Atherosclerosis 239 (2015) 21–30

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Weight loss improves fasting flow-mediated vasodilation in adults: A meta-analysis of intervention studies

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ARTICLE INFO

Article history:
Received 29 July 2014
Received in revised form
7 November 2014
Accepted 9 December 2014
Available online 31 December 2014

Keywords:
Flow-mediated vasodilation
Endothelial function
Weight loss
Intervention studies
Meta-analysis

ABSTRACT

Background: Obesity is associated with vascular endothelial dysfunction. Effects of weight loss on endothelial function are however not clear. Therefore, we performed a meta-analysis to quantify effects of weight loss on flow-mediated vasodilation (FMD) of the brachial artery, a measurement of endothelial function.
Methods: Studies with experimental (RCTs) and quasi-experimental designs published before June 2014 were identified by a systematic search. Changes in FMD were defined as the difference between measurements before and after the study. For RCTs, changes were corrected for those in the no-weight loss control group. Summary estimates of weighted mean differences (WMDs) in FMD and 95% confidence intervals (CIs) were calculated using random-effect meta-analyses. The impact of subject characteristics, type of weight-loss treatment, and dietary composition on changes in FMD was also investigated.
Results: Four RCTs involving 265 subjects were included. Weight loss increased FMD vs. control by 3.29% (95% CI: 0.98–5.59%; $P = 0.005$; mean weight loss: 8.6 kg). A total of 1517 subjects participated in 33 studies with 49 relevant study arms. It was estimated that each 10 kg decrease in body weight increased fasting FMD by 1.11% (95% CI: 0.47–1.76%; $P = 0.001$). Effects were more pronounced when participants had coexisting obesity-related morbidities. Also, effects may be larger when subjects received low-fat diets or weight-reduction regimens including exercise therapy or weight-loss medication.
Conclusion: Weight loss significantly improves fasting FMD in adults, which is a risk marker for cardiovascular disease. Effects may depend on subject characteristics, type of weight-loss treatment, and dietary composition.

1. Introduction

Overweight and obese people have an increased risk to develop multiple metabolic disorders such as dyslipidemia, hypertension, and insulin resistance. All these metabolic risk markers are associated with vascular endothelial dysfunction, which is characterized by a decreased arterial response to stimuli that triggers the release of vasodilators from the endothelium, and predicts long-term atherosclerotic disease progression and cardiovascular event rates [1,2]. Although the mechanisms underlying the association between excess adipose tissue and reduced endothelial function [3–5] have not been fully elucidated, enhanced oxidative stress and inflammatory cytokines may play an important role. In addition, resistance to the vasomotor function of insulin and leptin, activation of the renin-angiotensin-aldosterone system (RAAS), and direct adverse effects of several adipokines and other vasoactive factors may be involved [3–7].

In two reviews, it was concluded that lifestyle changes leading to weight reduction may improve vascular endothelial function [8,9]. Results, however, were not quantitatively summarized and results of recent large clinical trials were not included. In addition,

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http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.056
0021-9150/

effects of weight loss on endothelial function were not consistent between studies. It was therefore concluded [8,9] that the impact of subject and treatment characteristics on the outcomes warranted further research. We therefore performed a meta-analysis of human intervention studies on the effects of weight loss on flow-mediated vasodilation (FMD) of the brachial artery, the current gold standard [10] and a robust [11] non-invasive measurement of vascular endothelial function. Objectives were (i) to quantitatively summarize for the first time the effects of weight loss on FMD and (ii) to examine sources of heterogeneity between studies to identify the impact of subject characteristics, type of weight-loss treatment, and dietary composition.

2. Methods

The PRISMA statement checklist for this meta-analysis is available online as supporting information (Supplemental Checklist 1).

2.1. Search strategy

Potentially relevant studies published before June 2014 were identified by a systematic search of the database PubMed (http://www.ncbi.nlm.nih.gov/pubmed). The following search terms were used to search in titles and abstracts: (weight loss or weight reduction or weight change or BMI loss or BMI reduction or BMI change or diet) and (flow mediated vasodilation (or vasodilatation or dilation or dilatation) or endothelial (or endothelium) dependent vasodilation (or vasodilatation or dilation or dilatation) or endothelial (or endothelium) function (or dysfunction) or FMD or vascular reactivity or brachial artery). The search was limited to studies in humans and to the English language. Reference lists from the selected articles were also screened manually for potentially relevant publications.

2.2. Selection of trials

Human intervention studies, that investigated the relationship between weight loss and fasting FMD of the brachial artery with experimental (RCTs) and quasi-experimental (before-and-after design) designs, were selected.

The selection was performed in two steps. First, titles and abstracts were screened. Studies were selected if they met the following inclusion criteria: human intervention study with adults, intervention with weight loss as experimental variable, no intentional co-intervention that made it impossible to estimate the effect of weight loss, and assessment of fasting vascular endothelial function by measuring FMD. In the second step, full-texts of the selected articles were read and studies were excluded based on the following criteria: missing data on FMD, no appropriate measures of variability reported, and no suitable diet-induced weight-loss intervention (i.e. weight loss achieved by exercise alone or no statistically significant weight change). Two of the authors (P.J.J. and R.P.M.) completed the literature search independently. When inconclusive, eligibility was discussed until consensus was reached.

2.3. Data extraction

For each of the selected studies, data were extracted using a custom-made database including identification of the study (first author's name and year of publication), study design (experimental or quasi-experimental), subject characteristics (sample size, age, gender, body mass index (BMI), waist circumference, baseline FMD level, and health status), treatment characteristics (type of weight-loss treatment, duration and amount of weight reduction, and dietary composition) and FMD values including measures of variance.

2.4. Statistical analysis

Statistical analyses were performed using Stata 12.0 software (Stata Corporation, College Station, TX, USA). The FMD response was quantified as the maximal percentage change in post occlusion arterial diameter relative to baseline diameter, which is the diameter of the brachial artery before the introduction of a flow stimulus in the artery. The post occlusion arterial diameter is the diameter observed within minutes of reperfusion following the release of an inflated cuff.

For RCTs including a no-weight loss control group, changes in the experimental group were first corrected for those in the no-weight loss control group. Changes in FMD were then calculated as the difference between measurements after the study (end-of-the-study values). For RCTs and intervention studies with quasi-experimental designs that did not include a no-weight control group, changes in FMD were calculated as the difference between measurements before (start-of-the-study values) and after the study (end-of-the-study values). For trials that performed FMD measurements more than one time during the study, only results of the last measurement were used.

Summary estimates of weighted mean differences (WMDs) in FMD and 95% confidence intervals (CIs) were calculated using fixed-effect meta-analyses and visualized using forest plots. The inverse of the variance ($1/SE^2$) (SE = between-subject variance) was used as a weight factor. Heterogeneity was evaluated using the Cochran's Q test ($P < 0.1$ indicates statistical significant heterogeneity) and quantified using the I^2 statistic [12–14], i.e. the percentage of variability in effect estimate that is due to heterogeneity rather than sampling error. An I^2 value above 50% indicates relevant heterogeneity between studies [15]. In case of heterogeneity, random-effect meta-analyses were used as described by DerSimonian and Laird [13].

As the number of RCTs was limited, a subgroup analysis to identify sources of heterogeneity between studies could only be performed for studies without a no-weight loss control group. As it was evident that the amount of weight loss was an important source of heterogeneity, first a lower-weight loss and a higher-weight loss group were defined. For this, the median value of weight loss for the entire group was used as cut-off point. Subgroup analyses were performed within each weight-loss group by comparing the summary results of the study arms grouped by baseline BMI, baseline FMD level, health status (healthy or coexisting obesity-related morbidities), mean age, population size, study duration, type of weight-loss treatment (diet alone, diet and exercise, diet and weight-loss medication or surgery), and dietary composition (low-fat defined as $\leq$ 30% of energy from fat or low-carbohydrate defined as $\leq$ 45% of energy from carbohydrates [16]). Median values of continuous variables in both weight-loss groups were used as cutoff values to create the binary variables. Univariate meta-regression analyses were performed to investigate the relationships between changes in body weight or waist circumference with changes in FMD. A cumulative meta-analysis was performed to evaluate the change in summary effects of weight loss on FMD over time. For this, studies were chronologically ordered by publication year, and then the cumulative WMDs were calculated at the end of each year. For all statistical analyses, two-sided tests were used. A P-value <0.05 was considered as statistically significant.

Publication bias was evaluated visually by inspecting the symmetry of funnel plots. The degree of funnel plot asymmetry was assessed with the Egger's weighted regression test. Absence of