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Relation of Cumulative Weight Burden to Vascular Endothelial Dysfunction in Obesity

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Abstract

Although excess fat mass is broadly linked to increased cardiovascular risk, the relation between vascular phenotype and degree of obesity in extreme weight categories is unknown. We examined brachial artery vasomotor responses using ultrasound in 203 consecutive patients mainly afflicted with severe obesity (mean age 44 ± 11 yr; body mass index (BMI) 46 ± 9 kg/m^2, range 30–72 kg/m^2; and body weight 128 ± 29kg, range 69–207 kg). We studied a unique population with >70% of subjects characterized as morbidly obese (BMI ≥ 40) including a 31% group of super-obese individuals (BMI ≥ 50). Brachial artery flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD) were examined as measures of endothelium-dependent and -independent dilation, respectively, in relation to clinical, hemodynamic, and metabolic parameters. Endothelial function was significantly impaired in the highest as compared to lowest tertile of body weight (FMD 6.5 ± 4.6 vs. 9.8 ± 4.8%, p<0.001), whereas NMD was similar in all groups. Univariate correlates of FMD were gender, weight, waist circumference, BMI, diastolic blood pressure, and creatinine. In multivariate analysis, weight was a strong independent significant predictor of FMD (β= −0.23, p=0.005) in addition to gender. Within an overweight population, cumulative weight burden remains strongly linked to progressive arterial dysfunction. In conclusion, these results suggest that cardiovascular risks intensify with escalating obesity, and underscore the importance of therapeutic weight loss interventions in the context of the expanding obesity epidemic.

Keywords

endothelium; obesity; vasculature

Introduction

While obesity is broadly linked to impaired vasoreactivity when compared to lean populations, the relation between degree of obesity and vascular phenotype across a wide range of individuals with excess fat remains unknown.[1] In addition, whether vascular dysfunction

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progresses or reaches a plateau as body weight increases throughout the extremely obese range remains an open question. Thus, the purpose of this study was to examine the relationship between arterial dilator responses and overall weight burden in expressly overweight individuals.

Methods

We enrolled 216 consecutive obese men and women (BMI ≥ 30 kg/m^2; range 30–72 kg/m^2), age ≥18 years, from 2002 to 2006 receiving care at the Boston Medical Center Nutrition and Weight Management Center. This high-volume ambulatory center provides outpatient comprehensive dietary, medical, behavioral, or surgical treatments to promote lifestyle modification and weight loss. Patients with unstable medical conditions such as active coronary syndromes, heart failure, systemic infection, malignancy, or pregnancy were excluded. All subjects gave written, informed consent and the study was approved by the Boston Medical Center Institutional Review Board. A significant portion of individuals in this specialized ambulatory clinic exhibited extreme obesity, as 71% of the study population was morbidly obese (class 3 obese, BMI ≥ 40) and 31% of total subjects were super-obese (BMI ≥ 50).

Ultrasound studies were performed in a temperature-controlled room with subjects lying supine in a fasting state. Studies were performed during a weight-stable period prior to initiation of any weight loss intervention. Trained sonographers examined brachial artery vasomotor responses using a noninvasive, standardized method of ultrasound imaging as previously described, using a Toshiba Powervision 6000 system.[2,3] Flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD) of the brachial artery were examined as measures of endothelium-dependent and -independent dilation, respectively. Brachial artery FMD responses were examined following a 5-minute cuff occlusion in an upper arm position above the antecubital crease. Pulsed-Doppler flow velocity signals at baseline and after cuff deflation provided measures of reactive hyperemia. Sublingual nitroglycerin (0.4 mg) was omitted if the subject declined or had a history if migraines, blood pressure <100 mmHg, previous adverse reaction to nitrates, or used phosphodiesterase type-5 medications. An investigator blinded to clinical information performed all off-line analyses of digitized end-diastolic images. 203 subjects had technically analyzable ultrasound data and were included in the analyses.

Concomitant with the vascular studies, clinical characteristics along with blood pressure, heart rate, height, weight, BMI, and waist circumference were recorded for each subject. Biochemical analyses included lipids, glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), hemoglobin A1c, and renal function were quantified from blood samples collected in a fasting state.

Analyses were completed using SPSS for Windows, version 12.1 (SPSS Inc.). Data are presented as mean ± SD, unless otherwise indicated. Correlations between vascular parameters and clinical or biochemical data were examined using linear regression analysis. Examined variables included age, gender, weight, BMI, waist circumference, heart rate, blood pressure, lipids, glucose, insulin, HOMA-IR, hemoglobin A1c, creatinine, FMD, NMD, hyperemic flow, history of diabetes, hypertension, coronary artery dieasease, and smoking. Univariate correlates of vascular function ($p<0.05$) were entered into a stepwise multiple regression analysis to identify independent predictors of FMD. Clinical and vascular parameters were compared among tertiles of body weight using analysis of variance (ANOVA) or chi-square tests, as appropriate. Data were categorized and presented in tertiles of body weight based on independent correlations between weight and flow-mediated dilation.

Results

A total of 203 patients (mean age 44 ± 11 yr, 80% female) completed the study. All subjects were obese with average BMI 46 ± 9 kg/m^2 (range 30–72 kg/m^2), total body weight 128 ± 29 kg (69–207 kg) and waist circumference 130 ± 19 cm (94–180 cm). As expected in this demographic group, nearly half of the patients had hypertension and approximately one third was diabetic. Using a cut-point HOMA-IR value of 1.7, 74% of the study population exhibited insulin resistance.[4,5] Patient characteristics displayed in tertiles of body weight categories are shown in Table 1. Adiposity measures including BMI and waist circumference increased with rising tertiles of weight status ($p<0.001$ by ANOVA). Other clinical parameters that varied significantly between groups included blood pressure, plasma insulin, gender, and smoking status.

For the entire population, average flow-mediated dilation was 8.1 ± 4.8% (n=203) and nitroglycerin-mediated dilation was 11.6 ± 6.2% (n=95). As shown in the Figure, brachial artery FMD was significantly impaired in the highest vs. lowest tertile of body weight (6.5 ± 4.6% vs. 9.8 ± 4.8% respectively, $p<0.001$) lending support for graded vascular impairment with escalating obesity status. Additional brachial artery parameters are displayed in Table 2. In addition to impaired endothelium-dependent FMD, the heavier groups also exhibited lower reactive hyperemia, a marker of microvascular dilator dysfunction. In contrast, nitroglycerin-mediated, endothelium-independent dilator responses were similar between all groups.

As displayed in Table 3, univariate correlates of flow-mediated dilation were gender, weight, BMI, waist circumference, diastolic blood pressure, and creatinine. Multivariate analysis identified body weight ($\beta = -0.23$, $p=0.005$) as a significant independent predictor of FMD whereas other adiposity measures of waist circumference or BMI were not significant determinants of flow-mediated dilation when total weight was included as a variable in the analysis. Gender was also independently associated with endothelial function ($\beta = 0.21$, $p=0.009$). Waist circumference was weakly independently linked to arterial dilation ($p=0.01$) only if weight was excluded from the multivariate model.

Discussion

In the present study which included a large number of severely obese patients, we demonstrated that body weight is a significant predictor of vascular dysfunction after adjusting for covariates in a population afflicted with morbid obesity. Most importantly, weight burden was strongly linked to arterial dysfunction without evidence for a threshold cut-point in relation to degree of vascular impairment, lending strong support to our growing recognition that cardiovascular risk continues to rise with escalating obesity. Brachial artery flow-mediated dilation correlated with body weight, but not independently with BMI in severely obese subjects, suggesting that this conventional measure of adiposity may be limited in its discriminatory power with regard to cardiovascular risk in extreme obesity.

Our findings provide a clinical opportunity to gain insight into the pathophysiological link between morbid obesity and vascular function, as prior population studies examined vascular physiology in primarily mildly obese subjects. The Framingham database demonstrated an inverse association between brachial artery flow-mediated dilation and BMI, although the relation to other anthropometric measures was not reported.[6] A similar study in Hispanics observed a gender difference noting a link between BMI and impaired vascular responses in women.[7] Smaller cross-sectional studies suggest that weight distribution, in particular central localization of fat, may be a more important determinant of vascular phenotype. For example, in 2 studies of overweight adults, flow-mediated dilation correlated with waist-to-hip ratio, but not BMI or metabolic parameters.[8,9] In other studies, accumulation of visceral fat quantified

by abdominal computed tomography (CT)[10] or ultrasound imaging[11] was linked with impaired vasoreactivity, though a report in older men failed to confirm this relationship.[12] Collectively, these studies brought to our attention that various adiposity measures relate to vascular diathesis, but very few studies to date examined vasomotor responses in expressly severe obesity (BMI ≥ 40) and a significant gap in knowledge exists with regard to this issue.

We offer novel data by providing evidence for progressive loss of vascular homeostasis with advancing weight burden into the extreme range, and from a clinical standpoint refute any potential notion that added increase in fat mass beyond a specific threshold cut-point fails to contribute to further health risks. Our results are in agreement with recent clinical data by McTigue et al demonstrating rising mortality across weight groups ranging from normal to the extremely obese.[13] These findings combined with a growing population in highest weight categories underscore the danger in simplifying obesity as a homogeneous condition. Our present data suggest that progressive impairment in endothelial function may represent a pathophysiological mechanism linking obesity to cardiovascular risk. Although adiposity is associated with insulin resistance and dyslipidemia, we did not identify a specific relation between these conventional metabolic parameters and vasomotor function, an observation that has been fairly consistent across other studies that examined this issue in the obese.[9,10] This can be partly explained by the already high prevalence of abnormal HOMA-IR in these subjects thus limiting its discriminatory power. Overall, since variables beyond traditional metabolic risk factors were determinants of vascular diathesis across weight tertiles, our identification of a specific impairment in endothelial function with progressive weight assumes even greater functional significance, and lends further support to the growing recognition that excess fat burden itself may be detrimental to vascular homeostasis.

Our study has several limitations. Waist-to-hip ratio assessment was not available in our study subjects. In addition, we did not quantify fat percentage or distribution as physical size limitations pose significant challenges for advanced imaging with CT and MRI, or X-ray absorptiometry as many morbidly obese subjects do not fit into scanners. Lastly, only a subset of patients received NTG, thus we cannot exclude a change in endothelium-independent dilation, although no such effect was seen in previous similar investigations.[8,10] Overall, these inherent study limitations are counterbalanced by the relatively large and unique study population, clinical relevance of examining vascular function in severe obesity, and importance of filling a gap in knowledge with regard to this issue.

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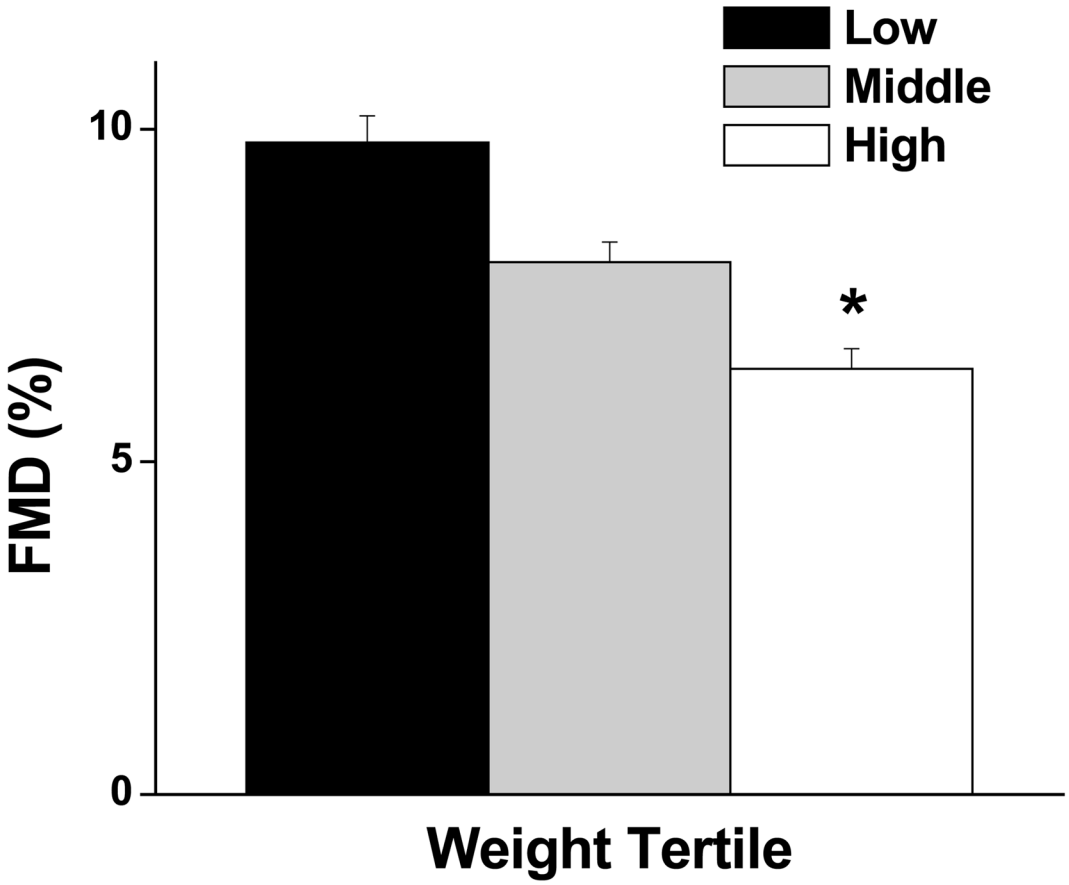

Figure.
Brachial artery flow-mediated dilation (FMD) stratified according to body weight tertiles (low < 113 kg, middle 113–137 kg, and high >137 kg). As shown, FMD was significantly impaired in the high vs. low tertile (*$p < 0.001$). Data are presented as mean ± SE.

Table 1

Subjects characteristics by weight tertile

Variable	<113 kg (n = 67)	113–137 kg (n = 67)	>137 kg (n = 69)	*P*
Age (years)	46 ± 12	45 ± 11	41 ± 11	0.055
Weight (kg)	98 ± 11	124 ± 7	161 ± 17	<0.001
Body Mass Index (kg/m^2)	38 ± 4	45 ± 5	55 ± 7	<0.001
Waist circumference (cm)	114 ± 10	129 ± 9	150 ± 15	<0.001
Systolic blood pressure (mm Hg)	127 ± 14	135 ± 14	127 ± 15	0.002
Diastolic blood pressure (mm Hg)	71 ± 9	75 ± 11	72 ± 12	0.103
Total cholesterol (mg/dl)	193 ± 38	194 ± 37	188 ± 41	0.636
Low density lipoprotein cholesterol (mg/dl)	115 ± 32	112 ± 31	112 ± 37	0.883
High density lipoprotein cholesterol (mg/dl)	51 ± 12	50 ± 16	46 ± 11	0.058
Triglycerides (mg/dl)	134 ± 61	163 ± 103	152 ± 104	0.197
Glucose (mg/dl)	109 ± 37	113 ± 47	104 ± 21	0.428
Insulin (μU/mL)	16 ± 14	15 ± 12	21 ± 11	0.030
HOMA-IR	3.5 ± 3.3	3.9 ± 6.6	4.3 ± 3.0	0.725
Heart rate (beats per minute)	71 ± 10	73 ± 11	73 ± 13	0.351
Creatinine (mg/dl)	0.7 ± 0.1	0.7 ± 0.2	0.8 ± 0.2	0.134
Hemoglobin A1c (%)	6.2 ± 1.1	6.5 ± 1.6	6.1 ± 1.0	0.283
Men	8%	15%	38%	<0.001
Smoker	48%	24%	48%	0.011
Hypertension	36%	48%	48%	0.469
Diabetes mellitus	30%	30%	29%	0.993
Angiotensin converting enzyme inhibitor use	13%	19%	17%	0.642
HMGCo-A reductase inhibitor use	27%	21%	17%	0.400

Table 2

Brachial artery parameters by weight tertile

Variable	<113 kg (n = 67)	113–137 kg (n = 67)	>137 kg (n = 69)	*P*
Flow-mediated dilation (%)	9.8 ± 4.8	8.0 ± 4.5	6.5 ± 4.6	<0.001
Flow-mediated diameter increase (mm)	0.36 ± 0.16	0.32 ± 0.17	0.27 ± 0.18	0.011
Reactive hyperemia (% increase)	694 ± 352	520 ± 298	518 ± 398	0.011
Nitroglycerin-mediated dilation (%)	12.6 ± 5.3	11.5 ± 7.3	11.1 ± 5.8	0.664

Table 3

Univariate correlates of flow-mediated dilation

	Regression Coefficient	*P*
Gender	0.31	<0.001
Weight (kg)	−0.28	<0.001
Body Mass Index (kg/m^2)	−0.14	0.048
Waist circumference (cm)	−0.24	0.001
Systolic blood pressure (mm Hg)	−0.13	0.058
Diastolic blood pressure (mm Hg)	−0.17	0.015
Total cholesterol (mg/dl)	0.05	0.530
Low density lipoprotein cholesterol (mg/dl)	0.11	0.121
High density lipoprotein cholesterol (mg/dl)	−0.04	0.547
Creatinine (mg/dl)	−0.16	0.030
Triglycerides (mg/dl)	−0.08	0.271
Hemoglobin A1c (%)	−0.08	0.306
Glucose (mg/dl)	−0.05	0.466
Insulin (μU/mL)	−0.05	0.584
HOMA-IR	−0.08	0.388