Hypogonadism as an additional indication for bariatric surgery in male morbid obesity?

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Abstract

Objective: Male obesity is often associated with reduced levels of circulating total (TT) and calculated free testosterone (cFT), with normal/reduced gonadotropins. Bariatric surgery often improves sex steroid and sex hormone-binding globulin (SHBG) levels. The aim of this study was to assess the effects of bariatric surgery on waist circumference (WC) and BMI, and on TT levels, in morbidly obese men, stratified, according to the gonadal state, in eugonadal and hypogonadal (TT < 8 nmol/l) subjects.

Design: A cohort of morbidly obese patients (29 with hypogonadism (HG) and 26 without) undergoing bariatric surgery (37, 10, 6, and 2, with Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, biliopancreatic diversion and gastric sleeve, respectively) was studied at 6 and 12 months from the operation.

Methods: Anthropometric parameters (weight, BMI, WC) and sex hormones (gonadotropins, TT, cFT, estradiol (E₂), SHBG) were assessed.

Results: WC was the only parameter significantly correlated with androgens, but not with E₂, SHBG, and gonadotropins, at baseline. After surgery, a significant increase in TT, cFT, and SHBG, accompanied by a decrease in E₂, was evident in the two groups. However, both TT and cFT, but not E₂, SHBG, and gonadotropin variations, were significantly higher in the hypogonadal group at follow-up, with an overall 93% complete recovery from HG. Reduction in WC, but not BMI, was significantly greater in hypogonadal men ($\Delta WC = -29.4 \pm 21.6$ vs -14.4 ± 17.4 at 12 months, $P = 0.047$).

Conclusions: Recovery from obesity-associated HG is one of the beneficial effects of bariatric surgery in morbidly obese men. The present findings suggest that the gonadal state is a predictor of WC decrease after bariatric surgery.

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Introduction

Obesity and its associated comorbidities have been exponentially increasing during the last 40 years, representing a medical and socio-economic burden, not only in industrialized, but also in developing countries (1). Treatments for obesity include a wide range of interventions, such as dietary prescriptions, structured exercise, lifestyle modification programs, specific drugs, and bariatric surgery. The currently recognized indications of bariatric surgery are limited to morbid obesity, i.e. BMI > 40 kg/m², or BMI ≥ 35 kg/m² associated with risky comorbidities, such as cardiovascular (CV) diseases and type 2

diabetes (T2DM), which are significantly ameliorated after the intervention (2, 3, 4).

Alterations in sex steroid hormones are often associated with male obesity. In particular, low circulating levels of total (TT) and free (FT) testosterone in the presence of reduced gonadotropins, characterizing central secondary hypogonadism (HG), with elevated estrogens, have been described in male metabolic syndrome (5, 6). Obesity and HG are linked in a vicious cycle, in which low testosterone favors weight gain, and adiposity induces HG (6, 7). Interestingly, both obesity and HG are associated with

increased all-cause and CV mortality (6, 8). Several studies demonstrated that weight loss and reduction in waist circumference (WC) induce an increase in testosterone levels. A recent meta-analysis (9) comparing bariatric surgery with lifestyle modifications programs has shown a greater recovery in TT and FT with the surgical approach, probably due to a greater effect on body weight. On the other hand, it is possible that androgen levels, in men, contribute to the regulation of body weight. Hypogonadal subjects, who have reduced muscle mass and lower muscular strength, could also have a reduced energy expenditure as described for aging males (10); in addition, androgens could play a role in the regulation of adipose tissue metabolism (11).

The aim of this study was to verify whether hypogonadism (TT < 8 nmol/l) modulates the effects of bariatric surgery on abdominal adiposity, body weight, and TT.

Subjects and methods

Patients

The clinic-based survey was performed on a consecutive series of morbidly obese (BMI > 40 kg/m²) patients who were undergoing bariatric surgery at Careggi University Hospital in Florence (*n*=55). All patients were enrolled for a subsequent 6- and 12-month follow-up, after intervention. The study was approved by the Local Ethical Committee and Institutional Review Board (protocol number 83/13). All patients enrolled gave signed informed consent after receiving written and oral information on the study.

Study design

All male patients in the list for bariatric surgery at the Metabolic and Bariatric Surgery Unit of Careggi

University Hospital in Florence, Italy, between July 1, 2009 and June 30, 2011, who gave their consent were enrolled in the study, provided that they had a BMI > 40 kg/m² and no history of present or past treatment for HG. The choice of surgery and type of surgery was made by a team composed of a surgeon, an endocrinologist, and a dietitian, depending on the overall evaluation of the patient's history. Among the 55 patients studied, 37, 10, 6, 2, underwent Roux-en-Y gastric bypass (67%), laparoscopic adjustable gastric banding (18%), biliopancreatic diversion (11%), and gastric sleeve (4%), respectively.

In the prospective observation, pre-surgery baseline evaluation (T0) was performed at hospital admission for bariatric surgery. The follow-up evaluation was performed 6 (T1) and 12 (T2) months after surgery.

Biochemical and anthropometric measurements

- Anthropometric measures: height, weight, and WC were measured for each subject at the three time points, according to the cohort.
- Sex hormones: serum TT, estradiol (E₂) follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone-binding globulin (SHBG) were measured by immunoassay (Immulite 2000, M-Medical System, Milan, Italy) on a sample of venous blood drawn in the morning. The analytical sensitivity of the assays was 0.5 nmol/l for TT, 55 pmol/l for E₂, 0.1 mIU/ml for FSH, 0.05 mIU/ml for LH, and 0.02 nmol/l for SHBG. TT measurement by immunoassay has been validated by isotopic dilution-liquid chromatography-tandem mass spectrometry method for values higher than nanomolar (12). Calculated free testosterone (cFT) was calculated as demonstrated previously (13).

Table 1 Anthropometric and sex steroid parameters before bariatric surgery in the obese cohort enrolled (*n*=55). Mean ± s.d. values at baseline before surgery (T0) and at 6 (T1) and 12 months (T2) from surgery are indicated, as well as *P* significance between the indicated time points after Student's *t*-test for paired data. Significant *P* values are indicated in bold.

	T0 (<i>n</i> = 55)	T1 (<i>n</i> = 50)	<i>P</i> _{T1-T0}	T2 (<i>n</i> = 42)	<i>P</i> _{T2-T0}
Age (years)	42.3 ± 11.6				
BMI (kg/m ²)	46.6 ± 7.4	37.5 ± 6.7	0.000	32.2 ± 6.8	0.000
Weight (kg)	148.4 ± 26.1	120.7 ± 26.3	0.000	101.8 ± 24.1	0.000
WC (cm)	140.1 ± 18.0	121.5 ± 17.1	0.000	113.6 ± 16.6	0.000
TT (nmol/l)	9.02 ± 4.71	14.77 ± 6.35	0.000	14.6 ± 6.0	0.000
cFT (nmol/l)	0.224 ± 0.132	0.263 ± 0.111	0.038	0.265 ± 0.097	0.339
E ₂ (pmol/l)	139.6 ± 49.5	135.6 ± 52.7	0.347	126.7 ± 44.9	0.007
SHBG (nmol/l)	21.7 ± 8.9	42.3 ± 19.7	0.000	42.2 ± 20.0	0.000
FSH (mIU/ml)	4.03 ± 2.56	5.59 ± 3.00	0.000	6.21 ± 3.90	0.000
LH (mIU/ml)	3.09 ± 1.96	4.34 ± 2.14	0.000	4.47 ± 2.60	0.001

Statistical analysis

Patients were included in the analysis when evaluations at baseline and at least one follow-up were available. Parametric distribution of data was evaluated by Kolmogorov-Smirnov test. Data have been expressed as mean $\pm$ s.d. Correlations were performed using Spearman's analysis. Student's *t*-test was used for comparisons of two sets of paired or independent data, as appropriate. A $P < 0.05$ value was used for statistical significance. Stepwise multiple linear regression was applied for multivariate analysis. All statistical analyses were performed on SPSS 20.0 for Windows (Statistical Package for the Social Sciences).

Results

Among the 58 morbidly obese patients initially enrolled, 55 were available for analysis ($n=55$, 1.2% dropout), having clinical data and blood sampling before surgery (T0, $n=55$) and at 6 (T1, $n=50$, 10% dropout) and/or 12 (T2, $n=42$, 24% dropout) months. In the sample analyzed, the mean age was 42.3 ± 11.6 years, and mean BMI was 46.6 ± 7.4 kg/m². Among those patients, 37, 10, 6, and 2, underwent Roux-en-Y gastric bypass (67%), laparoscopic adjustable gastric banding (18%), biliopancreatic diversion (11%), and gastric sleeve (4%), respectively. Six months after bariatric surgery, the decrease in adiposity (reduction in BMI, weight, and WC) was associated with a significant increase in TT and SHBG and decrease in estradiol (E₂) levels, which were further maintained at 12 months (Table 1). cFT significantly increased at 6 months, but the significance was lost at 12 months (Table 1). Gonadotropins (FSH and LH) increased, although not significantly, at both time points. When patients were stratified according to the gonadal status at baseline, in hypogonadal ($n=29$) and eugonadal ($n=26$) subjects (cutoff TT=8 nmol/l), a significant increase vs baseline was observed in both TT and cFT (Table 2), but not in E₂ (Table 2), SHBG, and gonadotropins, only in the hypogonadal group (Fig. 1). Differences between hypogonadal and eugonadal patients in variations from baseline were significant only for Δ TT and Δ cFT. No significant differences between the two groups were observed in either BMI or weight changes, but the mean variation in WC was significantly higher in hypogonadal men at 12 months (Table 2). Receiver operating characteristics (ROC) curve analysis was used to confirm the ability of the hypogonadal state (TT<8 nmol/l) to predict the WC reduction at 12 months (Fig. 2). Hypogonadal condition (TT<8 nmol/l), in fact, identified a WC decrease ≥ 23 cm,

Table 2 Variation in anthropometrical and sex hormone parameters after bariatric surgery in the cohort of obese men stratified in hypogonadal and eugonadal by a basal TT = 8-nM cutoff. Mean $\pm$ s.d. variation in all parameters at 6 (Δ T1) and 12 (Δ T2) months after surgery is indicated. Statistical significance in parameter variations within groups at T1 ($P_{\Delta T1}$) and T2 ($P_{\Delta T2}$) between hypogonadal and eugonadal subjects is indicated (P between groups) at both T1 and T2, with P significant values in bold.

	Hypogonadal (n = 29)				Eugonadal (n = 26)				P between groups	
	ΔT_{11}	ΔT_2 (n = 21)		$P_{\Delta T_2}$	ΔT_{11} (n = 24)	$P_{\Delta T_{11}}$	ΔT_2 (n = 21)	$P_{\Delta T_2}$		
BMI (kg/m ²)	-8.8 ± 6.7	-15.6 ± 9.4	0.000	-9.6 ± 4.8	0.000	-12.5 ± 8.6	0.000	0.650	0.276	
Weight (kg)	-22.6 ± 19.8	-51.6 ± 35.0	0.000	-28.7 ± 13.4	0.000	-41.2 ± 29.5	0.000	0.297	0.305	
WC (cm)	-22.3 ± 16.7	-29.4 ± 21.6	0.000	-16.6 ± 8.8	0.000	-14.4 ± 17.4	0.011	0.200	0.047	
TT (nmol/l)	7.52 ± 5.57	9.11 ± 6.69	0.000	3.56 ± 7.26	0.020	1.51 ± 7.11	0.342	0.037	0.001	
cFT (nmol/l)	0.164 ± 0.08	0.251 ± 0.097	0.002	-0.013 ± 0.174	0.719	-0.052 ± 0.157	0.148	0.009	0.001	
E ₂ (pmol/l)	-1.1 ± 50.9	-12.6 ± 51.1	0.271	-14.1 ± 59.1	0.255	-35.3 ± 57.3	0.011	0.413	0.184	
SHBG (nmol/l)	21.0 ± 16.1	24.0 ± 21.1	0.000	19.2 ± 15.9	0.000	18.9 ± 19.9	0.000	0.697	0.425	
5αDHT (mIU/ml)	1.40 ± 1.72	2.36 ± 3.85	0.013	1.55 ± 1.69	0.000	2.35 ± 4.43	0.025	0.759	0.993	
LH (mIU/ml)	0.99 ± 1.48	1.39 ± 2.57	0.022	1.78 ± 2.49	0.002	1.61 ± 2.98	0.022	0.187	0.796

Figure 1

Variation in anthropometric and sex hormone parameters after bariatric surgery in the cohort of morbidly obese men stratified in hypogonadal and eugonadal by a basal TT=8 nmol/l cut-off. Mean $\pm$ S.D. values of all parameters (A: TT, B: cFT, C: SHBG, D: E₂, E: FSH, F: LH, G: BMI, H: weight, I: waist) at baseline before

surgery (T0) and at 6 (T1) and 12 (T2) months of follow-up. Statistical significance: * P <0.05 and ** P <0.0001 between hypogonadal and eugonadal at T0; vs T0 in each group: ^a and ^d P <0.0001, ^b and ^e P <0.01, ^c and ^f P <0.05, in hypogonadal and eugonadal respectively.

with an accuracy (area under the ROC curve) of $71.2 \pm 9.9\%$ (P <0.05), with a 67% sensitivity and 71% specificity.

E₂ significantly decreased at 12 months, only in the eugonadal group (Fig. 1 and Table 2).

Bariatric surgery resulted in a complete recovery from HG (TT<8 nmol/l) in 93% of the hypogonadal subjects (27/29), already starting at 6 months from surgery (Fig. 1). No statistically significant differences were evident for baseline parameters between the two groups (BMI, weight, and gonadotropins) but for WC (P <0.05), TT and cFT (P <0.0001), SHBG, and E₂ (P <0.05; Fig. 1 and Table 2). The distribution of the type of bariatric surgery was similar between hypogonadal and eugonadal groups (data not shown), and the prevalence of T2DM was 5/29=17% and 2/26=8%, respectively, with no significant differences.

A strong positive correlation was found at baseline between BMI and WC in hypogonadal subjects ($r=0.811$, P <0.0001, $n=29$), which was still significant but weaker in eugonadal subjects ($r=0.465$, $P=0.045$, $n=26$). Conversely, the correlation was statistically significant between Δ BMI and Δ WC at 12 months from surgery in hypogonadal ($r=0.864$, $R^2=0.747$, P <0.0001, $n=21$) subjects, but not in eugonadal ($r=0.412$, $R^2=0.169$, $P=0.144$, $n=21$) subjects. The relationship between 12-month Δ BMI (x) and Δ WC (y) was $y=2.132x+0.858$ and $y=0.759x-4.556$ in hypogonadal and eugonadal subjects respectively.

Among all parameters considered to define adiposity (BMI, weight, WC), only WC at baseline showed a statistically significant correlation with androgens ($r=-0.375$, $P=0.013$ and $r=-0.411$, $P=0.006$ for TT and cFT respectively), but not with E₂, SHBG, and gonadotropin

Figure 2

Hypogonadal condition predicts WC reduction at 12 months from surgery. The receiver operating characteristics (ROC) curve shows that baseline hypogonadism ($TT < 8 \text{ nmol/l}$) identifies a reduction in waist circumference greater than -23 cm (indicated by the arrow, ΔWC_{T2}) at 12 months from surgery with an accuracy (area under the ROC curve) of 71% ($P < 0.05$), a 67% sensitivity, and 71% specificity. The ROC curve was constructed by plotting the sensitivity (true positive) vs the false positive rate (1-specificity) for different ΔWC values at 12 months from surgery.

levels (not shown). Such negative correlations remained statistically significant, even after adjustment for age as a further confounding factor (adj. $r = 0.373$, $P = 0.013$ and adj. $r = -0.400$, $P = 0.008$ for TT and cFT respectively).

Discussion

Bariatric surgery has been extensively described to ameliorate sex hormone and SHBG levels in morbidly obese patients (9, 14, 15, 16, 17, 18, 19), with an effect that may exceed what is predictable on the basis of weight loss (17). In this study, we demonstrate that the increase in androgens (cFT and TT) occurs only in hypogonadal patients ($TT < 8 \text{ nmol/l}$). Conversely, estrogen levels, which were significantly lower before surgery in hypogonadal individuals, significantly decreased in eugonadal patients only. Remarkably, bariatric surgery resulted in an almost complete and rapid recovery of HG, even starting at 6 months from surgery, similarly to what was found for T2DM recovery (20).

Interestingly, baseline testosterone levels appear to moderate the effect of bariatric surgery on sex hormone recovery. The previous works reported that BMI (9, 17) and age (18) were among the best predictors of androgen recovery after bariatric surgery. However, such cohorts of morbidly obese patients included both hypogonadal and eugonadal subjects. In this study, we show that HG is the best predictor of the decrease in WC after surgery. It can be speculated that the rapid weight loss induced by bariatric surgery eliminates disturbances in the regulation of gonadotropin and androgen secretion determined by excess adiposity, resulting in an improvement in testosterone levels in hypogonadal subjects. Conversely, in patients who remain eugonadal despite morbid obesity, feedback from appropriate levels of circulating testosterone could prevent any further increase in androgen secretion. It can also be observed that the role of E_2 in the determination of obesity-related hypogonadism could be smaller than what has been previously hypothesized (10, 21); in fact, E_2 levels at baseline are lower in hypogonadal subjects compared with eugonadal subjects. In addition, in eugonadal subjects, the reduction in E_2 determined by surgery does not produce an increase in testosterone, whereas recovery of hypogonadism occurs without any significant increase in E_2 levels.

At enrolment, WC was higher in hypogonadal than in eugonadal patients, despite a similar BMI. This confirms that WC is one of the major predictors of obesity-associated hypogonadism (6, 9), suggesting that abdominal fat has a greater impact on the regulation of sex hormone secretion than peripheral fat.

Interestingly, the reduction in WC in patients with hypogonadism was more pronounced than that observed for eugonadal subjects with a similar weight loss, suggesting that bariatric surgery could have a specific effect on abdominal adiposity in hypogonadal subjects. It can be speculated that the improvement in testosterone levels induced by bariatric surgery, which is greater in hypogonadal patients, contributes, to a greater extent in those subjects, to the preservation of lean mass, resulting in a greater reduction in abdominal adiposity. Unfortunately, no measures of body composition were available in this study. Further limitations were the absence of insulin sensitivity and glycemic parameters at baseline and follow-up, and the variety of surgery procedure used, which did not allow a subgroup analysis for type of intervention. Moreover, 89% (49/55) of the patients undergoing bariatric surgery had $BMI \geq 40 \text{ kg/m}^2$. Further studies carried out on subjects with BMI between 35 and 40 kg/m^2 are necessary to evaluate whether

hypogonadism could be considered as a novel comorbidity to be considered for bariatric intervention.

In conclusion, recovery from obesity-associated hypogonadism is one of the positive clinical outcomes of bariatric surgery in morbidly obese men. In addition, male hypogonadism appears to be a predictor of reduction in WC after surgery.

Declaration of interest

Dr E Mannucci has received: consultancy fees from Novo Nordisk, Eli Lilly, AstraZeneca, and GSK; speaking fees from Novo Nordisk, Eli Lilly, AstraZeneca, and Sanofi; research grants from Novo Nordisk, Eli Lilly, and AstraZeneca. Prof. M Maggi has received consultancy fees or research grants from Eli Lilly, Bayer, and Prostrakan. The other authors have no conflicts to declare.

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