Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Cross-sectional, Primary Care–Based Study of the Prevalence of Hypoandrogenemia in Nondiabetic Young Men with Obesity

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Objective: Obesity-associated hypoandrogenemia is increasing in parallel to the obesity epidemic. The prevalence of hypoandrogenemia in nondiabetic young men with obesity is not known. This study aimed to evaluate the prevalence of hypoandrogenemia and associated risk factors in this population.
Methods: This cross-sectional study included 266 nondiabetic men < 50 years of age with obesity who were referred from primary care. Total testosterone (high-performance liquid chromatography mass spectrometry), sex hormone–binding globulin, free testosterone (FT), luteinizing hormone (LH), high-sensitivity C-reactive protein, and homeostatic model assessment of insulin resistance were determined. Body composition and erectile function were also assessed. Hypoandrogenemia was defined as FT level < 70 pg/mL.
Results: Subnormal FT concentrations were found in 25.6% of participants. Hypoandrogenemia prevalence was different along the BMI continuum, being > 75% in individuals with BMI ≥ 50 kg/m^2. A multivariate regression analysis indicated that increasing BMI ($P < 0.001$), age ($P = 0.049$), and reduced LH levels ($P = 0.003$) were independent risk factors for hypoandrogenemia.
Conclusions: In a primary care–based cohort of nondiabetic young men with obesity, hypoandrogenemia was a very prevalent finding and was directly associated with adiposity. Obesity, age, and reduced LH levels were independent risk factors associated with hypoandrogenemia. Further prospective studies are needed to evaluate the long-term consequences of hypoandrogenemia in this population.

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Introduction

In men, obesity is considered the major cause of hypogonadism, a clinical syndrome characterized by low serum total testosterone (TT) and/or free testosterone (FT) concentrations and associated symptoms and signs of testosterone deficiency (1). More specifically, hypoandrogenemia is the term coined to denominate the finding of subnormal testosterone concentrations in men, independently of associated clinical symptoms or signs of decreased testosterone levels (2).

According to several epidemiological studies, hypoandrogenemia affects 20% to 40% of men with obesity (3), which contrasts with the prevalence of 4% to 5% in the general male population (4). However, most of the studies that have evaluated hypoandrogenemia in men with obesity have been conducted in elderly patients with cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), or chronic diseases, conditions all associated with subnormal testosterone levels (5,6). Also, many studies have assessed patients undergoing bariatric surgery or attending specialized care, factors linked to increased likelihood of presenting with hypoandrogenemia (7).

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The finding of a subnormal level of testosterone is not a trivial issue. Although often overlooked and underdiagnosed, hypoandrogenemia is associated with visceral obesity, reduced lean body mass, T2DM, the metabolic syndrome, sexual dysfunction, impaired erectile function, and decreased quality of life (8). Also, testosterone deficiency has been associated with multi-morbidity and with mortality risk (9,10).

Nevertheless, despite the capital importance of testosterone concentrations in men, no studies have yet specifically been conducted in a very prevalent population, the nondiabetic young man with obesity. This population represents a large percentage of people at risk and may potentially benefit from an early assessment of testosterone status.

Therefore, the aim of this study is to assess the prevalence of subnormal testosterone concentrations in a primary care–based cohort of young nondiabetic men with obesity.

Methods

Patients

From June 2013 to June 2015, we randomly selected six primary care centers located in the metropolitan area of Malaga, Spain. Next, in each primary care center, we randomly selected five primary care physicians and asked each primary care physician to consecutively invite 10 young (<50 years old) adult men with obesity (defined by BMI [weight in kilograms divided by height in meters squared] ≥ 30 kg/m^2) to participate in this study.

Exclusion criteria were a previous diagnosis of hypoandrogenemia, hemochromatosis, or T2DM (diagnosed if a potential participant was taking medication for diabetes, had fasting plasma glucose ≥ 126 mg/dL [7 mmol/L], or had hemoglobin A1c (HbA1c) ≥ 6.5%, as confirmed by repeated testing). Use of androgens or treatment with phosphodiesterase 5 inhibitors or alprostadil was also not allowed. In addition, participants with hepatic or renal impairment, CVD, or cancer were excluded from the study. All participants had normal pubertal development, intact sense of smell, and no increased luteinizing hormone (LH) levels or evidence of intercurrent pituitary disease or additional pituitary hormone deficiencies (thyrotropin, free thyroxine, prolactin, adrenocorticotropin, cortisol, and insulinlike growth factor 1 levels were all within the normal range).

Study protocol

Study participants were instructed to eat a light meal the evening before the clinical evaluation and to fast from 10 PM. Fasting blood samples were collected before 10 AM and were centrifuged at 4°C. Plasma and serum were distributed in aliquots and stored at −80°C until analysis.

Participants completed a structured interview to obtain the following data: age, medical history, current diseases, and associated treatment. The following data were also collected: height, waist circumference (WC), blood pressure (BP), and heart rate. Height was obtained with a stadiometer. WC was measured using a specific abdominal circumference tape measure (200 cm in length). The tape measure was wrapped around the participants' waists at the midway point between the bottom of the ribs and the top of the iliac crest. The participants were encouraged to breathe naturally during the procedure, to relax their abdominal muscles, and to not hold their breath. BP was measured twice with the participant seated and at an interval of 5 minutes between measurements (Omron M6 Comfort blood pressure monitor; Omron Healthcare, Inc., Hoofddorp, Netherlands). Participants were considered to have hypertension if they were taking any antihypertensive medication or had BP of 140/90 mm Hg or greater.

TT was determined by high-performance liquid chromatography mass spectrometry (HPLC-MS), conducted in a triple quadrupole liquid chromatography mass spectrometry system (Model 6460; Agilent Technologies, Santa Clara, California). The lower limit of detection was 0.024 ng/mL, the interassay coefficient of variation was 8.43% at 0.20 ng/mL, 2.64% at 1.49 ng/mL, and 2.64% at 8.08 ng/mL, and the intraassay coefficient of variation was 2.09% at 0.20 ng/mL, 3.67% at 1.49 ng/mL, and 1.64% at 8.08 ng/mL. Accuracy was 104%, and recovery was 97%. The calibrators were human serum sample based. The material was lyophilized and contained six levels of 0.05, 0.25, 0.98, 2.94, 5.82, and 11.60 ng/mL and a blank. Quality control samples were prepared from different stock solutions of human serum samples at three levels (0.20-, 1.49-, and 8.08-ng/mL serum concentrations). Working calibrations and quality control were reconstituted with 3 mL of distilled water in each vial and incubated for 15 minutes at room temperature. The vials were swirled to dissolve the contents until homogeneity. The HPLC-MS system was controlled with the Agilent MassHunter Workstation software version B.06.00. For peak integration and quantitative calculation, the Agilent MassHunter Quantitative Analysis software version B.06.00 was used.

Sex hormone–binding globulin (SHBG) determination was done with an electrochemiluminescence immunoassay (Elecsys SHBG; Roche, Basel, Switzerland) (reference range: 15-50 nmol/L). FT was estimated from TT and SHBG using Vermuelen's formula (11). Hypoandrogenemia was defined when FT levels were <70 pg/mL (11,12). LH was determined by a direct chemiluminometric assay (ADVIA Centaur; Siemens Healthineers, Erlangen, Germany) (reference values: 1.5-7.7 mIU/mL). Serum insulin levels were measured by immunoassay using an ADVIA Centaur autoanalyzer (Siemens Healthineers, Erlangen, Germany). We used the homeostatic model assessment of insulin resistance (HOMA-IR) to determine the status of insulin resistance (13). Finally, high-sensitivity C-reactive protein (hs-CRP) was analyzed in a multiplex immunoassay platform (Bio-Plex System; Bio-Rad Laboratories, Irvine, California). All biochemical parameters (except TT, given its elevated sensibility, specificity, and accuracy) were measured in duplicate.

We retested TT in a random sample of patients ($n=25$) in a separate early-morning serum determination because a single measurement of TT could misdiagnose gonadal status in a significant percentage of men (1). In this subset of patients, the mean baseline TT was 3.32 (SD 0.5) ng/mL, and the mean repeated TT was 3.38 (SD 0.6) ng/mL ($P=0.562$). Also, we found a strong correlation between both TT measurements ($r=0.85$; $P<0.001$). Finally, all patients with extremely low TT levels (<1.5 ng/mL) ($n=6$) underwent magnetic resonance imaging, and no brain pathology was found in any case.

Erectile function

The International Index of Erectile Function (IIEF-5) questionnaire was used to assess erectile function. This questionnaire comprises five questions, and each IIEF-5 item is scored on a 5-point ordinal scale in which lower values represent poorer sexual function. The possible scores for

the IIEF-5 range from 5 to 25, and erectile dysfunction is determined as absent (>21 points) or present (≤21 points) (14).

Body composition

Weight and body composition were obtained using the Tanita multifrequency body composition analyzer (MC-180MA; Tanita Corporation, Tokyo, Japan), a weighing instrument that uses bioelectrical impedance analysis for the screening of body fat and composition. This instrument is continuously checked in relation to the reference standards of dual-energy x-ray absorptiometry and has been validated against other weighing methods (15).

Along with the standard parameters of body composition (fat mass, fat-free mass, total body water, etc.) this body composition analyzer indirectly estimates visceral fat through a specific rating: the visceral fat rating (VFR). Scores range from 0 to 59; ratings from 1 to 12 indicate that the participant has a healthy level of visceral fat, whereas ratings from 13 to 59 indicate that the patient has an excess level of visceral fat. The VFR has been extensively used in medical research as an indirect visceral fat measurement (16).

Ethics

This study was reviewed and approved by the Ethics Committee of the Virgen de la Victoria University Hospital and was conducted according to the principles of the Declaration of Helsinki. The participants (all volunteers) provided signed consent after being fully informed of the study goal and its characteristics.

Sample size calculation

Given that a previous systematic literature review showed that the prevalence of obesity-related hypoandrogenemia ranges from 15% to 78.8% (17), we set an expected prevalence of hypoandrogenemia of 20% in our study. This prevalence assumption was done because we planned to include young patients without T2DM or CVD (with a priori lower prevalence of hypoandrogenemia) to determine TT values with HPLC-MS (which normally yields higher TT values than immunoassay (18)), and we used FT to diagnose hypoandrogenemia (also related to a lower prevalence of hypoandrogenemia than TT (3)).

Hence, the sample size needed for the estimation of the prevalence of hypoandrogenemia in our study was set as 246 participants (precision level: 5%; confidence level: 95%). However, taking into account an approximate 15% of patients referred from primary care not meeting inclusion criteria after the initial assessment, we increased the sample size to 290 participants.

Statistical analyses

The analyses were performed using SPSS Statistics (version 25 for Windows; IBM Corp., Armonk. New York). Normal distribution of the variables was evaluated using the Kolmogorov-Smirnov test; normal distributed data were expressed as mean (SD). For variables with no Gaussian distribution, values were expressed as median (25th-75th percentile). For statistical analysis, values of variables that did not have a Gaussian distribution were logarithmically transformed. The hypothesis testing for continuous variables was performed using the *t* test (or the Mann-Whitney test in the event of non-normality after log transformation). The Wilcoxon signed rank test was used for repeated measurements of TT. Associations between the qualitative characteristics were tested using the χ^2 test. We tested trends in baseline FT levels across BMI groups using the Jonckheere-Terpstra trend test. The relationship between continuous variables was examined using partial correlation analyses (age adjusted). Univariate logistic regression was used to examine the associations of demographic, physical, medical, and biochemical factors with hypoandrogenemia. Finally, a parsimonious multivariate logistic regression model was constructed, taking into account multicollinearity (through the variance inflation factor). The criterion used for selecting the best model was based on the Akaike information criterion. Values were considered to be statistically significant when $P<0.05$.

Results

Study population

A total of 304 patients were referred for clinical assessment from primary care; 38 participants were excluded from the study after the initial evaluation: 1 patient with Klinefelter syndrome, 1 patient with familial hypogonadotropic hypoandrogenemia, 2 patients undergoing testosterone treatment, 12 patients with T2DM or on antidiabetic drugs (metformin for prediabetes mainly), 13 patients without obesity according to inclusion criteria, 2 patients ≥50 years of age, 6 patients with established CVD, and 1 patient with colon cancer. Thus, the final sample for this study comprised 266 nondiabetic male participants <50 years of age with obesity.

Characteristics of study population

The prevalence of hypoandrogenemia in the whole cohort (mean age: 36.9 [SD 7.6] years; mean BMI: 39.0 [SD 6.8]) was 25.6%. Clinical characteristics and laboratory parameters of participants with normal and subnormal FT levels are presented in Table 1. Briefly, participants with hypoandrogenemia had higher BMI, increased WC, higher prevalence of hypertension, increased insulin resistance, more elevated HbA1c levels, increased hs-CRP concentrations, and decreased LH levels. Regarding the body composition analysis, individuals with subnormal FT levels had a higher percentage of body fat mass, a lower percentage of fat-free mass, and increased visceral fat, thus configuring a more detrimental body composition. No differences were found in age, lipid profiles, glucose levels, SHBG levels, IIEF-5 questionnaire scores, or prevalence of erectile dysfunction (Table 1).

Importantly, mean FT levels decreased with increasing BMI, and consequently, the percentage of participants presenting with hypoandrogenemia differed across the BMI continuum; subnormal FT levels were found in 11.1% of participants with BMI of 30 to 34.9 (mean FT level: 97.6 [SD 28.1] pg/mL), in 19.8% of participants with BMI ranging from 35 to 39.9 (mean FT level: 94.0 [SD 35.7] pg/mL), in 33.8% of participants with BMI of 40 to 49.9 (mean FT level: 84.8 [SD 25.3] pg/mL), and in 78.3% of participants with BMI greater than 50 (mean FT level: 62.7 [SD 17.2] pg/mL). Accordingly, a Jonckheere-Terpstra test for ordered alternatives showed that there was a statistically significant trend of lower FT levels (TJT = 9,105.5; $z=-5.05$; $P<0.001$) with higher BMI.

Correlation analysis between FT and other variables

A partial correlation analysis (age adjusted) showed that FT was negatively associated with BMI, WC, fat mass percentage, visceral fat, hs-CRP levels, HbA1c levels, insulin levels, and HOMA-IR and was positively associated with LH concentrations and fat-free mass

TABLE 1 Clinical characteristics (anthropometric and biochemical characteristics and body composition and erectile function) of study population, according to the presence of hypoandrogenemia (FT < 70 pg/mL)

	Eugonadal ($n = 198$)	Hypoandrogenemia ($n = 68$)	*P* value	Test
Age, median (IQR), y	38 (31-42)	39 (33.2-45)	0.124	M
Ever smoked, %	46.7	54	0.169	χ^2
BMI, mean ± SD	37.3 ± 5.3	44.0± 8.2	<0.001	T
WC, mean ± SD, cm	120.9 ± 12.7	134.0 ± 17.9	<0.001	T
Fat mass, mean ± SD, %	33.0 ± 5.0	38.7 ± 6.6	<0.001	T
Fat-free mass, mean ± SD, %	66.3 ± 5.1	60.8 ± 6.4	<0.001	T
VFR, mean ± SD, points	16.5 ± 4.9	23.5 ± 8.1	<0.001	T
Impaired VFR, %	79.9	92.5	0.017	χ^2
Hypertension, %	45.5	60.3	0.035	χ^2
Glucose, median (IQR), mg/dL	90 (85-97)	92 (88-99.7)	0.133	M
Insulin, mean ± SD, uIU/mL	18.6 ± 14.7	24.5 ± 16.7	0.006	T
HOMA-IR, mean ± SD	4.4 ± 4.3	5.9 ± 3.9	0.032	T
HbA1c, mean ± SD, %	5.3 ± 0.3	5.5 ± 0.3	0.009	T
Triglycerides, mean ± SD, mg/dL	156.2 ± 81.1	144.9 ± 76.4	0.319	T
HDL cholesterol, mean ± SD, mg/dL	42.2 ± 9.4	41.4 ± 8.6	0.549	T
LDL cholesterol, mean ± SD, mg/dL	115.7 ± 30.3	108.6 ± 26.9	0.091	T
hs-CRP, median (IQR), mg/dL	1.3 (0.7-2.8)	2.6 (1.2-4.8)	<0.001	M
LH, mean ± SD, mIU/mL	4.1 ± 2.2	3.1 ± 1.4	0.001	T
TT, mean ± SD, mg/dL	4.2 ± 1.3	2.4 ± 0.5	<0.001	T
SHBG, mean ± SD, nmol/L	26.1 ± 13.3	24.7 ± 10.5	0.430	T
FT, mean ± SD, pg/mL	101.5 ± 27.1	56.7 ± 9.4	<0.001	T
IIEF-5 questionnaire, median (IQR), points	22 (20-24)	22 (18-24)	0.220	M
Erectile dysfunction, %	39.6	49.3	0.168	χ^2

P values calculated for difference among groups using T, M, or χ^2 test. $P < 0.05$ considered significant.
FT, free testosterone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IIEF-5, International Index of Erectile Function; IQR, interquartile range; LDL, low-density lipoprotein; LH, luteinizing hormone; M, Mann-Whitney test; SHBG, sex hormone–binding globulin; T, *t* test; TT, total testosterone; VFR, visceral fat rating (determined by bioelectrical impedance); WC, waist circumference.

percentage. However, no significant correlations were found between FT and IIEF-5 scores or between FT and glucose (Table 2).

Factors associated with hypoandrogenemia

To examine factors associated with having hypoandrogenemia, a univariate logistic regression was performed (Table 3). This univariate analysis showed that WC, fat mass percentage, BMI, diastolic BP, HbA1c levels, and hs-CRP concentrations were factors independently associated with lower FT. On the other hand, fat-free mass percentage and LH concentrations were found as protective factors. Interestingly, insulin resistance, IIEF-5 scores, and erectile dysfunction were not significant factors for presenting with hypoandrogenemia.

Finally, a multivariate model was constructed to identify factors independently associated with hypoandrogenemia. In this multiple logistic regression analysis, the optimal model that best explained the presence of hypoandrogenemia included increasing BMI ($P < 0.001$) and age ($P = 0.049$) and reduced LH levels ($P = 0.003$), with a Nagelkerke R^2 of 0.309 (Table 4).

TABLE 2 Partial correlation coefficients among FT, clinical characteristics, biochemical and hormonal parameters, and body composition analysis

	FT (pg/mL)	
	r	*P*
BMI	–0.343	<0.001
WC (cm)	–0.331	<0.001
Fat mass (%)	–0.384	<0.001
Fat-free mass (%)	0.338	<0.001
VFR (points)	–0.376	<0.001
HbA1c (%)	–0.194	0.003
Glucose (mg/dL)	–0.060	0.365
Insulin (uIU/mL)	–0.210	0.001
HOMA-IR	–0.179	0.005
hs-CRP (mg/L)	–0.169	0.009
LH (mIU/mL)	0.262	<0.001
IIEF-5 (points)	0.101	0.115

All correlation coefficients calculated after adjustment for age.
FT, free testosterone; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IIEF-5, International Index of Erectile Function; LH, luteinizing hormone; VFR, visceral fat rating; WC, waist circumference.

Discussion

Our results show that the prevalence of hypoandrogenemia in a primary care–based cohort of nondiabetic young men with obesity reaches

TABLE 3 Factors associated with hypoandrogenemia (FT < 70 pg/mL) in nondiabetic young men with obesity: univariate regression models

	Univariate analysis		
	OR	95% CI	*P*
Age (y)	1.03	0.99-1.07	0.117
WC (cm)	1.06	1.03-1.08	<0.001
BMI	1.16	1.10-1.21	<0.001
Fat mass (%)	1.19	1.11-1.26	<0.001
Fat-free mass (%)	0.85	0.80-0.89	<0.001
SBP (mm Hg)	1.02	0.99-1.04	0.060
DBP (mm Hg)	1.03	1.00-1.06	0.018
HbA1c (%)	2.87	1.29-6.40	0.010
Glucose (mg/dL)	1.01	0.98-1.04	0.482
Insulin (uIU/mL)	1.02	1.00-1.04	0.017
HOMA-IR	1.07	0.99-1.14	0.059
LH (IU/mL)	0.70	0.57-0.86	0.010
hs-CRP (mg/dL)	1.07	1.02-1.12	0.008
IIEF-5 questionnaire (points)	0.95	0.88-1.02	0.195
Erectile dysfunction (%)	1.48	0.84-2.59	0.170

Logistic regression analysis: risk (OR) of hypoandrogenemia; dependent variable: FT ≥ 70 pg/mL (0) vs. FT < 70 pg/mL (1).
DBP, diastolic blood pressure; FT, free testosterone; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IIEF-5, International Index of Erectile Function; LH, luteinizing hormone; OR, odds ratio; SBP, systolic blood pressure; WC, waist circumference.

TABLE 4 Factors associated with hypoandrogenemia (FT < 70 pg/mL) in nondiabetic young men with obesity: multivariate regression models

	Multivariate analysis		
	OR	95% CI	*P*
Age (y)	1.04	1.00-1.09	0.049
BMI	1.15	1.09-1.21	<0.001
LH (IU/mL)	0.72	0.58-0.90	0.003
HOMA-IR	0.99	0.93-1.07	0.972
hs-CRP (mg/dL)	1.04	0.98-1.10	0.156

Logistic regression analysis: risk (OR) of hypoandrogenemia; dependent variable FT ≥ 70 pg/mL (0) vs. FT < 70 pg/mL (1).
FT, free testosterone; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LH, luteinizing hormone; OR, odds ratio.

important figures, finding subnormal FT concentrations in more than 25% of the participants. Also, we report that the presence of hypoandrogenemia is closely related to increased BMI, with the highest hypoandrogenemia prevalence in those patients with more extreme obesity. Finally, we have found that the degree of obesity and increasing age are independent risk factors associated with the presence of hypoandrogenemia, whereas increased LH levels are a protective factor.

Previous studies have evaluated the relationship between obesity and testosterone concentrations in men. In the Hypogonadism In Males (HIM) study, nondiabetic men ≥45 years of age with obesity were evaluated for decreased levels of testosterone; 52% of these patients presented with subnormal TT concentrations, and 40% had reduced FT levels (5). In this study, decreased FT levels were related to increasing BMI; however, no data on low-grade inflammation or erectile function were reported. Hofstra et al. (6) found subnormal TT and FT levels in 57.7% and 35.6% of men referred for obesity treatment, respectively. In this clinical study, hypoandrogenemia was associated with the degree of obesity and with impaired erectile function, although the latter was assessed by anamnesis, not with a validated test such as the IIEF-5 questionnaire. Also, Calderón et al. (19), in a small study involving 100 male patients with moderate to severe obesity, found a prevalence of hypogonadism of 44% when considering decreased TT concentrations and of 34% according to reduced FT concentrations. On the other hand, when men with severe obesity are evaluated, the prevalence of hypoandrogenemia is even higher. Thus, in a recent systematic review and meta-analysis that included 382 men referred to bariatric surgery, the pooled prevalence of hypoandrogenemia was 64% (95% CI: 50%-77%) (20).

Although the prevalence of hypoandrogenemia described in this study was lower than that previously described in men with obesity, it is important to take into account that the design of our study was clearly different from previous studies: we included only patients <50 years of age to limit the well-known deleterious effect of age on testosterone levels (21,22), and patients with T2DM, CVD, and other chronic diseases (conditions directly associated with a reduction in testosterone levels) (23,24) were also excluded. In fact, in a recent study performed by Lotti et al. (25), men with metabolically complicated obesity (described as BMI ≥ 30 with hypertension or BP > 130/80 mm Hg, high-density lipoprotein cholesterol < 40 mg/dL, or T2DM) had a higher risk of secondary hypogonadism compared with participants with metabolically healthy obesity (described as BMI ≥ 30 without any metabolic abnormalities). In addition, patients were recruited directly from primary care to avoid a preselection of patients coming from the hospital (i.e., undergoing bariatric surgery) or specialized care, who potentially could have presented with more obesity-associated comorbidities, such as hypoandrogenemia itself (Berkson's bias) (26).

An important (yet unsolved) issue is the definition of hypoandrogenemia in men with obesity. In this regard, given that most circulating testosterone is bound to SHBG or albumin (and only 1%-3% circulates as FT), changes in SHBG levels greatly affect the interpretation of testosterone concentrations (27). Therefore, in SHBG-altering conditions (such as obesity), measuring FT concentrations instead of TT concentrations should be considered (28). However, a major difficulty in interpreting FT concentrations is the lack of standardization regarding FT assays, so it has been suggested that laboratories should establish their own specific reference ranges for FT (1). In absence of our own references ranges for FT, we based ours on a previous study from Bhasin et al. (12), who established reference ranges for FT in a community-based sample of healthy young men without obesity. In this study, performed in 456 young men without obesity (mean BMI: 25.5 [SD 2.7]), the 2.5th percentile value for FT was 70 pg/mL, which was the threshold that we used for diagnosing hypoandrogenemia in our study.

Our findings might have significant implications given the global epidemic of obesity; in Europe, the prevalence of obesity has increased threefold over the past 2 decades; in the United States, more than 97 million people have overweight or obesity (approximately 50% of the population); and overall, approximately 700 million people worldwide have obesity (29). Thus, if a similar prevalence of subnormal testosterone

concentrations were found in the population with obesity worldwide, more than 175 million men with obesity could present with inappropriately reduced FT levels. Moreover, given that the design of this study intentionally excluded patients with T2DM, CVD, and chronic diseases and patients ≥50 years of age (conditions all associated with subnormal testosterone concentrations), the prevalence of hypoandrogenemia in participants with obesity could be even more elevated.

Importantly, the presence of hypoandrogenemia is far from being an unimportant finding given that reduced levels of testosterone are intimately associated with multiple signs and/or symptoms, including gynecomastia, decreased lean body mass and muscle strength, visceral obesity, reduced sexual desire, erectile dysfunction, insulin resistance, high BP, T2DM, and the metabolic syndrome (30). Furthermore, subnormal testosterone concentrations have been related to the severity of coronary heart disease (31), and prospective studies have shown that individuals with lower testosterone levels have increased risk of atrial fibrillation, cerebrovascular disease, and cardiovascular death (32).

In our study, we found that the degree of obesity was directly related to the likelihood of presenting with hypoandrogenemia. In this line, grade 1 obesity (BMI: 30-34.9) and grade 2 obesity (BMI: 35-39.9) were associated with reduced concentrations of FT in no more than 10% to 20% of participants, whereas morbid obesity (BMI≥40) was associated with hypoandrogenemia in more than 30% of patients, and extreme obesity (BMI≥50) was associated with almost 80% prevalence of hypoandrogenemia. Furthermore, in the multivariate analysis, we observed a 1.15-fold increased risk of hypoandrogenemia for every 1-point increase in BMI. These results are in agreement with previous epidemiological data that suggested that the single most powerful predictor of low testosterone levels is obesity and with studies that have indicated that testosterone levels negatively correlate with the severity of obesity (33).

In addition, decreased LH concentrations and increasing age were also independent risk factors for hypoandrogenemia. Regarding LH levels, marked obesity was shown to be associated with low or inappropriately normal levels of LH, suggesting a dominant suppression occurring at the hypothalamic-pituitary level (34). On the other hand, aging has been repeatedly identified as a clear factor associated with the decrease in testosterone levels in multiple studies (21,22).

It is important to highlight the elevated prevalence of erectile dysfunction that we found in our study, affecting approximately 40% of the studied participants. Taking into account the clinical characteristics of our population (nondiabetic young men without CVD), we mainly attribute this finding to the degree of obesity of our patients because excess body weight is a known risk factor for erectile dysfunction (35). Interestingly, we found that IIEF-5 scores or erectile dysfunction was not related to hypoandrogenemia. In this line, previous authors have shown that androgen levels fail to yield predicting information about erectile function when age is adjusted (36), and that low testosterone levels, as an independent impact factor, is relevant only for men with severe erectile dysfunction (37). In addition, it is important to bear in mind that sexual dysfunction in men with obesity is a multifactorial condition and that psychological and sociocultural factors may play a relevant role, independently of testosterone concentrations (38).

Our study has certain limitations but also some important strengths. We studied a relatively small sample (although more elevated than those in many previous studies) derived from a single city in a single country. Also, another limitation is the inherent nature of the study, a cross-sectional design in which only an association and not a cause can be inferred. In addition, although serum testosterone determination was not repeated in all patients, a random subset of participants underwent a repeated determination of serum testosterone, and no significant changes were found between both assessments. On the other hand, the strengths of our study lie in our design, including the inclusion of only young nondiabetic participants with obesity and without chronic diseases or CVD, the assessment of sexual function using the IIEF-5 validated test, the extensive hormonal evaluation, the use of a body composition analysis, and the determination of testosterone levels using HPLC-MS, which is considered the gold standard technique for steroid determination (39).

Conclusion

In a primary care–based cohort of nondiabetic young men with obesity, hypoandrogenemia was found in approximately 25% of participants. Subnormal testosterone concentrations were independently associated with the degree of obesity, age, and reduced LH levels but not with erectile function.

Further prospective studies are needed to evaluate the long-term consequences of hypoandrogenemia in this population. Meanwhile, strategies to address excess body weight and maintain a healthy lifestyle and a balanced diet should be implemented to avoid obesity-associated comorbidities. O

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