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The relationship between cardiometabolic and hemostatic variables: influence of race

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Abstract

Elevated concentrations of hemostatic variables such as fibrinogen, plasma activator inhibitor 1 (PAI-1), and tissue plasminogen activator (t-PA)/PAI-1 complex have been implicated in the pathogenesis of arterial lesion progression and subsequent cardiovascular disease. In the present study, traditional cardiometabolic variables (CMV) associated with cardiovascular disease risk were examined in relation to hemostatic variables in a group of 36 White American (WA) and 30 African American (AA) overweight/obese women. There were 9 CMV significantly related to PAI-1 and/or the t-PA/PAI-1 ratio, but not fibrinogen. A significant race effect was found for 5 CMV in relation to fibrinogen and/or the t-PA/PAI-1 ratio, but not PAI-1. Significant race and high-density lipoprotein cholesterol interactions were found for fibrinogen (P = .021); and significant race and waist to hip ratio (P = .015), diastolic blood pressure (P = .013), and insulin (P = .037) interactions were found for PAI-1. No interactions were found for the t-PA/PAI-complex. Both PAI-1 and the t-PA/PAI-1 ratio are favored above fibrinogen in the diagnostic evaluation of health risk in both WA and AA women. Because of differences by race, independent consideration should be given in the clinical management of WA and AA women presenting with elevated CMV. Our findings indicated the t-PA/PAI-1 complex to be the most global indicator of health risk in both WA and AA overweight/obese women.

1. Introduction

Hemostatic variables have received much attention because coronary thrombosis is "considered" a critical element in the pathogenesis of cardiovascular disease, myocardial infarction, and sudden cardiac death [1]. Increased concentrations of fibrinogen, plasma activator inhibitor 1 (PAI-1), and the tissue plasminogen activator (t-PA)/PAI-1 complex indicate a prothrombotic, proinflammatory state that may result in arterial lesion progression and subsequent coronary events [2,3]. Investigators have also recommended that hemostatic factors be included in the metabolic syndrome based upon their strong association with insulin resistance, hyperinsulinemia, and other traditional cardiometabolic variables (CMV) closely associated with the risk for cardiovascular disease and diabetes [4-6].

Fibrinogen is part of the coagulation cascade that is culminated in its conversion to fibrin. Fibrin is a consistent component of atherosclerotic plaque found in occluded coronary arteries and may also serve as a precipitating factor in endothelial cell injury [4]. Plasma activator inhibitor 1 is the predominant regulator of hypofibrinolytic activity [7]. Increased PAI-1 levels are associated with angiographically determined heart disease [8] and, given its association with insulin, may be considered the antecedent variable predicting diabetes [9,10]. The t-PA/PAI-1 complex is significantly correlated with PAI-1 [5] and the more traditional CMV. Because it signifies general impairment of the fibrinolytic system, investigators have recommended that t-PA/PAI-1 be included in the metabolic syndrome [2,4,5].

Given the critical role of hemostatic variables in relation to cardiovascular disease risk, diabetes, and the metabolic syndrome, it would be important to examine all variables

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simultaneously to determine if any one factor is optimal in demonstrating a significant relationship with the more established CMV. Furthermore, it would be important to conduct this study in overweight/obese individuals who possess higher hemostatic values [2,11]; in women, who have not been evaluated as extensively as men in studies of hemostatic risk factors; and in minorities, who have been typically underrepresented in the research literature. Black adults have been reported to have higher fibrinogen levels [11], yet few studies have examined CMV in relation to various indices of hemostasis in both White American (WA) and African American (AA) women. The purpose of this study was to evaluate the relationship between CMV and hemostatic variables including fibrinogen, PAI-1, and the t-PA/PAI-1 complex in a group of overweight and/or obese premenopausal WA and AA women.

2. Subjects, materials, and methods

2.1. Subjects

All subjects consisted of volunteers interested in a weight loss program. Participants were required to be premenopausal; have stable weight for a minimum of 3 months; possess a body mass index (BMI) above 25; and be free of known metabolic disease such as diabetes, hyperlipidemia, or hypertension. Subjects who were pregnant or lactating; amenorrheic; or taking medications that would affect blood pressure, carbohydrate, or lipid metabolism were excluded from the study. A total of 66 subjects (36 WA, 30 AA) met the criteria necessary for participation in the study. Subjects gave informed consent and completed all testing procedures in accordance with the Institutional Review Board guidelines for the use of human subjects at the University of Miami.

2.2. Evaluations

Nutrient intake, alcohol consumption (in grams per day), and cigarettes smoked daily were recorded using a 3-day food log and analyzed using the Dine System (Buffalo, NY, 1994).

Subjects were administered the College Alumnus Questionnaire developed by Paffenbarger et al [12] for evaluating daily physical activity.

Education experience was measured using a categorical scale of 1 to 5 modified from Rosmond et al [13].

All subjects completed the Daily Stress Inventory that has been shown to be a significant correlate of endocrine measures of stress [14].

2.3. Physical and anthropometric measurements

Body weight was measured to the nearest 0.1 kg, height was measured to the nearest 0.5 cm, and BMI was calculated as weight (in kilograms) divided by the square of height (in square meters). Waist circumference was measured using a spring tension measuring tape (Country Technology, Inc., Gays Mills, WI) midway between the lower rib margin and iliac crest. Hip circumference was measured at the outermost points of the greater trochanters [15]. The waist to hip ratio (WHR) was calculated by using waist circumference divided by hip circumference. All anthropometric measurements were performed by the same investigator who recorded the mean of the 2 measurements to the nearest 1.0 mm.

After an overnight fast, systolic and diastolic blood pressures were taken in one setting after a 5-minute rest interval. Duplicate blood pressure measurements were taken from the left upper arm, averaged, and recorded to the nearest 2.0 mm Hg with a 5-minute interval separating measurements.

2.4. Magnetic resonance imaging

The abdominal region was examined by using magnetic resonance imaging with a 1.5-T instrument (Siemens Medical Systems, Iselin, NJ). Spin-echo imaging was performed using a T1-weighted sequence with a 147-millisecond repetition time and 4.8-millisecond echo time. During a single breath hold, image thickness was 10 mm with a 2.5-mm gap between images. A total of 7 images were obtained in each subject, with the central slice of the acquisition centered at the L4-5 intervertebral disk space. The volume of visceral adipose tissue in liters was computed by summing the visceral adipose tissue area in each slice multiplied by the nominal slice thickness of 10 mm and converting to liters.

2.5. Serum measurements

Blood was withdrawn from the antecubital vein after a 12-hour fast, and serum was analyzed within 1 week of withdrawal. All serum measurements were taken while subjects were seated in a quiet position for at least 5 minutes. Total cholesterol [16], high-density lipoprotein (HDL) cholesterol [17], its subfractions [18], and triglycerides [19] were measured by the Diabetes Research Institute Lipid Laboratory, University of Miami. Serum standards used for calibration were developed by the Diabetes Research Institute and calibrated against serum samples from the Centers for Disease Control and Prevention Laboratory, Atlanta, GA. Very low-density lipoprotein cholesterol was estimated by triglycerides divided by 5, and low-density lipoprotein (LDL) cholesterol was indirectly calculated by subtracting HDL cholesterol and very low-density lipoprotein cholesterol from total cholesterol [20].

Apolipoprotein B in serum was measured by turbidimetric immunoassay using a commercially available kit (Incstar, Stillwater, MN) according to procedures outlined by the manufacturers. All apolipoprotein B procedures have been developed in accordance with the guidelines set forth by the International Federation of Clinical Chemistry.

The peak particle diameter for major LDL subfractions was determined on a gel scan based upon standards of known diameter as described by Kraus and Burke [21]. The LDL size of the predominant peak for a subject was identified as the subjects' LDL peak particle size (pps).

Fasting glucose levels were determined spectrophotometrically at a wavelength of 340 nm using a hexokinase reaction developed by Roche Diagnostic System (Nutley, NJ).

Serum insulin was measured by radioimmunoassay of serum using a Coat-A-Count insulin procedure (Diagnostic Products, Los Angeles, CA). The insulin resistance was assessed by using the homeostasis model assessment index, which divides the product of fasting insulin and glucose by 22.5 [22].

Table 1
A comparison of subject characteristics in CA and AA women using Student *t* tests for unpaired samples

	CA women (n = 36)	AA women (n = 30)	*P* [a]
Characteristics			
Age (y)	41.94 ± 7.10	37.97 ± 9.94	.063
Height (m)	1.64 ± 0.07	1.62 ± 0.06	.168
Weight (kg)	94.79 ± 15.72	91.84 ± 14.03	.427
BMI (kg/m^2)	35.12 ± 5.35	34.88 ± 4.4	.850
Resting heart rate (beats/min)	73.67 ± 11.04	76.57 ± 10.90	.289
Stress [b]	67.71 ± 21.37	69.28 ± 31.64	.815
Education [c]	2.56 ± 0.50	2.30 ± 0.66	.077
Physical activity (kcal/wk)	983.65 ± 1,033.60	892.88 ± 895.74	.723
Cigarettes (no./d)	2.11 ± 6.96	1.53 ± 5.10	.707
Alcohol	5.56 ± 13.78	2.27 ± 5.65	.226
CMV			
Waist (cm)	107.29 ± 14.50	101.03 ± 11.27	.058
WHR	0.86 ± 0.06	0.87 ± 0.08	.536
VAT (L)	1.20 ± 0.48	0.76 ± 0.30	<.001
Insulin (μU/mL)	14.84 ± 8.13	14.75 ± 5.77	.957
Glucose (mmol/L)	4.80 ± 0.57	4.76 ± 0.41	.758
IR	3.13 ± 1.81	3.20 ± 1.39	.878
Systolic blood pressure (mm Hg)	126.67 ± 14.89	123.00 ± 14.21	.313
Diastolic blood pressure (mm Hg)	82.11 ± 10.13	82.20 ± 8.70	.970
Triglycerides (mg/dL)	144.50 ± 78.44	107.77 ± 67.58	.048
Total cholesterol (mmol/L)	5.34 ± 1.32	5.14 ± 1.41	.552
HDL (mmol/L)	1.44 ± 0.42	1.45 ± 0.29	.931
HDL_2 (mmol/L)	0.36 ± 0.23	0.41 ± 0.28	.428
LDL (mmol/L)	3.10 ± 0.96	3.13 ± 1.25	.909
LDL pps (nmol/L)	27.11 ± 0.71	27.15 ± 0.57	.799
Apo B (mg/dL)	106.50 ± 29.22	102.70 ± 30.69	.609
TC/HDL	3.91 ± 1.26	3.69 ± 1.35	.488
Hemostatic variables			
Fibrinogen (mg/dL)	269.15 ± 64.48	294.87 ± 60.01 (n = 29) [d]	.137
PAI-1 (ng/mL)	44.99 ± 27.96	49.54 ± 31.88	.562
t-PA/PAI-1 complex (ng/mL)	41.76 ± 16.34	49.88 ± 18.72	.084

Values are means ± SD. VAT indicates volume of visceral adipose tissue; IR, insulin resistance calculated as (insulin × glucose)/22.5; Apo B, apolipoprotein B; TC, total cholesterol.

[a] Values obtained from a Student *t* test for unpaired samples.

[b] Graded numerically, with the higher number indicating a higher stress level.

[c] Graded on a scale of 1 to 5, with the higher number indicating a higher level of education.

[d] One outlier was excluded from the analysis.

2.6. Hemostatic measurements

Fibrinogen was measured in plasma with an enzyme-linked immunosorbent assay (ELISA) (Asserachrom Fibrinogen; Diagnostica Stago, Asnieres-Sur-Seine, France) using a sandwich method in which the signal was obtained from an antifibrinogen monoclonal peroxidase-linked antibody. Results were reported as nanograms per milliliter.

Plasma activator inhibitor 1 was measured in citrated plasma obtained after discarding the first milliliter of blood. An ELISA assay (Asserachrom PAI-1; Diagnostica Stago) was used that measured total circulating PAI-1 levels using the "sandwich" method of a monoclonal anti–PAI-1 antibody to capture antigen and a second peroxidase-linked monoclonal antibody to produce the signal. Results were reported as nanograms per milliliter.

The t-PA/PAI-1 complex was measured in citrated plasma with a sandwich ELISA (Asserachrom t-PA; Diagnostica Stago) using an anti–t-PA, peroxidase-linked monoclonal antibody to produce the signal. Results were reported as nanograms per milliliter.

2.7. Statistical analysis

All statistical analyses were completed using the Statistical Package for the Social Sciences, version 10.1 (SPSS, Chicago, IL) [23]. Means ± SD of all variables were calculated for participants. Natural log transformation was performed on triglycerides to achieve normality of distribution. Student *t* tests for unpaired samples were used to assess differences between racial groups. Because one AA woman had abnormally elevated blood glucose (3 SDs above the mean) and another AA woman had hyperfibrinogenemia [24], their values were excluded from the Student *t* test and subsequent regression analyses. Multiple regression analyses were conducted to determine whether CMV and/or race and/or a CMV by race interaction was significantly related to hemostatic variables. The CMV, race, and CMV by race interactions were entered into the regression analyses in a series of steps. If significant relationships were found, then the regression weights (*B*) and semipartial r^2 were used to report the independent contribution of each variable in that model.

Because potential confounders such as age, physical activity, nutrient intake, smoking, stress, alcohol consumption, and education were not found to be significantly related to any hemostatic variables and, in addition, did not impact findings, they were not regressed out of the regression models in all multiple regression analysis. A Pearson product-moment correlation was calculated among hemostatic variables for the whole sample and by race. An α level of $P < .05$ was used to denote significance.

3. Results

Table 1 shows the subject characteristics (means ± SD) of WA and AA women. Comparison between groups indicated

Table 2
Significant relationships between CMV and hemostatic variables only

CMV (n = 66)	Hemostatic variables					
	PAI-1			t-PA/PAI-1 complex		
	B	r^2	*P*	*B*	r^2	*P*
Waist circumference	3.630	0.102	.015		–	
BMI	8.244	0.068	.050	1.120	0.086	.025
Insulin	1.626	0.156	.002	0.732	0.089	.023
Glucose [a]		–		7.198	0.069	.050
Insulin resistance	8.402	0.218	<.001	3.809	0.125	.008
Diastolic blood pressure		–		0.760	0.148	.003
HDL cholesterol	−0.726	0.138	.005		–	
Total-HDL cholesterol	8.591	0.144	.004		–	
LDL pps	−14.801	0.099	.018	−10.521	0.136	.005

B indicates regression weight; r^2, semipartial correlation coefficient^2.
[a] One outlier was excluded from the analysis.

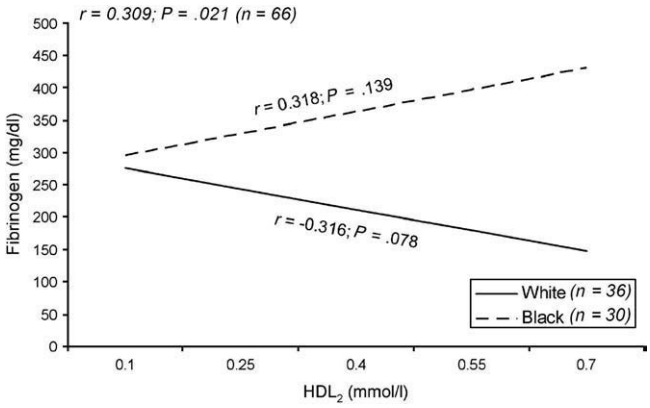

Fig. 1. Significant HDL cholesterol$_2$ by race interaction for fibrinogen (n = 66). Correlations and significance by race are also reported.

that WA women had significantly higher visceral adipose tissue and triglyceride levels than AA women ($P < .05$ for both). No other significant differences in CMV were observed between groups. Similarly, there were no differences in hemostatic variables ($P > .05$) between WA and AA women.

Table 2 shows the multiple regression results indicating significant relationships between CMV and hemostatic variables only. Waist circumference was significantly related to PAI-1, whereas BMI was significantly related to both PAI-1 and the t-PAI/PAI-1 complex. High-density lipoprotein cholesterol and the total cholesterol to HDL cholesterol ratio were significantly related to PAI-1, whereas diastolic blood pressure was significantly related to the t-PA/PAI-1 complex. Fasting glucose, insulin, and insulin resistance using the homeostasis model assessment were significantly related to both PAI-1 and the t-PA/PAI-1 complex, as was LDL pps. There were no significant relationships found between fibrinogen and any CMV; thus, fibrinogen was not included in this table.

Table 3 shows the significant CMV and/or race relationships for hemostatic variables. Results showed a significant relationship between waist circumference and race and visceral adipose tissue and race for fibrinogen. There was also a significant race effect for HDL cholesterol in relation to fibrinogen. For the t-PA/PAI-1 complex, significant waist, systolic blood pressure, and visceral adipose tissue and race effects were observed. Race, but not triglycerides, was significantly related to the t-PA/PAI-1 complex. No significant CMV and/or race relationships were observed for PAI-1; therefore, PAI-1 was excluded from this table.

Table 3
Significant relationships between CMV and/or race for hemostatic variables

CMV (n = 66)	Fibrinogen [a]			t-PA/PAI-1 complex		
	B	r^2	*P*	*B*	r^2	*P*
Waist circumference	1.451	0.073	.044	0.612	0.202	<.001
Race	43.086	0.092	.023	11.252	0.114	.010
Systolic blood pressure		–		0.479	0.128	.006
Race		–		10.315	0.091	.023
HDL	−1.106	0.053	.090		–	
Race	37.140	0.073	.045		–	
Visceral adipose tissue	0.056	0.110	.015	0.014	0.108	.012
Race	60.979	0.141	.004	14.508	0.131	.006
Triglycerides [b]		–		7.776	0.043	.122
Race		–		10.741	0.082	.031

[a] One person with hyperfibrinogenemia was excluded from the analysis.
[b] Natural log transformation was performed to achieve normality of distribution.

Fig. 1 shows the significant HDL$_2$ by race interaction for fibrinogen ($r^2 = .096$, $P = .021$). Upon further analysis, the relationship between HDL$_2$ and fibrinogen was not significant in either group; however, the directionality of the relationship was different by group. As HDL$_2$ increased in both groups of women, fibrinogen decreased in WA women yet increased in AA women, accounting for the significant interaction.

Shown in Fig. 2 is the significant insulin by race interaction for PAI-1 ($r^2 = .080$, $P = .037$). Insulin did not significantly contribute to the variance in PAI-1 in WA women ($P > .05$). In AA women, insulin contributed 36.7% to the variance in PAI-1 ($P = .002$).

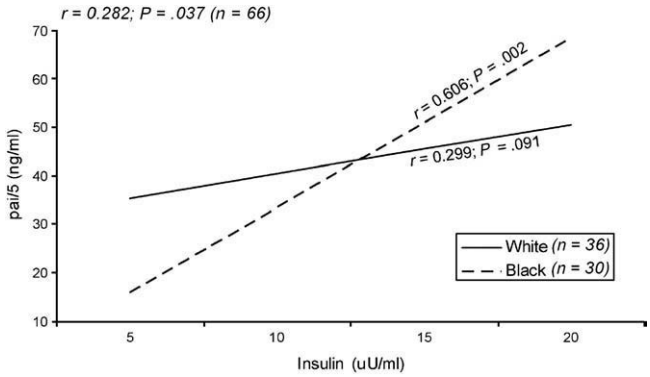

Fig. 2. Significant insulin by race interaction for PAI-1 (n = 66). Correlations and significance by race are also reported.

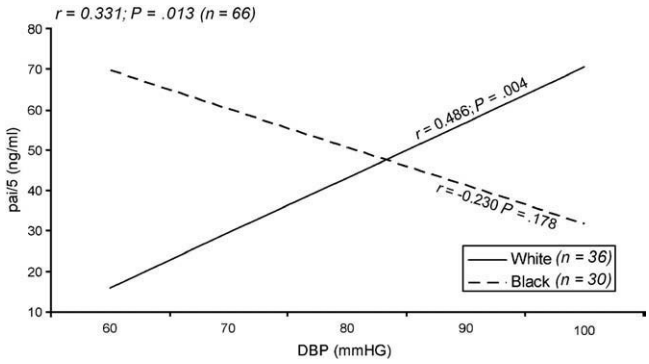

Fig. 3. Significant diastolic blood pressure by race interaction for PAI-1 (n = 66). Correlations and significance by race are also reported.

Fig. 3 shows the significant diastolic blood pressure by race interaction for PAI-1 (r^2 = .110, P = .013). Upon further examination and in WA women, diastolic blood pressure contributed to 23.7% of the variance in PAI-1 (P = .004); yet in AA women, diastolic blood pressure failed to contribute significantly to the variance in PAI-1 (P > .05).

Not presented in figure form was the significant WHR by race interaction for PAI-1 (r^2 = .106, P = .015).Upon further analysis, this relationship was not significant in WA women (P > .05), whereas in AA women, WHR accounted inversely for 26.3% of the variance in PAI-1 (P = .01). Because there were no significant interactions observed for the t-PA/PAI-1 complex, this ratio was subsequently omitted from figure form.

4. Discussion

Previous studies have linked fibrinogen, PAI-1, and the t-PA/PAI-1 complex with diabetes [9] and cardiovascular events [25-27]; however, we simultaneously examined the impact of CMV on 3 different hemostatic variables in a biracial group of young overweight/obese women.

Our findings showed lower visceral adipose tissue and triglycerides in AA compared with WA women. These results were also found in previous studies of overweight/obese WA and AA women [28,29]. It appears that lower visceral adipose tissue volume was directly responsible for the lower triglyceride levels observed in AA women. Upon comparing a subset of 13 WA and 13 AA women matched for visceral adipose tissue (within 2.0 cm^2), differences in triglycerides subsequently disappeared. In this subset of women, fibrinogen and PAI-1 were subsequently higher in AA women (P = .17 and P = .022, respectively), with a trend toward a higher t-PA/PAI-1 ratio in the same group (P = .066). Thus, the lack of significant differences in hemostatic factors between groups may have been due to the lower visceral adipose tissue found in AA women.

There were 9 CMV significantly related to PAI-1 and t-PA independent of race, thereby favoring the prediction of these hemostatic variables over fibrinogen. Interestingly, when we controlled for insulin resistance, all significant relationships with hemostatic factors were lost. Thus, in agreement with results from Potter van Loon et al [6], the relationship between CMV and hemostatic variables was modulated by insulin resistance. The mechanism underlying this relationship requires further clarification.

The influence of race was manifested in several data analyses. For example, at a given waist, HDL cholesterol, or visceral adipose tissue level, fibrinogen was always higher in AA women (Table 3). Likewise, at a given waist, systolic BP, visceral adipose tissue, and/or triglyceride level, the t-PA/PAI-1 complex was always greater in AA women. Thus, in overweight/obese women possessing similar CMV, AA compared with WA women will have higher hemostatic variables.

The influence of race was also manifested in several interactions. It is unknown why favorable increases in HDL_2 and decreases in WHR translated into beneficial reductions in hemostatic variables for WA but not AA women. Yet, beneficial reductions in fasting insulin did translate into favorable reductions in PAI-1 in AA women. Given the fact that diabetes is 2.4-fold greater for AA than WA women [30] and that serum insulin contributed to almost 37% of the variance in PAI-1 in AA women, PAI-1 can be a clinically useful marker of diabetes risk in this group.

Surprisingly, the relationship between insulin and PAI-1 was absent in WA women. Work by Vague et al [31] using younger obese men and women had shown insulin to modulate fibrinolytic activity through its actions on PAI-1 synthesis, independent of BMI. Evidence shows that PAI-1 is expressed in adipose tissue and that visceral adipose tissue has the greatest capacity to produce PAI-1 [32]. Because WA women in our study already possessed significantly greater visceral adipose tissue volume, it is possible that the relationship between insulin and PAI-1 may have been obscured by the stronger influence of visceral adipose tissue mass. This was not the case for AA women who possessed significantly lower visceral adipose tissue levels. Thus, the relationship between insulin and PAI-1 was clearly evidenced in AA but not WA women. Interestingly, serum insulin showed a significant relationship with the t-PA/PAI-1 ratio in both WA and AA women. This reinforces the more global utility of this hemostatic variable in relation to basal insulin levels.

The significant race by diastolic blood pressure interaction showed that in WA women, diastolic blood pressure contributed to almost 24% of the variance in PAI-1. This was not observed in AA women. Because diastolic blood pressure was significantly related to the t-PA/PAI-1 ratio in both WA and AA women, this points once again to the more global utility of t-PA/PAI-1 complex for both groups of women.

The influence of race also manifested itself with respect to the relationship among hemostatic variables themselves. As reported elsewhere, hemostatic variables are correlated among each other [5,33]. The significant relationship

observed between PAI-1 and the t-PA/PAI-1 complex was driven by the correlation found in WA women only (r^2 = 0.671, $P < .001$). Although endogenous fibrinolysis is regulated by t-PA, only a minor portion is active. Most of the t-PA is bound in inactive t-PA/PAI-1 and other complexes [5]. These data have not been examined in AA women; thus, it is possible that the relationship between free t-PA and inactive t-PA/PAI-1 complexes is different for WA and AA women. This would explain the apparent dissociation between the t-PA/PAI-1 complex and PAI-1 or fibrinogen found in AA women. More research is warranted examining why hemostatic relationships may differ by race.

There are several limitations that should be noted with regard to the study. First, the fibrinolytic system is regulated by a balance between activators and inhibitors; and in the present study, only inhibitors were studied. Furthermore, we used a baseline blood sample in a cross-sectional study; thus, conclusions regarding relationships between variables were based upon a single blood draw after an overnight fast. It would have been preferable to perform multiple samples examining hemostatic variables in response to dynamic, inflammatory, and/or prothrombotic events. Nonetheless, several analyses showed adverse hemostatic relationships with various CMV signifying impaired fibrinolytic activity.

Within the context of these limitations, several relevant findings were observed. First, our findings favored the use of PAI-1 and/or the t-PA/PAI-1 ratio over fibrinogen in the evaluation of health risk in both groups of women possessing elevated BMI values. Second, because of race effects for several hemostatic measurements, independent consideration should be given in the clinical evaluation and management of WA and AA patients presenting with elevated CMV. To our knowledge, this is the first study that clearly demonstrates racial disparities in the relationship between CMV and hemostatic variables in a young group of overweight/obese women. Finally, because there were no race interactions for the t-PA/PAI-1 complex, this may be considered the most global indicator of health risk in both AA and WA overweight/obese women. Future research should be directed toward examining race differences with respect to the relationship among hemostatic variables themselves because they differed between WA and AA women.

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