Meeting the Challenges of Diagnosing and Managing Male Hypogonadism

Written by Lori Alexander

Male hypogonadism raises many questions about who should be treated and what the treatment should be. The Endocrine Society (TES) published updated guidelines on testosterone therapy for androgen deficiency syndromes in adult men in 2010 [Bhasin S et al. *JCEM* 2010]. However, the evidence base for treatment recommendations is weak, making the guidelines "a framework rather than a cookbook," according to Alvin Matsumoto, MD, Veterans Affairs Puget Sound Health Care System and University of Washington School of Medicine, Seattle, Washington, USA, one of the authors of the guidelines.

Among the most important questions that remain unanswered are:

- How is male hypogonadism defined?
- Which testosterone measurement (total, free, bioavailable) should be used for diagnosis?
- Under what conditions should testing be done?
- What is the risk-benefit ratio of testosterone therapy for older men?

Definition of Hypogonadism

Late-onset hypogonadism is distinct from hypogonadism in younger male individuals. For boys and young men, hypogonadism is clearly related to a definable pathological entity, such as testicular failure, often associated with a congenital abnormality, such as Klinefelter syndrome, or pituitary disease, such as a tumor or developmental defects. The diagnosis is based on the absence of secondary sex characteristics and the presence of gynecomastia and small testes.

For older men, TES guidelines recommend that a diagnosis of androgen deficiency be made "only in men with consistent symptoms and signs and unequivocally low serum testosterone levels." However, many symptoms and signs of hypogonadism symptoms are vague, and it is unclear whether symptoms are caused by a reduction in testosterone or are a result of the normal physiological process of aging.

Hypogonadism should not be attributed to age until other factors have been ruled out, said Frances Hayes, MD, Saint Vincent's University Hospital, Dublin, Ireland. She discussed a recent report from the European Male Aging Study, in which nine symptoms were confirmed to be related to the total or free testosterone level (Table 1) [Wu FCW et al. *N Engl J Med* 2010]. The investigators found that a diagnosis of hypogonadism required at least three sexual symptoms in combination with a low testosterone level. Among physical symptoms, limited physical vigor was significantly associated with a low total testosterone level, and psychological symptoms had little or no association with testosterone level.

Table 1. Symptoms Related to Testosterone Levels in the European Male Aging Study.*

Type of Symptom	
Sexual	• Decreased frequency of morning erection • Decreased frequency of sexual thoughts • Erectile dysfunction
Physical	Inability to: • Engage in vigorous activity • Walk more than 1 km • Bend, kneel, or stoop
Psychological	• Loss of energy • Sadness • Fatigue

*Wu FCW et al. *N Engl J Med* 2010.

Measurement of Testosterone Levels

In general, high-throughput commercial "platform" testosterone assays lack accuracy, specificity, sensitivity, and precision, especially at low testosterone levels. TES guidelines recommend that the initial diagnostic test be performed in a reliable reference laboratory. Dr. Hayes noted that a diagnosis of hypogonadism should be confirmed by repeating the measurement of total testosterone, because studies have shown transient decreases in the testosterone level among healthy young men, particularly in the afternoon, and have also shown that a repeat test is normal in about one-third of older men.

A free or bioavailable testosterone level measurement is recommended for men who have a total testosterone level that is near the lower limit of the normal range. Dr. Hayes suggested the calculated free testosterone as the best testing method, because it more accurately reflects the level of bioactive testosterone than the measurement of only total serum testosterone. Calculators can be found online (such as at www.issam.ch/freetesto.htm).

Conditions for Testosterone Testing

The testosterone level fluctuates throughout the day, with peak serum concentrations in the morning. Thus, the initial testosterone level should be measured in the morning. In addition, Dr. Hayes recommended measuring testosterone in the fasting state. Because acute stress affects hormone levels, testosterone should not be measured during an acute or subacute illness.

Risk-Benefit Ratio of Testosterone Therapy

Dr. Matsumoto noted that treatment decision-making requires a value assessment, with careful consideration of the potential clinical benefits versus treatment burden and risks, and sound clinical judgment. Both practitioners and patients should be well informed. In general, testosterone therapy should be started when the benefits outweigh the risks. TES guidelines recommend testosterone therapy for symptomatic men with classic androgen deficiency syndromes, with a goal of inducing and maintaining secondary sex characteristics and improving their sexual function, sense of well-being, and bone mineral density.

Treatment should be given for organic causes (primary and secondary hypogonadism), such as Kleinfelter syndrome, cryptorchidism, damage from irradiation or chemotherapy, pituitary tumor, hemochromatosis, and other recognized etiologies. Transient causes, such as opioids, excessive exercise, anabolic steroids, central nervous system-active drugs, and glucocorticoids, should not prompt treatment, except in uncommon cases in which the offending cause cannot be ethically eliminated or medically corrected. The decision to treat is more difficult when low testosterone levels are due to functional causes, such as morbid obesity, aging, and excessive exercise. For men with a borderline case of hypogonadism, it is reasonable to start treatment and discontinue it if there is no clinical response after 6 months, said Dr. Matsumoto. In such cases, he added, "you should lower expectations and tell patients upfront that they may not respond."

Risks of Testosterone Therapy

Shehzad Sultan Basaria, MD, Boston University, Boston, Massachusetts, USA, noted that testosterone therapy has several adverse effects (AEs), including acne, oily skin, decreased spermatogenesis, gynecomastia, and possible exacerbation of obstructive sleep apnea. Dr. Basaria discussed adverse effects on the prostate cardiovascular (CV) system.

TES guidelines recommend against starting testosterone therapy for men with prostate cancer because of the dependency of prostate cancer on androgens. The concern has always been that testosterone therapy may result in progression of subclinical prostate cancer, however; this concern remains theoretical. An analysis of 18 population studies showed that endogenous serum testosterone levels were not associated with an increased risk of prostate cancer [Roddam AW et al. *J Natl Cancer Inst* 2008]. An increasing number of men with history of low grade prostate cancer who are considered cured are being treated with testosterone in clinical settings. Since the majority of men who are diagnosed with prostate cancer have low grade organ-confined disease, this patient population will increase with time. Therefore, Dr. Basaria recommended that randomized controlled trials are needed to determine the efficacy of testosterone treatment in these men. If efficacy is established, this should be followed by long-term safety studies to evaluate recurrence rates.

The relationship between testosterone treatment and CV disease remains unresolved. Data from epidemiologic studies are inconsistent regarding the association of serum testosterone levels and CV mortality. Dr. Basaria suggested that testosterone may simply be a biomarker of health rather than being causal. In a recent study of older men with mobility limitation, men randomized to testosterone gel experienced increased CV AEs [Basaria S et al. *N Engl J Med* 2010]. Since CV events were diverse in nature, a single mechanism appears unlikely to explain these events. Since the events started occurring within weeks after randomization, progression of atherosclerosis appears to be an unlikely mechanism. Serum estradiol levels were significantly higher in those men who experienced CV events compared with men who did not, possibly predisposing these men to increased risk of thrombosis. Dr. Basaria emphasized that the population in the TOM Trial was unique: men were older (mean age 74 years), had limitations in mobility, and the overall prevalence of chronic diseases (hypertension, diabetes, hyperlipidemia, and obesity) was high. Dr. Basaria also emphasized that the findings of the TOM Trial need confirmation and do not apply to young men with classic hypogonadism or to healthy older men