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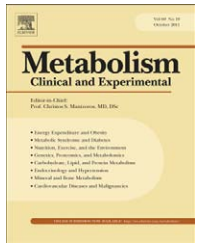

Head-to-head comparison of fibrates versus statins for elevation of circulating adiponectin concentrations: a systematic review and meta-analysis

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ABSTRACT

Background. Elevation of adiponectin levels is a potential therapeutic tool against cardiovascular and metabolic diseases. Clinical evidence suggests differences between fibrates and statins in improving circulating concentrations of adiponectin.

Aim. To compare the efficacy of fibrates vs. statins on circulating concentrations of adiponectin by meta-analysis of randomized head-to-head trials.

Methods. A systematic literature search of Medline was conducted to identify randomized head-to-head comparative trials investigating the efficacy of fibrates vs. statins on circulating levels of adiponectin. Inverse variance-weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for net changes in adiponectin concentrations using a random-effects model. Random-effects meta-regression was performed to assess the effect of putative moderators on adiponectin levels.

Results. Six trials with a total of 326 subjects (166 in the fibrate and 160 in the statin group) met the eligibility criteria and were selected for this meta-analysis. The estimated effect size for fibrate versus statin therapy was 0.42 μg/mL (95% CI: −0.34–1.17). This effect size was robust in the leave-one-out sensitivity analysis and not sensitive to any single study. Meta-regression indicated a borderline significant association between duration of treatment and the effect of fibrates vs. statins on adiponectin concentrations (slope: −0.20; 95% CI: −0.41–0.01; $p = 0.06$). However, baseline body mass index, glucose and lipid levels did not predict the effect of fibrate vs. statin therapy on circulating adiponectin concentrations ($p > 0.05$).

Conclusions. Monotherapy with either fibrates or statins has comparable effects on circulating concentrations of adiponectin. Thus, differential effects of statins and fibrates on the occurrence of cardiovascular events may not be attributed to the corresponding changes in adiponectin levels.

Abbreviations: BMI, Body mass index; CHD, Coronary heart disease; CI, Confidence interval; ELISA, Enzyme-linked immunosorbent assay; HDL-C, High-density lipoprotein cholesterol; HIV, Human immunodeficiency virus; Hs-CRP, High-sensitivity C-reactive protein; LDL-C, Low-density lipoprotein cholesterol; RIA, Radioimmunoassay; SD, Standard deviation; SEM, Standard error of the mean; WMD, Weighed mean difference.

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1. Introduction

Adiponectin is a 247 amino acid adipocyte-secreted hormone that occurs at high circulating concentrations [1–3]. This adipokine has attracted widespread attention because of its pivotal role in glucose and lipid metabolism [4–8], energy homeostasis [9] and cardiovascular health [10–14]. Experimental and clinical evidence has indicated significant lipid-modulating [15,16], insulin synthesizing [17], anti-atherogenic [18,19], anti-diabetic [18,20], antioxidant [21], anti-inflammatory [22,23], anti-thrombotic [24] and anti-obesity [19] effects for adiponectin. Circulating levels of adiponectin have been frequently reported to be inversely associated with the presence of type 2 diabetes [25], metabolic syndrome [26], dyslipidemia [27], hypertension [28], coronary artery disease [29] and myocardial infarction [30]. Due to the exuberance of findings on the beneficial actions of adiponectin, elevation of circulating levels of this adipokine has been proposed as a potential therapeutic tool against metabolic and cardiovascular disorders [11,31,32].

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (statins) and agonists of peroxisome proliferator-activated receptor-α (fibrates) are the most widely administered lipid-lowering agents that are at the frontline of pharmacotherapy for hypercholesterolemia and hypertriglyceridemia, respectively. Statins have been unequivocally shown to reduce the incidence of cardiovascular outcomes in both primary and secondary prevention [33]. The same findings have been reported for fibrates in populations with diabetic dyslipidemia or atherogenic dyslipidemia [coexistence of elevated triglycerides and diminished levels of high-density lipoprotein cholesterol (HDL-C)] [34–37]. Several lines of evidence have shown that the considerable cardiovascular benefits achieved by statin and fibrate therapy cannot be fully explained by lipid-lowering effects of these drugs. During the past two decades, a plethora of the so-called "pleiotropic" actions has been identified for stains and fibrates including antioxidant properties, down-regulation of pro-inflammatory cytokines and mitigation of vascular and systemic inflammation, improvement of vasodilation and endothelial function, and attenuation of platelet aggregation [38–41]. Another pleiotropic effect that has been reported for both statins and fibrates is induction of adiponectin and increasing circulating levels of this adipokine [42,43]. In light of these findings, it might be speculated that multiple pleiotropic effects of statins and fibrates are, at least in part, mediated through induction of adiponectin.

Although a number of head-to-head randomized controlled trials have been conducted to ascertain the impact of fibrate vs. statin therapy on circulating adiponectin levels [44–49], the results have been inconclusive. The present study aimed to resolve this uncertainty by systematically reviewing the literature, and meta-analysis and meta-regression of all head-to-head comparative trials investigating the effects of fibrates vs. statins on adiponectin 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 [50]. Medline (http://www.ncbi.nlm.nih.gov/pubmed) was searched using the combination of following search terms in titles and abstracts: ("fibrate" OR "fibric acid" OR "fenofibrate" OR "bezafibrate" OR "ciprofibrate" OR "clofibrate" OR "gemfibrozil" OR "procetofen" OR "clofibric acid") AND ("statin" OR "fluvastatin" OR "pravastatin" OR "lovastatin" OR "simvastatin" OR "atorvastatin" OR "rosuvastatin") AND (adiponectin). The search was limited to studies in human. The literature was searched from inception to July 19, 2013. Selected articles were hand searched to identify further relevant studies.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: i) be a randomized clinical case–control or case–cross-over trial, ii) investigated the impact of a fibrates vs. statins on circulating adiponectin levels, iii) presentation of sufficient information on adiponectin levels at baseline and at the end of study in both fibrate and statin groups. Exclusion criteria were i) non-clinical studies, ii) not having a head-to-head randomized controlled design, and iii) lack of sufficient information on adiponectin levels at baseline and/or at the study endpoint. Exclusion of an article for the latter reason was done if no feedback was received after contacting the author(s).

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) number of participants in the case and control groups; 5) age, gender and body mass index (BMI) of study participants; and 6) circulating concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides, high-sensitivity C-reactive protein (hs-CRP) and glucose.

2.4. Quality assessment

Eligible studies were systematically assessed for potential risk of bias using instructions described in the Cochrane Handbook for Systematic Reviews of Interventions [51]. The items used for the assessment of each study were adequacy of sequence generation, allocation concealment, blinding, addressing drop-outs (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "Yes" was indicative of low risk of bias, whilst "No" indicated high risk of bias. Labeling as 'Unclear' indicated unclear or unknown risk of bias.

2.5. Quantitative data synthesis

Meta-analysis was conducted using the Cochrane Program Review Manager version 5.1 (Cochrane Collaboration, Oxford, UK). Blood lipid and glucose levels were collated in mg/dL. A multiplication by 38.6, 88.5 or 18.0 was used to convert cholesterol (total cholesterol, HDL-C or LDL-C), triglyceride