Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis

Whitsel E A, Boyko E J, Matsumoto A M, Anawalt B D, Siscovick D S

Authors' objectives
To determine whether intramuscular administration of testosterone esters to hypogonadal men is associated with changes in plasma lipids.

Searching
MEDLINE was searched from 1966 to 1999, and Current Contents from July to December 1999. The full search strategy was reported in the paper. Studies reported in any language were considered. Two experts in the field screened the articles identified by the search for possible omissions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-experimental studies were eligible for inclusion. The authors defined quasi-experimental as studies in which pre-treatment measures were recorded on a single group of patients who later received a treatment, after which post-treatment measurements were recorded.

Specific interventions included in the review
Intramuscular testosterone ester. The dosage of testosterone ester ranged from 50 to 250 mg every 7 to 30 days, for a duration of 1 to 24 months.

Participants included in the review
Male patients with non-experimental hypogonadism.

Outcomes assessed in the review
Studies which reported pre- and post-treatment concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, or total triglyceride were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers determined by consensus which articles met the inclusion criteria for the review.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors do not state how many of the reviewers performed the data extraction.

The following data were extracted from the studies: name of the first author; publication year; sample size; design of study; age (mean); the percentage of patients with primary hypogonadism, as defined by study-specific criteria; total plasma testosterone; serum estradiol and plasma lipid concentrations; the type and dosage of testosterone ester, and the frequency and duration of treatment.

The raw mean and variance of the difference (post-treatment minus pre-treatment) in each plasma lipid subtype was calculated for each study.

Methods of synthesis
How were the studies combined?
The study-specific differences were combined using fixed-effect models and weighted random-effects models (see Other Publication of Related Interest no.1). The authors reported weighted mean difference (WMD) with 95% confidence intervals (CIs). The strength of the association between the mean difference and pertinent characteristics was measured using the correlation coefficient (r).

How were differences between studies investigated?
Between-study homogeneity was tested prior to pooling. The authors determined whether heterogeneity of the means could be explained in fixed-effect and random-effects models of mean difference on study and patient characteristics (see Other Publications of Related Interest nos.2-3) before and after excluding outlying observations, which were identified using a multiple-outlier procedure (see Other Publications of Related Interest no.4).

Results of the review
Nineteen studies (n=272) were eligible for inclusion in the review: 4 RCTs, of which 2 included a placebo treatment group, and 15 quasi-experimental studies.

Fixed-effect models demonstrated that the concentrations of total cholesterol (WMD -14 mg/dL, 95% CI: -17, -11), LDL cholesterol (WMD -5 mg/dL, 95% CI: -8, -1) and HDL cholesterol (WMD -4 mg/dL, 95% CI: -5, -2) decreased significantly after treatment, but that the concentration of triglyceride did not change (WMD -1 mg/dL, 95% CI: -6, 4).

For each lipid subtype, the study-specific differences were heterogeneous. Combining the differences in a weighted random-effects model meant that only total cholesterol (WMD -12 mg/dL, 95% CI: -22, -2) and HDL cholesterol (WMD -4 mg/dL, 95% CI: -6, -2) decreased significantly. The exclusion of a single study with an outlying pre-treatment HDL cholesterol concentration removed the heterogeneity in the remaining studies (fixed-effect WMD -3 mg/dL, 95% CI: -4, -2).

The post-treatment minus pre-treatment difference in HDL cholesterol varied inversely with testosterone dosage 9 = -0.53, p=0.055). Therefore, decreases in HDL cholesterol were larger at lower dosages of testosterone ester. These were not explained by attrition, regression to the mean, dosing frequency or duration, concomitant elevation of plasma total testosterone, aromatisation of testosterone to estradiol, or other study or patient characteristics.

Authors' conclusions
Intramuscular administration of testosterone esters to hypogonadal men was associated with a small, dosage-dependent decrease in HDL cholesterol and concomitant declines in total cholesterol and LDL cholesterol. The aggregate effect of these changes on cardiovascular risk remains unknown but deserves further study.

CRD commentary
The authors addressed a clear review question and reported good inclusion criteria. The search was fairly comprehensive and there were no language restrictions. It is unlikely that important publications were missed. The study selection and data extraction processes were described, but the number of reviewers who extracted the data was not specified. The validity of the included studies was not assessed. Details of the studies were tabulated clearly. The method of pooling appears to have been appropriate, and heterogeneity was investigated using random-effects models.

The authors' conclusions follow on from the results of the review.

Implications of the review for practice and research
The authors did not state any implications for further research and practice.

Funding
National Heart, Lung and Blood Institute and the Veterans Affairs Puget Sound Health Care System Health Services Research and Development Postdoctoral Fellowship Program, National Research Service Award, contract 5-T32-HL07055.
**Bibliographic details**

**PubMedID**
11566455

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Cholesterol, HDL /blood; Dose-Response Relationship, Drug; Humans; Hypogonadism /blood /drug therapy; Injections, Intramuscular; Lipids /blood; Male; Testosterone /administration & dosage

**AccessionNumber**
12001002345

**Date bibliographic record published**
30/11/2002

**Date abstract record published**
30/11/2002

**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.