Adiposity, but not Obesity, Is Associated With Arterial Stiffness in Young Nulliparous Women

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Abstract

Subclinical vascular dysfunction is increasingly recognized as an independent risk factor for cardiovascular events and adverse pregnancy outcomes. The evidence linking indices of obesity and vascular dysfunction is mixed. As an example, some data suggest that adiposity may be a better predictor of endothelial dysfunction than body mass index (BMI). The aim of the current study is to compare the association of obesity, as evaluated by BMI, and a direct measure of body fat to biophysical parameters of vascular function including flow-mediated vasodilation and pulse wave velocity (PWV) in healthy nulliparous reproductive-age women. This is a secondary analysis of data collected as a prospective study of prepregnancy physiology in healthy, nulliparous women. Body mass index was calculated as weight (kg)/height (m²). Total and android body fat were calculated by dual-energy X-ray absorptiometry. Brachial PWV and flow-mediated vasodilation were assessed ultrasonographically. Seventy-nine women were evaluated. Mean BMI was 24.4 (5.4) kg/m², and 15% of women were obese (BMI $\geq$ 30 kg/m²). In contrast, 39% were considered to have excess adiposity, with $\geq$ 39% android body fat. Brachial PWV was associated with increased adiposity, but not obesity. We found no differences in flow-mediated dilation associated with either BMI or body fat. Adiposity may be superior to BMI in identifying women with vascular dysfunction at increased risk of adverse pregnancy outcome and cardiovascular disease. Proper identification may allow implementation of prevention strategies to improve perinatal outcomes and maternal health.

Keywords

pregnancy, obesity, endothelial dysfunction, arterial stiffness, body composition

Introduction

Over one-third of reproductive-age women are obese with a body mass index (BMI) of $\geq$ 30 kg/m², and another 25% are overweight (BMI 25-29.9 kg/m²).^{1,2} During pregnancy, maternal obesity is a risk factor for adverse perinatal outcomes including gestational diabetes, gestational hypertension and preeclampsia, macrosomia, and cesarean delivery.³⁻⁵ Preeclampsia, in particular, is associated with significant maternal morbidity and contributes to 15% of premature births.⁶

In addition to traditional cardiovascular risk factors, including obesity, hypertension, and smoking, other factors, such as markers of endothelial dysfunction and vascular stiffness, are increasingly being recognized as independent risk factors for cardiovascular events in both nonpregnant and pregnant individuals. As a marker of vascular dysfunction, arterial stiffness describes the reduced capability of an artery to expand and contract in response to pressure change.⁷ Pulse wave velocity (PWV) is the gold standard for noninvasive measurement of arterial stiffness.^{7,8} Numerous studies have shown the independent predictive value of PWV on risk of coronary artery disease, stroke, cardiovascular, and all-cause mortality in nonpregnant adult populations.⁸⁻¹² Adverse pregnancy outcome, notably hypertension and preeclampsia, is also more

common in women with elevated PWV measured prior to conception¹³ or in the midtrimester.¹⁴ Additionally, van der Graff et al recently have shown that women with a history of early-onset preeclampsia have impaired vessel stiffness compared to women with prior uncomplicated pregnancy at 4 to 5 years postpartum.¹⁵ Endothelial function can be quantified by flow-mediated dilation (FMD). The FMD refers to the change in arterial diameter in response to a blood flow stimulus.¹⁶ Brachial FMD is inversely related to future cardiovascular events in nonpregnant adults.^{16,17} A recent systematic review found that compared to women without preeclampsia, those whose pregnancy was complicated by preeclampsia had lower FMD prior to the onset of preeclampsia, at diagnosis, and within 3 years postpartum.¹⁸

Evidence from studies examining the relationship between endothelial dysfunction, arterial stiffness, and BMI have been

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varied, with some studies showing an association and others not.^{12,19–21} Markers of central obesity, including waist circumference and body fat (BF) percentage, however, have been shown to be better predictors of arterial stiffness than BMI in some at-risk populations.^{12,22–24} The association of FMD and obesity is less well studied, especially in adults. Understanding the association between BMI, BF, and vascular function in young women prior to conception could enable improved pregnancy risk stratification and potentially allow for the initiation of risk-reducing strategies to improve pregnancy outcome. The aim of this study is to compare the association of obesity and BF with arterial stiffness and FMD in healthy nulliparous reproductive-age women.

Materials and Methods

Participants

The institutional review board of the University of Vermont approved this study. Healthy nulligravid women were recruited as part of a prospective trial characterizing the association of prepregnancy and late pregnancy maternal physiology between November 2010 and June 2014. Eligible participants were intending a first pregnancy within the next year and were 18 to 42 years of age with self-reported regular menstrual cycles (every 26–35 days). Women were excluded if they had hypertension, type 2 diabetes mellitus, autoimmune disease, or other major medical conditions. Written informed consent was obtained from each participant. For the current analysis, study participants were evaluated during the follicular phase of their menstrual cycle following a 3-day calorie- (based on weight), sodium- (3500 mg), and potassium- (3500 mg) controlled meal plan that was supplied to the participants followed by an overnight fast. Additionally, patients were instructed to refrain from the use of nonsteroidal anti-inflammatory medications and decongestants for 48 hours and caffeine and alcohol for 24 hours prior to the study.

Data Collection

All measurements were performed in the Clinical Research Center at the University of Vermont. Body mass index was calculated as weight in kilograms divided by the square of the height in meters, with a BMI ≥ 30 kg/m² considered obese.²⁵ Dual-energy X-ray absorptiometry (DXA) scans were performed to estimate total and android BF and body surface area (BSA). As there is no standard definition of “excess” adiposity, we applied the predicted %BF corresponding to BMI published by Gallagher et al and defined $\geq 33\%$ BF consistent with an overweight BMI and $\geq 39\%$ BF consistent with an obese BMI.²⁶ Blood pressure was measured using continuous noninvasive tonometric radial artery blood pressure monitoring (Finometer Pro; Finapres, Amsterdam, the Netherlands) in the seated position following a period of rest. All ultrasound measurements were obtained with a GE Vivid 7 ultrasound machine (GE Healthcare, Milwaukee, Wisconsin) and have

been previously described.^{27–29} Doppler echocardiography was used to determine baseline cardiac output. Cardiac index was calculated as cardiac output divided by BSA. Brachial pulse waveforms were obtained by Doppler ultrasound using either a 3.5-sector or a 10-MHz linear transducer. Time from electrocardiogram R wave to systolic flow in the brachial artery was used to determine PWV. The distance from the heart to the brachial artery was calculated post hoc as height $\times 0.33$, as described previously. Uterine blood flow was assessed using color Doppler ultrasound with an 8.0-MHz transvaginal transducer at the level of the internal cervical os. The calculation of FMD has been previously described. Briefly, baseline brachial artery diameter was established 2 finger breadths above the antecubital fossa under direct visualization with ultrasound. Brachial artery constriction was accomplished by inflating a sphygmomanometer to 60 mm Hg above systolic blood pressure across the distal extremity. After a period of 5 minutes, the cuff was deflated and brachial artery diameter was measured at 10-second intervals between 40 and 90 seconds postdeflation. Flow-mediated dilation was calculated as the difference in diameters divided by the baseline diameter and reported as percentage of FMD.

Statistical Analysis

Descriptive statistical methods were used to describe the characteristics of the study population. Confidence intervals were used to estimate cardiovascular outcomes for women with excess adiposity ($\geq 39\%$) and those with lean adiposity ($<33\%$). The *t* tests were used to test for differences in cardiovascular outcomes between these 2 groups. Correlation and linear regression analyses were performed to evaluate and compare the relationship between the predictor variables, BMI and % BF, and the outcome variable, PWV. Regression analyses are reported as unadjusted and while adjusting for maternal age and mean arterial pressure. A scatterplot demonstrating the relationship between BMI and %BF was created using unadjusted values; however, regression analyses were run using both raw and transformed values for BMI to account for non-normality and nonlinearity.

Results

Seventy-nine healthy nulligravid women were consented and enrolled in the study. Participant characteristics are listed in Table 1. The mean BMI was 24.4 kg/m², with 25 (32%) participants categorized as overweight or obese (BMI ≥ 25 kg/m²) and 15% categorized as obese with a BMI ≥ 30 kg/m². The mean total and android BF measured by DXA was 35.7% and 38.3%, respectively. Of the study population, 58% and 63% were characterized as having excess adiposity, defined as total and android BF $\geq 33\%$, respectively, while 37% and 43% had a total or android BF $\geq 39\%$, respectively. Both BMI and android BF were strongly correlated ($r = .80$, $P < .001$; Figure 1). The upper left quadrant of this figure is noteworthy and identifies women with a healthy BMI but excess android adiposity.

Table 1. Patient Characteristics.^a

Variable	N = 79
Age, years	30.6 (4.3)
Menstrual cycle, days	9.4 (3.4)
Body mass index, kg/m ²	22.5 (20.7, 26.7)
Obese by BMI (≥ 30 kg/m ²), n (%)	13 (15)
% Android body fat	38.3 (12.1)
Obese by android body fat ($\geq 39\%$), n (%)	34 (39)
% Total body fat	35.7 (9.2)
Obese by total body fat ($\geq 39\%$), n (%)	29 (33)
Body surface area, m ²	1.7 (0.2)
Pulse, bpm	66.1 (8.7)
Systolic blood pressure, mm Hg	116.7 (12.5)
Diastolic blood pressure, mm Hg	69.8 (7.2)
Mean arterial pressure, mm Hg	88.4 (7.4)
Cardiac output, L/min	4.5 (1.0)
Cardiac index, L/min/m ²	2.6 (0.5)
Uterine blood flow, mL/min	39.9 (21.9)
Brachial pulse wave velocity, m/s	4.2 (0.5)
Brachial flow mediated dilation, % dilation change	11.9 (10.8)

Abbreviation: BMI, body mass index.

^aData are expressed as mean (standard deviation) or median (interquartile range) unless otherwise specified.

Figure 1. Relationship between body mass index and percentage of android body fat.

Hemodynamic parameters and vascular function were compared in healthy weight and obese women and in those with lean ($<33\%$) and excess ($\geq 39\%$) android BF. Pulse, systolic, diastolic, and mean arterial pressure and cardiac output are all higher in obese compared to healthy weight nulliparous women (Table 2A), with no differences noted in brachial PWV or flow-mediated vasodilation. When android BF was evaluated instead of BMI, pulse and cardiac output remained significantly elevated in those with excess adiposity. Additionally, brachial PWV was significantly elevated in otherwise healthy women with excess compared to lean android BF (Table 2B). Systolic, diastolic, and mean arterial blood pressure, cardiac index, brachial flow-mediated vasodilation, and uterine blood flow did not differ between the groups. Similar findings were noted when adiposity was defined as total BF (data not shown).

Brachial PWV appears to be differentially affected by obesity and adiposity. Android BF more strongly correlates with brachial PWV than BMI (Table 3). Android BF accounts for 8% of the variability in brachial PWV. Neither android BF nor BMI was strongly associated with brachial FMD. Results were unchanged when adjusting for maternal age and mean arterial pressure.

Discussion

In our population of healthy nulliparous women, PWV, as a marker of arterial stiffness, was more strongly correlated with prepregnancy BF than with BMI. This finding is consistent with data from the Elderly Health, Aging, and Body Composition study, a large prospective cohort study, which showed that compared to other measures of BF, aortic PWV was most strongly associated with abdominal visceral fat, independent of body weight.³⁰ Similar findings were shown in middle-aged adults; markers of central obesity including waist circumference, waist to hip ratio, waist to height ratio, and visceral fat mass were more strongly associated with PWV than BMI.^{12,24} Other cross-sectional studies however have failed to show correlation between PWV and BMI or waist circumference.^{21,31} These studies involved older men and women including smokers and those with comorbidities including hypertension and diabetes. To our knowledge, this is the first study showing a stronger association of BF over BMI with arterial stiffness in a young, healthy, low-risk population. Our results are consistent with other studies showing increases in pulse and cardiac output with increasing obesity (as measured by either BMI or BF).^{32,33}

In our population, flow-mediated vasodilation, as a marker of vascular function, was not associated with BF or BMI. This is consistent with at least 1 study³⁴ but contrary to the large Framingham Heart Study which showed an independent relationship between BMI and brachial FMD as well as smaller cross-sectional studies showing correlations between abdominal obesity and FMD.³⁵⁻³⁹ Our lack of association may be due to our smaller numbers or due to our population being studied.

Of interest, blood pressure was not significantly different based on adiposity; however, obese women (as measured by BMI) had higher systolic, diastolic, and mean arterial pressures than healthy weight women. Given the association of adiposity with PWV, it is somewhat surprising that blood pressure was not different between the 2 groups. This difference in association may reflect the pattern noted in Figure 1 where an obese BMI is also associated with the highest levels of android adiposity, but where elevated adiposity can be associated with a nonobese BMI. As our definition of increased adiposity includes many with nonobese BMI, this subset may represent an intermediate group where the strength of the current association with elevated blood pressure is dampened.

Body mass index is the most commonly used measure to define obesity, as it is a simple, noninvasive method and is used extensively both in clinical practice and as a research tool. However, BMI is unable to distinguish between fat and lean

Table 2. Comparison of Cardiovascular Measures.^a

A. Excess ($\geq 39\%$) versus lean ($<33\%$) android adiposity			
Variable	Excess Adiposity, 34 (43%)	Lean Adiposity, 29 (37%)	P Value
Pulse, bpm	69.1 (66.1-72.1)	61.7 (58.8-64.5)	.001
Systolic blood pressure, mm Hg	119.2 (113.2-125.1)	114.4 (111.6-116.9)	.151
Diastolic blood pressure, mm Hg	71.1 (68.5-73.7)	68.5 (65.6-71.4)	.179
Mean arterial pressure, mm Hg	89.8 (87.0-92.6)	86.8 (84.2-89.5)	.126
Cardiac output, L/min	4.8 (4.4-5.2)	4.2 (3.9-4.5)	.018
Cardiac index, L/min/m ²	2.5 (2.4-2.7)	2.6 (2.4-2.8)	.669
Uterine blood flow, mL/min	38.8 (31.5-46.2)	38.7 (29.3-48.1)	.977
Brachial pulse wave velocity, m/s	4.4 (4.2-4.5)	4.1 (3.9-4.2)	.014
Brachial flow mediated dilation, % dilation change	12.8 (9.1-16.4)	11.0 (6.3-15.8)	.554
B. Obese ($\geq 30\%$) Versus Healthy ($<25\%$) Body Mass Index (BMI)			
Variable	Obese BMI, 13 (15%)	Healthy BMI, 54 (62%)	P Value
Pulse, bpm	71.5 (67.4-75.5)	64.1 (61.8-66.4)	.005
Systolic blood pressure, mm Hg	126.5 (112.2-140.8)	114.2 (112.2-116.2)	.002
Diastolic blood pressure, mmHg	74.6 (70.5-78.8)	68.2 (66.4-70.0)	.003
Mean arterial pressure, mm Hg	92.9 (88.4-97.5)	86.8 (85.0-88.6)	.005
Cardiac output, L/min	5.3 (4.6-6.1)	4.3 (4.1-4.5)	$<.001$
Cardiac index, L/min/m ²	2.6 (2.2-2.9)	2.6 (2.5-2.7)	.981
Uterine blood flow, mL/min	34.1 (22.1-46.2)	39.5 (33.7-45.3)	.411
Brachial pulse wave velocity, m/s	4.4 (4.1-4.7)	4.1 (4.0-4.2)	.067
Brachial flow-mediated dilation, % dilation change	16.9 (8.8, 25.0)	11.8 (8.6, 15.0)	.168

^aResults are reported as mean (95% confidence interval).

Table 3. Simple Linear Regression Models.

Predictor Variable	Coefficient (95% CI)	r	P Value
Outcome variable: Brachial pulse wave velocity			
% Android body fat	0.011 (0.003 to 0.020)	.29	.011
BMI	0.016 (−0.004 to 0.036)	.17	.124
Outcome variable: Brachial flow mediated dilation			
% Android body fat	0.066 (−0.144 to 0.277)	.08	.531
BMI	0.197 (−0.276 to 0.669)	.10	.409

Abbreviations: BMI, body mass index; CI, confidence interval.

body mass and is overestimated in individuals with increased muscle mass. A recent systematic review reported that BMI has poor sensitivity (50%) in identifying excess adiposity, that is, many individuals with a healthy BMI may be at risk of adverse outcome due to increases in BF that are not accurately reflected in their BMI.⁴⁰ Dual-energy X-ray absorptiometry has emerged as a simple, safe, and accurate modality to noninvasively measure total and regional lean and fat mass.⁴¹⁻⁴⁴ By comparing the differential attenuation of 2 energies, DXA can estimate fat mass, lean body mass, and bone mass and is associated with negligible radiation exposure.^{43,45} The use of DXA for measuring body composition has shown validity across BMI groups^{44,46} and is used in many clinical settings.⁴⁷ There are limitations, however. The DXA relies on the assumption of a constant lean mass, but this likely varies based on hydration and disease status. Additionally, trunk composition, relative to limb composition, relies more on predicted than actual

measurements.⁴⁸ In our population of young healthy women, DXA likely provides a reliable estimate of body composition.

Numerous studies have shown an independent association between PWV and cardiovascular events including coronary artery disease, stroke, and mortality in low- and high-risk non-pregnant populations.^{8,9,49} A large systematic review and meta-analysis pooled the results of 17 longitudinal studies evaluating PWV. These heterogeneous studies included middle-aged to elderly adults with varying comorbidities including diabetes, hypertension, and end-stage renal disease and showed an approximately 2-fold increased risk in cardiovascular events, cardiovascular mortality, and all-cause mortality in those individuals with a high compared to low aortic PWV.¹¹

In uncomplicated pregnancies, PWV decreases through the midtrimester, then rises until term.^{14,50} In previous work, we have shown that PWV is decreased postpartum compared to prior to pregnancy, suggesting a persistent remodeling effect of

pregnancy.²⁸ A 2012 systematic review and meta-analysis concluded that preeclampsia is associated with increased arterial stiffness both during and after pregnancy, up to 4 years postpartum.⁵⁰⁻⁵³ This trend was persistent at 10 years postpartum.⁵⁴ Ostlund et al, however, found that FMD, while decreased at 1 year postpartum in pregnancies complicated by preeclampsia compared to those without preeclampsia, normalized to match that of uncomplicated pregnancies at 11 years.⁵⁵ Longitudinal studies have been undertaken in an attempt to examine the predictive value of arterial stiffness on pregnancy outcome. Khalil et al identified women at high risk of developing preeclampsia (as identified by first trimester screening) and longitudinally measured brachial PWV and augmentation index beginning in the first trimester. Their results examine changes in hemodynamic parameters across gestation and showed that compared to women who remain normotensive, those who develop preterm preeclampsia have significantly higher PWV and augmentation index beginning in the first trimester and persisting throughout gestation.^{13,14} To our knowledge, our group was the first to observe an increase in PWV measured prior to conception in young, healthy nulligravidas who subsequently developed preeclampsia,¹³ suggesting that a prepregnancy phenotype of increased arterial stiffness may contribute to risk assessment for hypertensive disorders of pregnancy.

The strength of the current study is that it encompasses a group of young, healthy women. Cardiovascular measurements were performed rigorously in a clinical research center. Our study, however, is not without limitations. First, a standard definition of excess adiposity does not exist with regard to outcome. We believe our chosen BF percentile values corresponding to overweight and obese BMI are clinically relevant, but further study is needed to determine thresholds of BF that correspond to increased risk of disease. Brachial PWV was measured for convenience, but it is unknown which peripheral vessel may be most predictive of arterial stiffness and subsequent disease. Additionally, it may not be feasible or cost-effective to obtain DXA scans on a large population of women, especially prior to pregnancy, and DXA scans are not performed during pregnancy. Evaluation of other methods of determining BF should be explored and correlated with outcome. For example, waist to hip ratio is a simple noninvasive technique, and abdominal obesity has been associated with cardiovascular disease and all-cause mortality.⁵⁶ Finally, the overall cohort had a relatively low BMI, with only 16% of the population categorized as obese. This may limit the generalizability of results.

Ample evidence supports an increased risk of subsequent development of cardiovascular disease in women who develop preeclampsia during pregnancy.⁵⁷ It has been suggested that this increase in risk is mediated by changes in vascular hemodynamic properties and endothelial function as measured by arterial stiffness.⁵³ While maternal obesity is a risk factor for pregnancy complications and cardiovascular disease, BF may have advantages over BMI in predicting arterial stiffness, preeclampsia, and subsequent cardiovascular disease and may identify an at-risk group that has previously received little attention.

Declaration of Conflicting Interests

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