

T Trials shed light on benefits of testosterone therapy

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Serum testosterone levels naturally begin to decline gradually with age, but not necessarily to levels below those considered normal for healthy young men. In the NIH-sponsored Testosterone Trials, researchers evaluated the effects of testosterone therapy in 790 men aged 65 years or older with low testosterone and symptoms possibly attributable to low testosterone. In the studies, which were conducted at 12 sites across the country, researchers randomly assigned participants to therapy with testosterone gel or placebo gel, applied daily to the skin. They then measured serum testosterone levels in the participants at 1, 2, 3, 6, 9 and 12 months.

The effects of testosterone gel were evaluated in terms of improvements to sexual function, physical function and vitality, with results published in February 2016. Additional trials, published this year, assessed the effects of testosterone on anemia, bone mineral density, noncalcified coronary artery plaque and cognitive function.

Endocrine Today spoke with study researcher Susan S. Ellenberg, PhD, professor of biostatistics at the University of Pennsylvania's Perelman School of Medicine, about the design of the T Trials, their recently published findings, and what these findings may mean for clinical practice.

How were the T Trials designed? What were their objectives?

Ellenberg: We designed the trials based on the recommendations of what was then called the Institute of Medicine (IOM) of the National Academies of Science, now the National Academy of Medicine. Those recommendations were motivated by concern about the increased use of testosterone and the limited understanding of the benefits and risks. The IOM recommended that a series of coordinated, randomized studies be done that could determine whether there were any clear advantages to therapy. Then, if benefits were documented, it would be worth doing much larger studies to do a full comparison of the risks and benefits. The primary risk of concern with testosterone treatment has been prostate cancer. In epidemiologic studies, higher levels of testosterone are associated with increased risk for prostate cancer. The concern then is, if you supplement with testosterone, are you going to increase the risk? Of course, our study was too small to assess that — we had only a handful of cases of prostate cancer. More recently, concerns have also arisen regarding cardiovascular risk.

What have been the main findings so far?

Ellenberg: We published the first set of findings about a year ago in *The New England Journal of Medicine*. That paper reported the results of the three primary studies under the umbrella of the T Trials. Those studies focused on sexual function, vitality and physical function.

We found that there was definitely an improvement in sexual function, specifically in libido. Testosterone therapy did not seem to have any effect on vitality, although there were some indications

that it might affect mood. The third piece, physical function, was a bit harder to interpret. We focused that substudy on men who indicated they did not have the physical strength they once had, particularly with respect to walking ability, and who walked what would be considered slowly, based on a 6-minute walk test. Those men did not show a significant improvement in terms of walking ability, but when we looked at the entire group of men, almost 800, we did see an improvement in walking ability. We saw the effect in the group where we did not anticipate any effect. The impact on physical function remains unclear right now. Was this a coincidence, a fluke finding? Or was there a small effect that we just didn't see in one group, but saw in the larger group? We don't have the answer yet.

Now, the new studies that just came out have to do with the four other issues we addressed in these trials: anemia, bone, CV, and cognitive functioning.

What were the main findings from these substudies?

Ellenberg: Again, the results were mixed. We found strong improvements in trabecular bone density and strength, which was the primary endpoint in the Bone Trial, but the study was too small to determine whether this measure would have an impact on fracture, the ultimate outcome of interest in an elderly population. Testosterone therapy also improved hemoglobin levels in men with anemia.

Testosterone treatment did not seem to have any effect on cognitive functioning. Memory was the primary endpoint for that trial, and we focused on men who were considered to have age-associated memory impairment. Testosterone did not have any effect on those men or on the group as a whole. The fourth area we looked at was CV, focusing on noncalcified coronary artery plaque. We found that the volume of noncalcified plaque increased significantly more in those in the testosterone arm vs. the placebo arm. Again, the studies were too small to evaluate clinical events. Exactly what this finding is going to mean is unclear. We'll have to wait for larger studies to see if there is any impact on CV events. The FDA is requiring the manufacturers of testosterone to do a large study to look at the CV risks of testosterone, so we will eventually get information on whether there is, in fact, a difference in the risk for major CV events. You would need a study of several thousand men to be able to determine that.

How might these findings affect clinical practice?

Ellenberg: These studies, emerging from a rigorously designed and carefully conducted randomized placebo-controlled trial, provide substantially more, and more reliable, information on the effects of testosterone than were previously available. For physicians who are considering whether testosterone would benefit their patients, these studies will provide information on the potential benefits and risks of testosterone treatment that should help them make judgments based on the individual needs and interests of the particular patient. So, for instance, if you have an older male patient who comes in with low testosterone, and he is saying, "I can't remember things the way I used to, and I've heard that maybe testosterone will help," our study has shown that there is no reason to think that is going to help. If, on the other hand, a patient with low testosterone is concerned about his sexual function, then our data show that testosterone may be beneficial. The study is going to give physicians and patients more information to help them make these treatment decisions.

What questions do researchers still have about testosterone, and how will these be studied?

Ellenberg: Now that we have studied the potential benefits, people really want to know the actual risks. The concern about prostate cancer remains, and there is the newer issue of CV risk. A randomized trial that was done some years ago seemed to show an increased risk for CV events with testosterone, but other studies have suggested a possible benefit. My hope is that definitive answers about risks will be forthcoming from the large study the FDA is asking testosterone manufacturers to do. That is the big piece that's still missing. We now know a lot more about the potential benefits of testosterone, and some areas where it seems to not be beneficial, but we don't really know about the important risks.

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