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The Postprandial Effect of Components of the Mediterranean Diet on Endothelial Function

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OBJECTIVES This study investigated the postprandial effect of components of the Mediterranean diet on endothelial function, which may be an atherogenic factor.

BACKGROUND The Mediterranean diet, containing olive oil, pasta, fruits, vegetables, fish, and wine, is associated with an unexpectedly low rate of cardiovascular events. The Lyon Diet Heart Study found that a Mediterranean diet, which substituted omega-3-fatty-acid-enriched canola oil for the traditionally consumed omega-9 fatty-acid-rich olive oil, reduced cardiovascular events.

METHODS We fed 10 healthy, normolipidemic subjects five meals containing 900 kcal and 50 g fat. Three meals contained different fat sources: olive oil, canola oil, and salmon. Two olive oil meals also contained antioxidant vitamins (C and E) or foods (balsamic vinegar and salad). We measured serum lipoproteins and glucose and brachial artery flow-mediated vasodilation (FMD), an index of endothelial function, before and 3 h after each meal.

RESULTS All five meals significantly raised serum triglycerides, but did not change other lipoproteins or glucose 3 h postprandially. The olive oil meal reduced FMD 31% (14.3 ± 4.2% to 9.9 ± 4.5%, $p = 0.008$). An inverse correlation was observed between postprandial changes in serum triglycerides and FMD ($r = -0.47$, $p < 0.05$). The remaining four meals did not significantly reduce FMD.

CONCLUSIONS In terms of their postprandial effect on endothelial function, the beneficial components of the Mediterranean and Lyon Diet Heart Study diets appear to be antioxidant-rich foods, including vegetables, fruits, and their derivatives such as vinegar, and omega-3-rich fish and canola oils. (J Am Coll Cardiol 2000;36:1455–60) © 2000 by the American College of Cardiology

The Mediterranean diet, comprised largely of olive oil, pasta, fruits, vegetables, fish, and wine, is associated with a low rate of cardiovascular events (1,2). This observation is unexpected because this diet is associated with a serum cholesterol level similar to that of other countries with higher prevalences of heart disease. Other observational studies have found inverse correlations between coronary disease prevalence and the intake of fish, fruits, and vegetables (3–6). The Lyon Diet Heart Study reported a reduction in cardiovascular events in coronary heart disease (CHD) subjects randomized to a Mediterranean diet that substituted α-linolenic acid (omega-3 fatty acid) enriched canola oil for the traditionally consumed predominately omega-9 olive oil (7,8). This diet did not change serum lipoproteins, suggesting an alternative beneficial mechanism. Other prospective diet trials have found reductions in cardiovascular events in heart disease subjects advised to eat more fruits and vegetables, eat more fish, or take omega-3 fish oil supplements (9–12).

High-saturated fat diets are potentially atherogenic because they elevate serum cholesterol, increase coagulation, and impair endothelial function. Endothelial dysfunction may be an atherogenic factor (13). A high–saturated fat diet impairs endothelial function, possibly because of oxidative stress (14–18). Intravenously administered fat emulsions also produce endothelial dysfunction (19,20). Because the Mediterranean and Lyon Diet Heart Study diets are not associated with low serum cholesterol levels, we hypothesized that olive, fish, and canola oils have other vasoprotective properties, specifically, that they do not impair endothelial function postprandially. To evaluate this hypothesis, we measured brachial artery flow-mediated vasodilation (FMD) (21) before and 3 h after five high-fat meals, three of which contained olive, canola, or fish oils, and two that added antioxidant vitamins or foods to olive oil.

METHODS

Study population. We studied 10 healthy hospital volunteers (5 men, 5 women) ages 28 to 56 years with serum cholesterol and triglyeride levels <200 mg/dl. No subjects had coronary risk factors other than age and gender. All subjects were on ad libitum diets, and none was taking supplemental vitamins or medications, except one male subject who had been on an HMG-CoA reductase inhibitor for two years. All purposely refrained from exercise on the days of the study and fasted for 12 h overnight before being studied. All subjects gave written informed consent, and the

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Abbreviations and Acronyms
ANOVA = analysis of variance
BP = blood pressure
CHD = coronary heart disease
FMD = brachial artery flow-mediated vasodilation
MI = myocardial infarction

protocol was approved by the Institutional Review Board of the University of Maryland.

Intervention. All subjects ate five meals in varied order, starting at 8:00 to 10:00 AM, separated by at least a one-week interval. The meals contained 50 g fat and 900 kcal. Three meals contained different sources of fat:

1. extra-virgin olive oil (50 g) and nonpreservative whole-grain bread (120 g),
2. canola oil (50 g) and nonpreservative whole-grain bread (120 g), and
3. canned red salmon (420 g) and crackers (30 g).

The canola oil and salmon meals contained approximately 5 g and 6 g of omega-3 fatty acid, respectively. The other two meals evaluated the addition of antioxidant vitamins and foods to olive oil:

4. extra-virgin olive oil (50 g), nonpreservative whole-grain bread (120 g), and vitamins C (1 g) and E (*d,1* α-tocopherol, 800 IU), and
5. extra-virgin olive oil (50 g), nonpreservative whole-grain bread (120 g), balsamic vinegar (100 ml), and salad [romaine lettuce (1.5 cup), carrot (1 medium-sized), tomato (1 medium-sized)].

Clinical parameters. Fasting blood was drawn for total, low-density lipoprotein, and high-density lipoprotein cholesterol, triglycerides, and glucose determinations. Assays were performed in the hospital's clinical chemistry laboratory. Heart rate, blood pressure (BP), and FMD were then assessed, following which subjects ate one of the five meals. Three hours after completion of the experimental meal, all parameters were reassessed.

Brachial artery FMD was assessed by a previously described technique (22–27). Briefly, FMD was assessed in the subject's left arm in the recumbent position after a 15-min equilibration period in a temperature-controlled room (22°C) by a single dedicated ultrasonographer. Blood pressure and heart rate were monitored at 5-min intervals in the subject's right arm using an automated sphygmomanometer. Using 11.0-MHz linear array ultrasound, the brachial artery was longitudinally imaged approximately 5 cm proximal to the antecubital crease twice at baseline and once 1 min after a 5-min upper arm BP cuff (12.5 cm wide) arterial occlusion. Twelve-by-16-cm photographic images were obtained in ×8 magnification directly from the rolling digital image storage at end-diastole using R-wave electrocardiographic selection. All images were analyzed by two independent observers blinded to the study sequence. Arterial diameter was determined by caliper measurement. The FMD was determined as the percent diameter change of the post-occlusion measurement relative to the mean of the two baseline measurements. The interobserver variability was 0.09 ± 1.47%, and the interobserver linear correlation coefficient was 0.89.

Statistics. The study had an 80% power to detect a 3% reduction in FMD and a 90% power to detect a 3.6% reduction in FMD. Group values are expressed as mean ± SD. Statistical change was analyzed using analysis of variance (ANOVA) for repeated measures (StatMost, version 3.5) and the two-tailed paired *t* test. Multiple comparisons of the changes in FMD induced by the five meals were statistically compared using Duncan's Multiple Range Test and the Tukey test. A p value <0.05 was considered significant.

RESULTS

Serum lipoprotein and glucose determinations obtained before and 3 h after the five meals are shown in Table 1. Mean serum triglycerides rose significantly ($p < 0.05$) after each meal (range 27% to 45%). No significant changes were observed in serum total, low-density lipoprotein, and high-density lipoprotein cholesterol or glucose levels.

Preprandial and postprandial blood pressure, heart rate, baseline brachial arterial diameter, and FMD are shown in Table 2. No significant changes were observed in BP or heart rate. The olive oil and bread meal reduced FMD 31% (14.3 ± 4.2% to 9.9 ± 4.5%, $p = 0.008$). This change in FMD was significantly different from that following the canola and salmon meals by ANOVA ($p = 0.02$). The olive oil meal reduced FMD statistically more ($p < 0.05$) than the other four meals by Duncan's Multiple Range Test, and more ($p < 0.05$) than the other meals, excepting the olive oil, vinegar, and salad meal by the Tukey test. The reduction in FMD following the olive oil and bread meal was associated with a 2% decrease in post-occlusion arterial diameter ($p = 0.09$) and a 1.8% increase in baseline arterial diameter ($p = 0.14$). A significant inverse correlation was observed between postprandial changes in serum triglycerides and FMD ($r = -0.47$, $p < 0.05$) (Fig. 1). No significant changes in FMD were observed after any of the other four meals.

DISCUSSION

Current study. Contrary to part of our hypothesis, our study found that omega-9 (oleic acid)-rich olive oil impairs endothelial function postprandially. The change in FMD correlated with the change serum in triglycerides, so the effect probably results from triglyceride-containing lipoproteins. The mechanism appears to be oxidative stress because the decrease in FMD was reduced (71%) by the concomitant administration of vitamins C and E. Balsamic vinegar (red wine product) and salad reduced the postprandial impairment in endothelial function to a similar extent

Table 1. Lipoproteins and Glucose Before and After Five High-Fat Meals in 10 Healthy Subjects

	Olive Oil and Bread	Canola Oil and Bread	Salmon and Crackers	Olive Oil, Bread, and Vits C/E	Olive Oil, Bread, Salad, and Vinegar
Preprandial					
Glucose (mg/dl)	85 ± 4	80 ± 8	80 ± 5	83 ± 13	81 ± 6
Cholesterol (mg/dl)	173 ± 22	170 ± 19	174 ± 22	167 ± 17	174 ± 21
LDL-C (mg/dl)	104 ± 23	109 ± 17	112 ± 23	100 ± 17	106 ± 15
HDL-C (mg/dl)	53 ± 13	48 ± 11	49 ± 12	53 ± 10	52 ± 14
Triglyc (mg/dl)	78 ± 41	63 ± 28	66 ± 47	71 ± 36	82 ± 44
Postprandial					
Glucose (mg/dl)	76 ± 13	84 ± 12	81 ± 5	79 ± 11	89 ± 13
Cholesterol (mg/dl)	171 ± 23	174 ± 26	174 ± 23	166 ± 18	171 ± 18
LDL-C (mg/dl)	98 ± 27	108 ± 23	110 ± 23	95 ± 22	96 ± 21
HDL-C (mg/dl)	52 ± 13	49 ± 14	47 ± 14	51 ± 10	48 ± 12
Triglyc (mg/dl)	107 ± 74*	88 ± 49*	84 ± 58*	99 ± 69*	119 ± 50*

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Triglyc = triglycerides; Vits = vitamins.
*$p < 0.05$ compared with preprandial value.

(65%). In keeping with our hypothesis, the omega-3-rich canola oil and salmon meals did not reduce FMD significantly.

Related studies. We have previously reported that a high–saturated fat meal transiently impairs endothelial function (14,15), probably as a result of increased circulating levels of free fatty acid and/or remnant particles. Similar decreases in FMD have been reported with high–saturated fat meals in other studies (17,18). This impairment is reversed by prior administration of an angiotensin-converting enzyme inhibitor (18). A recent report that a high-oleic and linoleic acid (sunflower oil) meal impairs FMD in comparison with a low-fat meal supports our observations (28). Albumin-bound oleic and linolenic acids reduce vascular ring endothelium-dependent vasodilation (29). Remnant particles obtained from postprandial humans impair rabbit aortic ring endothelium-dependent vasodilation in a dose-dependent fashion (30). Fasting remnant particle levels are associated with endothelial dysfunction and coronary event risk (31,32), but fasting hypertriglyceridemia is associated with endothelial dysfunction in only one of three reported studies (33–35).

The parenteral administration of a triglyceride emulsion impairs endothelium-dependent vasodilation and may also reduce endothelium-independent vasodilation (19,20). An increase in baseline arterial diameter after a high-fat meal (endothelium-independent effect) has been reported (36) and might explain the absence of a decline in FMD after a high-fat meal in one study (37). We observed a trend increase (1.8%) in baseline arterial diameter in our study.

Table 2. Heart Rate, Blood Pressure, and Brachial Artery Blood Flow, Diameter, and Flow-Mediated Vasodilation Before and After Five High-Fat Meals in 10 Healthy Subjects

	Olive Oil and Bread	Canola Oil and Bread	Salmon and Crackers	Olive Oil, Bread, and Vits C/E	Olive Oil, Bread, Salad, and Vinegar
Preprandial					
Heart $rate_B$ (beats/min)	60 ± 7	64 ± 7	57 ± 7	62 ± 8	57 ± 7
Heart $rate_{PO}$ (beats/min)	59 ± 6	61 ± 7	58 ± 7	63 ± 8	59 ± 9
BP_B (mm Hg)	110/70 ± 9/5	116/74 ± 7/6	109/69 ± 7/4	111/71 ± 10/8	107/72 ± 8/8
BP_{PO} (mm Hg)	111/69 ± 12/6	115/71 ± 8/7	111/64 ± 8/8	112/69 ± 9/8	110/68 ± 10/7
Blood $flow_B$ (ml/min)	129 ± 82	119 ± 68	143 ± 96	145 ± 94	105 ± 47
Blood $flow_{PO}$ (ml/min)	810 ± 325	839 ± 360	924 ± 433	847 ± 365	900 ± 342
Arterial $diam_B$ (mm)	3.27 ± 0.62	3.29 ± 0.60	3.31 ± 0.66	3.34 ± 0.61	3.28 ± 0.57
FMD (%)	14.3 ± 4.2	13.0 ± 3.4	13.1 ± 5.2	13.3 ± 6.8	13.5 ± 3.5
Postprandial					
Heart $rate_B$ (beats/min)	63 ± 10	62 ± 7	58 ± 7	63 ± 12	59 ± 6
Heart $rate_{PO}$ (beats/min)	64 ± 9	63 ± 11	57 ± 7	65 ± 10	59 ± 8
BP_B (mm Hg)	112/71 ± 9/5	116/70 ± 11/7	110/69 ± 11/6	108/69 ± 12/6	108/70 ± 13/6
BP_{PO} (mm Hg)	110/70 ± 9/9	115/68 ± 9/8	109/64 ± 12/5	109/67 ± 12/6	110/72 ± 11/7
Blood $flow_B$ (ml/min)	124 ± 65	129 ± 87	122 ± 64	127 ± 77	122 ± 72
Blood $flow_{PO}$ (ml/min)	792 ± 328	856 ± 385	924 ± 318	856 ± 363	880 ± 336
Arterial $diam_B$ (mm)	3.33 ± 0.63	3.32 ± 0.68	3.32 ± 0.67	3.37 ± 0.68	3.31 ± 0.63
FMD (%)	9.9 ± 4.5*	11.6 ± 4.4	12.8 ± 5.1	12.1 ± 5.7	12.1 ± 3.5

Subscript B = baseline; BP = blood pressure; diam = diameter; FMD = flow-mediated vasodilation; subscript PO = postocclusion.
*$p = 0.008$.

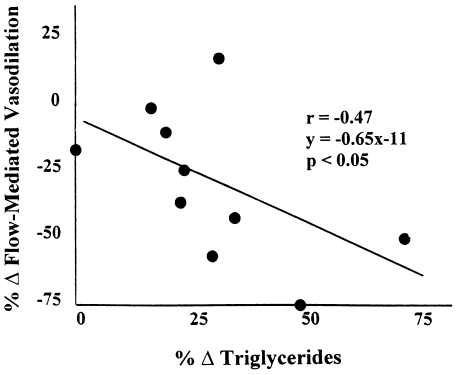

Figure 1. Correlation between percent change in brachial artery flow-mediated vasodilation (3 h postprandial compared with fasting value) and percent change in triglycerides following an olive oil and bread meal in 10 healthy subjects.

We have also reported that the impairment in endothelial function following a high–saturated-fat meal is reduced by the concomitant administration of vitamins C and E, suggesting an oxidative stress mechanism (15). Purple grape juice, rich in polyphenol antioxidants, has been shown to improve FMD in one of two reported studies (37,38). This proposed mechanism is supported, but not proven, by the finding of increased free-radical production by electron paramagnetic resonance spectroscopy in subjects fed a high-fat meal (16).

Diet studies. Considerable data support a vasoprotective effect of the Mediterranean diet, The Seven Countries Study found rates of CHD to be much lower on Crete than would be expected for the mean serum cholesterol level (1,2). Neither the mechanism of this vasoprotection nor the specific foods and/or lifestyle producing it have been clearly identified. The Lyon Diet Heart Study reported a reduction in cardiovascular events in CHD subjects given a Mediterranean diet modified by the substitution of α-linolenic acid (omega-3 fatty acid)-enriched canola oil for the traditionally consumed olive oil, compared with a prudent French diet (7,8).

Olive oil, a staple of the Mediterranean diet, has been presumed to have vasoprotective properties. It appears, however, to have mixed effects on serum cholesterol, endothelial function, and coagulation. Being highly monounsaturated (72%), it has beneficial effects on serum lipoproteins (39–41). The major unsaturated fatty acids in olive oil are oleic acid (18:1n-9) and linoleic acid (18:2n-6) (42). A high-oleic and linoleic acid meal has recently been shown to impair FMD in comparison with a low-fat meal (28). Oleic acid decreases vascular cell adhesion molecule-1 expression in endothelial cells, but not as effectively as polyunsaturated fatty acids, including omega-3 fatty acids (43). Whether the 17% saturated fat content of olive oil impairs this action is unknown. In a clinical study, olive oil was shown to activate coagulation factor VII to the same extent as does butter (44). Thus, olive oil does not have a clearly beneficial effect on vascular function.

Fish consumption is inversely associated with the incidence of cardiovascular events (4–6). Fish oils decrease serum very-low-density lipoproteins, triglycerides, platelet aggregation, and inflammation, and they increase membrane stability and endothelial function (45–53). The mechanism of the latter effect appears to act through changes in eicosanoid metabolism (45,46). The clinical benefit of fish and fish oil has been confirmed in prospective trials. One of two angiographic studies reported decreased progression of coronary artery disease in subjects given fish oil supplementation (54,55). The Diet and Reinfarction Trial (DART) found a 29% reduction in mortality in post–myocardial infarction (MI) patients advised to eat more fish (9), and the Indian Experiment of Infarct Survival trial found significant reductions in cardiac death, nonfatal MI, and cardiovascular events in subjects given either omega-3 fatty acid supplementation (2 g/day) or omega-3 fatty-acid-containing mustard oil (11). The GISSI (Gruppo Italiano per lo Studio della Sopravivenza nell' Infarto miocardico) study reported a 15% reduction in mortality in 11,324 post–MI patients given omega-3 fatty acid supplementation (1 g/day) (12).

The consumption of fruits and vegetables has also been associated with lower incidences of cardiovascular events (3). Postulated mechanisms include increased antioxidant intake, increased fiber intake (with resulting decreased serum low-density lipoprotein), increased potassium intake, and decreased BP (56). Support for the clinical benefit of fruits and vegetables comes from an Indian study in which the addition of fruits, vegetables, nuts, and grain products to a fat-reduced diet lowered cardiovascular events, including mortality, in post–MI patients (10).

Study limitations. Although considerable data support an atherogenic role for endothelial dysfunction, the assumption that endothelial function predicts progression of atherosclerosis and/or cardiovascular event risk is supported only by preliminary data (57). Our study documented postprandial changes after a large morning meal. Whether similar effects would be observed at other times is unknown, especially in view of circadian variations in hepatic and digestive metabolism. We studied a small subject group, but significant changes were observed after the olive oil and bread meal. Several other studies employing the brachial artery FMD technique have been of similar size. We did not measure responses to nitroglycerin in this study, because we and other investigators have reported them to be unaffected by a fatty meal (14–18). Our study does not establish that the decrease in FMD is entirely endothelium-dependent, because the majority, but not all, of the decline in FMD was due to a decrease in post-occlusion arterial diameter. Our data do not exclude a direct vasodilator effect (endothelium-independent) of the olive oil by itself (trend increase in baseline diameter). Two prior studies have observed a direct vasodilator effect of a high-fat meal (36,37); one study observed a direct vasodilator effect after intravenous lipid emulsion (20), but most other prior studies have not (14–18).

Conclusions. In terms of their effects on postprandial endothelial function, the beneficial components of the Mediterranean and Lyon Diet Heart Study diets appear to be the antioxidant-rich foods—vegetables, fruits, and their derivatives such as vinegar, and omega-3-rich fish and canola oils—not olive oil. Canola oil may share some of the unique vasoprotective properties of other omega-3-rich oils, such as fish oil. Dietary fruits, vegetables, and their products appear to provide some protection against the direct impairment in endothelial function produced by high-fat foods, including olive oil.

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