

PAPER

Insulin resistance but not visceral adipose tissue is associated with plasminogen activator inhibitor type 1 levels in overweight and obese premenopausal African-American women

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OBJECTIVE: To compare plasma plasminogen activator inhibitor type 1 (PAI-1) levels and to examine the association of PAI-1 with visceral adiposity and other components of the metabolic syndrome in overweight and obese premenopausal African-American (AA) and Caucasian (CC) women.

DESIGN: Cross-sectional study.

SUBJECTS: 33 CC and 23 AA healthy, overweight and obese, premenopausal women (age 19–53y, body mass index 28.1–48.9 kg/m²).

MEASUREMENTS: Body mass index, sagittal diameter, waist circumference, percentage body fat, visceral and subcutaneous adipose tissue (by anthropometry, magnetic resonance imaging (MRI), and bioelectric impedance techniques), PAI-1, leptin, lipids, glucose, insulin, and insulin resistance (by HOMA IR).

RESULTS: AA women had lower triglyceride levels and less visceral adipose tissue (VAT) volume than CC despite similar BMI. PAI-1 levels were not significantly different in the two groups. Insulin resistance was associated with PAI-1 in both groups but only in CC women were VAT, triglyceride, HDL cholesterol and blood pressure related to plasma PAI-1 levels. Multiple regression analysis showed that VAT in CC and insulin resistance in AA were independent predictors of PAI-1.

CONCLUSION: VAT is significantly associated with circulating PAI-1 levels in overweight and obese CC but not AA premenopausal women.

International Journal of Obesity (2003) 27, 82–87. doi:10.1038/sj.ijo.802192

Keywords: visceral adipose tissue; insulin resistance PAI-1; premenopausal women; fibrinolysis; metabolic syndrome

Introduction

It is well established that obesity in general and central obesity in particular increases the risk of cardiovascular disease.^{1,2} Central obesity is strongly linked to insulin resistance in Caucasian populations, and it tends to cluster with a variety of abnormalities that impact on cardiovascular risk, such as hypertension, hyperinsulinemia, dyslipidemia, and glucose intolerance.³ This constellation of findings is known as the Metabolic Syndrome, which is also associated with

impaired fibrinolysis characterized by elevated plasma plasminogen activator inhibitor type 1 (PAI-1) levels. PAI-1 is considered a potential link between central obesity, insulin resistance and cardiovascular disease.^{4,5} It is consistently elevated in obese individuals, and it correlates with each component of the Metabolic Syndrome, and in particular with insulin levels, central adiposity and triglycerides.^{6–14} It has been recently demonstrated *in vitro* that adipose tissue, and especially omental fat, secretes significant amounts of PAI-1,^{15–18} suggesting that visceral adipose tissue (VAT) may be an important contributor to PAI-1 levels in obese, insulin-resistant individuals. Whether the association between central obesity and elevated PAI-1 levels is a direct one related to the excess adipose tissue or an indirect one reflecting the link between visceral adiposity and insulin resistance is unclear.

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Received 2 April 2002; revised 25 July 2002;

accepted 13 August 2002

The prevalence of obesity among ethnic groups is highest in African-American (AA) women.^{19,20} Although anthropometric data from population studies suggest that obese AA women tend to have a more central distribution of fat than Caucasian (CC) women,^{21–23} the present authors and others have shown that AA women have less visceral fat than CC women of similar body mass index (BMI).^{24–26} Furthermore, ethnic differences in the relation of body fat distribution to insulin resistance and lipids have been shown in some but not all studies, suggesting a difference in the metabolic impact of VAT between AA and CC women.^{24,27–29} The majority of studies examining the relationship of PAI-1 with its associated metabolic disturbances have been conducted in CC populations. Although clinically evident cardiovascular disease in women occurs predominantly in post-menopausal individuals, it is believed that the origins of atherosclerosis occur earlier in life. Thus an understanding of mechanisms underlying cardiovascular risk in premenopausal women may be important to prevention of future disease. To our knowledge, there are no studies comparing the relationships between PAI-1 and metabolic risk factors in obese AA vs CC premenopausal women; therefore, we studied overweight and obese premenopausal AA and CC women to compare PAI-1 levels and to examine the relationship between PAI-1, body fat distribution, and other components of the metabolic syndrome in both ethnic groups.

Methods

Subjects

Thirty-three CC and 23 AA overweight and obese premenopausal women were evaluated. This group was a subset of women who participated in a study previously reported by us.²⁴ All subjects had a BMI greater than 25.0 kg/m², were in good health, and were not taking any medications known to affect blood pressure, carbohydrate or lipid metabolism. Both parents and both grandparents had to be of the same racial descent for the subject to be considered CC or AA. All subjects gave their written informed consent before participation, and the study was approved by the institutional review board of the University of Miami.

Anthropometry

Body weight was measured to the nearest 0.1 kg and height to the nearest 0.5 cm. BMI was calculated as body weight divided by height² (kg/m²). Waist circumference was measured midway between the lower rib margin and iliac crest. Sagittal abdominal diameter (SD) was measured in a reclining position with an anthropometer placed in the same position as that used to determine waist circumference. All anthropometric measurements were performed by the same investigator. Body composition analysis was performed using bioelectrical impedance techniques (RJL System, Clinton Township, MI, USA). Values recorded were entered into a gender- and obesity-specific equation reported by Segal *et al*.^{30,31}

Blood pressure

After an overnight fast, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken after subjects were in a seated position for a 5 min interval. Duplicate blood pressure measurements were taken from the left upper arm, averaged, and recorded to the nearest 2.0 mmHg with a 5 min interval separating measurements.

Laboratory measurements

Blood was drawn from the antecubital vein after a 12 h fast. Glucose was measured by a glucose oxidase method (Cobas Mira analyzer). Insulin was determined by radioimmunoassay with reagents obtained from Diagnostic Products, Los Angeles, CA, USA. Relative insulin resistance was expressed by the homeostatic model assessment HOMA IR (fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5).³² Total cholesterol and triglycerides were measured enzymatically using commercial kits (Roche Diagnostics). HDL cholesterol was measured after precipitation of the apo B-containing lipoproteins with dextran-sulfate and LDL cholesterol was calculated according to the formula of Friedewald *et al*.³³ Leptin concentrations were measured by radioimmunoassay (Linco Products). PAI-1 levels were determined by radioimmunoassay with reagents obtained from American Bioproducts Company (Parsippany, NJ, USA).

Magnetic resonance imaging

The abdominal region was examined using magnetic resonance imaging (MRI) with a 1.5 T instrument (Siemens Medical Systems, Insulin, NY, USA). Spin-echo imaging was performed using a T₁-weighted sequence with 147 ms repetition time and 4.8 ms echo time. Slice thickness was 10 mm with a 2.5 mm inter-slice gap. A total of seven slices was obtained in each subject with the central slice of the acquisition centered at the L4–L5 disc level. Acquisition time was 26 s using this imaging sequence, enabling imaging to be performed during a single breath hold. Once obtained, MRI data were stored on magnetic tape and transferred to a stand-alone Silicon Graphics (Indy) workstation (Silicon Graphics Mountain View, CA, USA) using specially designed image analysis (Tomovision Inc., Montreal, Quebec).³⁴ The VAT was defined as adipose tissue contained within the boundaries of the rectus abdominis, internal obliquus, quadratus lumborum and long back muscles. The subcutaneous adipose tissue (SAT) was defined as the adipose tissue located between the skin and this group of muscles. The VAT volume was computed by summing the VAT area in each slice multiplied by the nominal slice thickness of 10 mm and converting to liters. The SAT volume was computed using the identical technique.

Diet and physical activity

Subjects were asked to keep a 3 day food log typical of their eating habits for one weekend day and two week days during

the week proceeding testing. Nutrient and alcohol intakes were analyzed by using a computerized analysis system (Dine Health Systems 1994). Subjects were administered the College Alumnus Questionnaire to assess their participation in sports, recreational activities and every day physical activities. Subjects were also required to record the average number of cigarettes smoked daily.

Data analysis

Descriptive statistics are presented as mean \pm s.d. Differences between ethnic groups were assessed using Student's *t*-test for unpaired samples. Logarithmic transformation of triglycerides and square root transformation of PAI-1 was performed in order to normalize the distribution of these variables. Pearson's correlation coefficients, and partial correlation coefficients of PAI-1 with body fat distribution and metabolic variables adjusted by age and fat mass were calculated. To evaluate the independent association of PAI-1 with selected variables, multiple regression analysis was performed with PAI-1 as the dependant variable. Analysis was carried out separately for each ethnic group. A *P*-value of 0.05 was considered significant. All statistical evaluations were performed using Statistix software in an IBM personal computer.

Results

The characteristics of the CC women are compared to those of the AA in Tables 1–3. CC women were older, had higher triglyceride levels and despite similar BMI, had more VAT

Table 1 Clinical features

	Caucasian (n = 33)	African-American (n = 23)
Age	41.7 \pm 7.2	36.7 \pm 9.5*
BMI (kg/m ²)	34.5 \pm 5.0	34.3 \pm 4.1
Fat mass (kg)	42.5 \pm 9.5	40 \pm 8.7
Body fat (%)	44.8 \pm 3.0	44.3 \pm 2.8
SBP (mmHg)	125.7 \pm 14.5	121.0 \pm 11.1
DBP (mmHg)	81.1 \pm 9.9	81.1 \pm 7.7
Smokers (n)	6	3

Mean values \pm s.d.; **P* < 0.05.

Table 2 Regional fat distribution

	Caucasian (n = 33)	African-American (n = 23)
Sagittal Diameter (cm)	23.7 \pm 5.0	22.6 \pm 3.0
Waist Circumference (cm)	105.8 \pm 13.6	99.3 \pm 10.6
SAT area (cm ²)	475.4 \pm 120.8	451.6 \pm 137.4
SAT volume (ml)	4523 \pm 1140	4262 \pm 1365
VAT area (cm ²)	125.2 \pm 53.5	75.6 \pm 29.6***
VAT volume (ml)	1178 \pm 480	700 \pm 246***

Mean values \pm s.d.; ****P* < 0.001.

Table 3 Metabolic features

	Caucasian (n = 33)	African-American (n = 23)
Total cholesterol (mmol/l)	5.2 \pm 1.2	5.0 \pm 1.4
Triglycerides (mmol/l)	1.58 \pm 0.4	1.03 \pm 0.4**
HDL-Cholesterol (mmol/l)	1.45 \pm 0.4	1.43 \pm 0.3
LDL-Cholesterol (mmol/l)	2.94 \pm 1.3	3.11 \pm 1.5
Fasting glucose (mmol/l)	4.8 \pm 0.6	4.8 \pm 0.4
Fasting insulin (pmol/l)	102.6 \pm 58.8	104.0 \pm 40.9
HOMA IR	3.0 \pm 1.8	3.1 \pm 1.4
Leptin (ng/ml)	36.4 \pm 13.1	38.2 \pm 17.7
PAI-1 (ng/ml)	44.8 \pm 29.0	48.1 \pm 32.1

Mean values \pm s.d.; ***P* < 0.01.

area and volume. Percentage body fat, total fat mass, SAT area and volume, and SD were similar in the two groups. There was a trend for waist circumference to be higher in CC women (*P* = 0.051). There were no significant differences in PAI-1, insulin, glucose, and HOMA IR values between the two groups. The groups were also comparable in physical activity and nutrient intake (data not shown). Table 4 shows the Pearson's correlation coefficients and the partial correlation coefficients adjusted for age and fat mass of PAI-1 with various metabolic and adiposity variables. In univariate correlation analysis PAI-1 correlated significantly in both groups with HOMA IR and fasting insulin. In CC women, PAI-1 was linearly related to glucose, SBP, DBP, triglyceride, HDL, fat mass, waist circumference, SD and VAT. In AA women, however, there was no significant association between PAI-1 and any of these variables. Figure 1 shows the relationship of PAI-1 with HOMA-IR, VAT volume and triglyceride levels within each race. After adjusting for age

Table 4 Pearson correlation coefficients (*r*) and partial correlation coefficients adjusted for age and fat mass (partial *r*) between PAI-1 and selected variables

	Caucasian (n = 33)		African-American (n = 23)	
	<i>r</i>	Partial <i>r</i>	<i>r</i>	Partial <i>r</i>
Fat mass	0.39*	—	0.15	—
SD	0.48**	0.36	0.34	0.37
WC	0.45**	0.26	0.30	0.28
VAT volume	0.47**	0.38*	0.18	0.18
VAT area	0.45**	0.35	0.18	0.20
SAT volume	0.24	0.25	0.07	−0.16
SAT area	0.24	0.23	0.02	−0.30
Leptin	0.34	0.13	0.11	0.01
SBP	0.44*	0.34	−0.13	−0.14
DBP	0.46*	0.37*	−0.20	−0.22
Triglycerides	0.47**	0.46**	0.10	0.08
HDL	−0.50**	−0.42*	−0.34	−0.36
Glucose	0.39*	0.39*	0.27	0.25
Insulin	0.38*	0.18	0.60**	0.64**
HOMA IR	0.42*	0.26	0.59**	0.62**

P* < 0.05; *P* < 0.01.

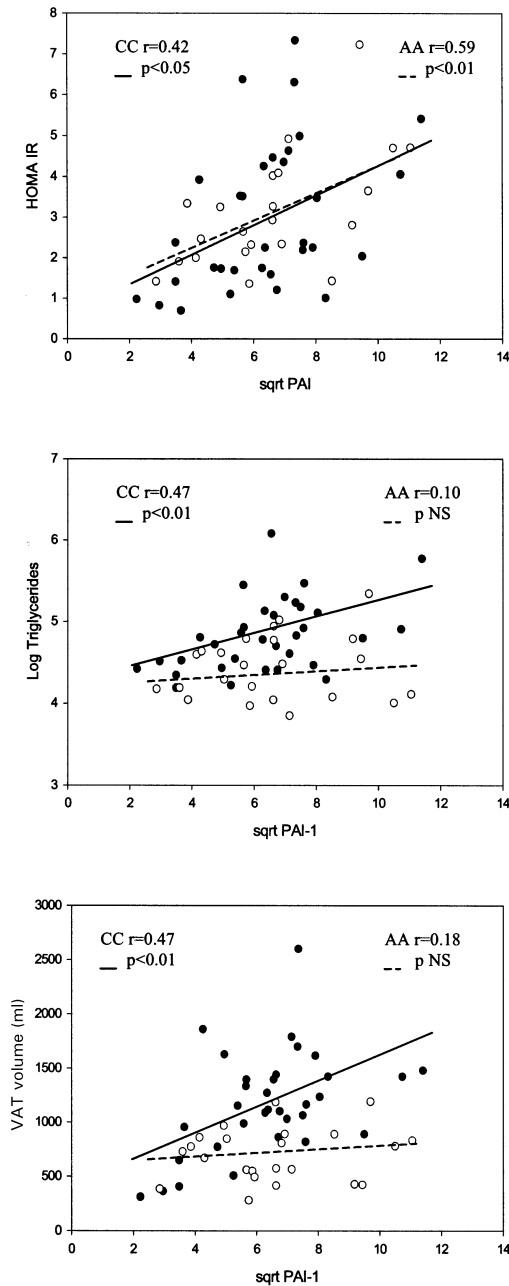


Figure 1 Relationships between PAI-1 and HOMA IR, VAT volume, and triglyceride levels in Caucasian (●) and African-American (○) women.

and fat mass in CC women, VAT volume, DBP, triglyceride, HDL cholesterol and glucose remained significantly associated with PAI-1 while the relationship of PAI-1 with insulin and HOMA-IR was lost. In AA women adjusting for age and fat mass did not affect the association of PAI-1 with HOMA-IR and fasting insulin. In multiple regression analysis (Table 5), VAT volume was an independent predictor of PAI-1 after adjusting for the effect of age, HOMA-IR, glucose, and

Table 5 Multiple regression models for the prediction of PAI-1 in Caucasian women (model r^2 0.45) and in African-American women (model r^2 0.40)

Independent variable	Estimated β	P
<i>Caucasian women</i>		
Age	-0.2	0.07
VAT volume	0.006	0.01
HOMA IR	-0.84	0.22
Triglyceride	2.36	0.19
Glucose	0.17	0.06
<i>African-American women</i>		
Age	0.03	0.78
VAT volume	0.04	0.36
HOMA IR	2.56	0.02
Triglyceride	-0.28	0.92
Glucose	-0.12	0.52

triglyceride levels in CC women. In AA women in the same multiple regression model, HOMA-IR was the only predictor of PAI-1 and it explained 30.6% of the variance of PAI-1.

Discussion

There is growing evidence that PAI-1 has a role in atherothrombotic vascular disease. A high plasma PAI-1 concentration is considered part of the metabolic syndrome and visceral adiposity appears to be particularly relevant in the link between PAI-1 and insulin resistance in CC populations. In this study we show that overweight and obese premenopausal AA and CC women of similar BMI had comparable PAI-1 levels despite significantly less VAT in the AA women. In both groups PAI-1 was associated with insulin levels and insulin resistance determined by HOMA IR. However, there were ethnic differences in the relationship between PAI-1 and the other components of the metabolic syndrome. We found a lack of association of plasma PAI-1 levels with parameters of general and visceral adiposity, blood pressure and lipids in AA women, whereas these associations were significant in the CC women.

A link between PAI-1 and insulin resistance in obesity was described more than 10y ago.⁹ Our results are consistent with those of several population studies that show a positive association between fasting insulin and plasma PAI-1 levels.⁶⁻⁸ The mechanisms underlying the elevated PAI-1 levels in obesity and insulin resistance have not been elucidated. Potential sources for the excess circulating PAI-1 include endothelial cells, hepatocytes and adipocytes. Insulin increases the expression of PAI-1 in hepatocytes and arterial endothelial cells *in vitro*.^{35,36} However, infusion of insulin failed to raise PAI-1 levels *in vivo*.³⁷⁻³⁹ It is therefore unclear if insulin resistance is related to PAI-1 through a direct effect of hyperinsulinemia or via its associated metabolic disturbances.

We found that the volume of VAT was independently associated with PAI-1 in CC women, which is in agreement

with clinical studies in CC populations showing that visceral fat accumulation is an important predictor of PAI-1 levels in obese and nonobese men and women.^{11,12} It has recently been proposed that adipose tissue and in particular visceral fat may contribute directly to the increased circulating PAI-1 levels in obesity. PAI-1 mRNA is found in visceral and subcutaneous fat but it increased only in visceral fat during the development of obesity in a rat model.¹⁵ It has also been demonstrated that human adipocytes produce PAI-1 under cultured conditions^{16–18} and PAI-1 expression and release in adipose tissue appear to be increased in obesity.¹⁷ Several but not all studies have shown that secretion of PAI-1 from human adipocytes is greater in visceral than subcutaneous fat.^{18,40} Moreover, PAI-1 lowering in obese women after weight loss correlated with the reduction of VAT and not with changes in insulin or triglyceride levels,¹¹ supporting an important role for VAT in the regulation of circulating PAI-1 levels.

The lack of association noted between PAI-1 and visceral adiposity in AA women is, therefore, surprising and challenges this view. It may suggest that it is hyperinsulinemia and/or insulin resistance *per se* that is the major factor associated with the excess circulating PAI-1 seen with obesity in this ethnic group. In this study, AA women had significantly less VAT than CC women despite similar BMI, which is in agreement with a number of reports showing that, for a given fat mass, AA men and women have less fat in the intra-abdominal compartment than their CC counterparts.^{24–26,41} Furthermore, some studies suggest differences between AA and CC subjects in the association of abdominal adiposity with insulin resistance,²⁸ blood pressure,⁴² and cardiovascular mortality risk.⁴³ The ethnic discrepancy between PAI-1 and VAT may be related to an ethnic difference in the metabolic impact of VAT accumulation or it may be attributed at least in part to the lower volume of VAT found in AA. As we previously reported, VAT volume was not associated with HOMA IR in AA women.²⁴ However, a report involving women who were more obese than those studied here and with comparable VAT between AA and CC showed no ethnic difference in the association between VAT and insulin resistance,²⁹ arguing in favor of the concept that a lower volume of VAT in AA might play a role in the ethnic differences we found. In order to clarify this point, we examined the relationship between VAT volume and PAI-1 in CC women in the lower one half of VAT values and found a strong positive correlation ($r = 0.66$, $P < 0.01$), indicating that, at lower levels of VAT comparable to those in the AA group, VAT remained associated with PAI-1 in CC women. This favors the view that a difference in the pathophysiologic impact of VAT may exist between the two ethnic groups.

Thus, while visceral fat appears to be a major predictor of PAI-1 levels in CC, it has little impact in AA where insulin resistance seems to be the dominant associated factor. It is of interest that a lack of association also exists between PAI-1 and other components of the metabolic syndrome, namely glucose, triglyceride, HDL cholesterol and blood pressure in

AA, despite a strong relationship found between these metabolic variables and PAI-1 in CC as has been noted by others.^{13,14,44–46} This suggests that the lack of a metabolic relationship between visceral fat and PAI-1 extends in parallel fashion to other components of the metabolic syndrome in premenopausal AA women.

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