ORIGINAL RESEARCH—ENDOCRINOLOGY

Testosterone Deficiency in Patients with Erectile Dysfunction: When Should a Higher Cardiovascular Risk Be Considered?

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ABSTRACT

Introduction. Low testosterone levels (low T) increase the cardiovascular (CV) risk of men with erectile dysfunction (ED). T levels associated with a higher CV risk are unknown.

Aim. To determine the prevalence of CV risk factors associated with low T as defined by European Guidelines and their contribution to low T, overall and at different ages.

Methods. Multicenter, cross-sectional, observational study conducted in Spain among men with ED aged ≥18 years visiting Urology/Andrology offices for sexual dysfunction. Anthropometric, clinical, and laboratory data, including total T (TT) values, were collected for 1,278 men.

Main Outcome Measures. Risk factors were assessed in men with TT ≤8, 8–12, and ≥12 nmol/L, and two-group comparisons were made. Bivariate and multivariate logistic regression analyses were performed to calculate odds ratios for low T after adjusting for possible confounding factors.

Results. Mean age (standard deviation) was 58.0 (9.2) years. Age and prevalence of CV risk factors was similar in men with TT ≤8 nmol/L or 8–12 nmol/L and significantly higher than in men with TT >12 nmol/L. Low T was therefore considered as TT ≤12 nmol/L, with a prevalence of 33.3%. Obesity, hypertension, hyperlipidemia, and severe ED were the variables most strongly associated with low T: obesity in middle-aged men; hyperlipidemia, and hypertension in older men. Severe ED was a risk factor in both groups. Hypolipidemic therapy had the greater effect in young men. Multivariate analysis showed that severe ED and obesity were the strongest predictors of low T.

Conclusion. T levels associated with increased CV risk could go as high as 12 nmol/L in men with ED, with distribution of risk factors showing differences according to age. Obesity and severe ED are the best predictors of low T-related CV risk. **Martínez-Jabaloyas JM. Testosterone deficiency in patients with erectile dysfunction: when should a higher cardiovascular risk be considered? J Sex Med 2014;11:2083–2091.**

Key Words. Testosterone; Hypogonadism; Cardiovascular Diseases; Androgen Deficiency; Erectile Dysfunction; Metabolic Syndrome; Diabetes; Hypertension; Hypercholesterolemia; Obesity; Abdominal Obesity; Sexual Dysfunction

Introduction

Erectile dysfunction (ED) is a common disorder in aging men affecting over 50% of men aged 40–70 years [1]. ED is frequently associated with modifiable risk factors such as diabetes, hypertension, hyperlipidemia, obesity, smoking, and a sedentary lifestyle [1–4]. ED has shown to increase the risk for cardiovascular (CV) events and all-cause mortality, showing also a trend to increase the risk for CV mortality [5]. ED nearly doubles the risk for CV events in men with diabetes [6]. Men with ED are therefore advised to undergo a detailed medical assessment for early intervention on cardiovascular health [7,8].

ED is one of the most common symptoms of testosterone deficiency syndrome (TDS), a condition associated with advancing age that is characterized by low levels of serum testosterone (low T) and the presence of compatible symptoms that are

not specific of the condition [9,10]. The relationship between ED and low T has been recently reviewed [11].

Low T is thought to be associated with diabetes, metabolic syndrome (MetS), and CV disease [12]. A meta-analysis of epidemiological data has shown that MetS is associated with lower levels of total T (TT) [13]. Longitudinal evidence has also shown that low T is associated with a higher risk for developing MetS, although it is unclear which is the cause and which is the consequence [14]. Some authors also support that low T might be a fundamental component of MetS [15].

Association between MetS and low T levels has shown to be more evident in men with ED [13], which may result in increased CV risk in these men. Comorbidities such as diabetes, hypertension, and obesity have been found to be associated with increased CV diseases in men with low T, independently of age [14]. Looking for low T among men with CV comorbidities and, conversely, identifying CV comorbidities when hypogonadism is found, is therefore of great importance [14].

Among symptoms associated with low T, ED is an important reason to seek medical advice. Most guidelines recommend the determination of serum T in men with ED signs [9,10]; however, a biochemical threshold for the definition of low T is still lacking, with differences among professional societies. Determining T thresholds may be of value as a reference to start testosterone replacement therapy (TRT) but also to adopt more intensive measures, beyond lifestyle modifications, to reduce CV risk. European Guidelines recommend TRT in men with ED and low T (defined as TT ≤8 nmol/L; 230 ng/dL) and also in those with "borderline" T levels (8–12 nmol/L) and a clinical picture of low T, where a short trial is advisable [9]. However, the T level associated with an increased CV risk in men with ED is unknown.

Aim

We analyzed the prevalence of common CV risk factors in a large cohort of men with ED with the aims of (i) analyzing which TT threshold, using the two thresholds proposed by European guidelines (8 and 12 nmol/L) as a reference, is associated with a higher prevalence of CV risk factors; and (ii) identifying which of these CV risk factors is associated with a higher likelihood for low T. The relative weight of each risk factor across the lifespan was also assessed.

Method

This was a multicenter, cross-sectional, observational study conducted in Spain with the objective of assessing the relationship of ED and cardiovascular risk factors, including the prevalence of low T levels, among men seeking specialized medical attention due to sexual dysfunction. Patients aged ≥18 years were consecutively recruited by 394 urologists and andrologists from January to September 2009. Inclusion criteria included a diagnosis of ED according to the Erectile Function domain of the International Index of Erectile Function (IIEF-EF) [16], the ability to answer a self-questionnaire, and to have provided written informed consent. The only exclusion criterion was refusal to participate in the study. An independent Ethics Committee approved the study protocol. All information was centralized in a coordination center.

Data Collection

Data were collected in a single visit and included: age, anthropometric data (body mass index [BMI] and waist circumference [WC]), tobacco use and alcohol consumption, and medical conditions (hyperlipidemia, diabetes, and hypertension). Information about the presence of these comorbidities was self-reported (confirmed by previous prescription of treatment and/or lifestyle changes for their correction) when not available in the clinical records. Diagnosis was based on current local guidelines targets. Hypolipidemic therapy was also recorded given the T-lowering effect of statins [17]. Obesity and abdominal obesity were defined as having a BMI ≥30 kg/m^2 and WC ≥102 cm, respectively [18]. Men were considered smokers when smoking for at least 1 year. Moderate alcohol consumption was defined as having up to two glasses of wine or beer per day or 3–4 hard alcohol drinks per week. Excessive intake was considered as any intake exceeding the stated amounts [19]. Severity of ED was assessed using the IIEF-EF, which includes questions 1–5 and 15 of the IIEF [16]. Questions are scored from 1 to 5 points, with ED defined as a total score value ≤25. Severity is classified as follows: mild (22–25), mild-to-moderate (17–21), moderate (11–15), and severe (6–10). A single point plasma TT level measurement was performed between 7 and 11 hours in subjects lacking a TT determination in the last 6 months. Laboratory tests were performed at the reference laboratory of participating centers. Serum TT was measured using a chemiluminiscent

immunoassay. In order to analyze and compare the prevalence of cardiovascular risk factors with respect to T levels, men were classified as those with TT ≤8 nmol/L (hypogonadic), 8–12 nmol/L (borderline), and ≥12 nmol/L (eugonadic).

Main Outcome Measures

Two-group comparisons of prevalence of CV factors were made among the three TT groups to analyze the low T threshold (8 or 12 nmol/L) associated with a higher CV risk. Once a threshold indicative of a higher cardiovascular risk was selected, the likelihood of low T was assessed and analyzed by age ranges.

Statistical Analysis

Normal distribution of variables was tested prior to analysis (Kolmogorov–Smirnov test). Percentages were used to describe categorical variables and compared using the χ^2 test. Quantitative variables were expressed as mean scores ± standard deviation (SD) and compared using the Student's *t*-test. The relationship between quantitative variables was assessed using the Pearson's correlation test. Bivariate and multivariate logistic regression analyses were used to calculate odds ratios (ORs) for low T and the 95% confidence interval. ORs were adjusted in bivariate analysis for variables showing relationship with T levels according to the literature in order to eliminate their possible confounding effect when analyzing the effect of cardiovascular risk factors and toxic habits, despite not having shown any relationship with T levels in our series. These included age, obesity, abdominal obesity, and severe ED. Stratification by age group was also performed. Receiver-operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of risk factors for the prespecified TT thresholds (≤8 and ≤12 nmol/L) and the area under the curve (AUC) for each variable analyzed showing a higher prevalence in men with either TT ≤8 or 8–12 nmol/L vs. men with TT ≥12 nmol/L. The Youden index and the optimal cut-point maximizing TT differentiating ability were also calculated. The SAS® 9.1.3 Service Pack 3 statistical software package was used (SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$.

Study Subjects

A total of 1,391 patients were recruited. Of these, 51 were ineligible because they did not meet some of the inclusion criteria, leaving a population of 1,340 men. Baseline characteristics of these patients (age, anthropometrics, prevalence of risk factors, and T levels) have been published elsewhere [20]. T values were valid for 1,278 men, constituting the population study for our analysis.

Results

Subjects' Characteristics

Participants were mainly white (98.4%), heterosexual (97.1%), with a stable partner (89.9%), with primary education, high school, or college degree (93.8%), and actively employed (64.5%). ED was diagnosed at the screening visit in 74.3% of subjects; a similar number of men (69%) had one or more comorbidities (hyperlipidemia, diabetes, or hypertension), with 46% of them having two or more comorbidities. Besides hypolipidemic therapy (16.7%), 36.9% of men were on antihypertensive therapy.

Testosterone Levels and Erectile Dysfunction

Distribution of TT levels were as follows: 13.7% TT ≤8 nmol/L (N = 175), 19.6% TT 8–12 nmol/L (N = 250), and 66.7% TT ≥12 nmol/L (N = 853). Prevalence of low T according to both preestablished thresholds was therefore 13.7% for TT ≤8 nmol/L and 33.3% for TT ≤12 nmol/L. Mean TT levels decreased with increasing ED severity [mean (SD), nmol/L]: mild [18.2 (14.2)], mild-moderate [16.4 (9.3)], moderate ED [15.5 (7.0)], and severe ED [14.9 (8.2)] ($P = 0.003$).

Risk Factors and Testosterone Levels

Mean TT levels were statistically lower in men with the following risk factors vs. those without [mean, nmol/L (SD)]: obesity [13.8 (7.6) vs. 16.3 (8.1), $P < 0.0001$], abdominal obesity [14.5 (6.7) vs. 16.5 (10.5), $P = 0.0002$], hyperlipidemia [14.8 (8.6) vs. 16.5 (9.3), $P = 0.0013$], or hypertension [15.0 (9.5) vs. 16.7 (8.7), $P = 0.0013$]. They were also lower in men receiving hypolipidemic therapy vs. those who were not [14.5 (8.6) vs. 16.1 (9.2), $P = 0.0173$]. No significant differences were found for age, diabetes, tobacco use, or alcohol consumption.

Prevalence of Risk Factors According to Testosterone Levels

Table 1 shows the prevalence of risk factors—overall and according to the three TT ranges—as well as the two-group differences. No significant differences were found between men with TT

Table 1 Prevalence of comorbid conditions and risk factors overall and according to the three TT ranges

	Overall N = 1,278	TT ≤8 nmol/L N = 175	TT 8–12 nmol/L N = 250	TT ≥12 nmol/L N = 853	*P* value		
					TT ≤8 nmol/L vs. 8–12 nmol/L	TT ≤8 nmol/L vs. ≥12 nmol/L	TT 8–12 nmol/L vs. ≥12 nmol/L.
Age, mean (years) (n = 1,117)	58.1 (9.3)	58.0 (9.5)	59.6 (8.2)	57.6 (9.5)	0.0965	0.6739	0.0079
18–44 years (n = 94)	94 (8.5)	16 (10.5)	9 (4.3)	69 (9.2)	0.0757	0.8055	0.057
45–64 years (n = 759)	759 (67.9)	100 (65.8)	148 (70.1)	511 (67.8)			
≥65 years (n = 264)	264 (23.6)	36 (23.7)	54 (25.6)	174 (23.0)			
Obesity (n = 1,245)							
BMI <30 (n = 971)	971 (78.0)	123 (71.1)	174 (70.5)	674 (81.7)	0.9136	0.0024	0.0002
BMI ≥30 (n = 274)	274 (22.0)	50 (28.9)	73 (29.5)	151 (18.3)			
Abdominal obesity (n = 1,011)							
WC <102 cm (n = 547)	547 (54.1)	69 (46.9)	102 (48.3)	376 (57.6)	0.8301	0.0215	0.0209
WC ≥102 cm (n = 464)	464 (45.9)	78 (53.1)	109 (51.7)	277 (42.4)			
Tobacco habit (n = 1,275)							
Yes (n = 549)	549 (43.1)	77 (44.0)	111 (44.4)	361 (42.5)	1.0000	0.7374	0.6112
No* (n = 726)	726 (56.9)	98 (56.0)	139 (55.6)	489 (57.5)			
Alcohol consumption (n = 1,262)							
No (n = 380)	380 (30.1)	47 (27.0)	64 (26.0)	269 (31.9)	0.7418	0.0080	0.0220
Medium (n = 784)	817 (62.1)	105 (60.3)	156 (63.4)	523 (62.1)			
Excessive (n = 98)	98 (7.8)	22 (12.7)	26 (10.6)	50 (6.0)			
Hyperlipidemia							
Yes (n = 426)	426 (33.3)	73 (47.7)	98 (39.2)	255 (29.9)	0.6161	0.0032	0.0069
No (n = 852)	852 (66.7)	102 (58.3)	152 (60.8)	598 (70.1)			
Diabetes							
Yes (n = 289)	289 (22.6)	49 (28.0)	69 (27.6)	171 (20.0)	1.0000	0.0256	0.0145
No (n = 989)	989 (77.4)	126 (72.0)	181 (72.4)	682 (80.0)			
Hypertension							
Yes (n = 609)	609 (47.6)	98 (56.0)	137 (54.8)	374 (43.8)	0.8431	0.0036	0.0024
No (n = 669)	669 (52.4)	77 (44.0)	113 (45.2)	479 (56.2)			
Hypolipidemic therapy							
Yes (n = 210)	210 (16.4)	38 (21.7)	52 (20.8)	120 (14.1)	0.9040	0.0152	0.0129
No (n = 1,068)	1,068 (83.6)	137 (78.3)	198 (79.2)	733 (85.9)			
DE severity†							
Severe (n = 264)	264 (22.3)	43 (27.0)	64 (27.7)	157 (19.8)	0.9085	0.0544	0.0139
Moderate (n = 771)	771 (65.2)	105 (66.0)	141 (61.0)	525 (66.3)	0.3377	1.0000	0.1579
Mild (n = 147)	147 (812.4)	11 (6.9)	26 (11.3)	110 (13.9)	0.1637	0.0182	0.3234

Data are expressed as N (%) unless specified. Specific population numbers when data are incomplete for all patients are indicated in brackets.
*Nonsmokers include never smokers and ex-smokers
†Comparisons are made between those who had each category vs. those who did not
BMI = body mass index; WC = waist circumference

Table 2 Crude and adjusted odds ratios (95% CI) for TT ≤12 nmol/L

Variables	Crude	Age adjusted	Obesity adjusted	Abdominal obesity adjusted	Severe ED adjusted
Obesity	**1.85** (1.40–2.43)	**1.83** (1.37–2.45)	—	**1.57** (1.15–2.15)	**2.01** (1.51–2.67)
Abdominal obesity	**1.48** (1.15–1.92)	**1.36** (1.03–1.79)	**1.10** (0.76–1.61)	—	**1.44** (1.10–1.88)
Hyperlipidemia	**1.58** (1.24–2.01)	**1.55** (1.19–2.01)	**1.43** (1.11–1.83)	**1.42** (1.08–1.86)	**1.66** (1.29–2.14)
Hypertension	**1.58** (1.25–2.00)	**1.51** (1.16–1.97)	**1.40** (1.10–1.79)	**1.34** (1.03–1.74)	**1.55** (1.21–1.98)
Diabetes	**1.53** (1.17–2.01)	**1.50** (1.12–2.01)	**1.40** (1.06–1.85)	**1.34** (1.00–1.81)	**1.49** (1.12–1.98)
Hypolipidemic therapy	**1.64** (1.21–2.22)	**1.77** (1.29–2.43)	**1.47** (1.08–2.00)	**1.55** (1.11–2.16)	**1.65** (1.20–2.26)
Alcohol consumption	**1.31** (1.01–1.70)	**1.36** (0.77–2.39)	**1.14** (0.75–1.73)	**1.1** (0.88–1.58)	**1.33** (1.01–1.74)
Severe ED	**1.53** (1.15–2.03)	**1.61** (1.19–2.19)	**1.47** (1.11–1.96)	**1.44** (1.06–1.95)	—

Statistically significant ORs ($P < 0.05$) are written in bold
ED = erectile dysfunction

≤8 nmol/L and TT 8–12 nmol/L for any of the risk factors assessed. Prevalence of these risk factors was statistically higher in men with either TT ≤8 or 8–12 nmol/L vs. those with higher TT levels. Only mean age and prevalence of severe ED were significantly higher in men with TT 8–12 nmol/L vs. men with TT ≥12 nmol/L.

Given the similar prevalence of CV risk factors among men with TT ≤8 nmol/L and TT 8–12 nmol/L, the TT ≤12 nmol/L threshold (from now "low T") was chosen to further analyze CV risk in these men.

Likelihood of Low T

Bivariate analysis showed that obesity was the risk factor showing a higher likelihood of low T. This effect remained after adjusting for other confounding variables analyzed: age, abdominal obesity, and severe ED (see Statistical analysis). The effect of hypertension and hyperlipidemia was slightly lower but also remained after individually adjust for other confounding variables. Hypolipidemic therapy had an effect similar to that of hyperlipidemia. The effect of other variables disappeared after individually adjusting for other confounding variables (Table 2).

When further analyzing the likelihood of low T in prespecified age groups, the distribution of the variables effect showed differences (Table 3). Obesity, abdominal obesity, and diabetes were risk factors for TT ≤12 nmol/L in men aged 45–64 years, whereas hyperlipidemia was a risk factor only in older men (≥65 years). Hypertension and severe ED were risk factors in men aged ≥45 years. Hypolipidemic therapy was a risk factor especially in young men. Multivariate logistic regression analysis including all variables showed that only obesity and severe ED were risk factors for low T (Table 4).

TT Thresholds for CV Risk Factors

Sensitivity and specificity of TT threshold ≤12 nmol/L vs. TT ≤8 nmol/L by means of ROC analysis showed that although sensitivity of TT ≤12 nmol/L is lower than that of TT ≤8 nmol/L, the sensitivity of this lower threshold is low. Any of these two thresholds has positive likelihood ratios (sensitivity/1-specificity) for any of the CV risk factors. The AUCs were in all cases ≤0.6, with obesity showing the higher value (Figure 1). Cut-points optimizing TT differentiating ability for each CV risk factor assessed are also shown in

Table 3 Crude odds ratios (95%CI) for low T (TT ≤12 nmol/L) by age group

Variables	18–44 years (n = 94)	45–64 years (n = 759)	≥65 years (n = 264)
Obesity	**3.16** (0.91–10.95)	**2.09** (1.47–2.98)	**1.18** (0.67–2.09)
Abdominal obesity	**2.22** (0.72–6.83)	**1.39** (1.00–1.94)	**1.21** (0.69–2.11)
Hyperlipidemia	**2.78** (0.95–8.13)	**1.31** (0.96–1.79)	**2.26** (1.34–3.81)
Hypertension	**1.86** (0.60–5.81)	**1.36** (1.00–1.84)	**2.41** (1.35–4.32)
Diabetes	**1.69** (0.45–6.34)	**1.48** (1.03–2.11)	**1.64** (0.96–2.78)
Hypolipidemic therapy	**5.13** (1.31–20.08)	**1.53** (1.04–2.26)	**2.14** (1.37–3.91)
Severe ED	**1.05** (0.33–3.35)	**1.68** (1.15–2.46)	**1.80** (1.02–3.19)

Statistically significant ORs ($P < 0.05$) are written in bold
ED = erectile dysfunction

Table 4 Multivariate analysis for TT ≤12 nmol/L

Variables	OR (95% CI)
Obesity	**1.51** (1.08–2.10)
Abdominal obesity	**1.20** (0.90–1.60)
Hyperlipidemia	**1.27** (0.87–1.74)
Hypertension	**1.14** (0.86–1.57)
Diabetes	**1.11** (0.80–1.53)
Hypolipidemic therapy	**1.27** (0.84–1.92)
Alcohol consumption	**1.21** (0.88–1.65)
Severe ED	**1.41** (1.02–1.93)

Statistically significant ORs ($P < 0.05$) are written in bold
ED = erectile dysfunction

Figure 1. These TT levels were higher than 12 nmol/L in all cases.

Discussion

Low T is known to be common among men consulting for ED [21]. Our study has revealed a prevalence of low T levels among men with ED ranging from 13.7% to 33.3% when thresholds are set at 8 or 12 nmol/L, respectively. Obesity and severe ED would be the strongest predictors of low T. In addition, we found that several CV risk factors that are commonly observed in men with ED [1–4] are more prevalent not only in formal hypogonadic men according to European Guidelines [9], but also in those having so-called "borderline" T levels (8–12 nmol/L). According to these data, the CV risk of men with ED could be significantly higher for T levels below a threshold as high as 12 nmol/L or even more.

Men with low T in our series were significantly older, although no differences were found among prespecified age categories probably due to the lack of homogeneity among subjects (nearly 70% of participants were 45–64 years old). However, we were able to identify differences in the risk factors associated with the likelihood of low T in different age groups. Rather than a selection bias in our study, age distribution may be representative of that of men seeking medical attention in our setting.

Prevalence of cardiovascular risk factors frequently associated with ED was high in our series. This may indicate factors with the strongest association with ED in our setting. However, as the aim of this study was to analyze differences in the prevalence of cardiovascular risk factors in men with ED with and without low T, we did not include a control group of men with normal erectile function that would have helped further understand the relevance of the high prevalence found. It is also important to take into account that the risk factors showing a strong association with ED, and probably with low T, are likely to show differences among countries according to the prevalence in the general population of men.

Among all cardiovascular risk factors analyzed, hypertension, followed by hyperlipidemia, were the most prevalent risk factors in our study (47.6% and 33.3%, respectively). Both have been found to be frequently associated with ED of any severity [22] and, according to an epidemiological study performed in Spain, they are also the most prevalent cardiovascular risk factors in the general male population [23]. Their prevalence increased significantly in men with low T compared with other risk factors. In men with ED, hypertension has

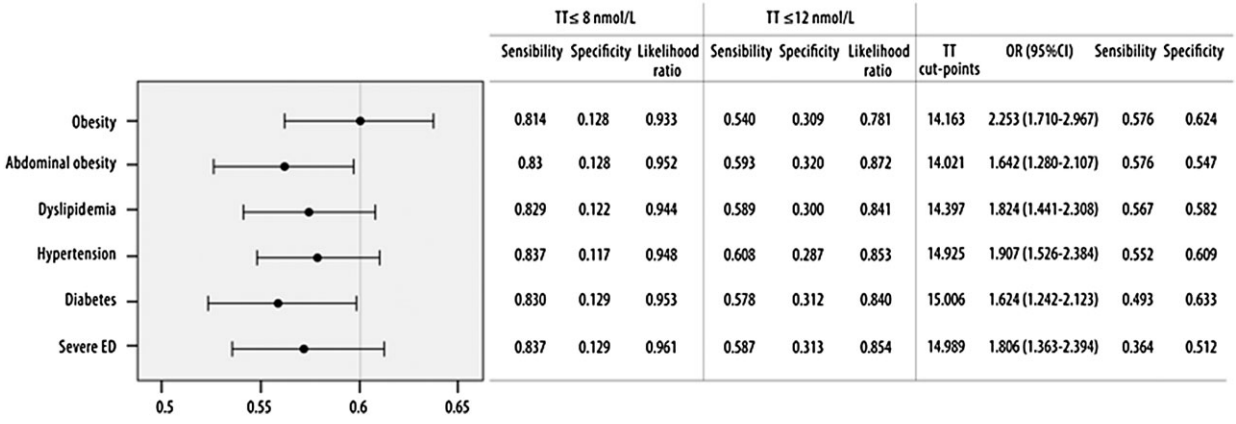

Figure 1 Area under the curve (95%CI) for each of the CV risk factors assessed according to the TT thresholds analyzed and cut-points (OR [95%CI]) optimizing TT differentiating ability for each CV risk factor (alcohol consumption excluded). TT = total testosterone; ED = erectile dysfunction.

shown to be independently associated with elevated pulse pressure (PP), an indicator of arterial stiffness [24]. Elevated PP has proven to be a marker of arteriogenic problems and low T and a predictor of major cardiovascular events in young men [21,25]. This is why it has been suggested that measurement of PP should become routine practice in sexual medicine [26].

Prevalence of diabetes was third in importance (22.5%), which is in agreement with the observations of an epidemiological study of ED performed in Spain where this comorbidity was the one showing the greatest odds for ED after adjusting for age in our setting [4]. Prevalence of diabetes did not increase as much, although it was statistically significant. Hypertension and hyperlipidemia were associated with an increased likelihood of low T in men aged ≥65 years, whereas diabetes did in middle-aged men. However, their contribution disappeared after adjusting for all confounding variables.

Prevalence of obesity was also relatively high (22.0%), increasing up to 29.5% in men with low T. Its relationship with low T levels has been described in detail [27,28]. Obesity was associated with an increased likelihood of low T in middle-aged men. Together with severe ED, obesity was the only risk factor associated with low T after adjusting for all confounding variables. This is in accordance with the observation that BMI was the most differentiating factor between hypogonadal (defined as TT <300 ng/dL) and eugonadal men in the Hypogonadism in Males study, an epidemiological study performed in men aged ≥45 years visiting primary care practices in the United States [29]. On the contrary, abdominal obesity, a fundamental component of MetS [5], which is also known to be a risk factor for ED [30], only had a relative low contribution to low T. This result is in contradiction with that reported by Corona et al., where elevated WC (>102 cm) was one of the MetS factors showing a higher association with low T in men consulting for sexual dysfunction [31]. The high prevalence of abdominal obesity found in our series (45.8%) may mask the relationship. Although WC has been proposed as a low T predictor in community dwelling men [32], our study suggests that it is not a good indicator in men with ED in our setting. Among toxic habits, only excessive alcohol consumption was more prevalent in men with TT ≤8 nmol/L. The small number of men in this group did not allow for the analysis of associations.

The type of hypolipidemic treatment was not recorded; however, statins are the most widely used hypolipidemic agents so far in our setting (nearly 95%). Their T lowering effect has been described [17]. Only half of men with hyperlipidemia were on hypolipidemic therapy. The relationship was significant across all age groups, but stronger in young men, where a fivefold increase was observed. Although it should be subject of further research, this finding would support the independent effect of statins on T levels, which would be stronger in younger ages.

Despite the evidence found in this study, it remains unknown whether the higher prevalence of CV risk factors is the cause of low T or its consequence [14]. This may explain why, despite the significant difference found in the prevalence of individual CV risk factors, any of the two thresholds assessed had good diagnostic properties. Even when TT thresholds for each CV factor were found, they were not adequate markers. The possibility of identifying a TT value associated with a higher CV risk, defined as a combination of individual CV risk factors, cannot be ruled out. However, we did not assess well-known indicators such as the Framingham risk score or other relevant indicators. It is also worth mentioning that, to date, the association of low T and a higher CV risk is still controversial. Although three recent meta-analyses have observed an association of low T levels and CV mortality, it cannot be ruled out that low T could merely be an indicator of poor health affecting prognosis rather than a CV marker itself [33–35]. In fact, evidence suggests that T may have an indirect role in maintaining CV health by modulating cardiac risk factors as those implicated in the MetS [12]. Losing weight (diet and exercise) is recommended in obese men with low T, as the existing evidence points to improved T levels and metabolic health [36]. These benefits would be more apparent in younger, nondiabetic subjects with a greater degree of obesity [37].

TRT is advisable in men with ED due to its synergic effect in conjunction with phosphodiesterase type 5 inhibitors (PDE5) [9]. Men at a higher CV risk could also benefit from the growing evidence regarding the metabolic positive effect of TRT [38]. Two recent retrospective studies have reported increased number of adverse effects among men on TRT, these including an increased risk of cardiovascular events and all-cause mortality in old men and/or with cardiovascular complications, therefore calling for a cautious use of TRT and the need for individually tailored treatment [39,40]. Prospective, randomized controlled trials

are needed to better determine the risks and benefits of TRT in older low T men.

Some limitations of the study have already been addressed. Although the results of our study strongly support a higher cardiovascular risk associated with T levels slightly above 12 nmol/L, it should be taken into account that these results are based on a single T measurement. Guidelines recommend repeating the analysis when values between 8 and 12 nmol/L are observed for confirmation purposes [9,10], in order to avoid transient low T values caused by acute conditions or stress. Low T diagnosis should always be based on repeated measurements, and treatment decisions should be based on low T confirmation. However, for epidemiological purposes, a single measurement may be considered a fairly approximation of men androgen status, as reported by Vermeulen and Verdonk, who observed that it was a reliable reflection of the annual mean T level in healthy middle-aged and elderly men [41]. On the contrary, the lack of centralization of laboratory tests may have affected, although relatively, the TT values observed. Comorbidities were self-reported when no clinical records were available. In this case, presence of the comorbidity was confirmed by a previous prescription of treatment and/or lifestyle changes. Nevertheless, the situation described in our study reproduces that of medical consultation, and therefore could help as a first approach for low T screening in men at different ages.

Conclusion

T levels associated with increased CV risk could go as high as 12 nmol/L in men with ED, with distribution of risk factors showing differences according to age. Obesity and severe ED are the best predictors of low T-related CV risk.

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Conflict of Interest: José M. Martínez-Jabaloyas is a scientific study/trial investigator for Bayer, Pfizer Inc, Lilly and GlaxoSmithKline.

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