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SYSTEMATIC REVIEW

Mediterranean dietary pattern, inflammation and endothelial function: A systematic review and meta-analysis of intervention trials

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Abstract *Background:* High adherence to a Mediterranean diet (MD) is associated with reduced all-cause and cardiovascular mortality risk. To our knowledge, there is no systematic review and meta-analysis of randomized controlled trials that has compared the effects of an MD on outcomes of endothelial function and inflammation.
Methods and results: Literature search was performed using the electronic databases MEDLINE, EMBASE, and the Cochrane Trial Register. Inclusion criteria were: randomized controlled trials, 19 + years of age, and minimum intervention period of 12 weeks. Study specific weighted mean differences (WMD) were pooled using a random effect model. Seventeen trials including 2300 subjects met the objectives. MD regimens resulted in a significantly more pronounced increase in flow mediated dilatation [WMD: 1.86%, 95% CI 0.23 to 3.48, $p = 0.02$; $I^2 = 43\%$], and adiponectin [WMD: 1.69 μg/ml, 95% CI 0.27 to 3.11, $p = 0.02$; $I^2 = 78\%$], while high-sensitive C reactive protein [WMD: −0.98 mg/l, 95% CI −1.48 to −0.49, $p < 0.0001$; $I^2 = 91\%$], interleukin-6 [WMD: −0.42 pg/ml, 95% CI −0.73 to −0.11, $p = 0.008$; $I^2 = 81\%$], and intracellular adhesion molecule-1 [WMD: −23.73 ng/ml, 95% CI −41.24 to −6.22 $p = 0.008$; $I^2 = 34\%$] turned out to be significantly more decreased.
Conclusion: The results of the present meta-analysis provide evidence that an MD decreases inflammation and improves endothelial function.

Introduction

The traditional Mediterranean diet (MD) first postulated by Ancel Keys in the 1960s [1] is defined by a high intake of virgin olive oil, vegetables, fruits, plant proteins, whole grains, fish, low-fat dairy, moderate alcohol intake, and low red meat consumption [2,3]. The Prevención con Dieta Mediterránea, a large intervention trial including 7447 subjects, showed that an MD rich in olive oil or nuts reduced the risk of cardiovascular disease (CVD) by 30% when compared to the low fat counterparts [4]. Systematic reviews investigated the effects of an MD on cardiovascular risk factors in overweight, obese and type 2 diabetic (T2D) subjects reporting improvements of these outcome parameters [5–9].

Low-grade, chronic inflammation is essential in the development of atherosclerosis, the main cause of coronary heart disease. Inflammation appears to play a key role from the initial phase to the final lesions of this disease [10] and is characterized by the infiltration of macrophages, deposition of lipids, and thickening of the vascular

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wall in response to chemo-attractant cytokines [11]. Increased expression and activation of C-reactive protein (CRP), or pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are associated with the development of atherosclerosis. A meta-analysis reported a significant association between elevated levels of IL-6, CRP and T2D risk, furthermore supporting the hypothesis that chronic inflammation is a predictor of T2D development [12]. Evidence from prospective cohort studies showed that endothelial dysfunction represents an independent risk factor for the development of many CVD [13]. Inflammation of the endothelium is regarded to play a major role in the destabilization of atherosclerotic lesions paving the way for future CVD events [13]. There is a causal link between inflammation, endothelial dysfunction and atherosclerosis. A meta-analysis reported a reduction of CRP for low- as compared to high glycemic index/load diets [14]. Furthermore, low carbohydrate diets were reported to impair flow mediated dilatation when compared to the corresponding effects of low fat diets [15]. From these observations, one may conclude that the decreased CVD mortality following MD can be explained by beneficial counter-regulatory effects of this regimen on inflammation and endothelial dysfunction. A review by the Cochrane Group concluded that the MD pattern reduces some cardiovascular risk factors in the primary prevention of CVD [16]. However, to our knowledge, there is no systematic review and meta-analysis of randomized controlled trials (RCTs) comparing the effects of an MD on outcomes of endothelial function and inflammation. Thus, it was the aim of the present study to summarize the available data regarding the impact of MD on these parameters.

Methods

Search strategy

Queries of literature were performed using the electronic databases MEDLINE, EMBASE, and the Cochrane Library until February 22nd, 2014 with restrictions to RCTs, but not to language and calendar date using the following search terms: *("Mediterranean diet" or "diet" or "Mediterranean" or "score" or "pattern" or "adherence")* in combination with *("inflammation" or "endothelial" or "vascular")*. This systematic review was planned, conducted, and reported in adherence to standards of quality for reporting meta-analyses [17]. Literature search was conducted independently by both authors, with disagreements resolved by consensus.

Selection criteria

Studies were included in the meta-analysis if they met all of the following criteria: *(i)* randomized controlled or cross-over design; *(ii)* minimum intervention period of 12 weeks; *(iii)* MD dietary intervention or provision of dietary factors relevant to the MD with at least two components from the following list required:

- High monounsaturated/saturated fat ratio (use of olive oil as main cooking ingredient),
- Low to moderate red wine consumption,
- High consumption of legumes,
- High consumption of grains and cereals,
- High consumption of fruits and vegetables,
- Low consumption of meat and meat products and increased consumption of fish,
- Moderate consumption of milk and dairy products;

(iv) comparison group was no intervention or minimal intervention ((ii) − (iv) according to Rees et al., 2013 [16]); *(iv)* participants ≥19 years of age; *(v)* sample size: no exclusion criteria (sensitivity analyses were performed according to study populations); *(vi)* assessment of the "outcome of interest" markers descriptive of chronic inflammation (CRP, IL-6, adiponectin, AD) and endothelial function (intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-Selectin, FMD); *(vii)* report of change from baseline values (if not available, post-intervention mean values were used instead) with standard deviation (or basic data to calculate these parameters: standard errors, 95% confidence interval, *p*-values). If data of ongoing studies were published as updates, results of only the longest duration periods were included.

Data extraction and quality assessment

The risk of bias assessment tool by the Cochrane Collaboration was applied specifying the following bias domains: selection, performance/detection, attrition, and reporting bias [18] (Supplemental Fig. S1). The following data were extracted from each study: the first author's last name, year of publication, study length, gender distribution and age, BMI, % diabetics, sample size, study design, description of MD intervention and comparison group, energy content of diets, outcomes and post mean values or differences in mean of two time point values with corresponding standard deviation. Data extraction was conducted by one author (L.S.), whereas quality assessment was independently performed by both authors (L.S. and G.H.), with disagreements resolved by consensus.

Data synthesis and analysis

For each outcome parameter, a meta-analysis was performed in order to determine the pooled effect of the intervention in terms of weighted mean differences (WMDs) between the change from baseline or post-intervention mean values of the MD and control groups. Combining both data in one meta-analysis is an accepted method described by the Cochrane Collaboration [19]. All data were analyzed using the REVIEW MANAGER 5.1 software, provided by the Cochrane Collaboration (http://ims.cochrane.org/revman). The random-effects model was used to estimate WMDs with 95% confidence intervals (CIs). Forest plots were generated to illustrate the study-specific effect sizes along with a 95% CI. Data were