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Review

Resveratrol supplementation and plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

The results of human clinical trials have revealed that the effects of resveratrol on adipokines are inconsistent. Our objective was to elucidate the role of resveratrol supplementation on adipokines through a systematic review and a meta-analysis of available randomized placebo-controlled trials (RCTs).[1] The search included PubMed-MEDLINE, SCOPUS and ISI web of sciences database till up to 6th November 2016. Weight mean differences (WMD)[2] were calculated for net changes in adipokines using fixed-effects or random-effects models; meta-regression analysis and publication bias were conducted in accordance with standard methods. Nine RCTs with 11 treatment arms were eligible for inclusion in this systematic review and meta-analysis. Meta-analysis of data from 10 treatment arms showed a significant change in plasma adiponectin concentrations following resveratrol supplementation (WMD: 1.10 μg/ml, 95%CI: 0.88, 1.33, $p < 0.001$); $Q = 11.43$, $I^2 = 21.29\%$, $p = 0.247$). There was a significant greater adiponectin-reducing effect in trials with higher than or equal to 100 mg/day (WMD: 1.11 μg/ml, 95%CI: 0.88, 1.34, $p < 0.001$), versus those with less than 100 mg/day dosage (WMD: 0.84 μg/ml, 95%CI: −0.62, 2.31, $p = 0.260$). Meta-analysis of data from 5 treatment arms did not find any significant change in plasma leptin concentrations following resveratrol supplementation (WMD: 3.77 ng/ml, 95% CI: −2.28, 9.83, $p = 0.222$; $Q = 8.00$, $I^2 = 50.01\%$). Resveratrol significantly improves adiponectin but does not affect leptin concentrations. Additional studies are required to further evaluate the potential benefits of resveratrol on adipokines in humans.

Contents

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[1] RCTs: randomized placebo-controlled trials.
[2] WMD: weight mean difference.

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1. Introduction

The adipose tissue, an active endocrine secretory cell, produces several cytokines and hormone-like proteins, including leptin, and adiponectin, termed adipokines, which have been a breakthrough in obesity and metabolic disorder research in the last few decades [1,2], due to their important role in the regulation of energy homeostasis by affecting several biological processes, including food intake, insulin action, lipid, and glucose metabolism [3]. Changes in plasma levels of these two adipokines result in metabolic disorders, such as insulin resistance and atherosclerosis [4]. The leptin/adiponectin ratio is now considered an index linked to adiposity, atherosclerosis and cardiovascular risk [5].

Adiponectin—as an insulin-sensitizing molecule that may couple with energy metabolism [6]—exerts several other actions, mostly by improving endothelial dysfunction, enhancing fatty acid oxidation, and reducing glucose production from the liver [2]. Moreover, adiponectin has emerged as an anti-inflammatory cytokine and cardio-protective molecule, with pleiotropic effects on the cardiovascular system, as it is negatively related to cardiovascular [7,8] and other disease risk factors like obesity, metabolic syndrome, hypertension and diabetes [6]. It also reduces the foam cell formation and adhesion molecule expression [9], and stimulates nitric oxide formation in the endothelium [6]. Moreover, hypoadiponectinemia is associated with insulin resistance, hyperinsulinemia, metabolic syndrome, and coronary artery disease [10,11]. Another adipokine—leptin—is elevated with increasing body fat stores, decreasing the appetite, and increasing the energy expenditure via its effects on specific receptors in the hypothalamus [12].

Some particular foods—such as red wine, chocolates, olive oil and walnuts—have beneficial effects on the cardiovascular system due to the presence of specific compounds like polyphenols [13]. In this respect, resveratrol in grapes and wine—belonging to the stilbenoid group [14]—has attracted attention for their beneficial effects on health through its antioxidant, anti-inflammatory, cardioprotective, and neuroprotective activities. Resveratrol also improves insulin sensitivity, and decreases the lipid accumulation in obesity-related disorders [15,16]. Resveratrol supplementation might affect adipokine homeostasis and also modulate the expression of adipokines in the visceral fat [17,18]. Though the effects of resveratrol on adipokines have been widely studied in animal models [19,22], the evidence in humans is particularly limited and inconclusive.

The effects of resveratrol supplementation on the concentrations of adipokines were assessed in various studies [23–26]. There were different results when the effects of resveratrol on adipokines were considered. Positive effects were reported in some trials [27], while no effect was demonstrated in adipokines in some of the interventions with resveratrol [24]. Therefore, because of the controversy about the effects of resveratrol on adipokines, we performed a systematic review of the literature and a meta-analysis of randomized placebo-controlled trials to evaluate the effects of resveratrol supplementation on levels of plasma adipokines. The meta-analysis was conducted in accordance with the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [28].

2. Methods and materials

2.1. Search strategy

PubMed-Medline, SCOPUS, and ISI Web of Science databases were searched for RCTs that assessed the effect of resveratrol on adipokines (leptin and adiponectin), using the following search terms in titles and abstracts and also in combination with MESH terms: **(((‘resveratrol’ [Supplementary Concept]) OR resveratrols [Title/Abstract])) AND ((((‘Adipokines’[Mesh]) OR adipocytokines[Title/Abstract]) OR ‘Adiponectin’[Mesh]) OR ‘Leptin’[Mesh])**. The literature was searched up to 6th November 2016 and the search was limited to studies published in English. References in the reference lists of selected articles as also previously published review articles were searched by hand to identify additional RCTs, testing the effects of resveratrol on leptin and adiponectin in humans. Two reviewers (S.SH and R.BB) separately evaluated each article. Discrepancies were resolved by discussion with M.MS.

2.2. Study selection

Studies with the following criteria were included: 1) the clinical trials (parallel or crossover design); 2) the studies with an appropriate controlled design, i.e., the only difference between the control and treatment groups was resveratrol; 3) the baseline and post-trial values for either adiponectin or leptin with standard deviations (SDs), standard error (SE), or 95% CIs were available for each group in the study; 4) subjects ingested resveratrol for at least 4 weeks; and 5) participants were adults (age $\geq$18 years). Exclusion criteria were: (i) non-interventional studies, (ii) studies without control or placebo groups, (iii) observational studies (case-control, cross-sectional or cohort design), and (iv) a lack of sufficient information on baseline or endpoint adiponectin and/or leptin.

2.3. Data extraction

We used a screening form to select eligible articles. Eligible RCTs were reviewed and data of eligible studies were extracted by two investigators (S.SH and R.BB), using a standardized electronic form. Characteristics of the studies were recorded, including: 1) first author’s name, 2) year of publication, 3) country where the study was performed, 4) study design, 5) number of subjects in each groups, 6) intervention assigned to the control group, 7) type and