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Laparoscopic Sleeve Gastrectomy Improves Reproductive Hormone Levels in Morbidly Obese Males - A Series of 28 Cases

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Rezumat

Gastrectomia longitudinală laparoscopică îmbunătățește nivelul hormonilor reproductivi la bărbații cu obezitate morbidă - o serie de 28 cazuri

Introducere: Bărbații obezi prezintă frecvent reduceri ale hormonilor androgeni ce pot fi modificate după scăderea ponderală obținută prin chirurgie bariatrică. Gastrectomia longitudinală laparoscopică (GLL) a fost folosită frecvent în ultimul deceniu pentru tratarea obezității severe. Scopul studiului a fost evaluarea modificărilor hormonilor reproductivi după GLL.

Materiale și metode: Studiu prospectiv ce a inclus 28 de bărbați cu indice de masă corporală (IMC) > 35 kg/m^2, ce au efectuat GLL. Testosteronul Total (TT), Sex Hormone Binding Globulin (SHBG) și Hormonul Luteinizant (LH), parametrii biochimici și antropometrici au fost evaluați înainte și după chirurgie bariatrică.

Rezultate: La momentul inițial pacienții prezentau o medie a IMC de 50,10 (±11,19) kg/m^2, SHBG 23,37 (±17,47) nmol/L, LH 3,83 (±1,76) mUI/ml și TT 8,31 (±3,24) nmol/L. După GLL, pacienții au prezentat modificări semnificative ale parametrilor evaluați, cu valori medii ale IMC de 35,87 (±7,02) kg/m^2 ($p < 0,001$), SHBG 37,81 (±18,95) nmol/L ($p < 0,05$), LH 4,76 (±2,49) mUI/ml ($p < 0,05$), TT 12,7 (±3,8) nmol/L ($p < 0,001$). Procentul de reducere a excesului ponderal (%EBL) a fost 43,07 (±9,56) iar prevalența sindromului metabolic s-a redus semnificativ de la 75% la 25% ($p < 0,001$).

Concluzii: În afara scăderii IMC, GLL a determinat o îmbunătățire semnificativă a hormonilor reproductivi la bărbați cu obezitate severă.

Cuvinte cheie: obezitate, scădere ponderală, chirurgie bariatrică, gastrectomie longitudinală, testosteron, nivel hormoni androgeni

Abstract

Background: Obese males frequently present with low androgen levels that may improve after weight loss achieved by bariatric surgery. Laparoscopic sleeve gastrectomy (LSG) has been used often in the last decade as treatment for morbid obesity. The aim of this study was to evaluate modifications in the male reproductive hormone profile after LSG.

Patients and Methods: The prospective study included 28 males with body mass index (BMI) > 35 kg/m^2 who underwent LSG. Total Testosterone (TT), Sex Hormone Binding Globulin (SHBG) and Luteinizing hormone (LH), together with biochemical and anthropometric data, were evaluated at baseline and after LSG.

Results: Baseline patients had a mean BMI of 50.10 (±11.19) kg/m^2, SHBG 23.37 (±17.47) nmol/L, LH 3.83 (±1.76) mUI/ml and TT 8.31 (±3.24) nmol/L. After LSG, patients showed a mean BMI of 35.87 (±7.02) kg/m^2 ($p < 0.001$), SHBG 37.81 (±18.95) nmol/L ($p < 0.05$), LH 4.76 (±2.49) mUI/ml ($p < 0.05$), whereas mean TT was 12.7 (±3.8) nmol/L ($p < 0.001$). The percentage of excess body weight loss (%EBL) was 43.07 (±9.56) and metabolic syndrome prevalence

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decreased significantly from 75% to 25% ($p < 0.001$).
Conclusions: Beyond BMI loss, LSG significantly improved reproductive hormone levels in morbidly obese males.

Key words: obesity, weight loss, bariatric surgery, gastric sleeve, testosterone, androgen level

Introduction

Obesity is defined by the World Health Organization criteria as a body mass index (BMI) of 30 kg/m^2 or higher and affected in 2008 nearly 200 million men and 300 million women worldwide, representing the fifth leading risk factor for death at global level (1). The reason behind this position is that it often harbours hypertension, dyslipidaemia, hyperglycaemia and increased waist circumference, a group of disorders that is known together under the name of "metabolic syndrome" and recognizes individuals with increased risk for coronary artery disease, stroke or type II diabetes (2). Obesity is associated in both sexes with various hormonal modifications, including that of gonadal steroids and gonadotropins (3,4). Male obesity has often been linked to male hypogonadism, a condition defined as reduced testosterone concentration and decreased sperm production (5,6). The pathogenic mechanism of this hormonal imbalance is complex and has not been completely defined, but consists of reduced gonadotropin secretion, reduced circulating Sex Hormone Binding Globulin (SHBG) bound and bio-available testosterone and increased peripheral conversion of androgens to estrogens (5). On the other hand, androgen deficiency might be responsible of further modifications in body composition seen in obesity, increasing the occurrence of metabolic syndrome features.

Many studies have shown the effect of weight loss on female reproductive function, with increased probability of ovulation and conception (7). In contrast, fewer studies have evaluated the effects of obesity treatment on the male reproductive axis. Besides low caloric diet and medical therapy, bariatric surgery has shown to be an effective treatment for morbid obesity, providing high rates of constant weight loss, improvement of numerous comorbidities and increase in life expectancy (8). Previous studies have evaluated the effect of bariatric surgery on reproductive hormones (Biliopancreatic Diversion, Vertical Banded Gastroplasty, Roux-en-Y Gastric By-Pass, Laparoscopic Adjustable Gastric Banding), most of them showing an increase in total testosterone (TT) (9-15). Laparoscopic sleeve gastrectomy (LSG) represents a restrictive bariatric procedure that has gained interest among surgeons in the last decade, with consistent modifications of the hormones involved in energy balance (16), but with few results concerning the consequences on the reproductive environment.

The goal of this study was to evaluate changes in reproductive hormones together with anthropometrical and biochemical parameters in a group of severely obese males who underwent LSG.

Materials and Methods

The study was conducted with approval of the local Ethics Committee and in accordance with the ethical standards of the Helsinki Committee for Human Rights. All patients gave signed informed consent.

The study group consisted of 28 consecutive obese males who underwent LSG between January 2008 and March 2011 at "Sf. Ioan Hospital Bucharest" Department of Surgery and were evaluated before and after surgery at the "Elias Hospital Bucharest" Department of Endocrinology, Diabetes and Nutrition Disorders. In all cases, LSG was performed only after unsuccessful attempts to reduce weight through programs consisting in low caloric diet and scheduled physical activity. All patients met the 1991 NIH Consensus Conference guidelines for bariatric surgery, with a BMI $\geq$ 40 kg/m^2 or a BMI $\geq$ 35 kg/m^2 with associated comorbidities and LSG was in all cases intended as the definitive procedure. Exclusion criteria were: patients younger than 18 or older than 60 years, history of primary gonadal failure (including radiation, chemotherapy, orchitis, testicular trauma, Klinefelter syndrome and cryptorchidism) or secondary gonadal failure (including tumors of the hypothalamic-pituitary region, head injury or surgery, hyperprolactinemia and isolated/idiopathic hypogonadotropic hypogonadism), any syndromic hypothalamic obesity (as Prader-Willi syndrome), underlying chronic systemic diseases (including heart failure, renal and hepatic impairment, chronic obstructive pulmonary disease, chronic infective diseases) or occurrence of critical illness during the last 6 months before surgery or in the follow-up period, patients regularly taking medication known to be associated with impairment of gonadal steroids (including opiates, anabolic steroids, ketoconazole) or history of previous androgen replacement therapy, patients with history of recreational drug use or excessive alcohol intake.

The decision to perform LSG instead of other techniques was made by the surgical team based on individual factors including BMI, age, metabolic variables, comorbidities and perioperative risk, in accordance with the "European Association for Endoscopic Surgery" Guidelines on Obesity surgery (17). The surgical technique of LSG was performed as previously described (18). After inducing general anaesthesia, pneumoperitoneum was obtained through introduction of a Veress needle into the left abdominal quadrant. Five trocars were used: a 10 mm optical trocar, placed 2-3 cm to the left side of the median line, 20 cm below the xiphoid; two 12-mm trocars placed on the left and right midclavicular line, respectively, on the same horizontal line with the optical trocar; a 5 mm trocar placed on the left anterior axillary line, just below the left costal margin; a 5/10 mm trocar (Ternamian canula, Karl Storz, Germany) placed in the epigastric region for the use of the Cuschieri liver retractor (Karl Storz, Germany), its position and diameter depending on the left hepatic lobe size.

The first surgical step was the complete dissection of the

greater curvature of the stomach, by using the 10 mm LigaSure device (Valleylab, Boulder, CO, USA). The dissection was initiated at the level of the incisura angularis, continuing firstly to the right, towards the antrum, then progressing cranially to the gastric fundus and finally exposing the left diaphragmatic crus, to ensure proper conditions for fashioning a uniform gastric tube. The gastric sleeve resection started 2-3 cm from the pylorus by using 5 to 7 green/blue Endo-GIA Cartridges (Covidien, US), guided by a trans-orally introduced 36 Fr calibration bougie. The remnant gastric tube was fashioned with the equal contribution of the anterior and posterior gastric wall in order to avoid any helicoidal twist. After completing the gastric resection, the lateral stomach was removed throughout the 12 mm left lateral access, and then, a left subhepatic drainage tube and a nasogastric tube were placed. A methylene blue test was performed in all patients searching for stapled line errors or leaks. The stapled line was over-sewn only at the suspected areas. On postoperative day 1, all the patients were submitted to a Gastrografin X-Ray Upper Gastrointestinal Study for the gastric repletion and depletion evaluation, searching for possible stapled line early leaks. Nasogastric and drainage tube removal were considered in the same day, before and after the Upper Gastrointestinal Study, respectively.

Clinical evaluations were performed at baseline in a time lapse of 3 to 4 weeks before surgery and after a follow-up period of approximately 6 months and included medical history, clinical examination with blood pressure measurement and complete anthropometric evaluation (including height, weight, waist and hip circumference). Blood samples were drawn from an antecubital vein between 8 and 9 A.M. after an overnight fast and standard biochemical laboratory measures were performed immediately (complete blood count, erythrocyte sedimentation rate, glucose, alanine aminotransferase, aspartate aminotransferase, creatinine, urea, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides), whereas serum samples for hormonal determinations were kept at -80°C until assay. TT, SHBG and luteinizing hormone (LH) levels were measured using commercial kits (Immulite 2000; Siemens Healthcare Diagnostic Products, USA). LH was measured using solid-phase two-site chemiluminescent immunometric assay with analytical sensitivity of 0.05 mUI/mL, normal range 0.8-7.6 mUI/mL, intra-assay CV was 3.04-5.11% and inter-assay CV was 6.2-7.1%. SHBG was measured using solid-phase two site chemiluminescent immunometric assay with analytical sensitivity of 0.02 nmol/L, normal range 13-71 nmol/L, intra-assay CV was 2.3-5.3% and inter-assay CV was 4.0-6.6%. TT was measured using solid-phase competitive chemiluminescent immunometric assay with analytical sensitivity of 0.52 nmol/L, intra-assay CV was 5.1-16.3% and inter-assay CV was 7.2-24.3%, normal range 8.5-55 nmol/L. It is well known that no single cut-off value for low TT exists for adult males, with low level limits ranging between 15 and 8 nmol/L (430 and 230 ng/ml) (19). In the present study the lowest threshold, of 8 nmol/l, was used to place obese males in the low-TT range.

Presence of metabolic syndrome was established according to the ATP-III definition (2) if patients had at least 3 of the following 5 risk factors: waist circumference greater than 102 cm; serum triglyceride level of at least 150 mg/dL or on treatment; HDL-cholesterol level less than 40 mg/dL or on treatment; blood pressure of at least 130/85 mmHg or on treatment; and serum glucose level of at least 110 mg/dL or diabetes mellitus. Excess BMI loss (%EBL) was calculated considering a normalized body weight at a BMI of 25 kg/m^2 and dividing (BMI(pre-operative) – BMI(post-operative)) by (BMI(pre-operative) – 25).

Data distributions were expressed as mean, standard deviations (SD), ranges and percentages, as appropriate. The Student's t-test for paired samples and Wilcoxon rank test were used when appropriate to analyze comparisons between baseline and follow-up results in the study group. Chi-squared test for proportions was used to compare subgroups. Possible correlations were tested using Pearson analysis or Spearman's rank correlation coefficient. The data were analyzed using Stata IC-11 (Stata Corp 2009 Release 11, Statistical Software, USA). Comparison with data from previous studies (11,15) was made after transformation of TT values to nmol/L.

Results

At baseline patients in the study group had a mean age of 43.07 (±9.56) years, a mean BMI of 50.10 (±11.19) kg/m^2, all men showing BMI >35 kg/m^2. Metabolic syndrome prevalence was 75% and 4 patients (14%) had diabetes mellitus treated with oral hypoglycaemic agents. The hormonal analyses showed a mean TT of 8.31 (±3.24)nmol/L, with values below the 8 nmol/L cut-off in 57.14% of males. Mean SHBG resulted 23.37 (±17.47) nmol/L with six patients (21.4%) showing values below the normal range. Mean LH resulted 3.83 (±1.76) mUI/ml. Preoperative and 6 month follow-up results from the cohort are presented in *Table 1*.

Six months after LSG, patients showed a %EBL of 43.07 (±9.56) and a significant reduction in BMI ($p<0.001$). Mean SHBG and LH increased to 37.81 (±18.95) nmol/L ($p<0.05$) respectively 4.76 (±2.49) mUI/ml ($p<0.05$), all men showing SHBG in the normal range. Mean TT reached 12.7 (±3.8) nmol/L ($p<0.001$), with low TT levels (<8 nmol/L) prevalence reduced to 10.71% ($p<0.001$) (*Fig. 1*). Mean values of components of metabolic syndrome (waist circumference, hypertension, blood glucose, HDL and triglycerides) showed a significant improvement after LSG (*Table 1*). Metabolic syndrome prevalence was reduced to 25% ($p<0.001$). Correlation analysis between changes in TT, SHBG, LH and baseline BMI, %EBL, presence or absence of metabolic syndrome or diabetes, metabolic syndrome parameters at baseline or post-operative, did not show significance (data not shown).

Discussion

Worldwide obesity has shown a dramatic increase in the last 3-4 decades, the numbers nearly doubling since 1980 (1). Reducing BMI is associated with a decrease in obesity related

Table 1. *Baseline and 6 month follow-up data of study cohort. Data expressed as mean value ± SD*

	Baseline	Six Month	P value
BMI (kg/m^2)	50.10 ± 11.19	35.87 ± 7.02	<0.001
Waist Circumference (cm)	146.15 ± 19.98	115.27 ± 17.57	<0.001
Waist/Hip ratio	1.03 ± 0.15	0.97 ± 0.09	<0.05
Systolic BP (mmHG)	141.4 ± 17.29	127.2 ± 13.23	<0.001
Diastolic BP (mmHG)	85.20 ± 12.94	76.40 ± 8.6	<0.01
Blood Glucose (mg/dl)	109.51 ± 37.34	89 ± 16.3	<0.01
Total Cholesterol (mg/dl)	211.36 ± 37.33	186.24 ± 32.64	<0.01
LDL Cholesterol (mg/dl)	131.75 ± 34.95	120.67 ± 28.68	NS
HDL Cholesterol (mg/dl)	38.80 ± 9.90	42.55 ± 11.27	0.07
Triglycerides (mg/dl)	194.61 ± 67.23	111.62 ± 68.70	<0.001
Metabolic Syndrome Prevalence	75%	25%	<0.001

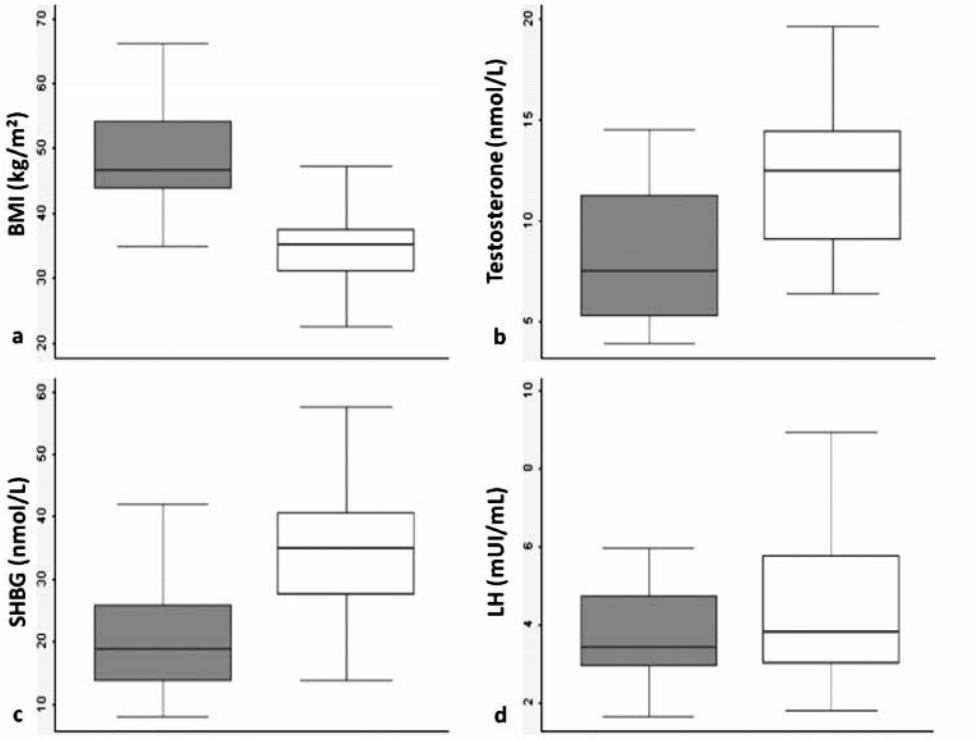

Figure 1. *Change in BMI, TT, SHBG, LH six month after LSG. Darker bars represent baseline values and lighter bars represent follow-up values (median and interquartile range). All p<0.05*

comorbidities in both men and women, but the best strategy to achieve this is still unknown. Low caloric diet together with sustained physical activity are known to be associated with low compliance and the few drugs that have shown efficacy were withdrawn due to important adverse effects, whereas bariatric surgery showed constant benefits for obesity treatment (20).

Starting from the 70ies, many studies have shown a negative correlation between TT and BMI (21,22). Obese males have shown low TT levels associated with alterations in amplitude but not in frequency of pulsatile LH secretion caused by high aromatase-induced androgen to estrogen conversion, pointing to a form of hypogonadotropic hypogonadism (23,24). A further feature that partially explains the possible low TT is low SHBG, thought to be the consequence of obesity-related hepatic function impairment (25). Finally, adipose derived hormones with role in body homeostasis like leptin, adiponectin, resistin and ghrelin, are also thought to influence testosterone metabolism (26). Mechanisms underlying the relationship between obesity and male hypogonadism remain therefore complex and not completely known but involve, for sure, all three levels of the hypothalamus-pituitary-gonadal axis as well as sex hormone transport and metabolism.

In the study group, levels of TT under the lowest cut-off for hypogonadism were present in more than half of the patient group, confirming a high rate of low androgen levels when BMI is > 35 kg/m^2. A considerable number of studies showed a link between reduced plasma testosterone and metabolic syndrome (27), but low TT did not show a significant correlation with presence of metabolic syndrome in our cohort. Cross-sectional and longitudinal studies of larger samples are needed to study the possible effect of low androgen levels in obese males with BMI > 35 kg/m^2.

To the best of our knowledge, this is the largest cohort of male patients that underwent LSG as the definitive bariatric

procedure to be evaluated for androgen status. The improvement of obesity related reproductive hormone modifications after bariatric surgery is well known in women, but less studied in men, in part because women more frequently undergo bariatric procedures (28). In our group significant changes in TT, SHBG and LH were observed six months after important weight loss induced by LSG. These results are consistent with previously published data that showed beneficial effects on the male reproductive profile in all types of bariatric surgery (9-15, 24,29). The 20 males treated with biliopancreatic diversion in the study conducted by Alagna et al. (11) showed mean baseline TT levels of 9.75±3.74 nmol/L and LH of 2.42±1.59 mIU/ml that significantly increased after 12 month to 16.39±6.56 nmol/L respectively 4.97±2.6 mIU/ml. Twenty obese patients, ten undergoing Laparoscopic Roux-en-Y Gastric Bypass, eight Laparoscopic Gastric Banding, and two Laparoscopic biliopancreatic diversions, were evaluated after a 6 month follow-up by Facchiano et al. (14), showing significant increase in TT (from mean 8.1 to 13.2 nmol/l, $P<0.001$), SHBG (from 19.0 to 39.4 nmol/L, $P<0.0001$) and LH (from 2.70 to 3.62 mIU/l, $P<0.05$). Seven patients treated with LSG were evaluated together with 25 undergoing Roux-en-Y Gastric Bypass in the study performed by Pellitero et al. (15), showing significant increase in TT (from 8.61±3.17 to 18.94±5,74 nmol/L, $p<0.001$) and SHBG (from 18.3±11.8 to 42.7±18.1 nmol/L, $p<0.001$), but not in LH. The different results on reproductive hormone improvement with different surgical techniques was evaluated in the metanalysis by Corona et al. (24), observing that non-malabsorbtive surgery determined a less consistent TT increase then malabsorbtive surgery, but this result was not confirmed after adjusting for percent weight loss of BMI.

A weaknesses of our study might be the small sample size, but obese women scheduled for bariatric surgery largely outnumber men. Moreover, evaluating obese male patients at 6 months after surgery might be too early to ensure a reassessment of the hypothalamus-pituitary-gonadal axis after consistent weight loss and this might explain the lack of correlation between TT, SHBG and LH modifications and BMI, %EBL or parameters of the metabolic syndrome. However, consecutive 6 and 12 month evaluation of patients that underwent LSG demonstrated important and stable %EBL as well as further significant changes in metabolic syndrome parameters (30), so we hypothesize that our on-going study in obese males who underwent this surgical procedure might keep the same trend of improvement of the hormonal status.

Conclusion

In contrast to obese women that often present with hyperandrogenism, obese males frequently show hypoandrogenism. The mechanisms of this imbalance remain unclear, as well as the predictive parameters of testosterone gain. Surgical weight loss seems to provide stable metabolic modifications and also prolonged effects on the reproductive environment. Many clinicians have therefore started to use the link between obesity and male hypogonadism to underline again, if still necessary, the importance of weight loss.

Conflicts of interest and source of funding

No conflicts of interest are declared.

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