pathogenetic role of glucocorticoids in human obesity has been suggested due to several clinical, metabolic, and cardiovascular similarities between the abdominal obesity phenotype and syndromes of endogenous or exogenous hypercortisolism (13, 49, 50). Similarly, a causal role of a functional GHD could be hypothesized as an example of maladaptation involved in the etiopathogenesis of obesity and obesity-related metabolic alterations (14, 16, 17, 50). We previously reported that severely obese patients with deficiency in the GH/IGF-I axis showed a significantly different body composition with higher FM and waist circumference and lower FFM than patients with a normal GH/IFG-I axis (35). Moreover, an increase in non-traditional predictors of cardiovascular events has been reported in a group of healthy obese women meeting criteria for GHD (51). This evidence is particularly relevant in severe obese patients considering the protective effect of IGF-I against cardiovascular disease, atherosclerosis (52, 53) and diabetes (54). In line with this evidence, distinct effects of GH and IGF-I on several features of the MetS have been recently reported (55), and low plasma IGF-I levels have been recently accounted as one of the possible determinant of a an early atherosclerosis observed in metabolically healthy but obese women (56). There are several limitations to our study. Mainly, causality cannot be evidenced in a cross-sectional study. Therefore, although our data evidenced that criteria for GHD ascribed to obese subjects a different cardiovascular risk profile, we cannot exclude that MetS prevalence is related to obesity *per se* rather than to the low GH status. Moreover, all the subjects included in the study meet the waist circumference as a criterion for MetS, independently of GH status. In this context, it has been recently evidenced the uselessness of waist circumference as a criterion of MetS in severely obese women (46). However, waist circumference values were higher in GHD than in GHS subgroups and showed the highest association with a low GH status. Waist circumference showed also a significant correlation with age and BMI. However, after adjustment for age and BMI, at the multivariate analysis both GH peak and IGF-I remained the major determinants of waist circumference, and age and IGF-I were the major determinants of MetS independently of anthropometric variables. Therefore, in line with a recent study in a population of lean, overweight and obese men (57), also in moderate-severe obese subjects waist circumference is a stronger predictor of GH response to standardized testing than weight. On the other hand, it has been to consider that should the visceral fat be the only determinant of GHD, all obese subjects with waist circumference higher than gender-specific cut off would have GHD. This is not the case, as no more than about 30% morbidly obese subjects generally met the criteria for GHD.

In summary, the results of our study show that MetS prevalence is higher in moderately-severely obese subjects who met criteria for GHD than in GHS subgroup. However, the cross-sectional nature of this data does not allow us to infer causality but lets hypothesize the relevance of the association of a low GH status with increased metabolic risk factors in severe obesity independently from BMI *per se*. This is a new evidence that needs to be further evaluated, in line with the increased risk of cardiovascular events in men and women with organic hypopituitarism. Nevertheless, our finding suggests that additional investigation for GH status might be warranted in obese subjetcs and considered in the clinical evaluation of their metabolic risk profile.

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