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Impact of statin therapy on plasma adiponectin concentrations: A systematic review and meta-analysis of 43 randomized controlled trial arms

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ABSTRACT

Background and aims: The effect of statin therapy on plasma adiponectin levels has not been conclusively studied. Therefore, we aimed to evaluate this effect through a systematic review and meta-analysis of available randomized controlled trials (RCTs).

Methods: Quantitative data synthesis was performed using a random-effects model with weighted mean difference (WMD) and 95% confidence interval (CI) as summary statistics.

Results: In 30 studies (43 study arms) with 2953 participants, a significant increase in plasma adiponectin levels was observed after statin therapy (WMD: 0.57 μg/mL, 95% CI: 0.18, 0.95, $p = 0.004$). In subgroup analysis, atorvastatin, simvastatin, rosuvastatin, pravastatin and pitavastatin were found to change plasma adiponectin concentrations by 0.70 μg/mL (95% CI: −0.26, 1.65), 0.50 μg/mL (95% CI: −0.44, 1.45), −0.70 μg/mL (95% CI: −1.08, −0.33), 0.62 μg/mL (95% CI: −0.12, 1.35), and 0.51 μg/mL (95% CI: 0.30, 0.72), respectively. With respect to duration of treatment, there was a significant increase in the subset of trials lasting ≥12 weeks (WMD: 0.88 μg/mL, 95% CI: 0.19, 1.57, $p = 0.012$) but not in the subset of <12 weeks of duration (WMD: 0.18 μg/mL, 95% CI: −0.23, 0.58, $p = 0.390$). Random-effects meta-regression suggested a significant association between statin-induced elevation of plasma adiponectin and changes in plasma low density lipoprotein cholesterol levels (slope: 0.04; 95% CI: 0.01, 0.06; $p = 0.002$).

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Conclusions: The meta-analysis showed a significant increase in plasma adiponectin levels following statin therapy. Although statins are known to increase the risk for new onset diabetes mellitus, our data might suggest that the mechanism for this is unlikely to be due to a reduction in adiponectin expression.

1. Introduction

Adiponectin is an adipocyte-derived plasma protein secreted mainly by white adipose tissue [1]. It impacts metabolism of carbohydrates and fatty acids in the liver cells and muscles, indirectly influencing the insulin resistance *via* decreasing hepatic gluconeogenesis, increasing glucose uptake and beta-oxidation in the muscles [2]. In the circulation, adiponectin exists in three oligomeric forms: a low-molecular weight trimer, a medium molecular weight hexamer and a larger High–Molecular Weight (HMW) adiponectin form [3]. The HMW adiponectin is in particular the major active form of protein, which is primarily associated with insulin resistance and the presence of metabolic syndrome [4]. The adiponectin gene (*ADIPOQ*) located at position 3q27 is considered the most important genetic factor regulating plasma adiponectin levels [5]. The levels of plasma adiponectin are higher in women than in men and vary by ethnicity, being lower in African-Americans than in Caucasians [6,7]. Several single nucleotide polymorphism (SNPs) of the adiponectin gene such as SNP45, SNP276, SNP11377 and SNP11391 were associated with low plasma concentrations of adiponectin and type 2 diabetes mellitus (DM) [8]. Moreover, a sedentary life and high fat diet seems to be associated with disturbances of plasma adiponectin concentrations [9]. Indeed, it has been recently shown that obesity induces a DNA hypermethylation of *ADIPOQ* gene [10]. Low plasma concentrations of adiponectin have been observed in patients with metabolic syndrome, DM, obesity, hypertension, and coronary artery disease (CAD) [11–14]. Nevertheless, increased plasma levels of adiponectin have been found to be associated with increased values of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), suggesting a role of adiponectin in inflammatory processes [15]. Adiponectin also stimulates endothelial production of nitric oxide (NO) and endothelin-1 (ET-1), inhibits monocyte adhesion to endothelial cells and macrophage-derived foam cell transformation, simulates angiogenesis through promotion of cross-talk between Akt signaling and AMP-activated protein kinase and attenuates TNF-α-induced expression of adhesion molecules in endothelial cells [16]. Plasma adiponectin levels were negatively correlated with triglyceride and low-density lipoprotein cholesterol (LDL-C), but positively correlated with high-density lipoprotein cholesterol (HDL-C) levels in clinical trials [17,18]. Similarly to HDL-C its level increases after physical exertion [19].

Statins have been shown to have pleiotropic effects, influencing endothelial function, platelet adhesion, thrombosis, plaque stability, and inflammation, however there have been recently a discussion whether this effect is not only related to potent LDL-C reduction [20,21]. Available data also suggest that statins may have an impact on the adiponectin levels and hence the use of statins should be recorded, as can be a potential confounder. On the other hand statin therapy increases the risk of new onset diabetes (NOD), and one of the investigated hypotheses of this mechanism might be adipokines related [22].

Taking into account that statin therapy might modulate plasma adiponectin concentrations, and the exact effects are not completely known, we evaluated the impact of statin therapy on plasma adiponectin concentrations in the systematic review and meta-analysis of randomized controlled trials (RCTs).

2. Materials and methods

The analysis was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [23]. Due to the study design (meta-analysis of randomized controlled trials) no Institutional Review Board (IRB) approval, as well as no patients' informed consents was obtained.

2.1. Search strategy

The analysis was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [23]. PubMed, Medline and SCOPUS databases were searched using the following search terms in titles and abstracts: (atorvastatin OR simvastatin OR rosuvastatin OR fluvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR) AND (adiponectin). Additional searches for potential trials included the references of review articles on that issue, and the abstracts from selected congresses: scientific sessions of the European Society of Cardiology (ESC), the American Heart Association (AHA), the American College of Cardiology (ACC), European Society of Atherosclerosis (EAS) and National Lipid Association (NLA). The wild-card term "*" was used to increase the sensitivity of the search strategy. All searches were limited to studies in human. The literature was searched from inception to March 1, 2015. Two reviewers (CS and AS) examined every article separately to minimize the possibility of duplication, investigating reviews, case studies and experimental studies. Disagreements were resolved by discussion with a third party (MB).

2.2. Study selection

Original studies were included if they met the following *inclusion criteria:* (i) having a randomized controlled design in either parallel or cross-over form, (ii) investigating the impact of statin therapy (in monotherapy or in the combined therapy) on plasma/serum concentrations of adiponectin, (iii) treatment duration of at least two weeks, (iv) presentation of sufficient information on plasma/serum adiponectin concentrations at baseline and at the end of follow-up in each group or providing the net change values.

Exclusion criteria were (i) non-clinical studies, (ii) lack of a control group in the study design, (iii) observational studies with case-control, cross-sectional or cohort design, and (iv) lack of sufficient information on baseline or follow-up adiponectin 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; 5) type, dose and duration of statin therapy; 6) age, gender and body mass index (BMI) of study participants; 7)