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THE JOURNAL of UROLOGY®
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Update to the Testosterone Guideline

Key Words: androgens, hormonal therapy, hypogonadism, diabetes, cardiovascular disease

SINCE the release of the AUA guideline on the evaluation and management of testosterone deficiency in 2018, there have been several notable updates in the testosterone space. Specifically, 2 new, landmark randomized controlled trials (RCTs) have been released and provide additional data to inform the guideline, particularly as it relates to the areas of cardiovascular (CV) disease, diabetes, erectile function and libido, obstructive sleep apnea (OSA), and prostate events.

CV DISEASE

Arguably one of the most notable studies to have ever been conducted in the testosterone space reported findings in 2023. The Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial was conducted in response to earlier Food and Drug Administration requests for more data on potential CV risks associated with testosterone therapy.[1] The RCT study involved 5246 men aged 45 to 80 with total testosterone levels < 300 ng/dL.[2] Study men received either placebo or testosterone gel 1.62%, which was dosed to keep therapeutic levels between 350 and 750 ng/dL.

After a mean treatment of 22 months, the percentage of myocardial infarctions, strokes, or CV-related death adverse events (AEs) was 7.0% for testosterone vs 7.3% for placebo. Secondary outcomes which were statistically higher in testosterone-treated men were of limited clinical relevance: +0.3 mm Hg systolic blood pressure vs −1.5 mm Hg, nonfatal arrhythmias (5.2% vs 3.3%), atrial fibrillation (3.5% vs 2.4%), and acute kidney injury (2.3% vs 1.5%).

Results overall provide more definitive evidence that testosterone therapy (when performed appropriately) does not increase the risk for major CV events after a mean 2 years of treatment. The secondary findings of increased arrhythmias, atrial fibrillation, and minimally elevated blood pressure may be due to a volume-expanding effect of testosterone and are of limited/unclear clinical relevance. It is also plausible that the CV risk profile of testosterone may differ depending on doses and agent/modality prescribed (ie, injectable vs topical), particularly given distinctive AE profiles observed (eg, erythrocytosis) by agent.[3]

Currently, statement #20 in the testosterone guideline notes that it is unclear if testosterone increases major CV events. However, these updated data confirm that testosterone therapy does not increase major CV event risks over at least a 2-year period when done according to prescribed protocols.

DIABETES

One landmark RCT (T4DM trial) was published in 2021 evaluating the impact of testosterone therapy on diabetes.[4] The study included 1007 obese men with total testosterone levels approximately < 400 ng/dL and newly diagnosed diabetes/impaired fasting glucose. Men were randomly assigned to receive lifestyle modifications and testosterone undecanoate injections (1000 mg) or placebo every 3 months for 2 years after an initial loading dose. Results demonstrated several notable findings, including better glucose tolerance (relative risk 0.59, $P < .001$) and improved 2-hour glucose (~14 mg/dL improvement between groups), indicating both a protective and treatment effect of testosterone. AEs were higher with testosterone and roughly mirrored those observed in the TRAVERSE study. Importantly, improvements in diabetic indices were independent of baseline testosterone values, suggesting that testosterone therapy may benefit men at high risk for diabetes, even when technically in a eugonadal range (ie, 400 ng/dL).

A follow-up analysis of T4DM data indicated that some benefits were secondary to improvements in fat and skeletal muscle mass.[5] However, despite these beneficial secondary effects, testosterone remained an independent contributor.

These data provide helpful, high-level information as it relates to the current testosterone guideline

THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000003855
Vol. 211, 608-610, April 2024
Printed in U.S.A.

statement #15, which states that the data are inconclusive as to whether testosterone therapy improves diabetic indices. Additionally, the data suggest a role for testosterone in men with impaired fasting glucose/glucose tolerance regardless of baseline testosterone levels.

ERECTILE FUNCTION AND LIBIDO

The previously cited TRAVERSE trial also included a subset of men who were concomitantly enrolled in a "Sexual Function Study."[6] These men (n = 1161) met all TRAVERSE inclusion criteria but also exhibited low libido on a standardized assessment. Results demonstrated that testosterone-treated men exhibited higher overall rates of daily sexual activity (approximately +0.5 events/d) and increased libido without improvements in erectile function.

Similarly, the T4DM trial also obtained various measures of sexual function (n = 815 with data) and demonstrated improvements in overall intercourse and sexual satisfaction, greater sexual desire, and improved orgasmic function. However, in contrast to the TRAVERSE study, results demonstrated a 2.1-point increase in a standardized assessment of erectile function (compared to ~1 point at 1 year and no difference at 2 years in the TRAVERSE study). It is notable that although findings were statistically different between groups, they failed to achieve the minimally clinically significant difference necessary to be clinically relevant (ie, +4 points).[7]

Currently, the AUA testosterone guideline statement #14 indicates that testosterone therapy may improve low sex drive and erectile function. These previously cited data would further support the beneficial effects of testosterone on libido and overall sexual function but would provide further conflicting data on whether it has a notable impact on erectile function itself. Most likely, these data suggest that treating erectile dysfunction with testosterone is a nuanced concept, where the modality employed, peak doses achieved, baseline erectile function, and comorbid contributing factors (eg, diabetes, obesity) all play important roles. To highlight this latter point, in the T4DM study, the statistical difference with therapy came as much because of an increase in the treated arm as a decrease in the placebo arm, whereas the TRAVERSE study exhibited similar increases in both arms. As such, it suggests that testosterone may ultimately have more of a protective effect against age- and comorbidity-dependent impacts on erectile function rather than a direct treatment/augmentation effect.

OSA

Evaluating the association between OSA and testosterone is challenging due to a paucity of high-level data, with some questioning whether the 2 have a causal relationship. While some hypothesize that OSA leads to low testosterone via central, hypoxia-induced impairments in the hormonal axis, others deny an independent correlation altogether. To address this controversy, 2 recent meta-analyses abstracted data from case-control studies and confirmed the association between OSA and low testosterone, even after controlling for comorbid conditions.[8,9] However, another meta-analysis failed to demonstrate any improvements in testosterone after treating OSA, arguing against a causative role.[10]

Although treating OSA may not improve testosterone levels, initiating testosterone therapy in men with OSA may lead to a worsening of symptoms. Specifically, multiple small studies over the past 4 decades (all n <100) have previously demonstrated the potential for acute worsening of OSA symptoms in men undergoing testosterone therapy supplementation.[3]

Given these observations, clinicians should exercise caution when starting a man with OSA on testosterone therapy. Additionally, men with low testosterone should be routinely screened for OSA and referred for treatment prior to initiating therapy. At the present time, the 2018 AUA testosterone guideline does not specifically address the potential risks of worsening OSA in men undergoing testosterone therapy and need for screening prior to initiation of treatment.

PROSTATE EVENTS

Both TRAVERSE and T4DM included various measures of prostate events as secondary outcomes. In the TRAVERSE study, men with prostate cancer/nodules, elevated PSA, or severe baseline urinary symptoms were excluded; while in the T4DM study, prostate cancer was an exclusion and severe urinary symptoms required urological review.

Regarding prostate events, the TRAVERSE study demonstrated no differences in rates of benign prostatic hyperplasia, nonstatistically higher rates of urinary retention in the testosterone arm (50 vs 34 events, $P = .08$), similar rates of prostate cancer (12 vs 11 events, $P = .87$) and high-grade disease (5 vs 3 events, $P = .51$), and higher PSA levels in testosterone-treated men (+0.2 vs +0.08 ng/mL, $P < .001$).

The T4DM study similarly demonstrated statistically higher rates of prostate-related events in testosterone-treated men (2.4% vs 1.6%). Events included benign prostatic hyperplasia–related hospital admissions and higher rate of PSA increases $\geq$ 0.75 μg/mL (23% vs 19%) but similar rates of prostate cancer (5 vs 4 events).

Overall, findings are similar to prior studies and reaffirm the current AUA testosterone guideline

statement #17, which indicates that testosterone supplementation is not correlated with an increased risk for development of prostate cancer.

TAKE-HOME MESSAGES

Two landmark RCTs evaluating testosterone therapy have recently been concluded and provide significant data on the risks and benefits of treatment. Key findings included no increased risks for severe CV events, but mild increases in blood pressure, rate of nonfatal arrhythmias, and risk of acute kidney injury. Testosterone also likely increases sexual activity, libido, and other aspects of sexual function, but has limited and likely clinically insignificant effects on erectile function. For diabetes, testosterone supplementation likely results in both preventative and treatment benefits for men with impaired fasting glucose/glucose tolerance, regardless of baseline testosterone levels. The studies also confirmed prior data demonstrating an increase in prostate-related events overall, without increasing the risk for prostate cancer (including high-grade disease). And finally, additional data suggest that OSA is correlated with low testosterone and should be screened for prior to initiation of testosterone and closely monitored during therapy.

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Submitted November 26, 2023; accepted January 17, 2024; published March 8, 2024.

Funding/Support: None.

Conflict of Interest Disclosures: The Author has no conflicts of interest to disclose.

Ethics Statement: This study was deemed exempt from Institutional Review Board review.

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