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Mediterranean diet supplemented with nuts reduces waist circumference and shifts lipoprotein subfractions to a less atherogenic pattern in subjects at high cardiovascular risk

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ABSTRACT

Objective: The PREDIMED trial showed that Mediterranean diets supplemented with either extra-virgin olive oil or nuts reduced incident cardiovascular events compared to a control diet. Consumption of both supplemental foods has been associated with reduced LDL-cholesterol, but it is unknown whether they can shift lipoprotein subfractions to a less atherogenic pattern. We investigated changes in adiposity and lipoprotein subfractions after consumption of the PREDIMED diets.

Methods: In a PREDIMED sub-cohort ($n = 169$), lipoprotein subclasses (particle concentrations and size) were determined by nuclear magnetic resonance spectroscopy at baseline and after intervention for 1 year.

Results: Participants allocated to the Mediterranean diet supplemented with nuts showed significant reductions from baseline of waist circumference (mean [95% CI]; −5 cm [−7; −3]) and concentrations of medium-small (−27 nmol/l [−46; −8]) and very small LDL (−111 nmol/l [−180; −42]); decreased LDL particle number (a nuclear magnetic resonance-specific measurement) (−98 nmol/l [−184; −11]); and an increase of large LDL concentrations (54 nmol/l [18; 90]), with a net increase (0.2 nmol/l [0.1; 0.4]) of LDL size. The Mediterranean diets with olive oil and nuts increased large HDL concentrations (0.6 μM [0.0; 1.1] and 1.0 μM [0.4; 1.5], respectively). Compared to the other two intervention groups, participants in the nut-enriched diet showed significantly reduced waist circumference ($p \leq 0.006$, both) and increased LDL size ($p < 0.05$, both).

Conclusion: Lipoprotein subfractions are shifted to a less atherogenic pattern by consumption of Mediterranean diets enriched with nuts. The results contribute mechanistic evidence for the reduction of cardiovascular events observed in the PREDIMED trial.

1. Introduction

Coronary heart disease (CHD) mortality in Mediterranean areas is low compared to Northern Europe [1,2] and the US [2]. This could be explained in part by local dietary habits, such as adherence to the Mediterranean diet (MeDiet), the most likely dietary model to provide protection against cardiovascular disease (CVD) [3,4].

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This notion is supported by results from the recent randomized controlled clinical trial PREDIMED (PREvención con DIeta MEDiterránea; www.predimed.org). In this study, conducted in 7447 participants at high cardiovascular risk but no CVD at enrolment, intervention with MeDiets supplemented with either extra-virgin olive oil (EVOO) or mixed nuts for nearly 5 years reduced by 30% the incidence of a composite endpoint of cardiovascular death, myocardial infarction and stroke in comparison with a control diet (advice on a low-fat diet) [5].

The precise mechanisms involved in the cardioprotection afforded by EVOO and nuts remain to be fully elucidated. Increased consumption of these foods is associated with decreased circulating inflammatory biomarkers related to atherogenesis [6]; therefore it is plausible that they might reduce CVD by delaying the development of atherosclerosis, the harbinger of most cardiovascular events. Atherosclerosis is triggered by the entry of LDL particles into the arterial intima and their oxidative modification, whereby inducing a self-perpetuating inflammatory response that eventually leads to the formation of atheroma plaques, the hallmark of the disease [7]. It has been known for some time that LDL particles are heterogeneous, comprising multiple distinct subclasses that differ in their metabolic behaviour and atherogenic potential. As opposed to large and buoyant LDL particles, small and dense LDL confer a greater atherogenic risk because of decreased removal by LDL receptors, increased residence time in the circulation, greater binding to arterial wall proteoglycans, easy penetration to the subendothelial space, greater susceptibility to oxidative modification, and enhanced uptake by scavenger receptors in macrophages [8,9].

There is increasing evidence that dietary modification can be a major determinant of LDL number and particle size (reviewed in Ref. [10]). Interventional studies consistently show that nut intake is associated with a reduction of total and LDL cholesterol [11,12]. Additionally, walnuts [13] and almonds (in combination with plant sterols, vegetable protein and viscous fibre) [14] have been reported to redistribute LDL subfractions and reduce the cholesterol content of small, dense LDL. Consumption of polyphenol-rich EVOO as replacement of common olive oil (with low polyphenol content) has also been associated with LDL cholesterol reduction [12,15], although an olive-oil based high-MUFA diet failed to show an effect on small, dense LDL in men undergoing a weight-losing diet [16]. We therefore hypothesized that, in subjects at high vascular risk, MeDiets supplemented with either EVOO or nuts for 1 year would shift lipoprotein subfractions to a less atherogenic pattern when compared to a control diet.

2. Subjects and methods

2.1. Design and study subjects

The present randomized clinical trial was conducted within the PREDIMED study (ISRCTN35739639). The protocol has been reported in detail elsewhere [17]. For this study we selected 169 participants recruited in the Barcelona-North site between December 2004 and January 2009. Participants were men aged between 55 and 80 years and women aged between 60 and 80 years at high cardiovascular risk but no CVD at enrolment. Inclusion criteria were either type-2 diabetes or at least three of the following risk factors: current smoking (>1 cigarette/day during the last month); hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or antihypertensive medication); LDL-cholesterol ≥160 mg/dl; HDL-cholesterol ≤40 mg/dl in men or ≤50 mg/dl in women, independently of lipid-lowering therapy; BMI ≥ 25 kg/m^2; and family history of premature CHD (definite myocardial infarction or sudden death in first-degree relatives before 55 years in men or before 65 years in women). Exclusion criteria were a prior history of CVD, any severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts (supplemental foods given in two arms of the study), and low predicted likelihood of changing dietary habits. At the first visit, participants provided data about medical history, medication use, and lifestyle, including dietary habits. Anthropometric and blood pressure measurements were performed and fasting blood samples were drawn at baseline and after intervention for one year. The study protocol was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the ethics committee of the institution. Written informed consent was obtained from all subjects.

A total sample size of 51 participants per group provides >90% power to detect a significant difference among dietary arms in changes of the main outcome (very-small LDL particle concentrations) with a two-sided type I error of 0.05. These calculations were based on published very-small LDL data before and after a dietary intervention including nuts [14].

2.2. Assessment of risk factors

Participants were considered as diabetic, hyperlipidemic or hypertensive if they had a previous diagnosis of these conditions and/or they were treated with antidiabetic, cholesterol-lowering, or antihypertensive agents, respectively. Smoking status was categorized into never, current or past smoking according to self-reports. Physical activity was determined with the validated Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire [18]. Height, weight, and waist circumference were measured with standard methods. Trained personnel measured systolic and diastolic blood pressure in triplicate with a validated semi-automatic oscillometer (Omron HEM-705CP; Hoofddorp, The Netherlands).

2.3. Diets

The dietary habits of participants were assessed using a validated 137-item food frequency questionnaire [19]. At the inclusion visit and after intervention for 1 year, the food frequency questionnaire was completed by a trained dietician in face-to-face interviews. Participants were asked about the frequency of consumption of each food item during the past year, specifying usual portion sizes (semi-quantitative assessment). Nine possibilities of frequency were offered, from never to more than six times a day. Nutrient intakes were computed using Spanish food composition tables [20] and were adjusted for energy intake by the residual method [21]. After the screening visit, suitable candidates were randomly assigned to one of the three interventions: MeDiet with EVOO, MeDiet with mixed nuts or control diet. The two groups allocated MeDiets received intensive education to follow the MeDiet and supplemental foods at no cost. EVOO (1 L/week) was provided to one group and 30 g/day of mixed nuts (15 g walnuts, 7.5 g hazelnuts and 7.5 g almonds) to the other group. To improve compliance, and to account for family needs, participants in the corresponding MeDiet groups were given excess EVOO or additional packs of nuts. In the control group, participants were given advice to follow a low-fat diet and received non-food gifts.

At baseline and quarterly, dieticians run individual and group sessions separately for each group. In each session, a dietary screener of adherence to the MeDiet was used to track changes of dietary habits. The score was determined by 12 questions on food consumption frequency and 2 questions on food intake habits considered characteristic of the MeDiet (each question scored 0 or 1) [22].