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Carotid intima-media thickness changes with Mediterranean diet: A randomized trial (PREDIMED-Navarra)☆

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ABSTRACT

Objective: Observational studies have reported inverse associations between adherence to the Mediterranean diet (MedDiet) and atherosclerotic disease. We tested the effect of two types of MedDiet on progression of subclinical carotid atherosclerosis.

Methods: We randomized 187 high-cardiovascular-risk asymptomatic subjects (51% women, mean age 67 years) to three treatment arms: MedDiet with supplemental virgin olive oil (VOO), $n = 66$; MedDiet with supplemental nuts, $n = 59$; and control diet, $n = 62$. Participants received nutrition behavioral counseling in quarterly group and individual educational sessions. Free supplemental foods were provided to the MedDiet groups. Changes in mean intima-media thickness (IMT) were measured ultrasonographically in the far wall of bilateral common carotid arteries after 1 year.

Results: Overall, no significant between-group differences in IMT progression were observed after 1-year. However, a significant interaction ($p = 0.03$) between baseline IMT and treatment effect was apparent. Among participants with baseline IMT ≥ 0.9 mm, 1-year IMT changes versus control showed significant differences of −0.079 mm (95% confidence interval, −0.145 to −0.012) for the MedDiet with VOO and −0.072 mm (−0.140 to −0.004) for the MedDiet with nuts. No IMT changes occurred in any intervention group among participants with lower baseline IMT values (<0.9 mm).

Conclusions: MedDiets enhanced with VOO or nuts were not effective in inducing ultrasonographic regression of carotid atherosclerosis after 1 year intervention. However, they were effective among subjects with elevated baseline IMT, suggesting that subclinical atherosclerosis may respond to dietary intervention within a relatively short time frame only among subjects with a high initial atherosclerotic burden.

1. Introduction

Cardiovascular atherosclerotic disease is the leading cause of death worldwide [1]. Because atherosclerosis progresses unnoticed over decades, preclinical markers contribute to early detection and prevention strategies [2]. Ultrasound measurements of carotid intima-media thickness (IMT) are well validated surrogate markers of preclinical atherosclerosis and future cardiovascular events [2–5].

Lifestyle and dietary habits are thought to powerfully affect cardiovascular risk [6,7]. Observational studies have reported that carotid IMT is inversely associated with adherence to dietary patterns characterized by high plant-food intake and low intake of processed and saturated fat-rich foods [8–10]. Few randomized trials have tested lifestyle interventions on carotid IMT progression rates, with discordant results [11–14]. This might be due in part to testing different interventions in specific population groups. Particularly, the effect of changes in the dietary pattern alone, without energy restriction or increased physical activity, cannot be ascertained from available trials.

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While the Mediterranean diet (MedDiet) is increasingly recognized as a cardioprotective food pattern [7,15], no clinical trial has specifically tested adherence to the MedDiet without energy restriction on IMT progression. A recent weight loss trial that examined energy-restricted diets (including a MedDiet) for 2 years in overweight and obese subjects reported non-significant carotid IMT changes, though there was a significant regression of mean carotid vessel wall volume in all weight-loss diet groups [16].

We conducted a randomized trial to compare the 1-year effects on carotid IMT progression of three non-calorie-restricted nutritional interventions, a low-fat diet (control diet), a MedDiet supplemented with virgin olive oil (VOO), and a MedDiet supplemented with mixed nuts.

2. Methods

2.1. Trial design

The PREDIMED (PREvención con DIeta MEDiterránea) study is an on-going cardiovascular primary prevention trial conducted in Spain comparing two interventions with MedDiet versus a control group. The trial was not designed to compare outcomes between the two MedDiets but between each one of them versus a single reference group (control diet). The design and methods of the overall PREDIMED trial have been the subject of a specific publication [17]. Further details are available at www.predimed.es. The present analysis deals with a subsample from one of the 11 recruitment centers (PREDIMED-Navarra).

2.2. Participants

Candidates were community-dwelling men (55–80 years) or women (60–80 years), without cardiovascular disease but at high risk because of the presence of type-2 diabetes or at least three traditional major cardiovascular risk factors [17]. A random subsample of 240 of the 1055 participants recruited in the PREDIMED-Navarra center was selected for sequential carotid IMT measurements. Among them, 199 participants successfully underwent baseline measurements of IMT and 187 of them completed again this measurement after 1-year follow-up. All participants provided informed consent to a protocol approved by the local Ethical Review board.

2.3. Nutrition interventions

A previously described behavioral intervention promoting the MedDiet was implemented [17,18]. Briefly, at inclusion and quarterly thereafter, dietitians gave personalized dietary advice to participants randomized to the two MedDiets, with instructions directed to upscale a 14-point score of adherence to the MeDiet [17–19]. Dietitians administered also group sessions, separately for each group. Sessions consisted of informative talks and delivery of written material including seasonal shopping lists, meal plans, and recipes. Participants assigned the MedDiet groups were given free allotments of either VOO (1 l/week) or raw, unprocessed nuts (30 g/day: 15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts). Participants allocated to the control (low-fat) group received recommendations to reduce all types of fat. Energy restriction was not advised, nor physical activity promoted. Observed changes in food and nutrient intake after 1 year were in the expected direction [18].

2.4. Measurements

At baseline and at the 1-year visit we administered questionnaires about lifestyle, medical conditions, medication use, a 137-item validated food frequency questionnaire [20] and a short 14-point questionnaire assessing adherence to the MedDiet [19]. Energy and nutrient intakes were calculated from Spanish food composition tables, as described [17,20,21].

2.5. Carotid ultrasonography

The primary outcome was the 1-year between-group change in carotid IMT. B-mode ultrasound imaging of the right and left carotid arteries was performed at baseline and after 1 year of intervention with a 5–12 MHz broadband linear array transducer, according to the recommendations of Mannheim carotid intima-media thickness consensus [5]. We used an HDI 1500 (ATL, Bothell, Washington, DC, USA) apparatus. Patients were examined in the supine position with the head turned 45° contralateral to the side of scanning. A standardized imaging protocol was used for the common carotid artery (CCA) IMT measurements. With the carotid dilatation and flow divider as anatomic landmarks, the sonographer obtained high-resolution images of the CCA 1 cm proximal to the bifurcation using a single lateral angle of insonation and optimizing the image for the arterial far wall. Two certified sonographers (PI, MMF) blinded to clinical information and to group allocation performed all procedures. Digital images from diastolic frame recordings were electronically transferred to either an offline workstation for quantification or stored on DVD for ensuing offline IMT measurements.

The outcome variable was mean CCA-IMT, defined as the average of multiple measurements of the far-wall IMT of the right and left CCA. Off-line measurements of IMT were performed for each side by using the edge-tracking software M'Ath (ICN-METRIS, Argenteuil, France), as described [22]. Between- and within-observer reproducibility of paired readings of mean CCA-IMT was adequate as previously reported, with regression coefficients of 0.76 ($p < 0.0001$) and 0.82 ($p < 0.0001$), respectively [23]. The between-observer CV of paired readings of mean CCA-IMT was 5%.

2.6. Statistical analyses

Regardless of actual compliance with the intended dietary intervention, we performed our analyses based on an intention-to-treat principle. Differences in baseline IMT and within-group changes after 1 year were adjusted for age, sex, and hyperlipidemic status at baseline. Between-group differences in changes of mean IMT versus the control group for the two MedDiet interventions were estimated using multivariable linear regression models, adjusting for the above-mentioned factors. Subgroup analyses were prespecified for baseline IMT, using 0.9 mm as the cutoff point, a value that has been defined by the European Societies of Cardiology and Hypertension as definitely abnormal [24] and that roughly corresponds to the 75th percentile of the distribution of mean CCA-IMT values for healthy Spanish men and women aged ≥ 65 years and indicates a high cardiovascular risk [25]. The interaction between baseline IMT and its change after intervention was appraised by introducing a product-term in the multivariable model.

3. Results

No significant differences were found for mean age, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, body mass index, waist circumference, blood pressure, proportion of men, proportion of diabetics or proportion of smokers between this subgroup undergoing repeated IMT measurements ($n = 187$) and the rest of PREDIMED participants in our center ($n = 868$) (not shown in tables).

Characteristics of participants who completed the trial were similar in the three groups at baseline (Table 1), albeit there was a small non-significant imbalance for hyperlipidemia. Within the group of participants ($n = 61$) with higher baseline IMT (≥0.9 mm),

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Table 1
Characteristics of participants according to group allocation and to baseline carotid intima-media thickness (IMT).

	MedDiet + VOO (n = 66)	MedDiet + nuts (n = 59)	Control (n = 62)	Baseline IMT < 0.9 mm (n = 126)	Baseline IMT≥0.9 mm (n = 61)
Age, years	67 ± 6	67 ± 6	67 ± 5	66 ± 6	68 ± 6
% male sex	49	56	42	41	66*
% family history of early-onset CHD	17	12	13	15	10
Smoking					
Current smoker	15	17	19	17	18
Former smoker	30	29	29	21	44*
Body mass index, kg/m^2	29.7 ± 3.9	29.2 ± 3.2	29.3 ± 3.1	29.2 ± 3.5	29.9 ± 3.2
Waist circumference, cm	97 ± 11	97 ± 11	95 ± 9	94 ± 10	100 ± 9*
% hypertension at baseline	73	85	79	80	75
% type-2 diabetes at baseline	42	31	27	29	43
% hyperlipidemia at baseline	70	59	73	62	79*
% use of statins	35	36	35	67	61
% antihypertensive medication	71	68	79	29	25
% antihyperglycemic agents	26	20	15	15	31
% antiplatelet drugs	14	10	10	10	10
Educational level					
Primary or lower level	76	68	63	70	67
Baseline adherence to MedDiet (14-point score)	9.1 ± 1.6	9.1 ± 1.8	8.7 ± 1.8	9.1 ± 1.6	8.6 ± 1.9*
1-year adherence to MeDiet (14-point score)	11.5 ± 1.7	11.7 ± 1.4	9.6 ± 1.5**	11.1 ± 1.6	10.7 ± 2.0

±SD or n (%).
MedDiet: Mediterranean diet; VOO: virgin olive oil; CHD: coronary heart disease.
* $p < 0.05$.
** $p < 0.0001$ for the comparison of means among the three groups (ANOVA).

no relevant between-group differences were found for baseline characteristics (data not shown). More men, higher prevalence of risk factors and lower baseline adherence to the MedDiet were found among participants with higher baseline IMT (Table 1, last two columns). Use of therapeutic agents that can influence IMT progression, such as statins or antihypertensive agents, was similar in participants with high or low IMT.

As intended, adherence to the MedDiet significantly improved in the two intervention groups as compared to the control group (Table 1, last row).

Baseline IMT values were well balanced in the three groups (Table 2). In all groups, mean IMT was reduced after one year (Table 2). However, this within-group reduction was only statistically significant for the second group (MedDiet + nuts) as both limits of the 95% confidence interval (CI) showed negative values: −0.031 mm (95% CI: −0.055 to −0.007). When we divided the sample according to baseline IMT (cut-off: 0.9 mm), significant reductions were observed for both intervention groups only among participants with baseline IMT ≥ 0.9 mm (Table 2, last row, Fig. 1).

When we compared the average change in both intervention groups versus the control group (reference category, i.e., mean = 0), no apparent between-group differences were observed for the overall cohort (Table 3). A significant interaction (p = 0.03) existed between baseline IMT (dichotomized at 0.9 mm) and the intervention. In the subset of participants with baseline IMT ≥ 0.9 mm,

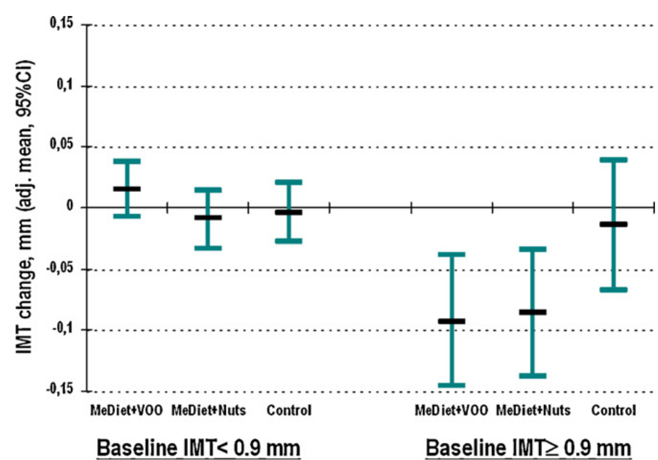

Fig. 1. Changes in Common Carotid Intima-Media Thickness (IMT) by baseline IMT and intervention group. MeDiet: Mediterranean diet; VOO: virgin olive oil.

significant adjusted 1-year differences in IMT changes for the two MedDiet arms versus the control group were found, either when considering them separately or when merged into a single group (Table 3). No between-group differences were observed for participants with a baseline IMT < 0.9 mm.

Table 2
Baseline common carotid artery IMT and within-group changes at 1 year by intervention group.

	MedDiet + VOO (n = 66)	MedDiet + nuts (n = 59)	Control (n = 62)	p value*
Baseline IMT, mm	0.825 (0.780; 0.870)	0.854 (0.817; 0.891)	0.840 (0.809; 0.871)	0.56
1-year IMT, mm	0.809 (0.774; 0.844)	0.821 (0.795; 0.848)	0.830 (0.798; 0.862)	0.38
1-year change in IMT, mm	−0.016 (−0.043; 0.011)	−0.033 (−0.058; −0.008)	−0.010 (−0.026; 0.005)	0.38
Adjusted 1-year change in IMT, mm**	−0.012 (−0.035; 0.011)	−0.031 (−0.055; −0.007)	−0.007 (−0.031; 0.017)	0.33
Adjusted 1-year change in IMT, mm**				
Baseline IMT < 0.9 mm	0.015 (−0.008; 0.037)	−0.009 (−0.033; 0.014)	−0.004 (−0.028; 0.020)	0.30
Baseline IMT ≥ 0.9 mm	−0.093 (−0.146; −0.039)	−0.086 (−0.138; −0.034)	−0.014 (−0.067; 0.039)	0.04

Values are means (95% confidence interval).
MedDiet: Mediterranean diet; VOO: virgin olive oil; IMT: intima-media thickness.
* Duncan post hoc test.
** Adjusted for age, sex, and hyperlipidemia at baseline.

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Table 3
Differences in changes of common carotid artery IMT among intervention groups, stratified by baseline IMT.

	n	Control (1)	MedDiet + VOO(2)	MedDiet + nuts(3)	*p* value (1 versus 2)	*p* value (1 versus 3)
Univariate analysis						
Baseline IMT < 0.9 mm	126	0 (ref.)	0.018 (−0.014; 0.050)	−0.007 (−0.040; 0.026)	0.27	0.67
Baseline IMT ≥ 0.9 mm	61	0 (ref.)	−0.064 (−0.129; 0.002)	−0.057 (−0.124; 0.009)	0.06	0.09
Univariate analysis *(both MedDiet groups merged)*						
Baseline IMT < 0.9 mm	126	0 (ref.)	0.006 (−0.022; 0.035)		0.66	
Baseline IMT ≥ 0.9 mm	61	0 (ref.)	−0.060 (−0.117; −0.004)		0.04	
Multivariate analysis*						
Baseline IMT < 0.9 mm	126	0 (ref.)	0.018 (−0.014; 0.051)	−0.006 (−0.039; 0.028)	0.26	0.74
Baseline IMT > = 0.9 mm	61	0 (ref.)	−0.079 (−0.145; −0.012)	−0.072 (−0.140; −0.004)	0.02	0.04
Multivariate analysis* *(both MedDiet groups merged)*						
Baseline IMT < 0.9 mm	126	0 (ref.)	0.008 (−0.021; 0.036)		0.61	
Baseline IMT > = 0.9 mm	61	0 (ref.)	−0.075 (−0.133; −0.018)		0.01	

Values are means (95% confidence interval).
MedDiet: Mediterranean diet; VOO: virgin olive oil; IMT: intima-media thickness.
* Adjusted for age, sex, and hyperlipidemia at baseline.

4. Discussion

In this randomized trial we did not find any significant effect on IMT progression for the overall cohort after 1-year intervention with MedDiets. The number of participants was relatively small and low statistical power might account for this non-significant result. However, in the subgroup of participants with higher baseline atherosclerosis the consumption of MedDiets was associated with ultrasonographic regression of carotid IMT after intervention for 1 year, suggesting that subclinical atherosclerosis may respond to dietary intervention within a relatively short time frame only in those with a high initial atherosclerotic burden. Thus, an apparent effect versus the control group was observed only in participants with baseline IMT ≥ 0.9 mm. It is likely that the thinning effect of any anti-atherosclerotic intervention on the arterial wall directly relates to baseline thickness with little benefit for subjects who already have a low IMT, as shown in clinical trials using high-dose statins [26,27]. Our results, though non-significant for the overall cohort, lend some support to the vasculoprotective role of the MedDiet in subjects with a higher degree of subclinical atherosclerosis [7,15]. This can be applied also to the key Mediterranean foods supplemented in the study, VOO [28] and nuts [29].

Increased carotid IMT is a well-known predictor of future cardiovascular events [3–5,30]. This suggests that the enhanced MedDiets used in our study might provide vascular benefit after intervention for just 1 year only in subjects with a higher initial degree of atherosclerosis. By showing reductions in cardiovascular risk factors levels [31] and the metabolic syndrome [32] with the MedDiets after 3 months and 1 year, respectively, earlier results of the PREDIMED trial are consistent with an anti-atherosclerotic effect. They are also in agreement with previous observational studies [15,33,34]. The MedDiets used in the PREDIMED study were found to downregulate cellular and circulating adhesion molecules and other inflammatory biomarkers [35], further supporting their anti-atherogenic effect.

Available trials of lifestyle interventions on carotid IMT progression have reported inconsistent results, partly because they were testing different interventions in specific population groups [11–14]. The DIRECT-Carotid study [16] assessed carotid IMT before and after 2 years of nutrition intervention with three weight-loss diets, including one MedDiet arm. Participants were younger, mostly male, and had a lower baseline IMT. No significant changes were reported, but a significant regression of carotid vessel wall volume was documented, suggesting an anti-atherosclerotic effect [16].

The increasing accrual of evidence showing that the consumption of both VOO and nuts is associated with improved lipid profiles, better insulin sensitivity, reduced oxidative stress and inflammation, and enhanced endothelial function further supports the biological plausibility of our results [28,29].

Two potential limitations to our study deserve to be mentioned. First, the generalization of our findings to younger and/or healthier individuals from other geographical locations is uncertain, although the beneficial effect on carotid IMT may be reproduced in other populations, as it has been shown for several benefits of the MedDiet in US populations [15]. Another limitation is the small number of subjects examined, as carotid ultrasound was not part of the initial examination of all the PREDIMED trial participants.

In conclusion, intervention with enhanced MedDiets was associated with carotid IMT regression only in participants with a high carotid IMT at baseline. The results suggest that a non-energy-restricted traditional MedDiet enriched with VOO or nuts can be a useful tool in the lifestyle management of subjects with measurable preclinical atherosclerosis. Longer follow-up of the entire PREDIMED cohort may eventually provide stronger evidence of the cardiovascular benefits of the MedDiet.

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Conflict of interest statement

ER has received research funding from the California Walnut Commission, Sacramento, CA and is a non paid members of its Scientific Advisory Committee. All other authors declare that they have no conflict of interest.

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