CLINICAL STUDY

IGF1 modifications after bariatric surgery in morbidly obese patients: potential implications of nutritional status according to specific surgical technique

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Abstract

Objectives: IGF1 is decreased in morbidly obese (MO) patients and its changes after bariatric surgery weight loss (WL) are not well known. The aim of this study was to analyse IGF1 modifications in MO patients after WL and its relationship to ghrelin and to different types of surgeries.

Design: Retrospective follow-up study at the University Medical Center.

Methods: One hundred and nine MO patients (age 44.1 ± 9.3 , BMI 51.74 ± 8.75 kg/m²) were evaluated at baseline and 1 year after surgery: 28 sleeve gastrectomy (SG), 31 distal modified (m), and 50 ringed (r) Roux-en-Y gastric bypass (RYGBP) surgery. Changes in IGF1, IGFBP3, ratio IGF1:IGFBP3, and ghrelin were evaluated 1 year after surgery.

Results: Baseline prevalence of low IGF1 (defined by S.D. $IGF1 < -2$) was 22%, and %WL 1 year after surgery was $34.9 \pm 8.9\%$. There was a significant decrease in IGFBP3 in all the procedures, an increase in IGF1:IGFBP3 ratio in rRYGBP and SG, but total IGF1 only increased significantly in SG. Albumin concentrations decreased in mRYGBP, did not change in rRYGBP, but increased in SG after surgery. Total ghrelin concentrations increased after both RYGBPs and decreased after SG ($P < 0.05$ in all cases). The prevalence of low IGF1 decreased in SG (28.6 vs 10.1%, $P = 0.03$) and did not change in RYGPBP techniques. The %albumin change was the only dependent variable associated with the % total IGF1 change.

Conclusions: Recovery of low IGF1 after bariatric surgery was specifically related to the albumin modifications induced by surgery and was not related to ghrelin modifications.

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Introduction

Obesity, defined as an increased amount of body fat, is a chronic clinical condition (1) associated with a high burden of severe chronic comorbidities such as diabetes (2) and renal dysfunction (3). Different studies have recently demonstrated the improvement of obesity-related endocrine comorbidities after treatment with bariatric surgery (4, 5, 6, 7, 8). In this context, it has also been demonstrated that GH secretion is impaired in obese patients (4, 9). In fact, GH levels in some obese patients have been found to be as low as in adult patients with organic GH deficiency (9, 10). Somatotrophic insufficiency has been associated with cardiovascular disease and an excessive cardiovascular morbidity and mortality in those patients with untreated GH deficiency (11), so obese subjects with functional deficiency of the somatotrophic axis could also have an additional reduction in their life expectancy due to this fact.

On the other hand, this GH functional deficiency may also contribute to maintain the obese condition. The mechanisms implicated in this impaired somatotrophic status are not fully understood. GH has an important anabolic function in hepatic and muscle tissues and lipolytic actions in adipose tissue (12). Insulin-like growth factor 1 (IGF1) has been reported to be low in a substantial proportion of patients with severe obesity in association with normal or high concentrations of its binding proteins (IGFBPs), mostly IGFBP3 (9, 12). This functional GH deficiency state in obesity is not always reversed after hypocaloric diet, while weight loss (WL) obtained by bariatric surgery seems to be more effective in doing so (13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24). However, as bariatric surgery may also have a catabolic and intense impact on nutritional status, changes in IGF1 may eventually be of an unfavorable nature. To date no reported studies have analyzed the potential differential effects on GH/IGF1 of specific

bariatric surgical procedures with a diverse component of restrictive vs malabsorptive nature. Ghrelin is a stimulator of GH secretion and therefore it is interesting to evaluate the relationship of ghrelin together with IGF1 after different bariatric surgical procedures.

Our main objective was to analyze the changes in IGF1, IGFBP3, and ratio IGF1:IGFBP3 concentrations in morbidly obese (MO) patients after substantial WL after treatment with different bariatric surgical procedures. Additionally, due to the potential influence of ghrelin in IGF1 axis homeostasis, modifications of this orexigenic peptide were also evaluated.

Subjects and methods

Patients

One hundred and nine patients with morbid obesity treated in our hospital from 2007 to 2008 were included in this retrospective follow-up study; all underwent surgical treatment according to criteria for bariatric surgery formulated by the 1991 National Institutes of Health Consensus Development Panel Report (25). All patients were evaluated with standardized medical history following the institutional protocol for bariatric surgery at baseline and at 12-month after being operated. Patients were studied after achieving weight stabilization (<4 kg of WL in the last month) at 12 months. Exclusion criteria were: i) liver, cardiac, or renal failure, cancer, acute, or chronic inflammatory diseases; ii) pregnancy; iii) organic pituitary disease; and iv) use of corticoids or having known drugs that affect the GH/IGF1 axis.

Demographic and clinical data, including age, history of diabetes, and hypertension were recorded in all subjects before bariatric surgery and at 12-month follow-up. Diabetes and hypertension were defined according to ATP criteria (26). Individuals with HbA1c $>7.5\%$ were excluded; none of the patients having diabetes was under insulin treatment. BMI was calculated as weight in kilograms divided by height per square meter. Waist circumference was measured at the top of the iliac crest by the same endocrinologist in all the patients (S P).

After surgery, patients were instructed to follow a specific and standardized dietary program for postbariatric surgery, including nutritional supplements as required following current guidelines (27). Light to moderate physical activity mostly consisting of 60 min/day moderate activity (e.g. brisk walking) was encouraged in all patients; no patient followed an intense exercise regime, muscle-improving capacity exercise, or endurance training that could affect the somatotrophic axis.

Patients were treated with three different types of bariatric surgical procedure in the same hospital; there were no specific criteria for assignation of a particular surgical technique. Sleeve gastrectomy (SG) was introduced in the last year in our institution. The series included a total of 109 patients in which in 31 patients a

modified Roux-en-Y gastric bypass (mRYGBP) was performed, in 50 a ringed RYGBP (rRYGBP), and in 28 a SG. The first two techniques combine a permanent restriction of volume ingested (gastroplasty), with about 25 cc in the mRYGBP and 75 cc in the rRYGBP, and induce moderate to mild malabsorption. In mRYGBP, a truncal vagotomy was performed in all cases. In this procedure, the gastric pouch was formed by transecting the stomach vertically just left of the gastroesophageal junction, and a distal Roux-en-Y was then made 80–100 cm proximal to the ileocaecal valve as previously described (28). In rRYGBP, the gastroplasty was performed as in vertical banded gastroplasty with two stapled lines, and the Roux-en-Y was made 150 cm proximal to the ileocaecal valve and the vagus was left intact (29). The SG was performed laparoscopically using along a 32-F bougie from the angle of his to ~ 5 cm orally to the pylorus (30). The percentage of WL (%WL) was calculated as the percentage of quotient between the difference of initial weight and 12-month weight divided by initial weight. The ideal body weight (IBW) was calculated according to Lorenz's formula: in men $(\text{IBW} = (\text{height (cm)} - 100) - ((\text{height (cm)} - 150)/4))$; in women $((\text{height (cm)} - 100) - ((\text{height (cm)} - 150)/2))$. The percentage of excess body WL (EBWL) was calculated as $((\text{baseline weight} - \text{actual weight}) / (\text{baseline weight} - \text{IBW})) \times 100$.

The study was approved by the institutional ethics committee in accordance with the Declaration of Helsinki and all participants gave their written informed consent before clinical data was collected.

Measurements

Biochemical measurements Blood samples were prospectively obtained by venipuncture between 0700 and 0800 h after an overnight fast at baseline and 12 months after surgery. Albumin was measured by routine clinical chemistry test immediately after extraction. HbA1c was measured in blood samples with EDTA by HPLC using a fully automated Adams Menarini HI-AUTO A1c 8160 analyzer manufactured by Arkray (Kyoto, Japan) with an inter-assay coefficient of variation (CV) $<1.8\%$. C-reactive protein (CRP) was measured in serum samples by nephelometry using BN-ProSpect (Dade Behring, GMBH, Marburg, Germany) with an inter-assay CV $<3.7\%$. Serum samples for the hormonal measurements were immediately frozen and stored at -80°C until assayed and were analyzed together under the same analytical conditions.

Hormonal measurements Immunoreactive insulin levels were determined using an automated electrochemiluminescence immunoassay (Modular E, Roche Diagnostics GmbH); the analytical sensitivity was 0.2 mUI/l and the inter-assay CV was $<2.8\%$. Insulin resistance was assessed by using the homeostasis model

assessment of insulin resistance (HOMA-IR) and calculated by the formula: fasting insulin (mUI/l) $\times$ fasting glucose (mmol/l)/22.5. Serum total IGF1 and IGFBP3 were measured by a chemiluminiscence immunoassay (Immulite 2000, Siemens Healthcare Diagnostics Products, Llanberis, UK), standardized against WHO NIBSC 1st IRR 87/518 (1 ng/ml $\times$ 0.13 = 1 nmol/l); the sensitivity was 20 ng/ml; the intra-assay and inter-assay CV were <3.9 and <7.7% respectively. IGFBP3 was standardized against WHO NIBSC Reagent 93/560 (1 μ g/ml $\times$ 34.78 = 1 nmol/l). The sensitivity was 0.1 μ g/ml; the intra-assay and inter-assay CV were <4.6 and <7.3% respectively. The ratio IGF1:IGFBP3 was calculated on molar basis (IGF1 nmol/l/IGFBP3 nmol/l). The number of SDS from an age-related reference population mean was calculated for each IGF1 value (31). IGF1 values were not adjusted by gender as there are no significant gender differences in middle-aged adults (31). Low IGF1 was defined by a s.d. of IGF1 below -2 . Ghrelin concentrations were measured using commercial RIA, which has an antibody specific for total ghrelin (Linco Research, Inc., St Louis, MO, USA). Intra-assay CV was below 10% and inter-assay CV below 16%. Assay sensitivity was 93 pg/ml. Total ghrelin measurements were available in 24 mRYGBP, 34 rRYGBP, and 16 SG patients at the baseline and after surgery.

Statistical analysis

Descriptive statistics were expressed as mean $\pm$ s.d. or median (interquartile range) when the sample distribution was not Gaussian (departure from normality was assessed by the Kolmogorov–Smirnov test). Differences between baseline and groups were tested by the paired Student's *t*-test or the non-parametric Wilcoxon signed-rank test when it was appropriate. Differences among groups were evaluated by ANOVA or Kruskal–Wallis when required. Categorical variables were analyzed with the χ^2 test or the Fisher exact test when indicated. Associations between variables were estimated using Spearman's correlation coefficient. A multiple linear regression analysis using a selection algorithm was performed for the change of total IGF1 after surgery as the dependent variable including those variables that showed a significant association in the univariate analysis. A logistic regression model was also performed for the identification of those factors influencing a low post-surgery SDS IGF1 < -2 as the dummy variable. *P* value < 0.05 was considered statistically significant. Data were analyzed using the SPSS 12.0 statistical package.

Results

IGF1 at baseline

The mean age of subjects was 44.1 ± 9.3 years and mean presurgical BMI was 51.74 ± 8.75 kg/m²; 38.5%

were men (42 men and 67 women). Preoperatively, five patients had diabetes and 13 had hypertension. Anthropometric and hormonal characteristics of subjects are shown in Table 1. Men were younger than women and had a significantly higher IGF1 and ratio IGF1:IGFBP3 than women (153.4 ± 69.6 vs 114.9 ± 55.2 , $P = 0.002$; 0.13 ± 0.05 vs 0.10 ± 0.03 , $P < 0.001$, respectively) before surgery. BMI was similar in all subjects irrespective of the surgical procedure performed. Demographic and treatment characteristics in each group of surgical treatment are shown in Table 2. Patients treated by SG (49.3 ± 9.9 years) were older than mRYGBP and rRYGBP (42.8 ± 9.5 and 42.7 ± 9.03 years respectively, $P = 0.002$).

Overall prevalence of low IGF1 status at baseline was 22% (24/109 patients) with no differences according to the surgical procedure that was subsequently performed (16.7% mRYGBP, 22% rRYGBP, 28.6% for SG, $P = \text{NS}$). No differences in age and BMI were observed in subjects with or without low IGF1 status at baseline. Serum IGF1 values were inversely correlated with age ($r = -0.3$, $P < 0.001$). No linear correlation was observed between BMI and IGF1 ($r = -0.1$, $P = 0.2$). Baseline IGF1:IGFBP3 ratio correlated negatively with age ($r = -0.3$, $P < 0.001$) but not with BMI ($r = -0.2$, $P = 0.09$).

IGF1 after 12 months of WL induced by bariatric surgery

Mean EBWL and %WL were of 63.1 ± 15.9 and $34.9 \pm 8.9\%$ respectively, corresponding to a mean WL of 50.6 ± 17.9 kg. Patients treated with SG showed a

Table 1 Clinical and analytical characteristics of patients before and after surgically induced weight loss. Data expressed as mean $\pm$ s.d. or median (interquartile range).

Variable	Preoperative	One year postoperative	<i>P</i>
Weight (kg)	142.9 $\pm$ 24.7	92.7 $\pm$ 16.9	<0.001
WC (cm)	137.7 $\pm$ 14.9	103.0 $\pm$ 14.2	<0.001
BMI (kg/m ²)	51.7 $\pm$ 8.7	33.6 $\pm$ 6.3	<0.001
HbA1c (%)	5.9 $\pm$ 1.45	4.9 $\pm$ 0.7	<0.001
Albumin (g/dl)	3.9 $\pm$ 0.4	4.1 $\pm$ 0.6	0.1
Total cholesterol (mmol/l)	4.8 $\pm$ 0.9	4.1 $\pm$ 0.9	0.06
HDL cholesterol (mmol/l)	0.9 $\pm$ 0.3	1.2 $\pm$ 0.4	<0.001
Triglycerides (mmol/l)	1.5 (1.2–1.9)	0.8 (0.7–1.1)	0.001
HOMA	4.5 (3.1–6.6)	1.4 (0.8–1.9)	<0.001
CRP (mg/l)	8.9 (4.6–15.9)	1.7 (0.8–4.1)	<0.001
IGF1 (ng/ml)	129.8 $\pm$ 63.7	133.1 $\pm$ 69.8	0.5
IGFBP3 (μ g/ml)	4.2 $\pm$ 1.4	3.5 $\pm$ 1.0	<0.001
Ratio IGF1:IGFBP3	0.11 $\pm$ 0.04	0.14 $\pm$ 0.05	<0.001
Ghrelin (pg/ml)	717.8 (628.6–867.7)	758.4 (613.5–968.1)	0.1

WC, waist circumference; CRP, C-reactive protein.

Table 2 Baseline demographic characteristics and treatments in mRYGBP, rRYGBP, and SG patients. Data expressed as mean $\pm$ s.d.

Variable	mRYGBP	rRYGBP	Sleeve gastrectomy
<i>n</i>	31	50	28
Gender (men/ women), <i>n</i>	10/21	21/29	11/17
Age (years)	42.8 $\pm$ 9.5	42.7 $\pm$ 9.03	49.3 $\pm$ 9.9*
WC (cm)	135.7 $\pm$ 14.9	138.8 $\pm$ 15	139 $\pm$ 16.9
BMI (kg/m ²)	51.8 $\pm$ 6.6	52.8 $\pm$ 9.9	49.6 $\pm$ 8.3
Diabetic patients, <i>n</i>	2	3	1
Oral antidiabetic (metformin)	2	2	1
Insulin therapy	0	0	0
Hypertension (%)	6	5	2
One oral antihyper- tensive treatment	4	4	2
Two or more oral antihypertensive treatments	2	1	0

WC, waist circumference; CRP, C-reactive protein. * $P < 0.002$: significance differences of mean variation inter-groups (ANOVA).

lower %WL in comparison with the other two surgical techniques used ($P = 0.001$ and 0.006 for mRYGBP and rRYBPG respectively) (Table 3).

The overall prevalence of low IGF1 status was of 19.3% (21/109 patients) at 12 months after surgery. There was a trend to a lower prevalence of low IGF1 in those individuals treated with SG 1 year after the procedure: 32.1% for mRYGBP, 16% for rRYGBP, and 10.1% for SG ($P = 0.06$). Interestingly, in those individuals treated with SG, the prevalence of low IGF1 was lower after surgery (28.6 vs 10.1% pre- and postsurgery values, $P = 0.03$); in contrast, no statistically significant changes were observed in the other two groups of surgical procedures: 22 vs 16% in rRYGBP ($P = 0.4$) and 16.7 vs 32.1% in mRYGBP ($P = 0.1$) respectively.

Low IGF1 at follow-up was associated with either a higher %WL (40.6 $\pm$ 9.1%WL among low IGF1 vs 33.5 $\pm$ 8.3% in normal IGF1; $P = 0.002$) and a higher %EBWL (69.9 $\pm$ 16.3%EBWL among low IGF1 vs 61.5 $\pm$ 15.5% in normal IGF1; $P = 0.04$), as well as a greater decrease in albumin (−8.4 (−22.4 to 3.7%) among low IGF1 vs 4 (−3.4 to 12.6%) among normal IGF1; $P = 0.03$). Low IGF1 state after surgery was not associated with age (45.6 $\pm$ 9.8 vs 43.7 $\pm$ 9.1 years, $P = 0.5$), baseline BMI (55.8 $\pm$ 12.2 vs 50.7 $\pm$ 7.4 kg/m², $P = 0.07$), and postsurgery BMI (32.8 $\pm$ 6.9 vs 33.7 $\pm$ 6.2 kg/m², $P = 0.5$). A significant decrease in HOMA, CRP, and HbA1c was observed after surgery as expected, and in relation to IGFBP3, a decrease was also found in all patients, irrespective of the surgical procedure used (Table 3). When evaluating the impact of the different surgical procedures in the changes of total IGF1, only those patients undergoing SG showed a significant increase in total IGF1 in

contrast to the other procedures. IGF1:IGFBP3 ratio showed a significant increase in patients operated by either rRYGBP or SG; however, there was a large variability in the percentage of change in IGF1:IGFBP3 ratio in rRYGBP patients (Table 3).

Albumin concentrations increased significantly in SG, decreased in mRYGBP, and did not change in rRYGBP 1 year after surgery (Table 3). Categorization by gender or diabetes mellitus was not associated with changes in somatotrophic hormones and to %WL at 12 months.

Ghrelin after 12 months of WL induced by bariatric surgery

Before surgery there were no differences in total ghrelin among the three groups of patients (733.2 (657.9–1007.5), 715.3 (644.3–862.3), 708.8 (590.2–790.1) in mRYGBP, rRYGBP, and SG respectively ($P = 0.2$)), but ghrelin concentrations were significantly different between the groups at 1 year follow-up after surgery ($P < 0.001$). In particular, postsurgical ghrelin was significantly lower in SG when compared with the other two groups, where no significant changes were found (Table 3). In addition, the magnitude and direction of change in total ghrelin after WL were different according to the type of surgical procedure: in SG there was a significant decrease while a significant increase in circulating ghrelin was observed in the other two groups when compared with baseline values (Table 3).

Bivariate correlations and multiple regression analyses

When all the patients were considered, changes in total IGF1 were significantly and positively correlated with the %WL ($r = 0.3$, $P = 0.001$) and with changes in albumin ($r = 0.3$, $P = 0.003$), while a negative correlation was found with changes in ghrelin concentrations ($r = -0.3$, $P = 0.006$). No correlation of IGF1 changes was observed with age, baseline BMI, and insulin or HOMA changes. In addition, ghrelin changes showed a significant negative correlation with age ($r = -0.2$, $P = 0.02$), %WL ($r = -0.3$, $P = 0.001$), change in IGF1:IGFBP3 ratio ($r = -0.2$, $P = 0.04$), and change in albumin concentration ($r = -0.3$, $P = 0.01$). However, when correlations were performed according to surgical procedure, only in mRYGBP patients was the significance retained in relation to change in ghrelin and the %WL ($r = -0.5$, $P = 0.01$), while no significant correlations were found among changes in ghrelin concentrations and changes in total IGF1 and IGF1:IGFBP3 ratio. On the other hand, the %WL was significantly and positively associated with age ($r = 0.3$, $P = 0.001$), and with the percentages of IGFBP3 ($r = 0.3$, $P = 0.001$), ratio IGF1:IGFBP3 ($r = 0.2$, $P = 0.02$), and albumin ($r = 0.2$, $P = 0.02$) changes in

Table 3 Clinical and analytical measurements in relation to surgery technique.

Variable	Preoperative	One year postoperative	P*	Mean or median variation (%)	P†
BMI (kg/m ²)					
mRYGBP	52.1±6.5	32.2±5.4	<0.001	−37.9±8.2	0.011
rRYGBP	52.8±9.8	33.6±6.9	<0.001	−35.9±9.2	
SG	49.4±8.1	34.9±5.9	<0.001	−29.8±7.1‡	
HOMA					
mRYGBP	4.7 (3.1–6.8)	1.0 (0.6–1.7)	<0.001	−78 (−84 to −53)	0.03
rRYGBP	4.5 (3.2–7.1)	1.5 (0.8–2.0)	<0.001	−70 (−75 to −59)	
SG	4.2 (2.3–5.9)	1.6 (1.2–2.2)	0.001	−59 (−76 to −42)§	
Albumin (g/l)					
mRYGBP	41.4±3.2	38.3±6.8	0.03	−4 (−16 to 4.8)	<0.001
rRYGBP	39.9±4.3	40.7±4.6	0.3	1.8 (−4.9 to 9.6)¶	
SG	38.6±4.9	42.8±3.3	<0.001	8.7 (3.6 to 16.3)‡	
CRP (mg/l)					
mRYGBP	12.9 (6.4–18.1)	1.8 (0.6–4)	<0.001	−83.5 (−95.5 to −58.4)	0.007
rRYGBP	8.9 (3.7–17.4)	1.7 (0.7–4.4)	<0.001	−79.7 (−90.2 to −54.6)	
SG	7.1 (3.7–12.3)	2.2 (0.9–4)	<0.001	−69.1 (−82.3 to −59.8)	
IGF1 (ng/ml)					
mRYGBP	131.9±57.1	121.3±77.1	0.3	−7.1 (−51.7 to 14.8)	0.007
rRYGBP	130.3±64.6	125.9±57.8	0.5	−1.7 (−22.8 to 20)	
SG	126.8±70.2	148.3±72.9	0.001	31.9 (11.7 to 56.1)†	
IGFBP3 (µg/ml)					
mRYGBP	4.3±1.3	3.4±1.02	<0.001	−19.1 (−51.7 to 14.8)	0.058
rRYGBP	4.0±1.3	3.4±0.87	<0.001	−16 (−27 to −4)	
SG	4.3±1.7	3.8±1.1	0.02	−5.9 (−16.1 to 6.8)	
Ratio IGF1:IGFBP3					
mRYGBP	0.12±0.06	0.13±0.06	0.2	5.1 (−18.7 to 35.3)	0.05
rRYGBP	0.12±0.04	0.13±0.03	0.01	18.3 (−15.6 to 36.4)	
SG	0.11±0.04	0.14±0.04	<0.001	35.6 (21.7 to 57.9)‡	
Ghrelin (pg/ml)					
mRYGBP	733.2 (657.9–1007.5)	847.7 (771.7–1042.4)	0.01	18.9 (4.1 to 34.3)	<0.001
rRYGBP	715.2 (644.3–862.3)	891.4 (719.5–1138.5)	0.001	19.5 (−0.9 to 43.2)	
SG	708.8 (590.2–790.1)	542.5 (501.5–607.7)	<0.0001	−23.4 (−31.3 to −6.29)‡	

mRYGBP, modified Roux-en-Y gastric bypass; rRYGBP, ringed Roux-en-Y gastric bypass; SG, sleeve gastrectomy; CRP, C-reactive protein. *P, significance differences between values preoperative vs 1 year intra-group (paired Student's *t*-test). †P, significance differences of mean or median variation inter-groups (ANOVA). ‡P<0.02 SG vs ringed RYGBP and modified RYGBP; §P<0.05 SG vs ringed RYGBP; ¶P<0.05 ringed vs modified RYGBP.

all patients. SDS IGF1 postsurgery showed a positive and significant correlation with the percentage of albumin change ($r=0.2$, $P=0.03$), the %WL ($r=0.3$, $P=0.005$), and the baseline BMI ($r=-0.3$, $P=0.001$) in all patients.

When performing a linear regression analysis, in a first model including %WL, albumin, and circulating ghrelin changes as the confounders, the percentage of albumin change was the only independent variable ($R^2=0.15$, $\beta=0.2$ (0.05–1.23), $P=0.03$) significantly associated with the percentage of total IGF1 changes.

When a logistic regression analysis was performed, the low IGF1 status after surgery was predicted by %albumin change (OR=0.93, $P=0.005$), after adjustment by %WL, and percentages of albumin and ghrelin changes (Table 4).

Discussion

Severe obesity is associated with important and sometimes severe comorbidities, most of them showing a reversal or amelioration after substantial WL.

Regarding this, there is substantial evidence on the improvement of endocrine abnormalities like hypogonadic state in obese men and type 2 diabetes mellitus reversal (5, 6, 7, 32). The somatotrophic axis is also affected by severe obesity, and reduced basal and stimulated GH secretion and IGF1 concentrations have been described in obese subjects (15, 16, 17, 18, 22, 23). The somatotrophic axis is relevant for healthy condition at all ages and it is understood that low IGF1 concentrations have been closely associated with cardiovascular disease (11), abnormal abdominal adiposity accumulation, low quality of life, decreased muscle mass, and abnormal bone homeostasis (11, 12). Moreover, in patients with untreated GH deficiency, resulting low IGF1 has been claimed to explain, at least in part, the excessive cardiovascular morbidity and mortality. It is tempting to assume that this may also be operative in MO subjects and therefore somatotrophic axis is another biological target that has to be taken into account at the time of evaluating improvement of the obese condition after therapeutic management. As a consequence, any treatment for obese subjects in which concomitant recovery of IGF1

Table 4 Multivariate regression analysis for factors predicting the persistence state of low IGF1 in morbidly obese men after bariatric surgery. Multiple logistic regressions were performed using low IGF1 after 12-month bariatric surgery as dependent variables, and weight loss and albumin and ghrelin changes as confounders. Data are expressed as OR (95% CI).

	Odds ratio (95% CI)	P value
Low IGF1 postsurgery		
%Ghrelin change	0.9 (0.9–1.0)	0.5
%WL	0.9 (0.8–1.0)	0.07
%Albumin change	0.9 (0.8–0.9)	0.005

is not achieved may have deleterious consequences in the long term and has to be assessed accordingly. In our series, we found an overall prevalence of low IGF1 values of 22% before surgery. IGF1 variations after surgery were mostly related to the change in circulating albumin while WL showed a statistical trend, and moreover, the former was related to the surgical procedure used. Notably, IGF1 normalized predominantly in subjects in which SG was performed in comparison with the two types of by-pass procedures. This is relevant as IGF1 is an anabolic hormone, and its deficiency contributes not only to a persistent condition of excessive cardiovascular risk but also to a decreased lean mass due to muscle mass loss after surgery. It is known that surgical techniques with a high malabsorptive component for treatment of morbid obesity could be more effective for WL at short and midterm than restrictive ones, but it is also known that those surgical procedures are also more frequently associated to nutrient deficiency (33, 34, 35). This was also confirmed in our study, as patients undergoing mRYGBP, which has a high malabsorptive component, showed a higher percentage of WL together with a substantial decrease in serum albumin than those in which rRYGBP or SG were performed. However, it could not be ruled out that a certain degree of malnutrition may be related to an additional insufficient intake of protein dietary supplements in these patients. Nutrient deficiencies are frequent after bariatric surgery and they may also be related to a selective reduction in protein intake as well as the physiological impact of surgically induced anatomical changes in the gastrointestinal tract; a certain protein-rich food intolerance as well as poor digestion has been described in these patients (34, 35). It is also well known that there are greater nutritional risks related to the increased length of by-passed small intestine. All patients received the same nutritional recommendations according to published guidelines depending on type of bariatric surgery (27), and although all the patients were apparently highly compliant, it can be speculated that an amelioration of IGF1 after distal gastric by-pass may be possible with higher protein supplementation. Also, it may be argued that evaluation of malnutrition considering only albumin concentration may be insufficient. Albumin

may increase, decrease, or present no changes after bariatric surgery. Circulating albumin concentration is considered an inflammatory marker in a way that its concentration decreases when inflammation occurs (36), so their changes in obesity had to be interpreted with caution because the tendency of albumin changes may be influenced by opposed dynamic factors after bariatric surgical procedures. When a combined analysis of albumin and CRP is performed, for segregation of the inflammatory component from the potentially induced protein nutritional status, all patients irrespective of the surgical technique showed a significant decrease in CRP concentrations, thus indicating an amelioration of the low inflammatory condition associated with morbid obesity. However, only patients undergoing a SG presented an increase in albumin and decrease in serum CRP concentrations, suggesting that malnutrition is taking place to some extent in mRYGBP patients.

In this study, we also aimed to evaluate an estimation of free IGF1, which is thought to be the relevant fraction for its biological action. Free IGF1 was evaluated by calculation of IGF1:IGFBP3 ratio, and we found that WL after bariatric surgery was associated with a significant increase in IGF1:IGFBP3 ratio mostly due to a significant decrease in IGFBP3 for the whole group. Interestingly, the change in IGF1:IGFBP3 ratio was different in relation to the type of surgical procedure used, as only patients undergoing SG showed a significant increase in both total IGF1 as well as IGF1:IGFBP3 ratio. In this sense, the prevalence of low IGF1, defined as s.d. total IGF1 score < -2, decreased only significantly in patients treated by SG in contrast to rRYGBP and mRYGBP in which non-significant changes were observed. In fact, patients who underwent SG showed a significant increase in serum albumin despite WL. The catabolic vs the anabolic component of the post-surgical state may influence the normalization of IGF1 as well as albumin in a reciprocal way; and conversely, persistence of low IGF1 may also contribute to catabolism and to lower albumin. It may be hypothesized that a too rapid and intense loss of weight, obtained by some bariatric surgical procedures, mostly those with a malabsorptive component, may favor a persistent pathologically low IGF1. Galli *et al.* (23) showed a good correlation between a WL of about 23% and IGF1 increase, after 2 years of follow-up with banding. On the other hand, other investigators, i.e. Savastano *et al.* (21), also using banding, did not observe any correlation between these parameters after a 35–40% of EBWL at 6 months after surgery. These results suggest that a moderate WL obtained at 6 months probably requires more time for IGF1 recovery in contrast to what we found with SG, in which the recovery was observed at 1 year after surgery. As we did not measure IGF1 in our series at 6 months, we cannot report what happened at this time point of follow-up. Recently, Mittempergher *et al.* (24) have analyzed the

changes in GH, IGF1, IGFBP1, and IGFBP3 1 year after two different bariatric surgical procedures in a group of 35 patients with low preoperative GH. They observed a postoperative increase in all somatotrophic parameters, but no statistically significant differences were observed in IGF1 and IGFBP3 between biliopancreatic diversion and banding. However, no correlations with %WL and nutritional parameters were made, thus interpretation of such changes could not be made. Discrepancies observed in the modifications of IGF1 and their relationship with WL after bariatric surgery require taking into consideration the development of functional malnutrition, which may explain at least in part the different results obtained by different types of bariatric procedures. Also, the different periods of time of follow-up, which range from 6 to 24 months in most of the reports, is an important issue as the intensity of WL in relation to time may lead to a modification and a dynamic adaptation of the somatotrophic axis response (16, 17, 18, 19, 20, 21, 22, 23, 24). In this study, evaluation at 12 months of follow-up after bariatric surgery was chosen in order to avoid the first 6 months in which rapid WL usually takes place, which may greatly influence IGF1 concentrations.

We also observed that IGF1 postsurgery was correlated with BMI at baseline, independently of the type of bariatric procedure, thus indicating that the consequences of obesity with regard to somatotrophic disturbance runs in parallel to the severity of obesity.

Ghrelin is a well-known orexigenic hormone as well as a stimulator of GH secretion; therefore, we were interested in evaluating the potential role of ghrelin changes in relation to IGF1 after surgery. Our results seem to indicate that modifications of IGF1 in this setting are only a little or not influenced by ghrelin; thus, even with an increased ghrelinergic stimulus, as was observed in RYGBP groups, total IGF1 concentration was not related to ghrelin changes after surgery when surgical procedures were considered individually. In SG, there was a significant increase in total IGF1 concentration despite a significant decrease in ghrelin concentrations at 12 months after surgery. These results clearly indicate that the driving mechanism operating for IGF1 modifications is much more dependent on the nutritional changes than ghrelin ones.

Hyperinsulinism and insulin resistance, increased free fatty acids, and hyperleptinemia are additional factors that may contribute to the functional disturbances of the somatotrophic axis in MO subjects (9, 24). Most of these factors, if not all, show dramatic changes after surgically induced WL and may participate with more or less impact in the improvement of IGF1 after surgery. On the other hand, the difference in ghrelin changes observed in our patients depending on the surgical procedure is in agreement with previous studies (37, 38, 39, 40). These results confirm that the resection of the fundus by SG, the main location of

ghrelin-producing cells, is the basis of the observed decrease in ghrelin concentrations (38, 40).

We are aware of the descriptive nature of our work and these results should be interpreted with caution. Despite the fact our data require further investigation, we believe that the evaluation of the IGF1 axis should be included in the clinical follow-up when an extremely rapid WL is observed. Moreover, the potential deleterious outcomes in the persistently low IGF1 condition in the long term after bariatric surgery deserve specific studies. In conclusion, we showed that low IGF1 is related substantially to presurgical high BMI and its recovery or persistence after surgery is mostly related to the nutritional modifications induced by the specific surgical procedure.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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