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Effects of weight loss on insulin sensitivity and arterial stiffness in overweight adults

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Abstract

Obesity is characterized by metabolic and vascular abnormalities. We examined the effects of weight loss on insulin sensitivity and arterial stiffness in overweight adults. Twelve (9 females; 3 males) overweight (body mass index, 30.3 ± 3.7) adults (54.9 ± 3.9 years) without diabetes or vascular disease were counseled by a registered dietician to lose weight over 6 months. Vascular structure, function, and wall mechanical properties were measured via ultrasound. Intravenous glucose tolerance test, 24-hour blood pressure, body composition (dual-energy x-ray absorptiometry), and lipids were also assessed. There were significant reductions in body mass (86.3 ± 14.2 vs 79.5 ± 13.8 kg, $P < .0001$) and percentage of fat (44.3% ± 7.0% vs 41.0% ± 8.5%, $P < .01$) after weight loss. There were significant improvements in total cholesterol (6.0 ± 0.9 vs 5.0 ± 0.8 mmol/L, $P < .0001$), low-density lipoprotein cholesterol (3.9 ± 0.7 vs 3.2 ± 0.6 mmol/L, $P < .0001$), triglycerides (3.4 ± 2.3 vs 2.4 ± 0.9 mmol/L, $P < .05$), and insulin sensitivity (3.3 ± 1.7 vs 5.4 ± 1.6 $\mu U \times 10^{-4}$ min^{-1} mL^{-1}, $P < .0001$) after weight loss. Brachial artery compliance ($P < .05$) and distensibility ($P < .05$) curves over the physiologic pressure range improved, whereas endothelial function and intima-media thickness remained unchanged. In overweight adults, 6 months of weight loss resulted in improvements in body composition, insulin sensitivity, lipid profile, and brachial artery compliance and distensibility.

1. Introduction

Overweight individuals are at increased risk for developing cardiovascular disease. A limited amount of data assessing the effects of dietary modification on weight loss and subsequent changes in vascular structure and function have been inconclusive; with some trials demonstrating benefit and others no change. Brook et al [1] showed that 3 months of weight loss improved the metabolic profile, but failed to improve endothelial function or vascular compliance. In contrast, Ziccardi et al [2] reported that 1 year of weight loss plus exercise improved both the vascular response to L-arginine and the inflammatory profile in obese women. Further support for an improvement in vascular structure and function comes from Balkestein et al [3] who found that 3 months of energy restriction increased carotid artery distensibility in obese men.

Many overweight individuals are insulin resistant, and the relationship between insulin resistance and vascular structure and function is complex, especially in regard to dietary-induced weight loss. The effects of weight loss on the combined end points of vascular structure and function and insulin resistance are inconclusive, and few studies have included detailed and comprehensive measures of the functional, mechanical, and structural changes that occur in the arteries with weight loss. Therefore, the purpose of this investigation was to assess the effects of 6 months of energy restriction on insulin sensitivity, detailed measures of arterial endothelial function, and wall mechanical properties in middle-aged, overweight, and obese adults. We hypothesized that weight loss would significantly improve insulin resistance and vascular structure and function in these overweight individuals.

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2. Methods

2.1. Subjects

Twelve (males, 3; females, 9) overweight and obese (body mass index, 30.3 ± 3.7), middle-aged (54.9 ± 3.9 years), sedentary participants from the Minneapolis/St Paul Metropolitan area were recruited and volunteered to participate in this study. All subjects were 50 to 65 years of age with normal screening laboratory measures and without hypertension, dyslipidemia, impaired fasting glucose, or history of cardiovascular, peripheral vascular, or cerebral vascular disease. Exclusion criteria included body weight of more than 200% of the ideal, significant underlying medical illness, or use of medications known to alter vascular or metabolic function. None of the women were using hormone replacement therapy. No subjects had undergone a surgical procedure within 6 months preceding this study. All participants enrolled in this study after being advised of the protocol and collection of written informed consent. The protocol was approved by the University of Minnesota Institutional Review Board, and the procedures followed were in accordance with institutional and Health Insurance Portability and Accountability Act of 1996 (HIPAA) guidelines.

2.2. Assessment of vascular structure and function

Full details of the vascular techniques and reproducibility of the measurements in our laboratory have been previously published [4-6]. Vascular structure and function measurements were conducted in a quiet, temperature-controlled environment, and were performed in the morning after a 12-hour overnight fast. An arterial pressure waveform was obtained using a tonometer (Colin 7000, Colin Electronics, San Antonio, TX) placed over the radial artery and calibrated to a standard blood pressure cuff placed on the contralateral arm. The resting diameter, change in diameter throughout the cardiac cycle (for the determination of compliance and distensibility), and intima-media thickness (IMT) of the carotid and brachial arteries were measured with the subject resting in the supine position using a wall tracking system (PIE Medical WTS V2, Maastricht, The Netherlands) with a 10.0-MHz linear array ultrasound transducer held in place by a stereotactic device.

Assessment of flow-mediated dilation (FMD) was performed by imaging the left brachial artery at the distal third of the upper arm using the ultrasound system described above. A rapid inflation pneumatic cuff (Hokanson E20 Rapid Cuff Inflator, DE Hokanson, Bellevue, WA) was positioned on the forearm approximately 2 to 8 cm distal to the olecranon process to induce forearm ischemia when inflated. The forearm cuff was inflated to 250 mm Hg for 5 minutes. Brachial artery diameter was recorded immediately after cuff deflation and continued for approximately 2 minutes after cuff deflation. Percentage of dilation was calculated as the percentage of increase above resting diameter at 60 seconds after cuff release. To assess endothelium-independent dilation (EID), we administered 0.4 mg sublingual nitroglycerin, and the diameter of the brachial artery was measured at 5 minutes postadministration.

2.3. Assessment of insulin sensitivity

On a separate day, participants were assessed for insulin sensitivity with a frequently sampled intravenous (IV) glucose tolerance test. Participants were studied in the supine position. An intravenous catheter was inserted into an antecubital vein in one arm for the injection of insulin and glucose. Another catheter was inserted into the antecubital vein of the contralateral arm. Beginning 20 minutes after the insertion of IV lines, 3 baseline blood samples for glucose and insulin were drawn, and blood pressure and heart rate were measured at 5-minute intervals. Baseline values were calculated as the mean of these 3 measurements. Next, 50% glucose (300 mg/kg) was administered as an IV push over 30 seconds. Blood samples (3 mL) were collected at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 70, 80, 90, 100, 120, 130, 140, 150, 160, 170, and 180 minutes after the glucose bolus. Insulin (0.02 U/kg) was administered IV over 30 seconds, 20 minutes after the glucose injection to further stimulate insulin secretion. Blood samples for plasma glucose and insulin were collected into chilled glass tubes containing sodium heparin, stored on ice, and separated by centrifugation immediately after each study. Plasma was stored at −80°C until assay. Glucose and insulin levels were measured using Analox GL5 (Analox Instruments, Lunenburg, MA) and an enzyme immunoassay kit (ALPCO, Windham, NH), respectively. The insulin sensitivity index

Table 1
Clinical characteristics before and after weight loss

	Before weight loss	After weight loss	*P*
Body weight (kg)	86.3 ± 4.1	79.5 ± 4.0	.0003
Lean body mass (kg)	46.5 ± 27.3	45.0 ± 26.9	.04
Fat mass (kg)	37.1 ± 25.9	27.9 ± 30.8	.02
Percentage of body fat	44.3 ± 2.0	41.0 ± 2.5	.003
Total cholesterol (mmol/L)	6.0 ± 0.3	5.0 ± 0.2	.0001
LDL-C (mmol/L)	3.9 ± 0.2	3.2 ± 0.2	.0001
HDL-C (mmol/L)	1.4 ± 0.1	1.4 ± 0.1	.26
Triglycerides (mmol/L)	1.5 ± 0.3	1.1 ± 0.1	.06
Fasting glucose (mmol/L)	5.4 ± 0.1	5.3 ± 0.1	.32
Fasting insulin (pmol/L)	12.3 ± 0.7	10.6 ± 0.7	.52
Daytime blood pressure (mm Hg)			
Systolic	128 ± 3	124 ± 3	.03
Diastolic	81 ± 2	78 ± 2	.05
Mean arterial	98 ± 2	93 ± 2	.01
Nighttime blood pressure (mm Hg)			
Systolic	119 ± 5	115 ± 3	.37
Diastolic	70 ± 2	68 ± 2	.36
Mean arterial	86 ± 3	84 ± 2	.37

Data are presented as mean ± SD.

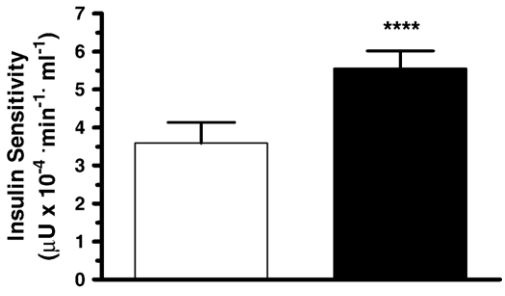

Fig. 1. Insulin sensitivity (S_I) ($\mu U \times 10^{-4}$ min^{-1} mL^{-1}) before and after weight loss. Data are presented as mean ± SD. ****$P < .0001$.

(S_I) and glucose effectiveness (S_G) were calculated from a least squares fitting of the temporal pattern of glucose and insulin throughout the frequently sampled IV glucose tolerance test using the MINMOD program [7].

2.4. Assessment of blood lipids

Blood samples were drawn into chilled tubes containing EDTA, and plasma was separated by centrifugation at 4°C for analysis of triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). These values were measured by standard clinical venous blood assay methods. Baseline measurements were made after a 2-week weight stabilization period and within 1 week of beginning the dietician guided weight loss program. Follow-up measurements were assessed within 1 week of the final dietician-guided meeting.

2.5. Assessment of ambulatory blood pressure

Ambulatory blood pressure was measured with the blood pressure cuff on the nondominant arm over a 24-hour period (Space Labs model 90207, Issaquah, WA). Blood pressure readings were obtained at the same time of day with activity stabilized to minimize intraindividual variation. All recordings were started on a weekday, other than Friday. Blood pressure readings that were different by more than 15 mm Hg from any other blood pressure within 1 hour and could not be explained by changes in physical activity noted in the activity logs were manually edited.

2.6. Assessment of body composition

Dual-energy x-ray absorptiometry was used to measure body fat percentage, fat-free mass, and fat mass. The specific unit used (Prodigy, 3M, Madison, WI) uses an x-ray source at a constant 78 kVp and K-edge filter (cerium) to achieve a congruent beam of dual-energy radiation with effective energies of 40 and 70 keV. The dual-energy x-ray absorptiometry scanner performed a series of transverse scans of the participant from head to toe at 1-cm intervals. The detector system collected information from 120 pixels during each scan. The scans were performed using a fast transverse speed mode, taking approximately 10 to 15 minutes for total body measurement.

2.7. Weight loss protocol

After all baseline measurements were completed, participants were counseled by a registered dietician in a behavioral modification/weight loss program one time per week for 6 months. Participants were counseled in positive eating behaviors and instructed to restrict food intake by 1255 to 2092 kJ/d (300 to 500 kcal/d). Adherence was monitored by a review of day by day food records and meeting with subjects weekly to discuss eating behaviors and food records. Basiotis et al [8] have demonstrated that energy intake can be accurately estimated from food intake records.

2.8. Statistical analysis

All statistical analysis and graphic presentation were accomplished using Graphpad Prism (v 4.0, San Diego, CA). All data are reported at baseline and follow-up. Paired sample Student t tests and repeated-measures analysis of variance were used to determine the effect of weight loss on each of the variables. Data are presented as mean and standard deviation. A P value of less than .05 was considered statistically significant.

3. Results

There were significant reductions in both body weight and percentage of fat, which resulted in significant decreases in both lean body ($P = .04$) and fat mass ($P = .02$) (Table 1). The weight loss intervention did not stimulate a significant change in fasting glucose or insulin (Table 1). There was however a 63.6% improvement in insulin sensitivity (3.3 ± 0.5 vs 5.4 ± 0.5 $\mu U \times 10^{-4}$ min^{-1} mL^{-1}, $P < .0001$) from baseline to after weight loss (Fig. 1). There were significant reductions in total cholesterol by 16.7%, LDL-C by 17.9%, and TG by 29.4%, and no significant change in HDL-C (Table 1).

Daytime (6:00 AM–6:00 PM) systolic ($P = .03$), diastolic ($P = .05$), and mean arterial blood pressure ($P = .01$) improved significantly. There was no change in nighttime (6:00 PM– 6:00 AM) systolic ($P = .37$), diastolic ($P = .36$),

Table 2
Vascular characteristics before and after weight loss

	Before weight loss	After weight loss	P
Brachial artery			
FMD (%)	5.5 ± 1.1	6.3 ± 1.2	.71
FMD (Δmm)	0.18 ± 0.1	0.19 ± 0.1	.81
EID (%)	20.4 ± 7.2	17.0 ± 5.6	.21
Diameter (mm)	3.52 ± 0.76	3.64 ± 0.64	.38
IMT (mm)	0.39 ± 0.05	0.40 ± 0.05	.36
Wall CSA	4.85 ± 1.49	5.05 ± 1.19	.38
Carotid artery			
Diameter (mm)	6.81 ± 0.61	6.93 ± 0.71	.33
IMT (mm)	0.69 ± 0.1	0.68 ± 0.1	.36
Wall CSA	16.55 ± 5.04	16.56 ± 5.10	.98

Data are presented as mean ± SD.

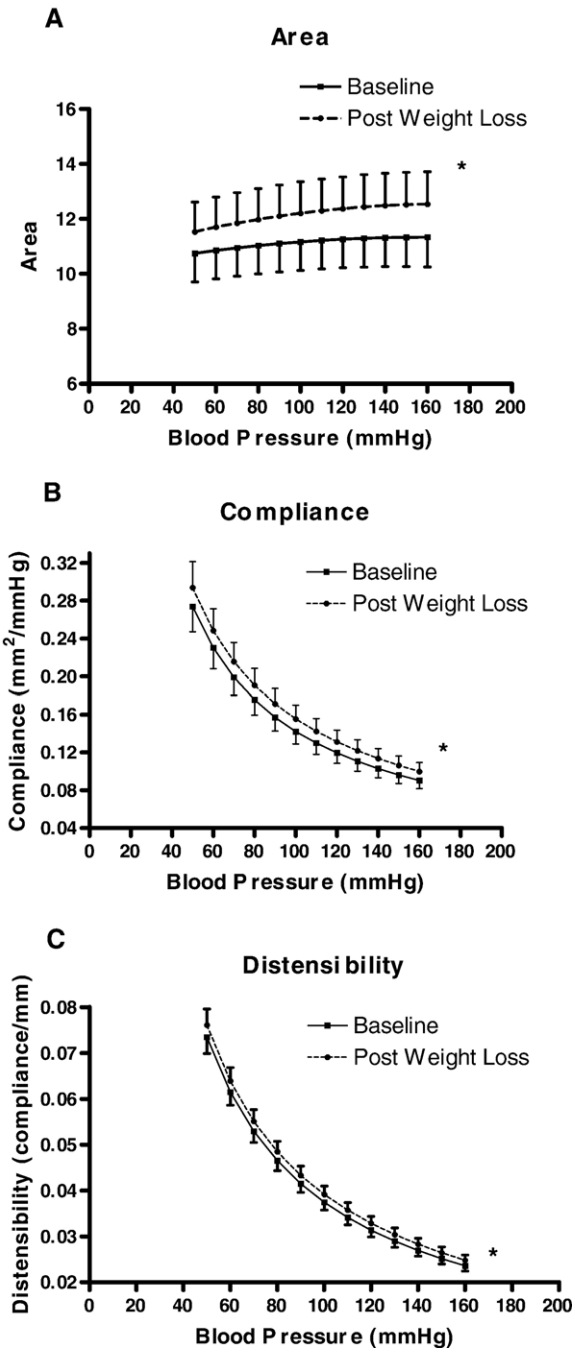

Fig. 2. Effect of weight loss on brachial artery pressure-area relationship (A), brachial artery compliance (B), and brachial artery distensibility (C). Data are presented as mean ± SD. *$P < .05$.

and mean arterial blood pressure ($P = .37$) with 24-hour mean arterial pressure, displaying a trend toward improvement (92 ± 2 vs 89 ± 2 mm Hg, $P = .08$).

There were no significant changes in brachial and carotid artery diameter, IMT, and wall cross-sectional area (CSA) as a result of the weight loss intervention (Table 2). The brachial artery FMD (%), absolute FMD (Δmm), and EID did not change after weight loss (Table 2). Brachial artery pressure-area ($P < .05$), compliance ($P < .05$), and distensibility ($P < .05$) curves over the physiologic pressure range improved (Fig. 2).

4. Discussion

The results of this study indicate that 6 months of energy restriction improves insulin sensitivity and arterial wall mechanics in conjunction with positive changes in other metabolic and lipid indices, but does not alter arterial structure or endothelial function.

Similar to our data, Balkestein et al [3] reported that 3 months of energy restriction alone or combined with aerobic exercise had a tendency to increase both brachial ($P = .06$) and carotid ($P = .06$) artery compliance in 37 obese men. There was no difference between the 2 interventions in regard to changes in brachial or carotid artery compliances. In addition, the authors reported that carotid artery distensibility was significantly increased as a result of the 2 weight loss interventions; however, the weight loss and exercise group did not differ statistically from the weight loss-only group. Both interventions resulted in similar decreases in body weight (15%) and mean arterial blood pressure (6%).

In the current study, brachial artery area, compliance, and distensibility improved throughout the physiologic pressure range after weight loss. The increase in brachial artery area may have been due to a reduction in vascular tone or due to outward remodeling of the artery. The structural components of the brachial artery, the wall CSA and IMT, did not change with weight loss, suggesting that the increase in brachial artery area was a result of decreased vascular tone. Brachial artery distensibility decreased, demonstrating a reduction in vessel wall stiffness. This likely occurred as a result of increased arterial smooth muscle relaxation, thereby decreasing smooth muscle contribution to wall tension and stiffness. The increase in brachial artery compliance was likely a result of both an increase in vessel size and a decrease in wall stiffness because both of these parameters independently affect arterial compliance [5].

The significant reduction in daytime blood pressure is consistent with the findings of decreased vascular tone and increased vascular compliance. The change in arterial tone and blood pressure may have occurred as a response to a decrease in sympathetic stimulation and pressor response. This may have been an important mechanism as previous research has shown a strong relationship between insulin resistance and sympathetic stimulation [9] and our subjects displayed significant improvements in insulin sensitivity. However, in the current study, there were no significant changes in fasting insulin, which has been suggested as the main mechanism responsible for changes in sympathetic stimulation. We cannot confirm the conclusion that improvements in insulin sensitivity may have been a potential mechanism in the causal pathway of arterial tone regulation because we did not measure neurohormonal factors or sympathetic activity.

Despite significant improvements in brachial artery area, compliance, and distensibility, we did not observe any changes in FMD or EID. Because the brachial artery pressure-area relationship changed as a result of the intervention, we also analyzed the absolute increase in brachial artery diameters (Δ mm) during FMD to account for possible changes in resting diameter. As with FMD expressed as percentage, we found no change after weight loss. The current results support the previous findings of Brook et al [1] who reported that 3 months of weight loss in obese men and women did not improve endothelial function.

The lack of improvement in FMD is somewhat surprising in light of the relatively large improvements in other cardiovascular risk factors such as the lipid profile, blood pressure, and insulin sensitivity. It may be that a larger decrease in weight and/or a longer duration of weight loss is required to elicit changes in endothelial function in overweight individuals. Alternatively, weight loss may not improve endothelial function directly, but rather through indirect mechanisms that may not have improved to a sufficient magnitude with the current intervention. Potential candidates that were not measured in the current study include adipokines, inflammatory cytokines, and markers of oxidative stress. Further research should examine the complex relationships among weight loss and changes in these novel cardiovascular risk factors.

A limitation of the current study is the small sample size and the lack of a control group. A larger sample size would have increased the statistical power to detect improvements in other variables measured, namely, endothelial function. In addition, inflammatory cytokines and adipokines were not measured. Because these markers are related to both insulin resistance and endothelial function, measuring changes might have provided additional insight into the lack of improvement in FMD.

In conclusion, the present study provides evidence that in overweight adults, 6 months of weight loss improves insulin sensitivity and arterial wall mechanical properties with positive changes in other metabolic and lipid parameters. Overall, these positive physiologic changes with weight loss may serve to decrease the metabolic and cardiovascular risk factor profile in overweight individuals.

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