ORIGINAL CONTRIBUTION

Effect of a Mediterranean-Style Diet on Endothelial Dysfunction and Markers of Vascular Inflammation in the Metabolic Syndrome

A Randomized Trial

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Context The metabolic syndrome has been identified as a target for dietary therapies to reduce risk of cardiovascular disease; however, the role of diet in the etiology of the metabolic syndrome is poorly understood.

Objective To assess the effect of a Mediterranean-style diet on endothelial function and vascular inflammatory markers in patients with the metabolic syndrome.

Design, Setting, and Patients Randomized, single-blind trial conducted from June 2001 to January 2004 at a university hospital in Italy among 180 patients (99 men and 81 women) with the metabolic syndrome, as defined by the Adult Treatment Panel III.

Interventions Patients in the intervention group (n=90) were instructed to follow a Mediterranean-style diet and received detailed advice about how to increase daily consumption of whole grains, fruits, vegetables, nuts, and olive oil; patients in the control group (n=90) followed a prudent diet (carbohydrates, 50%-60%; proteins, 15%-20%; total fat, <30%).

Main Outcome Measures Nutrient intake; endothelial function score as a measure of blood pressure and platelet aggregation response to L-arginine; lipid and glucose parameters; insulin sensitivity; and circulating levels of high-sensitivity C-reactive protein (hs-CRP) and interleukins 6 (IL-6), 7 (IL-7), and 18 (IL-18).

Results After 2 years, patients following the Mediterranean-style diet consumed more foods rich in monounsaturated fat, polyunsaturated fat, and fiber and had a lower ratio of omega-6 to omega-3 fatty acids. Total fruit, vegetable, and nuts intake (274 g/d), whole grain intake (103 g/d), and olive oil consumption (8 g/d) were also significantly higher in the intervention group ($P<.001$). The level of physical activity increased in both groups by approximately 60%, without difference between groups ($P=.22$). Mean (SD) body weight decreased more in patients in the intervention group (−4.0 [1.1] kg) than in those in the control group (−1.2 [0.6] kg) ($P<.001$). Compared with patients consuming the control diet, patients consuming the intervention diet had significantly reduced serum concentrations of hs-CRP ($P=.01$), IL-6 ($P=.04$), IL-7 ($P=0.4$), and IL-18 ($P=0.3$), as well as decreased insulin resistance ($P<.001$). Endothelial function score improved in the intervention group (mean [SD] change, +1.9 [0.6]; $P<.001$) but remained stable in the control group (+0.2 [0.2]; $P=.33$). At 2 years of follow-up, 40 patients in the intervention group still had features of the metabolic syndrome, compared with 78 patients in the control group ($P<.001$).

Conclusion A Mediterranean-style diet might be effective in reducing the prevalence of the metabolic syndrome and its associated cardiovascular risk.

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THE METABOLIC SYNDROME CONsists of a constellation of factors that increase the risk of cardiovascular disease and type 2 diabetes. Recent estimates indicate that the metabolic syndrome is highly prevalent in the United States, with an estimated 24% of the adult population affected.[1] Its clinical identification is based on measures of abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, and glucose intolerance.[2] The etiology of this syndrome is largely unknown but presumably represents a complex interaction between genetic, metabolic, and environmental factors including diet.[3,4] Several recent studies also suggest that a proinflammatory state is one component of the metabolic syndrome.[5-8] Moreover, evidence has accumulated indicating that low-grade inflammation is associated with endothelial dysfunction.[9,10]

See also pp 1433 and 1490.

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Although aspects of diet have been linked to individual features of the metabolic syndrome,[11] the role of diet in the etiology of the syndrome is poorly understood and limited to only a few observational studies.[12,13] The Adult Treatment Panel III recommendations for patients with the metabolic syndrome are consistent with general dietary recommendations.[14] Recently, the scientific advisory committee of the American Heart Association has stated that a Mediterranean-style diet has impressive effects on the progression of cardiovascular disease.[15]

The aim of this study was to assess the effect of a Mediterranean-style diet on endothelial function and vascular inflammation in patients with the metabolic syndrome. We studied endothelial function by assessing the vascular responses to L-arginine, the natural precursor of nitric oxide. Moreover, we characterized the low-grade inflammatory state of patients with the metabolic syndrome by measuring circulating levels of high-sensitivity C-reactive protein (hs-CRP) as well as of interleukins 6 (IL-6), 7 (IL-7), and 18 (IL-18). These proinflammatory ILs have been prospectively associated with thrombotic cardiovascular events[16,17] or have been suggested to be involved in plaque destabilization.[18] We then performed a randomized controlled trial of a Mediterranean-style diet designed to increase consumption of foods rich in phytochemicals, antioxidants, α-linolenic acid, and fiber.

METHODS

Men and women were recruited from June 2001 to January 2004 among those attending the outpatient department of the Division of Metabolic Diseases at the Second University of Naples, Naples, Italy. The study participants were sedentary (engaging in less than 1 hour per week of physical activity) and within the previous 6 months had no evidence of participation in weight reduction programs and had maintained a stable weight (±1 kg). None of the study participants had previously participated in dietary studies. Each patient was asked to complete a personal health and medical history questionnaire that served as a screening tool.

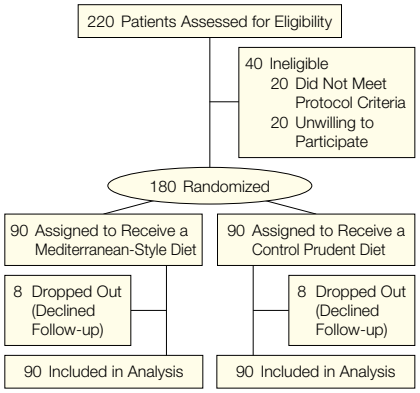
To be enrolled in the study, patients had to have 3 or more of the following criteria to meet the diagnosis of the metabolic syndrome, as defined by the Adult Treatment Panel III[2]: (1) abdominal adiposity (defined as waist circumference >102 cm [men] or >88 cm [women]); (2) low levels of serum high-density lipoprotein cholesterol (<40 mg/dL [men] or <50 mg/dL [women]); (3) hypertriglyceridemia (triglycerides level of 150 mg/dL or greater); (4) elevated blood pressure (130/85 mm Hg or greater); and (5) impaired glucose homeostasis (fasting plasma glucose concentration of 110 mg/dL or greater). Patients were excluded if they had cardiovascular disease, psychiatric problems, a history of alcohol abuse (alcohol consumption ≥500 g/wk in the last year), if they smoked, or if they took any medication. The study was approved by the institutional committee of ethical practice of the Second University of Naples, and all of the study patients gave written informed consent.

Patients were randomly assigned to either the intervention or the control diet using a computer-generated random number sequence (FIGURE 1). Allocation was concealed in sealed study folders that were held in a central, secured location until after informed consent was obtained. The nurses who scheduled the study visits did not have access to the randomization list. However, the staff members involved in the intervention had to be aware of the group assignment; thus, the study was only partly blinded. Laboratory staff did not know the patients' group assignments.

Patients consuming the intervention diet were given detailed advice about the usefulness of the experimental diet. Through a series of monthly small-group sessions, intervention patients received education in reducing dietary calories (if needed), personal goal-setting, and self-monitoring using food diaries. Behavioral and psychological counseling was also offered. The dietary advice was tailored to each patient on the basis of 3-day food records. The recommended composition of the dietary regimen was as follows: carbohydrates, 50% to 60%; proteins, 15% to 20%; total fat, less than 30%; saturated fat, less than 10%; and cholesterol consumption, less than 300 mg per day. Moreover, patients were advised to consume at least 250 to 300 g of fruits, 125 to 150 g of vegetables, and 25 to 50 g of walnuts per day; in addition, they were also encouraged to consume 400 g of whole grains (legumes, rice, maize, and wheat) daily and to increase their consumption of olive oil. Patients were in the program for 24 months and had monthly sessions with the nutritionist for the first year and bimonthly sessions for the second year. Compliance with the program was assessed by attendance at the meetings and completion of the diet diaries.

Patients consuming the control diet were given general oral and written information about healthy food choices at baseline and at subsequent visits but were offered no specific individualized program. However, the general recommendation for macronutrient composition of the diet was similar to that for the intervention group (carbohydrates, 50%-60%; proteins, 15%-20%; and total fat, <30%). Moreover, patients in the control group also had bimonthly sessions with study personnel during the 2-year study. All patients in both groups also received guidance

Figure 1. Flow of Patients Through the Trial



on increasing their level of physical activity, mainly by walking for a minimum of 30 minutes per day but also by swimming or playing aerobic ball games (eg, soccer).

Height and weight were recorded with participants wearing lightweight clothing and no shoes using a Seca 200 scale with attached stadiometer (Seca, Hamburg, Germany). Twenty-four–hour nutrient intakes were calculated with food-composition tables and patients' weekly diet diaries. To assess dietary adherence and exercise activity, all patients were asked to complete a 3-day food record and to record occupational,[1] household, and leisure-time physical activity. Foods were measured using standard measuring cups and spoons and weight-approximation diagrams.

Endothelial Function

Endothelial function was assessed with the L-arginine test, as previously described.[19,20] Briefly, after applying a device for automatic measurements of blood pressure and heart rate (Omheda 2300; Finapres, Englewood, Calif), an intravenous bolus of 3 g of L-arginine (10 mL of a 30% solution of L-arginine monochloride), the natural precursor of nitric oxide, was injected intravenously within 60 seconds. Blood pressure and platelet aggregation response to 1.25 µM adenosine diphosphate were measured before L-arginine injection and after 10 minutes.

We developed a score in which both responses were summed. For blood pressure, 1 point was attributed for a mean blood pressure response less than 2 mm Hg, 2 points for a response between 2 and 3 mm Hg, 3 points for a response between 3 and 4 mm Hg, 4 points for a response between 4 and 5 mm Hg, and 5 points for a response greater than 5 mm Hg. For platelet aggregation, 1 point was attributed for a response less than 2.5%, 2 points for a response between 2.5% and 5%, 3 points for a response between 5% and 7.5%, 4 points for a response between 7.5% and 10%, and 5 points for a response greater than 10%. In our laboratory, the mean (SD) blood pressure and platelet aggregation decreases following the L-arginine bolus (difference between basal and 10-minute values) in a matched control group of healthy men and women (n=50 for each) were –6.5 (1.5) mm Hg and –13% (3%), respectively, which correspond to the maximal score of 10.

Laboratory Analysis

Estimation of insulin sensitivity in the fasting state was assessed with homeostasis model assessment (HOMA) and calculated with the formula: fasting plasma glucose (mmol/L) × fasting serum insulin (µU/mL) divided by 25, as described by Matthews et al.[21] With such a method, high HOMA scores denote low insulin sensitivity (insulin resistance). Assays for serum levels of total cholesterol and high-density lipoprotein cholesterol, triglycerides, and glucose were performed in the hospital's chemistry laboratory. Plasma insulin levels were assayed by radioimmunoassay (Ares, Serono, Italy).

Serum samples for cytokine and hs-CRP levels were stored at –80°C until assay. Serum concentrations of IL-6, IL-7, and IL-18 were determined in duplicate using a high-sensitivity, quantitative sandwich enzyme assay (Quantikine HS, R&D Systems, Minneapolis, Minn). High-sensitivity CRP was assayed by immunonephelometry using a Behring Nephelometer 2 (Dade Behring, Marburg, Germany). In our laboratory, the median (interquartile range) for these values in a group of 100 healthy participants of both sexes (n=50 for each) were as follows: hs-CRP, 0.7 mg/L (0.2-3.2 mg/L); IL-6, 2.1 pg/mL (0.3-5.2 pg/mL); IL-7, 1.8 pg/mL (0.5-5.2 pg/mL); and IL-18, 129 pg/mL (50-275 pg/mL).

Statistical Analysis

Data are presented as mean (SD) unless stated otherwise. Data were analyzed by intention-to-treat. We compared baseline data using a *t* test for continuous variables and a Wilcoxon test for hs-CRP, IL-6, IL-7, and IL-18. We classified all study patients as having 3, 4, or 5 components of the metabolic syndrome and assessed for evidence of a relation of median hs-CRP level and mean HOMA and endothelial function scores across these groups using the Jonckheere-Terpstra test. We compared risk factors and nutrient intakes after 2 years using a test based on the values at the end of follow-up and a *t* test based on differences from baseline. Results of the analysis omitting patients lost in the follow-up did not differ from that including their last available records; data are therefore shown for the analysis that includes all participants as randomized. Spearman rank correlation coefficients were used to quantify the relations between metabolic variables and cytokine levels. The effects of treatment on HOMA and endothelial function scores, cytokine levels, and each of the components of the metabolic syndrome were tested by means of paired *t* tests and a Wilcoxon matched test, after adjustment for changes in body weight. The χ^2 test was used for comparing proportions of participants in the 2 groups with the metabolic syndrome after treatment. $P<.05$ was considered statistically significant. All analysis were conducted using SPSS version 9.0 (SPSS Inc, Chicago, Ill).

RESULTS

One hundred eighty patients were randomly assigned to the intervention (n=90) or control (n=90) group (Figure 1). Both groups were comparable, including the number of components of the metabolic syndrome (TABLE 1). There was an increase in hs-CRP levels and HOMA scores as the number of components of the metabolic syndrome increased; by contrast, there was an inverse relation between the number of components of the metabolic syndrome and the endothelial function score ($P<.001$ for trend for all) (FIGURE 2). Spearman rank correlation coefficients showed that endothelial function score was negatively associated with waist circumference ($r=-0.30$, $P=.01$), hs-CRP level ($r=-0.33$, $P=.01$), HOMA score ($r=-0.24$, $P=.02$), and IL-6 level ($r=-0.21$, $P=.02$).

After 2 years of follow-up, 8 participants in the intervention group and 8 in the control group dropped out of the

study; all dropouts occurred after 24 weeks of follow-up. Patients who dropped out from the intervention group showed a decrease in body weight after 24 weeks of follow-up, suggesting that they were adhering to the lifestyle changes.

Baseline data showed no important difference in the nutrient intake between the 2 groups (TABLE 2). After 2 years, patients following the intervention diet consumed a greater percentage of calories from complex carbohydrates and from polyunsaturated and monounsaturated fat; had a greater intake of fiber; had a lower ratio of omega-6 to omega-3 fatty acids; and had lower energy, levels of saturated fat, and levels of cholesterol than did controls. Total fruit, vegetable, nuts, and whole grain intakes and olive oil consumption were also significantly higher in the intervention group (Table 2). The level of physical activity increased in both groups (intervention group: from 48 [SD, 10] min/wk to 84 [SD, 36] min/wk, $P<.001$; control group: from 51 [SD, 9] min/wk to 81 [SD, 38] min/wk, $P<.001$) without any difference between them ($P=.22$).

After 2 years, patients in the intervention group had significant decreases in body weight; body mass index; waist circumference; HOMA score; blood pressure; and levels of glucose, insulin, total cholesterol, and triglycerides and a significant increase in levels of high-density lipoprotein cholesterol, all of which were greater than those recorded in the control group (TABLE 3). There was no difference for sex. Serum concentrations of IL-6, IL-7, IL-18, and hs-CRP were significantly reduced in patients in the intervention group compared with those in the control group. Endothelial function score improved in the intervention group but remained stable in the control group. There was an inverse relation between changes in endothelial function score and changes in hs-CRP levels ($r=-0.36$, $P=.01$) and HOMA scores ($r=-31$, $P=.01$).

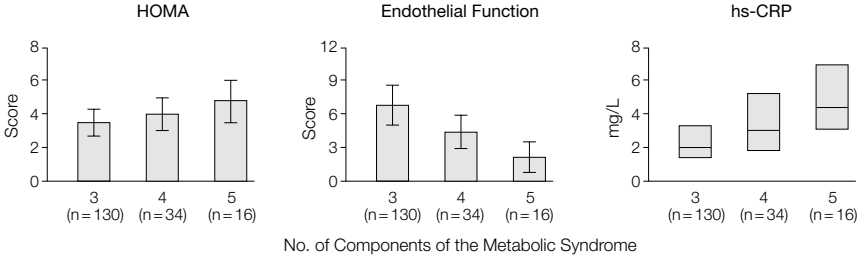
At 2 years of follow-up, 60 participants in the intervention group had experienced reductions in the number of components of the metabolic syndrome (Table 3), so that only 40 patients could still be classified as having the metabolic syndrome. This was significantly different from the control group, in which 78 patients were still classified as having the metabolic syndrome ($P<.001$). The data unad-

Table 1. Characteristics of the Study Participants

Characteristics	Mean (SD)		*P* Value
	Intervention Diet (n = 90)	Control Diet (n = 90)	
Sex, No. (%)			
Men	49 (54)	50 (56)	.70
Age, y	44.3 (6.4)	43.5 (5.9)	.56
No. of components of the metabolic syndrome, No. (%)			
3	74 (82)	76 (84)	.34
4	18 (20)	16 (18)	
5	8 (9)	8 (9)	
Body weight, kg	78 (8)	77 (8)	.36
Body mass index*	27.9 (3.4)	28.1 (3.2)	.55
Waist circumference, cm	92 (9)	93 (10)	.62
Plasma glucose, mg/dL	113 (10)	114 (10)	.43
Serum insulin, µU/mL	15 (6)	16 (7)	.15
HOMA score	3.7 (0.7)	3.8 (0.7)	.18
Serum lipids, mg/dL			
Total cholesterol	199 (34)	193 (32)	.18
HDL-C	41 (9)	42 (9)	.35
Triglycerides	168 (57)	172 (54)	.24
Blood pressure, mm Hg			
Systolic	134 (9)	136 (10)	.11
Diastolic	85 (6)	86 (7)	.21
Endothelial function score	6.0 (1.2)	5.9 (1.1)	.13
hs-CRP and cytokines, median (IQR)			
hs-CRP, mg/L	2.8 (0.7-5.4)	2.9 (0.5-5.7)	.25
IL-6, pg/mL	2.1 (0.5-4.8)	1.9 (0.5-4.7)	.14
IL-7, pg/mL	2.4 (0.6-5.9)	2.6 (0.7-6.0)	.12
IL-18, pg/mL	167 (102-232)	175 (104-238)	.10

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA, homeostatic model assessment; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IQR, interquartile range.
SI conversion factors: To convert glucose to mmol/L, multiply values by 0.0555; to convert insulin to pmol/L, multiply values by 7.715; to convert total cholesterol and HDL-C to mmol/L, multiply values by 0.0259; to convert triglycerides to mmol/L, multiply values by 0.0113.
*Calculated as weight in kilograms divided by the square of height in meters.

Figure 2. Distribution of HOMA Score, Endothelial Function Score, and hs-CRP Levels Among the 180 Patients at Baseline, by Presence of 3, 4, and 5 Components of the Metabolic Syndrome



HOMA indicates homeostasis model assessment; hs-CRP, high-sensitivity C-reactive protein. Error bars in 2 left panels indicate standard deviation; horizontal lines in boxes in right panel, median; boxes, interquartile range.

justed for changes in body weight showed a greater reduction in the number of components of the metabolic syndrome, such that at 2 years of follow-up, 30 patients in the intervention group and 73 patients in the control group were classified as having the metabolic syndrome ($P<.001$).

COMMENT

In this study, consumption of a Mediterranean-style diet by patients with the metabolic syndrome was associated with improvement of endothelial function and a significant reduction of markers of systemic vascular inflammation. Moreover, participants who followed the intervention diet showed a reduction in the number of the components of the syndrome such that the overall prevalence of the metabolic syndrome was reduced by approximately one half. Because data were adjusted for changes in body weight, the overall reduction in the prevalence of the metabolic syndrome after the intervention is likely to represent a conservative measure. Taken together, these findings suggest that a Mediterranean-style diet is a safe strategy for treatment of the metabolic syndrome and for helping to reduce the associated cardiovascular risk.

Current guidelines on the management of the individual components of the metabolic syndrome emphasize that lifestyle modification (weight loss and physical activity) is a first-line therapy, whereas drug therapy is considered secondary, unless otherwise indicated by current cardiovascular disease prevention guidelines.[22] In our study, the effect of the intervention diet was associated with modest changes in body weight, which has been shown to have no effect on CRP levels,[23] as well as an increment in physical activity not different from the control group. Because the results were adjusted for body weight changes, our findings suggest that, largely independent of concomitant changes in body weight, a Mediterranean-style diet might play a role in reducing the inflammatory state and endothelial dysfunction associated with the metabolic syndrome.

The mechanism by which a Mediterranean-style diet can reduce the low-grade inflammatory state associated with the metabolic syndrome is unclear. Macronutrient intake produces oxidative stress that leads to a proinflammatory state.[24] This intriguing evidence is also supported by the ability of antioxidant vitamins[25,26] or food antioxidants[20] to improve the transient endothelial dysfunction seen in healthy individuals after consumption of a single high-fat meal. Moreover, modulation of the fiber content of the meal may influence the cytokine milieu: increasing the fiber content (from 4.5 g to 16.8 g) of a high-carbohydrate meal was associated with significant reduction of circulating IL-18 levels in both healthy persons and in patients with type 2 diabetes.[27] Because dietary fiber may have anti-inflammatory roles, at least in intestinal functions,[28] it can be speculated that the fiber content of the intervention diet, eventually magnified by some other components with antioxidant capability, may influence the transient oxidative stress that occurs after macronutrient ingestion. An anti-inflammatory effect for omega-3 fatty acids also has been suggested,[29] although most of this effect was seen with supplement use.

Our results show a linear increment in hs-CRP levels and a linear impairment of endothelial function score associated with increase in the number of components of the metabolic syndrome. This leads to the speculation that

Table 2. Nutrient Indices at Entry to Study and After 2 Years

	Intervention Diet (n = 90)				Control Diet (n = 90)				Between-Group Comparison of Change	
	Mean (SD)				Mean (SD)					
Nutrient	Baseline	2 Years	Mean Change	*P* Value	Baseline	2 Years	Mean Change	*P* Value	Difference (95% CI)	*P* Value at 2 Years
Total energy, kcal/d	2235 (188)	2065 (168)	−170	<.001	2254 (198)	2184 (174)	−70	<.001	−100 (−178 to −21)	<.001
Carbohydrates, %	57.3 (2.1)	58.0 (2.0)	+0.7	.02	57.0 (2.2)	57.1 (2.3)	+0.1	.10	+0.6 (0.1 to 1.1)	.02
Complex carbohydrates, %	44 (2.0)	50 (2.1)	+6	<.001	43 (2.0)	42 (2.2)	−1	.06	+7 (4 to 12)	<.001
Fiber, g/d	14 (1.2)	32 (2.8)	+18	<.001	15 (1.3)	17 (1.5)	+2	.02	+16 (4 to 30)	<.001
Protein, %	13.7 (1.3)	14.0 (1.4)	+0.3	.06	13.4 (1.4)	13.5 (1.3)	+0.1	.09	+0.2 (−0.1 to 0.4)	.07
Fat, %	29.0 (2.8)	28.0 (2.7)	−1	.01	29.6 (2.9)	30.0 (2.8)	+0.4	.04	−1.4 (−2.8 to −0.2)	.02
Saturated	13.0 (2.8)	8.0 (1.1)	−5	<.001	13.4 (2.7)	13.7 (2.6)	+0.3	.06	−5.3 (−9.5 to −2.0)	<.001
MUFA	9.0 (1.2)	12.4 (1.7)	+3.4	<.001	9.2 (1.1)	9.6 (1.2)	+0.4	.05	+3 (1.0 to 5.0)	<.001
PUFA	7.0 (0.9)	7.6 (0.9)	+0.6	.001	7.0 (1.1)	6.7 (0.9)	−0.3	.06	+0.9 (0.3 to 1.5)	.01
Omega-3 fatty acids, g/d	0.6 (0.15)	1.5 (0.3)	+0.9	<.001	0.61 (0.17)	0.68 (0.2)	+0.07	.10	+0.86 (0.25 to 1.4)	<.001
Omega-6/omega-3 fatty acid ratio	11.2 (2.1)	6.7 (1.1)	−4.5	<.001	11.4 (2.1)	11.2 (1.9)	−0.2	.08	−4.3 (−8.3 to −1)	<.001
Cholesterol, mg/d	325 (39)	236 (29)	−89	<.001	316 (40)	307 (31)	−9	.09	−80 (−135 to −25)	<.001
Olive oil, g/d	15.0 (2.4)	26.7 (3.5)	+9.7	<.001	14.4 (2.7)	15.9 (2.9)	+1.5	.02	+8.2 (3.3 to 12.4)	<.001
Fruits, vegetables, nuts, and legumes, g/d	198 (20)	487 (89)	+289	<.001	186 (23)	201 (35)	+15	.01	+274 (176 to 372)	<.001
Whole grains, g/d	87 (17)	198 (46)	+111	<.001	94 (20)	102 (26)	+8	.02	+103 (45 to 159)	<.001
Alcohol, g/d	39 (7)	38 (10)	−1	.12	37 (8)	38 (8)	+1	.13	−2 (−5.6 to 1.6)	.10

Abbreviations: CI, confidence interval; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

CRP, which is produced by the liver under the influence of IL-6,[9] may be one link between the altered cytokine milieu and endothelial dysfunction associated with the metabolic syndrome. In addition to being a powerful risk marker, recent evidence suggests that CRP may directly participate in lesion formation through leukocyte activation and endothelial dysfunction.[30,31] Moreover, it has been suggested that increased inflammatory responses could lead to insulin resistance and compensatory hyperinsulinemia attributable in large part to the important role of inflammatory cytokines released from adipocytes.[9] Alternatively, insulin resistance may be responsible for the higher production of cytokines as a consequence of reduced anti-inflammatory effect of insulin in insulin-resistant states.[32] Regardless of the mechanisms, the proinflammatory state that accompanies the metabolic syndrome is associated with both insulin resistance and endothelial dysfunction, providing a connection between inflammation and metabolic processes that are highly deleterious for vascular function.

One limitation of our study is the inability to determine whether individual components of the diet can account for the changes observed or whether the changes in metabolic risk factors are a result of the sum of all the dietary changes. Although multiple dietary interventions, as in the study herein, render difficult the assessment of the effect of each intervention separately, the clinical usefulness of a whole-diet approach in the prevention of cardiovascular disease has been emphasized.[33] The Lyon Heart Study[34] has shown that diet can help reduce the risk of fatal and nonfatal cardiovascular events in individuals with cardiovascular disease. Singh et al[35] tested an Indo-Mediterranean diet in 1000 patients with existing coronary disease or at high risk for coronary disease. As compared with the control diet, the intervention diet reduced the rate of fatal myocardial infarction by one third and the rate of sudden death from cardiac causes by two

Table 3. Changes in Assessed Variables After 2 Years

Variable	Intervention Diet (n = 90) Mean (SD) 2 Years	Intervention Diet (n = 90) Mean (SD) Change	Intervention Diet (n = 90) *P* Value	Control Diet (n = 90) Mean (SD) 2 Years	Control Diet (n = 90) Mean (SD) Change	Control Diet (n = 90) *P* Value	Between-Group Comparison of Change Difference (95% CI)	Between-Group Comparison of Change *P* Value at 2 Years
Weight, kg	74 (7)	−4 (1.1)	<.001	75.8 (7)	−1.2 (0.6)	.02	−2.8 (−5.1 to −0.5)	<.001
Body mass index*	26.7 (3.1)	−1.2 (0.3)	<.001	27.7 (3.1)	−0.4 (0.4)	.06	−0.8 (−1.4 to −0.2)	.01
Waist circumference, cm	90 (8)	−2 (0.5)	.01	93 (10)	0 (0.01)	.74	−2 (−3.5 to −0.5)	.01
Plasma glucose, mg/dL	105 (9)	−8 (3)	<.001	112 (9)	−2.0 (1.5)	.21	−6 (−11 to −2)	<.001
Serum insulin, μU/mL	11 (5)	−4 (1.9)	.01	15.5 (7)	−0.5 (1.0)	.45	−3.5 (−6.1 to −1.7)	.01
HOMA score	2.5 (0.6)	−1.2 (0.5)	<.001	3.7 (0.7)	−0.1 (0.2)	.12	−1.1 (−1.9 to −0.3)	<.001
Serum lipids, mg/dL								
Total cholesterol	188 (29)	−11 (6)	.01	191 (30)	−2 (2)	.23	−9 (−17 to −1)	.02
HDL-C	45 (10)	+4 (2)	.01	43 (9)	+1 (1)	.08	+3 (0.8 to 5.2)	.03
Triglycerides	150 (49)	−18 (8)	.01	173 (53)	+1 (3)	.15	−19 (−32 to −6)	.001
Blood pressure, mm Hg								
Systolic	130 (8)	−4 (2)	<.001	135 (10)	−1 (1)	.06	−3 (−5 to −1)	.01
Diastolic	82 (5)	−3 (1)	<.001	85 (6)	−1 (1)	.05	−2 (−3.5 to −0.5)	.03
Endothelial function score	7.9 (1.3)	+1.9 (0.6)	<.001	6.1 (1.1)	+0.2 (0.2)	.09	+1.7 (1.0 to 2.4)	<.001
hs-CRP and cytokines, median (IQR)								
hs-CRP, mg/L	1.7 (0.4-4.9)	−1.1 (0.4)	.01	2.8 (0.5-5.5)	−0.1 (0.3)	.12	−1 (−1.7 to −0.3)	.01
IL-6, pg/mL	1.4 (0.4-3.8)	−0.7 (0.3)	.02	1.8 (0.5-4.5)	−0.1 (0.2)	.21	−0.6 (−1.1 to −0.1)	.04
IL-7, pg/mL	1.9 (0.5-5.2)	−0.5 (0.2)	.04	2.6 (0.7-6.0)	0 (0.1)	.78	−0.5 (−0.9 to −0.1)	.04
IL-18, pg/mL	148 (92-219)	−19 (9)	.03	171 (100-230)	−4 (3)	.08	−15 (−28 to −2)	.03
No. of components of the metabolic syndrome, No. (%)								
Adjusted for weight changes								
3	31 (34)	−43		59 (66)	−17		−26	
4	10 (11)	−8		12 (13)	−4		−4	<.001
5	1 (1)	−7		7 (8)	−1		−6	
Unadjusted for weight changes								
3	24 (27)	−50		55 (61)	−21		−29	
4	6 (7)	−12		11 (12)	−5		−7	<.001
5	0	−8		6 (7)	−2		−6	

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA, homeostatic model assessment; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IQR, interquartile range.

SI conversion factors: To convert glucose to mmol/L, multiply values by 0.0555; to convert insulin to pmol/L, multiply values by 7.715; to convert total cholesterol and HDL-C to mmol/L, multiply values by 0.0259; to convert triglycerides to mmol/L, multiply values by 0.0113.

*Calculated as weight in kilograms divided by the square of height in meters.

thirds. In a population-based study involving 22 043 apparently healthy adults in Greece, adherence to a traditional Mediterranean diet was associated with significantly lower total mortality, mortality from coronary heart disease, and mortality from cancer.[36] Despite a robust inverse association between the overall Mediterranean-diet score and mortality, no appreciable associations were seen for most of the individual dietary components, which would suggest that the cumulative effects (synergistic or interactive) of multiple dietary components may be substantial. In other words, the effect appears to be more than the sum of its parts.

The results of this study represent the first demonstration, to our knowledge, that a Mediterranean-style diet rich in whole grains, fruits, vegetables, legumes, walnuts, and olive oil might be effective in reducing both the prevalence of the metabolic syndrome and its associated cardiovascular risk. One of the mechanisms responsible for the cardioprotective effect of such a diet may be through reduction of the low-grade inflammatory state associated with the metabolic syndrome. Although weight reduction remains a cornerstone of therapy for the metabolic syndrome, from a public health perspective adoption of a diet similar to that investigated herein may provide further benefit on cardiovascular risk, especially in patients who do not lose weight.

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