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Statin therapy and plasma cortisol concentrations: A systematic review and meta-analysis of randomized placebo-controlled trials

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ABSTRACT

This study aimed to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) in order to calculate the effect size of statin therapy in changing plasma cortisol concentrations. Following a systematic search in Medline, SCOPUS, Web of Science and Google Scholar databases (by up to March 01, 2015), 7 eligible RCTs were selected. Random-effects meta-analysis suggested a significant increase in plasma cortisol concentrations following statin therapy (WMD: 6.34%, 95% CI: 1.80, 10.87, $p = 0.006$). Subgroup analysis confirmed the significance of the effect with lipophilic statins comprising atorvastatin, simvastatin, and lovastatin (WMD: 7.00%, 95% CI: 2.21, 11.79, $p = 0.004$) but not with hydrophilic statins (rosuvastatin and pravastatin) (WMD: 0.60%, 95% CI: −13.46, 14.66, $p = 0.933$). In the meta-regression analysis, changes in plasma cortisol concentrations following statin therapy were found to be independent of treatment duration. Results of this meta-analysis of RCTs suggest a significant elevation in plasma cortisol levels following statin therapy.

1. Introduction

Owing to their effective plasma low-density lipoprotein (LDL) lowering, statins have been used for primary and secondary prevention of cardiovascular events for several years. Statins act through inhibition of the key enzyme in the cholesterol biosynthesis pathway—3-hydroxy-3-methylglutaryl-CoA reductase. Statins have been uniformly reported to reduce cardiovascular endpoints and mortality in both primary and secondary prevention trials [1,2]. Statin-induced plasma cholesterol lowering seems to be more likely mediated by an increased hepatic intake of LDL particles, which is itself due to the up-regulation of hepatic LDL receptors, than the reduction of endogenous cholesterol synthesis [3,4].

Apart from their beneficial effects in reducing cardiovascular morbidity and mortality [5], statins possess several pleiotropic effects that are independent of the putative lipid-modifying effects of this class of drugs [6]. The most well-known pleiotropic actions of statins include anti-inflammatory, antioxidant and immunomodulatory effects [7,8] In this manner, statins can improve endothelial function by promoting the production of endothelial nitric oxide (NO) by eNOS both through cholesterol-dependent and -independent pathways [9]. Statins can also inhibit the expression of crucial cell adhesion molecules (e.g. VCAM-1 and E-selectin) involved in the inflammation of endothelium during atherogenesis beyond the lipidlowering effects [10,11], inhibit T-lymphocyte activation [12], reduce increased levels of high-sensitivity C-reactive protein (hsCRP) as demonstrated in JUPITER study [13], improve plaque composition [14], plus a variety of other positive effects on the biomarkers of vascular homeostasis and systemic coagulation [15].

With respect to the molecular mechanism, these pleiotropic effects seem to be mediated by reduced synthesis of mevalonate and isoprenoids, the important lipid anchors for many proteins involved in cell metabolism. Indeed, statins at clinically relevant concentrations are able to inhibit isoprenylation of small GTPases (e.g. Rho-family) resulting in up-regulation of NO production, inhibition of smooth muscle cell proliferation and inhibition of macrophage activity and accumulation in the vessel wall [16,17].

Cortisol, the leading member of glucocorticoids, is a steroid hormone derived from the conversion of cholesterol by an enzymatic

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

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side chain cleavage mediated by the P450 cytochrome [18]. Cortisol production and secretion is regulated by a hypothalamic-pituitary axis, specifically by the adrenocorticotrophic hormone with a negative feedback on its production when the cortisol concentrations reach sufficient levels. Cortisol circulates in plasma either in its free (active) form or in its inactive form, reversibly bound to its carrier proteins [19]. Because of its lipophilic nature, cortisol can enter the cell and modulate gene expression [20].

Apart from their metabolic, immunomodulatory and cardiovascular effects, glucocorticoids have been described to have a role in the stress response, maintaining the stress-related homeostasis. The stress response is associated with a rise in serum cortisol levels, which in turn cover the demands of the body for glucose supply to insulin-dependent cells, maintain heart and vessel reactivity during the stress period and modulate the stress immune response [21]. Glucocorticoids and cortisol are potent anti-inflammatory agents. Several lines of evidence have demonstrated inhibition of pro-inflammatory cytokines production, suppression of COX-2 and iNOS expression and inhibition of cell adhesion molecule (e.g. ICAM-1) expression by cortisol or its analogs, as comprehensively reviewed by Prigent et al. [21].

Some authors describe an increased incidence of antisocial behavior or severe depressive symptoms in the context of low serum cholesterol concentrations in humans [22,23]. Since cortisol notably takes part in keeping stress-related homeostasis and cholesterol is a precursor of cortisol synthesis, we might speculate about an association between the inhibition of cholesterol synthesis mediated by statin therapy and a possible impact on the stress response in the lack of cortisol synthesis.

However, the direct link between statin therapy and cortisol level changes has not been clearly outlined. Most of the randomized controlled trials (RCTs) evaluating statins' effects on plasma cortisol levels have been in small sample sizes, and produced inconsistent results. In the light of these observations, the objective of this study was to perform a systematic review and meta-analysis of RCTs, at the highest level of evidence, investigating the impact of statin therapy on plasma cortisol levels.

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [24]. PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (atorvastatin OR simvastatin OR rosuvastatin OR fluvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR "statin therapy" OR statins) AND (cortisol OR glucocorticoid OR glucocorticoids) AND (placebo). The wild-card term "*" was used to increase the sensitivity of the search strategy. The search was limited to articles published in English language. The literature was searched from inception to March 01, 2015.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: (i) being a randomized placebo-controlled trial with either parallel or cross-over design, (ii) investigating the impact of statin therapy, either as monotherapy or combination therapy, on serum/plasma concentrations of cortisol, (iii) presentation of sufficient information on cortisol concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were (i) non-interventional trials, (ii) lack of a placebo control group for statin therapy, (iii) observational studies with case-control, cross-sectional or cohort design, and (iv) lack of sufficient information on baseline or follow-up cortisol concentrations.

2.3. Data extraction

Eligible studies were reviewed and the following data were abstracted: (1) first author's name; (2) year of publication; (3) study location; (4) study design; (5) number of participants in the statin and control groups; (6) type of statin administered in the study; (7) dose of statin therapy; (8) treatment duration; (9) age, gender and body mass index (BMI) of study participants; (10) baseline levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, high-sensitivity C-reactive protein (hs-CRP) and glucose; (11) systolic and diastolic blood pressures; and (12) data regarding baseline and follow-up concentrations of cortisol.

2.4. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [25]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias. Labeling an item as "unclear" indicated an unclear or unknown risk of bias.

2.5. Quantitative data synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [26]. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up – measure at baseline. For single-arm cross-over trials, net change in plasma concentrations of cortisol were calculated by subtracting the value after control intervention from that reported after treatment. All values were collated as percent change from baseline in each group. Standard deviations (SDs) of the mean difference were calculated using the following formula: $SD = \text{square root } [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and range (or 95% confidence interval [CI]), mean and standard SD values were estimated using the method described by Hozo et al. [27]. To convert interquartile range into Min–Max range, the following equations were used: $A = \text{median} + 2 \times (Q_3 - \text{median})$ and $B = \text{median} - 2 \times (\text{median} - Q_1)$, where A, B, Q_1 and Q_3 are upper and lower ends of the range, upper and lower ends of the interquartile range, respectively. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: $SD = SEM \times \text{sqrt}(n)$, where n is the number of subjects.

Net changes in measurements (change scores) were calculated for parallel and crossover trials, as follows: (measure at end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at end of follow-up in the control group – measure at baseline in the control group). All values were collated in percentage change in cortisol levels. A random-effects model (using DerSimonian–Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of populations being studied and also differences in study design and