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Prevalence of male secondary hypogonadism in moderate to severe obesity and its relationship with insulin resistance and excess body weight

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SUMMARY

To study the prevalence of male obesity-secondary hypogonadism (MOSH) in patients with moderate to severe obesity, we performed a prospective prevalence study including 100 male patients with moderate to severe obesity at a university tertiary hospital. Total testosterone (TT) and sex hormone-binding globulin (SHBG) concentrations among others were assayed in all patients. Serum-free testosterone (FT) concentration was calculated from TT and SHBG levels. Semen analysis was conducted in 31 patients. We found a prevalence of 45% (95% CI: 35–55%) when considering decreased TT and/or FT concentrations. Serum concentrations of TT were correlated negatively with glucose ($r = -0.328$, $p < 0.001$) and insulin resistance ($r = -0.261$, $p = 0.011$). The same occurred with FT and glucose ($r = -0.340$, $p < 0.001$) and insulin resistance ($r = -0.246$, $p = 0.016$). Sixty-two percent (95% CI: 39–85%) of the patients with seminogram also presented abnormal results in semen analysis. The frequencies of low TT or low FT values were similar in patients with abnormal or normal semen analysis ($p = 0.646$ and $p = 0.346$, respectively). Ejaculate volume inversely correlated with BMI ($\rho = -0.400$, $p = 0.029$) and with excess body weight ($\rho = -0.464$, $p = 0.010$). Our data show the prevalence of MOSH in patients with moderate to severe obesity is high. Low circulating testosterone is associated with insulin resistance and low ejaculate volume with higher BMI and excess body weight. Semen analysis must be performed in these patients when considering fertility whether or not presenting low circulating testosterone.

INTRODUCTION

The prevalence of overweight and obesity have increased markedly during the past decades, reaching epidemic figures (Finucane *et al.*, 2011). Obesity is a significant risk factor for increased mortality, mainly because of its association with diabetes, cardiovascular disease and cancer (Berrington de Gonzalez *et al.*, 2010). Obesity is also associated with gonadal dysfunction, including polycystic ovary syndrome (PCOS) and male obesity-associated secondary hypogonadism (MOSH) (Alvarez-Blasco *et al.*, 2006; Saboor Aftab *et al.*, 2013).

PCOS and MOSH have been found in approximately 50% and 60% of severely obese female and male patients submitted to bariatric surgical procedures (Escobar-Morreale *et al.*, 2005; Calderon *et al.*, 2014). Of note, the marked weight loss that occurs after bariatric surgery results into remission of the hormonal derangements present in PCOS (Escobar-Morreale *et al.*, 2005) and MOSH (Botella-Carretero *et al.*, 2013; Calderon *et al.*, 2014; Samavat *et al.*, 2014) in almost all patients. The latter has been confirmed by a recent meta-analysis showing that bariatric surgery induces an increase in both total testosterone (TT) and free testosterone (FT), the normalization of serum sex hormone-binding globulin (SHBG), and the remission of MOSH in a large proportion of patients (Corona *et al.*, 2013). Therefore, it is not surprising why MOSH have been recently proposed as an indication for bariatric surgery (Lucchese & Maggi, 2013; Samavat *et al.*, 2014).

However, there are still some controversies regarding how obesity affects gonadal function and fertility in men and what are the best options for treatment (Stokes *et al.*, 2015). First, MOSH has been normally defined as low circulating testosterone levels with normal or reduced gonadotropins in the majority of the studies, without evaluating semen quality (Hofstra *et al.*, 2008; Dhindsa *et al.*, 2010). These studies demonstrated a high prevalence of MOSH, when defined by low serum testosterone levels, in patients presenting with obesity, from grade one to morbid obesity. Several mechanisms have been proposed to explain low circulating testosterone levels in obese men including, among others, increased aromatase activity and production of estradiol in adipose tissue, decreased SHBG levels thereby reducing TT concentrations, central leptin resistance, insulin resistance, and the direct effects of several adipokines (Zumoff, 1988; Gautier *et al.*, 2013; Landry *et al.*, 2013).

Whether infertility and semen abnormalities are directly related to the low androgens levels present in MOSH or to other factors related to obesity is unclear, but it is known that increased body weight is associated with abnormalities in semen parameters, and the percentage of men with abnormalities in sperm volume, concentration and total counts, increases with increasing body size (Eisenberg *et al.*, 2014).

We here aimed to assess the prevalence of MOSH and the presence of semen abnormalities in a series of moderate to severe obese men focusing on the anthropometric and biochemical parameters associated with these alterations.

SUBJECTS AND METHODS

Subjects

We studied 100 consecutive male patients with moderate to severe obesity referred to our Obesity Surgery Unit for counseling about metabolic surgery. Inclusion criteria required a body mass index (BMI) of at least 35 kg/m^2 and the compromise to attend the scheduled visits, irrespective of whether or not the patients finally underwent a bariatric procedure. Exclusion criteria included previous diagnoses of hypogonadism, thyroid disease, heart disease, kidney or liver failure and hyperprolactinemia or treatment for sexual dysfunction or drugs that could interfere with normal gonadal function. Thirty-one patients gave consent for semen analysis and completed the simplified International Index of Erectile Function test, in which a value equal or less than 21 is considered abnormal (Rosen *et al.*, 1997; Rhoden *et al.*, 2002). Twenty healthy controls were matched with patients in terms of age for establishing reference ranges for calculated FT concentrations and insulin resistance. Written informed consent was obtained and the study was approved by the Institutional Review Board of our Hospital, and according to the Declaration of Helsinki.

Anthropometric parameters were recorded. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured as the smallest perimeter between the costal border and the anterior suprailiac spines. Ideal body weight was calculated as the weight corresponding for a BMI of 25, given previous lack of consensus for the precise definition (Shah *et al.*, 2006; Montero *et al.*, 2011). Excess body weight (EBW) was calculated as the difference between body weight and ideal weight.

Analytical procedures and reference ranges

Serum creatinine, alanine aminotransferase, aspartate aminotransferase, and serum glucose concentrations were measured by standard colorimetric methods, using the Architect ci8200 analyzer (Abbot Diagnostics, Berkshire, UK). Levels of HDL cholesterol were measured in supernatant after plasma precipitation with phosphotungstic acid and Mg^{2+} (Boehringer Mannheim GmbH, Mannheim, Germany). Levels of total cholesterol and triglycerides were measured by enzymatic methods (Menarini Diagnostica, Florence, Italy). The LDL cholesterol concentration was calculated by using Friedewald's formula.

Fasting insulin, TT, SHBG, ferritin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol were also assayed (Escobar-Morreale *et al.*, 2005). Briefly, TT was measured by radioimmunoassay (Spectria; Orion Diagnostica, Espoo, Finland). FT concentration was calculated from total testosterone and SHBG concentrations (Vermeulen *et al.*, 1999). Serum ferritin, LH, FSH, estradiol, and insulin were measured by immunochemoluminescence (Immulite 2000; Siemens Healthcare Diagnostics Inc., Gwynedd, UK). Insulin resistance in the fasting state was estimated by the homeostasis model assessment method (HOMAIR). A commercial enzyme-linked immunosorbent assay (ELISA) was employed for the measurement of 25-hydroxyvitamin D concentrations (IDS Ltd., Boldon, UK). The specificity of this assay is 100% for 25-hydroxyvitamin D_3 and 75% for 25-hydroxyvitamin D_2, with negligible cross-reactivities with vitamin D_3 and vitamin D_2 (<0.01% and <0.30%, respectively). All the assays had a coefficient of variation <10%.

Normal ranges were 10.4–31.2 nmol/L for TT, and 13–71 nmol/L for SHBG as provided by the Central Laboratory of Hospital Universitario Ramón y Cajal. We used the 95% confidence interval of the mean of a group of 20 healthy men to obtain the reference range for FT, which was set at 225–635 pmol/L.

Semen parameters and reference ranges

Sperm samples were produced by masturbation and ejaculated into a clean wide-mouthed container, following a standardized 4-day sexual abstinence period. Sperm concentration was determined in a Bürker hemocytometer. The number of motile spermatozoa was analyzed using a Sperm Class Analyzer ® SCA 2002 (Microptic Inc., Barcelona, Spain). For semen analysis, we used the reference values proposed by the World Health Organization (Cooper *et al.*, 2010).

Statistics

We used the Ene 3.0 software (http://www.e-biometria.com) for *a priori* power analysis. Ninety-six patients were required to identify correctly a putative 50% prevalence of MOSH in moderately to severely obese men, with a confidence interval of 95% and a precision error (omega) of 10%. Results are expressed as means ± SD unless otherwise stated. The Kolmogorov–Smirnov statistic was applied to continuous variables. Logarithmic transformation was applied as needed to ensure normal distribution of the variables. Unpaired *t*-test or Mann–Whitney *U*-test were used to compare the central tendencies of the different groups as needed. To evaluate the association between discontinuous variables, we used the χ^2 test and Fisher's exact test as appropriate. Bivariate correlation was employed to study lineal association between two quantitative variables

using Pearson's or Spearman's tests as appropriate. Finally, a backwards multiple linear regression model was applied to evaluate the effects of several dependent variables on the changes of serum TT and FT concentration. Analyses were performed using SPSS 18 (SPSS Inc, Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

RESULTS

Prevalence of MOSH

The prevalence of MOSH was 45% (95% CI: 35–55%) when considering decreased TT and/or FT concentrations. One patient presented normal TT with reduced FT, 11 patients presented reduced TT with normal FT, and 33 patients presented both reduced TT and FT concentrations. Hence, when considering only decreased TT concentrations for defining MOSH a 44% (95% CI: 34–54%) prevalence of this condition was found, and when taking decreased values of FT, the prevalence of MOSH diminished to 34% (95% CI: 25–44%). None of the patients reported a decrease in beard or body hair growth, gynecomastia, or loss of strength. Forty-five patients had symptoms of fatigue, but all of them had sleep apnea or were active smokers. Fourteen patients also reported a decreased sex drive.

Characteristics of men diagnosed as having MOSH

Patients with or without MOSH had similar BMI, but patients with MOSH were older and had higher serum FSH, estradiol/TT ratio and fasting glucose concentrations (Table 1). There were no differences depending on the presence or absence of MOSH in the percentages of active smokers (16 vs. 20 in patients with or without MOSH, respectively, $p = 0.817$), diagnosis of sleep apnea (12 vs. 9, $p = 0.295$), or use of non-invasive mechanical ventilation (4 vs. 2, $p = 0.416$), and of patients reporting fatigue (23 vs. 22, $p = 0.547$) or decreased sex drive (7 vs. 7, $p = 0.808$). When defining MOSH only by decreased TT or only by decreased calculated FT similar results were obtained (data not shown).

Table 1 Comparison of clinical and biochemical characteristics of patients with and without MOSH

	With MOSH ($n = 45$)	Without MOSH ($n = 55$)	p
Age (years)	44 ± 11	37 ± 8	<0.001
Weight (kg)	144 ± 23	140 ± 21	0.459
Height (cm)	174 ± 7	174 ± 7	0.931
Body mass index (kg/m^2)	47.2 ± 7.2	46.2 ± 6.6	0.484
Excess body weight (kg)	68 ± 22	64 ± 20	0.450
Waist circumference (cm)	140 ± 16	139 ± 13	0.888
Systolic blood pressure (mmHg)	141 ± 16	142 ± 17	0.768
Diastolic blood pressure (mmHg)	87 ± 11	85 ± 12	0.415
Serum creatinine (μmol/L)	80 ± 18	80 ± 18	0.419
Aspartate aminotransferase (U/L)	27 ± 14	23 ± 9	0.118
Alanine aminotransferase (U/L)	49 ± 38	43 ± 23	0.330
Total cholesterol (nmol/L)	5.0 ± 0.9	5.1 ± 1.1	0.489
High-density lipoprotein cholesterol (nmol/L)	1.0 ± 0.2	1.0 ± 0.2	0.297
Low-density lipoprotein cholesterol (nmol/L)	3.1 ± 0.8	3.2 ± 0.8	0.650
Triglycerides (nmol/L)	1.9 ± 0.8	1.8 ± 1.0	0.518
Total testosterone (nmol/L)	8.0 ± 1.8	15.3 ± 4.2	<0.001
Sex hormone binding globulin (nmol/L)	2.2 ± 0.9	2.7 ± 0.9	0.072
Free testosterone (pmol/L)	200 ± 45	367 ± 105	<0.001
Luteinizing hormone (U/L)	3.2 ± 1.5	3.4 ± 1.2	0.507
Follicle-stimulating hormone (U/L)	4.2 ± 2.0	3.2 ± 1.5	0.022
Estradiol (pmol/L)	121 ± 40	125 ± 48	0.896
Estradiol/total testosterone ratio	0.15 ± 0.05	0.08 ± 0.03	<0.001
Fasting Insulin (pmol/L)	215 ± 167	174 ± 139	0.178
Fasting glucose (mmol/L)	7.2 ± 3.1	5.9 ± 1.7	0.011
Homeostasis model assessment of insulin resistance	9.5 ± 6.9	7.2 ± 7.9	0.131

Data are means ± SD.

Serum concentrations of TT and FT correlated inversely with glucose ($r = -0.328$ and $r = -0.340$, respectively, $p < 0.001$) and HOMAIR ($r = -0.261$, $p = 0.011$ and $r = -0.246$, $p = 0.016$, respectively). A multivariate linear regression model, introducing TT as dependent variable and age, BMI, EBW, fasting glucose, and insulin as independent variables, retained glucose as the only variable explaining the variability in TT levels (Table 2). A similar model introducing FT as dependent variable retained glucose and age as the only variables associated with the variability in FT values (Table 2).

Semen analysis

Thirty-one patients gave consent for semen analysis. This subgroup of patients was representative of the whole sample of obese men in terms of age (39.9 ± 6.6 year) and BMI (48.01 ± 8.45 Kg/m^2). Fifteen patients (48%, 95% CI: 29–68%) presented abnormal semen results, but one patient was finally excluded from the statistical analysis because of azoospermia. The hormonal profile of patients with or without abnormal semen did not differ, including TT and FT (Table 3).

These 31 patients completed the simplified International Index of Erectile Function test, with 19 men (62%, 95% CI: 43–81%) scoring below normal. There were no differences in the results of this test when comparing patients with or without abnormal semen (Mann–Whitney U = 86.000, $p = 0.324$), or when comparing them with or without MOSH (Mann–Whitney U = 94.000, $p = 0.674$).

We found that ejaculate volume inversely correlated with BMI ($\rho = -0.400$, $p = 0.029$) and with excess body weight ($\rho = -0.464$, $p = 0.010$). Furthermore, we found that serum estradiol inversely correlated with sperm counts ($\rho = -0.411$, $p = 0.027$), total mobility ($\rho = -0.404$, $p = 0.030$), and normal morphology ($\rho = -0.433$, $p = 0.024$). No other variable correlated with abnormal semen parameters (data not shown).

DISCUSSION

Our present results show a large prevalence of MOSH in patients with moderate to severe obesity and that semen

Table 2 Multivariate linear regression analysis

	R^2	F	β	p
Model I	0.164	6.161		0.001
Dependent variable				
Total Testosterone				
Retained independent variables				
Glucose			−0.261	0.010
Model II	0.211	6.221		<0.001
Dependent variable				
Free testosterone				
Retained independent variables				
Age			−0.296	0.003
Glucose			−0.222	0.024

Age, BMI, EBW, glycemia, and insulinemia were introduced as independent variables in both backwards stepwise linear regression models.

Table 3 Sperm analysis[a]

	Subnormal semen (n = 14)	Normal semen (n = 16)	p
Age (years)	42 (15)	40 (8)	0.382
Body mass index (kg/m^2)	46.0 (7.0)	45.4 (15.0)	0.589
Excess body weight (kg)	68.3 (26.6)	66.7 (34.0)	0.901
Total testosterone (nmol/L)	11.4 (6.8)	12.0 (8.3)	0.835
Sex hormone binding globulin (nmol/L)	2.7 (1.6)	3.0 (1.8)	0.819
Free testosterone (pmol/L)	282 (190)	265 (211)	0.708
Luteinizing hormone (U/L)	3.6 (2.7)	2.9 (1.2)	0.280
Follicle-stimulating hormone (U/L)	3.3 (2.3)	2.9 (1.9)	0.318
Estradiol (pmol/L)	128 (77)	114 (51)	0.382
Estradiol/total testosterone ratio	0.1 (0.06)	0.1 (0.07)	0.694
Fasting insulin (pmol/L)	151 (150)	174 (125)	0.467
Fasting glucose (mmol/L)	5.3 (1.5)	5.4 (1.9)	0.394
Volume (mL)	2.0 (2.0)	2.5 (2.0)	0.314
Sperm concentration (10^6/mL)	9.5 (28)	53 (41)	0.001
Progressive motility (%)	18 (26)	43 (5)	0.001
Liabilities (%)	5 (5)	10 (10)	0.001
Immobile (%)	75 (30)	50 (8)	0.131
Normal form (%)	29 (8)	37 (17)	0.382

One patient was excluded from the statistical analysis because of complete azoospermia. Data are shown as median (interquartile range). SHBG, sex hormone binding globulin. [a]Classified according to WHO criteria.

abnormalities are also very frequent. However, there is a dissociation between circulating concentrations of testosterone and semen abnormalities in these men, the former being mainly associated with age, glycemia, and insulin resistance, and the latter being associated with BMI, EBW, and circulating estradiol. Moreover, considering that clinical symptoms did not serve to discriminate patients with MOSH from those showing normal androgen levels, the identification of this disorder would require universal screening by measuring serum androgens in all male patients with moderate or severe obesity, even if asymptomatic. Semen analysis should also be performed in those seeking fertility, whether or not presenting with low testosterone, given the potential need for specific therapies such as exogenous gonadotropins with the aim of improving spermatogenesis.

Male hypogonadism is a condition characterized by inadequate testicular production of sex steroids and spermatozoa; however, the term is more commonly used to identify testosterone deficiency (Bhasin *et al.*, 2010). When considering androgens alone, the prevalence of MOSH was studied in the past in a cross-sectional study in the Netherlands (Hofstra *et al.*, 2008). The authors of this study involving 160 patients showed that TT was subnormal in 57.5% and FT in 35.6% of the subjects, similar to our results, and both were inversely related to BMI. They also found decreased libido and more erectile dysfunction in these patients, yet semen analysis was not investigated (Hofstra *et al.*, 2008). Recent studies performed in patients before and after metabolic surgery have yielded even higher proportion of MOSH, up to 79% when using TT as the diagnostic criteria (Pellitero *et al.*, 2012; Corona *et al.*, 2013). However, this very large figure of MOSH may represent a selection bias overestimating the prevalence of MOSH because this study included only patients who underwent bariatric procedures, and obesity-associated comorbidities are an indication for surgery.

Semen abnormalities are associated with increased body weigh as the percentage of men with abnormal sperm volume, concentration, and total sperm counts increased with increasing body size (Eisenberg *et al.*, 2014). In contrast, a recent meta-analysis pooling five studies has found no relationship between BMI and semen parameters (MacDonald *et al.*, 2010). However, the main limitation of this meta-analysis was that data from most studies could not be aggregated, and the authors concluded that population-based studies with larger sample sizes and longitudinal studies were required (MacDonald *et al.*, 2010).

The precise physiopathology of MOSH is not completely understood, but the increased estrogen production by enhanced conversion of testosterone to estradiol by the enzyme aromatase cytochrome P450 that is abundantly present in the adipocyte (Zumoff, 1988) has been proposed as one of the factors involved. Serum estradiol exerts a negative feedback on pituitary LH secretion (Hofstra *et al.*, 2008) and may also down-regulate GLUT4 by an augmentation of the estrogen receptor beta expression with a resultant increase in insulin resistance (Cohen, 2008). The role of increase aromatization in MOSH has also been supported by the efficacy of the aromatase inhibitor letrozole to treat this condition (Loves *et al.*, 2008). Although we could not find differences in serum estradiol between patients with or without MOSH, we found a higher estradiol/TT ratio in patients with MOSH, and also that serum estradiol concentrations inversely correlated with sperm counts and indexes of sperm health.

Other factors associated with obesity such as central leptin resistance and the increase in some adipokines (Fischer-Posovszky *et al.*, 2007; Gautier *et al.*, 2013; Landry *et al.*, 2013) may also participate in the physiopathology of MOSH by inhibiting gonadotropin pulses and/or secretion. In our study, we found negative correlations with glucose and insulin resistance in agreement with previous data showing that glycemia and insulin resistance are clearly associated with secondary hypogonadism in men: first, testosterone concentrations have been shown to be diminished not only in obese men but also in those with type 2 diabetes (Yeap *et al.*, 2009; Zitzmann, 2009); second, an association with other features of the metabolic syndrome (in which insulin resistance is a hallmark) has also been observed (Dandona *et al.*, 2008); third, we have recently shown that correction of MOSH after metabolic surgery is accompanied by a reduction in both glucose concentrations and insulin resistance (Botella-Carretero *et al.*, 2013; Calderon *et al.*, 2014); and fourth, it has been recently shown that hyperinsulinism induces DAX-1 in Leydig cells of mice which in turn inhibits testicular steroidogenesis (Ahn *et al.*, 2013).

It has been shown that testosterone therapy is effective in achieving sustained weight loss in obese hypogonadal men, irrespective of the severity of obesity (Saad *et al.*, 2015). Therefore, testosterone therapy might be advocated as a valid treatment for MOSH – such as other weight loss strategies and aromatase inhibitors – when fertility is not an issue, although MOSH is still not considered a 'classic' form of hypogonadism (Nguyen *et al.*, 2015). Long-term cardiovascular adverse effects in the long term have to be balanced against, and the uncertainties about how long testosterone therapy might be needed are still not solved yet (Nguyen *et al.*, 2015). On other hand, when patients have an indication for metabolic surgery, this has been proved to be a highly effective treatment for reversing MOSH (Samavat *et al.*, 2014).

The physiopathology of the relationship between abnormal sperm production and adiposity is uncertain and complex. Alterations in the hypothalamic–pituitary–gonadal axis, as mentioned

above, can lead to relative declines in gonadotropin levels (Hofstra *et al.*, 2008; Michalakis *et al.*, 2013). However, in our study we could not find low levels of gonadotropins in patients with subnormal semen parameters, but we found that serum estradiol inversely correlated with the number of spermatozoa. We also found that the alterations in the semen parameters were associated with BMI and excess body weight, in agreement with a recent study (Eisenberg *et al.*, 2014). It is possible that other factors may play a role in the physiopathology of semen alterations beyond that of gonadotropins in the obese patient, including a putative increase in testicular temperature, and other lifestyle, nutritional or environmental factors among others (Sharpe & Franks, 2002).

Our study have several limitations: first, it is possible that the small sample size of the subgroup used for semen analysis in our study may have precluded us from finding any significant difference in the aforementioned nutritional factors. Second, not all patients consented in having their spermatozoa analyzed, so the net effect of multiple positive and negative biases on sperm concentration is difficult to estimate in our study (Handelsman, 1997). This possibility is further supported by the fact that, in our study, all patients reporting a decreased sex drive consented for semen analysis. Third, patients with MOSH were significantly older than those without MOSH, and a previous study demonstrated that free testosterone had a curvilinear relationship with weight change in the same direction, as those patients who gained or lost >15% of weight showed this significant change (Camacho *et al.*, 2013). Unfortunately data on when patients started being obese and longitudinal changes in weight were not available in our study, so we were not able to analyze this issue.

In conclusion, the prevalence of MOSH in patients with moderate or severe obesity is high and, because clinical symptoms of gonadal dysfunction were not useful for its detection, routine screening for this condition is warranted before obesity surgery, even in asymptomatic men. Also, regardless of the testosterone concentrations, a semen analysis should be performed in moderate or severely obese patients considering fertility since sperm abnormalities are also prevalent in these men.

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CONFLICT OF INTEREST

The Authors declare that they have no conflict of interest.

AUTHORS CONTRIBUTIONS

B.C., J.G.-M., B.V.-P., and J.I.B.-C. contributed to data acquisition and revision. B.C. and J.I.B.-C. wrote the manuscript. J.I.B.-C and H.F.E.-M. designed the study. All authors contributed to data interpretation, drafted and revised critically the article for important intellectual content, and approved the final version of the manuscript.

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