

# The Mediterranean diet and endothelial function: Why some dietary fats may be healthy

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### ABSTRACT

Evidence from both diet and physiologic studies suggests that some dietary fats—but not others—impair endothelial function in the short term, possibly by a mechanism of oxidative stress. This insight may affect our advice to patients about heart-healthy eating.

**I**T MAY BE TIME TO CHANGE our standard advice about limiting cholesterol and high-fat foods, and take into account the effect

of specific dietary fats on endothelial function.

To be sure, cholesterol is important: six large trials in the past 5 years demonstrated that lowering the serum cholesterol level with HMG-CoA reductase inhibitors (statins) decreased the rates of mortality, cardiovascular events, and disease progression. As we shall see however, cholesterol is only part of the story.

### THE STANDARD MODEL AND THE MEDITERRANEAN DIET

Partially owing to the success of the large cholesterol-lowering trials, many people may view coronary artery disease in simplistic terms: high cholesterol leads to atherosclerosis, which leads to coronary events.

Against this background, the results of the Lyon Diet Heart Study<sup>1</sup> came as a surprise: patients with coronary artery disease who followed a so-called Mediterranean diet had a 70% lower rate of coronary events compared with controls. Yet their serum cholesterol levels were no lower.<sup>1</sup> Fish and fish-oil supplements were also found to be beneficial in the DART,<sup>2</sup> Indian,<sup>3</sup> and GISSI<sup>4</sup> studies.

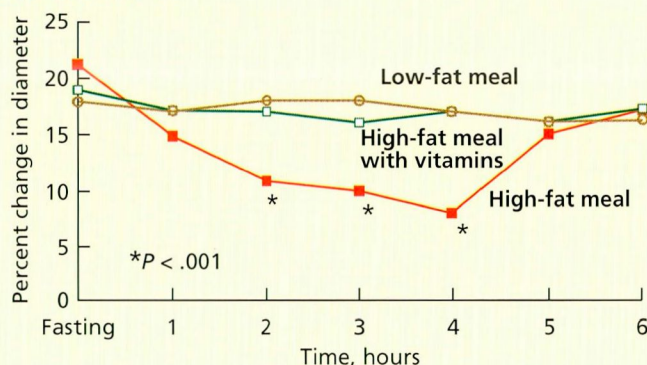
### HIGH-FAT FOODS INHIBIT ENDOTHELIAL FUNCTION

How can diet affect cardiovascular disease risk without changing cholesterol levels?

Certain foods have direct effects on endothelium-dependent vasoactivity. We can observe and measure these effects by noninvasively measuring the diameter of the brachial artery with ultrasound before and after eating.<sup>5</sup>

A blood pressure cuff is placed on the arm, inflated for 5 minutes, then released. In normal subjects in the fasting state, the artery responds to the increase in blood flow by

## A high-fat meal decreases flow-mediated vasodilation, but antioxidant vitamins maintain it



**FIGURE 1.** Effect of three different 900-calorie meals on flow-mediated endothelium-dependent vasodilation, expressed as percent change in the diameter of the brachial artery.

FROM PLOTNICK GD, CORRETTI MC, VOGEL RA. EFFECT OF ANTIOXIDANT VITAMINS ON THE TRANSIENT IMPAIRMENT OF ENDOTHELIUM-DEPENDENT BRACHIAL ARTERY VASOACTIVITY FOLLOWING A SINGLE HIGH-FAT MEAL. JAMA 1997; 278:1682-1686.



dilating by approximately 20% (FIGURE 1). This flow-mediated vasodilation lasts a few minutes and depends on the presence of endothelial nitric oxide, the most potent antiatherosclerotic molecule known.

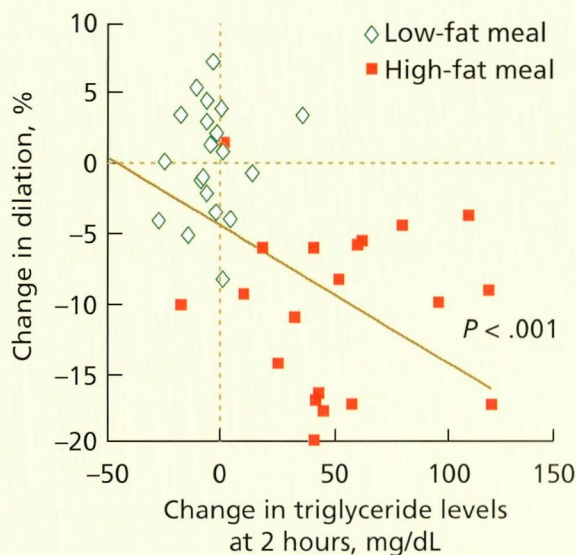
### Short-term effects of a high-fat vs low-fat meal

**Effects on vasodilation.** When we performed this experiment in healthy hospital employees,<sup>6</sup> we found that a 900-calorie, low-fat meal (5.5 oz Kellogg's Frosted Flakes, 8 oz skimmed milk, and 16 oz orange juice, containing 0 mg of fat) had no effect. The arteries continued to dilate by approximately the same amount as at baseline. On the other hand, a 900-calorie, high-fat meal (one Egg McMuffin, one Sausage McMuffin, two hash brown patties, and a noncaffeinated beverage containing 50 mg of fat) reduced the amount of flow-mediated vasodilation by approximately half at 4 hours ( $P < .001$ ). Surprisingly, subjects who took 1 g vitamin C and 800 IU vitamin E immediately before eating a high-fat meal showed no change in flow-mediated vasodilation (FIGURE 1).

**Effects on triglycerides.** In the same experiment we measured serum triglyceride levels before and 2 hours after eating. The mean value at baseline was 97 mg/dL; this did not change after the low-fat meal but increased to 147 mg/dL after the high-fat meal, with or without vitamins ( $P < .005$ ). Levels of cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) did not change significantly. In the subjects who ate the high-fat meal without vitamins, the change in vasodilation had a statistically significant inverse correlation with the change in triglyceride levels ( $r = -0.54$ ,  $P < .001$ ; FIGURE 2).

**Proposed mechanism: oxidative stress.** How to interpret these results? I believe that high-fat foods impair endothelial function by a mechanism of oxidative stress that involves triglyceride-rich lipoproteins. Triglyceride-rich remnant particles and/or free fatty acids may stimulate the endothelial cells to increase production of free-radical superoxide anions, which deactivate nitric oxide. Oxidative stress also contributes to the pathogenesis of atherosclerosis.<sup>5,6</sup> (Cigarette smoking, a powerful risk factor for athero-

### The greater the postprandial rise in triglycerides, the less the vasodilation



**FIGURE 2.** Correlation between mean change in vasodilation 2, 3, and 4 hours after a high-fat or low-fat meal vs change in triglyceride levels at 2 hours.

FROM PLOTNICK GD, CORRETTI MC, VOGEL RA. EFFECT OF ANTIOXIDANT VITAMINS ON THE TRANSIENT IMPAIRMENT OF ENDOTHELIUM-DEPENDENT BRACHIAL ARTERY VASOACTIVITY FOLLOWING A SINGLE HIGH-FAT MEAL. JAMA 1997; 278:1682-1686.

sclerosis, also increases oxidative stress and abolishes endothelial function in the short term.<sup>7</sup>) This mechanism may explain why the antioxidant vitamins C and E seem to preserve endothelial function.

### ■ WHAT ABOUT OLIVE OIL?

Different fats have different effects on endothelial function. We recently evaluated the effects of four different meals that each contained 50 g of fat (TABLE 1).<sup>8</sup> Three meals derived the fat from olive oil, and one from fish oil in the form of salmon. Surprisingly, olive oil, a predominantly omega-9 fatty acid, produced almost the same decline in flow-mediated vasodilation as did the fast-food breakfast. However, mixing olive oil with vitamins C and E or with balsamic vinegar and salad (which contain natural antioxidants) substantially reduced the impairment of endothelial function. The fish oil contained in salmon had very little effect on endothelial function.





TABLE 1

### Olive oil, but not fish oil, decreases flow-mediated vasodilation

CHANGE FROM BASELINE AT 3 HOURS	OLIVE OIL, BREAD	OLIVE OIL, BREAD, VITAMINS C + E	OLIVE OIL, BALSAMIC VINEGAR, SALAD, BREAD	SALMON
Triglycerides	+60%	+60%	+74%	+32%
Flow-mediated vasodilation	-31%*	-9%	-11%	-3%

\* $P < .05$ 

DATA FROM VOGEL RA, CORRETTI MC, FISHER AB, PLOTNICK GD.  
THE DIRECT EFFECT OF COMPONENTS OF THE MEDITERRANEAN DIET ON ENDOTHELIAL FUNCTION:  
OLIVE OIL, VITAMINS AND FISH. [ABSTRACT] J AM COLL CARDIOL 1999; 33: 296A.

**Canola oil  
impairs  
endothelial  
function less  
than olive oil  
does**

One would expect that olive oil, a staple of the diet in the Mediterranean region, would be relatively benign, in view of the results of the Lyon study. However, the Lyon study's Mediterranean diet used canola oil, not olive oil. Canola oil, containing an omega-3 fatty acid akin to fish oil, produced only an insignificant impairment in endothelial function compared with olive oil.

#### ■ DIET: WHAT IS IMPORTANT?

In view of these findings, the ideal diet would be high in fruits, vegetables, and breads and low in red meat and fat. One menu could be based on the one we used in our study: baked salmon along with bread, greens served with canola oil and vinegar, and fruit. In general, we should encourage our patients to eat more breads, vegetables, fruits, beans, and fish, and less meat, and to substitute canola oil margarine for butter and cream. These were the diet recommendations in the Lyon Diet Heart Study.<sup>1</sup>

As for alcohol, moderation is advised. However, red wine, with or without alcohol, has been found to improve flow-mediated vasodilation in a small study.<sup>9</sup>

#### ■ WHAT SHOULD WE RECOMMEND TO PATIENTS?

Based on what we know about the effects of poor diet and other risk factors for cardiovascular disease, the following recommendations are reasonable:

- Don't smoke cigarettes or cigars
- Avoid exposure to secondhand smoke
- Eat less
- Eat more fruits and vegetables
- Exercise. This need not be strenuous—walking 1.5 miles per day decreases the cardiovascular risk of a 70+ year old man by 50%.<sup>10</sup> Even without going to the gym, individuals who are physically active have the same cardiovascular benefit as those who work out regularly.

#### ■ TRADITIONAL RISK FACTORS STILL IMPORTANT

This discussion should in no way detract from the need to target all the well-established modifiable risk factors—cigarette smoking, sedentary lifestyle, hypertension, truncal obesity, hyperinsulinemia, insulin resistance, hypertriglyceridemia, low HDL, high LDL, and hypercoagulability. This is especially true in patients with more than one risk factor, since the average patient with coronary disease has 3.5 risk factors. However, lipid-lowering drugs should be used in addition to lifestyle changes—ie, diet and exercise. ■

#### ■ REFERENCES

1. De Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994; 343:1454-1459.
2. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART) *Lancet* 1989; 334:757-771.
3. Singh RB, Niaz MA, Sharma JP, et al. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: The Indian experiment of infarction survival-4. *Cardiovasc Drug Ther* 1997; 11:485-491.
4. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999; 354:447-455.
5. Vogel RA. Brachial artery ultrasound: a noninvasive tool in the assessment of triglyceride-rich lipoproteins. *Clin Cardiol* 1999; 22 Suppl 6:II-34-II-39.
6. Plotnick GD, Corretti MC, Vogel RA. Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal. *JAMA* 1997; 278:1682-1686.
7. Lekakis J, Papamichael C, Vemmos C, et al. Effects of acute cigarette smoking on endothelial-dependent arterial dilatation in normal subjects. *Am J Cardiol* 1998; 81:1225-1228.
8. Vogel RA, Corretti MC, Plotnick GD. The direct effects of components of the Mediterranean diet on endothelial function [abstract]. *J Am Coll Cardiol* 1999; 33:296A.
9. Hashimoto M, Kim S, Eto M, et al. Acute intake of red wine improves flow-mediated vasodilatation of the brachial artery in men. *Circulation* 1998; 98 Suppl 1:244.

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