

Pericardial Adipose Tissue, Atherosclerosis, and Cardiovascular Disease Risk Factors

The Jackson Heart Study

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OBJECTIVE — Pericardial adipose tissue (PAT), a regional fat depot that surrounds the heart, is associated with an unfavorable cardiometabolic risk factor profile. The associations among PAT, cardiometabolic risk factors, and coronary artery calcification (CAC) and abdominal aortic artery calcification (AAC) in African American populations have not been explored.

RESEARCH DESIGN AND METHODS — A total of 1,414 African Americans (35% men; mean \pm SD age 58 ± 11 years) drawn from the Jackson Heart Study (JHS) underwent multidetector computed tomography assessment of abdominal visceral adipose tissue (VAT) and PAT between 2007 and 2009. Cardiometabolic risk factors, CAC, and AAC were examined in relation to increments of PAT and VAT.

RESULTS — PAT was significantly correlated with BMI, waist circumference, and VAT ($r = 0.35, 0.46, \text{ and } 0.69$; all $P < 0.0001$). PAT (per 1-SD increase) was associated with elevated levels of systolic blood pressure ($P < 0.04$), fasting glucose, triglycerides, and C-reactive protein and lower levels of HDL (all $P \text{ values} < 0.0001$). PAT was also associated with metabolic syndrome (odds ratio [OR] 1.89; $P < 0.0001$), hypertension (1.48; $P < 0.0006$), and diabetes (1.40; $P < 0.04$); all associations were diminished after further adjustment for VAT (most $P > 0.05$). However, the association of PAT with CAC but not with AAC remained significant (OR 1.34 [95% CI 1.10–1.64]; $P < 0.004$) after multivariable and VAT adjustment.

CONCLUSIONS — PAT is significantly correlated with most cardiometabolic risk factors and CAC in the JHS cohort. The results suggest that PAT is an important VAT depot that may exert a local effect on the coronary vasculature.

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Pericardial adipose tissue (PAT) is an ectopic fat depot associated with measures of adiposity and metabolic risk factors and a predictor of coronary heart disease events (1–5). As a newly proposed marker of the visceral fat depot, PAT may exert a paracrine effect on nearby anatomic structures by actively se-

creting a number of proatherogenic and proinflammatory hormones, cytokines, and chemokines (1,6,7). However, the understanding of the relationship between the extra-abdominal visceral fat depot including PAT and cardiovascular disease (CVD) risk factors in nonwhite populations is lacking. In particular, Afri-

can Americans have much higher rates of obesity and have experienced different levels of CVD risk in relation to obesity (8,9). Therefore, additional data are needed to clarify the role of PAT in relation to CVD in this population. Thus, to better understand the impact of obesity on metabolic risk factors in African Americans, the purpose of this study was to examine the associations of computed tomography (CT) measures of PAT with other measures of adiposity, such as BMI and abdominal visceral adipose tissue (VAT) as well as cardiometabolic risk factors.

RESEARCH DESIGN AND METHODS

The JHS recruited 5,301 African Americans from the Jackson, Mississippi, metropolitan area between September 2000 and March 2004. The cohort was composed of four components: 1) ~31% of the cohort members were participants from the Atherosclerosis Risk in Communities (ARIC) study recruited to the JHS; 2) 30% were representative community volunteers who met census-derived age, sex, and socioeconomic status eligibility criteria from the Jackson, Mississippi, metropolitan area; 3) 17% were randomly ascertained from the Jackson, Mississippi, metropolitan area through methods described previously (10,11); and 4) 22% were in the JHS Family Study. The sampling frame for the family study was participants in any one of the ARIC, random, or volunteer samples whose family size met eligibility requirements as detailed previously (10,11). The cohort consisted of 5,035 adults aged 35–84 years old, and an additional 266 participants (251 participants aged 21–34 and 15 participants aged >85) who were added as a part of the JHS Family Study. This resulted in a final age range of 21 to 94 years (10,11). The present study included participants who underwent multidetector CT scanning from 2007 to 2009 as a part of the second JHS examination.

Overall, 4,200 participants attended

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the JHS examination 2. Of these, 1,414 (35% men) underwent multidetector CT assessment for VAT and PAT. Of these 1,414 participants, 1,402 had a complete covariate profile, 1,378 had an available measure of VAT, and 1,298 were free of CVD. The study protocol was approved by the institutional review boards of the participating institutions: the University of Mississippi Medical Center, Jackson State University, and Tougaloo College. All of the participants provided informed consent.

Multidetector CT scan protocol for measuring adiposity

The research CT protocol included the heart and lower abdomen, using a 16-channel multidetector CT system equipped with cardiac gating (Lightspeed 16 Pro; GE Healthcare, Milwaukee, WI). Quality control and image analysis was performed at a core reading center (Wake Forest University School of Medicine, Winston-Salem, NC). The protocol included scout images, one electrocardiogram gated series of the entire heart, and a series through the lower abdomen from L3 to S1 used for assessing VAT. The estimated average whole-body effective dose for the entire protocol was 4 mSv. The scanning procedure for cardiac gated CT scans of the coronary arteries was based on the standard protocols developed as a part of the National Heart, Lung, and Blood Institute's Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) studies.

PAT measurement was performed on the CT images after segmentation of the heart and surrounding adipose tissue from the remainder of the thorax using specific anatomic landmarks. Because it is difficult to distinguish pericardial fat from epicardial fat by the CT images, the PAT in our study was measured by combination of pericardial fat and epicardial fat. For pericardial fat volume, 18 slices, 2.5 mm thick, starting 1.5 cm above and ending 3.0 cm below the superior extent of the left main coronary artery were included for coverage of 4.5 cm along the head-foot (*z*-axis) of the individual. The anterior border of the volume was defined by the chest wall and the posterior border by the aorta and the bronchus. This region of the heart was selected because it includes the pericardial adipose tissue located around the major epicardial coronary arteries (left main coronary, left anterior descending, right coronary, and

circumflex arteries). Volume Analysis software (Advantage Windows; GE Healthcare, Waukesha, WI) was used to segment and characterize each individual voxel as a tissue attenuation of fat using a threshold range of -190 to -30 Hounsfield units. The PAT volume was the sum of all pericardial fat voxels over the 4.5-cm volume (cubic centimeters/4.5 cm). A similar approach was used for measuring abdominal fat depots. Twenty 2.5-mm-thick slices centered on the lumbar disk space at L4–L5 were analyzed. In this study, a randomly selected sample of 60 participants, the correlation coefficient between two different readers was 0.95 for VAT and subcutaneous adipose tissue and 0.96 for PAT, indicating excellent reproducibility of CT imaging measurements.

Coronary artery calcium and abdominal aortic calcium measurements

CT images were read by experienced and trained technologists for quantity of coronary artery calcium (CAC) and abdominal aortic calcium (AAC). The Agatston score, modified to account for slice thickness, was used to quantify the amount of calcified artery plaque, which was computed by multiplying each lesion (area) by a weighted attenuation score (in Hounsfield units) on a TeraRecon Aquarius Workstation (TeraRecon, San Mateo, CA). The reproducibility for CAC and AAC was 0.99. The presence of CAC and AAC was defined as Agatston score >0 .

Risk factors and covariate assessment

Risk factors and covariates were measured at examination 1 (2000–2004). BMI was defined as weight in kilograms divided by the square of height in meters. Two measures of the waist (at the level of the umbilicus, in the upright position) were averaged to determine baseline waist circumference for each participant. Fasting blood samples were collected according to standardized procedures, and the assessments of plasma glucose, lipids, and C-reactive protein (CRP) were processed at the Central Laboratory (University of Minnesota) as described previously (10,11). Sitting blood pressure was measured twice at 5-min intervals, and the average of two measurements was used for analysis.

Participants were considered to have dyslipidemia if their HDL cholesterol levels were <40 mg/dl in men and 50 mg/dl in women and/or if they had LDL chole-

sterol >160 mg/dl or used lipid-lowering medication. Participants were considered to be hypertensive if they were taking antihypertensive medications, if they self-reported a diagnosis of hypertension, and/or if their systolic pressure was ≥ 140 mmHg or diastolic pressure was ≥ 90 mmHg. Diabetes was defined as a fasting plasma glucose level ≥ 126 mg/dl or treatment with insulin or a hypoglycemic agent. Modified National Cholesterol Education Program Adult Treatment Panel III criteria were used to define the metabolic syndrome (8,12).

The JHS Physical Activity Cohort (JPAC) survey, which was derived from the modified ARIC physical activity survey was administered by trained interviewers at a home visit preceding the JHS clinical examination. The total physical activity score was calculated as the sum of the four different domains of physical activity (active living, work, home and garden, and sport and exercise indexes) (13). Alcohol use was defined as consumption of alcoholic beverages within the past 12 months. Current smoking status was defined as smoking at the time of the interview.

Statistical analysis

PAT was normally distributed, and CRP was normalized by logarithmic transformation and the central tendency and spread represented by the median and interquartile ranges. Age-adjusted Pearson correlations of PAT and VAT were performed with each of the metabolic risk factors including systolic and diastolic blood pressure, fasting plasma glucose and insulin, triglycerides, HDL cholesterol, and CRP, hypertension, diabetes, and dyslipidemia. To estimate the standardized effect size of PAT on continuous risk factors or the odds ratio (OR) on dichotomized risk factor prevalence, PAT was standardized to a mean of 0 and a SD of 1. Next, a multivariable regression model was constructed with PAT as the independent variable and each of the metabolic risk factors as the dependent variable. Three models were generated in stages: 1) the multivariable-adjusted models, for which covariates in all models included age, sex, smoking and alcohol, treatment for hypertension, diabetes, and dyslipidemia; 2) a second model in which the first model was additionally adjusted for BMI; and 3) a final model, in which the first model was additionally adjusted for VAT. Sex interactions were examined in the first model. Sex interactions were not significant in this study (all $P > 0.05$),

Table 1—Clinical characteristics of study participants

	Women	Men
<i>n</i>	925	489
Age (years)	60 ± 11	58 ± 11
Pericardial fat (cm ³)	67.1 ± 29	79.8 ± 37.1
Visceral abdominal fat (cm ³)	789.5 ± 363	850.4 ± 402.5
BMI (kg/m ²)	32.4 ± 7.0	29.4 ± 5.1
Waist circumference (cm)	99.2 ± 16.2	100.2 ± 12.9
CAC present	41 (372)	49 (224)
AAC present	61 (553)	65 (301)
Height (cm)	164.2 ± 6.4	178.1 ± 6.6
Triglyceride (mmol/l)	1.12 ± 0.56	1.21 ± 0.69
HDL cholesterol (mmol/l)	1.41 ± 0.36	1.16 ± 0.29
Total cholesterol (mmol/l)	5.21 ± 1.04	5.05 ± 1.02
Systolic blood pressure (mmHg)	124.4 ± 16.5	125.9 ± 15.6
Diastolic blood pressure (mmHg)	77.3 ± 9.6	82.1 ± 9.8
Fasting glucose (mmol/l)	5.33 ± 1.26	5.41 ± 1.44
CRP (nmol/l)	3.3 (1.3, 6.7)	1.3 (0.6, 2.9)
Obesity (BMI ≥30 kg/m ²)	58.5	38.5
Diabetes	15.6	13.5
Metabolic syndrome	41.2	33.2
Hypertension	62.5	59.2
Current smokers	7.9	12.3
Alcohol use	37.2	60.1
Physical activity score	8.3 ± 2.4	8.9 ± 2.6

Data are means ± SD, % (n), or median (25th, 75th percentile) unless indicated otherwise.

and the results presented are for women and men combined.

The association between PAT and the presence of CAC and AAC was assessed using logistic regression analysis to estimate the OR of the presence of CAC and AAC per 1-SD increase in PAT after adjustment for 1) age and sex; 2) age, sex, and VAT; 3) age, sex, smoking, alcohol, total and HDL cholesterol, systolic blood pressure, diabetes, hypertension treatment, and lipid treatment; and 4) model 3 plus VAT. $P < 0.05$ was considered significant. All computations were performed by SAS software (version 9.2, SAS Institute, Cary, NC).

RESULTS— Overall, 925 women and 489 men were available for analysis. The mean age of the study sample was 54 years. The mean ± SD PAT volume was 67.1 ± 29 cm³ in women and 79.8 ± 37.1 cm³ in men (Table 1). Approximately 52% of participants were obese, 61% had hypertension, 39% had metabolic syndrome, and 15% had diabetes.

Correlations with PAT

Age- and VAT-adjusted correlation coefficients of PAT with metabolic risk factors are displayed in Table 2. PAT was correlated to all of the cardiometabolic risk fac-

tors tested, with the notable exception of total cholesterol and diastolic blood pressure. PAT was also inversely related to physical activity score. However, the partial correlation coefficients of PAT with cardiometabolic risk factors did not remain significant after additional adjustment for VAT.

Multivariable-adjusted regression with PAT and metabolic risk factors

To investigate the strength of the association of PAT with both continuous and di-

chotomous metabolic risk factors, we performed multivariable regressions as summarized in Table 3. We observed significant associations per 1-SD increment of PAT and continuous measures of systolic blood pressure, fasting glucose, triglycerides, HDL cholesterol, and log CRP. However, the significant effect of PAT on these risk factors became weaker or diminished when BMI or VAT appeared in the same model (Table 3). Significant associations with PAT were also observed for dichotomous metabolic traits. The ORs of metabolic syndrome (1.89), hypertension (1.48), and diabetes (1.40) per 1-SD increase in PAT were significant (all $P < 0.05$). These relations became weaker or diminished after additional adjustment for BMI or VAT (Table 4).

Logistic regression analysis with PAT and CAC

Generally, men had a slightly higher percentage for the presence of CAC than women (49 vs. 41%) with a similar value for AAC (65 vs. 61%). The relationship between PAT and the presence of CAC was found to be significant in the minimally adjusted model (OR 1.37 [95% CI 1.20–1.56]; $P < 0.0001$). This association was not materially different with additional adjustment for VAT (OR 1.37 [1.15–1.64]; $P < 0.0004$) and persisted after additional adjustment for VAT and CVD risk factors (1.34 [1.10–1.64]; $P = 0.004$), including smoking, alcohol, total and HDL cholesterol, systolic blood pressure, diabetes, hypertension treatment, and lipid treatment. Conversely, there was no association between PAT and AAC in the multivariable-adjusted model (1.03 [0.82–1.29]; $P = 0.80$).

Table 2—Partial Pearson correlation coefficients between pericardial fat volumes and metabolic risk factors

	Age-adjusted	Age- and VAT-adjusted
BMI	0.35†	0.01
Waist circumference	0.46†	0.08*
Visceral abdominal fat	0.69†	NA
Triglycerides	0.23†	0.05
HDL cholesterol	−0.20†	−0.04
Total cholesterol	0.01	−0.01
Systolic blood pressure	0.09†	0.01
Diastolic blood pressure	0.07*	0.04
Fasting glucose	0.14†	0.02
Log CRP	0.17†	−0.01
Physical activity score	−0.11†	−0.02

* $P < 0.05$; † $P < 0.0001$. NA, not available.

Table 3—Multivariable adjusted regression coefficients between pericardial fat (per 1 SD) and metabolic risk factors

Model	MV adjusted	P value	MV adjusted + VAT	P value	MV adjusted + BMI	P value
Systolic blood pressure (mmHg)	0.95 ± 0.46	0.04	0.46 ± 0.61	0.45	0.46 ± 0.49	0.34
Diastolic blood pressure (mmHg)	0.20 ± 0.29	0.48	0.03 ± 0.38	0.95	0.03 ± 0.31	0.91
Fasting plasma glucose (mmol/l)	2.09 ± 0.63	0.0009	0.66 ± 0.84	0.43	1.60 ± 0.68	0.02
Triglycerides (mmol/l)	9.25 ± 1.59	0.0001	1.11 ± 2.09	0.59	7.14 ± 1.72	0.0001
HDL cholesterol (mmol/l)	−1.95 ± 0.41	0.0001	−0.20 ± 0.54	0.71	−0.79 ± 0.47	0.07
Log CRP	0.28 ± 0.04	0.0001	0.11 ± 0.05	0.03	0.09 ± 0.04	0.02

Data are multivariable (MV) regression coefficients (means ± SE) adjusted for age, sex, smoking, alcohol and treatment of hypertension, diabetes, or dyslipidemia.

CONCLUSIONS

Principal findings

Among the JHS cohort of 1,414 participants undergoing multidetector CT scanning, PAT was found to be significantly associated with cardiometabolic risk factors. However, most of the observed associations were attenuated or diminished with additional adjustment for BMI or VAT, suggesting that PAT is not more strongly correlated to cardiometabolic risk factors than VAT or BMI. In contrast, commensurate with its proposed primary role as a locally acting fat depot, PAT was predominantly associated with CAC but not with AAC even after VAT and other relevant CVD risk factors were accounted for.

Our findings have important implications for the role of PAT in relation to cardiometabolic risk factors and vascular calcification. Anatomically, the coronary arteries and the myocardium of both the right and left ventricles are surrounded by or in direct contact with this small fat depot. Consequently, this close proximity of PAT to the coronary artery and the underlying myocardium may exert a local toxic effect on the nearby organs rather than a systemic effect on cardiometabolic risk factors. Our data support the hypotheses that PAT is associated with cardiometabolic risk factors because of shared risk factors with VAT and that the independent association of PAT with CAC is probably due to its close anatomic relationship with the coronary vasculature. More importantly, despite lower amounts of VAT at similar levels of BMI in African Americans (14), the associations of PAT with cardiometabolic risk factors and

CAC found in this African American cohort is consistent with the findings from the Framingham Heart Study (1–5).

In the context of current literature

PAT has been found in several clinical studies to be significantly associated with clinical key components of metabolic syndrome and insulin resistance including BMI, waist circumference, elevated levels of blood pressure, glucose, LDL cholesterol, HDL cholesterol, triglycerides, and inflammatory cytokines including high-sensitivity CRP (3,4,7,15), and it has been proposed as a new indicator of cardiovascular risk (4). However, such an association may result from the systemic effects of the abdominal visceral fat depot because PAT is highly correlated with abdominal visceral fat. Furthermore, a large sample from the Framingham Heart Study demonstrated that the association of PAT with these cardiometabolic risk factors was weaker or diminished when VAT was taken into account (1,3). These data suggest that PAT may be a residual marker of visceral adiposity.

As a part of the metabolically active visceral fat depot, PAT is an important local source of free fatty acids and a number of proatherogenic, proinflammatory, and prothrombotic hormones, and cytokines, including leptin, monocyte chemoattractant protein-1, interleukin-6, and tumor necrosis factor- α (6,16–19). In addition, PAT is usually located in close proximity to the coronary vasculature compared with other fat depots. Such distinguishing biochemical properties and the unique anatomic location of PAT are hypothe-

sized to enhance its paracrine role in the development of coronary atherosclerosis (1,20,21). Therefore, a local interaction between PAT and the nearby coronary vasculature may explain the association between PAT with CAC observed in our data.

Strengths and limitations

Strengths of this study include the large sample size from a community-based cohort of African Americans, simultaneous volumetric quantification of PAT and VAT, and multiple adjustments for potential confounders. Limitations include 1) the cross-sectional study design, which limits our ability to infer causality; 2) the primarily African American sample (although this may be seen as a limitation of the current study, it is important to note that our results are consistent with the findings from the Framingham Heart Study [1], suggesting that our findings may apply across the ethnic groups); and 3) the potential misclassification of PAT due to combined measurement of pericardial and epicardial fat inherent in our methodology. In addition, because the CT-measured PAT and VAT were collected several years after clinical data were collected, this time gap between clinical data collected and CT measurements could result in misclassification of risk factors. However, this limitation should not affect the relative association among PAT, VAT, and CAC, which were measured contemporaneously on the same CT scans.

In summary, PAT is correlated with most cardiometabolic risk factors but not

Table 4—Multivariable ORs adjusted for hypertension, diabetes, and metabolic syndrome with an increase in pericardial fat (per 1 SD)

Model	MV adjusted	P value	MV adjusted + VAT	P value	MV adjusted + BMI	P value
Hypertension	1.48 (1.18–1.84)	0.0006	1.41(1.05–1.91)	0.03	1.44(1.13–1.83)	0.003
Diabetes	1.40(1.01–1.94)	0.04	1.06 (0.67–1.69)	0.78	1.29(0.90–1.86)	0.16
Metabolic syndrome	1.89 (1.62–2.21)	0.0001	1.32 (1.01–1.60)	0.006	1.48(1.25–1.74)	0.0001

Data are multivariable (MV) ORs (95% CI) adjusted for age, sex, smoking, alcohol, and treatment of hypertension, diabetes, or dyslipidemia.

more strongly than VAT. However, PAT is significantly associated with CAC, suggesting that PAT may exert a local toxic effect on the coronary vasculature in the JHS cohort.

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