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Effects of dietary carbohydrate restriction versus low-fat diet on flow-mediated dilation

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Abstract

We previously reported that a carbohydrate-restricted diet (CRD) ameliorated many of the traditional markers associated with metabolic syndrome and cardiovascular risk compared with a low-fat diet (LFD). There remains concern how CRD affects vascular function because acute meals high in fat have been shown to impair endothelial function. Here, we extend our work and address these concerns by measuring fasting and postprandial vascular function in 40 overweight men and women with moderate hypertriacylglycerolemia who were randomly assigned to consume hypocaloric diets (~1500 kcal) restricted in carbohydrate (percentage of carbohydrate-fat-protein = 12:59:28) or LFD (56:24:20). Flow-mediated dilation of the brachial artery was assessed before and after ingestion of a high-fat meal (908 kcal, 84% fat) at baseline and after 12 weeks. Compared with the LFD, the CRD resulted in a greater decrease in postprandial triacylglycerol (−47% vs −15%, $P = .007$), insulin (−51% vs −6%, $P = .009$), and lymphocyte (−12% vs −1%, $P = .050$) responses. Postprandial fatty acids were significantly increased by the CRD compared with the LFD ($P = .033$). Serum interleukin-6 increased significantly over the postprandial period; and the response was augmented in the CRD (46%) compared with the LFD (−13%) group ($P = .038$). After 12 weeks, peak flow-mediated dilation at 3 hours increased from 5.1% to 6.5% in the CRD group and decreased from 7.9% to 5.2% in the LFD group ($P = .004$). These findings show that a 12-week low-carbohydrate diet improves postprandial vascular function more than a LFD in individuals with atherogenic dyslipidemia.

1. Introduction

Endothelial dysfunction is an early event in coronary heart disease that can be detected using a noninvasive technique that evaluates flow-mediated dilation (FMD) of the brachial artery using high-frequency ultrasound [1]. A high-fat meal can transiently impair FMD of the brachial artery [2-4], and some studies report that the lipemic response is related to vascular dysfunction [5,6]. Although single meals high in fat induce hypertriacylglycerolemia, adaptation to high-fat diets with a low carbohydrate content dramatically decreases the postprandial lipemic response in normal-weight [7-9] and overweight [10] individuals. Thus, low-carbohydrate diets, by virtue of their potent triacylglycerol (TAG)-lowering effect, may improve vascular function if subjects are allowed to make metabolic adaptations.

There are other adaptations to carbohydrate-restricted diets (CRD) that could have a benefit on endothelial function, specifically those associated with the metabolic syndrome (insulin resistance syndrome). Metabolic syndrome represents a group of seemingly disparate physiologic signs that indicate a predisposition to obesity, diabetes, and cardiovascular disease. Its origins are generally believed to reside in impairment of insulin action; and its intellectual impact is embodied in a unifying principle for control of the broad range of physiologic effects, which now include vascular dysfunction [11]. Consistent with the idea that an intolerance to carbohydrate is an underlying feature of metabolic

JSV, WJK, and MLF had overall responsibility of the study and contributed to experimental design, data analysis and interpretation, and manuscript preparation. KDB, RS, and DAJ performed vascular measurements and analysis as well as biochemical assays. EEQ and CEF were responsible for the dietetic aspects of the study and overseeing the data collection protocols. All authors agreed on the final version of the manuscript, and none had any conflict of interest.

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syndrome, we have presented results showing that reduction in dietary carbohydrate results in global improvement in traditional and emerging markers associated with metabolic syndrome, particularly the cardiometabolic profile (high-density lipoprotein [HDL] is increased, and TAG and small low-density lipoprotein cholesterol are decreased) [12,13].

The status of CRD as a method to alter vascular function cannot be adequately addressed by single-meal experiments [14]. Therefore, the primary purpose of this study was to assess postprandial vascular function in the brachial artery after a high-fat meal in subjects with hypertriacylglycerolemia who consumed a CRD for 12 weeks. Their responses were compared with a control group who consumed a low-fat diet (LFD). We also measured an array of cardiometabolic markers implicated in vascular dysfunction including postprandial circulating TAG [5], fatty acids [15], total leukocytes [16], leukocyte subpopulations [17], and proinflammatory markers [18]. Our recent findings in this cohort showed that a CRD was more likely than an LFD to effect global improvement in markers associated with insulin resistance [19,20]. Here, we extend these findings by showing that a CRD also has a beneficial effect on postprandial lipemia and FMD of the brachial artery compared with an LFD.

2. Methods

2.1. Study design and participants

This study was a randomized, controlled, dietary intervention trial that compared a CRD to an LFD over a 12-week period in overweight subjects with atherogenic dyslipidemia. Participants were men and women aged 18 to 55 years with a body mass index (BMI) greater than 25 kg/m^2. Exclusion criteria were any metabolic and endocrine disorders; use of glucose-lowering, lipid-lowering, or vasoactive prescriptions or supplements; consumption of a CRD at baseline; or weight loss greater than 5.0 kg in the past 3 months. Eligible subjects had a 12-hour fasting blood sample taken, and subjects with both moderately elevated TAG (150-500 mg/dL) and low HDL cholesterol (<40 [men] or <50 [women] mg/dL) were randomly assigned to the CRD or LFD group after being matched by age and BMI. Twenty men and 20 women completed the study. All procedures were approved by the Institutional Review Board, and all subjects provided written informed consent. At baseline (week 0) and after the diet intervention (week 12), subjects came to the laboratory after a 12-hour overnight fast and 24-hour abstinence from alcohol and strenuous exercise to perform an oral fat tolerance test using standard procedures in our laboratory [9,21].

2.2. Dietary intervention

Subjects received individual and personalized dietary counseling from registered dietitians before the dietary intervention. Detailed dietary booklets, specific to each dietary treatment, were provided outlining dietary goals, lists of appropriate foods, recipes, sample meal plans, and food record log sheets. Throughout the intervention, subjects received weekly counseling during which time body mass was measured, compliance to the diet protocol was assessed, and further dietetic education was provided. Habitual physical activity was maintained throughout the study intervention and was documented daily by all subjects.

The main goal of the CRD was to restrict carbohydrate to a level that induced a low level of ketosis. Subjects monitored their level of ketosis daily using urine reagent strips that produce a relative color change in the presence of one of the primary ketones, acetoacetic acid. In this diet, there were no restrictions on the type of fat from saturated and unsaturated sources or cholesterol levels. Examples of foods consumed by the subjects included unlimited amounts of beef, poultry, fish, eggs, oils and heavy cream; moderate amounts of hard cheeses, low-carbohydrate vegetables, and salad dressings; and small amounts of nuts, nut butters, and seeds. Subjects restricted fruit and fruit juices, dairy products (with the exception of heavy cream and hard cheese), breads, grains, pasta, cereal, high-carbohydrate vegetables, and desserts. Subjects were instructed to avoid all low-carbohydrate breads and cereal products, and were limited to a maximum of 1 sugar alcohol-containing, low-carbohydrate snack per day. The LFD was designed to provide less than 10% of total calories from saturated fat and less than 300 mg cholesterol. Foods encouraged included whole grains (breads, cereals, and pastas), fruit/fruit juices, vegetables, vegetable oils, and low-fat dairy and lean-meat products. Standard diabetic exchange lists were used to ensure a macronutrient balance of protein (~20% energy), fat (~25% energy), and carbohydrate (~55% of energy).

All subjects were given a multivitamin/mineral complex that provided micronutrients at levels not exceeding 100% of the recommended dietary allowance and instructed to consume 1 pill every other day. No explicit instructions were provided regarding caloric intake for either diet. Seven-day weighed food records were kept during the week before baseline testing to assess habitual intake and during weeks 1, 6, and 12 of the intervention. Diet records were analyzed for energy and macro-/micronutrient content (NUTRITIONIST PRO, Version 1.3; First Databank, Hearst, San Bruno, CA). The nutrient analysis program had no missing values for the nutrients reported, and the database was extensively updated with new foods and individualized recipes.

2.3. Oral fat tolerance test

A flexible catheter was inserted into a forearm vein, and blood samples were obtained from a 3-way stopcock. The catheter was kept patent with a constant saline drip. Before consumption of the test meal, subjects rested in a seated position for 10 minutes; and a baseline blood sample was obtained, followed by assessment of FMD (described below). After these measurements, a high-fat meal (225 mL whipping

cream, sugar-free instant pudding, 28.5 g macadamia nuts) was consumed within a 15-minute time frame, providing 908 kcal, 13% carbohydrate, 3% protein, and 84% fat. Postprandial blood samples were obtained immediately (0 hour) and hourly (1, 2, 3, 4, 5, and 6 hours) after the meal; and vascular function was assessed again at 1.5, 3, and 4.5 hours. Subjects rested quietly in a seated position and consumed only water during the postprandial period.

2.4. Flow-mediated dilation

Subjects rested supine for 10 minutes in a quiet room position before data collection. Vascular function of the brachial artery was assessed by FMD using an Acuson 13.0-MHz linear array transducer and an Aspen cardiac ultrasound system (Acuson, Elmwood Park, NJ). Electrocardiographic leads were attached to the subject to monitor heart rate throughout the procedure. A longitudinal image of the brachial artery was located above the antecubital crease on the right arm. When a clear image of the artery anterior and posterior vessel wall was visualized, the transducer was held in place with a clamp; and the subject's arm was held steady with the use of an air cast throughout the duration of the protocol. Resting baseline images of the brachial artery were recorded for 30 heart beats. Arterial occlusion was then created by inflating a sphygmomanometric cuff on the right arm just above the medial epicondyle of the humerus. After 5 minutes of occlusion, the cuff was rapidly deflated; and postocclusion images were obtained immediately for 300 heart beats. Placement of the transducer on the arm was marked, and an image of the vessel was printed to provide external and inernal landmarks to standardize the location of the artery during repeated measurements. Brachial artery images were digitized and stored on a PC. The system uses a Data Translation (Marlboro, MA) DT 3152 frame grabber programmed to acquire a specified number of interleaved video frames in response to the R wave of the electrocardiogram. The digitized images were stored using 640 × 480-bit resolution using 8-bit/256–gray scale color encoding. The image format used was an enhanced version of Microsoft (Redmond, Wa) Windows device-independent bitmap.

Ultrasound images were analyzed using a semiautomated software (Vascular Tools 4; Medical Imaging Applications, Coralville, IA) that allows identification of brachial artery borders [22]. The near and far vessel walls were determined using a graph-searching approach, and quality control mechanisms were applied to recognize and minimize border segmentation variability. During the postocclusion sequence, average vessel diameter over 20 continuous frames was reported for 1 minute postdeflation and peak vessel diameter. Percentage changes for postocclusion measurements were determined through comparison with average resting baseline diameter. One trained, blinded technician performed all analyses. Coefficients of variation for arterial diameter on repeated scans with repositioning on a group of men and women (N = 10) in our laboratory were 2.2% for measurements made the same day and 2.2% for measurements made on 2 consecutive days.

2.5. Biochemical analyses

During each blood collection period, approximately 3 mL of blood was drawn from the catheter and discarded. Thereafter, whole blood was collected into a 3-mL tube with EDTA and a 10-mL tube with no preservative. The EDTA tube was sent to a certified medical laboratory (Quest Diagnostics, Wallingford, CT) for a white blood cell differential count. The 10-mL tube was centrifuged at 1500*g* for 15 minutes and 4°C, and promptly aliquoted into separate tubes that were stored at −75°C until analyzed for serum TAG, insulin, fatty acids, and interleukin-6 (IL-6). Triacylglycerols were determined by use of Roche Diagnostic (Indianapolis, IN) kits, which adjust for free glycerol. Insulin concentrations were analyzed in duplicate by I^{125} radioimmunoassay (Diagnostic Systems Laboratory 1600, Webster, TX). Nonesterified fatty acids were analyzed in duplicate using an acyl-CoA synthetase-acyl-CoA oxidase (ACS-ACOD) method (Wako Chemicals, Richmond, VA). Interleukin-6 was analyzed using the Evidence Investigator Biochip Array technology (Randox Laboratories, Antrim, United Kingdom) that uses sandwich chemiluminescent immunoassays to simultaneously detect multiple analytes from a single sample.

2.6. Statistical analyses

Dependent *t* tests were used to compare baseline values between the 2 diet groups. Vascular response and blood markers were compared using analysis of variance (ANOVA) with 1 between effect (CRD vs LFD) and time (week 0 vs week 12) as a within factor. Significant main or interaction effects were further analyzed using a Fisher least significant difference post hoc test. For postprandial biochemical variables, area under the curve was calculated using the trapezoidal method; and comparisons between groups were made by ANOVA. If there were significant differences between diet groups at the start of the experiment, analysis of covariance with baseline values as a covariate was used. Relationships among selected variables were examined using Pearson product-moment correlation coefficient. The α level for significance was set at .05.

3. Results

3.1. Baseline characteristics, dietary intake, and weight loss

We previously reported the baseline characteristics, dietary intake, and responses in fatty acid composition [19,20]. Briefly, the 2 diet groups were equally matched for sex; and there were no significant differences between groups in age, body composition, or metabolic profiles (Table 1). Energy intake was not different between diets, but

Table 1
Baseline characteristics

	CRD (n = 20)	LFD (n = 20)
Sex (M/F)	10/10	10/10
Age (y)	32.6 ± 11.3	36.9 ± 12.5
Body mass (kg)	96.5 ± 13.7	94.4 ± 15.2
BMI (kg/m^2)	33.5 ± 5.2	32.1 ± 4.1
Body fat (%)	40.6 ± 7.3	39.0 ± 7.9
Total cholesterol (mg/dL)	208.0 ± 26.0	204.0 ± 31.5
LDL cholesterol (mg/dL)	130.4 ± 21.8	127.9 ± 31.3
HDL cholesterol (mg/dL)	35.8 ± 6.9	38.7 ± 6.2
TAG (mg/dL)	210.9 ± 57.9	187.1 ± 57.6

Values are mean ± SD. No significant differences by independent *t* test. LDL indicates low-density lipoprotein.

the nutrient composition varied significantly between the CRD (1504 kcal; percentage of carbohydrate-fat-protein = 12:59:28) and LFD (1478 kcal; percentage of carbohydrate-fat-protein = 56:24:20) (Table 2). Dietary cholesterol was significantly higher and fiber was significantly lower on the CRD compared with the LFD. During weeks 2 to 12 of the CRD intervention, subjects reported the presence of urinary ketones above trace on 85% of the days, indicating a high degree of compliance. Despite similar reductions in calories, weight loss in the CRD group was, on average, 2-fold greater than that in the LFD group (10.1 vs 5.2 kg).

3.2. Postprandial TAG, insulin, and fatty acids

At baseline, the high-fat meal induced a dramatic rise in serum TAG in both diet groups that peaked about 3 to 4 hours after ingestion and remained above fasting levels for the duration of the 6-hour postprandial period. After 12 weeks, the postprandial TAG pattern was dramatically decreased at all time points in the CRD group, representing a 47% decrease in the total area under the curve compared with a more moderate 15% decrease in the LFD group (P = .007 for diet × time interaction) (Fig. 1). Serum insulin peaked 1 hour after the meal and returned to fasting levels at the 3-hour time point. After 12 weeks, the total insulin area under the curve was significantly decreased in the CRD group (−51%) compared with the LFD group (−6%) (P = .009 for diet × time interaction) (Fig. 1). Nonesterified fatty acids gradually increased throughout the postprandial period, peaking at the 6-hour time point. After 12 weeks, there was a slight increase in the total fatty acid area under the curve in subjects after the CRD, whereas the response was decreased in subjects after the LFD (P = .033 for diet × time interaction) (Table 3).

3.3. Postprandial leukocyte and IL-6 responses

Postprandial total leukocyte and neutrophil concentrations were significantly increased at the 2-, 4-, and 6-hour time points; but there were no other significant main or interaction effects (Table 3). Lymphocyte concentrations gradually increased over the 6-hour postprandial period, and the response was significantly blunted after 12 weeks in the CRD group (P = .050 for diet × time interaction) (Fig. 2). The total lymphocyte area under the curve was decreased after the CRD (−12%) but not the LFD (−1%) (P = .082 for diet × time interaction). Serum IL-6 increased significantly over the postprandial period, doubling in concentration at the 6-hour time point; and the response was significantly increased after 12 weeks in the CRD group (P = .024 for diet × time interaction) (Fig. 2). The total IL-6 area under the curve was increased after the CRD (46%) but decreased after the LFD (−13%) (P = .038 for diet × time interaction).

3.4. Vascular function

There was a significant difference in fasting peak FMD between diet groups at baseline (P = .043). Peak FMD in the fasted state increased slightly from 5.0% ± 3.0% to 5.5% ± 2.5% in the CRD group and decreased from 7.1% ± 3.3% to 6.1% ± 3.0% in the LFD group, which did not reach significance when the baseline FMD was used as a covariate in the ANOVA. There was a significant difference in the postprandial FMD response in the groups (Fig. 3). After 12 weeks, peak FMD at 3 hours increased from 5.1% ± 2.7% to

Table 2
Nutrient intake from 7 days of food records at baseline (week 0) and 21 days of food records during the intervention (week 12)

	CRD (n = 20)		LFD (n = 20)		*P* value[a]	
	Wk 0	Wk 12	Wk 0	Wk 12	Time	D × T
Energy (kcal)	2351 ± 617	1504 ± 494	2082 ± 445	1478 ± 435	.000	.154
Protein (g)	94.6 ± 28.5	104.8 ± 33.6	82.3 ± 17.6	71.5 ± 21.3	.756	.009
Protein (%)	16.2 ± 3.1	28.1 ± 4.4	15.8 ± 2.6	19.6 ± 4.4	.000	.000
Carbohydrate (g)	270.3 ± 67.2	44.8 ± 18.9	266.8 ± 74.7	208.3 ± 69.6	.000	.000
Carbohydrate (%)	46.6 ± 7.7	12.4 ± 5.2	50.9 ± 10.1	55.8 ± 7.9	.000	.000
Total fat (g)	97.0 ± 35.2	100.2 ± 37.9	78.5 ± 29.5	40.0 ± 17.5	.004	.001
Total fat (%)	36.2 ± 6.7	58.9 ± 5.4	33.0 ± 9.8	23.8 ± 6.8	.000	.000
Saturated fat (g)	34.2 ± 14.3	36.4 ± 12.9	26.0 ± 11.1	11.7 ± 5.9	.012	.002
Alcohol (%)	0.9 ± 1.8	0.7 ± 1.4	0.3 ± 0.5	0.9 ± 2.0	.232	.056
Cholesterol (mg)	354 ± 120	605 ± 262	267 ± 111	144 ± 80	.044	.000
Dietary fiber (g)	13.1 ± 3.5	9.4 ± 4.9	15.8 ± 6.6	17.3 ± 9.6	.083	.021

Values are mean ± SD. D indicates diet; T, time.
[a] 2 (diet) × 2 (time) ANOVA.

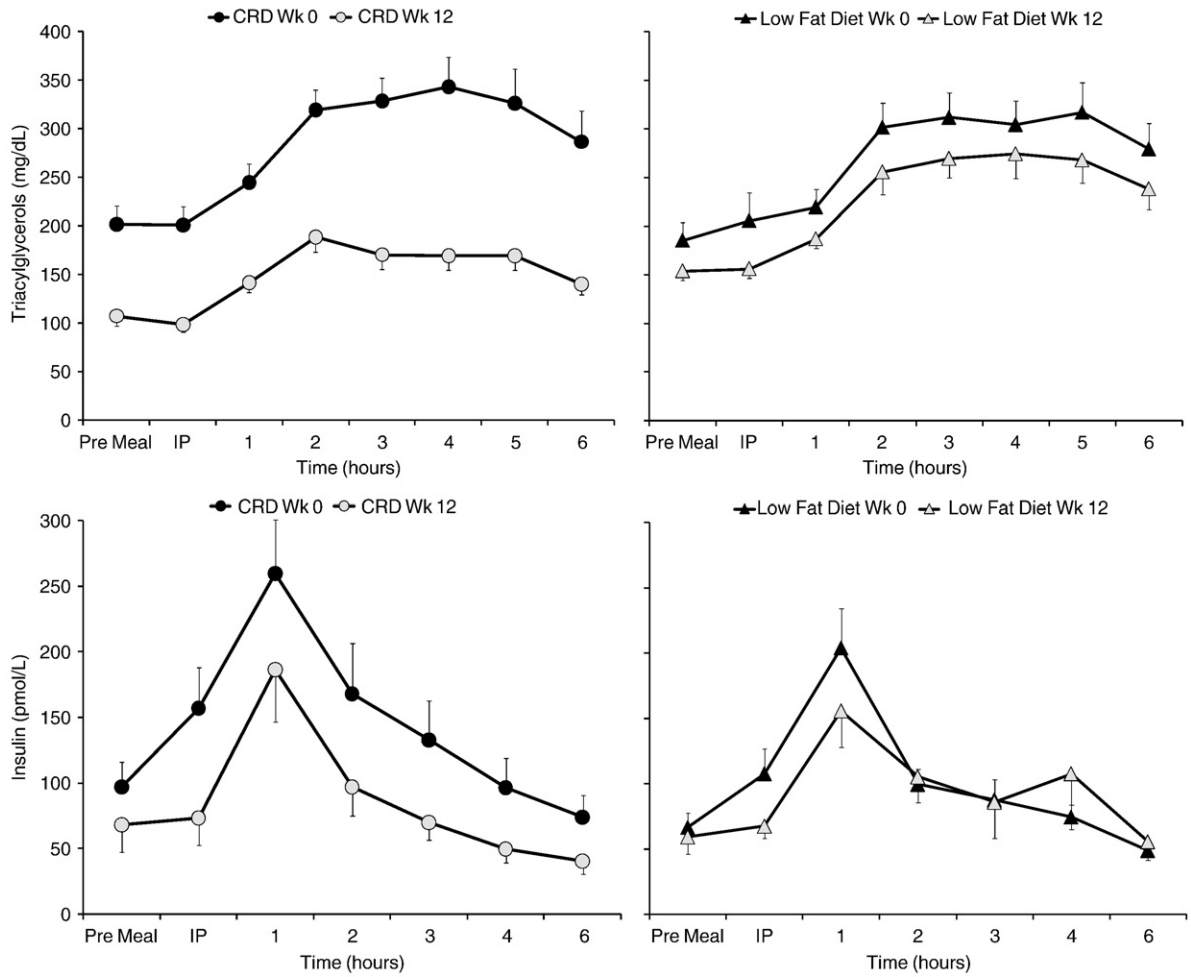

Fig. 1. Postprandial TAG (upper panels) and insulin (lower panels) responses to a high-fat meal in subjects who consumed a CRD or an LFD for 12 weeks. Mean total area under the curve was significantly different between the CRD and LFD for both TAG and insulin responses ($P = .007$ and .009 for diet × time interaction, respectively).

6.5% ± 3.3% in the CRD group and decreased from 7.9% ± 5.3% to 5.2% ± 2.9% in the LFD group ($P = .004$ for diet × time interaction). The differential response at 3 hours for peak FMD remained significant with use of baseline FMD and weight loss as covariates. The change in body mass was not correlated with the change in peak FMD at 3 hours in the CRD ($r = -0.06$) and LFD ($r = -0.36$) groups. Similarly, the change in peak FMD at 3 hours was not correlated with the change in postprandial lipemia or any other biomarkers.

Table 3
Leukocyte and fatty acid responses at baseline (week 0) and week 12

Variables	CRD (n = 20)		LFD (n = 20)	
	Wk 0	Wk 12	Wk 0	Wk 12
Leukocytes ($\times 10^9$/L)				
Pre	6.1 ± 1.4	5.8 ± 1.4	5.9 ± 1.8	5.9 ± 2.2
IP	6.2 ± 1.3	5.7 ± 1.3	5.9 ± 1.6	6.0 ± 2.0
2 h	6.5 ± 1.2	5.8 ± 1.1	6.4 ± 2.2	6.3 ± 1.9
4 h	6.6 ± 1.3	5.9 ± 0.9	6.5 ± 2.0	6.4 ± 1.9
6 h	6.5 ± 1.3	6.3 ± 1.3	6.8 ± 2.3	6.8 ± 2.2
Fatty acids (mEq/L)				
Pre	0.23 ± 0.09	0.28 ± 0.13	0.30 ± 0.15	0.24 ± 0.12
IP	0.21 ± 0.12	0.24 ± 0.12	0.26 ± 0.1	0.20 ± 0.10
2 h	0.28 ± 0.14	0.31 ± 0.12	0.25 ± 0.12	0.22 ± 0.08
4 h	0.39 ± 0.11	0.39 ± 0.11	0.41 ± 0.14	0.36 ± 0.13
6 h	0.43 ± 0.11	0.41 ± 0.09	0.47 ± 0.18	0.42 ± 0.18

Values are mean ± SD.
IP indicates immediate post.

4. Discussion

The adverse effects of single meals high in fat, especially saturated fat, on postprandial lipemia [2-4] and vascular and inflammatory function [14] have been used as evidence to discourage low-carbohydrate diets. The prior diet history, however, has a fundamentally important effect on the metabolic response to meals. For example, we have repeatedly shown that adaptation to a very low carbohydrate diet results in a substantial reduction in the postprandial lipemic response to a standardized fat challenge [8-10]. Thus, studies that show deleterious acute effects of a high-fat meal on vascular function and inflammation may show very

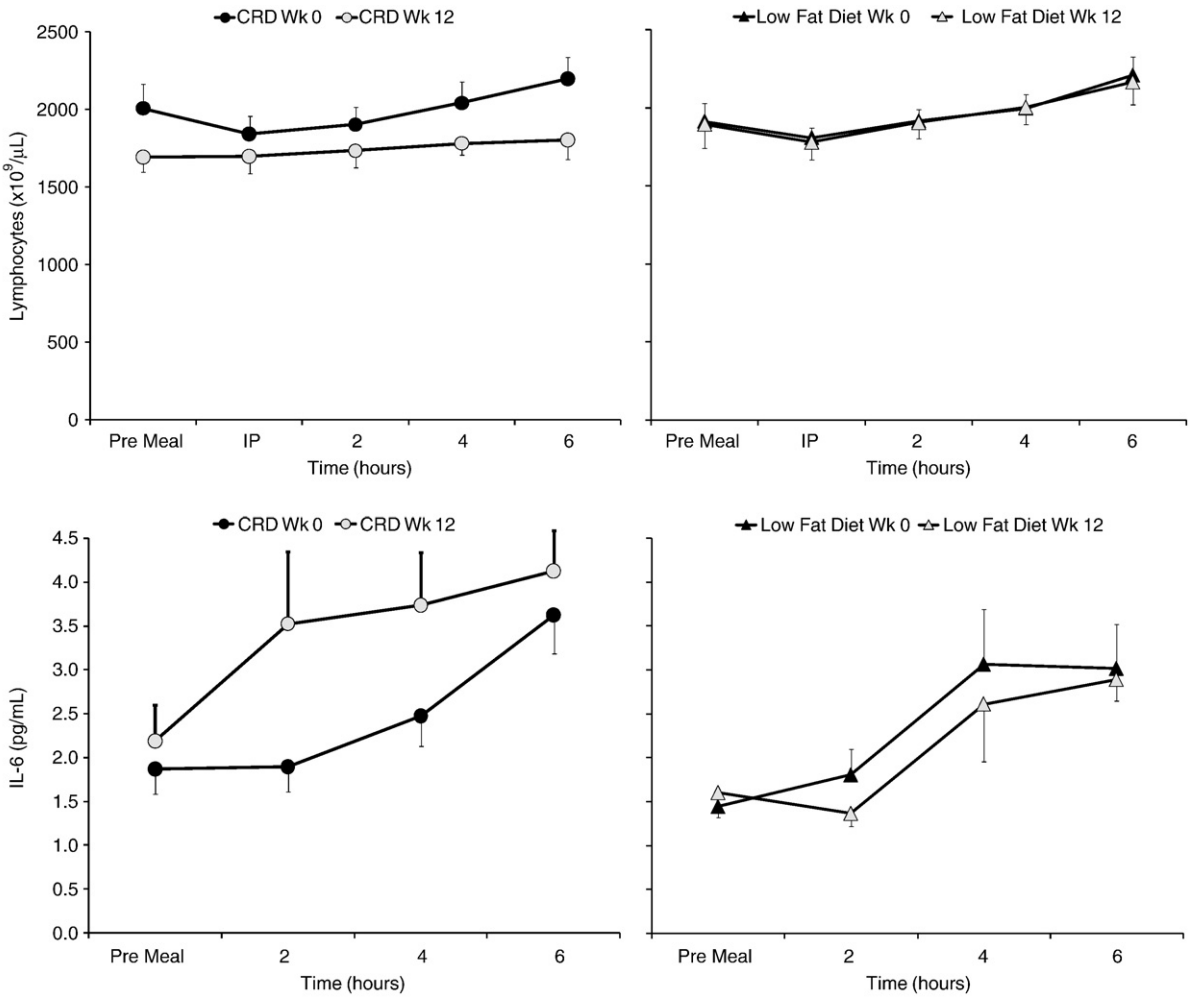

Fig. 2. Postprandial lymphocyte (upper panels) and IL-6 (lower panels) responses to a high-fat meal in subjects who consumed a CRD or an LFD for 12 weeks. Mean total area under the curve was significantly different between the CRD and LFD for both lymphocytes and IL-6 responses ($P = .050$ and .024 for diet × time interaction, respectively).

different results after subjects are adapted. Here we tested the effects of a high-fat meal on vascular function in subjects with atherogenic dyslipidemia who consumed a high-fat diet that was very low in carbohydrate. Consistent with our prior work, we showed a marked decrease in the lipemic response to the high-fat meal, whereas controls consuming an LFD showed little change. The major finding was that 12 weeks of adaptation to a very low carbohydrate diet improved postprandial FMD 3 hours after a high-fat meal compared with subjects consuming an LFD.

Studies that have assessed vascular responses after adaptation to diets varying in carbohydrate are sparse. Previous work showed no effect of a low-carbohydrate diet on fasting brachial artery FMD during weight loss or a weight maintenance phase [23,24]. Philips et al [25] reported a small decrease in fasting FMD after 6 weeks of a low-carbohydrate diet; but this was due to a larger baseline (preocclusion) diameter in those subjects, as peak postocclusion diameter actually increased more in the low-carbohydrate compared with the LFD group. These studies all assessed FMD responses to a CRD in the fasted state, whereas assessment of vascular function in the postprandial state is probably more revealing and clinically relevant because of the perturbations in metabolic homeostasis that have been linked to endothelial dysfunction.

There was a significant 2-fold increase in postprandial IL-6 concentrations, with levels increasing more rapidly after the CRD compared with the LFD. Although typically viewed as a proinflammatory cytokine, alternative roles have been demonstrated. Exercise is a potent stimulus for increasing IL-6 concentrations, which are attenuated when carbohydrate is provided [26]. Recent findings showed that IL-6 infusion increased glucose disposal and fatty acid oxidation [27]; and therefore, it has been hypothesized that IL-6 may actually prevent insulin resistance and type 2 diabetes mellitus through improved metabolic functioning in muscle [28].

There are several reasons to explain the significantly greater improvements in FMD in subjects' restricting carbohydrates in the present study. One possibility is that

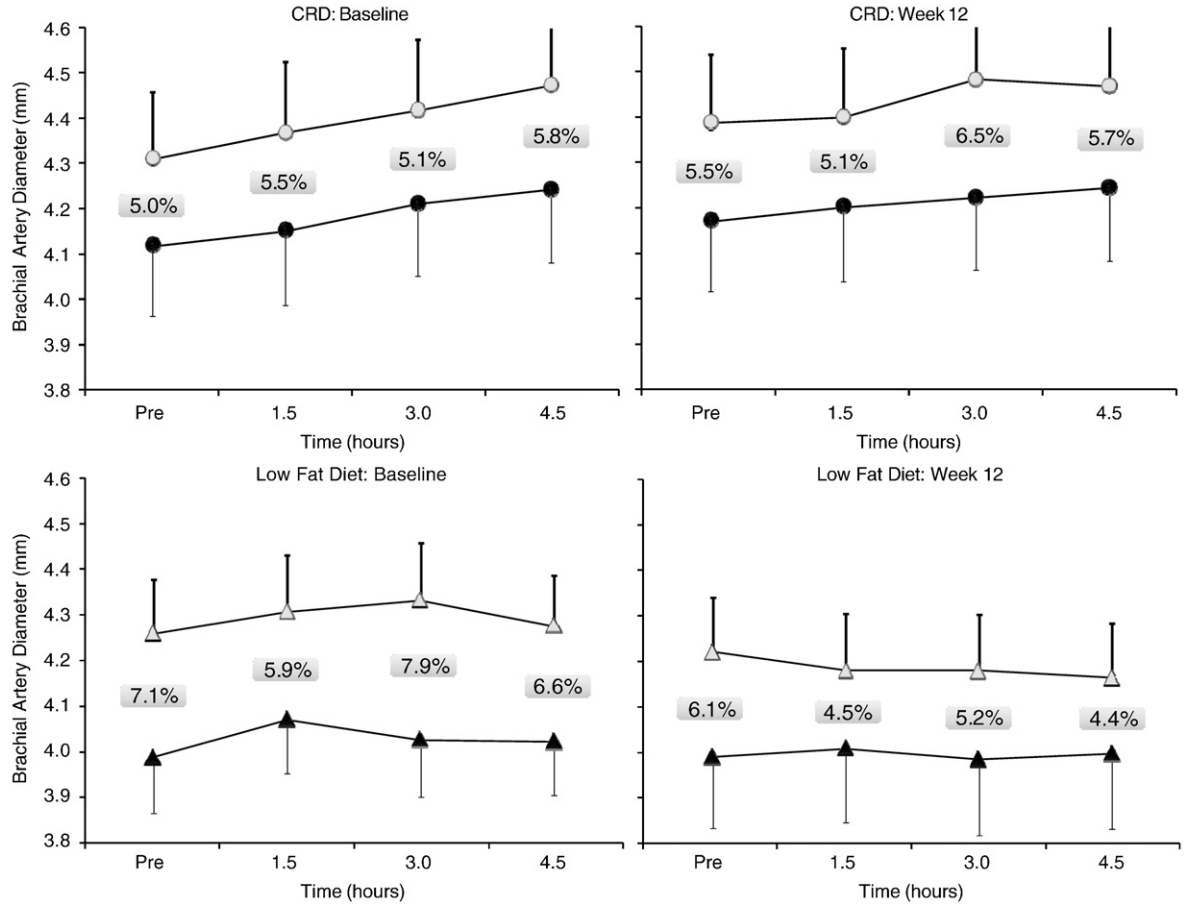

Fig. 3. Vascular responses to a high-fat meal before and after 12 weeks in subjects who consumed a CRD (upper panels) or an LFD (lower panels). Values represent resting brachial artery diameter before occlusion (closed circles) and peak diameters (open circles) after 5 minutes of cuff occlusion (mean ± SE). This procedure was performed before a high-fat meal and at 1.5, 3.0, and 4.5 hours postprandial. Average peak FMD ([postocclusion diameter − preocclusion diameter]/preocclusion diameter) values are shown between corresponding pre- and postocclusion diameters. After 12 weeks, there was an improvement in peak FMD in the CRD group, whereas the response decreased in the LFD group ($P = .004$ for diet × time interaction).

weight loss, which was greater in the CRD, contributed to better vascular function. However, weight loss has been shown not to affect FMD assessed in the fasting state [29]. There was also no correlation between weight loss and change in FMD in the present study. The dramatic decrease in postprandial lipemia in the CRD group could have played a role in the vascular responses. Previous studies have shown that FMD responses to a high-fat meal are related to the extent of postprandial lipemia [30,31]; however, not all studies have reported this relationship or an impairment in FMD after a high-fat meal [32]. In this study, there were no significant associations between the lipemic and vascular responses. Thus, the improved response in postprandial FMD in the CRD group compared with the LFD group appears to be independent of weight loss and lipid changes.

The clinical significance of the changes in FMD is uncertain. Lower FMD levels have been shown to predict future cardiovascular events in asymptomatic low-risk individuals (hazard ratio = 1.12 for every 1% decrease in FMD) [33]. Tertile analysis in that study indicated a significant increase in cardiovascular events in individuals in the 2 lowest tertiles (<3.60% and 3.60%-7.49%) compared with the highest tertile (>7.50%). Based on these findings, the changes in FMD in the present study on the order of 1% to 2% would be viewed as significantly altering risk status and clinically relevant.

The brachial artery reactivity protocol used in this study is generally considered an index of nitric oxide bioavailability [34]. Insulin resistance in endothelial cells is due to impairment in the phosphatidyl inositol 3-kinase–dependent signaling pathway that leads to production of nitric oxide [35], which is consistent with work showing that insulin resistance is associated with vascular dysfunction [36]. The beneficial effect of a CRD compared with reducing fat on vascular function in this study is consistent with our thesis that carbohydrate restriction targets features of insulin resistance [12,13]. The finding that FMD was improved by a low-carbohydrate diet in a rat model of obesity-induced impairment of coronary endothelial function [37] is further support for carbohydrate restriction having a positive effect on vascular function.

In conclusion, subjects who adapted to a diet very low in carbohydrate showed no evidence of vascular dysfunction in response to a high-fat meal. The findings are consistent with our proposed theory that carbohydrate restriction uniquely benefits features of metabolic syndrome [12,13] including endothelial function.

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