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Effect of atorvastatin on testosterone levels (Protocol)

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[Intervention Protocol]

Effect of atorvastatin on testosterone levels

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effect of treatment with atorvastatin on serum testosterone in males and females and the effects of various doses of atorvastatin on withdrawals due to adverse effects.

BACKGROUND

Testosterone, C_{19} H_{28} O_2, is the main male sex hormone and plays a crucial role in several bioprocesses, particularly, in males such as regulating sex drive and the production of sperm. Testosterone is also involved in regulating some other functions in both males and females, for example, bone mass, muscle mass and strength, fat distribution, and the production of red cells (Finkelstein 2013).

Testosterone circulates in the blood in three different forms: as testosterone firmly attached to sex hormone binding globulin (SHBG) (roughly 45% of total testosterone), which is biologically inactive; as free testosterone (approximately 2% to 3% of total testosterone); and as testosterone weakly bound to other proteins, mainly albumin (approximately 50% of total testosterone). Both free testosterone and testosterone attached to albumin are bioavailable for use by tissues (Dunn 1981).

Bioavailable and free testosterone are better measures than total serum testosterone to diagnose abnormal androgen status and their clinical sequelae. However, bioavailable and free testosterone tests are time-consuming, expensive and not always available. Therefore, determining total testosterone level, which is easy and relatively cheap, is commonly used to diagnose overt male hypogonadism. However, it is an unreliable marker in patients who have total testosterone levels just below the normal range or in the low-normal range. To overcome this issue and provide a more reliable indicator, some researchers use the SHBG and total testosterone with a formula to calculate an approximate estimate of bioavailable or free testosterone (Stanworth 2008).

The normal ranges of the serum total testosterone are significantly higher in adult men than adult women and vary widely depending on various factors, including the laboratory methods used and age. There is a significant increase in total testosterone in males after puberty and approximately 1% reduction in total testosterone per year in males over thirty years old (Brawer 2004; Pagana 2015; Feldman 2002; refer to Table 1).

Studies and reports suggest that low serum testosterone in men is associated with health problems, such as reduction in fertility and decreased libido. Low testosterone in both males and females can increase body fat and the incidence of depression. It can also decrease mass and strength of muscles, decrease body hair, decrease the production of red cells leading to anaemia, and decrease bone density (Demers 2010). Furthermore, some studies have suggested a link between low serum testosterone in males and an increased incidence of prostate cancer (Mearini 2013).

Description of the condition

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, a class of drugs mainly prescribed to lower blood cholesterol. They are widely used in adult patients for secondary and primary prevention of cardiovascular events (Stone 2014). They are also used to lower cholesterol in people of all ages with heterozygous familial hypercholesterolaemia and mixed dyslipidaemia Schaiff 2008. They are considered to be a highly effective class of drugs in reducing low-density lipoprotein (LDL) cholesterol (Schaiff 2008). Statins are also used to treat women with polycystic ovary syndrome (Sun 2015).

Description of the intervention

Atorvastatin is the most prescribed member of the statin class, which are among the most commonly prescribed medications worldwide (Ioannidis 2014; IQVIA 2017). In Canada, approximately 3 million people aged 20 to 79 (12%) have taken a statin during the period 2007 to 2011 and one in four Canadians are potentially eligible for statin treatment (Hennessy 2016). Studies illustrate that long-term statin therapy in secondary prevention significantly reduces all-cause mortality and major adverse cardiovascular events (myocardial infarction (MI), and stroke). However, it remains controversial whether they reduce mortality in primary prevention patients (Vrecer 2003).

Atorvastatin is rapidly absorbed after oral administration; reaching peak plasma concentration within one to two hours. Atorvastatin is extensively metabolised by cytochromes P-450 3A4 and P-450 3A5 to two active metabolites ortho- and para hydroxylated derivatives, which contribute to approximately 70% of the inhibitory activity for HMG-CoA reductase. These two active metabolites also increase the half-life of inhibitory activity for HMG-CoA reductase (about 20 to 30 hours). A Cochrane Review shows that atorvastatin 2.5 mg/day to 80 mg/day reduces total blood LDL-cholesterol by between 27.3% and 52%, respectively (Adams 2015; FDA 2011).
Although atorvastatin is generally well tolerated, it is associated with potential adverse effects. Such adverse effects can be divided into two groups: minor adverse effects, such as headache, nausea, vomiting, constipation, diarrhoea, and rash, and more serious adverse effects, such as statin-associated muscle symptoms, ranging from muscle pain and weakness to rhabdomyolysis, new onset diabetes mellitus, and an increase in hepatic transaminases (Thompson 2016).

How the intervention might work

Atorvastatin inhibits the enzyme that converts HMG-CoA into a cholesterol precursor called mevalonic acid in hepatocytes. Atorvastatin molecules bind reversibly to the active site, change the conformation of the enzyme, which leads to preventing the enzyme from acquiring a functional structure. Inhibition of HMG-CoA reductase, leads to a decline in the intracellular cholesterol, resulting in the activation of a protease which cleaves the sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum. SREBPs, in their turn, are translocated in the nucleus and increase the gene expression for LDL receptors in hepatocytes, which leads to a reduction of the circulating LDL and both intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL), precursors for LDL (Stancu 2001).
Atorvastatin decreases the availability of cholesterol, which is a crucial substrate for testosterone production, and may lead to a decline in serum testosterone (Schooling 2013).

Why it is important to do this review

Due to the widely increasing use of atorvastatin and the important role of serum testosterone in both men and women, concerns have been raised about the influence of atorvastatin on serum testosterone in men and women. A non-Cochrane systematic review, conducted by Schooling 2013, attempted to address the effect of statin therapy on testosterone. However, this review is out of date and several concerns regarding this review have been identified. These include its search strategy had language limitations (English language only); database search was limited to MEDLINE and ISI web; the risk of bias for each included study was not assessed; and the review was limited to adults. Furthermore there are some potential errors in the data. At present, there is no Cochrane Review available which has addressed this important question.

OBJECTIVES

To assess the effect of treatment with atorvastatin on serum testosterone in males and females and the effects of various doses of atorvastatin on withdrawals due to adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include randomised controlled trials of at least three weeks duration.

Types of participants

Participants may be of any age, with and without evidence of cardiovascular disease. They can have normal lipid parameters or any type of hyperlipidaemia or dyslipidaemia. We will include participants with various comorbid conditions, including type 2 diabetes mellitus, hypertension, metabolic syndrome, chronic renal failure, polycystic ovary syndrome, or cardiovascular disease.

Types of interventions

Atorvastatin (2.5 mg/day to 80 mg/day) administered at a daily dose for at least three weeks duration compared to placebo or no treatment. We have chosen this time window to allow at least three weeks for a steady-state effect of atorvastatin to occur.

Types of outcome measures

Primary outcomes

- Mean percentage change of total testosterone from baseline of different doses of atorvastatin minus mean percentage change from baseline with placebo in males and females
- End of treatment total testosterone of different doses of atorvastatin minus end of treatment total testosterone with placebo in males and females

Secondary outcomes

- Mean percentage change from baseline or end of treatment sex hormone binding globulin (SHBG) concentration; testosterone/SHBG ratio; and serum free testosterone for different doses of atorvastatin minus the same value for placebo in males and females
- Withdrawals due to adverse effects

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist will search the following databases without language or publication status restrictions.

- Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web).
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web).
- MEDLINE Ovid, MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (from December 2013).
- Embase Ovid (from December 2013).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (www.who.it.trialsearch).

The subject strategies for databases will be modelled on the search strategy designed for MEDLINE in Appendix 1. Where appropriate, these will be combined with subject strategy adaptations of the sensitivity- and precision-maximising search strategy designed by Cochrane for identifying randomised controlled trials (RCTs) (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Box 6.4.d; Higgins 2011)). We will screen references from a related Cochrane Hypertension Review (Adams 2015), therefore we will run database searches from December 2013, the last month in which searches were run for that review.

Searching other resources

- The Hypertension Information Specialist will search the Hypertension Specialised Register segment (which includes searches of MEDLINE, Embase and Epistemonikos for systematic reviews) to retrieve published systematic reviews related to this review title, so that we can scan their reference lists to identify additional relevant trials. The Specialised Register also includes searches of CAB Abstracts and Global Health, CINAHL, ProQuest Dissertations and Theses and Web of Science.
- We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.
- We will contact experts/organisations in the field to obtain additional information on relevant trials.
- We may contact original authors for clarification and further data if trial reports are unclear.
- We will also search the following resources for additional information.
    - Pfizer website (www.pfizer.ca/en/our_products).
    - US Food and Drug Administration website (www.fda.gov).
    - European Patent Office website (worldwide.espacenet.com).

Data collection and analysis

Selection of studies

Initial selection of trials will involve retrieving and reading the titles and abstracts of each paper found from the electronic search databases or bibliographic citations. We will provide a PRISMA flow diagram. Two review authors (BB, MIS) will analyse the full text papers independently, to decide on the trials to be included. We will resolve disagreements by recourse to a third review author (VM, JMW or SA). Two review authors (BB, MIS) will independently extract the appropriate data from each of the included trials. If there is disagreement over a value, we will reach consensus by data recalculation and involving a third review author (VM, JMW or SA) to determine the correct value.

Data extraction and management

We will directly extract the mean percentage change from the data or will calculate it from the baseline and endpoint values. We will add the calculated data to the 'Data and analyses' section of the review. If the calculated data differ from the given data by more than 10%, we will move the trial to the 'Excluded studies' section. We will extract standard deviations and standard errors from the report and calculate them when possible. In the event of no standard deviation data, we will impute it as was done in Adams 2015. We will enter data from placebo-controlled randomised trials as continuous data (measurement of total testosterone level; hormone binding globulin concentration; testosterone/SHBG ratio; and the level of free testosterone), or as dichotomous data (withdrawal due to adverse effects) using Review Manager 5 (RevMan 2014).

Assessment of risk of bias in included studies

MIS and BB will independently assess the risk of bias of each included study using the 'Risk of bias' tool. We will assess seven domains: adequate sequence generation; allocation concealment; blinding of participant and physician, blinding of outcome assessor; incomplete outcome reporting; selective reporting of outcomes; and other potential sources of bias, including funding information of each trial. We will resolve disagreements by recourse to a third review author (VM, JMW or SA). We will produce 'Risk of bias' tables as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8 (Higgins 2011). We will report this information in the 'Risk of bias' tables associated with each included trial.

Measures of treatment effect

We will summarise continuous outcomes (measurement of total testosterone level; sex hormone binding globulin (SHBG) concentration; testosterone/SHBG ratio; and the level of free testosterone) using mean differences (MDs) with 95% confidence intervals (CIs). We will summarise dichotomous data (withdrawal due to adverse effects) using risk ratios (RRs) with 95% CIs.

Unit of analysis issues

The unit of analysis will be the mean changes from baseline for the people completing the trial for each trial. We expect follow-up to be reasonably high for these short-term trials.

Dealing with missing data

When data are missing we will request them from the authors. The most common type of value that is not reported is the standard deviation (SD) of the change.

In the case of a missing SD for the change in the outcomes, we will impute the SD using the following hierarchy (listed from high to low preference).

- SD of the baseline or end of treatment value.
- Average weighted standard deviation of the change from other trials in the review (Furukawa 2006).

Because it is common for the SD to be miscalculated and in order not to overweight trials where it is inaccurately calculated and lower than expected, when SD values are less than 40% of the average weighted SDs, we will use the imputed value as used in Furukawa 2006.

Assessment of heterogeneity

The Chi^2 test to identify heterogeneity is not appropriate because it has low power when there are few studies but has excessive power to detect clinically unimportant heterogeneity when there are many studies; the I^2 is a better statistic. I^2 calculates between-study variance/(between-study variance + within study variance. This measures the proportion of total variation in the estimate of the treatment effect that is due to heterogeneity between studies. This statistic is also independent of the number of studies in the analysis (Higgins 2002). If $I^2 \geq 50\%$, we will use the random-effects model to assess whether the pooled effect is statistically significant and attempt to explore the cause of the heterogeneity (Adams 2016).

Assessment of reporting biases

If 10 or more studies meet the inclusion criteria, we will assess publication bias using funnel plots, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 10 (Sterne 2011).

Data synthesis

We will enter all placebo-controlled studies into Review Manager 5 as MDs using fixed-effect model data to determine the weighted treatment effect and 95% CIs for all outcomes (RevMan 2014). If $I^2 \geq 50\%$, we will use the random-effects model to assess whether the pooled effect is statistically significant. In the case when RCTs evaluate several doses of atorvastatin, we will divide participants

in the control group by the number of groups in order to avoid double-counting. Throughout, we will use 95% CIs. In addition, we will carry out a sensitivity analysis based on different levels of bias to address differences in risk of bias in the analyses.

'Summary of findings' tables

We will use the GRADE approach to assess the certainty of the supporting evidence behind each estimate of treatment effect (Schünemann 2011a; Schünemann 2011b). We will present key findings of the review, including a summary of the amount of data, the magnitude of the effect size, and the overall certainty of the evidence in a 'Summary of the findings' table. We have preselected the following important outcomes for inclusion in the 'Summary of the findings' table: the effect of atorvastatin on serum total testosterone, free testosterone, testosterone/SHBG ratio, and withdrawal due to adverse effects.

We will use GRADEpro GDT software to generate the 'Summary of findings' table (GRADEpro GDT 2015). We will consider five factors in grading the overall certainty of evidence: limitations in study design and implementation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision in results, and high probability of publication bias. This approach specifies four levels of certainty: high-, moderate-, low-, and very low-certainty evidence. The highest certainty rating is for RCT evidence. The certainty rating is downgraded by one level for each factor, up to a maximum of three levels for all factors. If there are severe problems for any one factor (when assessing limitations in study design and implementation, in concealment of allocation, or attrition over 50% of participants during follow-up), randomised trial evidence may fall by two levels due to that factor alone.

Subgroup analysis and investigation of heterogeneity

We will analyse subgroups based on the following factors.

- According to various doses.
- Males versus females.
- Age $\geq$ 60 years versus < 60 years.
- Children (age < 18 years) versus adult ($\geq$ 18 years).

We will assess heterogeneity using the I^2 statistic (Higgins 2002). If $I^2 \geq 50\%$ we will attempt to identify possible causes of heterogeneity by carrying out a number of planned subgroup analyses, provided there are sufficient numbers of trials (see below).

Sensitivity analysis

We will test the robustness of the results by performing several sensitivity analysis including:

- trials with low risk of bias versus high risk of bias; and
- trials with reported SDs of change versus imputed SDs of change.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Total testosterone and free testosterone levels by sex and age

Tests of blood: normal findings		
	Free testosterone pg/mL	
Age/Tanner stage	Male	Female
Postmenopausal		0.6-3.8
7 months-9 years (Tanner stage I)	≤ 3.7	< 2.2
10-13 years (Tanner stage II)	0.3-21	0.4-4.5
14-15 years (Tanner stage III)	1.0-98	1.3-7.5
16-17 years (Tanner stage IV)	35.0-196	1.1-15.5
18-19 years (Tanner stage V)	41.0-239	0.8-9.2
	Free testosterone %	
Adult male	1.6-2.9	
Adult female	0.1-0.3	
	Total testosterone ng/dL	
	Male	Female
7 months-9 years (Tanner stage I)	< 30	< 30
10-13 years (Tanner stage II)	< 300	< 40
14-15 years (Tanner stage III)	170-540	< 60

Table 1. Total testosterone and free testosterone levels by sex and age (*Continued*)

16-19 years (Tanner stage IV, V)	250-910	< 70
20 years and over	280-1080	< 70
	Dihydrotestosterone	
Adult male	240-650 pg/mL	
Adult female	≤ 300 pg/mL	

Total testosterone and free testosterone levels by sex and age Pagana 2015.

APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) <1946 to Present with Daily Update>, Ovid MEDLINE(R) Epub Ahead of Print <April 27, 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 27, 2018>

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1 atorvastatin calcium/

2 (atorvastatin$ or atorlip or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or lipitor or liprimar or liptonorm or lowlipen or sortis or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).tw,kf.

3 or/1-2

4 randomized controlled trial.pt.

5 controlled clinical trial.pt.

6 randomized.ab.

7 placebo.ab.

8 drug therapy.fs.

9 randomly.ab.

10 trial.ab.

11 groups.ab.

12 or/4-11

13 animals/ not (humans/ and animals/)

14 12 not 13

15 3 and 14

16 15 and (2013 12$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$).dt.

CONTRIBUTIONS OF AUTHORS

MIS, BB, VM, SPA and JMW contributed to the design of the protocol.

DECLARATIONS OF INTEREST

Muhammad Ismail Shawish: nothing to declare.

Bahador Bagheri: nothing to declare.

Vijaya Musini: nothing to declare.

Stephen Adams: nothing to declare.

James Wright: nothing to declare.

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