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Does statin therapy reduce plasma VEGF levels in humans? A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background. The effect of statins on plasma concentrations of vascular endothelial growth factor (VEGF), the main angiogenic growth factor with pro-inflammatory and atherogenic properties, is controversial. A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to obtain a conclusive result in humans.

Methods. PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched to identify RCTs investigating the impact of statins on plasma VEGF concentrations. A random-effects model and the generic inverse variance method were used for quantitative data synthesis. Meta-regression, sensitivity analysis and publication bias assessments were performed using standard methods.

Results. Eight RCTs examining the effects of statins on plasma VEGF concentrations were included. Meta-analysis suggested a significant reduction of plasma VEGF levels following statin therapy (weighed mean difference: −19.88 pg/mL, 95% CI: −35.87, −3.89, $p = 0.015$). VEGF reductions were observed in the subsets of trials with treatment durations ≥4 weeks (−19.54, −37.78, −1.30, $p = 0.036$), LDL-C reductions ≥50 mg/dL (−28.59, −43.68, −13.50, $p < 0.001$), lipophilic statins (−22.31, −40.65, −3.98, $p = 0.017$), and diseased populations (−21.08, −39.97, −2.18, $p = 0.029$), but not in the opposite subsets. Meta-regression also suggested a significant association between changes in plasma VEGF levels and LDL-C changes, treatment duration, but not molar dose of statins.

Conclusions. These results suggest a significant reduction in plasma VEGF concentrations following statin therapy. This effect depends on duration of treatment, LDL-lowering activity, lipophilicity of statins, and health status of studied individuals. Further RCTs are needed to explore if the VEGF reduction is implicated in the statin benefits on cardiovascular outcomes.

Abbreviations: BMI, body mass index; CI, confidence interval; EPCs, circulating endothelial progenitor cells; hs-CRP, high sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; VEGF, vascular endothelial growth factor; WMD, weighed mean difference.

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1. Introduction

Vascular permeability, vasculogenesis and angiogenesis are regulated by a complex interplay among several growth factors and their associated receptors. In this process, vascular endothelial growth factor (VEGF) family and its receptors play an essential role [1,2]. The VEGF family consists of different isoforms with several subtypes; each isoform performs a different role in the endothelial and vascular physiology and pathology, as comprehensively reviewed [1–4]. In particular, VEGF is involved in vascular development, integrity, homeostasis, thrombogenicity modulation, recruitment of hematopoietic precursors and migration of monocytes and macrophages. The angiogenic, permeability-enhancing and pro-inflammatory properties of VEGF determine its role in pathological conditions, such as cancer, ischemia and inflammation [1–4]. At a cardiovascular level, VEGF is implicated in the progression of atherosclerosis, instability of atherosclerotic plaque through induction of neoangiogenesis inside the plaque, prediction of worse clinical outcomes in acute coronary syndromes, and cardiac hypertrophy through a nitric oxide (NO)-dependent mechanism [1–7].

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) are known to exert beneficial effects on the clinical outcomes of cardiovascular diseases both by their lipid-lowering, anti-inflammatory, antioxidant and antithrombotic effects and by improving endothelial function, attenuating vascular/myocardial remodeling and stabilizing atherosclerotic plaques [8,9]. Alternative additional mechanisms by which statins may reduce cardiovascular events beyond their lipid reduction effects may be the modulation of angiogenesis by reducing VEGF levels, as suggested by some case–control human studies performed almost a decade ago [10,11]. More recently, the effects of different statins on the reduction of VEGF levels have been shown [12–19]; however, the results of human studies have not been fully conclusive [20–26]. In addition, some experimental *in-vitro* and animal studies have suggested a statin-induced stimulation of VEGF expression after endothelial and vascular injuries [27–32]. Furthermore, there is evidence indicating that statins could directly augment circulating endothelial progenitor cells (EPCs) through mechanisms independent of VEGF [17,19,21,22,33]. Therefore, at present the role of statins on the VEGF homeostasis is very controversial.

The aim of the present study was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to clarify the effect of statin treatment on plasma concentrations of VEGF in humans.

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 [34]. 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 (VEGF OR "vascular endothelial growth factor" OR VEGF-A). 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 humans. The literature was searched from inception to January 08, 2015.

2.2. Study Selection

Original studies were included if they met the following inclusion criteria: (i) being a randomized controlled trial with either parallel or cross-over design, (ii) investigating the impact of statin therapy on plasma/serum concentrations of VEGF, (iii) treatment duration of at least two weeks, (iv) presentation of sufficient information on VEGF concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were (i) non-randomized trials, (ii) lack of an appropriate 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 VEGF 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 VEGF.

2.4. Quality Assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [35]. 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) [36]. 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 VEGF was calculated by subtracting the value after control