OBES SURG (2010) 20:211–220
DOI 10.1007/s11695-009-9926-3

CLINICAL RESEARCH

Relationship Between Growth Hormone/Insulin-Like Growth Factor-1 Axis Integrity and Voluntary Weight Loss After Gastric Banding Surgery for Severe Obesity

Silvia Savastano · Luigi Angrisani · Carolina Di Somma · Francesca Rota · Maria Cristina Savanelli · Teresa Cascella · Francesco Orio · Gaetano Lombardi · Annamaria Colao

Received: 3 February 2009 / Accepted: 10 July 2009 / Published online: 28 July 2009

Abstract
Background The aim of this observational study was to determine, in a retrospective analysis, whether growth hormone (GH) and insulin-like growth factor-1 (IGF-1) at baseline or changes in the GH/IGF-1 axis after laparoscopic adjustable gastric banding (LAGB) is associated with weight loss and body composition changes in severely obese nondiabetic patients.
Methods Weight loss (expressed as percent excess weight loss [EWL%]), anthropometry, body composition by bioelectrical impedance analysis (BIA), serum IGF-1, and GH peak after GH-releasing hormone (GHRH) plus arginine (ARG) test were measured and expressed as standard deviation scores (SDS) of reference values in 104 women and 36 men, age (mean ± SD) 34±11 and 30.2±11 years, and BMI 44±5.7 and 39±3.2, respectively, before and 6 months after LAGB.
Results After LAGB, 25% of women and 22.5% of men had GH deficiency, while 30.8% of women and 33.3% of men had IGF-1 deficiency or insufficiency. The median EWL was 36.8% in women and 40.0% in men. In both genders, percent decrease of waist circumference, EWL, and fat mass (FM) and percent increase of fat-free mass (FFM) was greater in patients with normal GH secretion and IGF-1 levels. The GH peak after GHRH + ARG, IGF-1 levels, and IGF-1 SDS were inversely correlated with EWL% ($r=-0.50$, $r=-0.53$, and $r=-0.42$, respectively; $p<0.0001$) and percent FM ($r=-0.41$, $r=-0.36$, and $r=-0.35$, respectively; $p<0.0001$). In stepwise linear regression analysis, the GH peak after GHRH + ARG was the major determinant of EWL% ($p<0.0001$) and FM ($p=0.001$).
Conclusions The efficacy of LAGB was greater in the patients with a normal GH response to GHRH + ARG and with normal IGF-1 levels. The percent of FM, FFM, and EWL were significantly correlated with the GH response to GHRH + ARG and with IGF-1 levels.

Keywords Obesity · Fat mass · Fat-free mass · GH · IGF-I · LAGB

S. Savastano (✉) · C. Di Somma · F. Rota · M. C. Savanelli · T. Cascella · G. Lombardi · A. Colao
Division of Endocrinology, Department of Molecular and Clinical Endocrinology and Oncology, University of Naples Federico II,
via S. Pansini 5,
80131 Naples, Italy
e-mail: sisavast@unina.it

L. Angrisani
Department of Surgery, S. Giovanni Bosco Hospital of Naples,
via F.M. Briganti 255,
80144 Naples, Italy

F. Orio
Endocrinology, Parthenope University of Naples,
via Ammiraglio F. Acton 38,
80133 Naples, Italy

C. Di Somma
SDN Foundation IRCCS,
Naples, Italy

Introduction

There is a strict link between deficiency of growth hormone (GH) secretion and obesity [1–6]. On one hand, adult patients with GH deficiency (GHD) characteristically develop increases in abdominal obesity, total cholesterol, triglycerides, and fibrinogen levels and a decrease in HDL cholesterol levels, so depicting the "metabolic syndrome" [7–12]. On the other hand, obese patients have multiple endocrine abnormalities that parallel changes in body composition, i.e., increased visceral fat and decreased fat-free mass (FFM) [3–

5, 13, 14]. In obese patients, either 24-h spontaneous GH secretion or stimulated GH release or both are impaired, including GH secretion in response to all traditional pharmacological stimuli acting on the hypothalamus, such as insulin-induced hypoglycemia or arginine (ARG), and/or targeting directly the somatotrophs by exogenous GH-releasing hormone (GHRH) [15–17].

Although GH secretion in obesity may be suppressed as a consequence of increased energy intake and is reversible [18], it has nonetheless been speculated that reduced GH secretion may further maintain overweight because of the absence of potent lipolytic GH actions.

In fact, changes in GH and insulin-like growth factor-1 (IGF-1) secretion modify the response to surgery in obesity. Edén Engström et al. [19] investigated a well-characterized group of severely obese patients before and after weight reduction by Roux-en-Y gastric bypass (RYGBP) surgery and examined their basal levels of GH and IGF-1 in relation to body mass index (BMI) and markers of insulin sensitivity. RYGBP resulted in a decreased BMI from 45±6 to 35±6 and 32±6 kg/m^2 at 6 and 12 months, respectively; GH and IGF-1 increased at 6 months in women and at 12 months in both sexes by >300% and 11%, respectively. Despite some drawbacks in the study design, these results are interesting since they demonstrated that surgically induced weight loss only partially restores GH secretion.

In agreement with other authors [3, 4, 14], we reported that the GH secretory status influences body composition in obese patients [20]. In another prospective study that we conducted in 72 premenopausal obese women undergoing laparoscopic adjustable gastric banding (LAGB), we found that, 6 months after surgery, when the initial catabolic state should have already been overcome, 19.4% of 72 female patients were still diagnosed as GH-deficient and IGF-1-deficient (according to age normative ranges) and another 19.4% normalized their GH response to the GHRH + ARG test, but IGF-1 levels were still below normal ranges [21]. Interestingly, percent change of excess weight loss (EWL %) and fat mass (FM) lost were higher in 61.1% patients who normalized their GH/IGF-1 axis after LAGB than in the remaining 38.9% who did not. An important patho-physiological finding was that postoperative IGF-1 levels were the strongest determinant of percent changes of FM, FFM, and EWL in stepwise linear regression analysis [21].

In the present observational retrospective study, we extended our previously published database of 72 severely obese premenopausal women [21] to all our eligible patients who underwent LABG in order to determine the potential negative effect of persistently reduced GH and IGF-1 levels on loss of body weight and changes of body composition. We found that the prevalence of persisting GH and/or IGF-1 levels below the normal range 6 months after surgery was associated with a significantly reduced EWL%.

Patients and Methods

Inclusion Criteria

For the purpose of this study, the inclusion criteria were: (1) age between 16 and 60 years to limit the influence of age on the GH/IGF-1 axis; (2) normal glucose tolerance during standard oral glucose tolerance test to minimize any effects of glucose homeostasis on IGF-1 variability [22, 23]; and (3) inclusion criteria for bariatric surgery proposed by the 1991 National Institutes of Health Consensus Development Panel Report [24].

Exclusion Criteria

(1) Liver or renal failure, cancer, and acute or chronic inflammatory diseases were excluded by a complete medical examination and laboratory investigations; (2) chronic treatment with any type of medications, including oral contraceptives or hormone replacement therapy; (3) organic pituitary deficiency [25]; (4) bulimia nervosa according to DSM-IV; (5) ulcers demonstrated by esophagogastroduodenoscopy; (6) soft tissue overhydration, preliminarily evaluated by the BIA Vector by using the BIVA software [26], as previously reported [20, 21].

Patients

Out of 254 moderately and severely obese patients coming to our department since January 1, 2003 to December 31, 2007 and subjected to LAGB 6 months before admission, 140 patients (104 women and 36 men with baseline BMI of 43.1±5.4 kg/m^2 and postoperative BMI of 35.6±4.8 kg/m^2) with a mean age of 32.9±11.5 years (range 16–57 years) were included. Ten women were postmenopausal, while all premenopausal women were studied during the early follicular phase, 5–7 days after spontaneous menses. Patients were evaluated under standardized conditions after an overnight fast and were referred to our outpatient clinic.

Study Design

This is an observational, retrospective study. In the present study, we extended our previously published database of 72 severely obese premenopausal women [21] to all our eligible patients who underwent bariatric surgery. Then we combined the data having used the identical study protocol [21]. All patients gave their written informed consent to undergo every investigation mentioned in the study and they also agreed that their data would be used for scientific purposes. The study design was made in accordance with the Helsinki II Declaration for Study on human experimentation.

The main outcome measures were percent loss of excess body weight (EWL%), changes in FM, FFM, serum IGF-1, and GH peak after GHRH + ARG test, compared to normative, reference values. A secondary objective was determining relationships between GH/IGF-1 axis and EWL% and changes in FM and FFM.

Study Protocol

In the 2 weeks preceding LAGB and 6 months after, the following parameters were measured:

1. Anthropometric measurements, performed with the subjects shoeless, wearing only underwear.
2. Standing height was measured to the nearest centimeters 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 (in kilograms) divided by the height squared (in square meters) and used as an index for obesity. Waist circumference was defined as the largest circumference of the mid-abdomen. Ideal body weight (IBW) was calculated according to Lorenz' formula [$\mathrm{IBW} = \text{in women, height(cm)} - 100 - (\text{height(cm)} - 150/2)$; in men, $\text{height (cm)} - 100 - (\text{height(cm)} - 150/4)$] and was used to determine excess weight.
3. Body composition was determined by conventional bioelectrical impedance analysis (BIA) and by bioelectrical impedance vector analysis (BIVA) applying the software provided by the manufacturer [26]. Resistance (*R*) and reactance (Xc) were measured by a single investigator with a single-frequency 50-kHz bioelectrical impedance analyzer (BIA 101 RJL, Akern Bioresearch, Florence, Italy) according to the standard tetrapolar technique. All vectors fell in the lower left quadrant, outside the boundary line of the 75th tolerance ellipse, as expected in morbidly obese patients with normal hydration [27].
4. The GH/IGF-1 axis was evaluated by measuring the circulating IGF-1 levels and the GH peak after GHRH + ARG. The GHRH (1–29, Geref, Serono, Rome, Italy) + ARG (arginine hydrochloride; Salf, Bergamo, Italy) test was performed according to Ghigo et al. [28]. The GH response after GHRH + ARG was termed "deficient" (GHD) when the GH peak was ≤4.2 μg/L and "sufficient" (GHS) when the GH peak was >4.2 μg/L [17]. 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 0.02 μg/L. The intra-assay and inter-assay coefficients of variations (CVs) were 4.5% and 7.9%, respectively. Plasma IGF-1 was measured by IRMA after ethanol extraction at Diagnostic System Laboratories Inc. (Webster, Texas, USA). The normal ranges in men aged ≤20, 21–30, 31–40, 41–50, and 51–60 years old were 180–625, 118–475, 102–400, 100–306, and 95–270 μg/l, respectively, whereas in women they were 151–530, 118–450, 100–390, 96–288, and 90–250 μg/l, respectively [29]. The sensitivity of the assay was 0.8 μg/l. The intra-assay CVs were 3.4%, 3.0%, and 1.5% for low, medium, and high points of the standard curve, respectively. The inter-assay CVs were 8.2%, 1.5%, and 3.7% for low, medium, and high points of the standard curve. The *z* score or standard deviation score (SDS) for age and gender was also calculated according to our population reference values [29]. For the purpose of this study, IGF-1 levels were classified as "normal" when higher than −2 SD and "deficient" when lower than −2 SD [30]. However, a subanalysis was also performed in those patients having an IGF-1 SDS between −1.5 and −2 SD to investigate a possible role of insufficient IGF-1 levels.
5. A questionnaire to investigate eating pattern, smoking habits, and physical exercise (no exercise; ≤2–3 h/week; ≥2–3 h/week) was administered to all patients. Dietary intake was assessed by Winfood® (Medimatica software medico 1999, Rome, Italy) and described elsewhere [20, 21, 31].

LAGB All patients were operated at the Department of Surgery, S. Giovanni Bosco Hospital, Naples. The adjustable gastric banding device (Lap-Band™ System; Inamed Health, Santa Barbara, CA, USA) [32] was inserted laparoscopically according to Angrisani [33]. To minimize postoperative vomiting, the band was left completely unfilled at surgery [34]. The band was gradually inflated after weight stabilization (<4 kg of weight lost in the last month). At discharge, patients were instructed to follow a solid diet of "permitted" foods and a list of rules specifically developed for patients with gastric restriction [34]. After LAGB, to reduce any expected nutrition-driven influence on body composition and GH/IGF-1 axis, we used a well-balanced mildly hypocaloric diet with healthy food choices in all our patients coupled with conservative postoperative band management, as also previously reported [21]. In particular, previous investigations showed that nitrogen balance was not maintained in obese patients when energy intake was restricted to less than 4.6 MJ/day [35]. Thus, the diet was adapted for an energy intake of 5.7 MJ/day (55% carbohydrate, 25% fat, 20% protein, 30 g fiber) and moderate–intensity activity (brisk walking for 30–45 min/day) has been encouraged. Compliance was monitored by weekly telephone consultations and monthly control of food in which participants kept a record of their daily food intake. The repeated dietary assessments

demonstrated good nutritional compliance with behavioral changes of dietary and activity habits. Individual requirements were estimated from resting metabolic rate and physical activity pattern. Resting energy expenditure was measured by indirect calorimetry.

The study was approved by the Ethical Committee of the University of Naples Federico II School of Medicine, Italy.

Statistical Analysis

The statistical analysis was performed by the StatDirect Statistical Software (version 2.6.2 of April 23, 2007, Cheshire, UK; http://www.statsdirect.com/update.htm). Data distribution was analyzed by the Kolmogorov–Smirnov test. Values are given as the mean ± SD unless otherwise specified.

From a first analysis, we realized that our cohort was significantly represented by women who were more obese than the men (Table 1). Therefore, to avoid gender interference, the subsequent analysis was performed in women and men separately. According with the median values of EWL recorded 6 months after LAGB, the patients were classified as having a greater (group A) or lower (group B) EWL than the median for women and men. Then, the prevalence of GH and/or IGF-1 deficiency was calculated in the two groups. Comparison between these two groups was performed by Student's *t* test for unpaired data. We also determined whether baseline conditions were associated with EWL post-LAGB according with baseline GH and IGF-1 status. Comparison among different age and BMI groups was performed by the Kruskal–Wallis test followed by the Dunn's test for all pairs of columns. Pearson's correlation (the 95% confidence interval [95%CI] for *r*) was used to investigate the correlation between postsurgery GH peak after GHRH and IGF-1 levels as raw data and SDS. Furthermore, we first corrected for age, BMI, waist circumference, and FM variables the correlation between EWL, GH peak, and IGF-1 SDS. After, to analyze the major determinant of EWL between GH peak and IGF-1 SDS, we performed a multiple regression analysis with backward selection. Two-sided p values of <0.05 were considered to be significant.

Results

Patients' Profile Before Surgery

Before LAGB, 42 patients (30%) were diagnosed with GHD and ten (7.1%) were diagnosed with IGF-1 deficiency with no difference between women and men (Table 1). Another 14 patients (10%) had IGF-1 insufficiency (overall prevalence of IGF-1 insufficiency 17.1%). There were more women in this series and they were more obese than the men. Women had higher BMI, excess body weight (EBW), and FFM and lower FM than men. These differences did not depend on age since the number of cases above 50 years was similar in the two groups (seven and three, respectively; $p=0.96$).

Efficacy of LAGB

All patients completed the study and there were no postoperative complications. The composition of the diet corresponded to dietary prescriptions in all cases but none of the patients reported exercising regularly.

Median EWL% was 37 in women vs 40 in men (Table 2; not significant). The absolute EWL was greater in women, reflecting their higher preoperative BMI.

When considering the characteristics before LAGB, in the female population, the patients achieving a higher EWL were younger and less obese, both in terms of BMI, EBW, and waist circumference, than those achieving a lower EWL. In contrast, in the male series, the patients achieving a higher EWL were similar for anthropometric and body composition measurements as those achieving a lower EWL. In agreement with the EWL%, a significant reduction of waist circumference was only observed in the women while in the men no difference was observed and, similarly, no difference in the percent FM and FFM was noted (Table 2). Both in women and in men, the prevalence of postsurgery GHD was higher in the patients achieving a lower EWL% (Table 2). As for IGF-1 deficiency or insufficiency, there were no statistically significant differences in either sex. When the patients with IGF-1 deficiency and insufficiency were grouped together, a greater EWL% was associated with higher prevalence of normal IGF-1 levels only in women ($n=3$ vs 14; $p=0.008$) with a borderline significant finding in men ($n=1$ vs 6; $p=0.092$).

Efficacy of LAGB According to Presurgery GH and IGF-1 Secretory Status

In both men and women, while the percent decrease in BMI, waist circumference, EWL, and FM and the increase in percent FFM were significantly greater in patients with abnormal preoperative GH and IGF-1 secretion, BMI was significantly higher only in patients with abnormal preoperative GH secretion (Tables 3 and 4).

Efficacy of LAGB According to Postsurgery GH and IGF-1 Secretory Status

In women (Table 5), 25% of the patients were diagnosed as GHD and 30.8% (16.3) were IGF-1 deficient or insuffi-

Table 1 Patients' profile before LAGB

	Women	Men	*p* value
Number	104	36	<0.0001
Age (years)	33.8±11.4	30.2±11.3	0.104
BMI (kg/m^2)	44.±5.7	39±3.2	<0.0001
Waist circumference (cm)	119.0±7.9	113.5±3.5	<0.0001
Excess body weight (kg)	57.1±13.2	44.1±10.0	<0.0001
FM (%)	50.6±5.4	55.9±8.8	<0.0001
FFM (%)	49.3±5.4	44.3±8.8	<0.0001
Peak GH response (μg/L)	10.0±6.9	10.8±5.3	0.528
GH deficiency [*n* (%)]	34 (32.7)	8 (22.2)	0.330
IGF-1 (μg/L)	160.9±70.0	192.1±64.2	0.020
IGF-1 (SDS)	−0.68±0.93	−0.60±0.76	0.643
IGF-1 deficiency [*n* (%)]	9 (8.6)	1 (2.8)	0.49
IGF-1 insufficiency [*n* (%)]	8 (7.7)	6 (16.7)	0.2

According to the GH response after GHRH + ARG, GH deficiency was diagnosed when the GH peak is ≤4.2 μg/L. IGF-1 deficiency was diagnosed when the IGF-1 concentrations have an SD score <−2 for age and gender; IGF-1 insufficiency when the IGF-1 concentrations have SD scores <−1.5 to −2.0 for age and gender

cient. Concordance between GH and IGF-1 secretion failure was observed only in 16 of 26 patients (57.6%). While BMI did not differ in patients with normal or abnormal GH and IGF-1 secretion, the percent decrease in BMI, waist circumference, EWL%, and percent FM and increase of percent FFM was significantly greater in patients with normal GH secretion and normal IGF-1 levels (Table 3). Only in GHD women, the percent decrease of waist circumference was significantly lower than that recorded in those with a normal GH secretion (Table 3).

In men (Table 6), 22.5% of the patients were diagnosed as GHD and 33.3% were IGF-1 deficient or insufficient. Concordance between GH and IGF-1 secretion failure was observed in seven of eight patients (87.5%). BMI and waist circumference were significantly lower in patients with normal than in those with abnormal GH and IGF-1 secretion; the percent decrease in both parameters was significantly greater in patients with normal GH secretion but did not reach significance as related to IGF-1 secretion. EWL%, percent FM, and increase of percent FFM were significantly greater in the patients with normal GH secretion and normal IGF-1 levels (Table 3). As for net loss of kilograms of excess body weight, it was higher in patients with a normal IGF-1 secretion.

Correlation Study

In the entire series, 6 months after LAGB, a significant direct correlation was found between EWL% and the GH peak after GHRH + ARG (r=0.50; 95%CI=0.36–0.61; p<0.0001; Fig. 1 top), IGF-1 levels (r=0.53; 95%CI=0.40–0.64; p< 0.0001) and IGF-1 SDS (r=0.42; 95%CI=0.27–0.55; p< 0.0001; Fig. 1 bottom) but not with changes from baseline of GH peak (r=−0.02; 95%CI=−0.18 to 0.15; p=0.84) and IGF-1 levels (r=0.13; 95%CI=−0.03 to 0.29; p=0.12). Similarly, the GH peak after GHRH + ARG (r=−0.41; 95%CI=−0.54 to −0.26; p<0.0001), IGF-1 levels (r=−0.36; 95%CI=−0.49 to −0.20; p<0.0001), and IGF-1 SDS (r= −0.35; 95%CI=−0.48 to −0.19; p<0.0001) were significantly inversely correlated with percent FM. Multiple regression

Table 2 Results of anthropometry and body composition by BIA before LAGB, according to the median gender-related percent decrease of excess body weight lost (EWL)

	Women (n=52)			Men (n=18)		
	EWL <37%	EWL >37%	*p* value	EWL <40%	EWL >40%	*p* value
Age	36.3±11.9	31.4±10.5	0.028	32.3±13.4	27.5±6.7	0.18
BMI (kg/m^2)	46±6.1	42±4.2	<0.0001	39±3.2	38±3.2	0.17
Waist circumference (cm)	121.3±7.6	116.6±7.6	0.002	112.6±8.2	114.4±4.3	0.41
Excess body weight (kg)	63±13.2	51±10.3	<0.0001	47±9.5	42±10.1	0.13
FM (%)	50.6±5.0	50.7±5.8	0.925	57.5±9.1	54.2±8.3	0.27
FFM (%)	49.4±5.0	49.3±5.8	0.925	42.4±9.1	46.3±8.3	0.27
Prevalence of GH deficiency [*n* (%)]	27 (51.9)	7 (13.5)	<0.0001	7 (38.9)	1 (5.6)	0.045
Prevalence of IGF-1 deficiency [*n* (%)]	7 (13.5)	2 (3.8)	0.16	1 (5.6)	0 (0.0)	1.000
Prevalence of IGF-1 insufficiency [*n* (%)]	7 (13.5)	1 (1.9)	0.066	5 (27.8)	1 (5.6)	0.180

Table 3 Results of anthropometry and body composition by BIA in 104 women after LAGB, according to the presurgery prevalence of GH deficiency, IGF-1 deficiency, or IGF-1 insufficiency

	GHD	GHS	*p* value	IGF-1 deficient/insufficient[a]	IGF-1 normal	*p* value
n (%)	34 (32.7)	70 (67.3)		17 (16.3)	87 (83.7)	
BMI						
kg/m²	38±4.8	35±5.3	0.009	37±2.8	36±5.7	0.41
Percent change	−16.3±4.2	−19.8±4.7	<0.0001	−15.2±3.2	−19.4±4.8	<0.0001
Waist circumference						
cm	116.3±7.7	103.2±8.0	<0.0001	114.4±8.0	105.9±9.7	0.001
Percent change	−8.7±5.7	−12.9±6.9	0.003	−7.5±3.9	−13.3±7.1	0.05
Excess body weight loss						
kg	19±5.4	22±5.5	0.010	17±2.8	22±5.7	<0.0001
Percent change	32.7±8.9	41.7±12.2	<0.0001	31.4±7.4	40.4±12.2	0.002
FM (%)	46.5±7.4	41.3±10.2	0.009	48.3±7.1	41.8±9.8	0.008
FFM (%)	53.5±7.4	58.7±10.2	0.009	51.7±7.1	58.2±9.8	0.008

[a] Of the 17 patients who were IGF-1 deficient/insufficient, nine had clear deficiency and eight had insufficiency

analysis revealed that the postoperative GH peak after GHRH + ARG was the major determinant of EWL% ($p<0.0001$) and FM ($p=0.001$; Table 7).

Discussion

Our results at 6 months demonstrate that weight loss after LAGB, a well-established and beneficial bariatric procedure to cure moderately and severely obese patients, was greater in subjects with an intact preoperative response of GH to GHRH + ARG in the presence of normal serum IGF-1 levels corrected for age and sex. EWL%, an important outcome indicator, was significantly correlated with GH peak. Similar findings were made regarding FM and FFM measured by BIA. In multivariate analysis, GH peak contributes about 25% of the variance in EWL%, whereas serum IGF-1 contributed 18% in our study population. We detected a prevalence of 22–25% of severe GHD in men and women, and a 31–33% prevalence of low levels of serum IGF-1 that we arbitrarily considered below −1.5 SD from the mean.

At baseline in our study population, women had higher BMI, EBW, and FFM and lower FM than men, likely reflecting the possibility that a number of different parameters, such as endocrine variables, nutritional habits, or exercise training, might account for obesity phenotypic variability. In particular, obesity-related male hypogonadism with increased aromatase activity and testosterone/estradiol shunt [36], female hyperandrogenism, hypothala-

Table 4 Results of anthropometry and body composition by BIA in 36 men after LAGB, according to the presurgery prevalence of GH deficiency, IGF-1 deficiency, or IGF-1 insufficiency

	GHD	GHS	*p* value	IGF-1 deficient/insufficient[a]	IGF-1 normal	*p* value
n (%)	8 (22.2)	28 (77.8)		7 (19.4)	29 (80.6)	
BMI						
kg/m²	36±2.0	33±2.5	0.002	35±1.8	33±2.7	0.028
Percent change	−10.6±5.8	−14.3±3.2	0.023	−10.0±6.0	−14.3±3.2	0.12
Waist circumference						
cm	113.8±5.8	103.6±5.8	<0.0001	114.0±8.8	103.9±5.9	0.001
Percent change	−5.2±3.8	−8.3±3.7	0.045	−5.2±4.1	−8.2±3.7	0.63
Excess body weight loss						
kg	14±7.8	17±4.8	0.14	13±7.8	17±4.8	0.052
Percent change	26.8±12.1	40.7±9.3	0.001	26.0±12.9	40.4±9.2	0.002
FM (%)	62.5±6.5	47.9±8.7	<0.0001	62.5±7.0	48.4±9.0	0.001
FFM (%)	37.5±6.5	52.1±8.7	<0.0001	37.5±7.0	51.6±9.0	0.001

[a] Of the seven patients with abnormal IGF-1 levels, one had clear deficiency and six had insufficiency

Table 5 Results of anthropometry and body composition by BIA in 104 women after LAGB, according to the postsurgery prevalence of GH deficiency, IGF-1 deficiency, or IGF-1 insufficiency

	GHD	GHS	*p* value	IGF-1 deficient/insufficient[a]	IGF-1 normal	*p* value
n (%)	26 (25.0)	78 (75.0)		32 (30.8)	72 (69.2)	
BMI						
kg/m^2	37±3.4	35±5.7	0.079	37±4.0	36±5.8	0.33
Percent change	−15.8±3.2	−19.6±4.9	<0.0001	−16.3±3.7	−19.7±4.9	<0.0001
Waist circumference						
cm	115.1±8.1	104.9±9.2	<0.0001	112.9±7.7	105.0±9.9	<0.0001
Percent change	−6.5±2.5	−13.2±7.0	<0.0001	−7.4±4.1	−13.3±7.1	0.49
Excess body weight loss						
kg	19±3.7	22±5.9	0.004	19±4.3	22±5.8	0.0005
Percent change	31.9±7.1	41.0±12.4	<0.0001	34.1±8.9	40.8±12.2	0.0006
FM (%)	48.8±7.0	41.0±9.7	0.003	47.8±6.9	40.8±10.0	<0.0001
FFM (%)	51.2±7.0	58.9±9.7	0.003	52.2±6.9	59.2±10.0	<0.0001

[a] Of the 32 patients with abnormal IGF-1 levels, 15 had clear deficiency and 17 had insufficiency

mus–pituitary–adrenal axis hyperactivation, or GH hyposecretion might be sufficient to explain per se obesity phenotypic variability. This state, on turn, might have a great influence on body composition, especially in a nonexercise-trained obese male population, such as generally Southern Italy male obese population is reported to be [37]. Adams et al. also reported a marked difference in the BMI–percent fat relation observed in men and women across the entire range of BMI [38]. In line with this evidence, when comparing men and women body composition according to the gender-related EWL (Table 2), the percent FM differences are reduced in the subgroup of subjects with EWL higher than median values (p=0.054).

In previous studies, we already reported that the GH response to GHRH + ARG was significantly correlated with body composition before and after LAGB [20, 21] and that the patients who normalized their GH response to GHRH + ARG had a higher EWL% and a better body composition profile [21]. Similarly, in the latter study, we had already observed the persistence of low IGF-1 levels in association with an overall restoration of the GH response to the pharmacological stimulus. The same findings have been noted as well as by other authors after biliopancreatic diversion [39] or after RYGBP [19]. In the first case, however, low IGF-1 levels could be interpreted as a consequence of the catabolic state induced by malabsorptive surgical procedures, in analogy with other different catabolic conditions [40, 41]. Conversely, in patients undergoing RYGBP, a mixed restrictive and malabsorptive intervention, about one third of the patients had impaired

Table 6 Results of anthropometry and body composition by BIA in 36 men after LAGB, according to the postsurgery prevalence of GH deficiency, IGF-1 deficiency, or IGF-1 insufficiency

	GHD	GHS	*p* value	IGF-1 deficient/insufficient[a]	IGF-1 normal	*p* value
n (%)	8 (22.2)	28 (77.8)		12 (33.3)	24 (66.7)	
BMI						
kg/m^2	35.9±2.0	32.7±2.5	0.002	34.8±2.2	32.7±2.7	0.026
Percent change	−10.6±5.8	−14.3±3.2	0.023	−16.3±3.7	−15.0±2.5	0.22
Waist circumference						
cm	113.8±5.8	103.6±5.8	<0.0001	110.1±8.1	103.8±6.5	0.016
Percent change	−5.2±3.8	−8.3±3.7	0.045	−6.6±4.0	−8.1±3.8	0.28
Excess Body Weight Loss						
Kg	13.7±7.8	17.1±4.8	0.14	13.1±6.8	18.0±4.3	0.012
Percent change	26.8±12.1	40.7±9.3	0.001	28.3±12.6	42.2±7.5	<0.0001
FM (%)	62.5±6.5	47.9±8.7	<0.0001	57.8±10.3	47.9±8.7	0.005
FFM (%)	37.5±6.5	52.1±8.7	<0.0001	42.2±10.3	52.1±8.7	0.005

[a] Of the 12 patients with abnormal IGF-1 levels, four had clear deficiency and eight had insufficiency

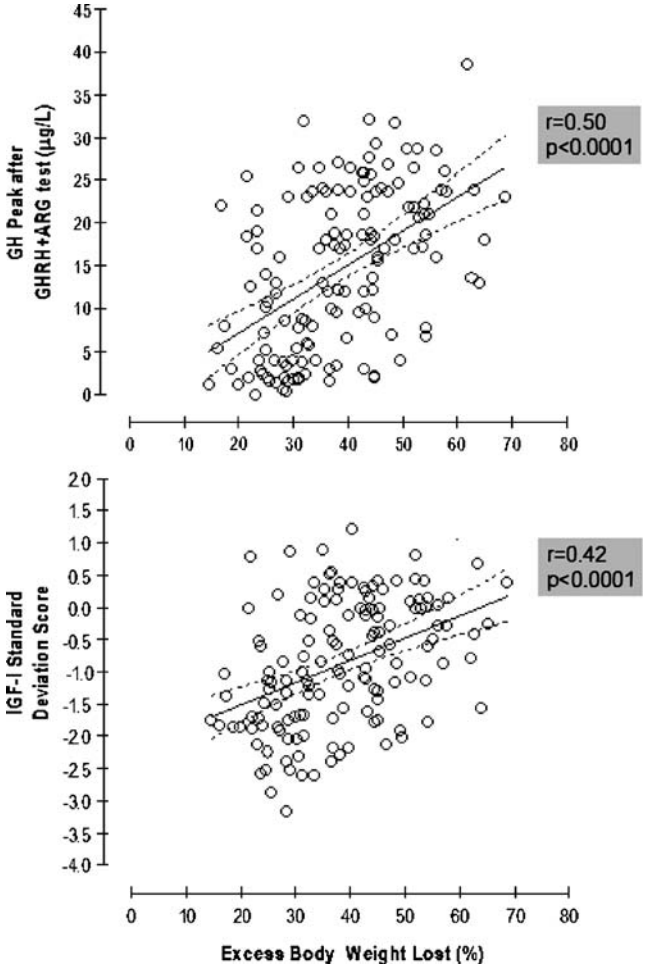

Fig. 1 Correlation between excess body weight lost and GH peak after GHRH + ARG (*top*) and IGF-1 levels expressed as SDS (*bottom*)

fasting glucose or diabetes before surgery [19]. A number of well-known factors had been reported to interfere with IGF-1 metabolism, such as age, gender, obesity, weight loss, malnutrition, or an altered glucose metabolism [22, 23, 42–44]. Therefore, it was of some interest to report the persistence of low IGF-1 levels in a group of severely obese patients with normal glucose tolerance after a nonmalabsorptive surgical procedure followed by a careful postoperative monitoring of their calorie intake [21]. Our previous study, however, had the limitation that it included women only. As significant gender differences exist in GH secretory status, the present retrospective study was designed to investigate the influence of the GH and IGF-1 secretory status on body composition in a larger number of moderately and severely obese patients, including both females and males. In that, this study extended our previous observations and confirms the discrepancy between the GH response to the pharmacological stimulus and circulating IGF-1 levels, further supporting a role for GH/IGF-1 axis as a maladaptive epiphenomenon of obesity. In this study, the IGF-1 reference ranges differ slightly from those that we reported in our previous series [21]. In particular, we used −1.5 SD as arbitrary cutoff to define a new category of obese patients with IGF-1 insufficiency, in analogy with the definition of partial GHD and in line with the clinical consequences of this condition, particularly on body composition [30]. In our previous study, however, IGF-1 was the major determinant of body composition changes. In the present investigation, conversely, the major determinant of EWL% and FM was the GH peak after GHRH + ARG, in line with previous evidence on the severity of clinical abnormalities in adult GHD [9, 10, 45]. In this context, the presence of the well-known dimorphism in GH secretion might have likely accounted for this difference. As in our previous study, however, diabetic patients were excluded from the analysis and all data were obtained 6 months after surgery, when weight is considered to be relatively stabilized after the initial acute negative energy balance.

The possibility that subtle, unrecognized failures of the GH/IGF-1 axis negatively influence the response to any surgical procedure for obesity, including LAGB, is highly likely. A general opinion is that weight loss normalizes the GH response to all stimuli [3, 4, 18]. However, IGF-1 secretion has been reported to show a long-lasting impairment, likely due to the actual caloric intake and thus reflecting the postoperative state of semistarvation. Our data demonstrate that a proportion of patients, that is approximately 25% in our cohort, had persistent abnormalities in the GH/IGF-1 axis. Therefore, semistarvation might certainly have contributed to lower IGF-1 levels, but at the same time GH secretion should have increased by inducing a kind of regulatory GH resistance state. This is not the finding we reported in our patients as the GH stimulation test does not fully support the existence of a specific (or isolated) GH resistance only. However, although low GH

Table 7 Results of the multiple regression analysis

Outcome	Parameters	β	r	t	p value
Percent excess body weight loss	GH peak after GHRH + ARG	0.49	0.32	4.01	<0.0001
	IGF-1 SDS	1.97	0.14	1.68	0.0946
Percent FM	GH peak after GHRH + ARG	−0.38	−0. 28	−3.36	0.001
	IGF-1 SDS	−1.67	−0.13	−0.58	0.12

values might be merely of a regulatory nature, just as low T_3 values in sick, nonthyroid illness patients are regulatory and not true hypothyroidism, the finding itself as well as any other consequence of this on body composition and surgical outcome have never been reported so far. In light of this, our results are original and suggest another mechanism to interpret data related to surgical outcome in severely obese subjects.

In conclusion, in the current study, we clearly demonstrated that the EWL% and changes in FM and FFM 6 months after LAGB were significantly associated with GH peak after GHRH + ARG and/or deficient/insufficient IGF-1 levels. Therefore, our data indicate that patients undergoing LAGB may require a preliminary study of the endocrine profile with special attention to the GH axis, using the GHRH + ARG test and a measurement of IGF-1 levels.

Acknowledgments This study has been partially granted by the Ministry of University Research of Italy, PRIN, with the number 2007N4C5TY_005. We thank Dr. Emanuele Nicolai (SDN Foundation IRCCS, Naples – Italy) for kindly providing DXA analyses.

References

1. Veldhuis JD, Iranmanesh A, Ho KK, et al. Dual defects in pulsatile growth hormone secretion and clearance subserve the hyposomatotropism of obesity in man. J Clin Endocrinol Metab. 1991;72:51–9.
2. Johannsson G, Bengtsson BA. Growth hormone and the metabolic syndrome. J Endocrinol Invest. 1999;22(5 Suppl):41–6.
3. Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormones secretion in experimental animals and the human. Endocr Rev. 1998;19:717–97.
4. Scacchi M, Pincelli AI, Cavagnini F. Growth hormone in obesity. Int J Obes Relat Metab Disord. 1999;23:262–71.
5. Maccario M, Tassone F, Grottoli S, et al. Neuroendocrine and metabolic determinants of the adaptation of GH/IGF-1 axis to obesity. Ann Endocrinol (Paris). 2002;63:140–4.
6. Savastano S, Di Somma C, Mentone A, et al. Growth hormone insufficiency in obese patients. J Endocrinol Invest. 2006;29:536–44.
7. de Boer H, Blok GJ, Van der Veen EA. Clinical aspects of growth hormone deficiency in adults. Endocr Rev. 1995;16:63–86.
8. Carroll PV, Christ ER, Bengtsson BA. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. J Clin Endocrinol Metab. 1998;83:382–95.
9. Colao A, Cerbone G, Pivonello R, et al. The growth hormone (GH) response to arginine plus GH releasing hormone test is correlated to the severity of lipid profile abnormalities in adult patients with GH deficiency. J Clin Endocrinol Metab. 1999;84:1277–82.
10. Colao A, Di Somma C, Cuocolo A, et al. The severity of growth hormone deficiency correlates with the severity of cardiac impairment in 100 adult patients with hypopituitarism: an observational, case-control study. J Clin Endocrinol Metab. 2004;89:5998–6004.
11. Gola M, Bonadonna S, Doga M, et al. Clinical review: growth hormone and cardiovascular risk factors. J Endocrinol Invest. 2005;90:1864–70.
12. Abs R, Feldt-Rasmussen U, Mattsson AF, et al. Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults—a KIMS database analysis. Eur J Endocrinol. 2006;155:79–90.
13. Pasquali R, Vicennati V, Gambineri A, et al. Hormones and pathophysiology of obesity. Eat Weight Disord. 2001;6(3 Suppl):9–20.
14. Franco C, Bengtsson BA, Johannsson G. Visceral obesity and the role of the somatotropic axis in the development of metabolic complications. Growth Horm IGF Res. 2001;11(Suppl A):S97–102.
15. Biller BM, Samuels MH, Zagar A, et al. Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab. 2002;87:2067–79.
16. Qu X, Gonzalo TGI, Al Sayed MY, et al. Influence of body mass index and gender on GH responses to GHRH plus arginine and insulin tolerance test. J Clin Endocrinol Metab. 2005;90:1563–9.
17. Corneli G, Di Somma C, Baldelli R, et al. The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. Eur J Endocrinol. 2005;153:257–64.
18. Rasmussen MH, Hviderbg A, Juul A. Massive weight loss restores 24-hour growth hormone release profiles and serum insulin-like growth factor-I levels in obese patients. J Clin Endocrinol Metab. 1995;80:1407–15.
19. Edén Engström B, Burman P, Holdstock C, et al. Effects of gastric bypass on the GH/IGF-1 axis in severe obesity—and a comparison with GH deficiency. Eur J Endocrinol. 2006;154:53–9.
20. Savastano S, Di Somma C, Belfiore A, et al. Growth hormone status in obese patients and correlation with body composition. J Endocrinol Invest. 2006;29:536–43.
21. Di Somma C, Angrisani L, Rota F, et al. Growth hormone and insulin-like growth factor-i deficiency are associated with reduced loss of fat mass after laparoscopic-adjustable silicone gastric banding. Clin Endocrinol (Oxf). 2008;69:393–9.
22. Frystyk J. Free insulin-like growth factors: measurements and relationships to growth hormone secretion and glucose homeostasis. Growth Horm IGF Res. 2004;14:337–75.
23. Maccario M, Ramunni J, Oleandri SE, et al. Relationships between IGF-1 and age, gender, body mass, fat distribution, metabolic and hormonal variables in obese patients. Int J Obes Relat Metab Disord. 1999;23:612–8.
24. Anonymous. NIH Conference. Gastrointestinal surgery for severe obesity. Consensus Development Conference Panel 1991. Ann Intern Med. 1991;115:956–61.
25. Lamberts SW, de Herder WW, van der Lely AJ. Pituitary insufficiency. Lancet. 1998;352:127–34.
26. Kotler DP, Burastero S, Wang J, et al. Prediction of body cell mass, fat-free mass, and total body water with bioelectrical impedance analysis: effect of race, sex, and disease. Am J Clin Nutr. 1996;64:489S–97S.
27. Piccoli A, Brunani A, Savia G, et al. Discriminating between body fat and fluid changes in the obese adult using bioimpedance vector analysis. Int J Obes. 1998;22:97–104.
28. Ghigo E, Aimaretti G, Gianotti L, et al. New approach to the diagnosis of growth hormone deficiency in adults. Eur J Endocrinol. 1996;134:352–6.
29. Colao A, Di Somma C, Cascella T, et al. Relationships between serum IGF1 levels, blood pressure, and glucose tolerance: an observational, exploratory study in 404 subjects. Eur J Endocrinol. 2008;159:1–10.
30. Ho KK, 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. 2007;157:695–700.

31. Hu FB, Rimm E, Smith-Warner SA, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. Am J Clin Nutr. 1999;69:243–9.
32. Kuzmak LI. A review of seven years' experience with silicone gastric banding. Obes Surg. 1991;1:403–8.
33. Angrisani L, Lorenzo M, Esposito G, et al. Laparoscopic adjustable silicone gastric banding: preliminary results of Naples experience. Obes Surg. 1997;7:19–21.
34. Busetto L, Pisent C, Segato G, et al. The influence of a new timing strategy of band adjustment on the vomiting frequency and the food consumption of obese women operated with laparoscopic adjustable silicone gastric banding (LAP-BAND®). Obes Surg. 1997;7:505–12.
35. Oi Y, Okuda T, Koishi H, et al. Effects of low energy diets on protein metabolism studies with [15N]glycine in obese patients. J Nutr Sci Vitaminol. 1987;33:227–37.
36. Micic DD, Cubrilo KM. Obesity and male reproduction function. Obes Metabol. 2006;2:13–27.
37. della Valle E, Stranges S, Trevisan M, et al. Self-rated measures of physical activity and cardiovascular risk in a sample of Southern Italian male workers: the Olivetti heart study. Nutr Metab Cardiovasc Dis. 2004;14:143–9.
38. Adams TD, Heath EM, LaMonte MJ, et al. The relationship between body mass index and per cent body fat in the severely obese. Diabetes Obes Metab. 2007;9:498–505.
39. De Marinis L, Bianchi A, Mancini A, et al. Growth hormone secretion and leptin in morbid obesity before and after biliopancreatic diversion: relationships with insulin and body composition. J Clin Endocrinol Metab. 2004;89:74–80.
40. Lukanova A, Soderberg S, Stattin P, et al. Nonlinear relationship of insulin-like growth factor (IGF)-I and IGF-1/IGF-binding protein-3 ratio with indices of adiposity and plasma insulin concentrations (Sweden). Cancer Causes Control. 2002;13:509–16.
41. Mauras N, Haymond MW. Are the metabolic effects of GH and IGF-1 separable? Growth Horm IGF Res. 2005;15:19–27.
42. Iranmanesh A, Lizarralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol Metab. 1991;73:1081–8.
43. Veldhuis JD. Gender differences in secretory activity of the human somatotropic (growth hormone) axis. Eur J Endocrinol. 1996;134:287–95.
44. van den Berg G, Veldhuis JD, Frölich M, et al. An amplitude-specific divergence in the pulsatile mode of growth hormone (GH) secretion underlies the gender difference in mean GH concentrations in men and premenopausal women. J Clin Endocrinol Metab. 1996;81:2460–7.
45. Colao A, Di Somma C, Pivonello R. Bone loss is correlated to the severity of growth hormone deficiency in adult patients with hypopituitarism. J Clin Endocrinol Metab. 1999;84:1919–24.