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Treatment with high dose salicylates improves cardiometabolic parameters: Meta-analysis of randomized controlled trials

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ABSTRACT

Introduction. There is conflicting evidence regarding the efficacy of high dose salicylates in improving cardiometabolic risk in healthy and type 2 diabetes patients. We aimed to determine whether treatment with salicylates at an anti-inflammatory dose (≥1 g daily) would improve cardiometabolic risk in healthy individuals and type 2 diabetes patients, compared to placebo.

Methods. Medline, Medline-in-process, Embase, and all EBM databases were searched for studies published up to December 2016. Twenty-eight articles from 24 studies comprising 1591 participants were included. Two reviewers independently assessed the risk of bias and extracted data from included studies. Meta-analyses using random-effects model were used to analyze the data.

Results. High dose salicylates (≥3 g/d) decreased fasting glucose (MD -0.4 mmol/l, 95% CI −0.54, −0.27) and glucose area under the curve (MD -0.41 mmol/l, 95% CI −0.81, −0.01). Salicylates (≥3 g/d) also increased fasting insulin (MD 2.4 μU/ml, 95% CI 0.3, 4.4), 2-h insulin (MD 25.4 μU/ml, 95% CI 8.2, 42.6), insulin secretion (MD 79.2, 95% CI 35, 123) but decreased fasting C-peptide (MD -0.11 nmol/l, 95% CI −0.2, −0.04), insulin clearance (MD -0.26 l/min, 95% CI −0.36, −0.16) and triglycerides (MD -0.36 mmol/l, 95% CI −0.51, −0.21) and increased total adiponectin (MD 1.97 μg/ml, 95% CI 0.99, 2.95). A lower salicylate dose (1–2.9 g) did not change any cardiometabolic parameters ($p > 0.1$). No significant difference was observed between those receiving salicylates and placebo following withdrawal due to adverse events.

Conclusions. High dose salicylates appear to improve cardiometabolic risk factors in healthy individuals and type 2 diabetes patients.

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Abbreviations: AMPK, Adenosine Monophosphate-Activated Protein Kinase; AUC, Area Under the Curve; CI, Confidence Interval; CRP, C-Reactive Protein; CVD, Cardiovascular Diseases; DPP, Diabetes Prevention Program; FFA, Free Fatty Acids; HbA1C, Hemoglobin A1C; HDL, High-Density Lipoprotein; HOMA-B, Homeostatic Model of Assessment of Insulin Secretion; HOMA-IR, Homeostatic Model of Assessment of Insulin Resistance; IL-6, Interleukin-6; LDL, Low-Density Lipoproteins; NF-κβ, Nuclear Factor Kappa Beta; MD, Mean Difference; mTOR, Mechanistic Target of Rapamycin; RCT, Randomized Controlled Trails; RD, Risk Difference; T2DM, Type 2 Diabetes Mellitus; TNFα, Tumor Necrosis Factor Alpha; WHO, World Health Organization; WMD, Weighted Mean Difference; QUICKI, Quantitative Insulin Sensitivity Check Index.

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1. Introduction

Cardiometabolic risk factors including obesity, type 2 diabetes (T2DM), dyslipidaemia, and hypertension are major health threats [1]. Although optimizing physical activity, dietary intake and weight loss remain the central targets for prevention of T2DM and cardiovascular disease (CVD), long-term adherence to lifestyle changes has remained a crucial challenge. Therefore, there is a need to explore additional strategies for prevention and treatment of T2DM and CVD [1,2].

Salicylates are esters or salts of the compound salicylic acid and exist in either acetylated (aspirin) or non-acetylated forms (salsalate, sodium salicylate and others) [3]. High-dose salicylates have been primarily used for the treatment of rheumatic conditions based on their anti-inflammatory effects relating to inhibition of nuclear factor kappa beta (NF-κβ) activity [4–7]. Low-dose salicylates have alternatively been used for the treatment and prevention of cardiovascular events relating to their inhibitory effects on platelet function and thrombus formation [8]. Some [6,9,10] but not all [7,11] clinical trials have demonstrated that high-dose salicylates can improve cardiometabolic risk by reducing chronic low-grade inflammation. However, the results of these trials have been conflicting based on the population studied, measures of glucose metabolism and cardiovascular risk assessed and salicylate dose used.

While a previous meta-analysis compared the effect of salicylates and placebo on indices of glycaemic measures and lipid profile, it only included patients with T2DM, reported on a limited range of cardiometabolic parameters and published articles up to April 2010 [12]. The aim of this study was to conduct an updated meta-analysis on the effect of salicylates on a broad range of cardiometabolic risk factors in all individuals regardless of their glycaemic and health status.

2. Materials and Methods

2.1. Data Sources and Searches

A systematic search of databases was performed including: Medline (to 5/12/2016), Medline In-process and other non-indexed citations (to 2/12/2016), Embase (to 2/12/2016) and all EBM, incorporating Cochrane Database of Systematic Reviews (to December 2016), ACP Journal Club (to October 2016), Database of Abstracts of Reviews of Effects (1st Quarter 2015), Cochrane Central Register of Controlled Trials (to October 2016), Cochrane Methodology Register (3rd Quarter 2012), Health Technology Assessment (4th Quarter 2016), NHS Economic Evaluation Database (1st Quarter 2015). The full search string can be found in Supplementary Table 1. The International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/) and reference lists of all included articles were also searched.

2.2. Study Selection

Randomized controlled trials, including cross-over trials and cluster trials in adults (≥18 years of age) regardless of any other characteristics were included. Interventions were included where any type of salicylates at a daily oral dose of ≥1 g (to achieve anti-inflammatory effects) was used for any duration in comparison to placebo. Primary outcomes included measures of glucose homeostasis and cardiovascular risk factors. Secondary outcomes included markers of inflammation and endothelial dysfunction and withdrawal due to adverse events. The detailed outcome measures can be found in Supplementary Table 2. Studies that reported only antiplatelet effects such as platelet aggregation/activation, and coagulation were excluded. No restrictions were placed on year of publication or publication status. A reviewer (EB) screened the titles, abstracts and keywords of each retrieved article in consultation with a second reviewer (MM).

2.3. Data Extraction and Quality Assessment

Double data extraction was conducted by two independent reviewers (EB, NN). In the case of having more than one article describing a study, data from the most current and comprehensive article was extracted; and any additional reported outcome data were subsequently extracted. When a study had more than two treatment arms, data from all arms were extracted if they met the study criteria. In randomized cross-over studies, data were extracted from before and after cross-over based on the assumptions that there was no carry-over effect; that authors used adequate washout periods (defined as a washout period of equal/similar to the duration of intervention [13]) and relevant statistical tests to control the carry-over effect; and that the reported results were comparable to parallel studies. Authors were contacted for further data where appropriate.

Two independent reviewers (EB and NN) assessed the risk of bias of each included study using a descriptive component approach [14]. Any disagreements were resolved by discussion among reviewers (EB, NN & MM). The overall risk of bias was judged as low, moderate, high or insufficient information. Publication bias was assessed through visual inspection of funnel plots.

2.4. Data Synthesis and Analysis

Results of clinically and statistically homogenous trials were pooled and analyzed using a fixed-effects model to provide estimates of the efficacy of the interventions. Where data were clinically or statistically heterogeneous, a random effects model was used. Meta-analyses results were expressed as mean differences (MD) and risk differences (RD) with 95% confidence intervals (CI) for continuous and binary outcomes respectively. Subgroup analyses were conducted using a priori subgroups of dose of salicylates (1–2.9/≥3 g daily), types of salicylates (salsalate and aspirin), duration of follow up (<4/4–12/≥12 weeks), and health status of participants (non-T2DM/T2DM participants) for outcomes with high heterogeneity. As the observed cardiometabolic effects were evident only with higher doses of salicylates, we analyzed the adverse events by performing a subgroup analysis for participants taking ≥3 g per day. Sensitivity analysis was also performed in which studies with high risk of bias were excluded from the analysis. Data were analyzed using STATA software version 14.