Modestly Overweight Women Have Vascular Endothelial Dysfunction

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ABSTRACT

Background: Vascular endothelial dysfunction occurs early in the atherosclerotic process and is predictive of cardiovascular prognosis. However, the association between specific cardiovascular risk factors and endothelial dysfunction in women has not been well characterized. This study examined the relationship between endothelial dysfunction and cardiovascular risk factors (body mass index [BMI] ≥ 25 kg/m², current smoking, age, diabetes, hypertension, hypercholesterolemia, and family history of early coronary heart disease) in a population of women that included those already being treated for risk factors.

Methods: Endothelial function was assessed by brachial artery ultrasound flow-mediated vasodilation (FMD) in 185 consecutive women without a history of coronary heart disease. Women with hypertension, diabetes, or hyperlipidemia were allowed to continue on their usual therapy.

Results: There was an inverse linear association between age and FMD. Subjects who were active smokers had lower FMD compared with nonsmokers, and subjects with BMI ≥ 25 kg/m² had lower FMD than subjects with BMI < 25 kg/m². FMD in overweight women (BMI ≥ 25 and < 30 kg/m²) was similar to that of obese women (BMI ≥ 30 kg/m²). Multivariate analysis demonstrated that body mass index, current smoking, and age were independent predictors of endothelial dysfunction in this population.

Conclusion: Modestly elevated BMI, smoking, and age predict endothelial dysfunction in women, even in the presence of treatment for other atherosclerotic risk factors. These findings demonstrate the importance of modest elevation in BMI as a risk factor for impaired vascular health in women, and underscore the need for focusing further attention on lifestyle modification as a component of cardiovascular disease prevention.

Introduction

Vascular endothelial dysfunction develops early in the atherosclerotic process and cardiac risk factors are associated with vascular endothelial dysfunction. Several studies have demonstrated that the presence of vascular endothelial dysfunction predicts an increase in risk of future cardiac events^{1–5} in both men and women. Cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, smoking, and obesity have been observed to be associated with vascular endothelial dysfunction, even prior to the development of clinically evident coronary atherosclerosis. Furthermore, treatment of cardiovascular risk factors can reverse endothelial dysfunction^{6,7} in some patients.

Although the association between cardiac risk factors and endothelial dysfunction has been observed in prior studies,⁸ the relationship between specific risk factors and endothelial dysfunction in women in the current treatment era has not been well established. There is evidence that there are gender-based differences in vascular endothelial function, supporting the concept of investigating the relationship between atherosclerotic risk factors and endothelial dysfunction specifically in women.⁹ The purpose of this study was to examine the relationship between cardiovascular risk factors and endothelial function in a contemporary

population of women that included those being treated for risk factors.

Methods

Study subjects were recruited from advertisements, and the Division of Cardiology outpatient centers at Tufts Medical Center. The study was approved by the Institutional Review Board at Tufts Medical Center. Written informed consent was obtained from all participants. Subjects with a history of coronary artery disease, cardiomyopathy, or valvular heart disease were excluded from the study. The presence of hypertension, diabetes, hypercholesterolemia, smoking, or family history of coronary disease was determined by self-report from the study subjects and by documentation of a history of these conditions on review of medical records. Patients were considered to have hypertension, diabetes, or hypercholesterolemia if they reported having these conditions or if they were on pharmacologic therapy for these conditions. Subjects were considered to have a positive family history of coronary disease if they had a first-degree relative who was either male with coronary heart disease at age < 55 years, or female with coronary heart disease at age < 65 years. Elevated body mass index (BMI) was defined as a body mass index ≥ 25 kg/m².^{10,11} Subjects with a history of diabetes, hypertension, or hyperlipidemia were allowed to continue on their usual medications. The following clinical variables were considered to be cardiac risk

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factors: age >65 years, hypertension, hypercholesterolemia, diabetes mellitus, current smoking, family history of premature coronary artery disease, and BMI ≥ 25 kg/m².

Brachial Artery Imaging

Brachial artery flow-mediated vasodilation was measured under fasting conditions. Study subjects were instructed not to smoke for at least 8 h prior to testing. Baseline longitudinal axis images of the brachial artery were obtained using a 12 MHz transducer (Vingmed, General Electric, Norway). A sphygmomanometer cuff was placed on the proximal arm and inflated to suprasystolic pressures for 5 min. One min after cuff deflation, reactive hyperemia images of the brachial artery were obtained. The brachial artery end-diastolic diameters at rest and during hyperemia were measured as the distance from the anterior to posterior blood-lumen interface. The brachial artery diameter was determined by averaging 3 evenly-spaced measurements that were obtained by blinded observers using electronic calipers on the ultrasound unit. The %FMD was calculated as $100 \times (\text{hyperemic brachial artery diameter} - \text{baseline brachial artery diameter}) / \text{baseline brachial artery diameter}$. The mean values for intraobserver and interobserver variability for the percent change in brachial artery diameter in our laboratory are 1.9% and 2.8%, respectively.

Statistical Analysis

Endothelial dysfunction was defined as FMD less than the median level (12%). The predictive value of individual risk factors for endothelial dysfunction was analyzed by univariate logistic regression, as well as age-adjusted logistic regression analyses. Finally, multivariate adjusted logistic regression models were performed. The variables that were included in the multivariate adjusted model included those that showed significance in the univariate model (age, BMI, current smoking), as well as those with clinical relevance (hypertension, diabetes, hypercholesterolemia, family history of coronary artery disease [CAD]). Student *t* test or analysis of variance (ANOVA) followed by a Student-Newman-Keuls test was also used for the comparison of differences in FMD associated with the presence or absence of risk factors that were found to be predictors of FMD. Data are presented as mean $\pm$ SEM unless otherwise indicated.

Results

A total of 185 women were enrolled in the study. The study subjects ranged in age from 21 to 79 years old. A total of 111 women (60%) were postmenopausal. Baseline characteristics of the study population and use of medications for risk factor modification are shown in Table 1. Sixty-three women had no cardiovascular risk factors, 71 had 1–2 risk factors, and 51 women had 3 or more risk factors. The mean baseline brachial artery diameter was 3.1 ± 0.04 mm, and mean hyperemia brachial artery diameter was 3.5 ± 0.04 mm.

Table 1. Baseline Characteristics of the Study Population

Variables	(N = 185)
Age, years (mean, SEM)	51 $\pm$ 1
Hypertension, n	44 (24%)
Race	
White, n	153 (83%)
Black, n	18 (10%)
Asian, n	10 (5%)
Hispanic, n	4 (2%)
Diabetes, n	6 (3%)
Hypercholesterolemia, n	47 (25%)
Current smoker, n	8 (4%)
Family history, n	36 (19%)
Body mass index ≥ 25 kg/m ² , n	102 (55%)
Total cholesterol (mg/dL)	210 $\pm$ 4
Low density lipoprotein cholesterol (mg/dL)	126 $\pm$ 5
High density lipoprotein cholesterol (mg/dL)	58 $\pm$ 2
Triglycerides (mg/dL)	134 $\pm$ 11
Antihypertensive therapy, n	44 (24%)
Lipid-lowering therapy, n	26 (14%)
Hormone replacement therapy, n	17 (9%)

Mean FMD was $12.8 \pm 0.5\%$, and median FMD was 12%. Univariate linear regression analysis demonstrated that FMD declined with increasing age ($r = 0.311$, $p < 0.001$, Figure 1). In univariate analyses, linear regression analysis demonstrated a negative association between BMI and FMD ($r = 0.205$, $p = 0.011$), and FMD was significantly lower in patients with body mass index ≥ 25 kg/m² ($11.4 \pm 0.7\%$) compared to those with BMI < 25 kg/m² (14.6 ± 1.0 , $p = 0.005$, Figure 2). FMD was lower in current smokers compared to nonsmokers (Figure 3). There was no significant difference in FMD between subjects with BMI ≥ 30 kg/m² (FMD: $10.8 \pm 0.9\%$) and those with BMI ≥ 25 kg/m² but < 30 kg/m² (Figure 2). In addition, there was no difference in FMD between subjects who were former smokers and those who had never smoked.

To evaluate which clinical variables predicted endothelial dysfunction, endothelial dysfunction was defined as %FMD below the median value of 12%. By univariate logistic regression analysis, the following variables were significantly associated with endothelial dysfunction: age, body mass index, post menopausal status, smoking status, and

Figure 1. Linear regression analysis demonstrating the relationship between flow-mediated vasodilation (FMD) and age.

Figure 2. Flow-mediated vasodilation (FMD) in subjects with body mass index (BMI) <25 kg/m² (white bar, n = 50) compared to those with BMI ≥25 and <30 kg/m² (black bar, n = 54) and those with BMI ≥30 kg/m² (hatched bar, n = 48). *p = 0.035 compared to BMI <25 kg/m² †*p* = 0.018 compared to BMI <25 kg/m², *p* = 0.496 compared to BMI = 25 to <30 kg/m².

number of cardiac risk factors. In the age-adjusted model, the significance was sustained for all of the above variables except for postmenopausal status and number of cardiac risk factors. Finally, multivariate logistic regression analysis was performed for endothelial dysfunction including variables of age, BMI, presence or absence of current smoking, hypertension, diabetes, positive family history, hypercholesterolemia, and cardiovascular medications (Table 2). After adjustment for all of the above variables, age, body mass index and current smoking emerged as independent predictors of endothelial dysfunction. To further evaluate these findings, the same analyses were performed using other validated^{8,11} cut off levels for FMD (at 10% and at 15%),

Figure 3. Flow-mediated vasodilation (FMD) in subjects not currently smoking (white bar) compared to current smokers (black bar). *p = 0.01.

Table 2. Multi-Variate Logistic Regression Analysis for Endothelial Dysfunction

	Odds Ratio (95% CI)	P-value
Age	1.03 (1.002–1.068)	0.037*
BMI	1.10 (1.02–1.18)	0.014*
Family history of CAD	0.94 (0.34–2.56)	0.16
Current smoking	3.89 (1.09–13.8)	0.037*
Hypertension	1.01 (0.39–2.86)	0.98
Diabetes	0.21 (0.03–1.77)	0.15
Hypercholesterolemia	0.57 (0.22–1.47)	0.25
Anti-hypertensive medication	1.77 (0.59–5.28)	0.306
Lipid-lowering medication	0.82 (0.193–3.45)	0.248

BMI = body mass index; CAD = coronary artery disease *p < 0.05.

which generated similar results as the FMD cut off of 12%. To specifically examine the relationship between modestly increased BMI and endothelial dysfunction, multivariate logistic regression analysis (including variables of age, BMI, current smoking, hypertension, diabetes, positive family history, and hypercholesterolemia) was performed in patients with BMI <30 kg/m²; BMI remained an independent predictor of endothelial dysfunction in these patients (OR: 1.047; 95% CI: 1.01–1.09, *p* = 0.033).

Discussion

These findings demonstrate that modestly overweight body mass index, smoking, and increasing age are independent predictors of endothelial dysfunction in a contemporary population of women with a varied degree of risk factors.

Furthermore, these observations indicate that even in the context of ongoing treatment for other modifiable risk factors, such as hypertension or hypercholesterolemia, modestly increased body weight and smoking are important predictors of endothelial dysfunction. Since vascular endothelial dysfunction precedes clinically evident coronary atherosclerosis and predicts risk of cardiovascular events, these findings support the concept that overweight body mass index and smoking are important targets for coronary risk modification in women.

Endothelial Dysfunction and Cardiovascular Disease

The vascular endothelium plays a role in the regulation of vasomotor tone, platelet aggregation, vascular inflammation, and vascular smooth muscle proliferation. Endothelial dysfunction disrupts the balance of these factors, resulting in a proatherosclerotic milieu. A number of studies have demonstrated that vascular endothelial dysfunction may precede the development of angiographically apparent coronary disease.^{1–3} Furthermore, endothelial dysfunction in both the coronary system and the peripheral circulation is predictive of cardiac events.^{1–4,6}

Although there are gender-based differences in vascular endothelial function,⁹ there is evidence that the link between vascular endothelial dysfunction and cardiac prognosis is applicable to women as well as men. Bugiardini et al. observed that in women with angina and myocardial perfusion abnormalities with normal coronary angiograms, coronary endothelial dysfunction was associated with future coronary atherosclerosis.⁵ In a study of flow-mediated vasodilation in postmenopausal hypertensive women, Modena and colleagues have reported that a substantial portion of women may demonstrate improvement in endothelial function after treatment for hypertension, and that women whose endothelial function improves with therapy have a better prognosis than those whose endothelial dysfunction persists.⁶ These observations indicate that not only is endothelial dysfunction related to cardiovascular prognosis in women, but that the response of the vascular endothelium to cardiovascular risk factor modification is also linked to prognosis. The observation that endothelial function may improve in response to therapeutic interventions also likely explains the lack of association between FMD and traditional risk factors (such as hypertension, hypercholesterolemia) in our study, in which most subjects were undergoing treatment for such risk factors. The findings of the current study support the importance of smoking and increased BMI as contributors to endothelial dysfunction, even in the context of the treatment or absence of other risk factors.

Risk Factor Modification and Endothelial Function

While prior studies have reported that obesity, age, and smoking are associated with endothelial dysfunction,^{8,13–24} the predictive value of these risk factors for endothelial

dysfunction in women has not specifically been examined. The data from the current study indicate that even modestly elevated BMI (≥ 25 kg/m²) is associated with abnormal endothelial function, supporting the current recommendations for an ideal BMI of 18.5–24.9 kg/m² in women.¹⁰ These findings suggest that women who are overweight but do not meet criteria for obesity (i.e., BMI ≥ 30 kg/m²) may still be at increased risk for cardiovascular events.

Clinical data support the link between obesity and smoking and increased risk of cardiovascular events.^{25–28} Furthermore, there is some evidence that obesity may affect the efficacy of lipid-lowering therapy.²⁹ Despite these observations, patient counseling regarding weight loss and smoking cessation remains suboptimal,^{30–32} even amongst patients with other cardiovascular risk factors. Furthermore, there are some data suggesting that women may be counseled less frequently than men regarding smoking cessation.³¹ The observation that smoking and modestly elevated body mass index independently predict endothelial dysfunction in a population of women that includes patients being treated for other risk factors highlights the need for further risk factor counseling targeted at lifestyle modification.

Limitations

There are several limitations to this study that warrant comment. Since nitroglycerin-mediated vasodilation was not measured in this study, the relationship between risk factors and endothelium-independent vasodilatory properties cannot be determined. Additionally, we did not examine the relationship between FMD and other anthropomorphic measurements, such as waist circumference; the relationship between endothelial function and markers of obesity other than BMI is of great interest for future studies. Since the study aimed to assess the relationship between risk factors and endothelial function in the context of clinical practice, subjects did not withhold medications prior to endothelial function testing. However, previous data have indicated that brachial artery flow-mediated vasodilation is not significantly affected by ongoing use of chronic vasodilator therapy.³³

While the study population was not selected for specific risk factors, there were a relatively low number of diabetic subjects in this study population, thereby potentially limiting the ability to detect an association between endothelial dysfunction and diabetes. Interestingly, although the number of current smokers in this study was also relatively small, smoking was found to be an independent predictor of endothelial dysfunction. The use of self-reported risk factors may be viewed as a limitation; however, review of medical records was also used to corroborate risk factor data wherever available. Finally, hormonal levels were not evaluated in women participating in this study. However, BMI, current smoking, and age predicted FMD independent of menopausal status, indicating that hormonal status did not significantly impact these findings.

Conclusion

Modestly increased body mass index, smoking, and age are strong predictors of endothelial dysfunction in women, even in the presence of other treated atherosclerotic risk factors. These findings indicate that even modest elevation in BMI is associated with impaired vascular health, and highlight the need for focusing further attention on lifestyle modification as an important component of cardiovascular disease prevention.

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