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Clinical Investigations

Weight Changes and Obesity Predict Impaired Resting and Endothelium-Dependent Myocardial Blood Flow in Postmenopausal Women

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Summary

Background: Obesity has been associated with impaired endothelial function, but the influence of lifetime weight patterns on endothelial function has not been studied.

Hypothesis: We hypothesized that coronary vascular reactivity would be diminished in postmenopausal women with a history of obesity and frequent weight swings.

Methods: We performed dynamic N-13 ammonia positron emission tomography in 18 postmenopausal women with cardiac risk factors. Myocardial blood flow (MBF) was measured at rest, after the cold pressor test (CPT), and after adenosine infusion in order to determine baseline and endothelium-dependent and -independent flows, respectively. Myocardial blood flow was corrected for cardiac work by normalizing to the rate–pressure product. Weight history was obtained by standardized questionnaire.

Results: Normalized rest (n-rest) MBF correlated negatively with current weight ($r = -0.52$, $p = 0.026$) and weight at age 18 ($r = -0.47$, $p = 0.047$). Normalized CPT (n-CPT) MBF correlated inversely with current weight ($r = -0.55$, $p = 0.018$), weight at age 18 ($r = -0.605$, $p = 0.008$), and highest weight ($r = -0.62$, $p = 0.006$). Higher waist circumference predicted lower n-rest MBF ($r = -0.52$, $p = 0.028$) and n-CPT MBF ($r = -0.48$, $p = 0.04$). The same association was found with hip circumference ($r = -0.52$, $p = 0.028$; $r = -0.49$, $p = 0.038$, respectively), whereas higher body mass index (BMI) predicted lower n-CPT MBF ($r = -0.53$, $p = 0.02$). Women with at least four significant weight swings had lower MBF during rest, CPT, and n-CPT (0.88 vs. 1.19 ml/g/min, $p = 0.008$; 0.76 vs. 1.23 ml/g/min, $p < 0.001$; 0.74 vs. 1.10 ml/g/min, $p = 0.009$, respectively).

Conclusions: Increased waist and hip circumference, weight, and frequent weight swings are associated with impaired resting and endothelium-dependent MBF in postmenopausal women. These data suggest that lifetime weight patterns may influence cardiovascular risk in women.

Key words: endothelium, obesity, prevention, women

Introduction

Obesity is reaching epidemic proportions in the United States, with major implications for cardiovascular risk in the increasing numbers of individuals affected.[1]

Elevated waist-hip ratio (WHR) and waist circumference as well as increased body mass index (BMI) and moderate weight gain have been independently linked with raised coronary heart disease (CHD) risk in women.[2, 3] Recently, overweight and obesity have been associated with higher mortality in the general population,[4] and higher BMI and significant weight gains have been linked to higher mortality among women.[5] Although obesity is a major epidemic and a strong CHD risk factor, little is known about lifetime weight patterns and coronary vascular function.

Endothelial dysfunction is an early step in the development of atherosclerosis. The endothelium releases endothelium-

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derived relaxing factor, or nitric oxide (NO), in response to various factors including acetylcholine, serotonin, bradykinin, and thrombin, as well as in response to flow-induced shear stress. Furthermore, sympathetic stimulation of the intact endothelium results in mixed alpha- and beta-adrenergic stimulation and leads to vasodilation. Without an intact vascular endothelial layer, sympathetic stimulation leads to paradoxical vasoconstriction.[6] Zeiher *et al.* have shown that a noninvasive sympathetic stimulus such as the cold pressor test (CPT) can be used to assess the functional integrity of the coronary vascular endothelium. Exogenous adenosine exerts direct vasodilatory effects on vascular smooth muscle cells and exerts NO-mediated effects on the vascular endothelium as well.[7] Adenosine effects can be characterized as a composite index of vascular reactivity; clinically, the agent is used to assess maximal myocardial blood flow (MBF) and myocardial flow reserve (MFR). Risk factors for CHD such as hypercholesterolemia, hypertension, smoking, family history of premature CHD, and obesity have all been associated with impaired vascular reactivity, indicating abnormal endothelial function. Because invasive coronary flow measurements are difficult to justify in healthy women, we sought to use a noninvasive technique for measuring microcirculatory vascular reactivity and MBF. Dynamic positron emission tomography (PET) in combination with N-13 ammonia imaging can accurately measure MBF noninvasively.

We hypothesized that lifetime patterns of obesity would be associated with impaired coronary endothelial function as measured by PET in postmenopausal women.

Methods

Study Design and Criteria

Subjects included postmenopausal (without menses for ≥ 12 months) women with at least one CHD risk factor (n = 18). Subjects were excluded if they had evidence of CHD, recent (< 3 month) initiation of lipid-lowering therapy or use of hormone replacement therapy, inability to discontinue vasoactive medicines for 24 h prior to PET, and inability to give informed consent. Current weight, height, and waist and hip circumference were measured at the initial clinic visit, and WHR and BMI were subsequently calculated. All subjects underwent dobutamine echocardiography to exclude CHD. A standardized questionnaire was administered to collect information regarding weight history, including weight at age 18, highest lifetime weight, and the number of times a subject had had a significant weight swing, which was defined as a gain or loss of ≥ 10 pounds in a year, excluding pregnancy. All subjects underwent PET with N-13 ammonia. Myocardial blood flow was measured using a three-compartment model at rest in response to sympathetic stimulation with CPT, and after adenosine infusion in order to determine baseline, endothelium-dependent, and maximal flows, respectively. The study protocol was approved by the institutional review boards of the University of Michigan and the Ann Arbor Veterans Affairs Medical Center, as well as by the Radiation Safety Committee. Each subject gave informed consent.

Positron Emission Tomography Imaging Protocol

Subjects discontinued all vasoactive medications 24 h prior to PET. The women were fasting for at least 8 h prior and caffeine intake was stopped 12 h prior to PET. Positron emission tomography studies were acquired, processed, and analyzed as has been reported previously.[8]

Myocardial blood flow was measured at rest, during CPT, and after adenosine infusion. To account for interindividual differences in cardiac work, MBF at rest and during CPT was normalized to cardiac work by dividing MBF by the rate–pressure product (RPP) and multiplying by 10,000. As adenosine uncouples flow from cardiac work, maximal hyperemic MBF was not normalized to the RPP. Coronary flow reserve (CFR) was defined as the ratio between MBF in response to adenosine and MBF at rest.

Statistical Analysis

Summary statistics of groups were presented as mean ± standard deviation. A two-tailed Student's *t*-test was used to compare mean values between groups. Pearson correlation coefficients were calculated for continuous variables. Univariate associations of the group with ≥ 4 weight swings versus the group with < 4 weight swings were compared using the Pearson chi-square test or, when appropriate, the two-sided Fisher's exact test or Student's *t*-test. A p value of < 0.05 was considered significant. All analyses were performed with the Statistical Package for Social Sciences for Windows, version 11.0 (SPSS, Inc., Chicago, Ill., USA).

Results

Eighteen women were enrolled and underwent N-13 ammonia PET studies at rest, with CPT and with adenosine. Health questionnaire data were available from all 18 women. Lipid levels were available in 16 women; in two women, we were not able to obtain enough blood for lipid analysis despite multiple attempts.

Baseline Patient Characteristics

The mean age of the 18 women was 59.6 ± 6.7 years. Mean weight at age 18 and current weight was 57.9 ± 13.0 kg and 78.1 ± 13.5 kg, respectively. Mean waist and hip circumference were 95.7 ± 10.9 and 112.0 ± 10.3 cm, respectively, with a mean WHR of 0.85 ± 0.04. Mean BMI was 29.3 ± 4.1 kg/m^2. Mean number of weight swings was 4.0 ± 4.0 (range 0–15). In other words, the study population represented an overweight to obese group. Other CHD risk factors and medication use are summarized in Table I. Ten of the 18 women had only two CHD risk factors; 7 had three risk factors, and 1 had four risk factors.

TABLE I Patient characteristics

Age (years)	59.6 ± 6.7	CPT MBF	1.05 ± 0.29
Total cholesterol (mg/dl)	231.6 ± 45.2	Normalized CPT MBF	0.96 ± 0.30
Triglycerides (mg/dl)	193.8 ± 136.5	Adenosine rate pressure product	137.2 ± 28.6
Low-density lipoprotein cholesterol (mg/dl)	144.7 ± 30.0	Adenosine MBF	2.64 ± 0.93
High-density lipoprotein cholesterol (mg/dl)	47.6 ± 14.9	CFR	2.68 ± 1.33
Waist circumference (cm)	95.7 ± 10.9	Hypercholesterolemia (TC > 200 mg/dl,	
Hip circumference (cm)	112.0 ± 10.3	LDL > 130 mg/dl, or current statin use)	n = 16
Waist/hip ratio	0.85 ± 0.04	Smoking	n = 11
Weight at study entry (kg)	78.1 ± 13.5	Hypertension	n = 5
Weight at age 18 (kg)	57.9 ± 13.0	Diabetes	n = 2
Highest weight attained (kg)	82.9 ± 12.2	Family history of premature coronary	
Number of significant weight swings	4.0 ± 4.0	artery disease	n = 11
Height (cm)	162.7 ± 8.8	Aspirin use	n = 3
Body mass index (kg/m^2)	29.3 ± 4.1	Beta-blocker use	n = 2
Resting rate pressure product	94.0 ± 23.7	ACE inhibitor use	n = 3
Resting MBF	1.07 ± 0.25	Long-acting nitrate use	n = 0
Normalized resting MBF	1.16 ± 0.28	Lipid-lowering therapy use	n = 3
CPT rate pressure product	110.6 ± 22.7	Calcium-channel blocker use	n = 3

Values are given as mean ± standard deviation.

Abbreviations: MBF = myocardial blood flow in ml/g/min, CPT = cold pressor test, CFR = coronary flow reserve, ACE = angiotensin-converting enzyme, TC = triglycerides, LDL = low-density lipoprotein.

Quantitative Myocardial Blood Flow Analysis

There was a significant rise in RPP between rest and CPT (94.0 vs. 110.6, $p < 0.001$), and between rest and adenosine (94.0 vs. 137.2, $p < 0.001$); RPP between CPT and adenosine was also significantly different (110.6 vs. 137.2, $p = 0.001$). Mean RPP, MBF, and CFR are shown in Table I. We found no correlation between traditional risk factors in our population (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides, smoking, hypertension, family history of premature CHD, and diabetes) and MBF measurements. We further found that cardiac medication use (which was infrequent in our population) did not significantly predict MBF values.

We found a significant negative correlation between n-rest MBF and current weight ($r = -0.52$, $p = 0.026$, Fig. 1) and weight at age 18 ($r = -0.47$, $p = 0.047$). There was a significant inverse relationship between n-CPT MBF and a woman's highest lifetime weight ($r = -0.62$, $p = 0.006$, Fig. 2), current weight ($r = -0.55$, $p = 0.018$), and weight at age 18 ($r = -0.61$, $p = 0.008$). No relationship was found between current weight, weight at age 18, and highest lifetime weight with maximal blood flow or CFR. Those who had high weight at age 18 also tended to have higher lifetime weights and current weights ($r = 0.79$, $p < 0.001$; $r = 0.71$, $p = 0.001$, respectively). Current weight also correlated with highest weight ($r = 0.849$, $p < 0.001$).

Evaluation of markers of central and visceral obesity yielded similar relationships. There were three women with normal weight (BMI < 25), eight overweight women (BMI 25–29), and seven obese women (BMI ≥ 30). We found a significant inverse association between waist and hip circumference with n-rest MBF ($r = -0.52$, $p = 0.028$; $r = -0.52$, $p = 0.028$, respectively, Fig. 3). There was also a similar correlation for

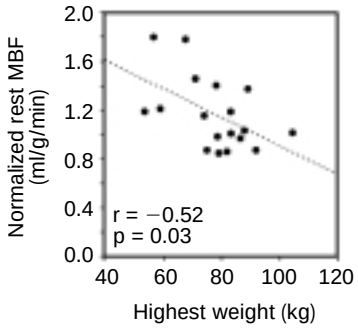

FIG. 1 Association between weight and resting myocardial blood flow (MBF).

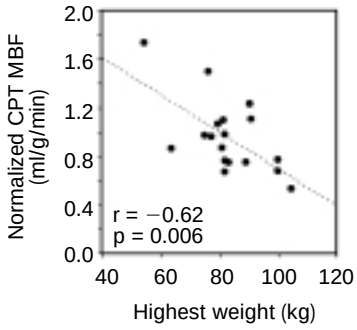

FIG. 2 Association between weight and endothelium-dependent myocardial blood flow (MBF). CPT = cold pressor test.

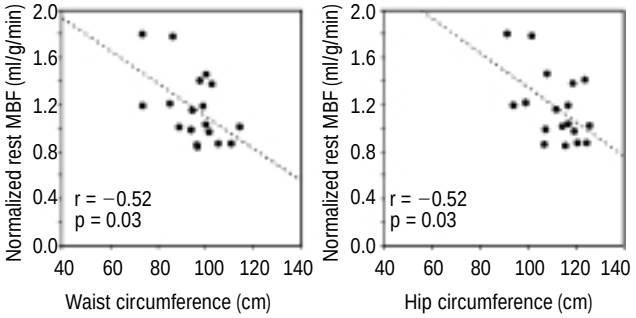

FIG. 3 Association between waist and hip circumferences and resting myocardial blood flow (MBF).

waist circumference, hip circumference, and BMI with n-CPT MBF ($r = -0.48$, $p = 0.04$; $r = -0.49$, $p = 0.038$; $r = -0.53$, $p = 0.023$, respectively, Fig. 4). There was no relationship between WHR and resting or endothelium-dependent MBF. Furthermore, no significant association was found between waist, hip, WHR, or BMI and endothelium-independent MBF in response to adenosine or CFR.

The number of times a woman had a significant weight swing correlated negatively with rest-MBF, CPT-MBF, and n-CPT MBF (Fig. 5). Women who had ≥4 significant weight swings had a markedly lower MBF during rest, CPT, and n-CPT than those who did not (Fig. 6). Using the Student's *t*-test, weight at age 18 was significantly higher in the group with ≥4 weight swings (67.7 ± 14.2 kg vs. 51.7 ± 7.4 kg, $p = 0.006$). It is interesting to note that current weight, highest weight, CHD risk factors, age, waist, hip, WHR, and BMI were similar between these two groups of women. Again, no relationship was found between weight swings and maximal flow or CFR. Multivariate regression analysis using the traditional risk factors mentioned in Table I, medications known to improve vascular endothelial function such as angiotensin-converting enzymes/angiotensin receptor blockers and statins, and the weight markers discussed above revealed that for resting MBF, only weight at age 18 remained a significant negative predictor. For the remaining measurements of MBF, multivariate analysis showed that no single predictor remained significant.

Discussion

The main finding of this study is that elevated weight at age 18, current weight, and highest weight are associated with lower endothelium-dependent and resting myocardial flows in postmenopausal women without known CHD, confirming our hypothesis that patterns of obesity adversely affect coronary vascular function. Furthermore, to our knowledge, this study is the first to examine the effect of weight fluctuations on coronary vascular reactivity. Specifically, more than four weight swings was a strong predictor of lower resting and endothelium-dependent MBF.

Our findings are supported by previous data showing that elevated BMI is associated with impaired coronary endothelial

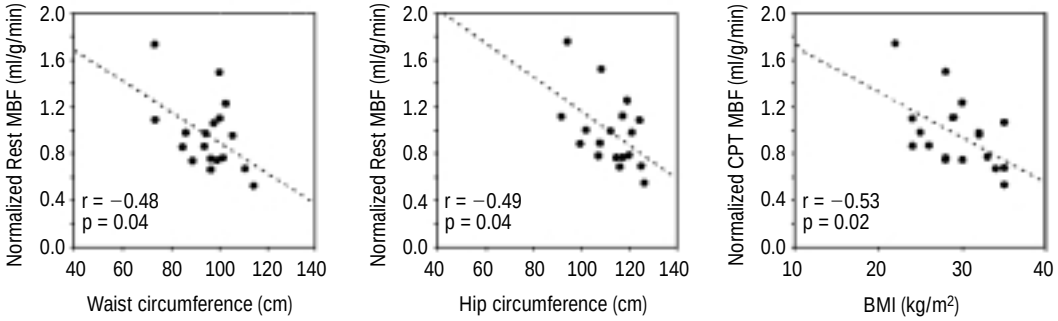

FIG. 4 Association between waist, hip, body mass index (BMI), and endothelium-dependent myocardial blood flow (MBF).

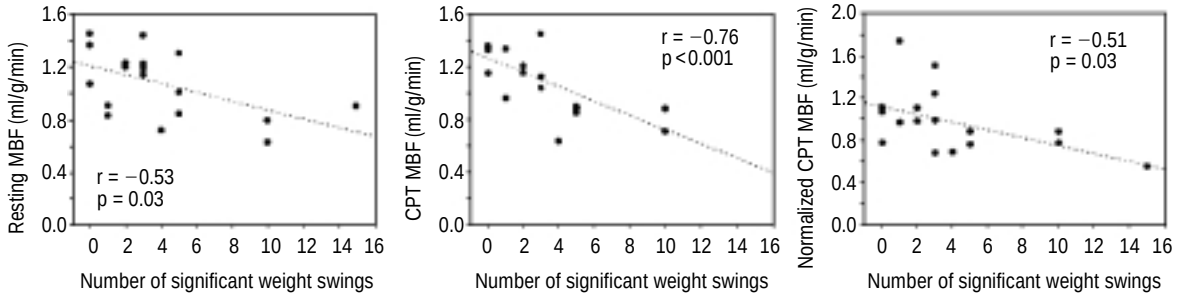

FIG. 5 Association between number of weight swings and resting myocardial blood flow (MBF), endothelium-dependent MBF, and normalized endothelium-dependent MBF.

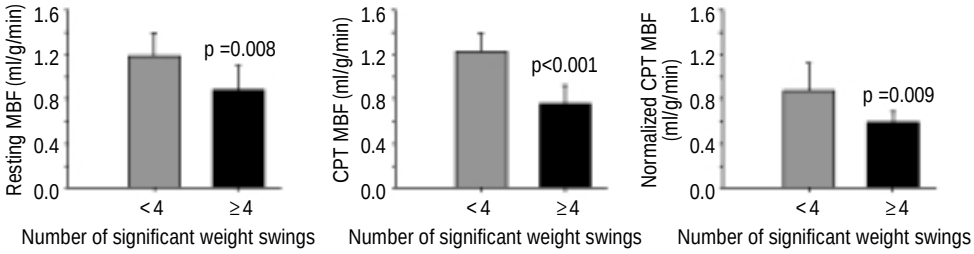

FIG. 6 Resting myocardial blood flow (MBF), endothelium-dependent MBF, and normalized endothelium-dependent MBF among women with ≥ 4 weight swings versus < 4 weight swings.

function in subjects with normal or mildly diseased coronary arteries.[9] Our findings also confirm those of Perticone *et al.*,[10] whose group found that in young men and women without CHD risk factors, BMI was an independent predictor of peripheral vessel endothelial dysfunction. They also found that WHR was a predictor of peripheral vessel endothelial dysfunction, a relationship which we did not observe in our study. One possible explanation for this discrepancy is that WHR may decrease more in response to weight loss in subjects with android rather than gynoid obesity.[11] In addition, waist circumference determined over the iliac crests may be a better predictor of visceral fat than WHR.[12]

In contrast to previous studies, we found that obesity and frequent weight swings are also strongly associated with lower resting MBF. These findings suggest that there is a basal level of NO release in the coronary circulation, which is lower in postmenopausal obese women. Lower myocardial flows have previously been shown in the distal epicardial coronary artery after inhibition of NO synthesis by N^G-monomethyl-l-arginine (L-NMMA) in male and female subjects with angiographically normal coronary arteries and no CHD risk factors, supporting the notion that NO exerts tonic effects in distal epicardial coronary arteries even in healthy subjects.[13] The importance of NO contribution to resting epicardial and coronary microvascular tone in subjects with angiographically normal coronaries and at least one CHD risk factor was subsequently shown by Quyyumi *et al*.[14] In subjects with CHD risk factors, L-NMMA caused a smaller increase in coronary vascular resistance and a smaller decline in coronary blood flow than in subjects without CHD risk factors, suggesting that basal NO bioavailability is lower in subjects with coronary risk factors. Subsequent studies have not found this association of lower resting MBF in the presence of markers of obesity. However, our study found a correlation with markers of obesity and resting MBF normalized to cardiac work, and previous studies did not normalize resting peripheral[10, 15, 16] or coronary flows. Furthermore, these associations have not previously been investigated solely in the postmenopausal population, and menopausal status is also associated with endothelial dysfunction.[17]

Our study is the first to examine the association of lifetime weight patterns with MBF and endothelial function. Our data show a significant negative correlation between MBF at rest, during CPT, and normalized CPT with the number of times a woman had had a significant weight swing. When women with ≥ 4 weight swings were compared with those who had less frequent weight swings, the only significant predictor was not current weight, but weight at age 18. It is interesting that current weight and highest weight, as well as other markers of obesity, were not associated with more weight swings. Lipid concentrations and total cholesterol/HDL cholesterol ratios were also similar between these two groups. By contrast, the Women's Ischemia Syndrome Evaluation (WISE) study[18] found lower HDL cholesterol levels and higher total cholesterol/HDL cholesterol ratios in women with self-reported weight cycling of ≥ 10 pounds at least three times. This association was directly related to the amount of weight cycled, with the strongest association found in women who lost ≥ 50 pounds/cycle. Our study may simply have been too small to detect this association; WISE enrolled 485 women, while our study included 18. In addition, we did not collect information regarding the amount of weight change per cycle, although current weight and BMI were indicative of a population that was in general still overweight and obese. In addition, the mean HDL cholesterol was lower in our subjects (47.6 ± 14.9 vs. 52 ± 12 mg/dl among weight cyclers in WISE, and 56 ± 14 mg/dl among non-weight cyclers in WISE), and the mean total cholesterol was higher in our study population (231.6 ± 45.2 vs. 201 ± 44 mg/dl among weight cyclers in WISE and 203 ± 46 mg/dl among non-cyclers in WISE). There was no difference in the finding of angiographic coronary disease between weight cyclers and non-cyclers in WISE. However, Ziccardi *et al.* showed that sustained weight loss over 1 year was associated with improved endothelial function in a group of premenopausal women, based on decreased inflammatory cytokine markers and improved vascular responses to intravenous L-arginine.[19]

Limitations

Our results are limited by the cross-sectional design, which precludes inference regarding causality between markers of obesity and myocardial flows. In addition, we are unable to control for unmeasured variables or draw conclusions regarding a pathophysiologic sequence of associations. Our study population consists mainly of an overweight and obese population. We did not include a sufficient number of age-matched lean controls or subjects who did not have CHD risk factors.

Another limitation is our small sample size, which did not allow us to correct adequately for multiple variables or to show significant correlations between myocardial flows and traditional CHD risk factors.

Conclusions

Results of this analysis support our hypothesis that lifetime weight patterns are associated with impaired coronary vascular reactivity in postmenopausal women with CHD risk factors. These findings suggest that the impairment of endothelium-dependent MBF that we observe in otherwise healthy postmenopausal women with a history of frequent weight swings may be linked to overweight and obese status in youth, highlighting the need for CHD prevention measures long before what our guidelines currently mandate. Our findings provide a possible mechanistic explanation for the consistent observation that obesity is a strong risk factor for CHD, and for the correlation between obesity, weight fluctuation, and higher mortality. Further study in this area should yield information regarding the best approach to primary prevention for postmenopausal women with CHD risk factors. Public health efforts are urgently needed to counter the epidemic of obesity among women in the United States and to provide weight control methods that can be successful and sustained over a lifetime.

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