ORIGINAL RESEARCH—ENDOCRINOLOGY

Are We Testing Appropriately for Low Testosterone?: Characterization of Tested Men and Compliance with Current Guidelines

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DOI: 10.1111/jsm.12730

ABSTRACT

Introduction. Direct-to-consumer ads for testosterone replacement therapies have significantly increased over the past several years. Subsequently, testing for low serum testosterone has correspondingly increased.
Aims. We sought to determine the testing behaviors of practitioners as well as the characteristics of men who are undergoing testing for low testosterone.
Methods. Men aged 18–85 years were queried from the institutional electronic data warehouse from 2009 to 2012. Men were considered "tested" if their serum total testosterone level had been measured for any purpose. Tested men (TM) were compared with those not tested (NT).
Main Outcome Measures. The frequency and timing of testing for low testosterone as well as patient demographics and clinical characteristics were compared between TM and NT using multivariable logistic regression models.
Results. Of the 321,674 total men, 10,133 (3.2%) underwent testing with a serum total testosterone (mean age of 55.2 ± 14.1 years). The frequency of testing increased from 2.5% to 3.6% during the study period ($P < 0.001$). Multivariable analysis demonstrated that TM were significantly ($P < 0.001$) more likely to be Caucasian and have increased body mass index. In addition, TM were significantly more likely to have comorbid conditions including decreased libido (adjusted odds ratio [aOR] 10.0, 95% confidence interval [CI] 8.5, 11.7), infertility (aOR 4.8, 95% CI 3.6, 6.6), erectile dysfunction (aOR 3.6, 95% CI 3.4, 3.8), osteoporosis (aOR 3.3, 95% CI 2.8, 3.8), depression (aOR 1.7, 95% CI 1.6, 1.8), prostate cancer (aOR 1.7, 95% CI 1.5, 1.8), hypertension (aOR 1.3. 95% CI 1.2, 1.4), chronic obstructive pulmonary disease (aOR 1.2, 95% CI 1.0, 1.4), and benign prostatic hyperplasia (aOR 1.2, 95% CI 1.1, 1.2). Among TM, only 889 (9%) men underwent testing between 7 AM and 12 PM.
Conclusions. The rate of testosterone testing is increasing with most testing practices directed toward a subset of men with comorbidities that are associated with hypogonadism. Compliance of physicians obtaining early morning serum testosterone levels is low. Further education of practitioners is required to appropriately test patients for hypogonadism. **Malik RD, Lapin B, Wang CE, Lakeman JC, and Helfand BT. Are we testing appropriately for low testosterone?: Characterization of tested men and compliance with current guidelines. J Sex Med 2015;12:66–75.**

Key Words. Hypogonadism; Low Testosterone; Serum Total Testosterone Testing; Diurnal Variation

Source of funding: Philanthropic support from the Division of Urology and the John and Carol Walter Center for Urological Health, NorthShore University Health System.

Introduction

Testosterone deficiency (TD) in adult males is characterized by a constellation of symptoms including sexual dysfunction, fatigue, mood disturbances, decline in bone mineral density, and change in body composition, with increased adipose tissue and decreased muscle mass, anemia, impaired cognition, and decline in feeling of general well-being [1–4]. Because of the influence on the endocrine and nervous system function, it is not surprising that TD has been linked to a number of comorbidities including obesity, type 2 diabetes, hypertension, osteoporosis, cardiovascular disease, metabolic syndrome, frailty, and Alzheimer's disease [1,5–17]. Prospective studies have shown a bidirectional association of low testosterone with type 2 diabetes and metabolic syndrome as well as evidence that the presence of baseline low testosterone may predict the occurrence of hyperlipidemia and hypertension [17]. While the pathophysiologic mechanism for these correlations is complex and includes multiple components, obesity-induced estrogens are postulated to contribute to low levels of testosterone by negative feedback inhibition at the pituitary level of the hypothalamic–pituitary–gonadal axis [16].

TD can be denoted as hypogonadism, or the presence of signs and symptoms of TD with the presence of a low serum testosterone level. Without symptoms, TD is a biochemical deficiency in serum testosterone levels. In the United States, it has been approximated that there are 2.4 million 40–69-year-old men with hypogonadism, as defined by the presence of both signs/symptoms and specific biochemical parameters (total testosterone < 200 ng/dL or total testosterone 200–400 ng/dL + free testosterone < 8.91 ng/dL), with a prevalence estimated between 6 and 12% [18]. The prevalence of biochemical TD, or serum total testosterone < 300 ng/dL, is estimated to be 38.7% [19]. In a recent study by Wu et al., evaluating approximately 3,400 random European men, the prevalence of biochemical hypogonadism alone (total testosterone < 11 nmol/L) was 17% and with the addition of symptomatic criteria that dropped to 2.1%, which increased to 5.1% for those aged 70–79 years old [20].

It is well known that levels of circulating testosterone decline with age in most men, with the prevalence of biochemical hypogonadism increasing significantly over 80 years old to rates as high as 49–50% [19,21]. The natural decline in circulating testosterone in aging men is compounded by the high incidence of obesity, diabetes, and other comorbidities, which further lowers serum levels of testosterone. Conversely, men above the age of 40 who self-report good or excellent health have been shown to display no decrease in serum testosterone levels [22].

Expert guidelines recommend the use of an early morning serum total testosterone for testing men with hypogonadal symptoms (e.g., decreased energy, decreased libido, change in hair patterns, etc). The Endocrine Society recommends a repeat early morning serum total testosterone in all patients and treatment in patients who have a serum level lower than the lower limit of normal established by the reference laboratory used by the physician [4]. Other societies indicate levels of testosterone lower than 200–230 ng/dL as an indicator for testosterone replacement therapy (TRT). If the serum total testosterone level is between 230 and 350 ng/dL, it has been suggested to repeat the measurement of total testosterone with sex hormone-binding globulin to calculate free testosterone or measure the free or bioavailable testosterone particularly in obese men [17]. Levels of free testosterone < 225 pmol/L are then considered in the hypogonadal range [23]. In addition to TRT, counseling for weight loss and lifestyle modifications, such as smoking cessation has been recommended.

While serum total testosterone testing is recommended, the results have been shown to be variable depending on the assay used and patient parameters. Serum total testosterone can be measured using immunoassay or mass spectrometry methods. Rapid automated immunoassay instruments are commonly used based on the principal of competitive binding to testosterone in the serum. While they are technically simple, rapid, and relatively inexpensive, they use proprietary reagents and reference ranges that are provided by the manufacturer with questionable accuracy and specificity, particularly in patients with low serum testosterone levels [24]. Mass spectrometry methods, considered the gold standard, isolate steroid hormones and detect them using chromatographic separation followed by detection by assessment of mass-to-charge ratio. These methods are highly specific and accurate, and with advancements allowing the use of liquid chromatography and tandem mass spectrometry, the sensitivity and specificity have been increased further [25]. However, individual mass spectrometry assays are developed using different procedures, instrumentation, reagents, and calibrators, result-