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Review

Impact of statin therapy on plasma resistin and visfatin concentrations: A systematic review and meta-analysis of controlled clinical trials

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ABSTRACT

The beneficial effects of statin therapy in reducing cardiovascular morbidity and mortality is not merely explained by the lipid-modulating effects. Although adipokines levels have been associated with cardiometabolic disorders, a few studies have explored the effect of statin on resistin and visfatin. We aimed to evaluate the impact of statin therapy on levels of resistin and visfatin through a meta-analysis of published studies. A systematic literature search in Medline and SCOPUS databases was conducted up to January 2015 to identify controlled trials assessing changes in plasma concentrations of visfatin and resistin during treatment with statins. Quantitative data synthesis was performed using a random-effects model, with weighed mean difference (WMD) and 95% confidence interval (CI) as summary statistics. 12 eligible studies with 14 treatment arms were included. Overall, 844 participants were studied. No significant change in plasma resistin concentrations was observed following statin therapy (WMD: −0.11 ng/mL, CI: −1.94,1.73, $p = 0.909$). This effect was robust and not affected by statin type, treatment duration and LDL-cholesterol concentrations. With respect to visfatin concentrations, there was a marginally significant reduction following statin therapy (WMD: −2.40 ng/mL, CI: −4.79,−0.002, $p = 0.050$). However, this effect size was weak and sensitive to three of the trials included in the analysis. This meta-analysis did not suggest any effect of statin therapy on plasma resistin levels, while a slight reduction in visfatin levels was found. The effect of statins on visfatin levels may represent a novel pleiotropic characteristic of these drugs.

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1. Introduction

Obesity, impaired glucose metabolism and dyslipidemia stimulate the atherosclerotic process and increase the risk of cardiovascular diseases (CVD) [1]. Beyond energy storage regulation, adipose tissue is an active endocrine organ that contributes to metabolic homeostasis by secreting bioactive molecules known as "adipokines", such as leptin, adiponectin, resistin, visfatin, *etc.* [2]. Therefore, adipokines represent interesting biologic substrates linking obesity, insulin resistance, atherosclerosis, and CVD [2].

Statin therapy is the cornerstone in the management of dyslipidemia and CVD [3]. Over recent years, it has been established that the beneficial effects of statins in reducing CV morbidity and mortality cannot be merely explained by the lipid-lowering effects but they may involve non-lipid – *i.e.* pleiotropic – mechanisms [4–10]. Among the latter, the question has arisen whether the potential insulin-sensitizing and anti-inflammatory effects of statins are attributable to the modulation of serum adipokines. In this context, conflicting results have been shown by previous studies that examined the effects of statins on adipokines [11–15]. In particular, less is known about the effect of statin therapy on circulating levels of restistin and visfatin because so far only a handful of papers have been published on this issue [15–25].

Resistin is a cysteine-rich adipokine with 108 amino acids and a molecular weight of 12.5 kDa, synthesized either by adipocytes or by immune cells [26]. It modulates pro-inflammatory actions in different settings. For instance, in human studies, resistin levels have been associated with increased expression of several pro-inflammatory biomarkers and are predictive of coronary atherosclerosis [27,28]. However, conflicting and/or null association has been also reported between resistin levels and obesity, as well as between resistin levels and insulin resistance [29,30].

Similarly, visfatin is a novel adipokine expressed by adipose tissue, human bone marrow, liver and muscles [31,32]. Recent evidence associates visfatin levels with endothelial dysfunction and pro-atherosclerotic pathways in several contexts [33,34]. Visfatin expression is regulated by cytokines and is increased in macrophages which are isolated from human unstable carotid and coronary atherosclerotic lesions, suggesting a potential role of this adipokine in plaque destabilization process [35]. Furthermore, visfatin has been reported to exhibit insulin-mimetic properties [36], and both tissue expression and plasma levels of visfatin have been shown to be up-regulated in subjects with obesity and type 2 diabetes [31,37].

Although many of the atheroprotective effects of statins have been well clarified, their influence on circulating levels of resistin and visfatin is still a subject of controversy [15–25]. Therefore, the aim of the present study was to evaluate the impact of statin therapy on circulating concentrations of both resistin and visfatin through a systematic review and meta-analysis of controlled trials.

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 [38]. SCOPUS (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) databases were used to search the following 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 (resistin OR visfatin). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature was searched from inception to January 19, 2015.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: (i) having a controlled design in either parallel or cross-over form, (ii) investigating the impact of statin therapy on plasma/serum concentrations of resistin or visfatin, (iii) treatment duration of at least two weeks, (iv) presentation of sufficient information on resistin or visfatin 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, (iv) trials that recruited subjects receiving stable statin therapy, and (iv) lack of sufficient information on baseline or follow-up resistin or visfatin 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 (in case of randomized design) groups; 5) age, gender and body mass index (BMI) of study participants; 6) 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; 7) systolic and diastolic blood pressures; and 8) data regarding baseline and follow-up concentrations of resistin or visfatin.

2.4. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [39]. The items used for