Protocol: Testosterone therapy and obesity among men and women: a systematic review and meta-analysis of randomized controlled trials

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**Introduction**

Observationally higher serum testosterone is associated with less central adiposity (1-3). Observational studies are open to uncontrollable confounding by socio-economic factors, health behavior and physiological changes with aging and ill-health. As such, it is difficult to know whether these observations mean that testosterone protects against obesity. Reviews and expert advice warn that testosterone is inversely associated with BMI (4), making self-medication with testosterone an attractive option. Currently, testosterone replacement is heavily promoted (5) and increasingly widely used (6, 7).

The most up-to-date meta-analysis of RCTs of testosterone therapy amongst middle-aged men suggests that testosterone treatment reduced total body fat by 1.6kg (95% CI: 2.5 - 6) (8).

**Review Question**

What is the effect of testosterone therapy on obesity?

**Eligibility criteria**

Studies will be eligible if they meet all the following criteria

- RCT of testosterone therapy compared with a placebo. Given, that many of these trials are in older people with chronic diseases, we will include trials where there is a comparison of testosterone therapy with placebo against the background of other drug use as long as the groups only differ in their use of testosterone.
- Duration of at least 4 weeks to ensure testosterone has had its full effects.
- Participants are adults, because hormone levels are different in children.
- Published study or registered trial where we are able to track down the results.
- Any date, because there is no reason to think that the effect of testosterone has changed over the years.
- Any setting, because there is no reason to think that the effect of testosterone varies by setting.
- Reported in English, because a preliminary search of the literature suggests most studies are in English.
- Provides information explicitly on at least one CVD risk factor by study arm.

We will consider total obesity and central obesity, because of the observational evidence linking low testosterone to central obesity (2-4). The outcomes considered will include

1. Total obesity
2. Central adiposity measured by waist circumference, DEXA or MRI

**Information Sources**

We will search the literature databases PubMed (1950-June 2013), EMBASE (1974-June 2013), Web of Science (1900-June 2013), as well as the WHO International Clinical Trials Registry for trials of testosterone therapy reporting any of the CVD risk factors given. The reference lists of all included articles and relevant reviews on this topic will be reviewed to identify additional studies not found through the database searches. In addition, Web of Science will be used to review citing articles of included studies where available. Where we find one report on a trial that gives one measure of obesity we will check all other publications on that same trial for reports concerning other measures of obesity. Where we find duplicate publications from the same trial we will include the most up-to-date relevant information. In cases where relevant trials are identified through the trial registry, but results have not been published in the literature, we will contact the trial investigators to request the results of their study.
Search
The complete search strategies used are presented in Appendix 1. Except in cases of database-specific syntax, search terms to describe obesity and testosterone will be identical across all databases. Wherever possible, database subject headings will be used. Validated filters for identifying clinically sound treatment studies will be applied to each search (9, 10). We will search for the terms (“placebo-controlled”) and (“trial”) in title, abstract or any field, because RCTs are not always tagged as such (11). The terms (“testosterone” or “androgen”) will be used to search the trial registry.

Study selection
Two people will search independently and compare their selections at the end of the search process. Any differences will be resolved by consensus or if necessary by reference to a third investigator. We will not exclude studies based on the number of participants, because we want to make full use of the evidence available. We will not exclude by participant characteristics’, because testosterone is used in a wide variety of people, and there is no reason to think that testosterone has different effects by sub-group.

Selection process
After the first automated query in the databases, we will use a three-step process for screening. First, we will screen the titles, and discard any study that can be excluded purely based on title. Secondly, we will screen the abstracts and exclude any study that can be excluded purely based on abstract. Thirdly, we will screen the remaining publications on the basis of the corresponding full text reports of obesity by trial arm.

Data extraction
An investigator will abstract data from the selected studies, using a standard template. A second investigator will check all the extracted data.

We will not contact authors for confirmation of their published numbers because we assume the authors would have corrected or withdrawn their papers if a major error came to light. We will contact the authors twice for clarification, if necessary. In the event of no response we will make conservative assumptions.

Data items
We will extract the following information for each trial

- Publication details (author, year of publication, title, journal)
- Study population, including number by study arm, sex, health status, age and setting
- Primary study outcome
- Duration of follow-up
- Number of participants in each arm at start and end (testosterone and placebo groups)
- Type of testosterone
- Mean and standard deviation of CVD risk factors by trial arm at the start and finish of the trial.
- Funding source
- Affiliations and competing interests of investigators
- Trial implementation and reporting including information on
  - randomization
  - treatment allocation
- comparison of groups at baseline
- trial eligibility criteria
- ‘blinding’ of outcome assessors, care providers, adverse event assessors and participants
- Type of analysis, intention to treat, per-protocol or other

**Bias assessment for individual studies**
We will use the Jadad scoring system (12) to assess the methodological quality of each RCT. Two investigators will independently rate each study and settle any differences by consensus or reference to a third investigator.

**Summary Measure**
The principal summary measure will be a pooled weighted mean difference of pre- to post-treatment differences for continuous outcomes and a measure of relative risk for dichotomous outcomes.

**Synthesis of results**
We will obtain the weighted mean difference for obesity and central adiposity for testosterone versus placebo using inverse variance weighting with random or fixed effects depending on the heterogeneity between trials. We will obtain a measure of relative risk using a Mantel-Hazal estimator. We will use meta-analysis regression, with inverse variance weighting, to assess whether the effects of testosterone therapy varies by specified sub-group. Heterogeneity will be assessed using the $I^2$ statistics. $I^2$ is the proportion of total variation observed between the trials attributable to differences between trials rather than to sampling error (chance), with values less than 30% representing low variation, less than 60% moderate variation, and greater than 60% high variation.

**Bias Assessment for all studies**
We will use funnel plots to assess publication bias. We will use the trim and fill method to assess the impact of publication bias on the pooled effect.

**Subgroup analysis**
We will do sub-group analysis primarily by sex and source of funding. Although it is unusual for the effect of the same hormone to vary by sex (13), we cannot rule it out. A previous meta-analysis of the effects of testosterone therapy on cardiovascular-related events found different associations by source of funding (14). We will also do sub-group analysis by age, type of testosterone, dose of testosterone and baseline testosterone, if possible.

**Statistical analysis**
We will use R to do the analysis, using functions, such as ‘metacont’ and ‘metabin’ from the R package ‘meta’, and ‘rma’ from the R package ‘metafor’ (R Development Core Team, Vienna, Austria).
References

Appendix 1: Search Strategies

**Pubmed**
(testosterone[MeSH Terms] OR testosterone* OR androgens[MeSH Terms] OR androgen*) AND
("Obesity"[Mesh] OR obesity OR obese OR "Body Weight"[Mesh] OR "Body Weight" OR "Body Mass
Index"[Mesh] OR BMI OR "body mass" OR "Adiposity"[Mesh] OR adiposity OR "Waist-Hip Ratio"[Mesh] OR
"Waist-Hip Ratio" OR "Skinfold Thickness"[Mesh] OR "skinfold thickness") AND ("randomized controlled
trial"[ptyp] OR Randomized OR Randomized OR placebo)

**Embase (OvidSP)**
1. exp testosterone/
2. testosterone$.mp.
3. exp androgen/
4. androgen$. mp.
5. 1 or 2 or 3 or 4
6. exp obesity/
7. obese.mp.
8. obesity.mp.
9. exp body mass/
10. body mass.mp.
11. BMI.mp.
12. exp body weight/
14. adiposity.mp.
15. exp waist-hip ratio/
16. waist-hip ratio.mp
17. exp skinfold thickness/
18. skinfold thickness.mp
19. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
21. placebo.mp.
22. double-blind.tw.
23. 20 or 21 or 22
24. 5 and 19 and 23

**Medline in Process (OvidSP)**
1. testosterone$.mp.
2. androgen$.mp.
3. 1 or 2
4. obesity.mp.
5. obese.mp.
6. BMI.mp.
7. Body Weight.mp.
8. body mass.mp.
9. adiposity.mp.
10. waist-hip ratio.mp
11. skinfold thickness.mp
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Randomized.mp.
14. Placebo.mp.
15. Double-blind.mp.
16. 13 or 14 or 15
17. 3 and 12 and 16

Web of Science
1. Topic=(testosterone*) OR Topic=(androgen*)
2. Topic=(obes*) OR Topic=(BMI) OR Topic=("body weight") OR Topic=("body mass") OR Topic=(adiposity) OR Topic=("waist-hip ratio") OR Topic=("skinfold thickness")
3. Topic=(randomized) OR Topic=(placebo*) OR Topic=("double-blind")
4. #3 AND #2 AND #1

WHO International Clinical Trials Registry Platform
Testosterone OR Androgen