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Effect of orlistat on plasma lipids and body weight: A systematic review and meta-analysis of 33 randomized controlled trials

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ABSTRACT

Orlistat, an inhibitor of intestinal lipase, promotes body weight reduction. The lipid-lowering efficacy of orlistat is controversial and the effect of orlistat-induced body weight reduction on lipid changes has not been explored in meta-regression analyses. A systematic literature search was conducted to identify randomized controlled trials investigating the efficacy of orlistat on plasma total, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides and lipoprotein(a) levels. Thirty-three studies were included in the meta-analysis (5522 and 4210 participants in the orlistat therapy and control groups, respectively). Orlistat reduced body weight (weighted mean difference: −2.12, $p < 0.001$), total-cholesterol (weighted mean difference: −0.30 mmol/L, $p < 0.001$), low-density lipoprotein cholesterol (weighted mean difference: −0.27 mmol/L, $p < 0.001$), high-density lipoprotein cholesterol (weighted mean difference: −0.034 mmol/L, $p < 0.001$) and triglyceride (weighted mean difference: −0.09 mmol/L, $p < 0.001$) concentrations, while no effect on lipoprotein(a) was observed. Total- and low-density lipoprotein cholesterol-lowering were associated negatively with duration of orlistat treatment and positively with body weight changes. In conclusion, Orlistat treatment slightly reduces cholesterol and triglyceride levels, but not lipoprotein(a) levels. Total- and low-density lipoprotein cholesterol levels reductions are more consistent in patients with greater body weight reduction and shorter duration of orlistat treatment.

1. Introduction

Orlistat is a reversible pancreatic and gastric lipase inhibitor that blocks absorption of 30% of ingested fat when eating a hypocaloric diet that roughly contains 30% of energy as fat [1]. It is an effective adjunctive therapeutic option to lifestyle modifications in the treatment of obesity. Accordingly, there is evidence that orlistat plus lifestyle changes achieve greater body weight (BW) loss than lifestyle changes alone [2]. A 4-year-long study supported additional beneficial effects of treatment with orlistat, in that this drug reduced the development of diabetes mellitus in people with prediabetes [3]. In addition, orlistat has a good long-term safety profile and serious adverse events are rare; hence, it is approved for use also in adolescents [4]. Despite this evidence, a high rate of gastrointestinal side effects limits adherence to treatment and its popularity among the patients [5].

Dyslipidemia is an established risk factor for ischemic cardiovascular disease (CVD) [6,7]. The relationship between most of the dyslipidemias, such as hypercholesterolemia, i.e. elevated total and/or low-density lipoprotein (LDL)-cholesterol (LDL-C), hypertriglyceridemia and low high density lipoprotein (HDL)-cholesterol (HDL-C) levels, and the risk of CVD is consistent [8–12]. Also, the combination of multiple lipids and lipoprotein abnor-

Abbreviations: BMI, body mass index; BW, body weight; CI, confidence interval; CMA, Comprehensive Meta-Analysis; CVD, cardiovascular disease; HDL, high density lipoprotein; HDL-C, high density lipoprotein-cholesterol; LDL, low density lipoprotein; LDL-C, low density lipoprotein-cholesterol; Lp(a), lipoprotein(a); PRISMA, preferred reporting items for systematic reviews and meta-analysis; RCT, randomized controlled trial; SD, standard deviations; SEM, standard error of the means; TC, total cholesterol; TG, triglyceride; WMD, weighted mean difference.

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malities is common [13] and shows a detrimental cumulative impact on CVD risk [6]. Interestingly, the association of multiple lipid and lipoprotein abnormalities is frequent in obese patients, considering that approximately 60–70% of obese patients are dyslipidemic [14]. Obese patients often have elevated triglycerides, decreased HDL-C, and usually only moderately elevated LDL-C but an increased number of small, dense LDL-particles which are considered highly atherogenic [15,16]. Hence, therapeutic strategies which are effective in positively influencing all these lipid parameters are warranted; this need is felt especially in obese patients, in whom it would be desirable to have drugs that act simultaneously on BW and on plasma lipids as well. As BW loss has itself an effect on plasma lipids, it is, however, challenging to distinguish between the BW-dependent and the drug-dependent effects on plasma lipid levels.

There are data indicating that after 1 year of treatment, orlistat might be associated with a significant improvement in cardiovascular risk factors, including reductions in systolic and diastolic blood pressures, fasting glucose and blood lipids [17]. As regards specifically lipid levels, a number of randomized controlled trials (RCTs) has explored the impact of orlistat on plasma total-cholesterol (TC), LDL-C, HDL-C or triglyceride (TG) levels [18–50]. Only few studies examined whether plasma lipoprotein(a) [Lp(a)] levels are affected by orlistat treatment [40,46]. Some of these studies reported that orlistat may improve lipid profile, while in other studies orlistat failed to have any significant effect on most lipids and lipoproteins. Thus, data regarding the effects of orlistat on the plasma lipid profile are still controversial.

Because high dropout rates have been reported in long-term BW loss trials with orlistat [3], the potential confounding effect of duration of treatment on orlistat-induced lipid changes is a matter of particular interest. In addition, because the main goal of treatment with orlistat is to ensure a permanent BW reduction [1,2,4,5] and diet-associated BW loss is commonly associated with beneficial changes in lipids levels [51,52], one may expect that BW changes during orlistat treatment should have a significant impact on plasma lipid and lipoprotein levels.

In order to answer these questions, we performed a systematic review of the literature and a meta-analysis of RCTs to elucidate the impact of orlistat therapy on plasma TC, LDL-C, HDL-C, TG and Lp(a) concentrations; moreover, we tested the impact of dose and duration of orlistat treatment and orlistat-induced BW changes on the possible changes in plasma lipid and lipoprotein concentrations.

2. Methods

2.1. Search strategy

The guidelines of the 2009 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [53] were exploited for the study design. A literature search through electronic databases PubMed-Medline, SCOPUS, Web of Science, and Google Scholar was carried out from inception to december 25, 2014. The following search terms in titles and abstracts (also in combination with MESH terms) were used: (orlistat) AND (hyperlipidemia OR hyperlipidaemia OR hyperlipidemic OR hyperlipidaemic OR dyslipidemia OR dyslipidaemia OR dyslipidemic OR dyslipidaemic OR hypercholesterolemia OR hypercholesterolaemia OR hypercholesterolemic OR hypercholesterolaemic OR "low-density lipoprotein" OR "high-density lipoprotein" OR cholesterol OR triglycerides OR LDL OR LDL-C OR LDL-cholesterol OR HDL-OR HDL-C OR HDL-cholesterol). The wild-card term "*" was used to increase the sensitivity of the search strategy and to avoid missing interchangeable formats of dyslipidemia, hyperlipidemia and hypercholesterolemia.

2.2. Study selection

Eligible studies were identified by the following criteria: (i) RCTs with either case-control or case-cross-over design, (ii) investigation of the effects of orlistat on plasma/serum concentrations of lipids and/or lipoproteins comprising TC, LDL-C, HDL-C, TGs and Lp(a), (iii) providing sufficient information on baseline and end-trial plasma/serum lipid concentrations in both orlistat and control groups. Exclusion criteria were (i) experimental studies, (ii) uncontrolled studies, and (iii) administration of lipid-lowering drugs (e.g. statins, fibrates, ezetimibe, bile acid sequestrants or *n*-3 polyunsaturated fatty acids and their esters) in the study groups without appropriate controlling, and (iv) lack of sufficient information on baseline or end-trial lipid concentrations. In case of the latter item, authors of the article(s) were contacted (single time *via* e-mail) and requested to provide necessary numerical data.

Articles were screened by two reviewers (AS and LES) to remove ineligible articles. Disagreements were resolved by discussion and referring to a third reviewer (MS), if required.

2.3. Data extraction

The following data were abstracted from reviewed eligible studies: 1) first author's name; 2) year of publication; 3) country where the study was performed; 4) study design; 5) number of participants in the orlistat and control groups; 6) dose of orlistat therapy; 7) treatment duration; 9) age, gender, and body mass index (BMI) of study participants; 10) baseline systolic and diastolic blood pressure values; and 11) data regarding baseline and follow-up plasma concentrations of TC, LDL-C, HDL-C, TGs and Lp(a).

Data extraction was performed by 2 reviewers (LES and MS), and disagreements were resolved by a third reviewer (AS).

2.4. Quality assessment

Risk of bias assessment in the included studies was performed according to the Cochrane instructions (2008). Each study was evaluated based on the following items: sequence generation adequacy, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. A judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias, according to the recommendations of the Cochrane Handbook. The item "unclear" was used to indicate either an unclear or unknown risk of bias.

Risk-of-bias assessment was performed by 2 reviewers (LES and MS), and disagreements were resolved by a third reviewer (AS).

2.5. Quantitative data synthesis

Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) was used in this meta-analysis [54]. 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 lipid indices were calculated by subtracting the value after control intervention from that reported after treatment. All values were collated to mg/dL. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, 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 methods described by Wan et al. [55] and the Cochrane handbook for systematic reviews of interventions. Missing SD values were imputed by the pooled SD of all studies. When only the standard error of the mean (SEM) was reported, standard deviation (SD) was esti-