Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials


CRD summary
This review concluded that testosterone use may be associated with a small positive effect on erectile dysfunction and a moderate improvement in libido, but the evidence was inconsistent and imprecise. Poor reporting about how different study designs were combined in the meta-analysis raises the possibility of bias in an otherwise well-conducted review. However, the authors’ cautious conclusions seem reliable.

Authors’ objectives
To evaluate the effect of testosterone on sexual function in men with sexual dysfunction and differing testosterone levels.

Searching
MEDLINE was searched to March 2005, while EMBASE and the Cochrane CENTRAL Register were searched to October 2004; the search terms were reported. The reference lists of reviews and eligible studies were also examined and a panel of experts was consulted.

Study selection

Specific interventions included in the review
Studies of any testosterone preparation versus placebo were eligible for inclusion. The types of testosterone in the review included: transdermal genital or nongenital patches (5 to 6mg/day) or gel (50 to 100mg/day); oral undecenoate (120 to 160mg/day) or micronised testosterone (400mg/day); transbuccal enanthate (10 to 20mg/day); and various intramuscular regimens. Testosterone was given for periods ranging from three weeks to 36 months.

Participants included in the review
Studies that enrolled hypogonadal men, or men with any testosterone level who were sexually dysfunctional, were eligible. The included participants formed two groups: those with low-normal or normal testosterone levels (mean age 38 to 65 years or older), and participants with low testosterone levels (mean age 35 to 66 years).

Outcomes assessed in the review
Eligible studies measured satisfaction with erectile function and/or with libido or overall sexual satisfaction. Studies that included only frequency of sexual function rather than satisfaction levels were not included in the primary analysis.

How were decisions on the relevance of primary studies made?
The studies were selected by reviewers working in pairs who consulted a third reviewer in the case of disagreement.

Assessment of study quality
The criteria for assessing study validity were randomisation method, adequacy of allocation concealment, blinding (participants, health care professionals, data collectors and outcome assessors) and extent of loss to follow-up. The assessment was conducted by reviewers working independently in pairs. Inter-rater reliability was checked.

Data extraction
The data were extracted by reviewers working in pairs using a standardised data extraction form. For continuous data, the standardised mean difference between groups and associated 95% confidence interval (CI) were calculated (difference in means divided by the pooled standard deviation). For dichotomous outcomes, the odds ratios reported by
the studies were converted to an effect size and standard error.

**Methods of synthesis**

**How were the studies combined?**
The data were pooled in a meta-analysis using a random-effects model.

**How were differences between studies investigated?**
Studies were analysed in two groups according to the participants’ testosterone level (low or low-normal/normal). Potential sources of heterogeneity were investigated by means of pre-specified subgroup analyses according to study quality, participant age and clinical characteristics, and type of intervention. Pre-specified sensitivity analyses were conducted to test the effect of varying the inclusion criteria for outcome measures. Statistical heterogeneity was tested by means of the I-squared statistic, which quantifies the amount of variability between studies that is likely to relate to between-study differences rather than chance.

**Results of the review**
The review included 15 randomised controlled trials (RCTs; 862 men), comprising eight parallel trials (781 men) and seven crossover trials (81 men). The 15 RCTs involved 17 comparison groups.

In general, the quality of the studies was limited. Only one study reported using allocation concealment. Blinding was fully reported in 4 studies, although all but one clearly or probably blinded the participants and treatment providers. Loss to follow-up exceeded 15% in 5 studies. The authors noted the possibility of reporting bias and publication bias.

Among men with low testosterone levels, testosterone had a large but not statistically significant effect on satisfaction with erection (effect size 0.80, 95% CI: -0.10, 1.60; 4 studies); there was a high level of inconsistency between the studies (I-squared 86%). The subgroup analysis showed a larger treatment effect in younger men (effect size 1.80, 95% CI: 1.00, 2.70; 2 studies) than among older men (effect size 0.10, 95% CI: -0.60, 0.80; 2 studies). Among men with low-normal or normal testosterone levels there was a small but statistically significant effect favouring testosterone over placebo for satisfaction with erection (effect size 0.34, 95% CI: 0.03, 0.65; 7 datasets from 6 studies). Inconsistency was very low (I-squared 5%).

Among men with low testosterone levels, testosterone had a large statistically significant effect on libido (effect size 1.31, 95% CI: 0.40, 2.35; 5 studies); there was a high level of inconsistency between the studies (I-squared >90%). Among men with low-normal or normal testosterone levels, there was no significant difference between the groups (5 datasets from 4 studies) and no inconsistency (I-squared 0%).

The meta-analysis found no significant effect of testosterone on overall sexual satisfaction, regardless of the testosterone level at baseline (10 studies).

Systematic subgroup and sensitivity analyses failed to explain inconsistencies between the groups. The outcomes did not differ significantly between the groups with low and low/normal testosterone levels at baseline.

**Authors’ conclusions**
Testosterone use may be associated with a small positive effect on erectile dysfunction and a moderate improvement in libido. Unexplained inconsistence between the studies, wide confidence intervals and possible reporting bias preclude more definite conclusions.

**CRD commentary**
The review objectives and inclusion criteria were clear, the search and validity assessment were thorough, adequate details were provided on the characteristics of the primary studies, and steps were taken to minimise bias in the review process. However, the review included data from crossover studies without specifying how these were dealt with in the meta-analysis, and also converted dichotomous results to continuous effect sizes without reporting the study results in their original format. This lack of statistical clarity raises the possibility of bias in an otherwise well-conducted review. Given this, the results of the meta-analysis should be treated with some caution. However, the authors’ conclusions reflect possible limitations of the review and seem reliable.
Implications of the review for practice and research
Practice: The authors stated that men with sexual dysfunction and clearly depressed testosterone levels should either avoid testosterone use or try it for a short period, as there is little evidence supporting its use and potential risk for harm (for evidence on harm the authors referred to another systematic review). An N-of-one trial may be a good option for individual patients considering the use of testosterone.

Research: The authors stated that researchers in this field should agree on valid patient-reported sexual outcomes measures such as the International Index of Erectile Function. Decision aids could be developed to help decision-making on the use of testosterone.

Funding
Mayo Foundation scholarship.

Bibliographic details

PubMedID
17285782

DOI
10.4065/82.1.20

Original Paper URL
http://www.mayoclinicproceedings.org/article/S0025-6196(11)60963-4/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Androgens /therapeutic use; Erectile Dysfunction /drug therapy; Hormone Replacement Therapy; Humans; Libido /drug effects; Male; Randomized Controlled Trials as Topic; Sexual Behavior /drug effects; Testosterone /deficiency /therapeutic use

AccessionNumber
12007005250

Date bibliographic record published
06/12/2007

Date abstract record published
01/12/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.