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Reductions in arterial stiffness with weight loss in overweight and obese young adults: Potential mechanisms

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ABSTRACT

Objective: Arterial stiffness decreases with weight loss in overweight/obese young adults. We aimed to determine the mechanisms by which this occurs.
Methods: We evaluated carotid-femoral pulse wave velocity (cfPWV) and brachial-ankle pulse wave velocity (baPWV) in 344 young adults (23% male, BMI 25–40 kg/m^2) at baseline, 6, and 12 months in a behavioral weight loss intervention. Linear mixed models were used to evaluate associations between weight loss and arterial stiffness and to examine whether improvements in obesity-related factors explained these associations.
Results: At 6 months (7% mean weight loss), there was a significant median decrease of 47.5 cm/s in cfPWV ($p < 0.0001$) and a mean decrease of 11.7 cm/s in baPWV ($p = 0.049$). At 12 months (6% mean weight loss), only cfPWV remained reduced. In models adjusting for changes in mean arterial pressure and obesity-related factors, changes in BMI ($p = 0.01$) and common carotid artery diameter ($p = 0.003$) were positively associated with change in cfPWV. Reductions in heart rate ($p < 0.0001$) and C-reactive protein ($p = 0.02$) were associated with reduced baPWV and accounted for the association between weight loss and reduced baPWV.
Conclusions: Weight loss is associated with reduced cfPWV independently of changes in established hemodynamic and cardiometabolic risk factors, but its association with reduced baPWV is explained by concurrent reductions in heart rate and inflammation.

1. Introduction

Obesity leads to poor vascular health and an increased risk of cardiovascular disease (CVD) [1,2]. The metabolic requirements of excess weight necessitate increases in total blood volume and cardiac output, and these hemodynamic changes elevate arterial wall stress, smooth muscle cell proliferation, vessel wall thickness and diameter, and eventually arterial stiffness [1,3]. These hemodynamic alterations, alongside other features of obesity, including chronic inflammation and endothelial dysfunction, impair vascular structure and function in obese individuals [4]. Weight loss lowers CVD risk [5,6] and reverses many adverse vascular changes, including arterial stiffness [6–10], an established predictor of vascular events [11,12]. Because weight loss improves many risk factors that correlate with arterial stiffness, such as blood pressure (BP) [13], inflammation [14], insulin resistance [13,14], and renin-angiotensin-aldosterone system hyperactivity [13], improvements in some of these risk factors likely explain the effect of weight loss on arterial stiffness.

Reductions in arterial stiffness with weight loss in overweight/obese adults [8–10,14,15] may be independent of concurrent reductions in BP [10], though not all studies agree [16]. Among hemodynamic factors, elevated blood volume and cardiac output in obese individuals may be more important drivers of arterial stiffening than elevated BP [10], particularly in young individuals. Few studies have evaluated mechanisms by which weight loss may reduce arterial stiffness, and these have included small numbers of either middle-aged and older overweight/obese adults [8,9] or

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severely obese adults [10]. The aim of this study was to determine potential mechanisms by which weight loss reduces arterial stiffness, as measured by carotid-femoral pulse wave velocity (cfPWV), a measure of aortic stiffness, and brachial-ankle pulse wave velocity (baPWV), a mixed measure of central and peripheral arterial stiffness, in young overweight/obese normotensive adults.

2. Methods

CfPWV and baPWV were measured at baseline and 6 and 12 month visits in overweight/obese adults participating in the Slow Adverse Vascular Effects of excess weight study (SAVE), a randomized-controlled trial (NCT00366990) evaluating the effects of weight loss, increased physical activity, and reduced dietary sodium intake on vascular health.

2.1. Study population

Eligible participants were men and women 20–45 years of age who were overweight/obese (body mass index (BMI) 25–39.9 kg/m^2) and physically inactive (<8 months of physical activity (PA) during the past 12 months). Exclusions included 1) diabetes, 2) hypertension or average screening BP≥140/90 mmHg, 3) cholesterol lowering, anti-psychotic, or vasoactive medication use and 4) current pregnancy or lactation. The study was approved by the University of Pittsburgh IRB and all participants provided written informed consent to participate in the study.

2.2. Intervention

All eligible participants received a one year lifestyle intervention consisting of diet and physical activity (PA). Participants were randomized to either 1) diet and PA alone (Control Na/lifestyle) or to 2) diet and PA plus reduced sodium intake (Low Na/lifestyle). The lifestyle intervention was delivered in group sessions that occurred weekly for months 1–4, biweekly for months 5–8, and monthly for months 9–12. The goal of the intervention was a 10% reduction in body weight over 6 months and continued maintenance of weight loss thereafter. The additional goal of the sodium reduction intervention was to gradually reduce daily sodium intake by approximately 50%.

2.3. Clinic visits

Participants were to complete clinic visits at screening, baseline, and 6, 12, and 24 months following randomization. The present study is a secondary analysis using data from baseline, 6 and 12 months.

2.4. Demographic and physical measures

Age, race, and smoking status were self-reported. Weight was measured in kilograms using a balance scale. Height was measured in centimeters using a stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured against the participant's skin at the narrowest part of the torso between the ribs and the iliac crest. BP was measured with a mercury sphygmomanometer after participants sat quietly for 5 min with feet flat on the floor.

2.5. Laboratory methods

Blood analytes were measured at the Heinz Laboratory at the University of Pittsburgh's Graduate School of Public Health as previously described [17]. Valid 24h urine collections had volume 500–4000 mL, duration 22–26 h, and total creatinine within the expected range [18]. Sodium and creatinine excretion were measured as previously described [17].

2.6. Pulse wave velocity

As earlier described [19], following 10 min of rest, cfPWV and baPWV were simultaneously determined using the VP2000 system (Omron Health Care Co., Kyoto, Japan), a noninvasive automated waveform analyzer. PWV was calculated as the path length between arterial sites of interest divided by the time delay between the foot of the respective waveforms. Intraclass correlation coefficients (ICC) for within technologist replicate measures were 0.76 (cfPWV) and 0.97 (baPWV) and for between technologists replicates were 0.60 (cfPWV) and 0.87 (baPWV).

2.7. Carotid ultrasound

Common carotid artery (CCA) intima-media thickness (IMT) and adventitial diameter (AD) measurements and readings were performed using an Acuson Sonoline Antares high resolution duplex scanner. IMT measures were determined as previously described [17]. CCA AD measures were calculated directly as the distance from the adventitial–medial interface on the near wall to the medial–adventitial interface on the far wall at end-diastole. The reading software used was the AMS system developed by Dr. Thomas Gustavsson [20]. For these analyses, the mean of the average IMT and AD values was used. Reproducibility of IMT and AD measures was excellent with between sonographer and within reader ICCs of >0.83.

2.8. Statistical analysis

Descriptive statistics were calculated to summarize study variables by visit and presented as median/inter-quartile range (IQR) or mean (SD) for continuous variables and frequency and percentages for categorical variables. Whether changes were significant at follow-up visits was determined by testing time, as a nominal variable, in linear mixed models. Non-normally distributed variables were transformed as necessary. Intervention arm was included in every model for consistency with trial design. Interaction between intervention arm and time since baseline was included if significant at $p < 0.10$. A mixed model was created for each PWV measure, adjusting for age, sex, race, smoking status, and years since baseline whenever significant at $p < 0.10$. All possible second order interactions were evaluated.

Next, baseline BMI and change in BMI (or weight or waist circumference) were added to the mixed models to simultaneously determine cross-sectional and longitudinal associations between measures of body size and PWV. The measure of body size change showing the most statistically significant association with each PWV measure was kept for additional analyses. Baseline mean arterial pressure (MAP) and change in MAP were then added to the models. Next, other cardiovascular and metabolic risk factors that could potentially explain the relationship between weight loss and reduced arterial stiffness were added. Linear mixed models were used to determine whether these factors' changes were associated with changes in BMI or waist circumference after adjustment for age, sex, race, and intervention arm. Only factors showing longitudinal association with at least one measure of body size were further examined.

Because participants who were not as successful with weight loss during the intervention may have been less likely to complete follow-up visits, non-ignorable mechanisms for the missing data were considered. Linear mixed effects pattern-mixture models