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ORIGINAL CONTRIBUTIONS

Effects of Bariatric Surgery in Male Obesity-Associated Hypogonadism

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Abstract

Introduction The prevalence of obesity has grown exponentially over the last several decades. Research has linked male obesity to changes in the gonadal axis, which can induce functional hypogonadism. Bariatric surgery provides sustained weight loss and metabolic improvement. This was a retrospective cohort study to evaluate the male gonadal axis and metabolic profiles of obese individuals during the bariatric pre- and post-operative periods while comparing them to a normal body mass index (BMI) group.

Methods Twenty-nine obese men, who underwent bariatric surgery between 2012 and 2016 at the Federal University of Santa Catarina Hospital and a control group (CG) of 29 age-matched men with normal BMI, were analyzed. Bariatric pre- and 6-month post-operative data were compared with the CG.

Results The study group (G1) presented an average age, weight, and BMI of 42.8 ± 9.5 years, 155.2 ± 25.8 kg, and 50.6 ± 7.1 kg/m^2, respectively. The pre-operative total testosterone (TT) G1 values were different from the CG (229.5 ± 96.4 versus 461.5 ± 170.8 ng/dL, $p < 0.01$). Bariatric surgery promoted a statistically significant improvement in weight, TT, and metabolic profiles in surgical patients.

Conclusion Functional hypogonadism is prevalent in obese men, and we must be aware of this diagnosis. Although studies defining the best diagnostic parameters and indication of adequate hormone replacement therapy are lacking, an increase in TT levels during the first 6 months after bariatric surgery was identified in our study. Previous studies have shown that gonadal function can normalize after metabolic improvement.

Keywords Obesity · Testosterone · Bariatric surgery · Hypogonadism

Introduction

Obesity has been increasing exponentially over the last several decades regardless of local socioeconomic status and has become a worldwide epidemic [1, 2]. The GBD study showed that between 1980 and 2015, obesity prevalence doubled in 73 countries and showed an increase in most of the other countries as well [3].

Excess weight is a significant risk factor for morbidity and mortality, not only associated with cardiovascular events but also with Type 2 diabetes mellitus (T2DM), malignant neoplasms, and musculoskeletal disorders, causing around three million deaths a year [4–6].

Several studies have associated male obesity with changes in sex hormones, which can lead to functional hypogonadism. This change is characterized by low levels of serum testosterone in addition to low or inappropriately normal levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the absence of pituitary disease [7–14]. As a consequence, sexual dysfunction (erectile dysfunction and low libido), loss of bone mass and risk of fracture, fatigue, altered moods and concentration, sarcopenia, increased adipose tissue, dyslipidemia, and other signs and symptoms may be observed [7, 15–17].

Mechanisms that culminate in an androgen decrease in obese individuals are not fully understood. However, it is

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known that the increase in adipose tissue is associated with enhanced activity of the aromatase enzyme and consequent elevation of the peripheral conversion of testosterone to estradiol. Through a negative feedback mechanism, this conversion inhibits the pituitary LH secretion, which is responsible for the stimulation, production, and secretion of testosterone by Leydig cells, leading to low serum testosterone levels [8–10]. Furthermore, in the physiological state, testosterone decreases triglyceride uptake in adipose tissue by inhibiting lipoprotein lipase activity and favoring lipolysis through the activation of the hormone-sensitive lipase. In the presence of lower levels of circulating testosterone, there is a greater activation of lipogenesis and inhibition of lipolysis [8].

Obesity is currently considered a low-grade inflammatory state since adipose tissue produces considerable amounts of pro-inflammatory molecules that are secreted into the circulation. Inflammation promotes insulin and leptin resistance in the hypothalamus, which impairs leptin stimulation of gonadotropin-releasing hormone (GnRH). On the other hand, it has been demonstrated that obesity-associated elevation in serum leptin concentrations may directly inhibit testicular function, contributing to hypogonadism pathogenesis [8, 9].

Several studies have demonstrated that intensive lifestyle interventions, including diet and physical activity, were able to reduce body weight and insulin resistance, thus preventing progression to T2DM and cardiovascular disease [18–20]. However, some studies have observed that in the long-term, the majority of individuals regain the weight they lose after these interventions [21, 22]. In addition, a few clinical studies have evaluated the impact of diet and physical activity on testosterone levels in obese men. The results were conflicting; some demonstrated increased testosterone [23–28], and others were neutral [17, 29, 30], whereas a small study, applying a long fasting period, demonstrated a reduction in the serum levels of this androgen [31].

Bariatric surgery, on the other hand, provides expressive and most often sustained weight loss, regardless of the selected surgical technique [32–35]. In addition, it is effective in resolution of many obesity-associated complications such as DM2, hypertension, dyslipidemia, and sleep apnea [35–37].

Lifestyle changes should always be encouraged for patients with hypogonadism associated with obesity, diabetes, and/or metabolic syndrome. However, the increase in total testosterone (TT) in studies with diet and physical activity appears to be discrete, while the results of bariatric surgery are superior in improving serum androgen levels [17, 36].

Considering the important role that testosterone plays in quality of life, metabolic diseases, and multiple organ and system functions, this study proposed to evaluate the male gonadal axis of obese patients before and after the surgical obesity treatment and compare it with that of patients of normal weight in addition to other clinical and laboratory parameters [38–40].

Subjects and Methods

Ethical Considerations

The study protocol was approved by the ethics committee and institutional review at Federal University of Santa Catarina and was compliant with the Helsinki Declaration. Informed consent was obtained from all participants.

Participants

We have included consecutively all male patients aged ≥ 18 years who underwent bariatric surgery at the University Hospital Polydoro Ernani de São Thiago, Federal University of Santa Catarina (HU-UFSC), during the period of January 2012 to December 2016 ($n = 34$).

Indications for bariatric surgery followed the criteria of the Brazilian Public Health Guidelines [41]: (1) body mass index (BMI) ≥ 50 kg/m^2; (2) BMI ≥ 40 kg/m^2, with or without comorbidities with no success in the longitudinal clinical treatment performed for at least 2 years; or (3) individuals with BMI ≥ 35 kg/m^2 with comorbidities without success in the longitudinal clinical treatment performed for at least 2 years. All patients were evaluated by a multidisciplinary team, and those considered to have a high surgical risk, based on pre-surgical BMI and other clinical characteristics, were selected for sleeve gastrectomy (SG) ($n = 22$). The remaining patients ($n = 12$) underwent Roux-en-Y gastric bypass surgery (RYGB).

In addition, male individuals who were matched for age but with a normal BMI were randomly selected among patient's visitors and hospital employees ($n = 34$).

Those patients with endocrine disorders that cause impaired sexual function (including hyperprolactinemia, primary testicular disease, and decompensated thyroid disease), patients being treated with testosterone or other medications that interfere with gonadal function in addition to those who did not present data or blood collection during the analyzed period or those who did not agree to participate in the study, were excluded.

We have done a separate analysis of the prevalence of laboratory hypogonadism in a larger group, encompassing all male candidates for bariatric surgery at HU-UFSC in the same period ($n = 72$).

Data Collection

Data were collected regarding preoperative characteristics, surgical data, and an average 6-month follow-up after surgery. Information was obtained concerning patients' ages, comorbidities, and type of surgery in addition to any medications used. A complete physical examination was performed; the BMI was calculated from the weight quotient (in kilograms) by the squared height (in meters).

All patients underwent standard evaluation process for bariatric surgery. The laboratory evaluation was performed using peripheral blood samples collected in the morning, after 12 h overnight fasting.

Serum samples were measured for TT, sex hormone binding globulin (SHBG), and LH by chemiluminescence immunoassay (Imulite2000). Calculated free testosterone (cFT) was calculated from TT, SHBG, and albumin using the Vermeulen equation [42].

In order to evaluate the hormonal profile after surgery, blood collection as close to 6 months as possible (between 3 and 9 months) was used with a mean of 157.21 ± 39.14 days after the procedure. We excluded patients who, for any reason, did not have a blood sample collected during this period.

The group of patients with normal BMI underwent the same clinical and laboratory procedures once.

Reference Ranges

For the analysis of this study, serum TT levels were categorized in three ways: (1) according to the reference range of the method, (2) according to the Endocrine Society guidelines [43], and (3) according to Anawalt et al. [44]. The method used by the HU-UFSC laboratory considers TT levels between 241 and 827 ng/dL as normal. According to the Endocrine Society's guidelines, men with TT levels < 264 ng/dL are classified as hypogonadal, levels between 264 and 400 ng/dL are borderline and would require calculation of free testosterone for definition, and TT levels > 400 ng/dL are defined as eugonadic [43]. For Anawalt's criteria, men with TT levels < 150 ng/dL are classified as hypogonadal, between 150 and 400 ng/dL borderline zone, and those with levels greater than 400 ng/dL are considered eugonadic [44]. Regarding cFT, serum levels were evaluated according to the Endocrine Society's guidelines with hypogonadism diagnosed as < 6.5 ng/dL [43].

According to the World Health Organization's (WHO) criteria, patients were categorized as BMI [45]: (1) normal weight (BMI between 18.5 and 24.9 kg/m^2), (2) overweight (BMI 25 to 29.9 kg/m^2), (3) obesity class 1 (BMI 30 to 34.9 kg/m^2), (4) obesity class 2 (BMI 35 to 39.9 kg/m^2), and (5) obesity class 3 (BMI ≥ 40 kg/m^2). Those with class 3 obesity were subdivided BMI between 40 and 49.9 kg/m^2, BMI between 50 and 59.9 kg/m^2, and BMI ≥ 60 kg/m^2 for better understanding of the data.

Statistical Analysis

The results are presented as mean ± standard deviation for continuous variables and as absolute numbers and percentages for categorical variables.

The normality of distribution of continuous variables was tested with the Kolmogorov–Smirnov test.

The association of continuous variables with the factors of interest was verified by the Student's *t* test.

All tests were two-tailed and performed using Statistica Ultimate Academic (TIBCO Software Inc., Palo Alto, CA, USA). A p value < 0.05 was considered statistically significant.

Results

Fifty-eight male patients were enrolled in the study. Of the 34 men who underwent bariatric surgery between 2012 and 2016, five were excluded due to lack of data, yielding a final sample of 29 individuals in the obese group who underwent the procedure and 29 age-matched normal weight men, forming the control group.

Baseline characteristics are shown in Table 1. The mean age of the groups was 42.79 ± 9.50 years for the study group and 42.76 ± 9.57 years for the control group.

Only one of the patients in the surgical group had class 2 obesity, while the other patients were class 3. The mean weight was 155.26 ± 25.88 kg, while the control group had a mean weight of 72.87 ± 9.72 kg. When categorized according to BMI, 3.4% of the obese had a BMI between 35.0 and 39.9 kg/m^2, 51.7% between 40 and 49.9 kg/m^2, 34.5% between 50 and 59.9 kg/m^2, and 10.3% presented BMI ≥ 60 kg/m^2.

As for the metabolic profile, obese patients presented fasting glycemia and triglycerides superior to the control group in addition to lower high-density lipoprotein (HDL)-c. However, there was no difference in low-density lipoprotein (LDL)-c and total cholesterol between the groups.

The preoperative hormonal assessment of the study group showed a mean TT of 229.53 ± 96.45 ng/dL, which is significantly lower than the control group with a mean TT of 461.53 ± 170.89 ng/dL ($p < 0.001$). For free testosterone, the study group presented a mean of 5.35 ± 1.91 ng/dL, while in the control group, the mean was 6.17 ± 2.19 ng/dL ($p = 0.133$).

When categorizing TT according to the reference values of the method, 44.82% of the obese patients presented normal values at baseline, while 55.17% of them were considered hypogonadic. According to the Endocrine Society's guidelines, only one patient in this group was eugonadic, 31.03% were in the borderline zone and 65.51% presented hypogonadism. Of those in the borderline zone, 55.56% presented cFT < 6.5 ng/dL. Categorizing TT by Anawalt et al. values, we found that 3.44% had normal TT, 75.86% were borderline, and 20.68% of them were hypogonadal. Of the patients in the borderline zone, 77.86% had cFT < 6.5 ng/dL.

The surgical techniques used were sleeve gastrectomy (65.5%) and Roux-en-Y gastric bypass (34.5%). When comparing bariatric patients before and after surgery, a significant metabolic improvement was observed as shown in Table 2. Among those who underwent sleeve surgery, there were no

Table 1 Clinical and laboratory characteristics of the participants

Variables	Obese group ($n = 29$) (mean ± SD)/n (%)	Control group ($n = 29$) (mean ± SD)/n (%)	p
Age (years)	42.79 ± 9.50	42.76 ± 9.57	0.989
Weight (kg)	155.26 ± 25.88	72.87 ± 9.72	< 0.001
BMI (kg/m^2)	50.61 ± 7.10	23.36 ± 1.92	< 0.001
Glucose (mg/dL)	108.42 ± 26.63	94.38 ± 8.09	0.009
HbA1c (%)	6.51 ± 1.21	5.12 ± 0.31	< 0.001
Total cholesterol (mg/dL)	183.07 ± 31.57	185.69 ± 31.02	0.753
HDL (mg/dL)	38.79 ± 10.09	52.17 ± 15.19	< 0.001
Triglycerides (mg/dL)	146.89 ± 75.66	92.21 ± 51.51	0.002
LDL (mg/dL)	114.91 ± 3.14	119.07 ± 24.88	0.593
TSH (μIU/mL)	2.23 ± 1.03	2.36 ± 129	0.664
LH (mIU/mL)	3.19 ± 1.63	4.03 ± 1.09	0.043
SHBG (nmol/L)	24.22 ± 11.54	66.00 ± 29.89	< 0.001
Total testosterone (ng/dL)	229.53 ± 96.45	461.53 ± 170.89	< 0.001
Reference range of the assay			
Normal	44.82% (13)	96.55% (28)	< 0.001
Hypogonadism	55.17% (16)	3.44% (1)	
Endocrine Society			
Normal	3.44% (1)	62.06% (18)	< 0.001
Borderline	31.03% (9)	27.58% (8)	
Hypogonadism	65.51% (19)	10.34% (3)	
Anawalt			
Normal	3.44% (1)	62.06% (18)	< 0.001
Borderline	75.86% (22)	37.93% (11)	
Hypogonadism	20.68% (6)	0	
Free testosterone (ng/dL)	5.35 ± 1.91	6.17 ± 2.19	0.133
BMI (kg/m^2)			
< 25		100% (29)	
30–34.9			
35–39.9	3.40% (1)		
40–49.9	51.70% (15)		
50–59.9	34.50% (10)		
> 60	10.30% (3)		
Surgical technique			
Roux-en-Y gastric bypass	34.50% (10)		
Sleeve	65.5% (19)		

Reference range of the assay (Immulite 2000): normal between 241 and 827 ng/dL, hypogonadism < 241 ng/dL. *Endocrine Society* [43]: normal > 400 ng/dL, borderline between 264 and 400 ng/dL, and hypogonadism < 264 ng/dL. Anawalt [44]: normal > 400 ng/dL, borderline between 150 and 400 ng/dL, and hypogonadism < 150 ng/dL

BMI body mass index (kg/m^2), *HbA1C* glycated hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low density lipoprotein, *TSH* thyroid stimulating hormone, *LH* luteinizing hormone, *SHBG* sex hormone binding globulin

differences in fasting glycemia ($p = 0.086$), HDL-c ($p = 0.152$), and LDL-c ($p = 0.259$). For those who underwent bypass surgery, there was a reduction in fasting glycemia ($p = 0.030$), and the difference in HDL-c and LDL-c was not significant ($p = 0.104$ and $p = 0.191$, respectively). When the 29 patients who underwent any of the two surgical techniques were evaluated, the entire metabolic profile showed an improvement, except for LDL-c values ($p = 0.077$).

After 6 months of sleeve surgery, there was an average reduction of 13.04 ± 4.57 kg/m^2 in BMI with patients being reclassified as 5.26% as overweight, 21.05% were class 1 obesity at that time, 26.32% were class 2 obesity, 42.11% with

Table 2 Clinical and laboratory evaluation before (baseline) and 6 months after bariatric surgery

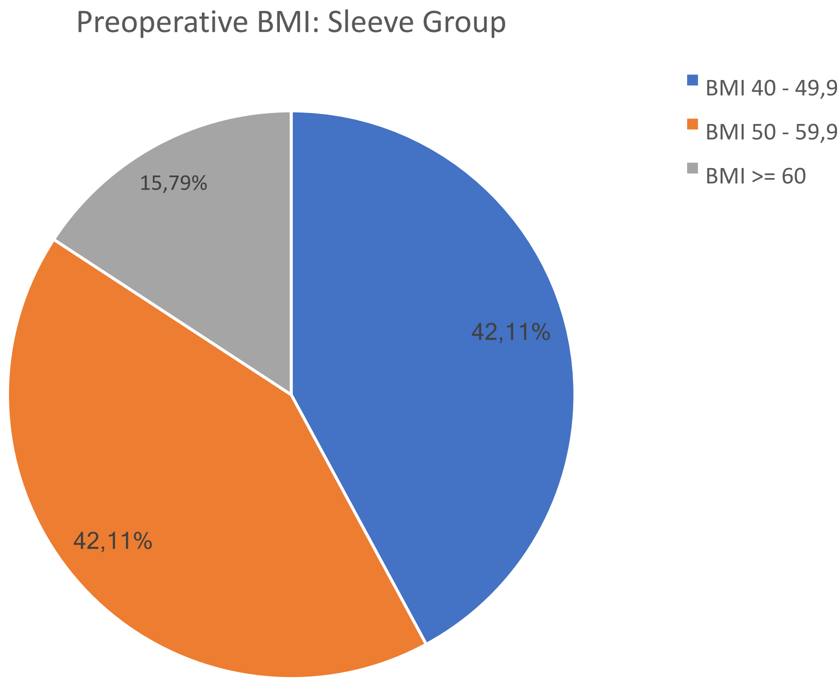
Variables	All patients ($n = 29$) (mean ± SD)			SLEEVE ($n = 19$) (mean ± SD)			Roux-en-Y ($n = 10$) (mean ± SD)		
	Preoperative	Postoperative	p	Preoperative	Postoperative	p	Preoperative	Postoperative	p
Weight (kg)	155.26 ± 25.88	115.98 ± 20.71	< 0.001	161.44 ± 25.26	121.28 ± 21.04	< 0.001	143.51 ± 23.95	105.92 ± 16.63	< 0.001
BMI (kg/m^2)	50.61 ± 7.10	37.82 ± 5.94	< 0.001	52.37 ± 7.12	39.33 ± 6.10	< 0.001	47.27 ± 6.03	34.94 ± 4.62	< 0.001
Glucose (mg/dL)	108.42 ± 26.63	94.03 ± 12/28	0.011	107.17 ± 30.87	93.47 ± 12.57	0.086	110.80 ± 17.06	95.10 ± 12.29	0.030
HbA1c (%)	6.58 ± 1.23	5.56 ± 0.45	< 0.001	6.71 ± 1.17	5.61 ± 0.39	0.003	6.37 ± 1.35	5.53 ± 0.55	0.040
Total cholesterol (mg/dL)	183.07 ± 31.57	160.10 ± 23.42	0.003	181.79 ± 25.90	165.16 ± 26.63	0.049	185.78 ± 42.91	148.89 ± 10.91	0.036
HDL (mg/dL)	38.79 ± 10.09	41.72 ± 9.35	0.027	40.63 ± 11.34	42.68 ± 10.38	0.152	34.89 ± 5.37	39.33 ± 7.33	0.104
TG (mg/dL)	146.89 ± 75.66	92.66 ± 30.35	0.001	133.00 ± 55.30	95.11 ± 33.58	0.003	176.22 ± 104.95	89.22 ± 25.06	0.035
LDL (mg/dL)	114.91 ± 33.14	102.47 ± 24.01	0.077	114.56 ± 28.33	105.68 ± 27.87	0.259	115.64 ± 43.58	95.44 ± 13.73	0.191
Total testosterone (ng/dL)	229.53 ± 96.45	388.38 ± 160.91	< 0.001	228.71 ± 112.29	386.07 ± 165.35	< 0.001	231.10 ± 60.99	392.75 ± 160.76	0.007
SHBG (nmol/L)	23.91 ± 11.62	51.30 ± 27.63	< 0.001	24.07 ± 12.70	47.23 ± 26.56	< 0.001	23.63 ± 10.01	58.64 ± 29.39	0.002
Free testosterone (ng/dL)	5.41 ± 1,92	6.28 ± 2.55	0.100	5.40 ± 2.24	6.59 ± 2.68	0.090	5.42 ± 1.23	5.72 ± 2.32	0.718
Weight loss (%)		25.14 ± 6.94			24.75% ± 7.25			25.88 ± 6.60	0.682
Absolute weight loss (kg)		39.28 ± 13.86			40.17 ± 14.43			37.59 ± 13.30	0.643
ΔTestosterone (ng/dL)[a]		158.84 ± 130.65			157.36 ± 124.41			161.65 ± 148.77	0.935
ΔBMI (kg/m^2)[b]		12.80 ± 4.32			13.04 ± 4.57			12.34 ± 3.99	0.687

BMI body mass index (kg/m^2), *HbA1C* glycated hemoglobin A1c, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TSH* thyroid stimulating hormone, *LH* luteinizing hormone, *SHBG* sex hormone binding globulin

[a] Difference between total postoperative and preoperative testosterone

[b] Difference in postoperative and preoperative BMI

Graph 1 Categorization of the preoperative BMI of patients undergoing sleeve surgery



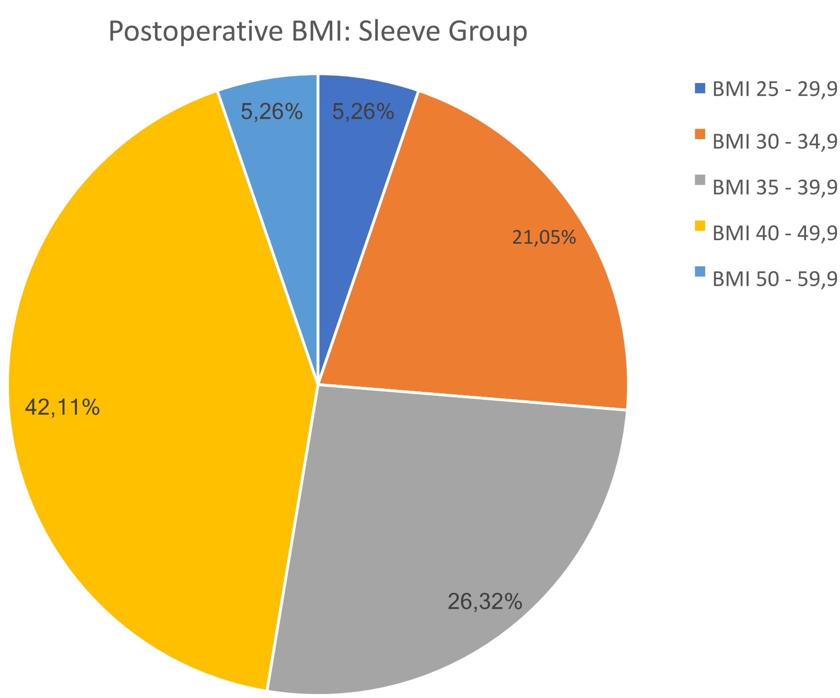
BMI between 40 and 49.9 kg/m^2, while only 5.26% had BMI between 50 and 59.9 kg/m^2 (Graphs 1 and 2).

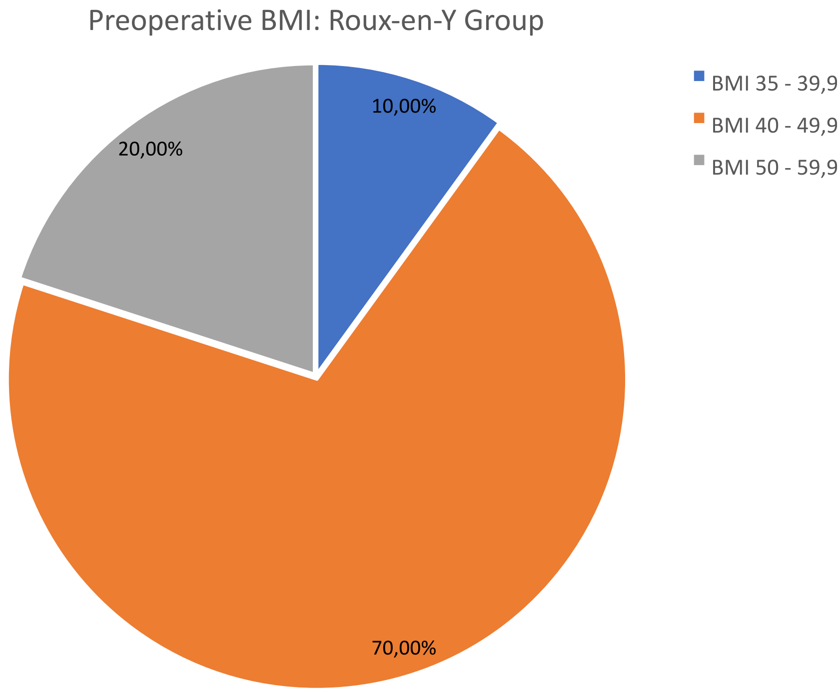
Patients who underwent the Roux-en-Y bypass technique presented a 12.34 ± 3.99 kg/m^2 reduction in BMI after 6 months, being reclassified as 20% overweight, 20% with class 1 obesity, 50% with class 2 obesity, and 10% with BMI between 40 and 49.9 kg/m^2 (Graphs 3 and 4).

The mean absolute weight loss after surgery was 39.28 ± 13.8 kg, totaling 25.14 ± 6.94% weight loss. Concurrently, the total preoperative testosterone of 229.53 ± 96.45 ng/dL increased to 388.38 ± 160.91 ng/dL after the procedure for an average increase of 69.2%, while values of SHBG increased from 23.91 ± 11.62 to 51.30 ± 27.63 nmol/L ($p < 0.001$).

Comparing bariatric patients' profile 6 months after surgery with the control group, a mean weight of 115.98 ± 20.71 kg was observed in the study group, while the control group presented a mean weight of 72.87 ± 9.72 kg ($p < 0.001$). However, at this time, no differences were observed between

Graph 2 Categorization of the postoperative BMI of patients who underwent sleeve surgery





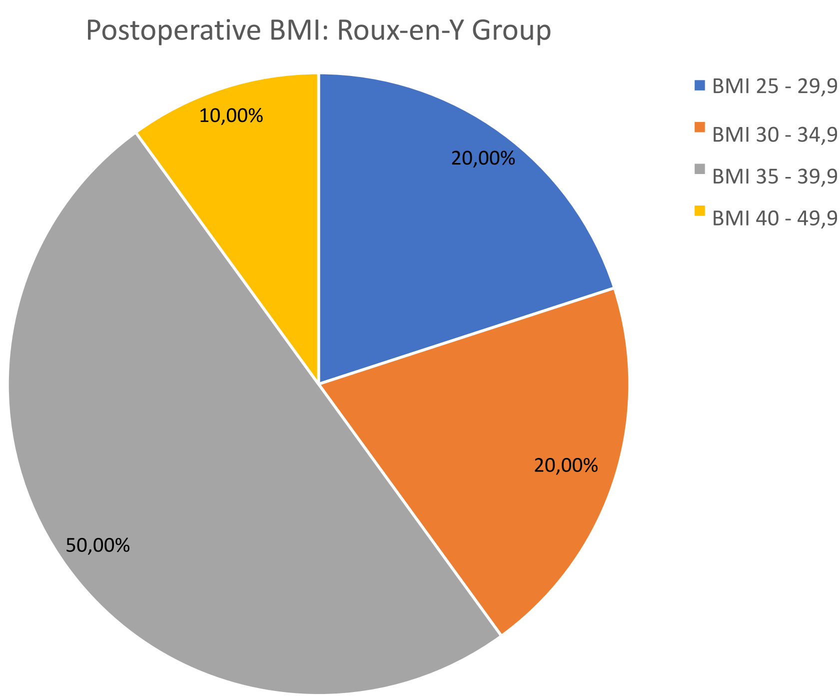
Graph 3 Categorization of the preoperative BMI of patients undergoing RYGB surgery

fasting glycemia levels and triglyceride values. Regarding TT values, 6 months after bariatric surgery, mean TT values were 388.38 ± 160.91 ng/dL, while the mean value in control group was 461.53 ± 170.89 ng/dL. Significant differences between the groups were no longer observed at this point (Table 3).

When we analyzed all male candidates for bariatric surgery at HU-UFSC in the same period ($n = 72$), mean TT was 232.15 ± 96.02 ng/dL, mean free testosterone 5.99 ± 2.65 ng/dL and mean BMI 51.44 ± 8.32 kg/m^2. The prevalence of hypogonadism was 58.33% according to the reference range of the method, 65.27% according to the Endocrine Society guidelines [43], and 20.83% in accordance with Anawalt's cutoff levels [44], which is consistent with the results obtained in the analysis of the study group.

Discussion

The present study demonstrated a high prevalence of biochemical hypogonadism in men with severe obesity and an improvement in hormonal and metabolic profiles 6 months after bariatric



Graph 4 Categorization of the postoperative BMI of patients who underwent RYGB surgery

Table 3 Clinical and laboratory comparison after bariatric surgery with control group

Variables	Postoperative ($n = 29$) (mean ± SD)	Control ($n = 29$) (mean ± SD)	p
Weight (kg)	115.98 ± 20.71	72.87 ± 9.72	< 0.001
BMI (kg/m^2)	37.82 ± 5.94	23.36 ± 1.92	< 0.001
Glucose (mg/dL)	94.03 ± 12.28	94.38 ± 8.09	0.900
HbA1c (%)	5.56 ± 0.45	5.12 ± 0.31	< 0.001
Total cholesterol (mg/dL)	160.10 ± 23.42	185.69 ± 31.02	0.001
HDL (mg/dL)	41.72 ± 9.35	52.17 ± 15.19	0.003
TG (mg/dL)	92.66 ± 30,35	92.21 ± 51.51	0.968
LDL (mg/dL)	102.47 ± 24.01	119.07 ± 24.88	0.012
Total testosterone (ng/dL)	388.38 ± 160.91	461.53 ± 170.89	0.099
SHBG (nmol/L)	51.30 ± 27.63	66.00 ± 29.89	0.059
Free testosterone (ng/dL)	6.28 ± 2.55	6.17 ± 2.19	0.863

BMI body mass index (kg/m^2), *HbA1C* glycated hemoglobin A1c, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TSH* thyroid stimulating hormone, *LH* luteinizing hormone, *SHBG* sex hormone binding globulin

surgery, regardless of the selected technique. When compared with same sex and age-matched individuals with normal weight prior to surgery, TT values were significantly higher in the control group, whereas after the procedure, significant differences were no longer observed between the two groups.

In view of the global obesity epidemic, hypogonadism associated with this condition is possibly one of the leading causes of low testosterone levels along with aging. Other causes such as metabolic syndrome and diabetes mellitus are also frequently associated with hypogonadism, ranging from 30 to 50% [12, 46]. Long-term lack of testosterone can affect an individual's sex life and quality of life in addition to contributing, along with other factors, to cardiovascular risk [39].

The mean TT levels below the recommended values characterize the hormone deficiency in this population. Corroborating the results found in this study, Aarts et al. [38] observed a mean TT of 276.66 ± 23.05 ng/dL and Pellitero et al. [39] 248.1 ± 91.4 ng/dL in patients with severe obesity before bariatric surgery.

The reference values of TT for a definition of hypogonadism vary greatly depending on the laboratory and assay methods. These variations are due to the absence of standardized tests, different calibrations, and the use of different populations to generate normality intervals [43]. In addition, there is no consensus in the literature regarding the most adequate cutoff point for hypogonadism for obese patients. The evaluation of symptoms compatible with the lack of testosterone in addition to an overall assessment of the patient is important for establishing the diagnosis.

When using reference values of the Immulite2000 assay, 44.82% of obese patients were considered eugonadic. However, when we used the criteria of the Endocrine Society [43] and Anawalt et al. [44], only 3.44% of them presented normal TT values and thus would not be further investigated for hypogonadism in clinical practice.

According to the Endocrine Society's guidelines [43], 31.03% of the patients were borderline and of these, 55.56% were hypogonadal considering a cFT < 6.5 ng/dL, which increased the hypogonadism diagnosis from 65.51 (TT < 264 ng/dL) to 82.75% when considering the value of TT and cFT in those individuals in the borderline areas. When classified according to the cut-off values of Anawalt et al. [44], 75.86% of the patients were borderline, of which 77.27% had cFT < 6.5 ng/dL, increasing the diagnosis of hypogonadism from 20.68 (TT < 150 ng/dL) to 79.31% after considering a cFT < 6.5 ng/dL. Both results appear to be clinically relevant. After taking into account the extensive methodological discussion in recent years, it is difficult to recommend one parameter over the other, suggesting the need for both evaluations.

In agreement with several studies [35, 37–39, 45, 47], as the weight/BMI went down, the TT levels increased. Weight reduction of 39.28 ± 13.86 kg was observed (25.14 ± 6.94% of the total weight) 6 months after surgery, associated with an absolute increase of 158.84 ± 130.65 ng/dL in testosterone levels. During the postoperative evaluation, 48% of the patients presented TT > 400 ng/dL, reclassifying them as eugonadic, whereas in the preoperative evaluation, only one of them was within this parameter.

Unlike previous studies [38–40], there was no significant increase in cFT after surgery. There were also no differences in cFT between normal weight individuals and the obese group both before and after the procedure. Studies involving bariatric surgery and correlation with the normal weight control group are scarce in the literature. The result may have been influenced by the limited sample size in addition to high SHBG values in the control group with no apparent explanation for these values.

SHBG values were lower in obese patients before bariatric surgery, compared to controls. As in previous studies [38, 39], there was a significant increase in their values 6 months after the surgery (23.91 versus 51.30 nmol/L, $p < 0.001$), which no longer presented a statistical difference in relation to the normal weight group ($p = 0.059$). This finding can be explained by the presence of insulin resistance in the obese patients, which results in compensatory hyperinsulinemia and, consequently, suppression of the hepatic SHBG production. After surgery, there is a large reduction in serum insulin and leptin resulting from the weight loss and, therefore, an increase in the hepatic production of SHBG [48, 49]. Unfortunately, it was not possible in the present study to assess insulin and leptin levels to corroborate the literature findings.

As assessed in other studies [38, 40, 47], the hormonal profiles clearly indicate a central origin for the observed hormonal dysfunction. LH was observed to be inappropriately normal (mean of 3.19 ± 1.63 mIU/mL), while circulating testosterone was low (mean of 229.53 ± 96.45 ng/dL). One limitation of the study was not evaluating the LH response after surgery, pre- and post-procedural FSH values, and also patients' spermogram.

Although patients selected for the study group did not present such remarkable metabolic disturbances, possibly because they were part of a population under constant medical care, there were improvements in most of these parameters. Possibly, the benefits of surgical treatment would be more evident in a population with a poorer baseline metabolic profile.

We should also consider that the time for evaluation after surgery was only 6 months, and yet, patients already presented hormonal profiles comparable to the normal weight group. A shorter evaluation interval after surgery is required in addition to a longer follow-up period in order to characterize the time course of recovery of the hypothalamic-pituitary-gonadal (HPG) axis and the evolution of hormone levels and weight loss over time.

The mean BMI of the study population was 50.61 kg/m^2, and it is the hospital's protocol to use the sleeve technique in patients with a higher BMI, which explains a higher prevalence of this technique among the individuals who underwent bariatric surgery (65.50%).

After analyzing the two types of surgery separately, the study demonstrated similar efficacy among the techniques in relation to weight loss (40.17 ± 14.43 kg in the sleeve versus 37.59 ± 13.30 kg in the bypass, $p = 0.643$) in addition to testosterone increase (157.36 ± 124.41 ng/dL in the sleeve versus 161.65 ± 148.77 ng/dL in the bypass, $p = 0.935$) 6 months after the procedure. Corona et al. [36] found a greater TT increase in malabsorptive surgeries compared to restrictive ones, but this finding was not confirmed after adjusting the percentage of weight loss by the BMI.

The patients showed improvement in their metabolic profiles after surgery but without significant LDL-c reduction (114.91 ± 33.14 mg/dL versus 102.39 ± 24.45 mg/dL, $p = 0.077$), probably due to the restricted sample size.

In relation to the postoperative period compared to the normal weight group, fasting glycemia that was higher in the obese group ($p = 0.009$) prior to surgery was no longer different after the procedure ($p = 0.900$). On the other hand, glycated hemoglobin (HbA1c) presented a reduction after surgery, placing it within normal values despite maintaining a statistically significant difference between the groups ($p < 0.001$). Regarding the post-surgical lipid profiles, obese patients presented lower total cholesterol and LDL-c than the control group ($p = 0.001$ and $p = 0.012$, respectively), whereas HDL-c remained lower in the patients who underwent the operation ($p = 0.003$).

Despite the increase in the prevalence of obese men, the latest guidelines do not discuss in depth how and when to treat hypogonadism in this population as soon as they are diagnosed. Testosterone replacement in obese men with deficiency was shown to be effective in reducing weight in addition to improving glycemic and lipid profiles in addition to reducing blood pressure values [50]. However, this replacement could possibly cause an increase in serum estradiol in these patients via aromatase activity. Studies, therefore, demonstrated improvement of the HPG axis after aromatase inhibitor treatment, showing reversion of hypogonadism associated with obesity [51, 52]. However, long-term confirmatory and safety studies are lacking to recommend the use of this therapeutic class of agents. Therefore, testosterone deficiency in obesity remains a clinically unresolved situation.

The treatment for hormonal improvement in obese patients who are candidates for bariatric surgery before and/or after surgery could be an adjuvant tool since it reduces adipose tissue and increases lean mass, but further studies are necessary before incorporating it into clinical practice.

We conclude from our study that biochemical hypogonadism is very prevalent in men with severe obesity and that these have a poorer metabolic profile than those with normal weight. With the surgical treatment of obesity, patients present, in addition to substantial weight loss, improved metabolic profile and testosterone production in the first 6 months. It is suggested, therefore, that testosterone deficiency should be considered as an associated factor for indication of bariatric surgery, since a significant improvement in the hormonal profile in these patients is demonstrated.

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Compliance with Ethical Standards

The study protocol was approved by the ethics committee and institutional review at Federal University of Santa Catarina and was compliant with the Helsinki Declaration. Informed consent was obtained from all participants.

Conflict of Interest The authors declare that they have no conflict of interest.

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