Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis

CRD summary
This review concluded that although haemoglobin and haematocrit increased and high density lipoprotein cholesterol decreased in men who received testosterone therapy, the clinical significance of these findings was unclear and the evidence base was deficient. The review had some limitations, but the authors were appropriately cautious regarding the reliability of the results given the limitations of the original studies.

Authors' objectives
To determine the adverse events associated with testosterone therapy in adult men.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 2003 to August 2008 without language restrictions. Studies published prior to 2003 were obtained from two existing systematic reviews (see Other Publications of Related Interest) augmented with a search to include previously excluded patients with HIV/AIDS. Reference lists and relevant experts were utilised as additional sources of information. Search terms were not reported but the search strategy was available on request from the authors.

Study selection
Comparative studies (randomised and non-randomised) of adult men with low or low-normal testosterone levels treated with any testosterone formulation were eligible for inclusion. Studies needed to be for at least three months and include a non-testosterone control group. Studies where testosterone was a cointervention with other hormones or drugs were ineligible.

Outcomes were specified in three categories: prostate outcomes (four measures and a composite outcome), cardiovascular events and cardiometabolic risk factors (12 outcomes) and indices of red cell mass (three outcomes). There was wide variation in patient setting, age, type and duration of intervention and length of follow-up across the studies. Details of the control interventions used were not provided for most studies.

Two reviewers independently assessed study eligibility. Discrepancies were resolved by consensus or arbitration.

Assessment of study quality
The study quality assessment evaluated randomisation sequence generation, allocation concealment, baseline imbalance, blinding, attrition, intention to treat and imputation methods.

Assessment was performed by two independent reviewers. Discrepancies were resolved by consensus or through arbitration.

Data extraction
Event rates and sample sizes were extracted in duplicate. Risk ratios and associated 95% confidence intervals were calculated. Mean values, sample sizes and standard deviations were extracted to calculate weighted mean differences (WMD) for continuous outcomes. Data were extracted from the longest time point where multiple time points were presented.

Study authors were contacted for clarification of methods and for missing data.

Methods of synthesis
Studies were pooled using meta-analysis (DerSimonian and Laird random-effects model). Heterogeneity was measured with $\chi^2$. Subgroup analyses were performed on patient age, testosterone level, formulation, route of administration and dose, duration of follow-up, loss to follow-up, concealment of allocation and blinding. Peto odds ratio and different continuity correction factors were analysed to assess sensitivity.
Results of the review
Fifty-one randomised controlled trials (2,701 patients, range 10 to 406) were included. Treatment duration ranged from three months to three years. Studies had high to medium risk of bias. Losses to follow-up ranged from zero to 45%. Allocation concealment was not reported in more than half of the included studies. Three trials had no blinding. Results for baseline imbalance and intention to treat were not reported. Five additional studies were relevant but did not report outcomes sufficiently for inclusion in meta-analyses.

Testosterone treatment was associated with an increase in haemoglobin (WMD 0.80g/dL, 95% CI 0.45 to 1.14), haematocrit (WMD 3.18%, 95% CI 1.35 to 5.01) and erythrocytosis (RR 3.15, 95% CI 1.56 to 6.35) and a decrease in high density lipoprotein cholesterol (WMD -0.49mg/dL, 95% CI -0.85 to -0.13). There was no significant effect on mortality, prostate or cardiovascular outcomes.

Heterogeneity was generally high and was explained partly by dose and route of testosterone administration.

Authors’ conclusions
Adverse events associated with testosterone therapy were increases in haemoglobin and haematocrit and a small decrease in high density lipoprotein cholesterol. The clinical significance of these findings was unclear. The evidence-base was deficient because of low-quality studies with inadequate duration.

CRD commentary
This review used appropriate methods to minimise bias when identifying, selecting and synthesising studies. Study quality, inadequate follow-up and potential reporting bias all introduced uncertainty. Numerous subgroup analyses were performed to explore the high heterogeneity. Judicious interpretation suggested that dose and route of testosterone administration merited further investigation as reasons for variation in adverse events. Results for some of the study quality criteria were not reported and there was a lack of reporting of control interventions, which made interpretation of the data more difficult.

The review had some limitations, but the authors were appropriately cautious about the reliability of the results given the limitations of the original studies.

Implications of the review for practice and research
Practice: The results supported guidance that haemoglobin and haematocrit should be monitored in androgen-deficient men receiving testosterone therapy.

Research: Studies were needed to assess patient-important outcomes of longer duration and follow-up as the available evidence was insufficient to weigh up the relative benefits and harms of testosterone treatment.

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