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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Does my patient have testosterone deficiency?

A: Diagnosis of testosterone deficiency (TD) requires the presence of relevant signs or symptoms along with biochemical evidence. Testosterone deficiency can prove challenging to diagnose and treat. The American Urological Association (AUA) endorses a total serum testosterone cutoff of less than 300 ng/dL in support of a diagnosis.[1] The prevalence of TD varies from 12% to 39% across men in their 50s to 80s.[2] Testosterone levels decline by approximately 1% yearly after the fourth decade of life.[3]

SIGNS, SYMPTOMS, AND COMORBIDITIES

The symptoms of TD are often nonspecific, particularly in older men, and include fatigue and poor memory and concentration. However, decreased libido, depression, erectile dysfunction, delayed ejaculation, and diminished facial and body hair growth are more specific indicators.[4] Physical examination findings that can support a diagnosis of TD include testicular atrophy, testicular masses, varicoceles, gynecomastia, and large waist circumference.[1]

Several comorbidities are commonly associated with TD. Evidence for a relationship between TD and obesity (body mass index > 30 kg/m^2) exists, with approximately half of men with obesity exhibiting reduced testosterone levels.[5] The low total testosterone observed in these patients may result from the lower sex hormone–binding globulin levels associated with obesity; however, free (biologically active) testosterone levels may be normal. Diabetes also has been identified as a comorbidity, with evidence suggesting that higher testosterone levels decrease the risk of having the disease.[6] Conditions that affect sleep are also related to TD. Diurnal variation in testosterone levels, with highest values in the morning hours, is associated with sleep. Sleep disturbances, therefore, can interfere with nocturnal testosterone production. Obstructive sleep apnea, in particular, has been described as a comorbidity with TD.[7] Other potential associated conditions include hypertension, hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease, and rheumatoid arthritis.[2,8]

WHAT ARE THE CAUSES OF TESTOSTERONE DEFICIENCY?

The etiology of TD can be divided into acquired and congenital causes. The acquired causes include aging, obesity, testicular trauma or removal, pituitary disease (prolactinoma), infection, environmental factors, autoimmune processes, and medications such as narcotics, antidepressants, and glucocorticoids.[2,9,10] More recently, it has been suggested that cannabis use may result in reduced testosterone levels; however, higher-quality studies are needed to establish a definitive association.[11] Congenital causes of TD include Klinefelter syndrome, Kallmann syndrome (hypogonadotropic hypogonadism with anosmia), and disorders of sexual development.

HOW IS IT DIAGNOSED?

Historically, a lack of consistency in serum testosterone cutoffs has made TD challenging to diagnose. As noted, a total testosterone value of 300 ng/dL is considered the lower threshold for diagnosis. While age-specific cutoffs may be more appropriate, such cutoffs have not yet been adopted by guidelines. This AUA-endorsed cutoff was determined based on statistical evidence suggesting that below this value, men tend to experience more symptoms and respond better to treatment.[12] Importantly, in addition to biochemical evidence of the condition, related symptoms must be present.

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Serum testosterone collection is a crucial component of diagnosis. Total testosterone should be measured between 7:00 and 11:00 AM except for shift workers. At least 2 measurements showing a low testosterone value sampled at least 2 to 3 weeks apart are needed to meet diagnostic criteria.[1] If low testosterone is confirmed, serum luteinizing hormone should be measured in an effort to elucidate the cause. Higher luteinizing hormone values suggest primary TD (testicular failure of production) and lower values, secondary TD (hypothalamus or pituitary malfunction). If luteinizing hormone levels are low or normal (suggesting secondary TD), serum prolactin should be measured to help evaluate for the presence of a prolactinoma, a recognized potential cause of TD. In a patient who presents with gynecomastia, serum estradiol should be measured, as this sign can be caused by a decrease in the testosterone:estrogen ratio.[1] In patients with obesity who have low total testosterone, measuring free testosterone to confirm the diagnosis may be useful.

WHICH PATIENTS SHOULD BE TREATED?

Treatment is indicated if diagnostic criteria are met, symptoms are present, and the patient understands the risks and benefits of treatment. The primary goal of treatment is to alleviate associated symptoms. There are, however, additional benefits that testosterone therapy may provide for patients with certain comorbidities. Specifically, it may improve bone mineral density, blood glucose control, lean body mass, and anemia. Screening for related conditions (eg, osteoporosis, diabetes) also may be reasonable for patients presenting with TD. If TD can be explained by another condition, then that condition should be treated before testosterone therapy is started.[12]

The 2018 AUA guideline endorses a strong recommendation that men actively trying to conceive should not receive exogenous testosterone, as it will suppress the hypothalamic-pituitary-gonadal axis, inhibiting spermatogenesis.[1] In addition, the guideline suggests that testosterone therapy not be commenced for a period of 3 to 6 months after a cardiovascular event because of the potential for worse outcomes; however, further study of this association is warranted.[1,13]

TREATMENT OPTIONS

Multiple treatment options and protocols exist depending on the patient's preference and desire to maintain fertility. Routes of administration for exogenous testosterone include intramuscular and subcutaneous injections, subcutaneous pellet implantation, topical therapies, oral agents, and intranasal spray. For patients with fertility concerns, endogenous testosterone production can be promoted with selective estrogen receptor modulators such as clomiphene citrate, human chorionic gonadotropin, aromatase inhibitors such as anastrozole, or a combination of these. Of these agents for patients who wish to maintain fertility, only human chorionic gonadotropin is approved by the US Food and Drug Administration for use in males. The biochemical goal of treatment is to achieve a total testosterone level in the middle tertile of the normal reference range, approximately 450 to 600 ng/dL.[1]

RISKS AND CONSIDERATIONS OF TREATMENT

Testosterone replacement therapy has multiple benefits, but a few potential risks should be highlighted. Infertility is one of the more critical risks that must be discussed with the patient.[14] Other potential adverse effects include acne, fluid retention, exacerbation of obstructive sleep apnea, exacerbation of existing lower urinary tract symptoms related to benign prostate enlargement, and, while less commonly reported, gynecomastia.[12]

Elevated prostate-specific antigen is a notable phenomenon that is expected to occur after testosterone replacement therapy is started. Because the prostate is an androgen-sensitive organ, increased androgens will result in increased production of prostate-specific antigen. It must be remembered that in this case, the increase does not necessarily indicate a neoplastic process.[15] Based on clinical principle, the AUA recommends measuring prostate-specific antigen in men older than 40 before starting testosterone therapy in order to exclude a diagnosis of prostate cancer.[1] Beyond this, our practice is to use the prostate-specific antigen level measured after initiation of testosterone therapy as a baseline for future comparisons. The relationship between testosterone replacement therapy and prostate cancer risk is an area ripe for further research. When counseling patients, however, it should be made clear that currently there is no high-quality evidence linking testosterone therapy to prostate cancer development.

Another adverse effect that has been associated with testosterone therapy is an increased risk of venous thromboembolic events. This association has not been proven conclusively, however, and the AUA guideline recommends informing patients of this.[1] Furthermore, there is not yet robust, definitive evidence for testosterone therapy's effect on the risk for cardiovascular events (moderate recommendation; evidence level B).[1] While not yet incorporated into guidelines, results from the recent TRAVERSE (Testosterone Replacement

Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men) study[16] suggest that testosterone therapy in men with hypogonadism does not increase the risk of major adverse cardiac events.

FOLLOW-UP

Following up with patients on testosterone therapy at a specific time interval is necessary to optimize outcomes. Measuring testosterone levels 1 to 2 months after treatment initiation is recommended. If testosterone levels increase adequately and symptoms are improved, therapy can continue indefinitely, with testosterone measurements taken every 6 to 12 months while the patient is being treated. Prostate-specific antigen also should be monitored at the same time interval, as should the hematocrit, with a goal of maintaining a hematocrit below 54%. If symptoms fail to improve after 3 to 6 months of treatment, cessation should be discussed, as TD may not be the cause of symptoms. In the case of an inadequate increase in testosterone levels, dose adjustment or medication change can be considered.[1]

WHEN TO REFER TO UROLOGY

Urology referral should be pursued when a patient with TD wishes to maintain fertility or is currently infertile. Other situations warranting referral include prostate-specific antigen values increasing beyond the new post-treatment baseline or lack of improvement in erectile function after treatment. In addition, any patient who currently has prostate cancer or has been treated for prostate cancer should be referred to a urologist.

DISCLOSURES

Dr. Bajic has disclosed being an advisor or review panel participant for Endo Pharmaceuticals. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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