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Re: Effects of Testosterone Treatment in Older Men

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Experts' summary

In the February issue of The New England Journal of Medicine, Snyder and colleagues [1] report the primary outcomes in The Testosterone Trials. The Testosterone Trials are set of multi-institutional, double blind, placebo-controlled studies aimed primarily at determining the efficacy of testosterone supplementation therapy (TST) on sexual function, physical function, and vitality. Secondary studies investigating TST's effect on cognitive function, bone density, anemia, and cardiovascular function were not reported in this initial manuscript.

Seven hundred and ninety men over the age of 65 yr with symptoms of hypogonadism and a serum testosterone concentration of <275 ng/dl were randomized to receive either an initial dose of 5 g of 1% testosterone gel or placebo gel once a day. Serum testosterone levels and improvement in symptoms were assessed at baseline and at 3 mo, 6 mo, 9 mo, and 12 mo. Ninety-one percent of men maintained normalized testosterone levels throughout the duration of the study. TST improved sexual desire (DISF-M-II), frequency of sexual activity (Personality Diagnostic Questionnaire-4), and erectile function (International Index of Erectile Function). However, TST did not confer any significant benefits in terms of vitality (an improvement of ≥4 in the Functional Assessment of Chronic Illness Therapy fatigue score). In the physical function trial, there was no significant difference between TST and placebo in terms of the percentage of men with an increase of 50 m or greater in the 6-min walking distance. However, on inclusion of all men enrolled in the three trials, TST was associated with a significantly higher percentage of men with an increase of ≥50 m in the 6-min walking distance. TST resulted in a very modest improvement in secondary measurements of vitality or depressive symptoms. More men in the TST group had an increase in prostate specific antigen ≥1 ng/ml, but there was no difference in the number of men diagnosed with prostate cancer 1 yr after the study period. Similarly, there was no difference in the number of men who experienced major cardiovascular events or died during the study period.

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Conflicts of interest: Ranjith Ramasamy is a clinical trials participant for Beckman Coulter and a member of advisory board for Lipocine Inc. Samarpit Rai, Jason Scovell, and Joseph Palmer have nothing to disclose.

Experts' comments

The Testosterone Trials were designed to address the lack of definitive evidence [2–4] and controversy surrounding the risks and benefits of TST. The coordinated trials focused on symptoms that have been associated with low testosterone levels. The seven trials share similar inclusion criteria and methodologies that allow investigators to draw conclusions across all studies. The initial study report focusing on the three main trials (sexual function, physical function, and vitality) represents the most rigorously and appropriately designed study in the field of TST.

While the authors failed to provide the range of total testosterone levels at each measurement period despite collecting this data, they report that 91% of men maintained eugonadal levels throughout all time points during the study suggesting that therapy was effective in restoring testosterone levels.

The sexual function study identified that TST plays a positive role in improving sexual desire, frequency, and erectile function. Despite these improvements, the benefits are modest and may not be clinically meaningful. It is well described that an improvement of 4 or greater on the International Index of Erectile Function-Erectile Function is clinically relevant and is often used as the cut-off for clinical trials assessing erectile function. While many hoped that The Testosterone Trials would clearly prove or disprove the efficacy of TST, it is not surprising given the modest and mixed findings of previous smaller studies that the ultimate effect of TST on hypogonadal symptoms is mild. It is likely that in most patients TST has the capacity to improve sexual function, but this effect may not be sufficient as monotherapy.

There was no difference in the number of major cardiovascular events in men treated with TST or placebo. While the benefits of TST appear to be mild in this population, the risks appear to be even smaller. A small proportion of men had an increase in prostate specific antigen, although the study period was too short to identify de-novo prostate malignancy. We hope that long-term follow-up of these patients will be similarly reassuring.

After screening >50 000 men, only 790 (<2%) of them were found eligible to be enrolled in the trial. The average participant was aged 72 yr and many men had comorbidities including a high rate of obesity, hypertension, sleep apnea, and diabetes. The strict inclusion criteria enhanced the study's ability to identify treatment efficacy. Because participation was limited to this narrow population, it is important not to generalize these findings to a larger population. While the majority of the controversy in TST has been focused on the older male population due to concerns over adverse events, there is a lack of high-quality evidence guiding therapy in younger men with hypogonadism.

This landmark study and future results that will be subsequently published will contribute significantly in shared decision making about the role of TST in older men with low testosterone levels.

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