Determinants of testosterone recovery after bariatric surgery: is it only a matter of reduction of body mass index?

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Objective: To explore the correlation models between body mass index (BMI) and sex hormones constructed from a male cross-sectional survey and evaluate the effects of surgery-induced weight loss on sex hormones in morbidly obese subjects that are not predicted by the constructed BMI correlation models.
Design: Cross-sectional population and longitudinal studies.
Setting: Bariatric surgery center in a university hospital.
Patient(s): A cross-sectional survey of a male general population of 161 patients (BMI median [interquartile range] = 29.2 [24.8–41.9] kg/m^2) in addition to 24 morbidly obese subjects (BMI = 43.9 [40.8–53.8] kg/m^2) who were undergoing bariatric surgery were prospectively studied for 6 and 12 months.
Intervention(s): Bariatric surgery on 24 morbidly obese men.
Main Outcome Measure(s): Cross-sectional population: construction of the best-fitting models describing the relationship between baseline BMI with total (TT) and calculated free (cFT) testosterone, E_2, sex hormone–binding globulin (SHBG), FSH, and LH levels. Longitudinal study deviation between the observed sex hormone levels at 6- and 12-month follow-up and those expected on BMI bases.
Result(s): The correlation of BMI with sex hormones was not univocally linear (E_2), but the best-fitting model was exponential for TT, cFT, FSH, LH, and TT/E_2 and power for SHBG. In addition to the significant improvement of all parameters observed after surgery in the longitudinal cohort, the increase in TT and SHBG, but not in cFT, was significantly higher than expected from the corresponding weight loss at 6 months from surgery (14.80 [12.30–19.00] nM vs. 12.77 [10.92–13.64] nM and 40.0 [28.9–54.5] nM vs. 24.7 [22.5–25.8] nM for TT and SHBG, respectively), remaining rather stable at 12 months.
Conclusion(s): The increase in TT and SHBG, but not the increase in cFT, after bariatric surgery is greater than expected based on weight loss. (Fertil Steril® 2013;99:1872–9. ©2013 by American Society for Reproductive Medicine.)
Key Words: Morbid obesity, BMI, weight loss, bariatric surgery, testosterone

Male obesity is associated with reduced levels of T and SHBG as well as with increased levels of estrogens. Despite the evidence of the negative feedback on the hypothalamus-pituitary-gonad axis or directly on the testis exerted by some adipose tissue–derived products, such as excess estrogens and leptin, kisspeptin, and other adipokines (1–7), the complex mechanisms underlying sex steroid hormone impairment in obesity are still unclear (7, 8–12). The majority of the studies reporting any association between male obesity and altered sex hormones suffer from population recruitment biases, which may ultimately affect results. In particular, cohorts are collected among patients

Received November 29, 2012; revised and accepted February 20, 2013; published online March 16, 2013.
M.L. has nothing to disclose. J.S. has nothing to disclose. G.S. has nothing to disclose. G.I. has nothing to disclose. M.L. has nothing to disclose. C.R. has nothing to disclose. G.F. has nothing to disclose. M.M. has nothing to disclose. E.M. has nothing to disclose.
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Fertility and Sterility® Vol. 99, No. 7, June 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.02.039

referred to andrology clinics for fertility and/or sexual dysfunction (8, 9, 13, 14) and/or are composed mainly of subjects with mild forms of obesity (body mass index [BMI] <40) (13, 15–18). Conversely, very few studies have focused on morbid obesity (9, 12, 19–24). Even fewer studies analyze modifications in circulating levels of sex hormones in obese patients after weight loss induced by dietary and life style changes (16, 17, 22) or by bariatric surgery (9, 12, 20, 22), showing an increase in T levels after weight loss. In these observational studies, the reported gain in T but not in E_2 levels has been shown to have a direct correlation with weight loss (8, 20); however, no attempt was made at either analyzing in detail the exact mathematical models correlating BMI with different sex hormones or at identifying further determinants of changes in sex hormone levels in patients who are losing weight.

Although evidence from randomized controlled trials is still limited to one single study (20), the role of excess body fat in the regulation of androgen levels can be considered well established. On the other hand, other hormones correlated with adiposity, such as leptin, are regulated not only by fat mass but also by its variation—that is, variations of adipose mass induce modifications of hormone levels even after adjusting for fat mass itself (25, 26).

There are many metabolic, hormonal, and clinical parameters that are altered in morbid obesity and can benefit from weight loss. However, for some of those (e.g., leptin levels), the observed variation after weight reduction is greater than expected (2, 3), whereas for others (e.g., blood pressure) the improvement is smaller than could be predicted by cross-sectional observations (27, 28).

The aim of the present work is to assess the potential effects of weight loss on sex steroid hormone levels in morbidly obese male patients, compared with those predicted by applying the mathematical models of BMI correlation with the different sex hormones obtained from a cross-sectional survey containing a 1:2 ratio of morbidly obese subjects.

MATERIALS AND METHODS

Patients

The clinic-based part of the cross-sectional survey was performed on a consecutive series of morbidly obese (BMI >40 kg/m^2) patients referred to a bariatric surgery unit (n = 56). The patients who actually underwent surgery were enrolled for a subsequent 6- and 12-month observation. The population-based sample (n = 105) was a part of the European Male Ageing Study (EMAS), Florence, random population sample of men enrolled between 2003 and 2005 in the Department of Clinical Physiopathology, University of Florence, for the EMAS multicenter, prospective, population-based study funded by the European Commission Fifth Framework Program, Quality of Life and Management of Living Resources (29).

Study Design

The study was approved by the Local Ethics Committee and Institutional Review Board. All patients enrolled gave signed informed consent after receiving written and oral information on the study.

All male patients referred to the Metabolic and Bariatric Surgery Unit of Careggi Hospital in Florence, Italy, between July 1, 2009, and June 30, 2010, were enrolled in the cross-sectional survey provided that they had a BMI >40 kg/m^2 and no history of present or past treatment for hypogonadism, were considered adequate for the surgical procedure by the investigators, and gave their informed consent. For those patients enrolled after January 1, 2010, who actually underwent surgery before December 31, 2010, a 6- and 12-month follow-up was performed after surgery. The choice of whether to have surgery and the choice of type of surgery were made by a team composed of a surgeon, an endocrinologist, and a dietitian, depending on the overall evaluation of the patient's history.

For the cross-sectional survey, all parameters specified below were recorded at first visit in both series of subjects. In the prospective observation, a presurgery baseline evaluation (T1) was performed at hospital admission for patients undergoing surgery and the follow-up evaluation was performed 6 (T2) and 12 (T3) months after T1. These follow-up time intervals were chosen to explore both short- (T2) and longer term (T3) effects of weight loss.

Measurements

Anthropometric measures. Height, weight, and waist circumference were measured for each subject at the three time points, according to the cohort.

Sex hormones. Serum TT, E_2, FSH, LH, and SHBG were measured by immunoassay (Immulite 2000, M-Medical System) on a sample of venous blood drawn in the morning. The analytical sensitivity of the assays was 0.5 nM for TT, 55 pM for E_2, 0.1 mIU/mL for FSH, 0.05 mIU/mL for LH, and 0.02 nM for SHBG. The ratio TT/E_2 was calculated on the bases of TT and E_2 values. TT and E_2 (30, 31) measurement by immunoassay has been validated by the isotopic dilution–liquid chromatography–tandem mass spectrometry (MS) method for values higher than nanomolar. In particular, using MS as the gold standard immunoassay ascertains low T compatible with hypogonadism (<11 nmol/L) with 75% sensitivity and 96.3% specificity; the parameters for detection of high E_2 (>120 pmol/L), as detected in all our morbidly obese subjects, are 88.4% and 88.6% (31). Calculated free T (cFT) was calculated as demonstrated elsewhere (32).

Mathematical Models

In the cross-sectional study, the best-fitting model was chosen for the description of the relation between BMI and sex hormones using SPSS 18.0 for Windows. The best model was chosen among the linear, power, cubic, exponential, and logarithmic ones according to the best value of R^2. The equations thus obtained were used to predict sex hormone and SHBG values after bariatric surgery (expected), which were compared with actually observed levels at the two time points of follow-up (observed at T2 and T3).

Statistical Analysis

Data were expressed as median (interquartile range). Nonparametric Wilcoxon's test was used for comparisons of