Effect of a Single High-Fat Meal on Endothelial Function in Healthy Subjects

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Although there is a well-established relation between serum cholesterol and coronary artery disease risk, individual and national variations in this association suggest that other factors are involved in atherogenesis. High-fat diet associated triglyceride-rich lipoproteins have also been suggested to be atherogenic. To assess the direct effect of postprandial triglyceride-rich lipoproteins on endothelial function, an early factor in atherogenesis—10 healthy, normocholesterolemic volunteers—were studied before and for 6 hours after single isocaloric high- and low-fat meals (900 calorie; 50 and 0 g fat, respectively). Endothelial function, in the form of flow-mediated vasoactivity, was assessed in the brachial artery using 7.5-MHz ultrasound as percent arterial diameter change 1 minute after 5 minutes of upper-arm arterial occlusion. Serum lipoproteins and glucose were determined before eating and 2 and 4 hours postprandially. Serum triglycerides increased from 94 ± 55 mg/dl preprandially to 147 ± 80 mg/dl 2 hours after the high-fat meal ($p = 0.05$). Flow-dependent vasoactivity decreased from 21 ± 5% preprandially to 11 ± 4%, 11 ± 6%, and 10 ± 3% at 2, 3, and 4 hours after the high-fat meal, respectively (all $p < 0.05$ compared with low-fat meal data). No changes in lipoproteins or flow-mediated vasoactivity were observed after the low-fat meal. Fasting low-density lipoprotein cholesterol correlated inversely ($r = -0.47$, $p = 0.04$) with preprandial flow-mediated vasoactivity, but triglyceride level did not. Mean change in postprandial flow-mediated vasoactivity at 2, 3, and 4 hours correlated with change in 2-hour serum triglycerides ($r = -0.51$, $p = 0.02$). These results demonstrate that a single high-fat meal transiently impairs endothelial function. These findings identify a potential process by which a high-fat diet may be atherogenic independent of induced changes in cholesterol. *©1997 by Excerpta Medica, Inc.*

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Although there is a well-established relationship between serum cholesterol and coronary artery disease risk, individual and national variations in this association suggest that other factors are involved in atherogenesis.[1] High-fat diet-associated triglyceride-rich lipoproteins have also been suggested to be atherogenic.[2] A potential mechanism is through induction of endothelial dysfunction, an early factor in atherogenesis.[3] Flow-mediated brachial artery vasoactivity is a sensitive, nitric oxide–dependent index of endothelial function, which has been shown to correlate with acetylcholine-assessed coronary artery vasoactivity.[4–7] Recent studies suggest that coronary risk factors produce both brachial and coronary artery endothelial dysfunction.[8–11] In the case of hypercholesterolemia, this process may be mediated by increases in endothelial oxygen-free radical production, leading to nitric oxide deactivation.[12] To determine whether triglyceride-rich lipoproteins may be directly atherogenic through induction of endothelial dysfunction, we assessed the short-term effects of high- and low-fat single meals on flow-mediated brachial artery vasoactivity.

METHODS

Ten healthy, physically active, normocholesterolemic hospital employees (5 men, mean age 39 ± 10 years) were studied. None of the subjects had a history of hypertension, diabetes mellitus, or tobacco abuse. All had fasting serum cholesterol and triglyceride levels <200 mg/dl and low-density lipoprotein (LDL) cholesterol levels <130 mg/dl. The mean body mass index was 23 ± 2 kg/m^2. Eight of the subjects took no medications and 2 had been taking hydroxymethylglutaryl coenzyme A reductase inhibitor therapy for borderline elevated cholesterol levels for >1 year. Studies were begun at 8:00 A.M. after a 12-hour fasting period. Written informed consent was obtained from all subjects and the protocol was approved by the institutional review board of the University of Maryland at Baltimore. Fasting blood was drawn for serum total, LDL and high-density lipoprotein cholesterol, triglycerides, and glucose. Assays were performed in the hospital's clinical chemistry laboratory. Brachial artery vasoactivity, blood pressure, and heart rate were then assessed (see later). Following this, subjects ate either a high- or low-fat meal in varied order at least 1 week apart. The high-fat meal (900 calories, 50 g of fat, 14 g of saturated fat, and 255 mg of cholesterol) consisted of an Egg McMuffin®, Sausage McMuffin®, 2 hash brown patties, and a noncaffeinated beverage (McDonald's Corporation). The isocaloric low-fat meal (0 g of fat, 13 mg of cholesterol) consisted of Frosted Flakes® (Kellogg Company, Battle Creek, Michigan), skimmed milk, and orange juice. Lipoprotein and glucose determinations were repeated 2 and 4 hours after eating.

Endothelial function in the form of flow-mediated brachial artery vasoactivity was measured hourly for 6 hours after eating by a previously described non-

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TABLE I Baseline Arterial Diameter and Blood Flow and Hyperemic Flow Before and After High- and Low-Fat Meals

	Preprandial	Postprandial					
		1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours
High-fat meal							
Baseline arterial diameter (mm)	3.2 ± 0.6	3.2 ± 0.6	3.3 ± 0.5	3.3 ± 0.6	3.3 ± 0.6	3.2 ± 0.6	3.3 ± 0.6
Baseline blood flow (ml/min)	102 ± 85	108 ± 94	108 ± 76	131 ± 78	79 ± 67	112 ± 60	87 ± 53
Postocclusion blood flow (ml/min)	577 ± 287	554 ± 260	584 ± 211	624 ± 289	628 ± 249	640 ± 241	588 ± 287
Flow-mediated vasoactivity (% change)	21 ± 5	15 ± 5	11 ± 4*	11 ± 6*	10 ± 3*	13 ± 5	15 ± 6
Nitroglycerin vasoactivity (% change)	25 ± 4			23 ± 3			
Low-fat meal							
Baseline arterial diameter (mm)	3.1 ± 0.8	3.1 ± 0.8	3.2 ± 0.8	3.2 ± 0.8	3.2 ± 0.8	3.1 ± 0.9	3.1 ± 0.9
Baseline blood flow (ml/min)	110 ± 58	111 ± 50	140 ± 83	124 ± 95	85 ± 69	76 ± 55	83 ± 52
Postocclusion blood flow (ml/min)	589 ± 311	677 ± 284	734 ± 342	682 ± 258	667 ± 247	576 ± 297	636 ± 290
Flow-mediated vasoactivity (% change)	18 ± 6	18 ± 5	17 ± 6	17 ± 2	17 ± 6	17 ± 5	16 ± 4

* $p < 0.05$ high- versus low-fat meal.

invasive technique.[5] Blood pressure and heart rate were also assessed hourly. Briefly, flow-mediated vasoactivity was assessed in the subject's left arm in the recumbent position in a temperature-controlled room (22°C) after a 10-minute equilibration period by a single dedicated ultrasonographer. Using 7.5-MHz linear array ultrasound, the brachial artery was longitudinally imaged approximately 5 cm proximal to the antecubital crease, twice at baseline and then 1 minute after release of 5 minutes of blood pressure cuff (12.5 cm wide), upper arm, arterial occlusion. In 4 randomly chosen subjects (2 men), nitroglycerin (non–endothelium-dependent) vasoactivity was also assessed preprandially and 3 hours after the high-fat meal. Only a subgroup was evaluated because flow-mediated vasoactivity has been shown to be a endothelium-dependent phenomenon.[6] Fifteen minutes after acquisition of the postocclusion image, 2 additional baseline images were obtained, after which 0.4 mg nitroglycerin was given sublingually. Five minutes later, another image was acquired. Photographic images were obtained of end-diastolic (simultaneously recorded electrocardiogram) frames which were subsequently analyzed by 2 independent investigators blinded to the subject's identity, meal status, and temporal sequence. Arterial diameter was determined by caliper measurement at the single most equivalently imaged site using side-by-side presentation. Flow-mediated and nitroglycerin vasoactivity were respectively determined as the percent diameter change of the postocclusion or nitroglycerin arterial diameter measurement relative to the mean of the corresponding 2 baseline measurements. The 2 independent observer measurements were averaged. The reproducibility of the 2 baseline measurements (SD of difference) was 0.87% (coefficient of variation 4.3%). Blood flow velocity was measured by Doppler technique before (baseline) and immediately after (postocclusion) blood pressure cuff occlusion. Arterial blood flow was determined as arterial cross-sectional area times mean Doppler velocity.

Group values are expressed as mean ± SD. Statistical change was analyzed for repeated measurements using analysis of variance, followed by 2-tailed paired t test and by linear regression analysis. A p value <0.05 was considered significant.

RESULTS

Lipoprotein, glucose, blood pressure, and heart rate determinations before and after the high- and low-fat meals are listed in Table II. Mean serum triglycerides increased from 94 ± 55 mg/dl preprandially to 147 ± 80 and 158 ± 97 mg/dl 2 and 4 hours after ingestion of the high-fat meal, respectively ($p = 0.05$ and 0.20 compared with low-fat meal). No other significant changes or trends in lipoproteins or glucose were observed. No hemodynamic changes occurred after either meal.

Pre- and postprandial baseline arterial diameter, blood flow, postocclusion maximal flow, and flow-mediated vasoactivity are shown on Table I. Neither meal caused significant changes in baseline arterial diameter or resting or postocclusion blood flow.

Pre- and postprandial flow-mediated vasoactivity determinations are shown in Figure 1 and Table I. Following the high-fat meal, flow-mediated vasoactivity decreased significantly at 2, 3, and 4 hours, differing from values obtained after the low-fat meal ($p = 0.05$, 0.02, and 0.03, respectively). Preprandial flow-mediated brachial artery vasoactivity correlated inversely with fasting LDL cholesterol ($r = -0.47$, $p = 0.04$), but insignificantly with other lipoproteins including triglycerides. The mean change in flow-mediated brachial artery vasoactivity at 2, 3, and 4 hours correlated significantly with the 2-hour change in postprandial serum triglyceride determination ($r = -0.51$, $p = 0.02$): a greater decrease in vasoactiv-

ity was observed in those with a greater increase in serum triglycerides (Figure 2).

In the 4 subjects studied before and 3 hours after the high-fat meal, nitroglycerin (non–endothelium-dependent) vasoactivity did not change: 25 ± 4% and 23 ± 3% (p = NS), respectively. In these subjects, flow-mediated vasoactivity decreased from 20 ± 7% before eating to 8 ± 1% 3 hours after the high-fat meal.

DISCUSSION

Serum triglyceride levels have not been found to correlate as strongly with coronary artery disease risk as have cholesterol levels, although most studies have determined only fasting triglycerides.[13,14] Stronger correlations between triglyceride levels and heart disease risk have been found in women, diabetics, Japanese, and those with elevated LDL or decreased high-density lipoprotein cholesterol levels.[2,13,14] Coronary disease risk also appears to correlate more closely with postprandial triglyceride levels and delayed chylomicron remnant clearance has been reported in patients with coronary disease.[15,16] One mechanism by which chylomicron remnants and other triglyceride-rich lipoproteins may lead to atherosclerosis is through the induction of endothelial dysfunction. Several studies have demonstrated that all traditional coronary risk factors are associated with endothelial dysfunction, independent of the presence of coronary artery disease.[8–11]

This study found that a single high-fat (50 g) meal reduces flow-mediated (endothelium-dependent) vasoactivity in the 2- to 4-hour postprandial period. An equicaloric low-fat (0 g) meal did not affect endothelial function. This observation clinically supports the preliminary observation of Doi et al[17] who found that chylomicron and very low density lipoprotein remnants isolated from the postprandial plasma of normocholesterolemic, healthy volunteers impaired acetylcholine-induced vasodilation in precontracted rabbit aortic strips. Our findings that preprandial flow-mediated vasoactivity correlated inversely with fasting LDL cholesterol, but not triglyceride levels, support the prior observation that hypercholesterolemia is an independent determinant of endothelial function.[8–11] Importantly, the current study found a significant correlation between elevations in 2-hour postprandial serum triglyceride levels and mean 2-, 3-, and 4-hour impairment of endothelial function, suggesting that indeed postprandial triglyceride-rich lipoproteins, but not fasting triglycerides, are the offending factor. This may explain why fasting triglyceride levels do not correlate closely with coronary artery disease risk.

The current study found higher preprandial flow-mediated vasoactivity (21%, 18%, high- and low-fat meals, respectively) than did previous reports.[4,10,11] This study investigated subjects with smaller arteries at baseline (3.2 ± 0.6 mm, 3.1 ± 0.8 mm, high- and

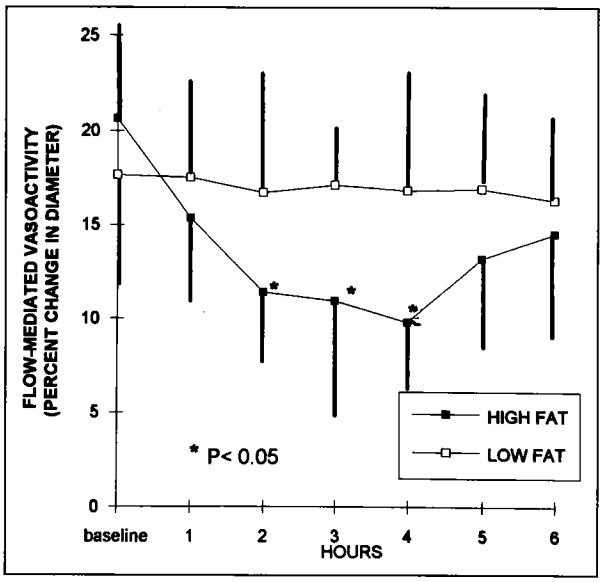

FIGURE 1. Flow-mediated brachial artery vasoactivity is plotted before and after ingestion of the high- and low-fat meals. Significant reductions in vasoactivity were observed 2, 3, and 4 hours after ingestion of the high-fat meal.

TABLE II Lipoproteins, Glucose, Blood Pressure, and Heart Rate Before and After High- and Low-Fat Meals

	Baseline		2 Hours		4 Hours	
	High-Fat Meal	Low-Fat Meal	High-Fat Meal	Low-Fat Meal	High-Fat Meal	Low-Fat Meal
Total cholesterol (mg/dl)	164 ± 21	177 ± 19	163 ± 22	171 ± 18	164 ± 22	171 ± 19
LDL cholesterol (mg/dl)	93 ± 24	104 ± 23	84 ± 22	99 ± 23	88 ± 19	100 ± 25
HDL cholesterol (mg/dl)	52 ± 14	56 ± 12	50 ± 13	54 ± 9	52 ± 14	52 ± 12
Triglycerides (mg/dl)	94 ± 55	91 ± 32	147 ± 80*	90 ± 29	158 ± 97†	104 ± 36
Glucose (mg/dl)	85 ± 8	83 ± 8	81 ± 9	77 ± 12	86 ± 10	85 ± 14
Blood pressure (mm Hg)	118/73 ± 9/7	113/72 ± 11/6	116/70 ± 10/6	115/69 ± 13/5	115/73 ± 9/9	113/71 ± 10/8
Heart rate (beats/min)	64 ± 9	67 ± 12	69 ± 8	72 ± 10	63 ± 9	64 ± 10

* p = 0.05; † p = 0.20.
LDL = low-density lipoprotein; HDL = high-density lipoprotein.

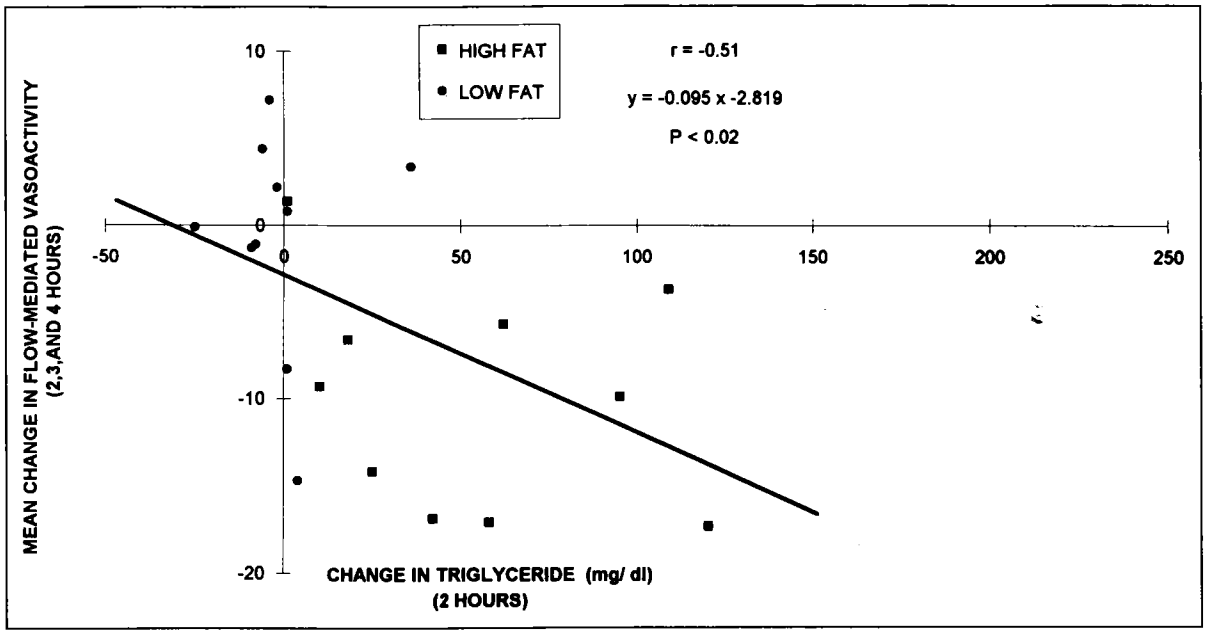

FIGURE 2. Individual subject mean change in flow-mediated vasoactivity (absolute change in percent change in arterial diameter) at 2, 3, and 4 hours after eating is plotted against change in serum triglycerides 2 hours after eating. Larger decreases in flow-mediated vasoactivity were significantly associated with greater increases in triglycerides.

low-fat meals, respectively), lower cholesterol levels (164 ± 21 mg/dl, 177 ± 19 mg/dl, high- and low fat meals, respectively), and a higher proportion of women (50%) than those in previous reports, all of which have been identified as factors associated with increased vasoactivity.[9–11] The observed changes in vasoactivity following only the high-fat diet appears to reflect impairment in endothelial function because no significant changes were observed in non–endothelium-dependent (nitroglycerin) vasoactivity, hemodynamics, baseline arterial diameter and blood flow, and postocclusion flow.

Study limitations: This study employed a large fat load (50 g). Such high-fat meals are commonly eaten, however, especially at ''fast-food'' restaurants.[18] The study did not attempt to determine whether lesser fat loads impair endothelial function, or whether high-fat meals lower in saturated fat have similar effects. Although postprandial triglyceride elevations correlated with impairment in endothelial function, the specific lipoprotein fraction or change in particle size, composition, or oxidative state responsible for the observed effect was not identified. Moreover, this study identified only a possible mechanism by which high-fat diets could lead to atherosclerosis independent of changes in cholesterol level.

Clinical implications: Angiographic studies of coronary disease progression have demonstrated that dietary consumption of saturated fat and serum levels of triglyceride-rich lipoproteins in the intermediate-density and very low density remnant lipoprotein fractions are independent predictors of coronary disease progression.[19,20] This study strongly supports these findings and suggests that a high-fat diet is atherogenic through a direct (endothelium-dependent) as well as indirect (cholesterol-dependent) pathway. The former may explain variations in the cholesterol–coronary artery disease risk relationship observed in populations with different diets. These data support the value of a low-fat diet as an important component for preventing and treating coronary artery disease, even in persons with ''desirable'' cholesterol levels and in those on lipid-lowering therapy.

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