Published in final edited form as:

Nat Clin Pract Endocrinol Metab. 2008 July ; 4(7): 374–375. doi:10.1038/ncpendmet0840.

Does testosterone supplementation improve health and function in elderly men?

Stephanie T Page [Assistant Professor of Medicine], John K Amory [Associate Professor of Medicine], and Alvin M Matsumoto [Professor of Medicine]^{*}
the University of Washington School of Medicine, Seattle, WA, USA.

Abstract

BACKGROUND—Low serum testosterone levels are associated with age-related changes in physical and cognitive function. Replacement therapy could, therefore, help alleviate symptoms of aging.

OBJECTIVE—To determine whether 6 months' supplementation with testosterone improved signs of aging in a population of elderly men with low-normal testosterone levels.

DESIGN AND INTERVENTION—This was a double-blind, randomized, placebo-controlled trial of testosterone supplementation conducted at a single center in the Netherlands between January 2004 and April 2005. Participants were recruited by direct mailing. Inclusion criteria included age 60–80 years and a serum testosterone level below the 50th percentile of the study population-based testosterone distribution (cutoff 13.7 nmol/l). Exclusion criteria included myocardial infarction, heart failure, malignancy, serious liver or renal disease, epilepsy, diabetes mellitus, elevated prostate-specific antigen, use of corticosteroids, and use of testosterone esters within the previous 60 days. Eligible participants were randomly allocated to receive either 80 mg oral testosterone undecanoate or placebo twice daily for 6 months. Functional ability was measured with the timed 'get up and go' test, the Stanford Health Assessment Questionnaire, an isometric handgrip strength test, and a maximal voluntary isometric leg strength test. Cognitive parameters assessed included verbal episodic memory, cognitive and perceptual speed, attention and mental flexibility, extrapersonal spatial perception, and visuospatial performance. BMD and total body composition were measured by dual-energy X-ray absorptiometry. Quality of life was assessed with the Short-Form 36 Health Survey (SF-36) and the Questions on Life Satisfaction Modules questionnaires.

OUTCOME MEASURES—The main outcome measures were functional mobility, cognitive function, BMD, anthropometry, body composition, biochemical measures, quality of life, and safety parameters.

RESULTS—The study enrolled 113 men in the testosterone group (mean age 67.1 years; mean serum testosterone level 11.0 nmol/l) and 110 men in the placebo group (mean age 67.4 years; mean serum testosterone level 10.4 nmol/l). Treatment adherence was >90% for both groups. When compared with the placebo group, treatment with testosterone was associated with increased lean body mass, decreased body fat mass and decreased body fat percentage ($P < 0.001$ for all comparisons); however, no significant changes in parameters of functional ability were observed in either group. Total cholesterol and HDL cholesterol decreased in the testosterone group, whereas insulin and glucose concentrations and measures of insulin resistance increased in the placebo group.

^{*}**Correspondence** Clinical Research Unit, Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care, System, S-182-GRECC, 1660 S Columbian Way, Seattle, WA 98108, USA, alvin.matsumoto@med.va.gov.

Competing interests

The authors have declared associations with the following companies: Ardana, Ascend Pharmaceuticals, GlaxoSmithKline, Merriem Pharmaceuticals, Solvay. See the article online for full details of the relationships.

Cognitive function improved in both groups but BMD and quality of life were unchanged. The mean number of adverse events per participant was 0.87 in the testosterone group and 0.90 in the placebo group.

CONCLUSION—The results of this study suggest that eugonadal or slightly hypogonadal men might not benefit substantially from short-term, low-dose testosterone supplementation.

Keywords

aging; androgen; supplementation; testosterone

COMMENTARY

The number of prescriptions for testosterone in men has increased over the past decade as additional therapeutic options have become available. When compared with studies in younger men with low mortality rates,¹ well-performed epidemiologic studies have demonstrated that low testosterone levels are associated with an increased risk of death in elderly men, independent of other risk factors and pre-existing medical conditions.² Nonetheless, long-term intervention studies are still lacking.

The study by Emmelot-Vonk *et al.* is the largest short-term study of testosterone supplementation in elderly men to date; however, the study does not provide clinicians with the crucial information required to determine whether testosterone therapy in these men does more good than harm. The largely negative results reported by Emmelot-Vonk *et al.* were difficult to interpret because the study was probably underpowered to detect changes in many of the outcome measures assessed. In addition, study duration was too short and the study population too small to demonstrate a change in the incidence of clinical outcomes (e.g. diabetes mellitus, cardiovascular disease, prostate cancer, or death).

Moreover, the study participants were not required to have clinical manifestations of androgen deficiency but were selected only on the basis of a total testosterone level below the 50th percentile for men aged 60–80 years. The use of this criterion means that only about 10% of the participants had testosterone concentrations similar to those associated with an increased risk of mortality in the epidemiologic studies.² The use of biochemical criteria alone for the diagnosis of hypogonadism led to the inclusion of many men in the study cohort who, by most current practice guidelines,³ would not normally have been treated with testosterone.

Emmelot-Vonk *et al.* demonstrated potentially beneficial increases in lean body mass and decreases in fat mass in the group treated with testosterone; however, functional mobility and muscle strength did not improve. A possible explanation for this discrepancy is that such improvements might only be observed with longer treatment duration or with higher doses of testosterone.⁴ Indeed, the dose and mode of delivery could be critical determinants of endorgan effects of testosterone therapy. As noted by the authors, trough testosterone levels did not increase after 6 months' treatment, an observation attributable to the pharmacokinetics of oral testosterone undecanoate.⁵ More-sustained increases in testosterone levels—rather than the bimodal peaks observed with twice-daily oral dosing⁵—might be critical to maximize potentially beneficial changes in elderly men.

Relatively small, short-term studies of testosterone administration in elderly men, including the study of Emmelot-Vonk *et al.*, have provided mixed results in terms of the potential benefits.³ Overall, such studies have repeatedly demonstrated improvements in body composition, but the morbidity and mortality benefits of these changes remain unproven. Moreover, concerns about possible adverse effects on prostate and cardiovascular disease persist. Long-term, carefully designed trials of testosterone replacement in a clinically relevant

population of elderly, androgen-deficient men are urgently required. In the meantime, however, careful selection and monitoring of patients administered testosterone therapy remain necessary.³

PRACTICE POINT

Assessment of testosterone therapy requires long-term, randomized trials of near-physiological replacement in genuinely hypogonadal elderly men that examine clinical outcomes, such as cardiovascular disease and prostate cancer

References

1. Araujo AB, et al. Sex steroids and all-cause and cause-specific mortality in men. *Arch Intern Med* 2007;167:1252–1260. [PubMed: 17592098]
2. Laughlin GA, et al. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab* 2008;93:68–75. [PubMed: 17911176]
3. Bhasin S, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006;91:1995–2010. [PubMed: 16720669]
4. Page ST, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab* 2005;90:1502–1510. [PubMed: 15572415]
5. Houwing NS, et al. Pharmacokinetic study in women of three different doses of a new formulation of oral testosterone undecanoate, Andriol Testocaps. *Pharmacotherapy* 2003;23:1257–1265. [PubMed: 14594344]

Acknowledgments

The synopsis was written by Vicky Heath, Associate Editor, *Nature Clinical Practice*. ST Page is supported by NIH grant K23 AG027238, JK Amory is supported by NIH grant K23 HD45386, and AM Matsumoto is supported by the Department of Veterans Affairs.