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Updates on Testosterone Therapy

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Aggressive direct-to-consumer advertising and development of more convenient formulations of testosterone (subsequently referred to as *T*) have played an important role in the dramatic increase of T prescribing rates in the United States.[1] The annual rate of T initiation has increased 3- to 4-fold from beginning in the year 2000 through 2011.[2,3] The largest change was with the topical T formulation with a 5-fold increase observed during the decade.[1] Increased utilization of T has been attributed to guideline nonadherence when initiating and monitoring testosterone therapy and an overall increase in routine population-level screening for testosterone deficiency and use of testosterone replacement therapy (TRT) for off-label indications.[4] The purpose of this review is to evaluate recent evidence focused on risks associated with TRT.

Background

The 2018 Clinical Practice Guidelines published by the Endocrine Society recommend against screening for testosterone deficiency (TD) in the general population due to the lack of clear benefit of early detection of androgen deficiency and long-term testosterone therapy in asymptomatic patients.[5] A diagnosis of hypogonadism should only be made in men with clinical symptoms suggestive of TD and consistently low serum T concentrations.[5] In general, the Endocrine Society recommends 300 ng/dL as the lower limit of the normal range for total testosterone level.

Symptoms of low T are variable. Sexual symptoms include diminished sexual libido, decreased frequency of sexual thoughts, decreased frequency of nocturnal erections, and erectile dysfunction (ED). Nonspecific symptoms include fatigue, decreased energy, depressed mood, irritability, and decreased sense of well-being. Low serum T concentrations may also be accompanied by other objective signs such as anemia, decreased bone-mineral density (BMD), reduced muscle strength and mass, increased body fat mass, and weight gain.

Testosterone levels are subject to circadian variation and are generally the highest in the morning. Therefore, measurement of testosterone levels should be performed in the morning as the normal ranges from serum testosterone are based on morning blood samples. There is no general consensus on the absolute level of low T below which a man can be considered androgen-deficient. For these reasons, the diagnosis should be based on both presence of clinical symptoms and confirmed low T levels

Low T levels can result from testicular failure caused by disruption of one or more levels of hypothalamic-pituitary-gonadal (HPG) axis.[5] Primary hypogonadism results from abnormalities at the testicular or gonadal level, whereas defects of the hypothalamus or pituitary could lead to secondary hypothyroidism. Examples of primary causes include genetic disorders, testicular trauma or chemotherapy and secondary causes include pituitary tumors and hyperprolactinemia. Distinguishing between primary and secondary hypogonadism is important as TD can be reversible in some cases of secondary hypogonadism by managing the underlying condition (e.g., obesity) or discontinuing the offending medication (e.g., opioids).

In general, testosterone levels tend to decline by 0.4-2% annually in men after the age of 30. Due to the extensive use of TRT in age-related hypogonadism, the Food and Drug Administration (FDA) published a statement in 2014 notifying providers that there is insufficient safety and efficacy data on the use of TRT for age-related hypogonadism.[6] Currently, the use of TRT is FDA-approved for men who have hypogonadism due to primary or secondary causes. The use of TRT is contraindicated in patients with pre-existing breast/prostate cancer, prostate-specific antigen (PSA) >4 ng/dL, hematocrit over 50%, untreated severe sleep apnea, severe lower urinary tract symptoms, uncontrolled or poorly controlled heart failure, or in those desiring fertility.[5] A thorough urological evaluation is recommended in patients with prostate nodule or induration or serum PSA level > 4 ng/mL or serum PSA level > 3 ng/mL in men at high risk for prostate cancer (e.g., African-Americans or men with first-degree relatives with prostate cancer) prior to initiation of TRT.[5]

The goal of TRT is to provide symptom relief by restoring serum T concentrations to levels within normal range of 300-1000 ng/dL.[5] Once initiated, monitoring recommendations for TRT include assessment of serum T levels, clinical response and adverse effects at 3 months following initiation and then annually thereafter. Common adverse effects associated with TRT include acne, gynecomastia, peripheral edema, and polycythemia. However, the serious concerns identified with TRT are an increased incidence of cardiovascular (CV) events and prostate cancer. It was these risks that prompted the FDA to issue a safety alert in January 2014 regarding TRT.

Oregon Health Plan (OHP) Fee-for service (FFS) policy requires prior authorization for all testosterone products. Covered indications include testicular hypofunction, hypopituitarism and related disorders, AIDS-related cachexia, and gender dysphoria.

Cardiovascular Events

The use of TRT in TD has been in clinical practice for over 70 years, however, there has been an increasing concern regarding the CV risks associated with TRT. The data available on the CV safety profile of TRT is conflicting. Earlier data supported the view that a low serum T level is associated with increased CV risk and therefore, TRT can have beneficial impact on CV risk reduction.[7] However, some studies within the last decade have suggested increased CV risk with the use of exogenous testosterone therapy. As a result, in 2014, the FDA released a statement mandating labeling changes for all testosterone products to inform patients about the possible increased risk of heart attacks and strokes associated with TRT.[6] Additionally, health care providers were also advised to prescribe TRT only for men with low T levels caused by primary or secondary hypogonadism, and not age-related hypogonadism.

The statement released by the FDA was based on five observational studies[8-13] and 2 meta-analyses[14-15]. The five observational studies were retrospective cohort studies that yielded conflicting results. Two of these studies[8-9] found statistically significant CV harm with TRT, two studies[10-11]found a decreased risk of all-cause mortality with TRT, and one study[12] was inconclusive. Due to the conflicting results and the retrospective nature of these studies, the generalizability of these results is limited.

Additional evidence from a meta-analysis that included 27 placebo-controlled testosterone studies of 12 weeks duration or longer showed an increase in CV events in the TRT group when compared with the placebo group.[13] However, this analysis only included trials that reported 1 or more CV events. As a result, failure to include any trials that did not show increased CV risk could have skewed the analysis. Furthermore, the results from 2 out of the 27 studies contributed to a third of the CV outcomes in the TRT group. Additionally, 18 of the 23 events reported in one of the studies would not generally qualify as CV events (e.g., edema, elevated blood pressure, chest pain and tachycardia with fatigue).[13] The high number of adverse events reported in one study could likely be due to the use of an unapproved oral formulation of micronized T at very high doses in men with cirrhosis of the liver, resulting in serum T concentrations approximately 20 times the upper limit of the normal range.[13] Therefore, the increased CV risk could potentially

be due to methodological issues, inclusion/exclusion criteria challenges and varying formulations of T included in trials.[13]

Recently, several systematic reviews and meta-analyses have been published to examine the association between TRT and CV disease and mortality. One analysis evaluated the association between exogenous TRT (injection, oral, or topical) and risk of serious CV events. It included 39 randomized controlled trials (RCTs) and 10 observational studies, including those mentioned above.[15] The included trials represented 5451 men, of which 3230 received exogenous T and 2221 received placebo. The duration of trials ranged from 6 weeks to 3 years and the mean ages of participants were 50-60 years. The findings of this systematic review did not reveal any significant association between TRT and myocardial infarction (MI) (odds ratio [OR] 0.87; 95% confidence interval [CI], 0.39-1.93; 16 RCTs), stroke (OR 2.17; 95% CI, 0.63-7.54; 9 RCTs), or mortality (OR 0.88; 95% CI, 0.55-1.41; 20 RCTs). Due to presence of high clinical trial heterogeneity, a pooled analysis was not conducted using data from the observational studies.[15]

Another analysis, The Testosterone Trials, were a multi-center set of 7 double-blind, placebo-controlled trials designed to determine whether testosterone would benefit older men.[16] Men 65 years of age or older (n=790) with serum T levels less than 275 ng/dL were assigned to receive either testosterone gel or placebo gel for 1 year. The primary endpoints included improvements in sexual function, physical function and fatigue. Results showed a modest benefit in sexual function and physical function in symptomatic older men with low T levels. Seven major CV events (MI, stroke, or death from CV causes) were observed in each study group during the treatment period. Two events in the testosterone group and nine events in the placebo group were observed in the subsequent year. However, given that the study was not designed to investigate CV events, it is not possible to draw a definitive conclusion on the impact of TRT on cardiovascular risk.[16]

Prostate Cancer

The theory of prostate cancer being an androgen-dependent disease was established by the work of Charles Huggins in 1941.[17] This is based on the concept that development of prostate relies on androgen stimulation and high levels of testosterone could contribute to the acceleration of prostate growth, not only in benign disease but also in cancer.[17,18] Furthermore, testosterone suppression, by the means of orchiectomy followed by use of medical castration with LHRH agonists, has historically been considered first line therapy for advanced prostate cancer since the 1980s.[17] However, this does not take into account that malignant prostate tumors become increasingly prevalent as men age and experience a decline in serum T levels. Therefore, the question of whether high levels of endogenous testosterone or testosterone supplementation stimulates the development of prostate cancer continues to remain controversial.

A recent systematic review and meta-analysis evaluated the possible relationship between endogenous and exogenous testosterone and prostate-specific antigen (PSA) and prostate cancer.[19] This meta-analysis examined the link between prostate cancer with endogenous testosterone levels and exogenous testosterone separately. Twenty prospective cohort studies that reported risk estimates for prostate cancer and endogenous testosterone levels were included. The meta-analysis results showed a summary relative risk (SRR) of prostate cancer for an increase of 5 nmol/L of testosterone of 0.88 (95% CI 0.96, 1.02). Additionally, 26 placebo-controlled randomized trials of TRT that reported data on PSA levels and/or prostate cancer were included. The overall difference in PSA levels after TRT initiation was 0.10 ng/mL (95% CI -0.28 to 0.48) and the SRR of prostate cancer as an adverse effect of TRT initiation was 0.87 (95% CI 0.30 to 2.50). These results did not reveal a statistical difference between endogenous testosterone levels and prostate cancer or between TRT and an increased risk of prostate cancer and/or change in PSA levels.

Conclusion

Studies have not demonstrated a clear association between testosterone therapy and CV events or prostate cancer. Given the limitations of currently available evidence on benefit-risk profile, current OHP policy restricts the use of testosterone therapy in patients with symptomatic hypogonadism due to primary or secondary causes.

For patients with a qualifying indication for testosterone replacement, preferred OHP FFS products are topical testosterone gel, testosterone cypionate and testosterone enanthate

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