ORIGINAL RESEARCH—ENDOCRINOLOGY

Marked Testosterone Deficiency-Related Symptoms May be Associated to Higher Metabolic Risk in Men with Low Testosterone Levels

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ABSTRACT

Introduction. Testosterone deficiency syndrome (TDS) is usually suspected on the basis of signs/symptoms. However, some men with low testosterone levels (low T) are asymptomatic or present mild, unnoticed symptoms. Would they have the same cardiovascular risk as symptomatic men?

Aims. This study aims to assess the relationship between presence/severity of low T-related symptoms and the likelihood of metabolic syndrome (MetS).

Methods. Data were taken from a multicenter, cross-sectional study conducted in Spain among men visiting men's healthcare offices aged ≥45 with low T (total T <8 nmol/L or <12 nmol/L and calculated free T <250 nmol/L). Only subjects whose MetS components and symptoms had been assessed were selected. Data available included anthropometrics, toxic habits, comorbidities, and total testosterone (TT) levels.

Main Outcome Measures. MetS was defined using the harmonized definition. Erectile dysfunction was classified using the International Index of Erectile Function questionnaire. The Ageing Male Symptoms (AMS) scale assessed symptoms. Symptom severity was classified as "none/mild" and "moderate/severe." Bivariate and multivariate logistic regression analyses were performed to calculate the effect of moderate/severe symptoms on the odds ratio (OR) for MetS.

Results. Mean age (SD) was 61.2 (8.1) years. Erectile dysfunction (ED), AMS, and MetS prevalence were 97.4%, 94.9%, and 69.6%. Prevalence of MetS was higher in men with moderate/severe symptoms vs. men with no/mild ones (75.3% vs. 57.9%, $P < 0.001$). Age and prevalence of TT <8 nmol/L, moderate/severe ED, and obesity were significantly higher in men with moderate/severe symptoms. Multivariate analysis showed that besides obesity and moderate/severe ED, moderate/severe symptoms increased the likelihood of MetS. This effect disappeared in men with severe ED and in the nonobese. Three symptoms showed relationship with MetS after adjusting for all confounding factors.

Conclusion. Severity of TDS symptoms may indicate higher cardiovascular risk in men with low T. **García-Cruz E, Leibar-Tamayo A, Romero-Otero J, Asiaín I, Carrión A, Castañeda R, Mateu L, Luque P, Cardeñosa O, and Alcaraz A. Marked testosterone deficiency-related symptoms may be associated to higher metabolic risk in men with low testosterone levels. J Sex Med 2014;11:2292–2301.**

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Introduction

Testosterone deficiency syndrome (TDS) is a clinical and biochemical syndrome characterized by a progressive decrease in serum testosterone (T) with age, which is associated with psychological, metabolic, and sexual disorders that have a negative impact on men's life [1–4]. It is believed that TDS remains largely underdiagnosed, which is mainly due to the lack of specificity of symptoms that can be attributable to aging and other medical conditions. Presence of low T levels (low T) is frequently associated with sexual disorders [5–7], these being usually the most evident consequences for men and the most likely driver to seek medical advice. Low T is also associated with a variety of medical conditions such as type 2 diabetes mellitus, metabolic syndrome (MetS), and cardiovascular disease (CVD) [8–11]. Pulse pressure, an index of arterial stiffness that has been suggested to be an independent CV risk factor, has also shown to be higher in men with arteriogenic erectile dysfunction (ED) and low T [12]. Recent meta-analyses have also associated low T with increased CVD and overall mortality [13–15]. Given the current burden of these diseases, efforts should be made to identify people at risk so that measures to reduce the risk of CVD can be adopted. This will undoubtedly benefit from an improvement of TDS diagnosis in urology and men's health offices. Although lifestyle modifications and treatment of the conditions associated with low T are the first-line approach in men with low T, especially in those with obesity, type 2 diabetes mellitus or MetS, two recent systematic reviews and one meta-analysis suggest that testosterone replacement therapy may improve metabolic outcomes in these patients [16,17]. Long-term randomized clinical trials are needed to prove this benefit.

Clinical practice guidelines define TDS as a biochemical and a clinical condition [1,2]. TDS is usually suspected on the basis of symptoms or signs and confirmed by laboratory tests. Despite the importance of symptoms in TDS diagnosis, they are typically nonspecific to the condition and similar to those of aging [1,2]. Furthermore, some men with low T are asymptomatic or present symptoms that are mild in nature, which might be due to differences in androgen sensitivity [18,19]. Mild symptoms are frequently not spontaneously noticed by men and therefore not reported. It is not known whether these "asymptomatic" men with low T are at the same cardiovascular risk as "symptomatic" men. In other words, would there be a potential risk in not detecting these "asymptomatic" men?

Our group has recently reported a high prevalence of MetS among men with low T, as well as the factors increasing the likelihood for MetS in these men, these being presence of moderate to severe ED, central obesity, or peripheral vascular disease and, to a lesser extent, alcohol intake [20]. Among the 1,094 men with low T participating in the study, presence and severity of symptoms was recorded in 999 men.

Aims

With the aim of further identifying men with low T at a higher risk for MetS, we assessed the existing relationship between the presence and severity of low T-related symptoms and the likelihood for MetS, beyond the aforementioned identified risk factors. Relationship was analyzed for overall symptoms as well as for each of the three domains. Relationship with specific symptoms was also assessed.

Methods

Study Sample

Between October 2009 and December 2010, men visiting urology, men's health, or endocrinology offices for any reason, and with confirmed or suspected low T, were invited to participate in a multicenter, cross-sectional, single-visit, observational study aimed at analyzing the relationship between low T and comorbidities, TDS symptoms, and ED. Inclusion criteria were being 45 years or older and having a diagnosis of low T defined as a total testosterone (TT) <8 nmol/L or <12 nmol/L and calculated free testosterone (cFT) ≤250 nmol/L. Exclusion criteria were patient refusal to participate in the study or being under testosterone substitutive or 5-alpha-reductase inhibitor treatments. An independent Ethics Committee approved the study protocol, and all patients gave written informed consent prior to the participation in the study. Among the 2,238 subjects eligible for the study, 1,094 with available data for MetS assessment were initially selected in order to analyze the risk factors for MetS in this cohort of men with low T. The results of this study have been published elsewhere [20]. TDS-related symptoms assessment was available for 999 subjects. Data collection, including anthropometrics and laboratory determinations,

has been previously described [20]. Central obesity was defined as body mass index (BMI) ≥30 kg/m^2. T was measured from fasting blood samples taken from 7 AM to 11 AM when testosterone values were older than 2 months or were not available. Calculation of cFT was made following Vermeulen's formula [21].

Main Outcome Measures

The harmonized definition was used to diagnose MetS [22]. This definition requires the presence of three abnormal findings out of the following five: elevated triglycerides (≥150 mg/dL), blood pressure (≥130/85 mm Hg), or fasting glucose (≥100 mg/dL); reduced high density lipoprotein (HDL)-cholesterol (<40 mg/dL); being under pharmacologic treatment for these conditions; and abdominal obesity (high waist circumference). Cutoff point for this latter component is left open to differences among countries. A threshold of 94 cm is recommended for people of European origin (Europid) by the International Diabetes Federation [23] and for Caucasian populations by the World Health Organization [24] and therefore is the most appropriate in our setting. Participants were asked to answer the Spanish version of the Ageing Male Symptoms (AMS) scale, a 17 item-scale rated 1–5 (none to very severe). On this scale, a score >26 might indicate testosterone deficiency, with 27–36 indicating mild symptoms, 37–49 moderate, and 50–85 severe. Seven items are related to somatovegetative complaints, with scores 9–12, 13–18, and 19–35 indicating severity of symptoms as above, and 7–8 no symptoms. Five items are related to psychological complaints, and another 5 to sexual complaints. Scores indicating severity as above were 6–8, 9–11, and 12–25 for psychological symptoms, and 6–7, 8–10, and 11–25 for sexual symptoms. A score of 5 indicates absence of symptoms in both cases [25]. Men also completed the abridged five-item version of the 15-item International Index of Erectile Function questionnaire in order to diagnose and classify ED. In this questionnaire, each question is scored from 0 to 5 points (total score range: 5–25). ED is defined as any total score value <21. Severity is classified as follows: mild (17–21), mild-to-moderate (12–16), moderate (8–11), and severe (5–7) [26].

Statistical Analysis

Collected data and determinations were summarized using descriptive statistics. Quantitative variables were compared using Student's *t*-test or the analysis of variance (ANOVA) test (more than two categories). Linear trends were assessed using Kendall's tau-c correlation test (categorical variables) or the ANOVA weighted linear trend index (quantitative variables). Given the small size of the population of asymptomatic men in our study (5%), influence of symptoms was analyzed gathering those having moderate or severe symptoms and comparing them vs. those having no or mild symptoms. Bivariate analyses were performed in order to identify the variables having a relationship with symptoms among those which known relationship (age and TT levels) and those previously identified as increasing the likelihood of MetS (central obesity, alcohol intake, peripheral vascular disease, and moderate or severe ED) [20]. Variables showing a relationship were included in a multivariate analysis, where odds ratios (ORs) for MetS and 95% confidence intervals (CIs) were estimated using logistic regression analysis. The same analyses were performed to assess the effect of different AMS domains. Previous verisimilitude analysis showed that none of these variables interacted with the relationship symptoms—MetS. On the contrary, all of them showed a confounding effect on the likelihood of MetS. Moderate/severe ED was the variable showing a higher effect of the symptoms—MetS relationship, thereby reducing the influence by a 40%. Despite the lack of interaction, the overall population was split into two groups according to the presence/absence of moderate/severe ED or to the presence/absence of central obesity, given the strong effect of those variables on the likelihood of MetS [20]. The same multivariate analyses were performed in these groups of men. The effect of AMS domains was investigated in those groups where an effect on overall symptoms was observed. Univariate contribution to MetS of individual symptoms was assessed by step-back logistic regression analysis. Symptoms showing a relationship with MetS were included in a multivariate analysis. Statistical analyses were performed using the SPSS v.18.0 statistical software package (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

Results

Participants and Symptoms Assessment

Mean age of participants was 61.2 ± 8.2 years. The characteristics of these men and the assessment of symptoms are summarized in Table 1. ED was present in 914 men (97.4%), half of them with

Table 1 Characteristics of men participating in the study (N = 999)

	Overall
Age and anthropometrics	
Age (years), mean (SD)	61.2 (8.2)
45–59 years, n (%)	434 (43.4)
60–69 years, n (%)	400 (40.0)
≥70 years, n (%)	166 (16.6)
BMI (kg/m^2), mean (SD) [N = 997]	28.9 (3.9)
Overweight (BMI = 25–29.9), n (%)	509 (51.0)
Obese (BMI ≥30 kg/m^2), n (%)	351 (35.2)
Waist circumference (cm), mean (SD)	106.8 (16.4)
Toxic habits	
Tobacco use, n (%)	
Active smokers	301 (30.1)
Ex-smokers	421 (42.1)
Alcohol intake, n (%) [N = 995]	645 (64.8)
Total testosterone (nmol/L), mean (SD)	6.6 (2.2)
ED assessment	
ED,* N (%) [N = 996]	726 (72.9)
IIEF-5 questionnaire score,§ mean (SD) [N = 938]	11.6 (5.1)
ED categories according to IIEF5 scores, n (%) [N = 938]	
No ED	24 (2.6)
Mild ED	135 (14.4)
Mild to moderate ED	301 (32.1)
Moderate ED	275 (29.3)
Severe ED	203 (21.6)
Symptoms assessment	
Prevalence of global symptoms, N (%)	948 (94.8)
Total score, mean (SD)	43.1 (11.8)
Psychological domain score, mean (SD)	11.5 (4.4)
Somatovegetative domain score, mean (SD)	17.4 (4.9)
Sexual domain score, mean (SD)	14.3 (4.0)

Percentages are given with respect to the whole population (N = 999) unless otherwise indicated.
*Comorbidities and ED were self-reported or included in the clinical history; §N = 939
SD = standard deviation; BMI = body mass index; ED = erectile dysfunction; WC = waist circumference

moderate or severe ED (50.9%). Symptoms were present in 948 men (94.8%). AMS scale scores indicated the presence of moderate overall symptoms, moderate-to-severe psychological and somatovegetative symptoms, and severe sexual symptoms. The most frequently reported symptoms (prevalence >90%) were the three sexual symptoms: "Decrease in ability/frequency to perform sexually" (95.9%), "Decrease in number of morning erections" (96.4%), and "Decrease in sexual desire/libido" (94.2%), followed by "Physical exhaustion/lacking vitality" (92%) and "Decline in the feeling of general wellbeing" (90.2%) (Table 2).

Variables Showing Relationship with Presence/Severity of AMS

Men with moderate/severe symptoms were older than their counterparts who had no or mild symptoms and showed a significant higher prevalence of central obesity, TT <8 nmol/L and, especially, moderate or severe ED (Table 3).

MetS and Presence/Severity of AMS

Prevalence of MetS was significantly higher in men with moderate or severe symptoms vs. those with mild or no symptoms (75.3% vs. 57.9%, $P < 0.001$) (Table 3) and having moderate/severe symptoms increased more than twofold the likelihood of MetS (OR 2.520 [95% CI 1.703–2.978]). The same was observed in men with moderate or

Table 2 Prevalence of individual Ageing Male Symptoms (AMS) scale: Overall and in men with and without metabolic syndrome (MetS)

Items	Overall (n = 999) n (%)	No MetS (n = 304) n (%)	MetS (n = 695) n (%)	*P* value
Decline in feeling of general well-being*	904 (90.4)	270 (88.8)	633 (91.1)	0.264
Joint pain and muscular ache*	815 (81.5)	226 (74.3)	688 (84.6)	<0.001
Excessive sweating*	647 (64.7)	170 (55.9)	476 (68.5)	<0.001
Sleep problems*	860 (86.0)	263 (86.5)	596 (85.8)	0.751
Increased need for sleep, often tired*	861 (86.1)	251 (82.6)	610 (87.6)	0.028
Irritability†	825 (82.5)	239 (78.6)	585 (84.2)	0.034
Nervousness†	813 (81.3)	225 (74.0)	587 (84.5)	<0.001
Anxiety†	675 (67.5)	187 (61.5)	488 (70.0)	0.007
Physical exhaustion/lacking vitality*	922 (92.2)	267 (78.8)	654 (94.1)	0.001
Decreased muscle strength*	889 (88.9)	265 (87.2)	623 (89.7)	0.253
Depressive mood†	754 (75.4)	214 (70.4)	539 (77.6)	0.016
Feeling that you have passed your peak‡	809 (80.9)	227 (74.7)	581 (83.6)	0.001
Feeling burnt out, hit rock-bottom†	610 (61.0)	160 (52.6)	449 (64.7)	<0.001
Reduced beard growth‡	641 (64.1)	177 (58.2)	463 (66.7)	0.011
Less ability/frequency to perform sexually‡	959 (95.9)	285 (93.8)	673 (97.1)	0.024
Decrease in number of morning erections‡	964 (96.4)	288 (94.7)	675 (97.1)	0.063
Decreased sexual desire/libido‡	942 (94.2)	282 (92.8)	659 (94.8)	0.201

AMS domains are indicated as follows: *somatovegetative symptoms; †psychological symptoms; ‡sexual symptoms

Table 3 Differences according to severity of symptoms with respect to a) variables potentially related to metabolic syndrome (MetS), and b) prevalence of MetS, MetS components, and the number of components

	No or mild symptoms (N = 337)	Moderate or severe symptoms (N = 662)	*P* value
a)			
Age, years, mean (SD)	59.8 (8.2)	61.8 (8.1)	<0.001
Central obesity	97 (28.8)	256 (36.7)	0.002
Alcohol intake*	207 (61.6)	438 (66.5)	0.121
TT <8 nmol/L	248 (73.6)	552 (83.4)	<0.001
Moderate or severe ED	90 (28.4)	389 (62.5)	<0.001
Peripheral vascular disease	17 (5.1)	53 (8.1)	0.086
b)			
MetS prevalence	195 (57.9)	500 (75.5)	<0.001
MetS components†			
Abdominal obesity	253 (75.1)	566 (85.3)	<0.001
Abnormal fasting glucose	165 (49.1)	419 (63.3)	<0.001
Elevated triglycerides	159 (47.2)	389 (58.8)	<0.001
Hypertension	265 (78.6)	586 (88.5)	<0.001
Low HDL-cholesterol	63 (18.3)	140 (21.1)	0.360
Number of components, mean (SD)	2.7 (1.2)	3.2 (1.1)	<0.001
1	52 (15.4)	33 (5.0)	0.128
2	82 (24.3)	118 (17.8)	0.925
3	112 (33.2)	226 (34.1)	0.415
4	62 (18.4)	218 (32.9)	0.046
5	21 (6.2)	56 (8.5)	0.207

Data are expressed as N (%) unless indicated. Percentages are based on valid values (see Table 1)
*Moderate or excessive
†Abnormal values or taking medication
ED = erectile dysfunction; SD = standard deviation; TT = total testosterone

severe somatovegetative or psychological symptoms (OR for MetS 2.070 [95% CI 1.488–2.872] and 1.683 [95% CI 1.262–2.245], respectively) but not with moderate or severe sexual symptoms (OR for MetS 1.436 [95% CI 0.709–2.907]) with respect to those with no or mild symptoms.

The number of MetS components increased in line with the severity of overall symptoms ($P < 0.001$) (Figure 1). Prevalence of individual components was significantly higher in men with moderate or severe symptoms vs. those with mild or no symptoms, except for low HDL-cholesterol (Table 3). Only men with moderate or severe symptoms presented four MetS components on a more frequent basis.

Effect of Symptoms on MetS

Multivariate analysis including known determinants for MetS in this population (central obesity and moderate or severe ED) [20] and variables showing relationship with the presence/severity of symptoms (see above) showed that having moderate/severe symptoms increased the likelihood of MetS independently of central obesity and moderate or severe ED (Table 4a). When the population was subdivided into two groups according to the severity of ED, the effect of symptoms remained present only in men with no ED or mild

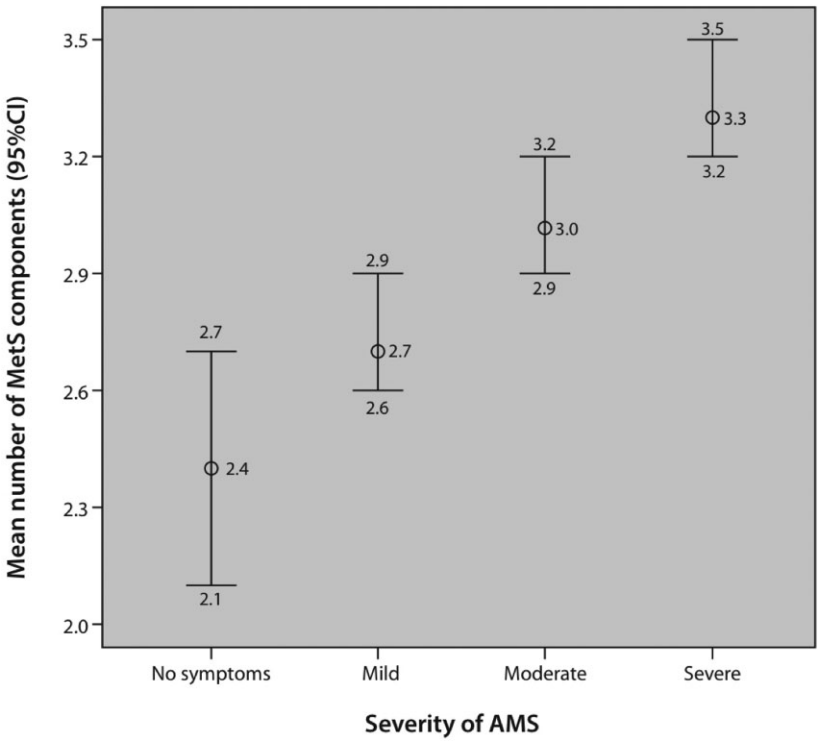

Figure 1 Number of metabolic syndrome (MetS) components according to the severity of overall symptoms (N = 999). AMS = Ageing Male Symptoms. P < 0.001 for lineal trend (ANOVA weighted linear trend index).

Table 4 Multivariate analysis: Odds ratios [95%CI] for metabolic syndrome (MetS). Confounding factors included in the analysis were those known to be associated with the presence of MetS in this population (central obesity and moderate or severe ED) [20] and those identified in this study to be associated with severity of symptoms (age, TT <8 nmol/L, moderate or severe ED, and central obesity)

a) Effect of moderate/severe overall symptoms in: the overall population and according to the presence/absence of moderate or severe ED or obesity

	Overall population (N = 999)	No ED + mild and mild-to-moderate ED (N = 460)	Moderate or severe ED (N = 478)	Non obese (N = 646)	Obese (N = 351)
Age	1.008 [0.990–1.027]	1.011 [0.986–1.036]	1.006 [0.979–1.033]	1.015 [0.995–1.037]	0.986 [0.949–1.025]
TT <8 nmol/L*	1.042 [0.723–1.501]	1.092 [0.690–1.729]	0.943 [0.513–1.732]	1.041 [0.683–1.585]	1.018 [0.487–2.127]
Central obesity†	**2.500** [1.794–3.482]	**1.958** [1.278–2.999]	**3.672** [2.116–6.374]	—	—
Moderate/severe ED‡	**1.947** [1.429–2.651]	—	—	**1.689** [1.187–2.403]	**3.004** [1.547–5.833]
Moderate/severe symptoms§	**1.579** [1.156–2.156]	**1.662** [1.130–2.446]	1.356 [0.794–2.317]	1.421¶ [0.995–2.030]	**2.029** [1.071–3.845]

¶$P = 0.053$

b) Effect of moderate/severe somatovegetative, psychological and sexual symptoms in the overall population, men with no or mild forms of ED, and obese men

	Overall population			Men with no or mild forms of ED			Obese men		
Age	1.008 [0.990–1.027]	1.011 [0.992–1.029]	1.010 [0.992–1.028]	1.011 [0.986–1.037]	1.014 [0.989–1.039]	1.013 [0.988–1.039]	0.982 [0.945–1.022]	0.986 [0.948–1.025]	0.985 [0.947–1.024]
TT <8 nmol/L*	1.060 [0.736–1.526]	1.094 [0.762–1.571]	1.101 [0.766–1.583]	1.135 [0.718–1.894]	1.166 [0.740–1.837]	1.173 [0.743–1.851]	1.092 [0.945–1.022]	1.145 [0.557–2.353]	1.218 [0.589–2.517]
Central obesity†	**2.501** [1.797–3.482]	**2.525** [1.815–3.514]	**2.547** [1.831–3.543]	**1.935** [1.266–2.957]	**1.928** [1.261–2.947]	**1.955** [1.280–2.987]	—	—	—
Moderate or severe ED‡	**2.111** [1.563–2.852]	**2.106** [1.557–2.848]	**2.212** [1.640–2.984]	—	—	—	**3.621** [1.925–6.810]	**3.742** [2.000–7.002]	**4.064** [2.174–7.596]
Moderate/severe symptoms§									
Somatovegetative	1.368 [0.953–1.964]	—	—	1.236 [0.803–1.904]	—	—	1.553 [0.713–3.382]	—	—
Psychological	—	1.279 [0.935–1.751]	—	—	1.347 [0.914–1.986]	—	—	1.211 [0.645–2.275]	—
Sexual	—	—	0.939 [0.429–2.058]	—	—	0.988 [0.473–1.851]	—	—	0.432 [0.090–2.070]

c) Effect of specific symptoms in the overall population

Age	1.005 [0.986–1.024]
TT <8 nmol/*	1.094 [0.761–1.028]
Central obesity†	**2.504** [1.783–3.517]
Moderate/severe ED‡	**2.001** [1.474–2.716]
Moderate/severe manifestations of:	
"Joint pain and muscular ache"§	1.339 [0.057–2.047]
"Sleep problems"§	**1.500** [1.311–1.804]
"Nervousness"§	**1.533** [1.044–2.253]
"Physical exhaustion/lacking vitality"§	**1.490** [1.032–2.008]

Data are expressed as odds ratio [95% CI]. Statistically significant values ($P < 0.05$) are shown in bold
*vs. total testosterone (TT) ≥8 nmol/L
†vs. no obesity
‡vs. no erectile dysfunction (ED)
§vs. no or mild symptoms

forms of ED (mild or mild-to-moderate ED), whereas the effect of central obesity was greater in men with moderate or severe ED. When the population was subdivided into nonobese and obese, the effect of moderate or severe symptoms was only evident in the latter group, where the effect of ED was also greater (Table 4a).

The effect of symptoms was further analyzed by domains in the groups where an effect of overall symptoms was observed: overall population, men with no or mild forms of ED, and obese men (Table 4b). Having moderate/severe somatovegetative, psychological, or sexual symptoms did not increase the likelihood of MetS in any of these groups.

Individual AMS Related to MetS

Men with MetS showed a significantly higher prevalence of 12 of the 17 AMS (Table 2). Among those with the highest prevalence (>90%), only the symptoms "Less ability/frequency to perform sexually" and "Physical exhaustion/lacking vitality" were more frequent in men with MetS. Analysis of the relationship between MetS and individual AMS scale components by step-back logistic regression analyses showed that having moderate or severe "Joint pain and muscular ache," "Nervousness," and "Physical exhaustion/lacking vitality" increased the odds for MetS (OR 1.654 [95% CI 1.166–2.345], 1.831 [95% CI 1.280–2.617], and 1.892 [95% CI 1.165–3.072], respectively), whereas "Sleep problems" reduced it (OR 0.635 [95% CI 0.413–0.976]). Replication of the multivariate analysis introducing these individual symptoms showed that besides having moderate or severe ED or obesity, having moderate or severe "Nervousness," "Physical exhaustion/lacking vitality," and "Sleep problems" also increased, although mildly, the odds for MetS (Table 4c).

Discussion

Symptoms associated to low T are a fundamental part of TDS and are essential to diagnosis of this condition [1,2]. The results of our study go further to suggest that in men with low T severity of TDS-related symptoms, as assessed by the AMS scale, is associated to a greater likelihood of MetS. Therefore, besides their utility to raise the suspicion of TDS in healthy men, severity of TDS-related symptoms may be useful to suspect a higher CV and metabolic risk in men with low T, which reflect the overall poor health status of these men.

Recognition of TDS symptoms is difficult given their nonspecific nature and the fact that they can be affected by several factors, including age, TDS duration, and coexistence of comorbidities [7]. Moreover, they also show a nonlinear relationship with serum T levels [6,7] and a high variability among individuals [27]. Despite this, several studies have been successful in finding a correlation between symptoms and T levels, once the confounding effect of age had been eliminated, and even symptom-specific T thresholds [6,7,27–29]. In our series of men with low T, AMS were present in 97.4% of subjects, with three sexual symptoms—"Less ability/frequency to perform sexually," "Decrease in number of morning erections," and "Decreased sexual desire/libido"—being among the most frequent symptoms (>90.0%) and with a greater affection. This is not surprising as sexual dysfunctions are one of the most prominent symptoms of low T [1–4] and, in our case, the reason to seek urological/andrological care. However, in the population-based European Ageing Male Study (EMAS), three sexual symptoms (decreased frequency of morning erection, decreased frequency of sexual thoughts, and ED), as assessed by the specific EMAS questionnaire, were also associated to lower T levels (TT <11 nmol/L and a cFT <220 pm/L) [7]. In contrast with this study, the majority of men in our series had ED, and this condition is not assessed in the AMS scale. In any case, these observations reinforce the importance of sexual symptoms when low T is suspected even in the general population. Furthermore, in a recent publication, the same study group has shown that both low T (TT <8 nmol/L), and the three sexual symptoms contribute independently to the higher risk of all-cause and CV mortality observed in men with TDS compared with eugonadal men [30].

Besides these, other symptoms reported to be more prevalent in men with low T such as fatigue ("Physical exhaustion/lacking vitality") [7,31] and "Decline in feeling of general well-being" were also among those with the highest prevalence. Among these, only the sexual symptom "Less ability/frequency to perform sexually" and specially the somatovegetative symptom "Physical exhaustion/lacking vitality" were significantly more prevalent in men with MetS. The higher prevalence of this sexual symptom is likely to be related to a higher severity of ED associated to the presence of MetS, as previously reported in this series [20].

Prevalence of MetS was 30% higher in men with moderate or severe AMS compared with those with no or mild symptoms. Only the severity of sexual symptoms did not increase the crude likelihood of MetS, probably due to their high prevalence and their severity in our series given the source of patients. The prevalence of each of the individual MetS components also increased in men with moderate or severe symptoms, except for low HDL-cholesterol, probably due to its lowest contribution to MetS in our setting [32].

As previously reported, prevalence of MetS in our series was related to increasing age and decreasing serum T levels, with moderate or severe ED, central obesity, alcohol intake, and peripheral vascular disease, being the risk factors associated to a higher likelihood of MetS after adjusting for confounding variables [20]. Of these, bivariate analysis showed that moderate ED and central obesity, together with age and T levels below 8 nmol/L, were confounding variables that increased the severity of AMS, indicating the close relationship between MetS and symptoms, probably due to its contribution to a poorer health and lower quality of life. Maybe because of this, the effect of moderate/severe symptoms was still evident after adjusting for all confounding variables for MetS, with central obesity, moderate or severe ED, and moderate/severe symptoms being the risk factors most strongly related to the likelihood of MetS. In contrast with our previous report [20], central obesity was the risk factor associated to a higher likelihood of MetS, rather than moderate or severe ED, when adjusting for severity of symptoms. The strong relationship existing among central obesity, MetS, and ED has been broadly described [33,34], and this effect might be explained by the strong relationship between ED and symptoms (especially sexual ones), which might bring down the contribution of ED alone. This relationship was evidenced in the nearly twofold prevalence of moderate/severe ED when moderate/severe symptoms were present. Likely due to the strength of this relationship, the effect of symptoms disappeared in men with moderate or severe ED, giving more prominence to the effect of central obesity. On the contrary, the effect of symptoms nearly disappeared in nonobese men, whereas the effect of symptoms and moderate or severe ED was enhanced in obese men. This finding is in contradiction with that reported in the Massachusetts Male Ageing Study (MMAS), where ED showed to be predictive of MetS only in nonobese men (defined as a BMI $<25\ kg/m^2$) [35]. Differences among the populations studied (ours with low T and very high prevalence of ED and obesity) and further adjustments for confounding variables may account for this difference. Interestingly, when analyzing on multivariate analysis, the contribution of severity of each of the AMS domains to the likelihood of MetS, any of them showed a significant effect. Maybe the lack of full independence of these domains may be the reason behind this finding [36]. On the contrary, when performing the same analysis with specific AMS that had been found to influence the likelihood of MetS, the severity of three symptoms—"Sleep problems," "Nervousness," and "Physical exhaustion/lacking vitality"—increased the likelihood of MetS after adjustment for all confounding factors and would therefore be the symptoms associated to a higher cardiovascular risk in our series of men with low T that would also have an impact on quality of life.

Besides the relevance of these findings, some limitations should be cited. To date, no recommendations on how to objectively evaluate TDS-related symptoms exist. Scientific societies involved in diagnosis, treatment, and management of TDS do not recommend the use of commonly used questionnaires such as the AMS scale or the Androgen Deficiency in Ageing Male [37] to diagnose TDS due to their low specificity [1,2]. However, these and other self-reported questionnaires such as the questionnaire used in the MMAS [38] and the New England Research Institute hypogonadism screener have demonstrated good sensitivity in cross-sectional surveys (although with variable specificity) and are useful in the collection of symptoms in the clinical practice [39]. Recently, Corona et al. [39] have recently reported the use of a 12-item structured interview (ANDROTEST), which allows the identification of severe hypogonadism with nearly 70% sensitivity and specificity. This research-administered instead of the self-reported approach may be translated into a better collection of symptoms in the clinical practice.

The high prevalence of ED may bias overall, and sexual scores of the AMS scale as these men are likely to score higher in questions addressing ability/frequency to perform sexually and the number of morning erections. However, symptoms found to be associated to MetS were not of a sexual nature, but rather psychological or somatovegetative. Specific symptoms associated to MetS are likely to vary among populations. As the AMS scale is a health-related quality of life ques-

tionnaire [36], prevalence and severity of symptoms are likely to be affected by chronic conditions commonly associated to low T that were not analyzed in our study (osteoporosis, frailty, cognitive impairment, depression, sleep apnea syndrome, mobility limitations, etc.) [4], some of which may also be related to MetS. Finally, as previously discussed [20], it should be noted that our results are based on a single T measurement when no measurements in the previous 2 months were available. Although these observations should be further confirmed with low T determined by repeated measurement, the approach presented herein is supported by the reliability of a single-point T measurement as an indicator of the annual mean T level reported by Vermeulen and Verdonck [40]. Treatment decisions should be also based on these premises. The high prevalence of ED may be a consequence of the patient selection process which, in any case, reflects the suspicion of low T in routine clinical practice.

Conclusion

The consistency of the results points to the severity of symptoms as an indicator of a higher cardiovascular risk and poorer quality of life in men with low T. Evaluation of symptoms in men with known low T is therefore highly advised.

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