REPRODUCTIVE ENDOCRINOLOGY

Testosterone-replacement therapy in older men with limited mobility: is it safe?

In men of 65 years of age or older with low testosterone levels and limited mobility, testosterone therapy may increase the risk of cardiovascular events, report researchers from the USA.

The randomized, placebo-controlled, Testosterone in Older Men with Mobility Limitations (TOM) trial was designed to determine the effect of testosterone administration on leg muscle strength. Participants were community-dwelling men ≥65 years of age with total serum testosterone levels of 3.5–12.1 nmol/l or free serum testosterone level <173 pmol/l and evidence of mobility limitations, such as trouble climbing 10 steps or walking two blocks. However, the trial was discontinued before the target enrolment of 252 men was reached owing to a significantly higher incidence of adverse cardiovascular events in the group treated with testosterone than the placebo group. "The findings in this study contrast with other interventional studies in which testosterone supplementation did not appear to result in increased cardiovascular events," comments Bu Beng Yeap of the University of Western Australia.

In men, age-related decline in circulating testosterone levels starts from middle-age onwards, and for some men low testosterone levels may contribute to mobility impairment later in life—a condition that is linked to disability, reduced quality of life and mortality. Although testosterone therapy improves muscle mass and strength in healthy older men with low serum testosterone levels, few studies have evaluated the effect of testosterone administration on physical function and mobility among older men with limited mobility.

The researchers randomly allocated participants to receive 10 g of a transdermal gel containing either 1% testosterone or placebo, which was applied once daily for 6 months. After 2 weeks of therapy, testosterone dose was adjusted to maintain total serum testosterone levels in the range 17.4–34.7 nmol/l. At the time the trial was discontinued, 129 of the 209 men randomly allocated to testosterone or placebo had completed 6 months of treatment and 47 others had received treatment for ≥12 weeks and had undergone at least one outcome assessment.

The researchers included these 176 men in the efficacy analyses, in which leg-press strength, chest-press strength and stair-climbing power while carrying a load were significantly more improved in the testosterone group than the placebo group. However, early termination of the trial limits the statistical power of these findings.

Significantly more men in the testosterone than the placebo group had cardiac, respiratory or dermatological events. Incidence of cardiovascular-related adverse effects—a broad category that included cardiac events, as well as events of a cardiovascular nature, such as peripheral edema, hypertension, arrhythmia and syncope—was also significantly higher in the testosterone group than the placebo group (23 men versus 5 men). These events remained significantly elevated in the testosterone group after adjustment for baseline risk factors, such as hyperlipidemia, HDL cholesterol level, hypertension and diabetes mellitus. Furthermore, time-to-event analyses revealed that the difference between the groups in incidence of cardiovascular-related adverse effects was maintained from outset to 6 months and did not diminish during the 3 months of post-treatment follow-up.

The researchers highlight that the total numbers of men experiencing events was small and, possibly, the observed results could have been due to chance alone. They caution against broad extrapolation of their findings to other populations, as the study recruited frail older men among whom chronic diseases such as obesity, hypertension, hyperlipidemia and diabetes mellitus were common and, therefore, cardiovascular risk would have been elevated.

"Additional studies are needed, both epidemiological studies to improve stratification of cardiovascular risk in aging men and randomized, placebo-controlled clinical trials to determine whether testosterone supplementation in middle-aged or older men would preserve health," concludes Yeap.

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