Effect of Short-Term Weight Loss on the Metabolic Syndrome and Conduit Vascular Endothelial Function in Overweight Adults

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Impaired vascular endothelial function may be an important mechanism linking obesity to increased cardiovascular risk. We investigated whether short-term weight loss improves conduit artery endothelial dysfunction in overweight adults. Forty-three otherwise healthy overweight patients with a body mass index ≥27 kg/m² completed an open-label 3-month trial consisting of a calorie-restricted diet and 120 mg of orlistat taken 3 times daily with meals. Endothelial function and parameters of the metabolic syndrome were measured before and after intervention. Subjects lost 6.6 ± 3.4% of their body weight. Low-density lipoprotein cholesterol, low-density lipoprotein concentration, fasting insulin, and leptin decreased significantly (all p < 0.009), and C-reactive protein decreased (p = 0.22). Conduit vascular function did not change as assessed by flow-mediated dilation (3.86 ± 3.54 vs 3.74 ± 3.78%, p = 0.86) and nitroglycerin-mediated dilation (17.18 ± 5.89 vs 18.87 ± 7.11%, p = 0.13) of the brachial artery. A moderate degree of weight reduction over 3 months improved the metabolic syndrome profile but not the vascular dysfunction associated with uncomplicated obesity. ©2004 by Excerpta Medica, Inc.

Methods

Human subjects: Potential subjects were recruited by local advertisements. Subjects were included if they were 18 to 50 years old, were overweight as defined by a body mass index ≥27 kg/m², and had a waist-to-hip ratio ≥0.80 for women and ≥0.85 for men. All subjects were apparently healthy by history and physical examination. Subjects were excluded for blood pressure >140/90 mm Hg, fasting total cholesterol >240 mg/dl, fasting glucose >126 mg/dl, or thyroid stimulating hormone >5.5 mU/L. All women had a negative pregnancy test before the trial. Other exclusion criteria were cardiovascular disease, cardiovascular risk factors other than obesity, medications for hypertension, hyperlipidemia, thyroid dysfunction, contraception use, or hormone replacement. Subjects were also excluded for other factors that could influence endothelial function (e.g., current tobacco use, antioxidants, folate, and fish oil). Subjects were instructed to maintain the same physical activity throughout the trial and were not permitted to initiate an exercise program.

Study protocol: The study was approved by the institutional review board at the University of Michigan Medical School, and each subject gave written informed consent. After an initial screening visit, subjects participated in a 12-week open-label weight-loss trial of dietary counseling plus 120 mg of orlistat 3 times daily with meals. The intervention included a calorie-restricted diet and orlistat, a pancreatic lipase inhibitor, because of its proved efficacy versus diet alone.

Experimental end points: Subjects fasted for ≥8 hours before testing. Endothelial function, anthropometric measurements, blood laboratory results, and an oral fat tolerance were assessed at baseline and 12 weeks after treatment in each subject, in the same order, and at the same time of day at the 2 visits.
Conduit vessel endothelial function was the primary end point and was determined by brachial arterial flow-mediated dilation (FMD) measured with high-resolution vascular ultrasonography. Nitroglycerin-mediated dilation (endothelial-independent vasomotion) also was determined as previously described. Subjects rested in a supine position in a temperature-controlled room for ≥15 minutes before each vascular study. Validation studies in 25 healthy subjects performed in the same laboratory demonstrated a high degree of FMD reproducibility consistent with published literature.

Waist (thinnest abdominal circumference below the xiphoid process), hip (circumference at the level of the femoral heads), and waist circumference (circumference at the level of the iliac crest) measurements were obtained from each subject. Percent body fat was calculated as the average of the values obtained by bioelectrical impedance and skinfold thicknesses at 3 sites (triceps, thigh, and suprailiac in women; chest, abdomen, and thigh in men). Blood was drawn for fasting levels of glucose, insulin, lipoprotein subfractions, CRP, and leptin, and then subjects performed a 6-hour oral fat tolerance test. Baseline triglyceride and insulin levels were measured before each subject consumed a milkshake containing 50 g of fat/m² of body surface area. Subjects drank the shake over 5 to 10 minutes, and triglycerides were measured at hours 2, 4, and 6 while subjects refrained from physical activity and food consumption.

CRP, lipoproteins, and leptin measurements: CRP and lipoprotein subclass levels (very-low-density lipoprotein [LDL] cholesterol, high-density lipoprotein cholesterol, LDL cholesterol, their patient particle diameters, and LDL particle concentration) were measured by LipoScience Incorporated (Raleigh, North Carolina). Lipoproteins were analyzed by nuclear magnetic resonance spectroscopy, and high-sensitivity CRP was analyzed by the Immuline 2000 analyzer (Diagnostic Product Corporation, Los Angeles, California), as described elsewhere.

Plasma leptin concentration was measured with a commercially available enzyme-linked immunosorbent assay kit (Linco Research, St. Louis, Missouri) according to the manufacturer’s instructions. The intra-assay coefficient of variation was 4.1%.

**Dietary intervention:** All dietary counseling and analyses were performed and standardized by the same registered dietician. A detailed 3-day food diary was collected and analyzed for intake of kilocalories, carbohydrates, proteins, fats, saturated fats, polyunsaturated fats, monounsaturated fats, vitamins, minerals, caffeine, and alcohol at baseline and completion of the study (Elizabeth Stuart Hands and Associates Food Processor 7.6 for Windows, ESHA Research, Salem, Oregon). Subjects were instructed to consume a moderately calorie-restricted diet during the study. Each subject was prescribed a diet that was 500 calories less than weight-maintenance needs, with 30% of calories coming from fat. If maintenance energy requirements were <1,500 calories/day, caloric

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**TABLE 1 Metabolic and Blood Pressure Responses to Weight Reduction**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Post-Treatment (12 wks)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Serum total cholesterol (mg/dl)</td>
<td>177 ± 32</td>
<td>164 ± 31</td>
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<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>114 ± 64</td>
<td>106 ± 64</td>
</tr>
<tr>
<td>Serum high-density lipoprotein (mg/dl)</td>
<td>46 ± 10</td>
<td>44 ± 10</td>
</tr>
<tr>
<td>Serum LDL (mg/dl)</td>
<td>114 ± 27</td>
<td>104 ± 25</td>
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<tr>
<td>Total cholesterol/high-density lipoprotein</td>
<td>3.96 ± 0.96</td>
<td>3.84 ± 0.94</td>
</tr>
<tr>
<td>LDL particle size (nm)</td>
<td>20.56 ± 0.67</td>
<td>20.57 ± 0.60</td>
</tr>
<tr>
<td>LDL particle concentration (mmol/L)</td>
<td>1,339 ± 359</td>
<td>1,222 ± 325</td>
</tr>
<tr>
<td>High-density lipoprotein particle size (nm)</td>
<td>8.74 ± 0.32</td>
<td>8.80 ± 0.36</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>88.3 ± 6.8</td>
<td>85.5 ± 9.2</td>
</tr>
<tr>
<td>Insulin (IU/ml)</td>
<td>8.8 ± 4.1</td>
<td>7.4 ± 2.7</td>
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<tr>
<td>CRP (mg/dl)</td>
<td>0.47 ± 0.41</td>
<td>0.40 ± 0.45</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>121 ± 13</td>
<td>120 ± 16</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>69 ± 10</td>
<td>68 ± 9</td>
</tr>
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Baseline values versus values after treatment by paired-samples t test.
*p < 0.05.
de\n
icit was adjusted to provide no fewer than 1,000 calories/day.

Subjects faxed or e-mailed detailed food records daily and received instruction, feedback, and support by the dietitian by telephone or e-mail. Subjects also had formal one-on-one nutrition counseling for at least 1 hour with the dietician every 4 weeks.

Statistical analyses: Paired-samples t tests were used to compare the effect of the weight-loss intervention on different variables. Univariate Pearson’s correlation coefficients were obtained between study variables and changes in FMD, nitroglycerin-mediated dilation, and arterial compliance. Given the expected 3.5% SD in FMD from our laboratory, we had 80% power to determine a 1.5% change in FMD after weight loss in 43 subjects. Statistical significance was defined as p < 0.05.

RESULTS

Seventy-one subjects completed the initial assessment and were enrolled into the trial. Ten men and 33 women (43 subjects) completed the study and the 2 assessments of vascular function. Only 1 subject left the trial because of an adverse event, abdominal cramping associated with the medication. Seven other subjects dropped out of the study because of their inability to adhere to the restricted fat content of the diet, which resulted in fecal urgency and oily stools. The remaining subjects were unavailable or unwilling to complete the final assessment. The mean age for the 43 subjects who completed the study was 38 ± 8 years.

The average daily meal compositions at baseline versus those at study completion were 2,216 ± 722 versus 1,622 ± 409 total calories, 35 ± 6% versus 29 ± 7% calories from fat, 11.2 ± 2.9% versus 1.1 ± 0.0% calories from saturated fat, 1.0 ± 0.0% versus 0.5 ± 1.0% calories from monounsaturated fat, and 0.5 ± 0.3% versus 0.6 ± 0.1% calories from polyunsaturated fat.

After 12 weeks, subjects lost an average of 6.6 ± 3.4% of their initial body weight, and 9 of 43 subjects lost ≥10%. All anthropometric measurements were significantly decreased (Figure 1). Overall, weight loss lessened the metabolic syndrome. Insulin, LDL particle concentration, LDL cholesterol, and high-density lipoprotein cholesterol decreased significantly, whereas fasting glucose, CRP, and high-density lipoprotein size trended toward improvement (Table 1). Despite these changes, brachial artery FMD, brachial nitroglycerin-mediated dilation (Figure 2), and blood pressure (Table 1) remained the same.

Oral fat tolerance improved modestly after intervention (Figure 3). The 2-hour postprandial increase in triglycerides was significantly decreased at study completion compared with the 2-hour postprandial increase at baseline. All other postprandial triglyceride levels and the area under the triglyceride curve did not change significantly as a result of the intervention.

Plasma leptin concentration decreased significantly after weight loss (Figure 4). This decrease in plasma leptin positively correlated with the change in FMD after weight loss (Figure 5). There were no other significant correlations between the changes in FMD
DISCUSSION

Orlistat-assisted weight reduction improved the metabolic syndrome profile of overweight adults after 3 months. LDL particle concentration also decreased significantly (Table 1). Despite the substantial metabolic benefits, a 6.6% body weight reduction over 3 months did not lessen conduit (brachial) arterial endothelial dysfunction (Figure 2).

A novel observation in this study was that the change in endothelial function after weight loss was predicted only by the change in plasma leptin concentration (Figure 5). From this finding and the ability of leptin to mediate endothelium-dependent vasodilation by the release of nitric oxide, it is plausible to speculate that the reduction in leptin may have blunted the expected improvement in FMD. This is the first observation to suggest that leptin positively modulates vascular endothelial function in humans. Further studies are required to directly test this hypothesis.

In at least 3 previous articles, endothelial function improved after comparable amounts of weight loss. The reasons for the discrepancy between our results and those of previous reports are not entirely clear, but small differences in the dietary prescriptions may have played a role. However, the dietary changes in our study (e.g., reductions in total and saturated fats) would be expected to improve vessel function. There were no other significant dietary nutrient or antioxidant changes observed in our study that could account for our results. Although we cannot exclude the possibility, it is unlikely that the use of orlistat was responsible. No significant effects on fat-soluble vitamins, plasma antioxidants, or other nutrients have been reported from larger weight-loss studies using orlistat that would be expected to impair FMD. The very small reduction in mean high-density lipoprotein cholesterol among our subjects could have played a role. However, this also seems unlikely given the substantial improvements in most other components of the metabolic syndrome (Table 1) and all other lipoprotein factors (e.g., total cholesterol/high-density lipoprotein ratio) and the reduction in postprandial lipemia.

The most probable explanation is that this is the first study to report the effect of weight loss on conduit (brachial) arterial endothelial function. In previous experiments, endothelial function was measured at the resistance arteriole level or by the plasma concentrations of soluble adhesion molecules. Vascular function may vary within the same patient when determined by different methodologies using different stimuli and at different vascular territories. Therefore, the lack of improvement in conduit vessel endothelial function instigated by shear stress (brachial FMD) does not contradict prior investigations that demonstrated enhanced endothelial-dependent flow at the resistance arteriole level after receptor agonist-mediated stimulation.

The implication from our findings is that, although resistance vessel endothelial function may improve, comparable time periods, dietary changes, and amounts of weight loss may not be capable of restoring conduit artery function. Although adequately powered (80%) with our sample size (n = 43) to determine a 1.0% change in FMD, improvements in conduit...
endothelial function may be seen with more subjects for a longer time and/or after a greater weight loss.

An additional study on weight loss and endothelial function has also been published. Raitakari et al demonstrated an improvement in brachial artery FMD (from 5.5 ± 3.7% to 8.8 ± 3.7%, p <0.0001) in 67 non-diabetic, obese adults after following a very low calorie diet (daily energy intake of 580 kcal/2.3 MJ) for 6 weeks. The increase in FMD was only related to a decrease in blood glucose and occurred independently of all other metabolic improvements. As in our study, there was no relation between the change in FMD and the overall similar amount of weight loss observed (11 kg). The only substantial difference among studies that can potentially explain their different findings is the extremely low-calorie diet. Taken together with our results, it appears that the lifestyle changes and diet used to achieve weight loss appear to be more important determinants of the change in vascular function than the actual decrease in adiposity.

 references