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ORIGINAL ARTICLE



Short-term effects of surgical weight loss after sleeve gastrectomy on sex steroids plasma levels and PSA concentration in men with severe obesity

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ABSTRACT

Male obesity is known to be associated with hypogonadism, which can be reverted after surgical weight reduction. However, the evidence about how rapidly this effect rises after surgery and what consequences each procedure have on prostate function and prostatic-specific antigen (PSA) concentration is scarce. So, we evaluated total testosterone, estradiol, luteinizing hormone, follicle-stimulating hormone and PSA plasma levels in a group of 29 Caucasian obese men ($BMI = 43.4 \pm 8.5 \text{ kg/m}^2$) before and one month after sleeve gastrectomy. 19 lean healthy male subjects were considered as controls. As expected, obese patients showed a high prevalence of hypogonadism (51.6%) at baseline, with reduced total testosterone compared to lean controls (10.8 ± 3.5 vs $15.7 \pm 4.2 \text{ nmol/l}$, $p < .01$), higher estradiol (124.4 ± 46.5 vs $78.7 \pm 39.6 \text{ pmol/l}$, $p < .01$), lower luteinizing hormone and follicle stimulating hormone (3.6 ± 1.3 and 2.5 ± 0.9 vs 5.2 ± 2.4 and $5.9 \pm 3.8 \text{ U/L}$, respectively, $p < .05$) plasma levels. One month after surgery, patients showed a significant body weight reduction ($-17.2 \pm 6.7 \text{ kg}$) with increased total testosterone (from 10.8 ± 3.5 to $18.9 \pm 4.9 \text{ nmol/l}$, $p < .001$), reduced estradiol (from 124.4 ± 46.5 to $96.1 \pm 34.3 \text{ pmol/l}$, $p < .05$) and increased PSA (from 0.74 ± 0.38 to $1.0 \pm 0.51 \mu\text{g/l}$, $p < .001$). These results confirm that hypogonadism is highly prevalent in obese males, but they also show that it can be early reversed after sleeve gastrectomy, further confirming the strong indication to surgery of hypogonadal patients with severely reduced quality of life. Higher testosterone levels may be responsible for the increase of PSA observed after surgery; however, PSA concentration has to be monitored over time to avoid underrating of potential severe prostate diseases.

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Introduction

Obesity is associated with a high burden of chronic complications, such as type-2 diabetes mellitus (T2D), dyslipidemia, cardiovascular diseases and also some forms of cancer. Treatments for obesity include different interventions such as lifestyle modification, pharmacological and surgical therapy, and several studies have shown the improvement of T2D and other associated diseases in morbidly obese patients after weight loss with lifestyle intervention but, above all, bariatric surgery [1–3].

Male hypogonadism represents another relevant endocrine abnormality related to obesity, with low circulating levels of total and free testosterone (TT and FT) now recognized as common features of metabolic syndrome [4,5]. The most accredited hypothesis for this association emphasizes the role of aromatization

of circulating testosterone to estradiol at the level of adipose tissue but also increased serum levels of leptin and pro-inflammatory cytokines may have a suppressive effect on testicular steroidogenesis [6,7].

Body weight loss appears to revert hypogonadism associated with obesity [8], with a greater androgen rise in those patients losing more weight [9]. To this regard, clinical studies which had specifically evaluated the impact of calorie restriction and physical activity on T level showed conflicting results [10–14], whether a recent meta-analysis has shown that weight loss after bariatric surgery is correlated with an increase in T levels greater than those obtained with lifestyle interventions alone [15]. However, to date, the majority of published studies have evaluated T and other sex hormones plasma levels after mid-long-term follow-up period from bariatric surgery, and only very

Table 1. Anthropometrical and hormonal parameters of obese patients before surgery and lean controls.

	Patients (29)	Controls (19)	<i>p</i>
Age (years)	40.5 ± 9.9	33.7 ± 9.6	n.s.
Weight (kg)	134.4 ± 28.9	70.9 ± 8.8	<.0001
BMI (kg/m ²)	43.4 ± 8.5	22.4 ± 1.9	<.0001
Waist circumference (cm)	135.0 ± 17.4	86.1 ± 6.3	<.0001
Testosterone (nmol/L)	10.8 ± 3.5	15.7 ± 4.2	<.01
Estradiol (pmol/L)	124.4 ± 46.5	78.7 ± 39.6	<.01
LH (UI/L)	3.6 ± 1.3	5.2 ± 2.4	<.05
FSH (UI/L)	2.5 ± 0.9	5.9 ± 3.8	<.05
PSA (µg/L)	0.74 ± 0.38	0.78 ± 0.3	n.s.

BMI: body mass index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PSA: prostatic-specific antigen.

few studies have considered the effects of surgery on prostatic-specific antigen (PSA) concentration and prostate function. The aim of our study was to observe the effects of weight loss after sleeve gastrectomy (SG) on sex hormones and PSA concentration in a group of morbidly obese male subjects already at one month from surgery, to define how rapid the effects of this bariatric procedure on male reproductive function are.

Subjects and methods

We evaluated 29 male obese patients referring to the Center for the Study and Integrated Treatment of Obesity (Ce.S.T.I.O.) of the Department of Medicine – DIMED, University of Padova, and 19 normal weight males as healthy controls. All subjects underwent a complete clinical history and physical examination (weight – balance Wunder Rtt 300; calibration Sigma precision S.r.l with minimum sensitivity of 0.1 kg, in the morning, after a fasting night – height, waist circumference, body mass index, blood pressure and general physical examination); furthermore, each patient underwent a clinical andrological evaluation (the presence of gynecomastia, International Index of Erectile Function (IIEF-5) questionnaire) and hormonal assessment (TT, estradiol (E2), LH, FSH, total and free PSA). The same patients were evaluated one month after SG in the same modality.

The study was approved by the local ethical committee and informed signed consent was obtained from all patients.

Statistical analysis

The results were expressed as means ± SD. Data obtained before and after weight loss were compared using Student's *t*-test. Correlations were performed by simple linear regression analysis and Spearman's correlation coefficients were used to evaluate the correlations between the different parameter considered. *p*

values <.05 were considered as statistically significant. The statistical analysis was carried out using GraphPad PRISM software (version 3.03; GraphPad Software Inc., San Diego, CA).

Results

In Table 1, the anthropometric and hormonal characteristics of the obese subjects and lean controls at baseline are reported. As expected, obese subjects present significantly different body weight, BMI and waist circumference compared with lean controls. At baseline, obese patients showed a high prevalence of hypogonadism (51.6%, TT <10 nmol/L). Furthermore, they showed a significantly lower TT and higher E2 plasma levels than lean controls. We also observed that FSH and LH concentration in obese patients were significantly lower than those of lean controls. However, the different age between the two groups could partially explain these results.

In obese patients, TT plasma levels showed a significant inverse correlation with BMI and waist circumference, whether there was a significant positive relationship between BMI and waist circumference with E2 plasma levels (Figure 1). Among obese patients, those with metabolic syndrome (according to the US National Cholesterol Education Program/Adult Treatment Panel III criteria [16]) showed lower TT plasma levels, although without reaching statistical significance difference (*p* = .09); on the contrary, IIEF-5 score was significantly lower in obese patients with metabolic syndrome with respect to patients without metabolic syndrome (*p* < .01, Figure 2).

After one month, patients were reevaluated, observing a rapid and significant weight loss (−17.2 ± 6.7 kg) with improvements in BMI, waist circumference, and hormonal parameters, as detailed in Table 2. We observed a significant increase in TT and a significant reduction of E2 plasma levels together with a significant increase in LH concentration, with only 11.6% of patients still showing hypogonadism. Considering that the IIEF-5 refers to the erectile function over the past six months, we did not perform a second evaluation of sexual activity with this questionnaire. Interestingly, we detected a significant increase of total PSA plasma levels early after surgery (Table 2).

Discussion

Bariatric surgery has been shown to be an effective method for weight loss, long-term weight maintenance and also for the amelioration of associated

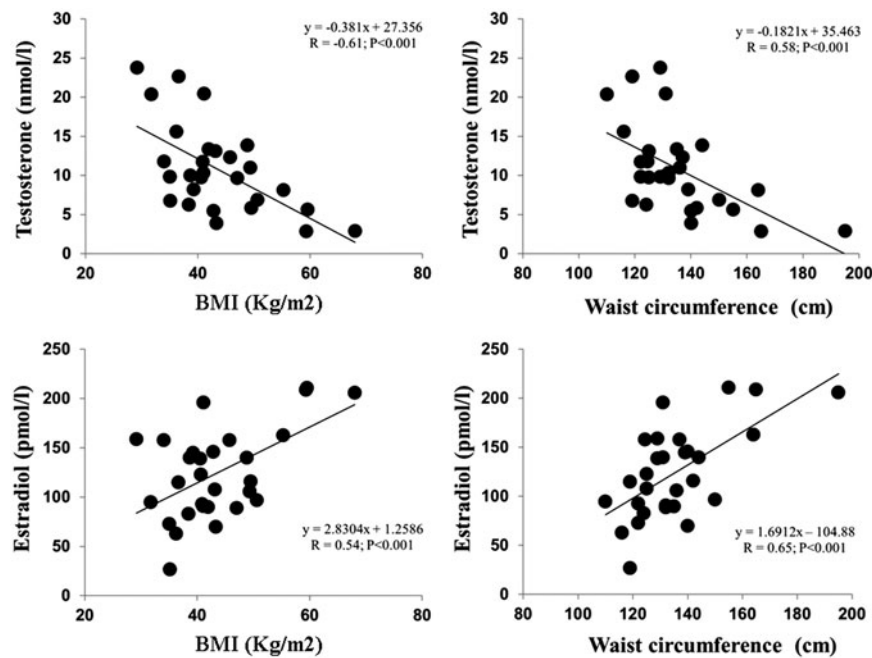


Figure 1. Correlations of anthropometrical parameters with testosterone and estradiol plasma levels in obese subjects before bariatric surgery.

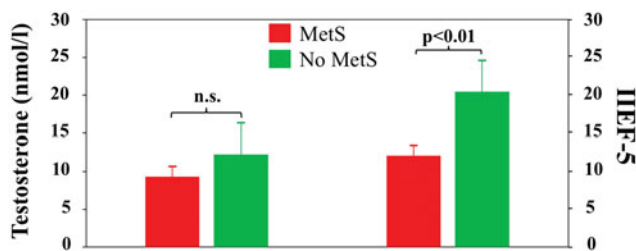


Figure 2. Baseline testosterone plasma levels (left panel) and IIEF-5 score (right panel) in obese patients with and without metabolic syndrome. MetS: Metabolic Syndrome; IIEF-5: International Index of Erectile Function-5.

Table 2. Anthropometrical and hormonal parameters in obese patients before and 30 days after laparoscopic sleeve gastrectomy (SG).

	Pre-SG (n = 29)	30 days after SG (n = 29)	p
Weight (kg)	134.0 ± 28.9	115.3 ± 24.8	<.001
BMI (kg/m ²)	43.4 ± 8.5	37.3 ± 7.2	<.001
Waist circumference (cm)	135.0 ± 17.4	121.5 ± 15.7	<.01
Testosterone (nmol/L)	10.8 ± 3.5	18.9 ± 4.9	<.001
Estradiol (pmol/L)	124.4 ± 46.5	96.1 ± 34.3	<.001
LH (UI/L)	3.6 ± 1.3	4.5 ± 1.2	<.01
FSH (UI/L)	2.5 ± 0.9	5.3 ± 1.8	n.s.
PSA (µg/L)	0.74 ± 0.38	1.0 ± 0.51	<.001

BMI: body mass index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PSA: prostatic-specific antigen.

comorbidities, including male hypogonadism. The most important determinant of T increase seems to be the percentage of reduction of BMI [8,9,13,14,17,18], pointing to adipose tissue as the main determinant of hypogonadism. It is well known that circulating T is aromatized to E2 within adipose tissue, and that the

high E2 plasma levels reduce LH-RH and LH secretion via negative feedback at the hypothalamic-pituitary level [19].

Our data confirm that obese male patients present a hypogonadotropic hypogonadism (51.6%), with a significant negative correlation of BMI and waist circumference with TT levels despite, as for the other related complications such as diabetes or hypertension, even hypogonadism can be not always observed in obese male, probably because of different duration of obese state and different compensatory mechanisms (e.g. LH compensatory secretion). This could explain the number of our patients without hypogonadism (48.4%).

Interestingly, when obese patients were grouped as having or not metabolic syndrome, those with metabolic syndrome showed a significant lower TT plasma levels, although without reaching the statistical significance. On the contrary, obese patients with metabolic syndrome showed a significant lower IIEF-5 score (Figure 2). These results can be expression of a more complex impairment of gonadal function occurring in the metabolic syndrome: in these patients, the progression of metabolic alterations and the consequent complications, such as neuro-vascular or microvascular abnormalities, may be responsible for a greater clinical severity of reproductive function abnormalities, together, with consequent more clinically relevant manifestations as shown by the significantly lower IIEF-5 score. However, considering that metabolic

patients were older than subjects without metabolic syndrome, we cannot exclude the influence of age on this parameter. Finally, it is possible that the small number of patients evaluated could have biased the reach of statistical significance for TT plasma levels.

Several studies evaluated the effects of bariatric surgery on T levels and gonadal function in the long term [8,9,13,14,17–18], but the evidence on early postoperative period are scarce. In the present study, we evaluated the rapid effect of SG on sex hormones and gonadal function in male obese subjects. All patients showed a significant weight loss just after 30 days from SG; this rapid and important weight reduction is accompanied by a fast and significant increase in TT and a significant reduction in E2 plasma levels. The rapid decrease of the fat mass (where E2 is produced from the aromatization of circulating androgens) could explain the improvement of hypogonadotropic hypogonadism, because of the reduction of the negative feedback on LH mainly exerted by E2 both at hypothalamic and at pituitary level, finally leading to the increase of testosterone production. The observed increase in LH plasma levels after weight reduction confirms this hypothesis [19].

Hypogonadism, despite high prevalence in male obese subjects, is often unrecognized and undertreated. It is characterized by a constellation of symptoms, such as sexual dysfunction, reduced lean mass and muscle strength, and also depression and reduced cognitive performance, which can further negatively affect their quality of life. Then, a rapid reversibility of hypogonadism may have an important role for male obese patients undergoing bariatric surgery. In fact, the early postoperative period is critical and requires a correct self-management of patient for the prosecution of caloric restriction, physical activity and adherence to medications in order to prevent complications or unsuccessful procedure. To this regard, a rapid correction of hypogonadism may have an important role, promoting a higher compliance of the patient to the successive medical interventions. The pharmacological restoring of T plasma levels has been shown to be successful in obese hypogonadal men, without any significant complication [20]; however, the indications for bariatric surgery in obese patients are not referred to hypogonadism correction yet, and then the observed rapid increase of T plasma levels after surgery could be considered another relevant positive effect. Nonetheless, T replacement therapy (in addition to lifestyle modifications) could be an interesting option in hypogonadal obese male waiting for bariatric surgery or with contraindications for this option.

Only one study has evaluated the rapid effect of a surgically induced weight loss on sex hormones in morbidly obese males, showing similar results. However, that study involved Asian men undergoing different surgical procedures (SG and Roux-en-Y gastric bypass, RYGB) with possible confounding results [21]. Furthermore, many important hormonal parameters regulating testicular function were not evaluated. To our knowledge, the present study represents the first evaluating specific short-term effects of SG on testosterone levels in Caucasian obese men. Above the improvement of physical activity and mood, the rapid normalization of T levels could early influence also erectile function. To this respect, another limitation of our study is the lack on the reevaluation of sexual function after SG, but this because IIEF-5 questionnaire refers to the sexual activity in the previous six months, and therefore, the results would have had no validity.

Finally, we also observed a significant increase in the concentrations of total PSA levels one month after SG. A reduced PSA value in obese men might reflect hemodilution from a larger plasma volume, and many studies have demonstrated inverse relationships between PSA levels and total body mass, total lean mass and total fat mass [22,23]. These studies also suggest that men with a greater BMI have increased plasma volume that lowers their PSA concentration. Only one study evaluated PSA levels after bariatric surgery in Caucasian men underwent RYGB, showing a significant rise after bariatric surgery [24]. Our study evaluated the specific effects of SG showing the rise in PSA levels already after one month, probably due to a direct effect of the concomitant increase in T levels and not only reduction in plasma volume alone. So, this result should not be misinterpreted but should be monitored over time like the other biochemical parameters after bariatric surgery. In fact, the low PSA plasma levels typically observed in male obese patients may be artificially low because of hemodilution and hypogonadal state, then they should be taken into consideration since alert threshold of cancer markers may differ in this population and, as suggested recently, this could lead to an underrating of potential severe prostate disease [25].

Disclosures statement

None of the authors declare competing financial interests.

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