Effect of Weight Loss and Nutritional Intervention on Arterial Stiffness in Type 2 Diabetes

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OBJECTIVE — There is increased stiffness of the large central arteries in type 2 diabetic patients, and obesity is a risk factor. However, the effect of intentional weight loss on arterial stiffness is uncertain, and the purpose of the current study was to assess this effect.

RESEARCH DESIGN AND METHODS — Arterial stiffness was assessed by measuring aortic pulse wave velocity (aPWV) at baseline and at completion of a 1-year weight loss intervention. Metabolic control of type 2 diabetes was also appraised.

RESULTS — Mean weight loss at 1 year in 38 volunteers with type 2 diabetes was 7.8%. There were improvements in HbA_{1c}, LDL cholesterol, homeostasis model assessment of insulin resistance, and inflammatory markers (plasminogen activator inhibitor-1, tumor necrosis factor-α, interleukin-6, and C-reactive protein). There was also a significant improvement in aPWV at completion of weight loss intervention, from 740 to 690 cm/s ($P < 0.05$).

CONCLUSIONS — Moderate weight loss improves arterial stiffness in type 2 diabetes.

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Cardiovascular disease (CVD) is the leading cause of mortality in type 2 diabetes (1). It is therefore important to identify subclinical manifestations of vascular disease so that the effectiveness of early intervention can be assessed. One of the manifestations of subclinical vascular disease is arterial stiffness, which represents a loss of compliance and elasticity within large arteries. Increased stiffness in the aorta and along the aortic iliac pathways is predictive of CVD events (2–6), which may be attributable to the adverse effect of arterial stiffness on left ventricular after-load and coronary perfusion (7). Also, arterial stiffness is associated with reduced blood volume delivery to the lower extremities (8).

Arterial stiffness of central vessels can be assessed noninvasively by measuring aortic pulse wave velocity (aPWV) (9,10). Age and hypertension were the two risk factors earliest identified for arterial stiffness (11), and more recently insulin resistance and diabetes have also been associated (12–16). Obesity may account for much of the association between insulin resistance and arterial stiffness, as this has been found in adolescents, young and middle-aged adults, and the elderly (11,17–20). Matched for age, aPWV is ~50 cm/s higher in obese compared with nonobese individuals, an increase in aPWV that is equivalent to the effect of 5 to 10 years of aging (19). While there are findings that treatment of hypertension improves arterial stiffness and that lifestyle interventions improve endothelial function, there are, however, few data regarding the effect of intentional weight loss on arterial stiffness (21). There are suggestive findings from an observational study that changes in weight, in interaction with baseline weight, influences aPWV. Wildman et al. (22) observed that modest weight loss in young adults with a mean baseline BMI of 27 kg/m^2 was associated with lowering of aPWV over a mean period of 2 years observation, whereas modest weight gain was associated with increased aPWV. The present study was designed to evaluate the effect of weight loss on aPWV as well as measures of metabolic control and markers of inflammation in overweight and obese participants with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The study population completed a 1-year behavioral weight loss intervention that included double-blinded randomization to orlistat or placebo. Details of this trial, including results of intervention at 6 months, have been published (23). Briefly, this was a single-center, randomized, double-blinded, placebo-controlled, clinical trial of a behavioral weight loss intervention combined with orlistat (Int+O group) or placebo (Int+P group) in overweight and obese patients with type 2 diabetes. The goal was to achieve at least a 7% weight loss. Research volunteers who meet inclusion criteria of *1*) a confirmed diagnosis of type 2 diabetes, *2*) 20–70 years of age, *3*) BMI >27 kg/m^2, *4*) stable current weight (defined as current weight ±3 kg during the past 6 months), *5*) adequate blood pressure control, and *6*) good general health other than type 2 diabetes were recruited from the general community by advertisement. Those with prior history of myocardial infarction, stroke, or clinical evidence of peripheral vascular disease and individuals who currently smoked were excluded. Individuals with abnor-

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Abbreviations: aPWV, aortic pulse wave velocity; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; IL, interleukin; PAI, plasminogen activator inhibitor; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Clinical characteristics at baseline and 1 year of weight loss intervention*

	Orlistat + intervention		Placebo + intervention	
	Baseline	Year 1	Baseline	Year 1
n	17		21	
Weight (kg)	97.0 ± 15.1	86.9 ± 13*	101.8 ± 19.3	92.4 ± 16.4*
BMI (kg/m^2)	34.0 ± 5.2	30.4 ± 4.1*	37.0 ± 8.1	33.6 ± 7.2*
Fasting plasma glucose (mg/dl)	182 ± 52	138 ± 46†	154 ± 43	119 ± 20†
A1C (%)	8.1 ± 1.2	6.7 ± 1.0*	7.8 ± 1.5	6.6 ± 1.1†
Fasting plasma insulin (μU/ml)	20.7 ± 2.9	20.2 ± 3.8	26.6 ± 4.0	25.8 ± 3.8
Systolic blood pressure (mmHg)	127 ± 15	131 ± 17	131 ± 15	128 ± 19
Diastolic blood pressure (mmHg)	80 ± 8	78 ± 6	81 ± 12	81 ± 8
LDL cholesterol (mg/dl)	130 ± 35	114 ± 37†	129 ± 27	120 ± 27†
HDL cholesterol (mg/dl)	44 ± 10	49 ± 13†	47 ± 11	56 ± 14*

Data are means ± SD. *$P < 0.01$, †$P < 0.05$ year 1 vs. baseline.

mal values for liver and renal function tests were also excluded. The protocol was approved by the University of Pittsburgh Institutional Review Board, and volunteers gave written informed consent. Thirty-nine participants of 52 individuals randomized in this clinical trial completed the 1-year intervention, and this report concerns the 38 participants in whom aPWV was measured at baseline and at 1 year. Blood specimens, following a 12-h fast, were obtained at baseline and 1 year for analysis of lipids, glucose, insulin, HbA_{1c} (A1C), markers of inflammation, and liver enzymes. Weight and height were measured using a calibrated scale. To measure fat mass and fat-free mass, dual-energy X-ray absorptiometry was performed, as previously described (24).

Weight loss intervention

Nutritional therapy was based on healthy food selections (25), emphasizing reduced fat consumption (≤30% of daily calories), and restriction of portions to create a daily negative energy balance of ~500 kcal/day. The goal was to achieve at least a 7% weight loss, and participants met weekly with a nutritionist for the first 6 months then every 2 weeks for the next 6 months. Participants were also encouraged to undertake physical activity (40–60 min of moderate-intensity physical activity, such as walking or cycling) on most days of week. Additionally, participants were randomized to receive orlistat (120 mg before each meal) or placebo. Pill counts were obtained monthly to monitor medication compliance. A daily multivitamin supplement was provided.

Laboratory methods

Glucose, insulin, and lipids were measured as previously described (23). Markers of inflammation (tumor necrosis factor [TNF]-α, interleulin [IL]-6, fibrinogen, plasminogen activator inhibitor [PAI]-1, and C-reactive protein) were assayed in the Laboratory for Clinical Biochemistry at the University of Vermont. Fibrinogen was measured in a BBL fibrometer (Becton Dickinson, Cockeysville, MD) (26) with Dade fibrinogen calibration reference (Baxter-Dade, Bedford, MA) and bovine thrombin (Parke-Davis, Lititz, PA). C-reactive protein was measured by colorimetric competitive immunoassays (C-reactive protein antibodies and antigens; Calbiochem, La Jolla, CA; [27]). PAI-1 assay was done as a two-site enzyme-linked immunosorbent assay measured by ultrasensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) and is sensitive to free PAI-1 (both latent and active) but not PAI-1 in complex with tissue plasminogen activator (28). TNF-α is measured by an ultrasensitive, solid-phase sandwich enzyme-linked immunosorbent assay using a monoclonal antibody specific for TNF-α (R&D Systems). Insulin resistance was estimated using the previously validated homeostasis model assessment of insulin resistance (HOMA-IR) based on fasting glucose and insulin levels: HOMA-IR = fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5 (29).

Measurement of PWV

PWV determinations were performed as previously described (17). Briefly, aPWV was measured by taking simultaneous recordings of the arterial flow waves from the right common carotid and right femoral arteries using unidirectional transcutaneous Doppler flow probes (model 810-a, 10 MHZ; Parks Medical Electronics, Aloha, OR). Three data collection runs were performed, each obtaining a minimum of 10 pairs of simultaneously recorded flow waves. During scoring, the flow waves were averaged and the time from the R wave of the electrocardiogram to the foot of the pressure wave was established. Results from all acceptable runs were averaged for the final aPWV measure used in these analyses. aPWV was calculated on the distance between the carotid and femoral arteries and the time differential in the arrival of the pressure wave at these locations, as previously described (11). Stiffer vessels are associated with a higher value for aPWV.

Statistical analysis

Data are presented as means ± SD for normally distributed variables, as percentages for categorical variables, or as median (interquartile range 25th–75th percentile) for nonnormal continuous variables. For within-group comparisons (baseline versus 1-year follow-up), a paired Student's *t* test was used for parametric data and Wilcoxon signed-rank test for nonparametric data. Comparisons between groups were performed using the unpaired *t* test and ANOVA for normally distributed variables, the Mann-Whitney and Kruskal-Wallis for nonnormal variables, and the χ^2 test and Fisher's exact test, when appropriate, for categorical variables. All statistical tests were two tailed, and *P* values of <0.05 were considered to be statistically significant. All analyses were performed using the SPSS (version 11.5; SPSS, Chicago, IL).

Table 2—*Inflammatory markers*

	Orlistat + intervention		Placebo + intervention	
	Baseline	Year 1	Baseline	Year 1
n	17		21	
IL-6 (pg/ml)	2.13 (1.56–2.88)	1.48 (1.18–2.04)*	2.44 (1.62–3.20)	1.37 (0.96–2.43)*
TNF-α (pg/ml)	3.68 ± 1.00	2.64 ± 0.71†	3.90 ± 1.22	3.05 ± 0.93*
C-reactive protein (mg/l)	2.84 (1.16–6.28)	2.03 (1.00–3.46)	3.16 (1.43–5.50)	1.97 (0.75–4.63)*
PAI-1 (ng/ml)	51.4 (36.0–87.0)	24.0 (10.4–33.2)*	78.6 (46.4–113.3)	54.0 (22.6–80.2)‡
Fibrinogen (mg/dl)	247.5 ± 64.3	342.6 ± 62.2†	254.7 ± 104.7	332.0 ± 74.2*

Data are means ± SD or median (interquartile range 25th–75th percentile). *$P < 0.05$, †$P < 0.001$ year 1 vs. baseline; ‡$P < 0.05$ placebo vs. orlistat.

RESULTS

Weight loss

Baseline and 1-year clinical characteristics by intervention status are listed in Table 1. At 1 year, mean weight loss was 7.8%, representing a decrease of 3.3 ± 4.1 BMI units. Approximately 42% of volunteers attained ≥10% weight loss, another 40% achieved ≥5%, and therefore just 18% had <5% weight loss. Weight loss was equivalent in the orlistat and placebo arms at 1 year, as was also observed at 6 months of intervention (23), reflecting the intensity of the behavioral intervention in this weight loss program.

Effect of weight loss on metabolic control. At 1 year of intervention, mean A1C was 6.6 ± 0.8%, improved from a baseline value of 8.0 ± 0.8%. Improvement in A1C correlated with amount of weight loss ($r_s = 0.35$; $P < 0.05$). There was also a significant decrease in HOMA-IR (8.0 ± 1.4 to 6.6 ± 1.0, baseline to year 1; $P < 0.001$). These metabolic improvements did not differ by treatment group. Blood pressure was well controlled at baseline and did not change at 1 year. LDL cholesterol tended to be lower in the Int+O group at 1 year, though the difference was not statistically significant. HDL cholesterol increased significantly and similarly at 1 year in the Int+O and Int+P groups.

Because of the association between obesity and circulating markers of inflammation, and of the potential relation to vascular function, a panel of circulating inflammatory markers was assessed at baseline and at 1 year. These data are shown in Table 2. There were significant decreases of ~30–40% in IL-6, TNF-α, and C-reactive protein. PAI-1 also decreased significantly. Intriguingly, fibrinogen increased significantly by 30–40% in each arm.

Effect of weight loss on arterial stiffness. aPWV at baseline was significantly correlated with BMI ($r = 0.61$; $P < 0.001$) but was not significantly associated with A1C, lipid parameters, baseline levels of inflammatory markers, or blood pressure (Figs. 1 and 2). The mean value (range) for aPWV at baseline was 817 (357–1,857) and at 1-year follow-up decreased to 680 cm/s (415–984), which represented a significant change ($P = 0.008$), as shown in Fig. 1. The effect remained statistically significant ($P = 0.014$), after excluding one participant who had a markedly elevated baseline value for aPWV (>1,500 cm/s) and a dramatic decrease in aPWV. A decrease in aPWV occurred in 25 (66%) of 38 participants. Individual changes in aPWV are shown in Fig. 2. As is evident in Fig. 2, those individuals with the highest baseline values for aPWV manifested the largest improvements and, indeed, the strongest correlate of improvement in aPWV following weight loss was baseline aPWV ($r = 0.88$; $P < 0.001$). After taking baseline aPWV into account, there was no significant correlation between the amount of weight loss and change in aPWV, though the largest decrease in aPWV occurred within the tertile of largest weight loss. Changes in aPWV were not different in patients receiving orlistat compared with those receiving placebo; 12 in the Int+O group and 13 in the Int+P group had improved aPWV. No statistically significant association was observed between improvement in aPWV and the concomitant improvements in inflammatory markers, insulin resistance, or other metabolic parameters (e.g., A1C).

CONCLUSIONS — Diabetes and obesity are recognized to be important risk factor for arterial stiffness (11,15,17,18), but the effect of intentional weight loss is uncertain. The main finding of the current study is that a moderate weight loss significantly improved aPWV. In response to a mean weight loss of ~8%, median values for aPWV decreased from 740 to 690 cm/s. This 50-cm/s improvement that was induced by nutritional intervention and weight loss is nearly identical to the average difference in aPWV that has been observed in comparing lean and obese adults (19). Furthermore, based on estimations derived from cross-sectional studies, a 50- to 100-cm/s increase in aPWV occurs with aging 10 years (19), so an improvement of 50

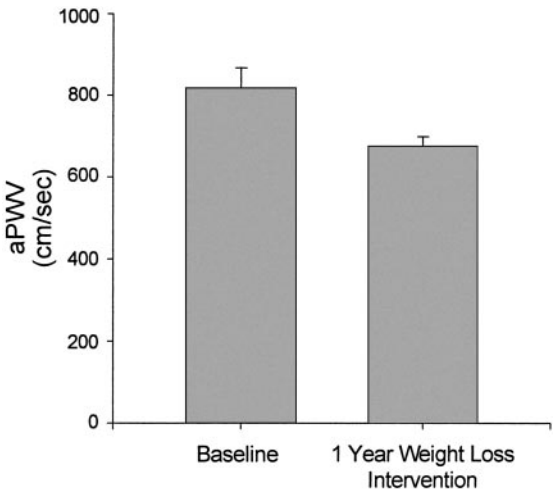

Figure 1—*Mean values for aPWV in 38 men and women with type 2 diabetes at baseline and following a 1-year weight loss and nutritional intervention are shown. The decrease in aPWV was statistically significant (P < 0.01).*

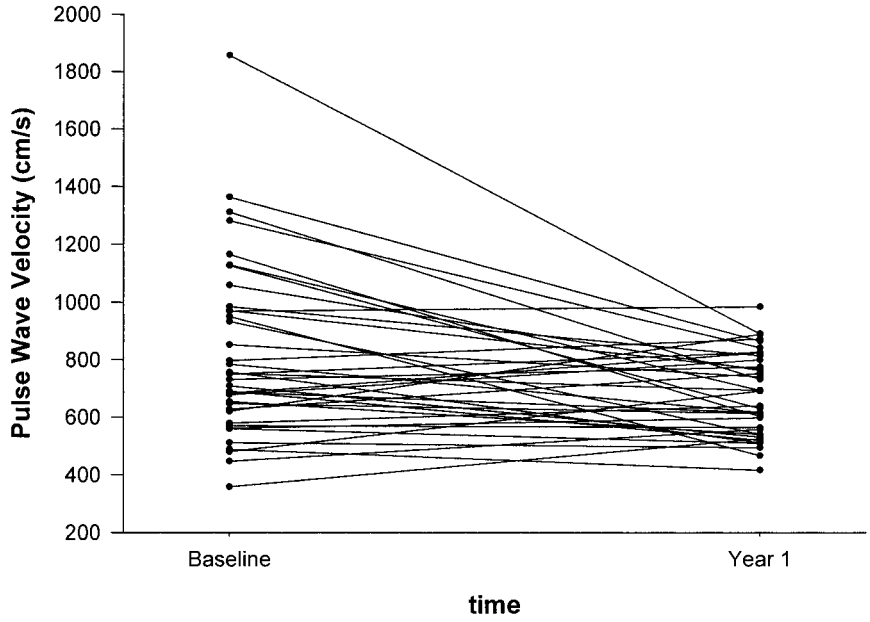

Figure 2—*Individual values for aPWV in 38 men and women with type 2 diabetes at baseline and following a 1-year weight loss and nutritional intervention are plotted. Improvement in aPWV was significantly correlated with the baseline value for aPWV.*

cm/s induced by weight loss can be regarded as a substantial clinical effect. It remains to be determined whether intentional weight loss reduces CVD events in type 2 diabetes (30), but the improvement in arterial stiffness following 1 year of weight loss intervention should be regarded as a positive finding in this regard.

Arterial stiffness within the aortic and aorto-iliac vessels is an independent risk factor for the development of CVD (2–5). Stiff arteries do not distend effectively during systole. This loss of elasticity causes adverse hemodynamic effects (7,8). Hypertension is strongly associated with arterial stiffness, and prior intervention studies have shown that treatment of hypertension improves arterial stiffness (21). However, in the current study, we can reasonably conclude that this was not the mechanism for weight loss–induced improvement in aPWV since blood pressure was well controlled at baseline and did not change during the 1-year weight loss intervention. There was a significant improvement in fasting hyperglycemia and A1C at 1 year, consistent with the effect now expected from 5 to 10% weight loss (31). There was a more modest, but nevertheless significant, reduction in LDL cholesterol and HOMA-IR. As well, there were significant decreases in PAI-1, TNF-α, IL-6, and C-reactive protein. Improvement in aPWV following weight loss may be related to improved metabolic control and changes in obesity-related inflammation. However, these metabolic factors did not significantly correlate with the improvement in aPWV. While such an association may have been anticipated from prior, much larger, cross-sectional studies, it is probable that both the relatively small size of the current intervention-based study and the relative homogeneity of metabolic response to a successful behavioral weight loss (>80% of participants achieved at least 5% weight loss) limited exploration of these potential correlations. Instead, in the current study, improvement in aPWV following weight loss was greatest in those with higher baseline values. Greater improvement also occurred in the tertile of largest weight loss. These findings suggest that in overweight and obese patients with type 2 diabetes and elevated values for aPWV, moderate weight loss is an effective intervention to improve arterial stiffness.

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