Close adherence to a Mediterranean diet improves endothelial function in subjects with abdominal obesity[1–3]

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ABSTRACT

Background: Abdominal obesity (AO) is associated with increased risk of cardiovascular disease and type 2 diabetes, whereas the Mediterranean diet exerts a cardioprotective effect.

Objective: We examined whether a close adherence to a Mediterranean-style diet improves endothelial function in individuals with AO.

Design: We recruited 90 subjects with AO without cardiovascular disease or type 2 diabetes. Participants were randomly assigned to the intervention or control group. Both groups were instructed to follow a Mediterranean-style diet for 2 mo. Subjects in the intervention group additionally had to follow a specific relevant daily and weekly food plan with close supervision by a dietitian and provision of basic foods. Flow-mediated dilatation (FMD), lipids, C-reactive protein (CRP), and insulin resistance with the homeostasis model assessment (HOMA-IR) were measured.

Results: After 2 mo, subjects in the intervention group increased their intake of total fat due to higher consumption of monounsaturated fatty acids as well as intakes of dietary fiber, vitamin C, and alcohol compared with the control group (all $P < 0.05$). The intervention group also increased FMD (2.05%; 95% CI: 0.97, 3.13%), whereas no effect was found in the control group (−0.32%; 95% CI: −1.31, 0.67%). Changes in lipids and CRP concentrations did not differ between the 2 groups, whereas diastolic blood pressure decreased in the intervention group (−6.44 mm Hg; 95% CI: −8.57, −4.31 mm Hg) compared with the control group (−0.76 mm Hg; 95% CI: −2.83, 1.31 mm Hg). Finally, there was a trend for a reduction in HOMA-IR in the intervention group compared with the control group ($P = 0.072$).

Conclusion: Close adherence to a Mediterranean-style diet achieved by close dietetic supervision improves endothelial function in subjects with AO. *Am J Clin Nutr* 2009;90:263–8.

INTRODUCTION

According to National Cholesterol Education Program (NCEP) criteria (1), one-third of men and one-half of women globally have abdominal obesity (AO), which is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes (2, 3). The IDEA (International Day for the Evaluation of Abdominal obesity) Study found that AO, measured by waist circumference, showed a graded relation with both CVD and type 2 diabetes at all values of body mass index (BMI; in kg/m^2) (2). According to several experts, AO is the obesity phenotype most likely to be associated with insulin resistance, atherogenic dyslipidemia, increased production of inflammatory cytokines, coagulation abnormalities, and CVD (4–6).

Numerous epidemiologic and intervention studies have shown that the Mediterranean diet is associated with a lower incidence of coronary heart disease (7–10). The exact mechanism through which the Mediterranean diet has cardioprotective effects is uncertain (11). It has been suggested that reduction of oxidative stress, antiinflammatory effect, improvement in endothelial function, and favorable effect on lipid profile are possible mechanisms. Although there are contradictory results about the effect of the Mediterranean diet on endothelial function (12–14), compliance has been a major problem in achieving dietary intervention. Results from the MARGARIN (Mediterranean Alpha linolenic enRiched Groningen dietARy INtervention) Study showed that a posted leaflet available to participants was not as effective as intensive dietary counseling in group sessions in changing dietary behavior (15). In another study, nutritional intervention to promote the Mediterranean diet under close dietetic supervision was associated with a decrease in oxidized LDL concentrations in healthy French-Canadian women (16). The PREDIMED (Prevención Dieta Mediterránea) Study reported that nutritional intervention promoting the Mediterranean diet in group sessions, coupled with free provision of Mediterranean-related dietary products, was more effective in improving dietary habits of participants than were verbal instructions and a leaflet recommending the third NCEP Adult Treatment Panel dietary guidelines (17). The aim of this study, therefore, was to assess the effect of the Mediterranean diet

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combined with close dietetic supervision on endothelial function in individuals with AO.

SUBJECTS AND METHODS

Subjects

Ninety subjects with AO (waist circumference >102 cm for men and >88 cm for women) were recruited from the outpatient Cardiology Department of the University Attikon Hospital and Hygeias Melathron Infirmary in Athens, Greece, between June 2005 and June 2008. They were selected from a pool of 340 healthy subjects who were employees in a national bank who had been referred for their annual check-up. Exclusion criteria were presence of type 1 or 2 diabetes or CVD, age >70 y, use of multivitamins, extensive alcohol drinking (>500 g alcohol/wk), and presence of malignancy or any disease state that might influence inflammatory markers. Furthermore, during the previous 6 mo participants should not have taken part in any weight-reduction program or other nutritional interventions or have practiced regular extreme physical activity (>6 h vigorous exercise/wk). The study was approved by the ethics committee of our institution, and all subjects provided informed consent.

Study design

On enrollment participants were assigned to the intervention (n = 46) or the control (n = 44) group with the use of a sequence of random binary numbers (ie, 001110110 in which 0 represented the intervention group and 1 the control group). At their first appointment with the dietitian, all participants were informed about the study, asked to keep a 3-d food diary, and completed a basic questionnaire to determine age, socioeconomic status, medical history, family history, physical activity, and smoking and alcohol consumption habits. All participants were provided with a copy of the Greek Mediterranean diet and were counseled on this type of eating pattern.

The intervention group received more counseling on food groups and specific items, frequency, and portion size of each food group to be consumed, and they were asked to follow a specific daily and weekly food plan. The food plan included daily consumption of whole-wheat grains and products, 2–3 portions of low-fat dairy products, 2 salads (one of which should contain ≥1 tomato) and ≥3 fruit together with a concentrated fruit juice made without preservatives (provided by ELAIS-Unilever Hellas SA), 5 mL (ie, 1 teaspoon) olive oil–based margarine (provided by ELAIS-Unilever Hellas SA), extra virgin olive oil as the main source of fat (provided by ELAIS-Unilever Hellas SA), 45 mL (ie, 3 tablespoons) extra virgin olive oil with 1 of the 2 salads, 6 whole raw almonds, and 150 mL (1 wine glass) red wine (provided by Harlaftis Ltd, Greece) with their main meal. According to the food plan, the intervention group was required to consume ≥1 portion of fish and at the most 1 portion of red meat weekly. The intervention group was closely supervised by a dietitian who made weekly phone calls and attended weekly appointments with participants. During these sessions body weight was measured, and participants handed in their 3-d food diary (every second session), completed a 24-h recall, and returned the empty packets of the products they had received previously along with the food plan check lists.

The objective of the 24-h recall was to check subjects' compliance and to reinforce the key principles of the Mediterranean diet. Additional 3-d food diaries were used to measure dietary intake at both the beginning and the conclusion of the study. Subjects in the control group met with the dietitian only at the beginning and the end of the study.

The duration of dietary intervention was 2 mo in both groups. Height, body weight, and waist circumference were measured in all participants at the beginning and at the end of the study. BMI was calculated.

Energy and nutrient intake

Both groups kept food diaries for 3 d at the beginning and at the end of the study. The analysis of the food diaries was carried out with the use of NUTRITIONIST V diet analysis software (version 2.1, 1999; First Databank, San Bruno, CA).

Compliance

Compliance was monitored by participants who made weekly telephone contacts with the dietitian; attended the arranged sessions; provided 3-d food diaries, 24-h recalls, and a check list of the foods they consumed daily; and returned the empty packages of the food they had been provided.

Blood sampling and laboratory methods

The volunteers attended the Department of Cardiology at Attikon Hospital twice for blood collection, ie, at the beginning and the end of the study. Venous blood samples were obtained at 0800 after a 12-h overnight fast. Samples were centrifuged at 3000 rpm for 10 min at 4°C within 2 h of blood collection and stored at −80°C until analyzed.

Serum total cholesterol, triglycerides, and HDL-cholesterol concentrations were determined by enzymatic colorimetric assays with the use of an ACE analyzer (Schiapparelli Biosystems Inc, Fairfield, NJ). LDL cholesterol was calculated by the Friedewald equation (18). C-reactive protein (CRP) was assayed by high-sensitivity particle-enhanced immunonephelometry (N Latex; Date-Behring Marburg GmbH, Marburg, Germany) with a range from 0.175 to 1100 mg/L.

Plasma glucose concentrations were measured enzymatically, whereas plasma insulin concentrations were measured by radioimmunoassay. Insulin resistance was assessed with the homeostasis model (HOMA). Insulin resistance scores (HOMA-IR) were calculated with the following formula: fasting plasma glucose (in mmol/L) × fasting plasma insulin (in μU/mL) divided by 22.5 (19). High HOMA-IR values indicated low insulin sensitivity, ie insulin resistance, whereas low HOMA-IR values denoted high insulin sensitivity. Previous studies have shown that HOMA-IR is closely related with the "gold standard" measurement of insulin resistance, the hyperinsulinemic euglycemic clamp procedure (20, 21).

Vascular tests

Flow-mediated dilatation (FMD) and nitroglycerin-induced dilatation of the brachial artery were evaluated by a single examiner (GV) blinded to the type of intervention according to the method described previously (22). All studies were performed in the morning after overnight fasting. After resting in a supine position for 10 min the diameter of the right brachial artery and baseline forearm blood flow were measured with an ultrasound machine (ATL HDI 3500) with the use of a 7.5-MHz linear array transducer. Increased forearm blood flow was induced by inflating a pneumatic blood pressure tourniquet placed around the wrist to a systolic blood pressure of 250 mm Hg for 5 min. Repeat blood flow scans were obtained immediately after cuff deflation, and the brachial artery was scanned continuously for 120 s thereafter, and its maximum diameter was defined. Ten minutes were allowed for vessel recovery, and analogous measurements were obtained before and 3 min after administration of sublingual nitroglycerin (400 μg). FMD was defined as the percentage of change of the artery's diameter (endothelial-dependent vasodilation). Similar measurements were also performed before and after the administration of nitroglycerin. The inter- and intra-observer variability for brachial diameter measurements previously calculated in our laboratory has been 0.1 ± 0.12 mm and 0.08 ± 0.19 mm, respectively.

Statistical analysis

Data are expressed as means ± SDs, whereas data on variables not normally distributed (eg, CRP) are expressed as medians and interquartile ranges. Differences of mean values within and between groups of subjects were analyzed by Student's *t* test or by Wilcoxon's signed rank test and Mann-Whitney *U* test, as appropriate. Pearson's correlation coefficients were used to assess relations between variables. Associations between categorical variables were tested by the chi-square test. Analysis of variance for repeated measures, with FMD as the dependent outcome and the intervention as the main fixed effect covariate, was applied to examine the research hypothesis. Normality was tested with the Shapiro-Wilk criterion, as well as the Q-Q plots of the continuous variables. A P value < 0.05 was considered significant. The SPSS version 13 statistical package (SPSS Inc, Chicago, IL) was used.

RESULTS

Baseline characteristics

Eighty-two of 90 recruited subjects completed the study (5 dropped out from the intervention group and 3 from the control group). In the intervention group 18 subjects (44%) had ≥3 components of the metabolic syndrome according to the third NCEP Adult Treatment Panel, whereas in the control group 16 subjects (39%) had ≥3 components of the metabolic syndrome (P = 0.823). Intervention and control groups were comparable for age (50.2 ± 6.4 y compared with 50.6 ± 8.1 y; P = 0.777), sex (56.1% compared with 48.8% men; P = 0.658), and smoking habits (34.1% compared with 29.3%; P = 0.812). In addition, lipid profile, weight, waist circumference, HOMA-IR score, and CRP concentrations did not differ between the 2 study groups (**Table 1**) as well as baseline FMD values (4.26 ± 3.0% compared with 4.37 ± 2.7%; P = 0.855) (**Figure 1**). Baseline waist circumference was associated with insulin concentrations (r = 0.445, $P < 0.001$) and HOMA-IR score (r = 0.405, $P < 0.001$).

Energy and nutrient intake

No significant differences were observed for baseline nutrient intakes between the 2 groups (**Table 2**). Baseline energy intakes were relatively low, possibly because of underreporting. After both interventions, energy intakes decreased, but the degree of reduction did not differ significantly between the 2 groups.

Analysis within the intervention group showed a decrease in intakes of saturated fatty acids (SFAs), cholesterol, carbohydrate, and protein, whereas total fat intake increased, because of higher intakes of monounsaturated fatty acids (MUFAs). Statistically significant increases occurred in intakes of dietary fiber, vitamin C, and alcohol. The control group showed no significant differences for intakes of macro- and micronutrients except a reduction in SFA intake. Between-group analysis showed that the intakes of total fat, MUFAs, fiber, vitamin C, and alcohol

TABLE 1
Characteristics of participants at baseline and 2 mo after dietary intervention[1]

	Intervention group (n = 41)			Control group (n = 41)			P for between-group comparisons[4]
	Baseline	2 mo after	P[2]	Baseline[3]	2 mo after	P[2]	
Body weight (kg)	94.1 ± 13.5[5]	91.4 ± 13.6	<0.001	94.0 ± 13.3	91.9 ± 13.3	<0.001	0.975
BMI (kg/m^2)	31.5 ± 3.8	30.6 ± 3.9	<0.001	32.8 ± 4.7	32.1 ± 4.6	<0.001	0.149
Waist circumference (cm)	106.1 ± 9.1	103.9 ± 9.3	<0.001	106.7 ± 9.5	105.7 ± 10.2	0.007	0.537
Glucose (mmol/L)	5.41 ± 0.89	5.28 ± 0.77	0.190	5.36 ± 0.67	5.31 ± 0.55	0.459	0.957
Insulin (μU/mL)	14.9 ± 7.8	11.8 ± 7.1	0.001	14.1 ± 5.8	15.3 ± 8.6	0.310	0.354
HOMA-IR score	3.5 ± 1.8	2.6 ± 1.3	<0.001	3.5 ± 1.7	3.8 ± 2.3	0.301	0.072
Total cholesterol (mmol/L)	5.49 ± 0.80	5.33 ± 0.78	0.038	5.39 ± 0.89	5.36 ± 0.83	0.705	0.581
Triglycerides (mmol/L)	1.67 ± 0.67	1.52 ± 0.42	0.071	1.46 ± 0.7	1.38 ± 0.64	0.898	0.100
HDL cholesterol (mmol/L)	1.24 ± 0.33	1.21 ± 0.32	0.152	1.28 ± 0.27	1.25 ± 0.25	0.105	0.693
LDL cholesterol (mmol/L)	3.71 ± 0.62	3.63 ± 0.65	0.304	3.52 ± 0.83	3.63 ± 0.72	0.026	0.556
C-reactive protein (mg/L)	2.1 (1.1–4.4)[6]	2.06 (0.8–3.3)	0.047	2.1 (1–1.7)	2.05 (1.6–4.2)	0.100	0.970
Systolic BP (mm Hg)	130.2 ± 14.4	122.5 ± 13.9	<0.001	129.6 ± 14.8	125.8 ± 13.7	0.016	0.647
Diastolic BP (mm Hg)	85.8 ± 7.6	79.6 ± 7.4	<0.001	86.3 ± 8	85.6 ± 8.8	0.465	0.041

[1] HOMA-IR, homeostasis model assessment–insulin resistance; BP, blood pressure.
[2] Derived by using Student's paired *t* test or Wilcoxon's test.
[3] Not significantly different from the corresponding baseline variables of the intervention group (unpaired *t* test or Mann-Whitney *U* test).
[4] Derived by using repeated-measures ANOVA.
[5] Mean ± SD (all such values).
[6] Median; 25th–75th percentiles in parentheses (all such values).

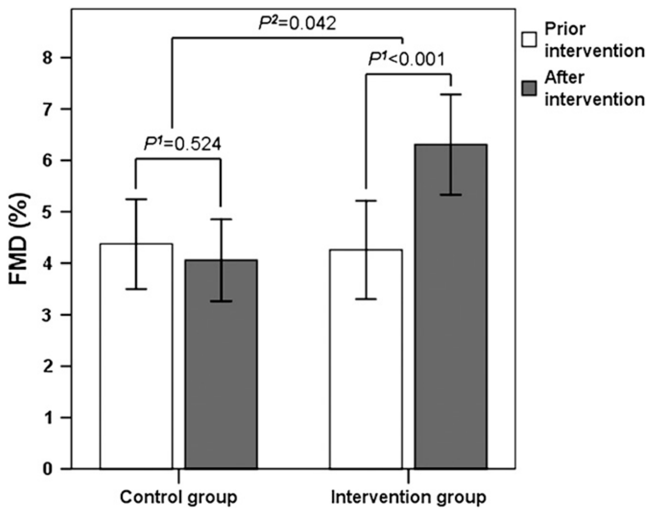

FIGURE 1. Mean (95% CI) flow-mediated dilatation (FMD) at the beginning and 2 mo after dietary intervention in individuals with abdominal obesity. P^1 values represent within-group comparisons (Student's paired *t* test); the P^2 value represents the between-groups analysis (repeated-measures ANOVA).

increased, whereas intakes of protein and SFAs decreased significantly in the intervention group compared with the control group. Finally, changes in n−6 and n−3 fatty acids as well as in α-linolenic acid did not differ significantly between the 2 groups (data not shown).

Serum lipids, insulin resistance, blood pressure, and FMD

Within-group comparisons showed that weight, BMI, and waist circumference decreased in both groups at the end of the study, but the degree of changes was similar when the 2 groups were compared. Changes in lipids and CRP concentrations did not differ between the 2 groups, whereas there was a trend for a reduction in HOMA-IR scores in the intervention group compared with the control group (*P* = 0.072). When changes in blood pressure were compared, only diastolic blood pressure decreased significantly in the intervention group compared with the control group (*P* = 0.041) (Table 1).

Finally, FMD increased significantly in the intervention group compared with the control group (*P* = 0.042) (Figure 1). Nitroglycerin-mediated dilatation remained unchanged in both intervention (10.3 ± 3.6% compared with 10.6 ± 3.5%; *P* = 0.816) and control (10.7 ± 3% compared with 10.7 ± 3.5%; *P* = 0.973) groups after the intervention period.

DISCUSSION

In our study a food plan based on the Mediterranean diet guidelines combined with the provision of free products and close dietetic supervision was more effective in improving dietary intake than was general verbal and written guidelines for the Mediterranean diet. Close dietitian supervision has been shown to have benefits toward a more successful intervention. The results from our study are in accordance with the results of 2 recent studies. In particular, Raatz et al (23) showed that a close supervision by a registered dietitian improves weight-loss success. In addition, results from the Heart to Heart Study (24) showed that case management, which includes nurse and dietitian advice, is more beneficial than the usual primary care approach in reducing the Framingham risk.

In our study, subjects in the intervention group increased their intake of total fat and MUFAs, caused by the increased consumption of olive oil through the daily addition of virgin olive oil in their salads, of olive oil–enriched margarine, and of almonds. The increase in alcohol was due to the intake of 1 glass of red wine during lunch. The increase in fiber and vitamin C could be the result of the planned consumption of 2 salads, ≥3 fruit, the concentrated fruit juice, and whole-grain products. In contrast, the

TABLE 2
Nutrient intakes of participants at baseline and 2 mo after dietary intervention[1]

	Intervention group (*n* = 41)			Control group (*n* = 41)			*P* for between-group comparisons[4]
	Baseline	2 mo after	P^2	Baseline[3]	2 mo after	P^2	
Total energy (kcal/d)	1841 ± 285[5]	1729 ± 304	0.045	1794 ± 514	1575 ± 491	<0.001	0.228
% Energy from							
Carbohydrates	41.9 ± 6.5	38.3 ± 5.3	0.009	42.4 ± 9.7	42.1 ± 7.6	0.839	0.107
Protein	16.1 ± 2.3	14.3 ± 2.5	0.002	16.6 ± 3.2	18.0 ± 4.8	0.079	<0.001
Total fat	40.7 ± 6.9	47.4 ± 6.4	<0.001	41.6 ± 9.4	40.3 ± 9.4	0.345	0.047
SFAs	13.9 ± 2.6	9.5 ± 1.7	<0.001	14.5 ± 3.3	11.8 ± 2.5	<0.001	<0.001
MUFAs	19.6 ± 4.2	26.4 ± 3.6	<0.001	20.5 ± 6.6	19.8 ± 7.7	0.534	0.007
PUFAs	6.6 ± 4.1	6.2 ± 2.9	0.653	5.7 ± 2.2	5.7 ± 3.0	0.910	0.145
Cholesterol (mg/d)	229.2 ± 71.3	142.1 ± 64.2	<0.001	235.9 ± 137	193.4 ± 120	0.074	0.119
Fiber (g/d)	17.0 ± 6.3	21.4 ± 8	0.009	16.3 ± 6.6	16.6 ± 7.5	0.833	0.023
Vitamin C (mg/d)	116.7 ± 80.9	167.8 ± 83.1	0.003	113.4 ± 68.8	117.1 ± 76.9	0.787	0.047
α-Tocopherol (mg/d)	4.5 ± 1.6	4.9 ± 4.1	0.494	5.1 ± 2.9	4.4 ± 3.1	0.160	0.978
β-Carotene (μg/d)	550.6 ± 532	595.9 ± 489	0.704	456.2 ± 480	418.4 ± 384	0.587	0.091
Alcohol (g/d)	5.9 ± 8.4	12.9 ± 5.3	<0.001	4.2 ± 8.6	4 ± 6.4	0.872	<0.001

[1] SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.
[2] Derived by using Student's paired *t* test.
[3] Not significantly different from the corresponding baseline variables of the intervention group (unpaired *t* test).
[4] Derived by using repeated-measures ANOVA.
[5] Mean ± SD (all such values).

reduction in SFA intake could be attributed to the instructions for less consumption of red meat, full-fat dairy products, and butter. Similar findings about the effectiveness of individual motivational interventions together with free provision of Mediterranean diet foods were observed in the PREDIMED Study (17). Positive results about the improvement of dietary intake after close dietetic supervision alone can be seen in a nutritional intervention promoting the Mediterranean food pattern in healthy women from the Quebec City Metropolitan Area (16), as well as in a nutritional intervention within the context of the MARGARIN project (15).

Achievements in dietary modification in the present study resulted in an improvement in endothelial function in individuals with AO. In addition, diastolic blood pressure was also reduced, and a trend was seen for an improvement in insulin sensitivity in the intervention group.

AO, a marker of visceral obesity, is associated with endothelial dysfunction (4), which represents the earliest abnormality in the development of vascular disease. This association is mediated through multiple mechanisms. Abdominal fat is characterized by the production of adipokines and proinflammatory cytokines, which induce oxidative stress leading to reduced nitric oxide availability. Lteif et al (25) reported that the contribution of central obesity on endothelial function is primarily mediated by insulin resistance. A reciprocal relation is also observed between insulin resistance and endothelial dysfunction (26). Insulin resistance is characterized by pathway-specific impairment in phosphatidylinositol 3-kinase–dependent signaling that in endothelium may cause an imbalance between the production of nitric oxide and the secretion of endothelin-1, leading to endothelial dysfunction and decreased blood flow that in turn worsens insulin resistance.

The favorable effect of the Mediterranean-type diet on endothelial function might be attributed to the various components of this diet such as olive oil, red wine, vegetables, and fruit (27, 28). Olive oil is a key component of the Mediterranean diet. In our study olive oil, provided as extra virgin olive oil, was the main source of fat. Olive oil has numerous beneficial effects on endothelial function attributed not only to the oleic acid, the main fatty acid contained in olive oil, but also to phenolic compounds, such as oleuropein, hydroxytyrosol, and tyrosol. In vitro studies have shown that oleic acid prevents endothelial activation by inhibiting the expression of leukocyte adhesion molecules (29), by scavenging intracellular reactive oxygen species (30), or by interfering with the activation of nuclear transcription factor κB (31). In addition, phenolic compounds are strong antioxidants and radical scavengers, increasing the bioavailability of nitric oxide (27, 32).

Red wine has also been reported to improve endothelial function, an effect most likely exerted by polyphenols shown to increase endothelial nitric oxide synthase expression (33–35). Furthermore, improvement in FMD has been observed after meals containing vegetables and fruit, an effect attributed to high concentrations of antioxidants in these foods (36, 37).

There are few and contradictory results about the effect of the Mediterranean diet on endothelial function. Fuentes et al (12) reported that the Mediterranean diet provided to healthy hypercholesterolemic men for 1 mo improved endothelial function as measured by FMD. In another study (13), a Mediterranean-style diet provided to patients with metabolic syndrome for 2 y showed an improvement in endothelial function as assessed by blood pressure and platelet aggregation response to L-arginine. On the contrary, Ambring et al (14) failed to report a beneficial effect on endothelial function of a Mediterranean-style diet given for 1 mo to healthy subjects. In their study endothelial function was measured invasively by venous occlusion plethysmography. However, it should be noted that our results are not directly compared with those findings because the recruited populations were different and the endothelial function was not assessed with FMD in all these studies.

In the present study, we report a trend for improvement in insulin sensitivity. Consistent with our findings, Esposito et al (13) showed an improvement in insulin sensitivity–style diet for 2 y. In another study high-risk asymptomatic subjects showed improvement in insulin sensitivity after 3 mo of Mediterranean diets supplemented with either olive oil or nuts (38). Finally, Tzima et al (39) showed that adherence to the Mediterranean diet was associated with better insulin sensitivity in overweight and obese subjects.

CRP concentrations were not affected significantly after dietary intervention. Previous studies have yielded conflicting results because the Mediterranean diet reportedly reduced inflammatory markers in some (13, 38, 40, 41) but not in other (42, 43) studies. This inconsistency may be due to different compositions of the Mediterranean diets provided and to variable duration of the intervention periods. Finally, the Mediterranean diet in our study was associated with a statistically significant reduction in diastolic blood pressure, an effect that has been reported previously (38, 44, 45).

In conclusion, we showed that a 2-mo dietary intervention, which included close dietetic supervision, improved the adherence to a Mediterranean-type diet and resulted in an improvement in endothelial function and a decrease in diastolic blood pressure in subjects with AO. This effect can probably explain, at least partly, the favorable effects of the Mediterranean diet on cardiovascular system.

The authors' responsibilities were as follows—LSR: collected and analyzed data and wrote the manuscript; JL: provided critical revision; AK: collected data (dietetic supervision); AZ: designed the study and provided critical revision; GV: collected data (performance of FMD); SE: collected data; and GD, SAR, and DTK: performed critical revision. None of the authors declared a conflict of interest.

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