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Testosterone Trials: what there is to know?

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In the last few weeks, the publication in JAMA and JAMA Internal Medicine of a series of studies on testosterone replacement therapy (TRT) has provided new data, following recent studies yielding conflicting results on cardiovascular risk in older men with age-related decline in testosterone levels. The new articles stem from a research network known as «Testosterone Trials», coordinated by Peter Snyder of the University of Pennsylvania. These studies, which involved 12 centers in the USA, have evaluated the role of TRT on several endocrine and metabolic parameters. Enrollment criteria in all the studies included age over 65 years, mean of two morning serum testosterone concentrations lower than 275 ng/dL (= 9.54 nmol/L), and symptoms attributable to androgenic deficiency (subjective and objective evidence of declining physical and sexual performance and reduced drive). In the arm randomized to active intervention, the dosage of testosterone gel was adjusted to maintain the hormone level within the normal range for young men, while the control group received a placebo gel.

Bone mineral density

The study on bone mineral density (BMD) (1) involved 211 patients (110 in the intervention arm, and 101 in the control group). At the end of the 12-month trial, the patients receiving TRT have shown a significant increase in BMD, whether measured as volume or area. This result confirms the potential role of TRT in preserving BMD in hypogonadic patients. The relatively small sample, and the limited duration of the study, however, did not allow evaluation of the incidence of fractures, which is the main clinical end-point. A larger and longer trial is required to determine whether TRT does reduce fracture risk in older men with low testosterone levels.

Anemia

The trial on the hematopoietic effects of TRT (2) divided the 783 participants on the basis of presence or absence of anemia (defined as Hb concentration < 12.7 g/dL), and its putative cause (based on routine laboratory evaluation), into three groups: anemia known cause, 64 patients; anemia unknown cause, 62 patients; absence of anemia, 657 patients. Within each group, the patients were randomized to TRT or placebo. The statistical analysis of the results shows that in older men with low testosterone levels and unexplained anemia, TRT corrected the anemia more than placebo. TRT also corrected anemia more than placebo in men who had anemia of known causes, such as iron deficiency. As expected, some patients without anemia developed eryhtrocytosis while on TRT. Several exploratory outcomes (like ability to walk, subjective well-being and memory) also showed improvement. While these data need to be confirmed in a larger number of patients, the study suggests that TRT may improve hematological parameters in anemic hypogonadic males, regardless of the cause of anemia.

Cognitive function

The trial on cognitive function (3) involved 788 men (493 with age-associated memory impairment) randomized to TRT (n = 394) or placebo (n = 394). The primary outcome, whether TRT improves memory function, was assessed through the score on the Delayed Paragraph Recall, a test of short-term memory, although several other tests were also performed. Contrary to what was shown in the two previous studies, 1 year of TRT, compared with placebo, was not significantly associated with improved memory or other cognitive functions. These results, however, do not rule out the hypothesis that response might have differed in a sample of different age or different degree of functional impairment.

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Cardiovascular risk

The fourth study, on cardiovascular risk in individuals receiving TRT (4), has raised a particularly intense debate. The sample was highly selected (only 170 of 790 screened individuals were enrolled) and the prevalence of diabetes, obesity and related vascular multi-pathology was high among all the participants. There was considerable loss to follow up, with only 138 patients completing the study, 73 receiving TRT and 65 placebo. The primary outcome of the study was non-calcified coronary artery plaque volume, as determined by coronary computed tomography angiography. Secondary outcomes included total coronary artery plaque volume and coronary artery calcium score. For the primary outcome, TRT compared with placebo was associated with a statistically significant greater increase in non-calcified plaque volume from baseline to 12 months (from median values of 204 mm^3 to 232 mm^3, vs. 317 mm^3 to 325 mm^3 in the placebo group). Similarly, for the secondary outcomes, TRT compared with placebo was associated with a statistically significant greater increase in the total plaque volume from baseline to 12 months (from median values of 272 mm^3 to 318 mm^3 in the TRT group, vs. from 499 mm^3 to 541 mm^3 in the placebo group). There were no differences in the calcification score and no death occurred in either group. These results need to take into account that, despite statistical adjustment, the different volume of the plaque at baseline may have affected the results. A larger and longer trial may be required, as suggested by the authors, to understand the clinical implications emerging from this study. The biology of the interaction between testosterone and plaque constituents needs to be better defined as well. Pending these data, the longstanding dispute on the CV risks and benefits of TRT in older hypogonadal men remains not adequately resolved.

References

1. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, et al. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. JAMA Intern Med 2017, 177: 471-9..
2. Roy CN, Snyder PJ, Stephens-Shields AJ, et al. Association of testosterone levels with anemia in older men: a controlled clinical trial. JAMA Intern Med 2017, 177: 480-90.
3. Resnick SM, Matsumoto AM, Stephens-Shields AJ, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017, 317: 717-27.
4. Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. JAMA 2017, 317: 708-16.