Traditional signs and symptoms commonly attributed to hypogonadism do not correlate with testosterone levels: the Cooper Center Longitudinal Study Experience

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ABSTRACT

Evidence suggests that substantial testosterone therapy is occurring without checking levels of testosterone, presumably based on the presence of symptoms alone. We sought to explore the relationship between total testosterone level and non-specific symptoms, metabolic abnormalities, and sexual dysfunction associated with hypogonadism. This cross-sectional study included 2994 generally healthy men aged 50–79 years examined at a preventive medicine clinic in Dallas, TX from January 2012 to March 2016. Symptoms of hypogonadism were assessed. Screening morning total testosterone levels were measured and categorized into low (<250 ng/dL), low normal (250–399 ng/dL), and normal (≥400 ng/dL). Multiple logistic regression models were used to test the associations between total testosterone and signs and symptoms of hypogonadism. When considering symptoms and signs of hypogonadism, only decreased libido (OR 1.31, 95% CI 1.00 to 1.70), fasting glucose ≥100 mg/dL (OR 1.47, CI 1.15 to 1.88), and hemoglobin A1c over 6% (OR 1.47, 95% CI 1.06 to 2.03) were associated with increased odds of low testosterone after adjustment for age, body mass index, and cardiorespiratory fitness. Testosterone levels were not associated with fatigue, depression, or erectile dysfunction in our study (p>0.6). In this preventive medicine cohort, symptoms commonly attributed to testosterone deficiency were not associated with low total testosterone levels.

Summary

What is already known about this subject?

- Risks associated with testosterone therapy are not fully understood.
- Threefold increase in testosterone prescriptions over the past decade.
- 25%–40% of men who receive testosterone prescriptions do not have appropriate pre-treatment testosterone levels measured to confirm the diagnosis of symptomatic low testosterone.

What are the new findings?

- No significant association was found between low serum testosterone (<250 ng/dL) and symptoms frequently attributed to hypogonadism (non-specific symptoms of fatigue and depression, and the more specific sexual symptom of erectile dysfunction), after adjustment for age, body mass index, and fitness level.

How might it impact on clinical practice in the foreseeable future?

- Symptoms alone should not be used to initiate treatment with testosterone.

INTRODUCTION

Testosterone deficiency diagnosed by clinical symptoms alone instead of unequivocally low testosterone levels plus associated symptoms as recommended by recent guidelines[1] has driven an increase in the use of testosterone replacement therapy, with the number of prescriptions globally increasing 12-fold from 2000 to 2011.[2] Surprisingly, 25%–40% of men who receive testosterone prescriptions do not have appropriate pre-treatment testosterone levels measured to confirm the diagnosis of symptomatic low testosterone.[3 4] A recent study evaluating records of 11 million US men showed a threefold increase in testosterone prescriptions over the past decade,[3] despite the possibility that there may be risks associated with taking testosterone that have yet to be fully understood.[5–9] In 2018, Endocrine Society guidelines outlined that testosterone use should be limited to those men with hypogonadism manifested by consistent symptoms, signs, and unequivocally low morning serum testosterone levels.[1]

In this cross-sectional study, we evaluated a sample of generally healthy men aged 50 years and older, who underwent a preventive health examination including an extensive medical questionnaire, a morning total testosterone measurement,

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and objective cardiorespiratory fitness (CRF) testing. A recent study from this population showed that testosterone level was inversely associated with body mass index (BMI) and directly associated with fitness.[10] The purpose of the current study was to evaluate the relationship between total morning testosterone levels and various parameters of sexual dysfunction, metabolic abnormalities, and other non-specific symptoms to test the hypothesis that the symptoms commonly attributed to hypogonadism are not routinely associated with low testosterone levels and that other etiologies for these symptoms should be considered.

MATERIALS AND METHODS

Data were collected from 3974 men who were self-referred or employer referred to the Cooper Clinic between January 2012 and March 2016 for a preventive medical examination. Participants were 50–79 years of age, generally healthy, primarily Caucasian, had higher educational levels, and had means for preventive healthcare. Men who were missing BMI or fitness (n=701) values, who were using any form of androgens, including testosterone, any form of estrogens, anti-estrogens, or 5-alpha reductase inhibitors (n=278), or who had testosterone >=3,000 were excluded, leaving a final sample of 2994 men. All participants provided written informed consent. The Cooper Institute institutional review board annually reviewed and approved the study protocol.

All patients completed a medical history and demographic questionnaire, a physical examination, blood chemistry tests following an overnight 12 hours fast and 24 hours of no exercise, anthropometric assessments, blood pressure measurements, and a maximal graded exercise test for assessment of CRF. A physician reviewed and confirmed the participant's responses to the standard medical history questions regarding sexual symptoms (decreased libido and erectile dysfunction), generalized symptoms (fatigue and depression), and the presence of self-reported diabetes. In addition, data on medication use for erectile dysfunction were available. For this analysis, erectile dysfunction was defined as self-report of erectile dysfunction and/or taking a prescription drug usually prescribed for this symptom such as Sildenafil.

Height and weight were measured using a standard physician's scale and stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured using the auscultatory technique with a standard sphygmomanometer. Hemoglobin A1c was measured directly using a high-performance liquid chromatography analyzer, the BioRad D-10 Hemoglobin Analyzer (BioRad Diagnostic Group, Benicia, CA, USA). The final grade and speed on a maximal modified-Balke treadmill test was used to estimate fitness in units of metabolic equivalent of tasks. A detailed description of the test has been published elsewhere.[11]

As part of their clinical assessment, a single morning total testosterone measurement, drawn between 07:00 and 09:00, was assayed within 2 hours. With serum separated at 2600 rpm for 10 min, total testosterone levels were analyzed on the Centaur Instrument (Seimen ADVIA Centaur CP, Tarrytown, NY, USA) or the Abbott Architect ci8200 (Abbott Park, IL, USA), using the standard chemiluminescence method. Standardized calibrators were utilized and instruments were calibrated as required in each manufacturer's package insert. Mean intra-assay coefficients of variation (CVs) were less than 10% and mean interassay CVs less than 10%. The Cooper Clinic laboratory participates in a standardized proficiency-testing programme to ensure accuracy. The reported reference ranges for the two machines were comparable on the low end of the range (Centaur, 241–827; Abbott, 240–1035). Testosterone levels were categorized into low (<250 ng/dL), low normal (250–399 ng/dL), and normal (≥400 ng/dL). Serum hormone binding globulin (SHBG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were not routinely obtained.

Statistical analysis

Participants were classified by age group (50–59, 60– 69, and 70–79 years) or by measured testosterone (low, low normal, and normal) level, and characteristics including symptoms and clinical findings were summarized. Trends were tested using the Jonckeere-Terpstra non-parametric method. Multiple logistic regression models were constructed to predict testosterone <250 ng/dL and test its association with signs and symptoms of hypogonadism, unadjusted and adjusted sequentially for age, BMI and fitness. SAS/STAT software, V.9.4, was used for all analyses.

RESULTS

Table 1 shows the baseline characteristics of the study population by age group. The average age was approximately 58 years. Older men were more likely to report symptoms and signs attributed to hypogonadism. The overall prevalence of self-reported decreased libido was 23.1%, erectile dysfunction 23.7%, fatigue 9.6%, and depression 7.4% in this cohort. Yet, 48.6% of men had none of these four symptoms commonly associated with hypogonadism.

Table 2 presents the sample characteristics by total testosterone level. Higher testosterone levels were inversely associated with prevalent decreased libido ($p<0.001$), erectile dysfunction ($p<0.001$), and unexplained fatigue ($p=0.005$), but not depression ($p=0.25$). Finally, an inverse relationship was noted between testosterone level and both fasting glucose and hemoglobin A1c levels. Mean BMI for all testosterone groups was either in the overweight or obese category. The mean BMI for those with low testosterone was 30.3 kg/m^2 compared with the mean BMI in those with normal testosterone of 26.8 kg/m^2 (p for trend<0.001). A positive association between fitness and testosterone level was observed. The prevalence of low total testosterone level versus the number of self-reported symptoms and signs is presented in figure 1. Men with three or more symptoms and signs attributed to hypogonadism were more likely to have a low total testosterone level than those with no symptoms or signs (p for trend<0.001).

Table 3 shows the OR of having a low testosterone level based on the presence of self-reported symptoms and signs attributed to hypogonadism. In the unadjusted models, all of the symptoms and signs evaluated in this study, except depression, were associated with low testosterone but, after adjustment for age, BMI, and fitness, this statistical significance generally disappeared. However, decreased libido ($p=0.049$), fasting glucose greater than 100 mg/dL ($p=0.002$) and hemoglobin A1c greater than 6% ($p=0.02$) remained significantly associated with low testosterone even after adjustment.

Table 1 Prevalence of symptoms and clinical findings by age groups, Cooper Center Longitudinal Study

	50–59 years	60–69 years	70–79 years	P value
N	1906	868	220	
Age, years, mean (SD)	54.1 (2.8)	63.6 (2.8)	73.5 (2.8)	
Decreased libido, %	19.2	29.0	34.5	<0.001
Erectile dysfunction*, %	18.3	31.0	41.8	<0.001
Unexplained fatigue, %	9.0	10.1	12.7	0.100
Depression, %	7.0	9.1	4.1	0.521
History of diabetes, %	2.1	3.8	3.2	0.015
Fasting blood glucose, mg/dL, mean (SD)	99.2 (14.8)	101.4 (16.0)	101.8 (19.5)	<0.001
Hemoglobin A_1c, %, mean (SD)	5.5 (0.5)	5.6 (0.5)	5.7 (0.6)	<0.001
Body mass index, kg/m^2, mean (SD)	28.0 (4.0)	28.0 (3.9)	26.7 (3.5)	0.017
Cardiorespiratory fitness, METs, mean (SD)	11.3 (2.1)	10.1 (2.0)	9.3 (2.1)	<0.001

SI conversion factors: to convert glucose to mmol/L, multiply values by 0.0555.
*Erectile dysfunction is defined by self-report and/or use of prescription medications used to treat this condition.
METs, metabolic equivalents.

DISCUSSION

In this sample of generally healthy men with screening morning testosterone levels, low serum testosterone (<250 ng/dL) was not associated with symptoms frequently attributed to hypogonadism (non-specific symptoms of fatigue and depression, and more specific sexual symptom of erectile dysfunction), after adjustment for age, BMI, and fitness level. Only decreased libido, fasting glucose greater than 100 mg/dL, and hemoglobin A1c greater than 6% were associated with increased odds of having low testosterone in this population. These results confirm the importance of treating with testosterone only after making a firm diagnosis of hypogonadism based on measurements of testosterone as well as the presence of supporting clinical symptoms and signs.

Previous studies have shown an association between symptoms suggestive of hypogonadism and low testosterone levels. For example, in a population of 434 men from an outpatient androgen clinic, investigators found increasing symptoms with decreasing testosterone levels, though there was no clear cut-point in testosterone level below which symptoms were likely to occur.[12] However, the symptoms occurred in three separate clusters at progressively lower testosterone levels. Non-specific symptoms, such as fatigue and depression, occurred at higher total testosterone levels than metabolic signs, such as elevated glucose, and these, in turn, were present at higher levels than sexual symptoms such as erectile dysfunction. In a study by Wu and associates with 3369 men between the age of 40 and 79 years who were randomly selected from eight European centers, symptoms suggestive of hypogonadism were only correlated with low testosterone if the testosterone level was below 11 nmol/L (317 ng/dL) and there were at least three sexual symptoms present.[13]

With respect to clinical signs, other investigators have shown a relationship between impaired fasting glucose, diabetes, and low testosterone. In one study of 355 men with type II diabetes, 17% were found to have total testosterone levels below 230 ng/dL (8 nmol/L) and symptoms of hypogonadism.[14] The Multi-Ethnic Study of Atherosclerosis showed this relationship between impaired fasting glucose, diabetes, and low testosterone which did not differ across ethnic groups.[15] Our finding of an association between fasting glucose, hemoglobin A1c, and low testosterone is therefore not surprising. Our data do not show a similar association between low testosterone and history of diabetes; perhaps this lack of association could be explained by the low prevalence of personal history of diabetes.

On the other hand, Emmelot-Vonk and colleagues administered the Androgen Deficiency in Ageing Males and the

Table 2 Prevalence of symptoms and clinical findings by total testosterone levels, Cooper Center Longitudinal Study

	<250 ng/dL	250 to <400 ng/dL	≥400 ng/dL	P value
N	326	994	1674	
Age, years, mean (SD)	57.7 (6.6)	58.2 (6.4)	58.5 (6.8)	0.106
Decreased libido, %	31.0	24.7	20.7	<0.001
Erectile dysfunction*, %	28.2	26.0	21.4	<0.001
Unexplained fatigue, %	13.2	10.5	8.4	0.005
Depression, %	8.0	8.0	6.9	0.247
History of diabetes, %	4.9	3.4	1.8	<0.001
Fasting blood glucose, mg/dL, mean (SD)	105.8 (23.8)	101.5 (15.5)	98.0 (13.0)	<0.001
Hemoglobin A_1c, %, mean (SD)	5.7 (0.8)	5.6 (0.6)	5.5 (0.5)	<0.001
Body mass index, kg/m^2, mean (SD)	30.3 (4.9)	28.9 (3.9)	26.8 (3.4)	<0.001
Cardiorespiratory fitness, METs, mean (SD)	9.7 (2.0)	10.4 (2.0)	11.3 (2.2)	<0.001

SI conversion factors: to convert testosterone to nmol/L, multiply values by 0.0347.
*Erectile dysfunction is defined by self-report and/or use of prescription medications used to treat this condition.
METs = metabolic equivalents.

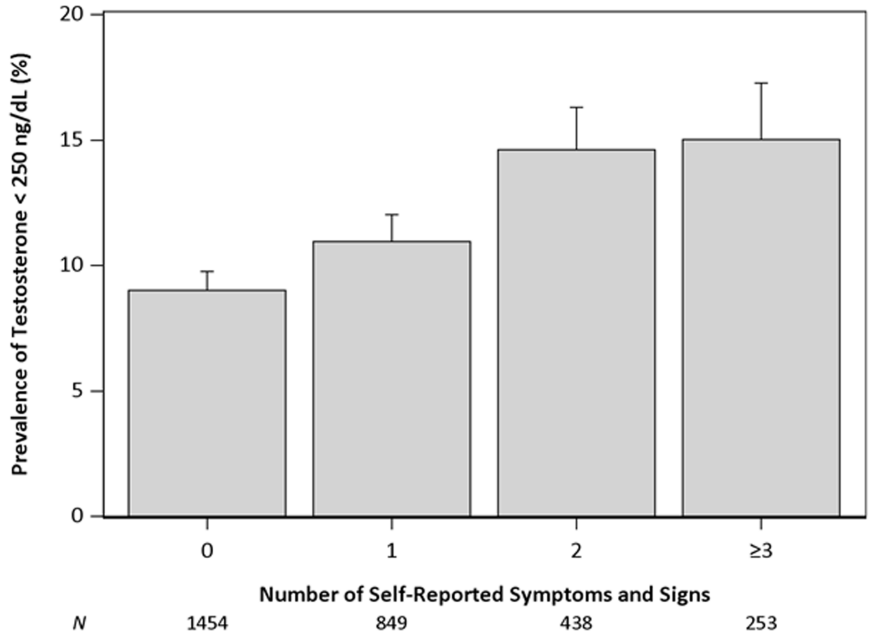

Figure 1 Prevalence of total testosterone<250 ng/dL versus number of self-reported symptoms and signs attributed to hypogonadism.

Ageing Males Symptoms screening questionnaires to 587 randomly selected men aged 60–80 years.[16] These brief questionnaires ask about typical symptoms attributed to androgen deficiency such as decrease in morning erections, decreased libido, and depressed mood. The questionnaire results were correlated with measured morning total testosterone levels yielding no significant association between total testosterone concentration and the scores on the two questionnaires. In other words, the presence of symptoms suggestive of low testosterone was an unreliable guide to the actual testosterone level. Finally, Araujo and colleagues carried out the Boston Area Community Health study, which looked at 1475 multi-ethnic men. In this study, 47.6% of the men with testosterone levels <300 ng/dL did not have any symptoms suggestive of hypogonadism.[17] There was no significant difference in the prevalence of symptoms based on race or ethnicity. Thus, it seems clear that symptoms of fatigue, depression, and sexual dysfunction are by no means tightly correlated with testosterone levels.

Overall, studies such as the current one support the need for screening or diagnostic testosterone level assessment before confirming a diagnosis of hypogonadism and initiating treatment with testosterone therapy. The results of our study demonstrate that using symptoms attributed to low testosterone levels as a surrogate for measured testosterone levels in making a diagnosis of hypogonadism is simply unreliable. This is not unexpected given that these symptoms may result from a number of other conditions. For example, erectile dysfunction may be due to vascular disease. In the study noted above, Wu and colleagues observed that the prevalence of even the most specific sexual symptoms of androgen deficiency was relatively high among men with

Table 3 ORs of having a low screening total testosterone level (<250 ng/dL), based on the presence of common self-reported symptoms and signs attributed to hypogonadism

	Unadjusted models OR (95% CI)	Age-adjusted models* OR (95% CI)	Age-adjusted and BMI-adjusted models† OR (95% CI)	Fully adjusted models‡ OR (95% CI)
Self-reported symptoms				
Decreased libido	1.57 (1.22 to 2.02)	1.65 (1.27 to 2.12)	1.45 (1.11 to 1.88)	1.31 (1.00 to 1.70)
Erectile dysfunction	1.31 (1.01 to 1.68)	1.39 (1.06 to 1.80)	1.18 (0.90 to 1.55)	1.07 (0.81 to 1.41)
Fatigue	1.50 (1.05 to 2.10)	1.52 (1.06 to 2.12)	1.27 (0.88 to 1.80)	1.05 (0.72 to 1.50)
Depression	1.10 (0.70 to 1.65)	1.10 (0.71 to 1.66)	1.06 (0.67 to 1.61)	0.93 (0.59 to 1.42)
Signs				
Glucose>100 versus<100 mg/dL	1.90 (1.51 to 2.40)	1.94 (1.54 to 2.46)	1.57 (1.23 to 2.00)	1.47 (1.15 to 1.88)
Self-reported diabetes	2.10 (1.16 to 3.59)	2.18 (1.20 to 3.72)	1.64 (0.89 to 2.87)	1.29 (0.69 to 2.28)
Hemoglobin A1c>6% versus<6%	2.18 (1.61 to 2.93)	2.34 (1.72 to 3.17)	1.70 (1.22 to 2.33)	1.47 (1.06 to 2.03)

*Multivariate model with age per year.
†Multivariate model with age per year and BMI per kg/m^2.
‡Multivariate model with age per year, BMI per kg/m^2, cardiorespiratory fitness per metabolic equivalent.
BMI, body mass index.

unequivocally normal testosterone levels.[13] Additionally, many of these symptoms are more likely to develop with increasing age unrelated to testosterone level. However, there was an association between low testosterone and laboratory markers of dysglycemia. This supports the American Diabetes Association recommendation that men with diabetes undergo testosterone screening.[18] Regardless of the number of symptoms and signs, low testosterone should be one of many considerations when work-up for fatigue, erectile dysfunction, or depression is initiated. Thus, the significant overlap of the symptoms common in hypogonadism with multiple other conditions and with the usual sequelae of ageing makes the task of using symptoms to diagnose hypogonadism challenging.

An important strength of our study is the large sample size with a wide breath of clinical data. The homogeneity of the sample (primarily Caucasian, highly educated, and with access to preventive healthcare) decreases the likelihood of unmeasured socioeconomic and comorbid confounders affecting the outcome. While our sample lacks racial/ethnic diversity, prior work has shown testosterone is not associated with race and ethnicity.[17] Another important strength relates to the careful review of symptoms for each participant by their physician, although specific androgen screening questionnaires were not used. Furthermore, a conservative cut-point for low total testosterone was chosen given the various ranges appearing in the literature (230–350 ng/dL)[13 14 17] and fell in the recommended range of the utilized assay. At this cut-point, symptomatic hypogonadism would be more likely to manifest. Limitations should similarly be acknowledged. An individual morning serum testosterone level was used in this analysis as only a single level was obtained as part of this clinical exam. Additionally, SHBG, LH, and FSH were not part of the routine clinical exam. Furthermore, some symptoms commonly attributed to low testosterone, such as frequency of morning erections, were not evaluated. It is also important to note that this is a preventive medicine population that does not undergo a validated history tool for the evaluation of hypogonadism such as the Psychosexual Daily Questionnaire[19] or other similar questionnaires. Importantly, this is a cross-sectional study; longitudinal changes in symptoms or testosterone levels could not be assessed.

In summary, it is clear that symptoms alone should not be used to initiate treatment with testosterone. Future research seems warranted to continue efforts to identify the most reliable signs and symptoms to accurately diagnose hypogonadism so that measurements of testosterone are made in those most likely to have hypogonadism. In addition, continued study of whether total testosterone, bioavailable testosterone, and estradiol levels are most reliable in making a diagnosis of hypogonadism is worthwhile. The optimal combination of symptomatology and reliable testosterone levels in making this currently common diagnosis is elusive. Finally, additional research is needed to better understand the physiological associations of glucose and diabetes with testosterone levels.

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