Testosterone supplementation therapy for older men: potential benefits and risks
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CRD summary
This review assessed the effects of testosterone supplementation for men older than 60 without severe illness. The authors concluded that supplementation may be helpful for men with low testosterone levels with or without hypogonadism. The review found only a few studies and the stated inclusion criteria were not consistently followed; hence, the conclusions should be interpreted with caution.

Authors’ objectives
To assess the effect of testosterone supplementation therapy in older men.

Searching
MEDLINE was searched from 1966 to October 2001; the search terms were stated and reports published in any language were eligible. The reference lists of reviews and identified studies were checked. Manual searches of the Proceedings of the Endocrine Society and the American Society of Andrology Annual Meetings (1992 to 2001), and the American College of Cardiology Annual Meetings (1999 to 2001), were also conducted. Duplicate reports were excluded and only the latest updates were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) published as either peer-reviewed studies or abstracts were excluded if the Jadad quality score was less than 2. Trials published as abstracts or letters were only included if they were clearly double-blind and placebo-controlled. Non-randomised trials and trials without a placebo control group that were published in peer-reviewed journals were excluded. Peer-reviewed, published crossover studies and studies that were not described as randomised were included. Dose-finding studies were excluded. The included studies were double- and single-blind RCTs, double- and single-blind crossover studies, double-blind studies with an unknown method of treatment allocation and non-randomised studies.

Specific interventions included in the review
Studies that compared any testosterone preparation with placebo were eligible for inclusion. In the included studies, testosterone was administered over variable periods of time, ranging from a single dose to 3 years’ treatment. The studies used different preparations of testosterone: transdermal, topical and scrotal testosterone; oral testosterone undecanoate; intramuscular preparations of testosterone, testosterone enanthate, testosterone cypionate and testosterone propionate; and intravenous testosterone.

Participants included in the review
Studies of men aged 60 years and over were eligible for inclusion. Studies in which the mean age of the participants was 50 years or less were excluded. Studies of men with severe or unstable systemic illness, and studies of men with hormone deficiencies due to specific disease (other than normal aging), were excluded.

The included studies were of men whose baseline testosterone levels varied from normal to moderately below the lower limit of the normal range for young men. Some studies only recruited men with a baseline testosterone value below a specified value, while others recruited men with a range of baseline testosterone values. The included studies were of the following groups (non-testosterone-level characteristics): healthy men; men with abdominal obesity; men with low bone mineral density; nursing home residents; men with mild to moderate obesity; men with erectile dysfunction; healthy and cognitively normal men; admissions to geriatric evaluation and management unit for rehabilitation; men with coronary artery disease; men with post-exercise ST depression; men undergoing knee or hip replacement; men with angina.
Outcomes assessed in the review
The inclusion criteria were not explicitly defined in terms of outcomes. The review assessed body composition, bone mineral density, muscle strength and functional ability, sexual function, mood and well-being, cognitive function, lipids and cholesterol, coronary heart disease, effect on prostate gland and erythrocytosis.

How were decisions on the relevance of primary studies made?
Any disagreements about study selection were resolved through discussion. The authors did not explicitly state how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using the Jadad scale, which considers randomisation, blinding and the handling of withdrawals and drop-outs (see Other Publications of Related Interest). Three reviewers independently assessed validity and resolved any disagreements through discussion.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The results from individual studies were classified as showing an increase, no change, or a decrease in the outcome measure for the treatment compared with placebo.

Methods of synthesis
How were the studies combined?
The studies were grouped by the outcome assessed and a narrative synthesis was undertaken.

How were differences between studies investigated?
The studies were grouped in the data extraction tables and in the text according to the baseline testosterone levels of the participants (baseline level below specified level versus no upper limit for testosterone levels) and the duration of treatment (single dose, 1 week to 3 months, and more than 3 months). Studies classified by the authors as high or lower quality were reported to have been analysed separately, but no details were reported.

Results of the review
Twenty-nine studies were included. There were 18 RCTs (613 men), 7 double-blind crossover studies (89 men), 1 single-blind crossover study (6 men), 1 double-blind study with an unknown method of treatment allocation (36 men) and 2 non-randomised studies (67 men).

Testosterone supplementation increased lean body mass (5 out of 7 studies) and decreased fat mass (7 out of 9 studies assessing some measure of body fat) in healthy men with low to slightly decreased testosterone levels. However, these changes were not significant in all cases.

For all studies, testosterone supplementation was associated with either an improvement or no change in lower body strength (5 studies: all reported no change), upper body strength (5 studies: 3 reported no change and 2 reported an improvement), function (7 studies: 4 reported no change and 3 reported improvements in some measures), sexual function (5 studies: 4 reported no change and 1 reported improvements in some measures), and mood (10 studies: 6 reported no change and 4 reported improved mood or energy).

Testosterone supplementation had mixed effects on cognitive function (5 studies). Improvement was found on some measures: spatial and verbal memory, spatial ability and spatial cognition improved in 2 studies, while working memory improved in 1 study. No improvement was found on other measures, i.e. memory recall and verbal fluency (1 study). In addition, verbal fluency failed to improve with practice (1 study).

Testosterone supplementation improved exercise-induced coronary ischaemia seen on electrocardiography (4 studies), but the results for angina were mixed (4 studies: 2 reported reduced angina and 2 reported no change).
A few studies found that men with low testosterone levels were more likely to show improvements in the following outcomes than men with a lesser degree of testosterone deficiency: lumbar bone mineral density (2 studies reported an increase for low testosterone men; no unrestricted studies assessed this outcome), self-reported functional status (4 studies reported no change for low testosterone men; 3 unrestricted studies reported an improvement), libido (3 studies reported an improvement for low testosterone men; 1 unrestricted study reported an improvement), erectile function (1 low testosterone study reported an improvement; 2 unrestricted studies reported no improvement), and exercise-induced coronary ischaemia (2 studies reported a benefit for low-normal testosterone men; 1 study reported a benefit for markedly reduced testosterone).

Testosterone supplementation had no major adverse effects on lipids: 4 studies reported that low-density lipoprotein cholesterol levels were reduced or unchanged, while 6 studies reported that high-density lipoprotein levels were unchanged.

Most of the studies reported that the mean haematocrit increased from baseline by 2.5 to 5%. Between 6 and 25% of men developed haematocrit levels above the normal range.

Nine studies found no increase in voiding symptoms, abnormal findings on examination of the prostate, or postvoid residual urine during treatment. One study found that the prostate increased in size by 12%. The results for prostate-specific antigen were mixed: 5 studies reported no effect, while 4 studies reported a significant increase even after 6 weeks’ treatment.

One study reported no change in sleep apnoea with testosterone supplementation.

Authors’ conclusions
Testosterone supplementation cannot be recommended for older healthy men with normal or low-normal testosterone levels. There was evidence that testosterone supplementation may be useful in men with reduced testosterone levels and clinical hypogonadism. Supplementation many also be helpful in older men with low testosterone levels, regardless of symptoms. The longer term (beyond 3 years) efficacy and safety are unknown.

CRD commentary
The review question was clear in terms of the intervention and participants. The inclusion criteria were defined in terms of the study design, but the criteria were not clearly stated or implemented. Several relevant sources were searched, the search terms were stated, and studies in any language were eligible. The methods used to select the studies and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Three reviewers independently assessed validity, which reduces the potential for bias and errors. The validity of all the studies was assessed using criteria validated for the reporting of RCTs, but methodological problems in the individual studies were not reported.

Some relevant information on the studies was tabulated. However, the tools used to measure the outcomes were not described for all outcomes, hence the validity of some outcome measures was unknown. The results from the individual studies were classified as increased, unchanged or reduced, but it was unclear whether these categories were based on statistically significant changes or not. A narrative synthesis was appropriate given the small number of studies, but the studies were combined without highlighting the better quality evidence and without taking account of the number of participants on which the evidence was based. However, the authors did analyse higher and lower quality studies separately, but these categories were not defined and the data were not reported.

The authors discussed some of the limitations of the review. In view of those highlighted above and the small number of men reported in a few trials, the evidence presented in the review was limited and the conclusions must be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that evidence from the review did not support the use of testosterone supplementation in healthy older asymptomatic men with normal to low testosterone levels. They further stated that testosterone may be
helpful for symptomatic men with symptoms due to low testosterone levels, and that a trial of testosterone in such men is reasonable unless there are contraindications. In addition, testosterone may help older men with marked reductions in their testosterone level, whether or not they have symptoms. The authors also stated that close monitoring is required in men receiving testosterone supplementation.

Research: The authors stated that well-designed, long-term placebo-controlled RCTs are required to determine the effectiveness of testosterone supplementation and its effects on function and quality of life.

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