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Review

The effects of bile acid sequestrants on lipid profile and blood glucose concentrations: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Aim: To undertake a systematic review and meta-analysis of prospective clinical studies to determine the effect of bile acid sequestrants (BAS) on lipid profile and blood glucose concentrations.
Method: PubMed-Medline, Web of Science, Cochrane Database and Google Scholar databases were searched (up until August 2016) to identify prospective studies evaluating the impact of BASs on the cardio-metabolic profile. Random effects model meta-analysis was used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. Heterogeneity was quantitatively assessed using the I^2 index. Systematic review registration: CRD42016035973.
Results: From a total of 769 entries identified, 15 studies were included in the final analysis. The meta-analysis indicated a significant reduction in fasting serum triglyceride concentrations following treatment with BASs (weighted mean difference [WMD] 0.54 mg/dL, 95% CI 0.43 to 0.65, heterogeneity p = 0.021; I^2 54.2%, n = 11 studies). The WMDs for total serum cholesterol (TC) was −1.18 mg/dL (95% CI −1.30 to −1.06, heterogeneity p = 0012; I^2 63.1%, n = 11 studies), 0.126 mg/dL (95% CI 0.02 to 0.22, heterogeneity p = 0.231; I^2 43.2%, n = 11 studies) for HDL-cholesterol, and −0.24 mg/dL (95% CI −0.35 to −0.14, heterogeneity p = 0.562; I^2 23.1%, n = 10 studies) for LDL-cholesterol, and −2.10 mg/dL (95% CI −2.84 to −1.36, heterogeneity p = 0.200; I^2 42.6%, n = 11 studies) fasting blood glucose (FBG) and −0.83% (95% CI −1.08 to −0.57, heterogeneity p = 0.856; I^2 20.9%, n = 11 studies) for HbA1c. These findings were robust in sensitivity analyses.
Conclusions: This meta-analysis suggests that therapy with BAS significantly improves HDL-C, LDL-C, and glycemic markers including fasting blood glucose, HbA1c levels, while deteriorating triglyceride levels.

1. Introduction

Available lipid modifying drugs used in the management of dyslipidemia include 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins), the cholesterol absorption inhibitor, ezetimibe, and bile acid sequestrants (BAS). BAS, also known as resins, are large, non-absorbable polymeric molecules that bind negatively charged bile salts in the intestine. This diverts bile acids from the enterohepatic cycle and increases their fecal excretion [1]. The end result is an increase in bile acid synthesis, and upregulation of the low-density lipoprotein (LDL) receptors. Clinical studies have shown that BASs in addition to their well-established cholesterol-lowering effects [2–4], can lower blood glucose and, may therefore be potentially beneficial in the treatment of patients with type 2 diabetes [5–7].

The mechanism(s) by which BAS exert their glucose lowering action is not completely understood. Data from in vitro and in vivo animal and human studies have suggested different mechanisms including enhanced glucose-stimulated release of the incretin hormone, glucagon-like peptide-1 (GLP-1) [8–12], and activation of the nuclear farnesoid X receptor, which is implicated in lipid and glucose metabolism [13,14]. The binding of bile acids to TGR5, a G protein-coupled receptor, has been reported to activate the downstream cyclic adenosine monophosphate signaling pathway in a wide array of tissues and cell types, and was proposed to represent an essential component in the pathway mediating GLP-1 release in response to BAS treatment [15].

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The glucose-lowering actions of GLP-1 are thought to be mediated by glucose-stimulated insulin secretion, inhibition of glucagon secretion and a suppressive effect on appetite and food intake [16].

Hypercholesterolemia and diabetes mellitus often co-exist, and this substantially increases the risk of cardiovascular disease [15]. Furthermore, there is good evidence that improved glycemic control prevents the microvascular complications of type 2 diabetes [6]. Hence the potential effects of BAS on the lipid profile and blood glucose concentrations provide the rationale for a systematic review to clarify the possible impact of BAS on these specific cardiovascular risk factors.

The single studies to date have been limited by sample size, research design and subject traits (gender, ethnicity, age, etc.), and therefore, underpowered to draw a robust conclusion. A meta-analysis of the available studies may overcome this limitation. This study was therefore designed to determine whether there is change in lipid profile and glucose levels subsequent to treatment with BASs.

2. Materials and methods

2.1. Literature search strategy

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [17,18]. Moreover the study protocol was registered with the International Prospective Register of Systematic Reviews, PROSPERO (registration no: CRD42016035973). The primary exposure of interest was treatment with BASs while the primary outcome of interest was changes in blood lipid and glucose levels subsequent to treatment with BASs. We searched multiple databases including PUBMED/Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Web of Science, and www.clinicaltrials.gov register; until August 2016 using a combination of search terms available in Supplementary Tables 1 and 2. This was complemented by hand search of the reference list of eligible articles, and email correspondences with authors for additional data where relevant.

2.2. Selection criteria

We included all prospective studies evaluating the effect of BAS on the outcomes of interest. Eligible studies had to meet the following criteria: (1) controlled trial with either parallel or crossover design, (2) prospective studies of patients treated with BASs compared to control group (either no BAS or placebo), (3) presentation of sufficient information on primary outcomes at baseline and at the end of follow-up in each group or providing the net change values. The following exclusion criteria were applied: (i) non-clinical studies; (ii) observational studies with a case–control, cross-sectional or cohort design; and (iii) studies that did not provide mean (or median) plasma, serum, or blood concentrations of our interested outcomes at baseline and/or at the end of trial. Narrative reviews, comments, opinion pieces, methodological, editorials, letters or any other publications lacking primary data and/or explicit method descriptions, were also excluded. Similarly, studies with incomplete data, and data that we could not obtain from the authors after several requests, were excluded. Study selection started with the removal of duplicates; followed by titles and abstracts screening by two reviewers. To avoid bias, reviewers were blinded to the names, qualifications or the institutional affiliations of the study authors. The agreement between the reviewers was excellent (Kappa index: 0.88; $p < 0.001$). Disagreements were resolved at a meeting between reviewers prior to the selected articles being retrieved.

2.3. Data extraction and management

The full text of studies meeting inclusion criteria was retrieved and screened to determine eligibility by two reviewers (MM, PR). Following assessment of methodological quality, the two reviewers extracted data onto a purpose-designed data extraction form, and independently summarized what they considered to be the most important results from each study. These summaries were compared and any differences of opinion resolved by discussion and consultation with a third reviewer (FA). Any further calculations on study data considered necessary, was conducted by the first reviewer and checked by the second reviewer. Descriptive data extracted included the first author's name, year of publication, country, design, Inclusion criteria, age range, total sample size, gender, dose (mg) of BAS, follow-up duration (week).

3. Quality assessment

A systematic assessment of bias in the included RCTs was performed using the Cochrane criteria [19]. The items used for the assessment of each study were the following: adequacy of random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, handling of 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' 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.

3.1. Data synthesis

Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up − measure at baseline. For RCTs, change scores were calculated as: (measure at end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at end of follow-up in the control group − measure at baseline in the control group). Where only the standard error of the mean (SEM) was reported, the standard deviation (SD) was calculated using the following formula: SD = SEM × square root (n), where n is the number of subjects [20,21]. If the outcome measures were reported in median and range (or 95% confidence interval [CI]), mean and standard SD values were estimated using the method described by Hozo et al. [22]. When the outcome variable was available only in the graphic form, the software GetData Graph Digitizer 2.24 [23] was used to digitize and extract the data. Blood lipid and glucose levels were collated in mmol/L; a multiplication factor of 0.0259, 0.0113 or 0.0555 was used to convert cholesterol (total cholesterol, high density lipoprotein cholesterol (HDL-C) or low density lipoprotein cholesterol (LDL-C)), triglycerides and glucose levels respectively from mg/dL to mmol/L as appropriate [21].

A random effects model (using the DerSimonian–Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of populations being studied and also differences in study design and type of BAS being studied [24]. Heterogeneity was quantitatively assessed using I^2 index. Effect sizes were expressed as weighed mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method, i.e. removing one study each time and repeating the analysis [25–27].

3.2. Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie 'trim and fill' and 'fail-safe N' methods were used to adjust the analysis for the effects of publication bias [28]. Meta-analysis was conducted using Comprehensive Meta-analysis (CMA) V3 software (Biostat, NJ) [29].

4. Results

4.1. Summary of searches and study selection process

A total of 765 unique citations where identified from searches, of which, 463 records remained after removing duplicates. After screening using article titles and abstracts, 47 articles remained for further evaluation, of which, 32 were excluded for the following reasons: non-human studies, genetic, or molecular studies (n = 22); reviews or editorial articles (n = 5); not RCT (n = 3), Fig. 1. Therefore, 15 studies were included in the meta-analysis.

5. Risk of bias assessment

Several of the included studies were characterized by lack of information about the allocation concealment (n = 4), blinding of outcome assessment (n = 3) and blinding of participants and personnel

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