Should Family Physicians Screen for Testosterone Deficiency in Men?

Yes: Screening for Testosterone Deficiency Is Worthwhile for Most Older Men

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This is one in a series of pro/con editorials discussing controversial issues in family medicine.

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Normal physiologic functioning of the testes is mandatory for virilization, male reproduction, and maintenance of lean muscle and bone mass. Testosterone deficiency is caused by inadequate production of serum testosterone and typically results in decreased libido, erectile dysfunction, decreased stamina, depressed mood, and decreased muscle and bone mass. In primary hypogonadism, impaired testosterone production at the level of the testes impedes spermatogenesis, with concomitant elevation of serum gonadotropin levels. Secondary hypogonadism results from disruption of the hypothalamic-pituitary-gonadal axis with low or normal serum gonadotropin levels. Suspicion of inadequate testosterone production in an aging man warrants a detailed investigation.

Prevalence estimates of testosterone deficiency in men vary widely across populations. The Boston Area Community Health (BACH) Survey, a population-based observational study of 1,475 black, Hispanic, and white men 30 to 79 years of age, found that 5.6% (95% confidence interval [CI], 3.6% to 8.6%) had symptomatic androgen deficiency, and the prevalence increased substantially with age.[1] The Hypogonadism in Males study evaluated 2,162 men in primary care outpatient practices and found that 38.7% of men 45 years and older had hypogonadism.[2] These men were more likely to have impaired sexual function, exhaustion, and low levels of general well-being than their eugonadal counterparts. Each year, up to 14 million men older than 45 years are at risk of symptomatic testosterone deficiency, based on serum total testosterone levels of 300 ng per dL (10.4 nmol per L) or less.[2] Despite these statistics, analysis of the data from the BACH Survey found that only 12.2% of symptomatic men with hypogonadism were being treated with testosterone replacement therapy, which highlights missed opportunities to test men who might benefit from treatment.[3]

Clinical practice guidelines from the Endocrine Society recommend that a diagnosis of androgen deficiency should be made in men with unequivocally low serum testosterone levels (300 ng per dL or less) who have persistent major symptoms.[4] The guidelines recommend against screening for androgen deficiency in the general population, although this recommendation is based on low-quality evidence. Nonetheless, substantial evidence supports screening men for testosterone deficiency.

A growing body of evidence shows a relationship between low serum testosterone levels and the development of chronic disease. A population-based cohort trial of men 20 to 79 years of age determined that low serum testosterone levels are associated with increased mortality (hazard ratio [HR] = 2.32; 95% CI, 1.38 to 3.89) and can predict risk of death from cardiovascular disease (HR = 2.56; 95% CI, 1.15 to 6.52) and cancer (HR = 3.46; 95% CI, 1.68 to 6.68), but not from respiratory diseases.[5] A study of 3,156 multiethnic men 45 to 84 years of age yielded evidence that the incidences of glucose intolerance and diabetes mellitus were inversely correlated with serum total testosterone levels.[6] Data from several studies—including the Study of Health in Pomerania trial, a population-based prospective cohort of 1,004 men 20 to 79 years of age, and the Massachusetts Male Aging Study, a population-based prospective cohort of 1,709 men—have demonstrated a relationship between low serum testosterone levels and the risk of metabolic syndrome.[7,8] These relationships strengthen the argument for screening for testicular hypogonadism in men with risk factors for chronic disease.

Although screening targets asymptomatic men, testosterone deficiency is unique because symptoms are not always well defined. This warrants casting a wider net to identify a treatable condition. Symptoms such as depression, fatigue, and inability to perform vigorous activity are related to low testosterone levels, whereas there is an inverse relationship between the number of sexual symptoms and testosterone levels.[9] ▶

The Testosterone in Older Men trial, a double-blind, randomized controlled trial of 209 men (mean age = 74 years), assessed the effects of testosterone replacement therapy in men with low serum testosterone levels and limited mobility.[10] The primary outcome was the change from baseline in maximal muscle strength in the leg press; secondary outcomes included the chest press, 50-meter walking speed, and stair climbing. Significant improvements were noted in the leg press, chest press, and stair climbing in the treatment group compared with the placebo group. However, the study was discontinued early because of a high incidence of adverse cardiovascular effects in the treatment group (HR = 2.4, $P = .05$). Advanced age and a high prevalence of hypertension, diabetes, hyperlipidemia, obesity, and metabolic syndrome among the participants may have contributed to these findings.

A recent study that reported an association between testosterone therapy and adverse cardiovascular outcomes had serious methodologic flaws, such as the omission of 1,132 men from the statistical analysis.[11] Thus, this study does not provide reliable information about the role of testosterone therapy in men with cardiovascular artery disease. It is not clear whether late-onset hypogonadism is directly linked to the pathogenesis of cardiovascular disease, is a marker of preexisting cardiovascular disease, or is a concomitant manifestation of another underlying disease.[12,13]

The possibility that hypogonadism may be involved in the pathogenesis of cardiovascular disease suggests that testosterone replacement therapy would result in improved cardiovascular outcomes. Data from the past 20 years support a beneficial effect of testosterone replacement therapy on cardiovascular outcomes. One study showed that mortality was reduced by one-half in men with a serum testosterone level less than 300 ng per dL who received testosterone replacement therapy.[14] A similar reduction in mortality was noted in men with diabetes and a serum testosterone level less than 300 ng per dL.[15] Another study noted a reduction in carotid intimal media thickness in men with hypogonadism who received testosterone replacement therapy, as well as a positive correlation between carotid intimal media thickness and the magnitude of increase in serum testosterone levels.[16]

For now, a cautious approach is warranted in treating men at risk of cardiovascular disease. With the possible exception of these patients, testosterone replacement therapy remains a potentially beneficial option in improving health-related quality of life in men. It is evident that many men likely have untreated symptomatic testosterone deficiency. Screening for testosterone deficiency with symptom questionnaires, coupled with testing the morning serum total testosterone level, can engage men and lead to an accurate diagnosis.[17] As with any therapeutic intervention, physicians should discuss the benefits and potential risks of hormone replacement therapy, as well as ongoing management, with patients before initiating treatment.

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