Endothelial Function and Weight Loss: Comparison of Low-Carbohydrate and Low-Fat Diets

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Abstract

The effect of weight loss on obesity-associated endothelial dysfunction is not clear because of conflicting data, demonstrating both improvement and no change in endothelial function after weight loss in obese subjects.

A two-year prospective study (n=121) was conducted to examine: 1) the effect of obesity and weight loss (either a low-carbohydrate or and low-fat diet) on flow mediated vasodilatation (FMD), a measure of endothelial function.

Participants reduced body weight by $7.1 \pm 4.4\%$, $8.7 \pm 6.8\%$ $7.1 \pm 7.8\%$ and $4.1 \pm 7.7\%$ at 3, 6, 12 and 24 months, respectively with no significant differences between the low-fat and low-carbohydrate groups. Endothelial function was inversely correlated with waist circumference, triglyceride level, and directly correlated with leptin in obese persons prior to weight loss. These weight losses did not confer any improvements in FMD. There were no differences between the low-fat and low-carbohydrate diets in FMD at any time point. At 6 months ($r = 0.26$, $p = 0.04$) and one year ($r = 0.28$, $p = 0.03$), there were positive correlations between change in FMD and change in leptin but not at two years.

There was no significant improvement in endothelial function after 7.1±7.8% weight loss at one year and 4.1±7.7% at two years, achieved by either a low carbohydrate or a low fat diet.

Keywords

Endothelium; Obesity; Leptin; Diet

Obesity is a serious, widespread problem in the United States and around the world. People who are overweight or obese are at risk for a variety of health complications, including coronary artery disease (CAD) and other cardiovascular conditions.[1] One central factor whereby obesity per se is thought to initiate atherosclerosis is via endothelial dysfunction.[2] Endothelial function is a marker of overall cardiovascular health and a predictor of future cardiovascular events.[3] Methods have been developed to measure endothelial function both invasively—through the measurement of forearm blood flow (FBF) after the infusion of acetylcholine—and non-invasively. One commonly used non-invasive measure is flow-mediated dilatation (FMD), in which the amount of arterial dilatation caused by the hyperemic response to arterial occlusion is compared to arterial diameter at rest.[4] Data from many studies examining endothelial dependent dilation in "healthy" obese patients,[5–9] and patients with comorbid conditions,[10–13] have found FMD is decreased compared with normal weight adults. FMD values in these studies ranged between approximately 4–10%,[14] compared with typical values found in healthy non-obese adults 12–20%.[15]

The effect of weight loss on obesity-associated endothelial dysfunction is not clear because of conflicting data from different studies, demonstrating both improvement [12, 16–19] and no change[7, 9, 11, 20–22] in endothelial function after weight loss in obese subjects. Additionally, several studies looking specifically at the effects of weight loss from high-carbohydrate vs. low-carbohydrate diets on endothelial function have produced differing results. Keogh et al[9] found no improvement in FMD after a 52 week weight loss on either high-carbohydrate or low-carbohydrate diets, while Phillips et al[23] reported decreased FMD after six weeks in subjects following a low-carbohydrate diet and increased FMD in subjects on a low-fat diet. Overall, studies evaluating the effect of weight loss on vascular function were small (11 to 67 subjects) and short duration (2 weeks to 6 months).[2]

Considering the great variability in the literature on obesity, weight loss, and endothelial function, we conducted a large (n= 121) two-year study to examine: 1) the relationship between obesity and FMD in obese patients seeking weight loss treatment and 2) the effects of weight loss via either a low-carbohydrate or and low-fat diet on endothelial function as measured by FMD.

METHODS

Study Population

The study population was enrolled in a National Institute of Health sponsored two-year, three-multicenter randomized trial of low-carbohydrate and low-fat diets on body weight. The study was approved by the Institutional Review Board of each respective institution. The subjects were randomized to either a low-carbohydrate diet or a low-fat diet as

described in detail elsewhere.[24] Approximately half of the participants were assigned to a low-carbohydrate diet, which limited carbohydrate intake but allowed unrestricted consumption of fat and protein. The other participants were assigned to consume a low-fat diet, which consisted of limiting energy intake to 1200 to 1500 kcal/d for women and 1500 to 1800 kcal/d for men, with approximately 55% of calories from carbohydrate, 30% from fat, and 15% from protein. Both groups included group behavioral treatment and a prescribed physical activity plan of 200 minutes per week.[24] The prescribed activity regimen was the same in both groups starting with 40 minutes per week (4 bouts of 10 minutes) at week 3 and progressing to 200 minutes per week (4 bouts of 50 minutes) by week 18. The primary form of physical activity was moderate to vigorous walking. Subjects with diabetes and heart disease were excluded from the study. This was a sub-study of the larger study and involved two of the three sites (University of Pennsylvania and the Washington University). All subjects at these two institutions (n=201) were approached to see if they would undergo evaluation of endothelial function at baseline and at 3, 6, 12 and 24 months. A total of 133 subjects were assessed at baseline. Subjects on vasoactive medications (n = 12) were excluded from all analyses. Of the remaining 121 subjects, follow-up assessments were conducted on 98 (81%) subjects at 3 months, 93 (77%) at 6 months, 80 (66%) at one year, and 59 (49%) at two years. There were a total of 9 subjects with unreadable images (2 at 3 months, 4 at 6 months, and 3 at one year). These data were not analyzed.

Brachial Artery Reactivity

The evaluation of endothelial function was assessed via the brachial artery reactivity test using a previously published method and according to guideline recommendations.[14,25] Sonographers were certified on this technique prior to patient enrollment. The blood pressure cuff was placed in the upper arm and the length of ischemia was 5 minutes. In brief, subjects were asked to fast for 12 hours except for water. Also, for 12 hours prior to the study, subjects were asked to adhere to the following restrictions: 1) no smoking, 2) no vasoactive medications (including over the counter medications such as high dose niacin, decongestants, vitamins C and E), 3) no vigorous physical activity. None of the subjects were taking an HMG Co-A reductase inhibitor (statin) before or during the study.

Ultrasound Measurements—The ultrasound images were acquired using an Acuson Sequoia 256 Cardiac ultrasound system with the use of a 15L8 MHz linear-array transducer. All subjects were supine during the study. The measurement of postdeflation brachial artery diameter was started before cuff release and the measurement used for analysis was at 1 minute after cuff release. The brachial artery diameter was measured offline on B-mode ultrasound images.

Image Analysis—Analyses of the images were completed using automated, edge-detection software (Brachial Analyzer for Research v 5.0.5, MIA Vascular Research Tools 5, Coralville, Iowa). Images were analyzed by an investigator proficient with the Brachial Analyzer software and blinded to patient information and study status.

Laboratory Assays

The lipid profile was measured according to previously published method.[24] Subjects were assessed at the respective clinical research centers after a 12-hour overnight fast. Whole blood was drawn into EDTA-containing tubes. After the blood was centrifuged, the plasma was removed and stored at −80°C until use. Plasma total cholesterol, HDL cholesterol, and triglyceride concentrations were measured enzymatically on a Cobas Fara II (Roche Diagnostic Systems Inc., NJ, USA) using Sigma reagents (Sigma Chemical Co., MO, USA) in a CDC-standardized lipid laboratory. LDL cholesterol was calculated using the Friedewald formula.

Leptin was measured in a subset of individuals (n=66) with a complete set of samples at each time point. Plasma concentrations of leptin were determined using the human leptin RIA kit (HL-81K, Linco Research, St. Charles, MO) according to manufacturer's instruction. Briefly, assay buffer, 100 μl standard, quality control or human sample (in duplicate), 100 μl ^{125}I- labeled human leptin, and 100 μl human leptin antibody were combined in borosilicate tubes, vortexed and incubated 24 hours at 4°C. Cold precipitating buffer was then added to each tube, incubated 20 minutes, then centrifuged at 2500 xg for 20 minutes at 4°C. The supernatant was decanted and the pellets counted in a gamma counter for one minute. The concentration of leptin in each sample was determined by interpolation of a reference curve constructed from the known standards. The duplicate samples had CV's less than 10% and the quality controls were within the expected range.

Statistical Analysis

Differences in participant characteristics at baseline between the low carbohydrate and low fat groups were tested using Wilcoxon rank sum tests for continuous variables and chi square tests for categorical variables. A linear mixed-effects model with a treatment-by-time interaction term was used to evaluate between-group differences in endothelial function at a specific time point, as well as within-group differences between specific time points. Subject-specific random effects were used to account for the correlation due to repeated measurements. The model included research site to adjust for differences across sites. Because mixed-effects models does not depend on observed outcomes and treatment, no effort was made to impute the missing data.[26] The two treatment groups were collapsed and bivariate correlations were used to assess the relationship between the endothelial function and variables measured at baseline and over time after controlling for treatment assignment. All statistical analyses were conducted using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Baseline Demographics and Endothelial Function

The baseline study characteristics of study participants are listed in Table 1. There were no statistically significant differences between the low-fat and low-carbohydrate groups on any baseline variable, including FMD. As shown in Table 2, after collapsing the two treatment groups, there were statistically significant correlations between FMD and waist circumference ($r = -0.27$, $p < 0.01$), triglycerides ($r = -0.27$, $p < 0.01$), and leptin ($r = 0.42$,

$p < 0.001$) at baseline and a marginally significant relationship with weight ($r = -0.18$, $p = 0.05$).

Weight Loss and Blood Pressure

Similar to the larger study,[24] participants reduced body weight by 7.1±4.4%, 8.7±6.8% 7.1±7.8% and 4.1±7.7% at 3, 6, 12 and 24 months, respectively. There were no significant differences in weight loss between the two groups at any time during the study. There was a decrease in systolic and diastolic blood pressure over time; −5.15 mmHg systolic and −1.71 mmHg diastolic for high carb and −3.55 mmHg systolic and −1.52 diastolic for low carb diets at two years. The decreases in blood pressure did not differ between diet groups (P = 0.91 for systolic and P = 0.44 for diastolic) at any time point.

Diet and Endothelial Function

There were no differences between the low-fat and low-carbohydrate diets in FMD at any time point (week 0, p = 0.17; 3 months, p = 0.66; 6 months, p = 0.80; one year, p = 0.86; two years, p = 0.29) (Figure 1). There were no significant changes in FMD from week 0 to two years in either the low-carbohydrate group (p = 0.16) or the low-fat (p = 0.10) group. As in the larger parent study, attrition increased over time but did not differ between the two groups.

Relationship Between FMD and Variables over Time

The relationship between endothelial function (FMD) and variables were compared over time (Table 3). There were no consistent and statistically significant relationships between changes in FMD or brachial artery diameter and these variables over time. At 6 months ($r = 0.26$, $p = 0.04$) and one year ($r = 0.28$, $p = 0.03$), there were positive correlations between change in FMD and change in leptin but not at 2 years. There was an inverse correlation between changes in triglycerides and FMD at 1 year ($r = -0.23$, $p < 0.05$) and a marginally significant inverse correlation at 2 years ($r = -0.24$, $p = 0.08$) for all subjects.

DISCUSSION

To our knowledge, this is the largest and longest study of weight loss on vascular function reported to date. There are several findings from this study. First, waist circumference and triglyceride level were inversely associated with endothelial dysfunction and leptin was positively associated with FMD prior to weight loss. Second, At one year, there were positive correlations between change in FMD and change in leptin and inverse correlation between triglycerides and FMD. Third, diet-induced weight loss of 7% at 1 year and 4% at 2 years with either a low-carbohydrate or low-fat diet did not improve (or worsen) endothelial dependent dilatation.

The findings from the present study are consistent with several published studies showing an association with WHR and FMD in obese subjects.[6, 17, 27, 28] One study showed that in normal-weight healthy subjects, modest fat gain results in impaired endothelial function.[29] Smaller published studies showed mixed results regarding endothelial function and weight loss. Most, however, do not show a significant improvement in endothelial function after

weight loss.[6, 7, 9, 11–13, 16–18, 20, 21] Our larger study also indicated there was no clinical improvement in endothelial function with weight loss at any point over two years.

The results of several clinical studies evaluating weight loss combined with exercise show improvement in endothelial function.[8, 12, 13, 30, 31] There are data to suggest that improvement in glucose and/or insulin sensitivity[17, 32] and the amount of LDL reduction[18] correlate with improvement in endothelial function for those enrolled in weight loss studies. Our data show no correlation with LDL. Thus, it seems that weight loss alone may not be enough to significantly improve endothelial function.

The type of diet subjects followed in obesity studies could potentially affect endothelial function discordantly. For example, it was reported that in hypercholesterolemic men, diets low in fat (especially saturated fat) and diets rich in monounsaturated fats improve endothelial function.[33] In another study, endothelial function improved in patients with metabolic syndrome after eating a Mediterranean-style diet.[34] However, diets that result in enhanced postprandial lipemia may adversely affect endothelial function.[35] One small study showed endothelial function is markedly impaired by a high-fat meal that causes an acute hypertriglyceridemia and was evident in dyslipidemic patients with baseline hypertriglyceridemia but not in normotriglyceridemic controls.[36] The results from our study did not demonstrate any significant difference in diet, either low carbohydrate or low fat, on endothelial function after weight loss. We did observe a significant association between changes in triglyceride levels and changes in endothelial function over time suggesting that lipemia likely affects endothelial function.

Leptin, a hormone derived from adipocytes, rises exponentially with body fat and is a vasodilator.[2] Leptin receptors are present throughout the vascular system indicating importance in normal vascular physiology. A rat model[37] and a human study[38] showed leptin directly causes vasodilatation via a nitric oxide-independent mechanism. It is a paradox that obese patients generally have elevated leptin levels and yet a reduced capacity for endothelium mediated vasodilatation. The reason for this paradox is thought secondary to leptin resistance.[39] Brook et al studied the effect of weight loss over three months on FMD in 43 obese but otherwise healthy subjects.[6] Although there was no overall significant change in FMD with weight loss, the change in endothelial function after weight loss was predicted only by the change in plasma leptin concentration. Our findings in larger sample confirm that changes in FMD are correlated with changes in leptin at both 6 months and 1 year. The reason for the leptin-FMD paradox with weight loss is unclear.

Limitations and Strengths

At year 2, significant attrition had occurred which increases the possibility of type II statistical error at this time point. A study by Hamburg et al showed that obesity was associated with lower arterial shear indicating a maladaptive vascular response which was reversed with weight loss.[40] Thus, there may be beneficial vascular effects to weight loss that were not evident from measuring FMD such as change in postprandial triglyceride level with weight loss. In addition, it is possible that our study population, that was free of known cardiovascular disease, may not show a significant improvement above baseline FMD level.

The strengths of our study include the large sample size, the two-year duration, and participants randomized to two different diets.

Conclusions

The results of this study indicate that endothelial function is inversely correlated with waist circumference, triglyceride level, and directly correlated with leptin in obese persons before weight loss. There was no significant improvement in endothelial function after approximately 7% weight loss at 1 year and 4% at 2 years, achieved by either a low carbohydrate or a low fat diet, despite decreases in waist circumference, serum triglyceride concentrations and other CVD risk factors. Changes in leptin were associated with changes in FMD.

Acknowledgments

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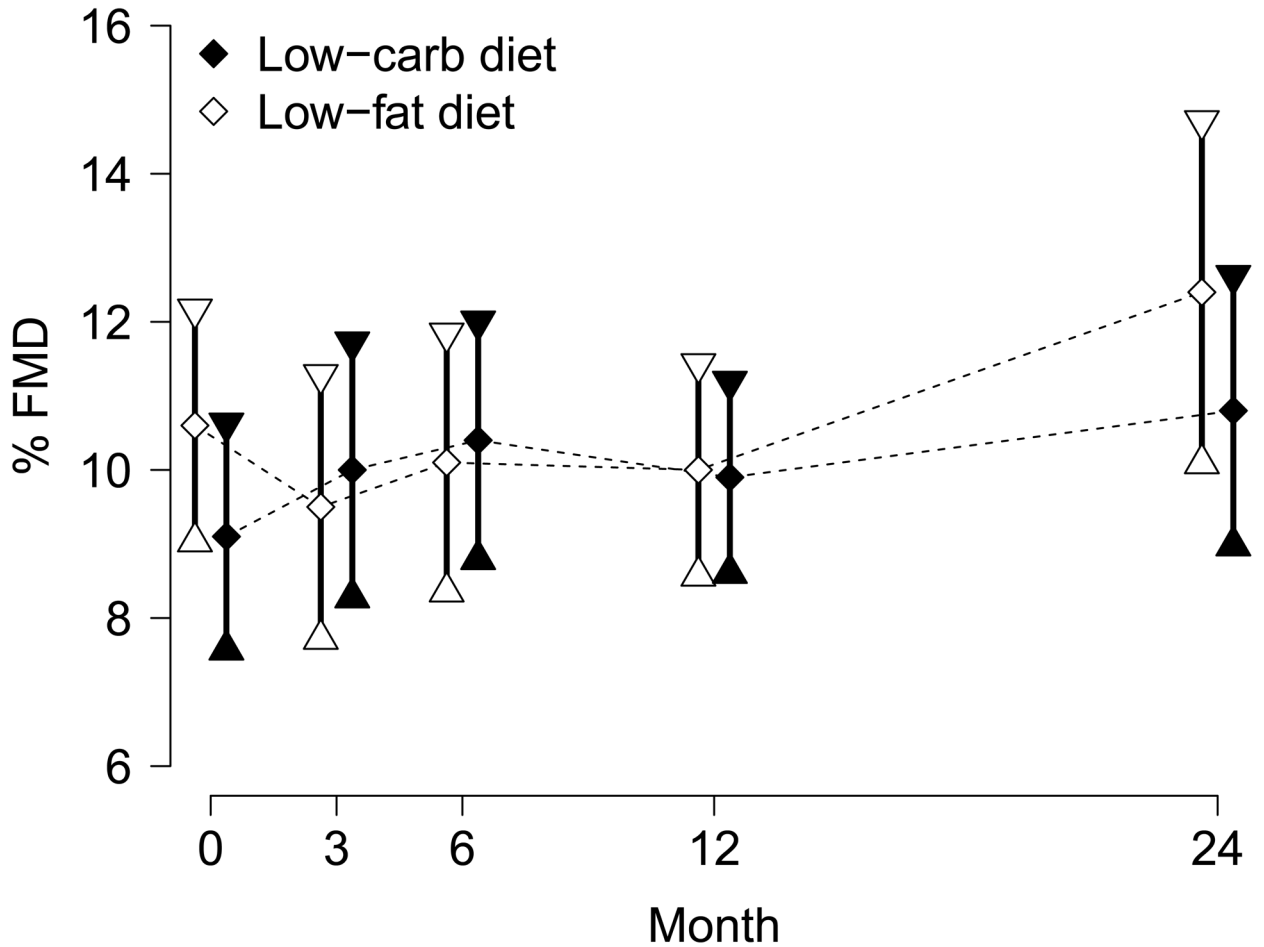
Figure 1.
Comparison of endothelial function, as measured by FMD, over time for low fat (n = 62) compared to low carbohydrate (n = 59) diets. Means and 95% confidence intervals were obtained from a linear mixed-effects model, which included time, treatment, and a treatment-by-time interaction term as principal explanatory variables and research site as a fixed effect. There were no differences between the low fat and low carbohydrate diets in FMD at any time (week 0, p = 0.17; 3 months, p = 0.66; 6 months, p = 0.80; 1 year, p = 0.86; 2 years, p = 0.29). There were no significant changes in FMD from week 0 to two years in either the low carbohydrate group (p = 0.16) or the low fat (p = 0.10) group. Likelihood ratio p value for interaction = 0.17.

Table 1

Participant Characteristics at Baseline

Variable	Total Participants	Low Fat	Low Carb	p-value
n	121	62	59	
Age (years)	45.7 ± 9.7	46.0 ± 10.6	45.4 ± 8.7	0.54
Female gender, %	65	63	66	0.71
Race/Ethnicity, %				0.63
African American	26.5	22.6	30.5	
Hispanic	3.3	4.8	1.7	
Other	1.7	1.6	1.7	
White	68.6	71.0	66.1	
Systolic blood pressure (mmHg)	126.5 ± 14.4	127.0 ± 14.8	126.4 ± 14.1	0.95
Diastolic blood pressure (mmHg)	75.0 ± 9.2	76.4 ± 0.2	73.5 ± 9.0	0.09
BMI (kg/m2)	35.8 ± 3.8	35.7 ± 3.5	35.9 ± 4.1	0.76
Weight (kg)	104.1 ± 14.8	103.6 ± 14.5	104.7 ± 15.3	0.82
Waist circumference (cm)	111.2 ± 11.1	111.1 ± 11.2	111.3 ± 11.1	0.95
Sagittal Diameter (cm)	20.4 ± 5.4	20.5 ± 5.5	20.4 ± 5.4	0.98
FMD	9.6 ± 6.1	8.9 ± 5.7	10.4 ± 6.4	0.23
Triglycerides (mg/dl)	108.1 ± 50.6	110.5 ± 49.7	105.6 ± 51.8	0.52
Cholesterol (mg/dl)				
Total cholesterol	193.0 ± 30.9	198.3 ± 30.8	187.5 ± 30.4	0.09
Low-density lipoprotein	125.2 ± 28.6	130.1 ± 29.1	120.1 ± 27.3	0.07
High-density lipoprotein	47.9 ± 12.7	57.6 ± 12.9	48.1 ± 12.5	0.70
Leptin (ng/ml)[*]	34.8 ± 18.0	33.7 ± 16.0	36.5 ± 20.8	0.65

Note. Summaries presented as mean ± standard deviation unless otherwise indicated as %. Differences between participants were tested using Wilcoxon rank sum tests for continuous variables and chi square tests for categorical variables.

[*] Collected on subset of participants (n = 66); low fat (n = 39), low carb (n = 27)

Table 2

Baseline Correlations with FMD

Variable	n	r	p-value
Weight	120	−0.17	0.05
BMI	120	0.03	0.76
Waist circumference	92	−0.27	<0.01
Sagittal Diameter	111	−0.09	0.34
Triglycerides	121	−0.27	<0.01
Total cholesterol	121	−0.12	0.18
Low-density lipoprotein	121	−0.14	0.13
High-density lipoprotein	121	0.14	0.12
Leptin	66	0.42	<0.001

Note. Partial correlations after controlling for treatment assignment; p values evaluate whether the partial correlation is equal to 0.

Table 3

Correlations Between Changes (from Baseline) in FMD and Variables

Variable	n	r	p-value
Weight			
3 months	95	−0.06	0.56
6 months	84	0.08	0.47
1 year	68	−0.08	0.53
2 years	57	−0.002	0.99
Waist Circumference[*]			
6 months	54	0.24	0.09
1 year	49	0.11	0.45
2 years	38	−0.09	0.60
Sagittal Diameter[*]			
6 months	66	−0.05	0.68
1 year	50	−0.02	0.91
2 years	25	−0.13	0.55
Triglycerides			
3 months	95	−0.03	0.75
6 months	81	−0.16	0.15
1 year	74	−0.23	0.046
2 years	57	−0.24	0.08
Total Cholesterol			
3 months	95	0.01	0.92
6 months	81	0.02	0.89
1 year	74	−0.05	0.69
2 years	57	−0.13	0.36
LDL			
3 months	95	0.05	0.62
6 months	81	0.02	0.88
1 year	74	−0.03	0.79
2 years	57	0.05	0.71
HDL			
3 months	95	0.04	0.69
6 months	81	0.14	0.23
1 year	74	0.18	0.12
2 years	57	−0.17	0.22
Leptin[*]			
6 months	59	0.26	0.04
1 year	58	0.28	0.03
2 years	50	0.08	0.60

Note. Partial correlations after controlling for treatment assignment; p values evaluate whether the partial correlation is equal to 0.

*
Variables were not collected at 3 months