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ORIGINAL ARTICLE

Erectile Dysfunction

# Prevalence of and risk factors for erectile dysfunction in young nondiabetic obese men: results from a regional study

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Erectile dysfunction (ED), a condition closely related to cardiovascular morbidity and mortality, is frequently associated with obesity. In this study, we aimed to determine the prevalence of ED and evaluate the associated risk factors in a cohort of 254 young (18–49 years) nondiabetic obese (body mass index [BMI]  $\geq 30$  kg m<sup>-2</sup>) men from primary care. Erectile function (International Index of Erectile Function [IIEF-5] questionnaire), quality of life (Aging Males' Symptoms [AMS scale]), and body composition analysis (Tanita MC-180MA) were determined. Total testosterone was determined using high-performance liquid chromatography–mass spectrometry. Multivariate logistic regression analysis was used to study the factors associated with ED. ED prevalence was 42.1%. Subjects with ED presented higher BMI, waist circumference, number of components of the metabolic syndrome, AMS score, insulin resistance, and a more unfavorable body composition than those without ED. Multivariate logistic regression analysis showed that a pathological AMS score (odds ratio [OR]: 4.238,  $P < 0.001$ ), degree of obesity (BMI  $\geq 40$  kg m<sup>-2</sup>, OR: 2.602,  $P = 0.005$ , compared with BMI 30–34.9 kg m<sup>-2</sup>), high-density lipoprotein (HDL)-cholesterol levels (OR: 0.956,  $P = 0.004$ ), and age (OR: 1.047,  $P = 0.016$ ) were factors independently associated with ED. In conclusion, we demonstrate that, in a primary care-based cohort of nondiabetic young obese men, ED affected >40% of subjects. A pathological AMS score, the degree of obesity, and age were positively associated with ED, while elevated HDL-cholesterol levels were inversely associated with the odds of presenting ED. Further prospective studies are needed to evaluate the long-term consequences of ED in this population.

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**Keywords:** Aging Males' Symptoms score; erectile dysfunction; International Index of Erectile Function-5 questionnaire; obesity; testosterone

## INTRODUCTION

Erectile dysfunction (ED) is the persistent inability to attain and maintain a sufficient erection to permit satisfactory sexual performance.<sup>1</sup> ED prevalence increases with age: 6% (range 1%–29%) in men aged 40–49 years, 16% (3%–50%) in men aged 50–59 years, 32% (7%–74%) in men aged 60–69 years, and 44% (26%–76%) in men aged 70–79 years.<sup>2</sup>

ED, a multifactorial affection, is associated with several endocrine and metabolic disorders including insulin resistance, hyperlipidemia, testosterone deficiency, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS).<sup>3,4</sup> ED is also related to decreased quality of life (QoL), impaired psychological health, and a higher risk of depression.<sup>5</sup> Finally, ED is also associated with increased likelihood of cardiovascular disease (CVD) and is considered an early marker of CVD.<sup>6,7</sup>

Obesity, considered as the epidemic of the 21<sup>st</sup> century in developed countries, is closely related to ED.<sup>8,9</sup> ED prevalence in obese men is 17%–36%.<sup>10–13</sup> However, inclusion/exclusion criteria in these studies are heterogeneous and include a significant percentage of patients with T2DM or CVD (both factors intimately linked to ED), assess elderly patients (as aging is another well-known risk factor for ED), or include patients from specialized care, who potentially could present more obesity-related comorbidities as ED.<sup>14,15</sup>

Noteworthy, to our knowledge, no studies have yet been performed in a prevalent population, young nondiabetic obese men, who could potentially benefit from an early assessment of the presence of ED, given the short- and long-term consequences of this condition.

Therefore, the aim of this study is to determine the prevalence of ED and evaluate the associated risk factors in a primary care-based cohort of young nondiabetic obese men.

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## PARTICIPANTS AND METHODS

### Study design and participants

From June 2013 to June 2015, 30 primary care practitioners from six primary care centers (Cruz de Humilladero Primary Care Center, Las Delicias Primary Care Center, Huelin Primary Care Center, Teatinos Primary Care Center, Tiro de Pichón Primary Care Center, and Carranque Primary Care Center) in Málaga (Spain) consecutively invited young men with obesity (defined by a body mass index [BMI]  $\geq 30 \text{ kg m}^{-2}$ ) to participate in this study. We defined young men as men aged 18–49 years old, since total and free testosterone decreases in men beyond 50 years of age, which potentially impairs erectile function.<sup>16</sup>

Exclusion criteria for the present study were a previous diagnosis of hypoandrogenemia, diabetes mellitus (diagnosed if a potential participant was taking medication for diabetes, had fasting plasma glucose  $\geq 126 \text{ mg dl}^{-1}$  [ $7 \text{ mmol l}^{-1}$ ], or glycated hemoglobin [HbA1c]  $\geq 6.5\%$ , as confirmed by repeated testing), use of any antidiabetic medication, or being under any treatment known to affect the gonadal axis, including any form of testosterone. In addition, subjects under treatment with phosphodiesterase 5 (PDE5) inhibitors or alprostadil, or with hepatic or renal impairment, established CVD or cancer were excluded. All subjects had a normal pubertal development, referred intact sense of smell, had no increased luteinizing hormone levels or evidence of intercurrent pituitary disease or additional pituitary hormone deficiencies (thyrotropin, free thyroxine, prolactin, adrenocorticotropin, cortisol, and insulin-like growth factor-I levels were all within the normal range).

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

### Erectile function, health-related QoL, and metabolic syndrome

To assess erectile function, all subjects were asked to complete the International Index of Erectile Function-5 (IIEF-5) questionnaire, a widely used validated tool for diagnosing ED because of its sensitivity and specificity.<sup>17</sup> ED was classified into four categories: severe (5–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25).<sup>17</sup> Thus, subjects presenting a score  $\leq 21$  were diagnosed of ED (ED+, cases), whereas those subjects with a score  $\geq 22$  were considered as not having ED (ED–, controls).

In addition, QoL was assessed using the Aging Males' Symptoms (AMS) scale. AMS scores range from 17 (minimum, asymptomatic) to 85 (maximum, extremely severe symptoms). AMS severity was graded as no/little complaints ( $\leq 26$ ), mild (27–36), moderate (37–49), and severe ( $\geq 50$ ).<sup>18</sup>

Finally, MetS was defined if the patient met three or more of the updated parameters for the diagnosis of MetS according to the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute definition.<sup>19</sup>

### Biochemical evaluation

Study participants were instructed to eat a light meal the evening before the clinical evaluation and to fast with effect from 10:00 p.m. Blood samples were collected from all participants between 08:00 a.m. and 10:00 a.m. Samples were centrifuged (3130 g), and plasma and serum were distributed in aliquots and stored at  $-80^\circ\text{C}$  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: weight and height (to calculate BMI), waist circumference (WC), blood pressure (BP), and heart rate (HR). BP was measured twice with the subject seated and an interval of 5 min between measurements. BP measurements were taken on the right arm, which was relaxed and supported by a table, at an angle of  $45^\circ$  from the trunk (Omron M6 Comfort Blood Pressure Monitor, Hoofddorp, The Netherlands).

Biochemical parameters were measured in duplicate using standard enzymatic methods. We used the homeostasis model assessment of insulin resistance index (HOMA-IR), as described by Matthews *et al.*<sup>20</sup> to determine insulin resistance. High-sensitivity C-reactive protein (hs-CRP) was analyzed in a multiplex immunoassay platform (Bio-plex System®; Bio-Rad Laboratories, Irvine, CA, USA), luteinizing hormone was determined using a direct quimiluminometric assay (ADVIA Centaur; Siemens Healthineers, Erlangen, Germany; reference values  $1.5\text{--}7.7 \text{ mIU ml}^{-1}$ ), total testosterone (TT) was determined using mass spectrometry techniques coupled with high-performance liquid chromatography (Model 6460; Agilent Technologies, Santa Clara, CA, USA), sex hormone-binding globulin was determined with an electrochemiluminescence immunoassay (Elecsys SHBG; Roche, Basel, Switzerland; reference range  $15\text{--}50 \text{ nmol l}^{-1}$ ), and free testosterone (FT) was calculated from TT and sex hormone-binding globulin using a law-of-mass-action equation.<sup>21</sup> According to previous reports, hypoandrogenemia was diagnosed when FT levels were lower than  $70 \text{ pg ml}^{-1}$  ( $<243 \text{ pmol l}^{-1}$ ).<sup>22</sup>

### Body composition analysis

Body composition was assessed using the Tanita Multi-Frequency Body Composition Analyzer MC-180MA (Tanita Corporation, Tokyo, Japan), a weighing instrument that uses bioelectrical impedance analysis to screen body fat and composition. This instrument has been validated against other weighing methods and is repeatedly checked in relation to the reference standards of dual-energy X-ray absorptiometry (DEXA).<sup>23</sup>

Fat mass (in kg) and fat-free mass (in kg) were measured, and visceral fat was calculated. Visceral fat was indirectly estimated, and the results were given as a specific rating: visceral fat rating (VFR;  $0 \pm 59$ ; no units). Ratings of 1–12 and 13–59 indicate that the subject has healthy and excess levels of visceral fat, respectively. VFR is extensively used in medical research for indirect visceral fat measurement in adults.<sup>24</sup>

### Statistical analyses

Normal distribution of the variables was evaluated using the Kolmogorov–Smirnov test; normally distributed data were expressed as mean  $\pm$  standard deviation (s.d.). For variables with no Gaussian distribution, the values were expressed as median (25<sup>th</sup>–75<sup>th</sup> percentile). For statistical analysis, the values of variables that did not have a Gaussian distribution were logarithmically transformed. Group comparisons between the quantitative data were performed using the Student's *t*-test (or the Mann–Whitney U test in the event of nonnormality after log-transformation), whereas group comparisons between the qualitative data were performed using the Chi-square test. Associations between continuous variables were tested using partial correlation analyses (age adjusted). Univariate logistic regression was used to examine the associations of demographic, physical, medical, and biochemical factors with ED. Finally, a parsimonious multivariate logistic regression model was constructed, considering multicollinearity (through variance inflation factor). The variables included in the multivariate regression model were those that were statistically significant in univariate analyses or were biologically

relevant. Regarding MetS components, given the low number of patients with no components, we grouped the number of MetS components as  $\leq 1$ , 2, 3, 4, and 5 for statistical analysis. We considered statistically significant if  $P < 0.05$ . Statistical analysis was performed using SPSS software (version 25.0 for Windows; SPSS Inc., Chicago, IL, USA).

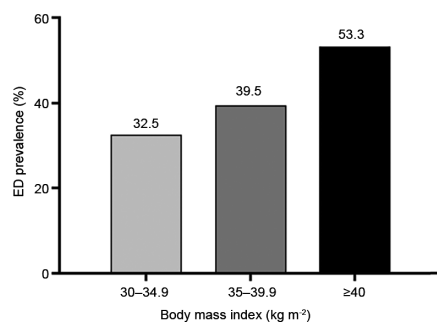
## RESULTS

Three hundred and four subjects were initially referred for clinical assessment; 50 were excluded from the study after the initial evaluation: 1 with Klinefelter syndrome, 1 with familial hypogonadotropic hypogonadism, 2 under testosterone treatment, 12 with T2DM or on antidiabetic drugs (metformin for prediabetes mainly), 13 overweight (not obese) individuals, 12 who were not in a committed relationship or were not sexually active, 2 with age  $\geq 50$  years, 6 with established cardiovascular disease, and 1 with colon cancer. Thus, the final sample for this study comprised 254 nondiabetic obese men aged  $< 50$  years.

The prevalence of ED in the whole cohort (median age: 38 [interquartile range, IQR: 32–43] years, median BMI: 37.4 [IQR: 33.3–42.9]  $\text{kg m}^{-2}$ ) was 42.1%. Clinical characteristics and laboratory parameters of the study groups (ED+ vs ED-) are shown in **Table 1**. Briefly, BMI, WC, fat mass percentage (FM%), VFR, AMS score, HbA1c, insulin, and HOMA-IR were significantly higher in the ED+ group than those in the ED- group (all  $P < 0.05$ ). However, fat-free mass percentage (FFM%), high-density lipoprotein (HDL)-cholesterol, and FT levels were significantly higher in the ED- group. However, no differences were observed in TT levels or hypoandrogenemia prevalence, smoking, employment, age, BP, low-density lipoprotein (LDL)-cholesterol, triglycerides, hs-CRP, or glucose concentrations (all  $P > 0.05$ ).

Although most ED+ patients presented mild ED, almost 25% had moderate or severe ED. In addition, the percentage of subjects presenting ED was different across the BMI continuum: ED was found in 32.5% of subjects with Grade I obesity (BMI 30–34.9  $\text{kg m}^{-2}$ ), in 39.5% of subjects with Grade II obesity (BMI 35–39.9  $\text{kg m}^{-2}$ ), and in 53.3% of subjects with morbid obesity (BMI  $\geq 40$   $\text{kg m}^{-2}$ ) ( $P = 0.018$ ; **Figure 1**). Consequently, IIEF-5 score also varied with the degree of obesity:  $21.8 \pm 3.8$  points in subjects with Grade I obesity,  $21.4 \pm 3.3$  points in subjects with Grade II obesity, and  $20.5 \pm 3.5$  points in morbidly obese subjects ( $P = 0.040$ ).

Next, we analyzed the relationship between ED and MetS in our population; we found no differences in ED prevalence between obese men with and without MetS (36.8% vs 45.9%,  $P = 0.145$ ). However, subjects with ED+ presented a higher median number of MetS



**Figure 1:** The prevalence of erectile dysfunction (ED) (defined by the International Index of Erectile Function-5 score  $\leq 21$  points) in nondiabetic obese young men, according to body mass index category.

components in comparison with ED- subjects (3.0 vs 2.7,  $P = 0.027$ ), and when we stratified the risk of ED according to the number of MetS components, we found that there was a higher probability of having ED as a function of the number of MetS components ( $P = 0.037$ ; **Table 2**).

Partial correlation analysis demonstrated that IIEF-5 score was positively associated with FFM% and HDL-cholesterol and was negatively associated with BMI, WC, FM%, VFR, insulin, HOMA-IR, and AMS score, after adjustment for age (all  $P < 0.05$ ). However, IIEF-5 score did not correlate with FT, TT, or number of components of MetS (**Table 3**).

We used univariate logistic regression to examine factors associated with ED. This univariate analysis showed that the presence of ED was significantly associated with BMI, number of components of MetS, WC, FM%, FFM%, insulin, HOMA-IR, HDL-cholesterol, FT levels, and pathologic AMS score (**Table 4**). Finally, a multivariate model was constructed to identify factors independently associated with ED. In this multiple logistic regression analysis, degree of obesity, a pathological AMS questionnaire, and increasing age were factors independently associated with a higher prevalence of ED, whereas elevated HDL-cholesterol levels were a protective factor for ED. Interestingly, a pathological AMS score was the most important determinant for ED ( $> 4$ -fold increase), followed by morbid obesity (which increased the odds for ED by 2.6-fold), in comparison with subjects with a BMI of 30–34.9  $\text{kg m}^{-2}$  (**Table 4**).

## DISCUSSION

We have investigated the prevalence of ED in a cohort of young nondiabetic obese men referred from primary care and analyzed associated risk factors for ED. Our main results indicate that ED is a prevalent finding in this population, affecting  $> 40\%$  of subjects, and that factors positively associated with ED were aging, degree of obesity, and a pathological AMS score, whereas elevated HDL-cholesterol levels were inversely associated with the odds of presenting ED. Interestingly, hypoandrogenemia was not related to ED in our study population.

Importantly, the ED prevalence here is not only higher than the previously reported prevalence of 1%–10% in young ( $< 40$  years) healthy men,<sup>25</sup> but also higher than the previous studies on obese men. Andersen *et al.*<sup>10</sup> reported an ED prevalence of 13% in obese men aged 20–45 years, Cheng and Ng<sup>11</sup> found a 36.5% ED prevalence in obese men aged 26–70 years, and Janiszewski *et al.*<sup>12</sup> found a 22.3% ED prevalence in obese men older than 20 years. In addition, in the European Male Ageing Study, ED was present in 24.8% of healthy weight men compared with 36.7% prevalence in obese men.<sup>13</sup> Finally, Sarwer *et al.*<sup>26</sup> reported that 36% of men undergoing bariatric surgery had ED.

Interestingly, we found this elevated ED prevalence despite the restrictive inclusion and exclusion criteria in our study: (1) only subjects  $< 50$  years were included to avoid the deleterious effect of age on ED;<sup>27</sup> (2) subjects with T2DM, CVD, chronic diseases, or previous diagnosis of hypoandrogenemia (conditions associated with increased prevalence of ED<sup>28</sup>) were excluded; and (3) the recruitment of patients was done directly from primary care to avoid a preselection of patients coming from the hospital or specialized care as these patients could present more obesity-associated comorbidities (Berkson's bias).<sup>29</sup>

Overall, when considering the clinical characteristics of our cohort, we mainly attribute the elevated prevalence of ED to the high degree of obesity of our patients because excess body weight is a recognized risk factor for ED.<sup>30</sup> Furthermore, we believe that many other aspects might have influenced this elevated ED diagnosis, such as sociocultural determinants, confidence with the medical team, self-esteem, or ED acceptance.<sup>31</sup>

**Table 1: Anthropometric, biochemical, and hormonal characteristics of the study population, according to the presence of erectile dysfunction (defined by the International Index of Erectile Function  $\leq 21$  points)**

Characteristics	ED- (n=147)	ED+ (n=107)	P	Test
Age (year), median (IQR)	37 (31–42)	39 (34–44)	0.018	M
Employment status, n (%)			0.605	$\chi^2$
Unemployed	41 (28.0)	38 (35.6)		
Working	92 (62.3)	59 (54.8)		
Other	14 (9.7)	10 (9.6)		
Smoking status, n (%)			0.277	$\chi^2$
Never	70 (47.4)	52 (49.0)		
Ex	36 (24.4)	34 (31.3)		
Former	41 (28.2)	21 (19.7)		
BMI (kg m <sup>-2</sup> ), median (IQR)	36.7 (33.1–40.7)	39.1 (34.1–45.3)	0.009	M
WC (cm), median (IQR)	119 (111–130)	124 (115–140)	0.004	M
Fat mass (%), mean $\pm$ s.d.	33.4 $\pm$ 5.7	35.9 $\pm$ 6.2	0.001	T
Fat-free mass (%), median (IQR)	66.3 (62.1–70.3)	63.9 (58.9–68.7)	0.003	M
VFR, median (IQR)	16 (13–20)	18 (14–25)	0.001	M
Pathological VFR, n (%)	113 (76.6)	97 (90.4)	0.005	$\chi^2$
Systolic blood pressure (mmHg), mean $\pm$ s.d.	132.9 $\pm$ 13.5	132.7 $\pm$ 11.8	0.917	T
Diastolic blood pressure (mmHg), mean $\pm$ s.d.	84.9 $\pm$ 10.8	86 $\pm$ 8.3	0.368	T
HbA1c (%), median (IQR)	5.3 (5.1–5.6)	5.4 (5.2–5.7)	0.059	M
Glucose (mg dl <sup>-1</sup> ), median (IQR)	90 (86–97)	91 (87–100)	0.210	M
Insulin ( $\mu$ U ml <sup>-1</sup> ), mean $\pm$ s.d.	17.6 $\pm$ 10.5	23.3 $\pm$ 19.8	0.003	T
HOMA-IR, mean $\pm$ s.d.	4.0 $\pm$ 2.6	5.6 $\pm$ 5.5	0.010	T
Triglycerides (mg dl <sup>-1</sup> ), mean $\pm$ s.d.	148.3 $\pm$ 75	159.2 $\pm$ 85.5	0.281	T
Total cholesterol (mg dl <sup>-1</sup> ), mean $\pm$ s.d.	187 $\pm$ 31.9	183.7 $\pm$ 34.7	0.442	T
HDL-cholesterol (mg dl <sup>-1</sup> ), median (IQR)	42 (38–48)	40 (34–46)	0.005	M
hs-CRP (mg l <sup>-1</sup> ), mean $\pm$ s.d.	2.7 $\pm$ 4.7	3.4 $\pm$ 5.3	0.320	T
LH ( $\mu$ U ml <sup>-1</sup> ), mean $\pm$ s.d.	3.8 $\pm$ 2.3	3.8 $\pm$ 1.7	0.999	T
Total testosterone (ng ml <sup>-1</sup> ), mean $\pm$ s.d.	3.8 $\pm$ 1.3	3.6 $\pm$ 1.5	0.258	T
Free testosterone (pg ml <sup>-1</sup> ), median (IQR)	89.4 (71.4–105)	82.1 (64.6–99.6)	0.047	M
Hypoandrogenemia, n (%)	34 (23.1)	33 (30.8)	0.168	$\chi^2$
IIEF-5 score (point), median (IQR)	24 (23–25)	19 (17–20)	<0.001	M
ED classification, n (%)			<0.001	$\chi^2$
No ED	147 (100)	0 (0)		
Mild	0 (0)	81 (75.7)		
Mild to moderate	0 (0)	21 (19.6)		
Moderate	0 (0)	4 (3.7)		
Severe	0 (0)	1 (0.9)		
AMS score (point), median (IQR)	30 (25–45)	43 (32–50)	<0.001	M
Pathological AMS score, n (%)	99 (67.3)	97 (90.7)	<0.001	$\chi^2$

P values were calculated for the difference among groups using t-test (T), Mann-Whitney (M) test, or Chi-square ( $\chi^2$ ) test. P<0.05 was considered statistically significant. ED: erectile dysfunction; BMI: body mass index; WC: waist circumference; VFR: visceral fat rating (pathological VFR  $\geq 13$ ); HbA1c: glycated hemoglobin; HOMA-IR: insulin resistance according to the homeostasis model assessment; HDL-c: high-density lipoprotein-cholesterol; hs-CRP: high-sensitivity C-reactive protein; LH: luteinizing hormone; IIEF-5: International Index of Erectile Function; AMS: Aging Males' Symptoms (pathological AMS scale  $\geq 27$  points)

Our study demonstrates that men with ED have higher WC and a more detrimental body composition, with an increased proportion of fat mass, decreased fat-free mass, and higher VFR scores than healthy subjects. In addition, negative correlations between IIEF-5 score and adiposity markers including BMI, WC, FM%, and VFR and a positive correlation with FFM% were noted. Accordingly, Cho *et al.*<sup>32</sup> found a U-shaped relationship between body fat percentage (measured using bioelectrical impedance) and ED (defined as an IIEF-5 score less than 18) in men older than 45 years. Men aged  $\geq 65$  years with the highest quartiles of total body fat percentage and trunk fat percentage (measured with dual-energy X-ray absorptiometry) had a greater prevalence of moderate to severe ED, according to the Massachusetts Male Aging Study (MMAS) questionnaire.<sup>33</sup>

In our study, we show that MetS is related to ED. Thus, although ED was not more frequently diagnosed in patients with MetS, increasing

numbers of MetS components were positively associated with ED. In line with this, Lotti *et al.*<sup>34</sup> also found that the risk of ED increased as a function of the number of MetS factors, even after adjusting for age and testosterone. Moreover, we observed that men with ED have a higher degree of insulin resistance; this may result in endothelial dysfunction in the corpus cavernosum, increased oxidative stress, reduced nitric oxide concentrations (which have vasodilator effect), and increased endothelin-1 levels (a potent vasoconstrictor), thereby affecting the erectile mechanism.<sup>35,36</sup> However, elevated serum homocysteine levels (not measured in our study) could also be an early predictor of ED because this amino acid is associated with endothelial dysfunction and atherosclerosis progression, as shown by Giovannone *et al.*<sup>37</sup>

Low serum testosterone levels are often present in men with ED, and obesity is frequently associated with hypoandrogenemia and ED in a complex and multidirectional relationship.<sup>38</sup> However, we have



**Table 2: Association of metabolic syndrome with erectile function**

Characteristics	ED- (n=147)	ED+ (n=107)	P	Test
MetS components (n), median (IQR)	2.7 (2-3)	3.0 (2-4)	0.027	M
MetS components, n (%)			0.037	$\chi^2$
≤1	24 (16.3)	9 (8.4)		
2	43 (29.3)	30 (28.0)		
3	47 (32.0)	29 (27.1)		
4	24 (16.3)	34 (31.8)		
5	9 (6.1)	5 (4.7)		

P values were calculated for the difference among groups using Mann-Whitney (M) test or Chi-square ( $\chi^2$ ) test. P<0.05 was considered statistically significant. ED: erectile dysfunction; MetS: metabolic syndrome

**Table 3: Partial correlation coefficients among International Index of Erectile Function score, clinical characteristics, biochemical and hormonal parameters, and body composition analysis**

	IIEF-5 (point)	
	r	P
BMI (kg m <sup>-2</sup> )	-0.215	0.001
WC (cm)	-0.201	0.001
Components MetS (n)	-0.095	0.132
Fat mass (%)	0.208	0.001
Fat-free mass (%)	-0.216	0.001
VFR	-0.220	0.001
Glucose (mg dl <sup>-1</sup> )	-0.091	0.156
Insulin ( $\mu$ U ml <sup>-1</sup> )	-0.281	<0.001
HOMA-IR	-0.275	<0.001
HDL-cholesterol (mg dl <sup>-1</sup> )	0.142	0.026
hs-CRP (mg l <sup>-1</sup> )	-0.060	0.347
Total testosterone (ng ml <sup>-1</sup> )	0.053	0.417
Free testosterone (pg ml <sup>-1</sup> )	0.110	0.095
AMS score (point)	-0.379	<0.001

All correlation coefficients were calculated after adjustment for age. IIEF-5: International Index of Erectile Function; BMI: body mass index; WC: waist circumference; MetS: metabolic syndrome; VFR: visceral fat rating; HOMA-IR: insulin resistance according to the homeostasis model assessment; TT: total testosterone; FT: free testosterone; AMS: Aging Males' Symptoms

**Table 4: Univariate and multivariate logistic regression analysis: risk of erectile dysfunction**

Independent variables	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age (year)	1.039	1.005-1.075	0.026	1.047	1.009-1.087	0.016
BMI (kg m <sup>-2</sup> )						0.018
≥30 to <35	1 (reference)		0.020	1 (reference)		
≥35 to <40	1.35	0.714-2.568	0.353	1.565	0.788-3.109	0.201
≥40	2.370	1.277-4.399	0.006	2.602	1.336-5.068	0.005
MetS components (n)	1.283	1.020-1.614	0.033	-	-	-
WC (cm)	1.026	1.009-1.043	0.003	-	-	-
Fat mass (%)	1.071	1.026-1.119	0.002	-	-	-
Fat-free mass (%)	0.932	0.892-0.974	0.002	-	-	-
VFR	1.073	1.031-1.118	0.001	-	-	-
Insulin (mU ml <sup>-1</sup> )	1.032	1.009-1.055	0.007	-	-	-
HOMA-IR	1.132	1.034-1.240	0.007	-	-	-
HDL-c	0.958	0.927-0.985	0.003	0.956	0.926-0.986	0.004
hs-CRP	1.026	0.975-1.080	0.328	-	-	-
Free testosterone	0.992	0.984-1.000	0.048	-	-	-
Pathological AMS scale	4.703	2.252-9.824	<0.001	4.238	1.978-9.079	<0.001

BMI: body mass index; MetS: metabolic syndrome; WC: waist circumference; VFR: visceral fat rating; HbA1c: glycated hemoglobin; HOMA-IR, insulin resistance according to the homeostasis model assessment; HDL-c: high-density lipoprotein-cholesterol; hs-CRP: high-sensitivity C-reactive protein; AMS: Aging Males' Symptoms (pathological AMS scale ≥27 points); -: not included in the analysis. Multivariate logistic regression analysis: risk (odds ratio [OR]) of erectile dysfunction. Dependent variable IIEF-5 score >21 points (0) versus IIEF-5 score ≤21 points (1). Independent variables: obesity (dummy variable): reference category Grade I obesity (BMI 30-34.9 kg m<sup>-2</sup>), Grade II obesity (BMI 35-39.9 kg m<sup>-2</sup>), Grade III obesity (BMI ≥40 kg m<sup>-2</sup>); HDL-cholesterol (in mg dl<sup>-1</sup>); pathological AMS scale (≥27 points); HOMA-IR (no units)

not found a significant relationship between FT levels and ED in the multivariate analysis. In line with this, previous authors have shown that low testosterone, as an independent impact factor, is only relevant for men with severe ED.<sup>39</sup> In addition, as previously noted, it is important to remember that sexual dysfunction in obese men is a multifactorial condition and that psychological and sociocultural factors may play a relevant role independently of testosterone concentrations.<sup>31</sup>

In agreement with previous reports, we also observed that ED is associated with an impaired QoL as evaluated using the AMS scale.<sup>3</sup> Although the AMS scale was originally designed to assess health-related QoL in aging men, no age-specific scales have been designed to evaluate male symptoms in young individuals and indeed there are no differences in AMS score between different age categories.<sup>40</sup>

Although we intentionally selected a population of young men (median age 38 years), we have observed a deleterious effect of age on erectile function, as reported by other authors.<sup>2,41</sup> In particular, the elevated prevalence of ED in this young population highlights the importance of considering the possibility of finding ED in a young patient. In line with this, Capogrosso *et al.*<sup>42</sup> reported that one in four patients seeking first medical help for new-onset ED is younger than 40 years. Furthermore, a negative relationship between HDL-cholesterol and ED was found in our study. Accordingly, previous reports have shown that hyperlipidemia and HDL-cholesterol are directly related to the probability of presenting ED<sup>43,44</sup> and that endothelial dysfunction is associated with ED.<sup>45</sup>

It is important to note that ED is an interesting early marker for future cardiovascular events, given that ED and CVD share pathophysiological links such as endothelial dysfunction and inflammation. In line with this, ED is associated with increased likelihood of cardiovascular events, cardiovascular mortality, myocardial infarction, cerebrovascular events, and all-cause mortality.<sup>6</sup> Indeed, ED precedes a cardiovascular event by 2-5 years.<sup>7</sup> Consequently, the third Princeton Consensus Conference has stated that the mere presence of ED should be enough to consider any individual as a high-risk patient for CVD.<sup>46</sup> Hence, more than 40% of our study population could be considered to be at high risk for cardiovascular events.

Our study has certain limitations, but also some important strengths. We have studied a relatively small sample derived from a single city in a single country; therefore, our findings cannot be generalized. Furthermore, our results could in part depend on sociocultural determinants, confidence with the medical team, self-esteem, or ED acceptance and hence should be interpreted with caution. In addition, we did not have partner status and we did not capture depression scores. 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. However, the strengths of our study lie in the careful design (including only young nondiabetic obese subjects without T2DM or CVD), the assessment of sexual function with the IIEF-5 validated test, the extensive hormonal evaluation, the use of body composition analysis, and the determination of testosterone levels with high-performance liquid chromatography–mass spectrometry, the gold standard technique for the determination of steroidal hormones.

Finally, when addressing the treatment of obese men with ED, targeting excess body weight is undoubtedly a key factor because a healthy lifestyle combining reduced caloric intake and increased physical activity can preserve or restore erectile function in men with obesity.<sup>47</sup> PDE5 inhibitors are the most effective oral drugs for treating ED, and, importantly, several studies have demonstrated that their efficacy is independent from baseline BMI.<sup>48</sup> Finally, bariatric surgery, considered the most effective long-term treatment for severe obesity, also improves erectile function.<sup>49</sup>

## CONCLUSIONS

In a primary care-based cohort of nondiabetic young obese men, ED is a frequent finding, affecting more than 40% of subjects. A pathological AMS score, the degree of obesity, and age were factors positively associated with ED, whereas elevated HDL-cholesterol levels were inversely associated with the odds of presenting ED. Larger multicenter studies should be done to confirm the high prevalence of ED we have found and also prospective studies should be carried out to assess the long-term consequences of ED in this population.

## AUTHOR CONTRIBUTIONS

MMV, MAP, MJBD, MDHO, SRM, FCD, JAT, LGS, FJT, and JCFG contributed to the manuscript concept and design, study implementation, and data collection. MMV, FJT, and JCFG performed data analysis. MMV, DCC, FJT, and JCFG drafted the first version of the manuscript. MMV, JJAM, PCS, FJT, and JCFG revised the manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declared no competing interests.

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