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Fatty Liver, Abdominal Adipose Tissue and Atherosclerotic Calcification in African Americans: the Jackson Heart Study

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Abstract

Objective—Both fatty liver and abdominal visceral fat (VAT) are associated with cardiometabolic risk factors. Whether fatty liver and VAT are jointly associated with coronary artery (CAC) or abdominal aortic (AAC) calcification is not clear.

Methods—Jackson Heart Study (JHS) participants (n=2884, mean age 60 years, 65% women) underwent non-contrast CT Exam for assessment of fatty liver, VAT, and CAC and AAC. Fatty liver was measured by liver attenuation (LA; low LA=high fatty liver). The Agatston score was used to quantify the amount of calcified artery plaque and the presence of calcified artery plaque was defined as Agatston score>0. Cross-sectional associations of LA and VAT with CAC and AAC were examined in logistic regression models.

Results—LA (per 1-standard deviation [SD] decrement) was associated inversely with CAC in age-sex-adjusted (OR 0.84, 95%CI 0.7–0.9, $p=0.0001$) and multivariable adjusted models (OR 0.89, 95%CI 0.8–0.9, $p=0.01$). The association persisted for LA with CAC when additionally adjusted for body mass index (BMI) (OR 0.89, 95%CI 0.8–0.9, $p=0.03$) or VAT (OR 0.90, 95%CI 0.8–0.9, $p=0.04$). Abdominal VAT (per 1-SD increment) was positively associated with CAC in age-sex-adjusted models (OR 1.27, 95%CI 1.2–1.4, $p=0.0001$), but the association was diminished with multivariable adjustment (OR 1.10, 95%CI 0.9–1.2, $p=0.09$) and with additional adjustment for LA ($p=0.24$) or BMI ($p=0.33$). For AAC, the associations with LA and VAT were only present in age-sex-adjusted models. Finally, we did not observe interactions between LA and VAT for CAC ($p=0.18$) or AAC ($p=0.24$).

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Conclusion—Fatty liver is associated with coronary atherosclerotic calcification independent of abdominal VAT or BMI in African Americans. Further investigations to uncover the clinical implications of fatty liver on coronary atherosclerosis in obesity are warranted.

Introduction

Artery calcification, measured in coronary artery or abdominal aortic artery, is a measure of subclinical artery disease and a marker of future cardiovascular disease (CVD) above and beyond associations with traditional cardiovascular risk factors (1; 2). Despite of a lower quantity of VAT and fatty liver found in African Americans (3; 4), our prior work indicates that high levels of both VAT and fatty liver in African Americans from the Jackson Heart Study (JHS) cohort is associated with a high prevalence of cardiometabolic risk factors, including hypertension, diabetes, dyslipidemia and the metabolic syndrome (5; 6). Based on the strong observed associations between cardiometabolic risk factors and atherosclerosis (7–9), it is conceivable that individuals with high levels of VAT or fatty liver are at greater risk for coronary artery (CAC) or abdominal aortic calcification (AAC) than those without.

Although abdominal VAT and the liver are metabolically connected, fatty liver is associated with obesity-related cardiometabolic complications independent of abdominal VAT (6; 10). Increased fatty liver may promote atherosclerotic calcification above and beyond the association of abdominal VAT. Several clinical studies have demonstrated that patients with nonalcoholic fatty liver disease have more severe coronary atherosclerotic burden (11–13). However, the association between fatty liver and coronary atherosclerotic burden in these studies is examined without consideration for potential associations with abdominal VAT. In addition, the studies are conducted in small, selected samples, potentially limiting their generalizability. To better understand whether fatty liver is an important correlate of artery atherosclerotic burden above and beyond abdominal VAT, we have comprehensively evaluated the association between fatty liver, abdominal VAT and atherosclerotic burden, measured by CAC or AAC, in participants of the JHS.

Methods

Study Sample

The original JHS cohort enrolled participants from September 2000 to March 2004 and comprises 5301 participants between the ages of 21–94 years (14). The present study includes a sub-set of participants (n=2884) who underwent multi-detector computed tomography (CT) scanning from 2007 to 2009 as a part of the second JHS Examination (JHS Exam 2).

Overall, 4203 participants attended JHS Exam 2 (from 2005 to 2008). Of these, 2884 (65% women) had measurements of abdominal VAT and fatty liver. Participants were excluded from the CT scan Exam if: 1) body weight was greater than 350 lbs (~160 kg); 2) pregnant or unknown pregnancy status; 3) female participant < 40 years of age; 4) Male participant < 35 years of age. Individuals imaged were further excluded if measurements were missing for total abdominal adipose tissue (n=1), for VAT (n=1), for CAC (n=4) and for AAC (n=1), resulting in a final sample size of 2880. The study protocol was approved by the institutional review board of the participating institutions: the University of Mississippi Medical Center, Jackson State University and Tugaloo College. All of the participants provided informed consent.

Multi-Detector CT Scan Protocol for Measuring Adiposity

The research CT protocol included the heart and lower abdomen using a 16 channel multi-detector computed tomography system equipped with cardiac gating (GE Healthcare Lightspeed 16 Pro, Milwaukee, Wisconsin). 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 ECG gated series of the entire heart, and a series through the lower abdomen.

The acquired abdominal imaging slices covering the lower abdomen from L3 to S1 were used to quantify VAT and SAT. Briefly, 24 contiguous 2.5-mm thick slices centered on the lumbar disk space at L4–5 were used for this analysis; 12 images before the center of the L4 - L5 disk space and 12 images after the disk space were used for quantification of VAT and SAT. The abdominal muscular wall was first manually traced and the adipose tissue volumes in different compartments were measured by semiautomatic segmentation technique. 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 -190 to -30 Hounsfield units. The VAT volumes were the sum of VAT voxels over 24 slices located within the intra-abdominal cavity (5; 6). In this study, the interclass correlation coefficient for inter-reader comparisons was 0.95 for VAT in a randomly selected sample of 60 participants (5; 6).

The CT diagnosis of fat infiltration in the liver can be made by measuring CT attenuation in Hounsfield Units (HU) or difference between liver and spleen, which have been shown to be inversely correlated with the fatty filtration of the liver seen on liver biopsy (15; 16). A recent study demonstrates that a simple measurement of liver attenuation on unenhanced CT scans is the best method of predicting pathologic fat content in the liver (17). In this study, measurement of LA in HU was performed in the right lobe of the liver of CT scans at the abdominal level of the T₁₂ – L₁ intervertebral space and was used to quantify fat deposit in the liver. As the amount of liver fat increases, the measured LA decreases based on the HU scale in which fat has negative values (low LA = high fatty liver) (6; 15). The LA was determined by calculating the mean HU of three circular regions of interest (ROI) measuring 100 mm² in the parenchyma of the right lobe of the liver (6; 15). Readers were trained to place the liver ROIs avoiding the large vessels and any focal liver lesions. The correlation coefficient between 2 different readers on a random selected sample of 60 participants was 0.98 for LA, indicating reliable reproducibility of CT measured LA in this study.

CAC and AAC Measurements

CT images were analyzed by experienced and trained technologists for the quantity of CAC and 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 Unit) on a TeraRecon Aquarius Workstation (TeraRecon, San Mateo, CA). The total CAC score is the sum of the score of the left main, left circumflex, left anterior descending and right coronary artery and the total AAC score is the sum of infrarenal abdominal aorta, left common iliac and right common iliac aorta. The reproducibility for CAC and AAC was 0.99. The presence of CAC and AAC were defined as Agatston score > 0.

Risk Factors and Covariate Assessment

Risk factors and covariates were measured at Exam 2 (2005 – 2008) (5; 6). 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 waist circumference (WC) for each participant. Fasting blood samples were collected

according to standardized procedures and the assessment of plasma glucose and lipids were processed at the Central Laboratory (University of Minnesota) as previously described (14). Sitting blood pressure was measured twice at 1-minute intervals after 5-minutes resting and the average of two measurements was used for analysis.

Participants were considered to have hypertension if they were taking antihypertensive medications, self-reported a diagnosis of hypertension, and/or if their systolic pressure was 140 mm Hg or diastolic pressure 90 mm Hg. Diabetes was defined as a fasting plasma glucose level 126 mg/dl or treatment with insulin or hypoglycemic agent. Participants were considered current smokers if they had smoked, used chewing tobacco or nicotine gum, or were wearing a nicotine patch at the time of interview. Daily alcohol consumption was assessed by a validated food frequency questionnaire (18) and participants were defined as alcohol drinkers if they drank more than 14 drinks per week (men) or more than 7 drinks per week in women. Obesity was defined by BMI of at least 30 kg/m² and modified National Cholesterol Education Program Adult Treatment Panel III criteria were used to define the metabolic syndrome (19).

In order to define the individuals with hepatic steatosis, a healthy referent sample was created by hierarchical exclusion of the presence of hypertension, triglycerides 150 mg/dl or taking lipid medications, HDL-C < 40 mg/dl in men or < 50 in women; fasting glucose 126 mg/dl or diabetes (n=2551); prevalent CVD (n=9); BMI < 18.5 kg/m² (n=115) and alcohol drinkers (n=31), resulting in final healthy referent sample size of 178. The lowest 10th percentile was chosen as a cutoff point from this healthy referent sample to define the prevalence of hepatic steatosis (6).

Statistical Analysis

LA and triglycerides were normalized by logarithmic transformation. Cardiometabolic characteristics by the presence or absence of CAC or AAC were compared with the use of analysis of variance for continuous variables and the chi-square test for categorical variables. To examine the association of fatty liver or VAT with CAC or AAC, age-sex-adjusted correlations of various risk factors with CAC or AAC score were performed after logarithmic transformation of the Agatston score plus 1. In addition, a logistic regression model was used and three models were generated in stages: (1) the first model was only adjusted for age and gender; (2) the second model was adjusted for age, gender, smoking and alcohol status, systolic blood pressure, treatments for hypertension, diabetes and dyslipidemia, plasma triglyceride and HDL-C levels; (3) the third model in which the second model was additionally adjusted for VAT or BMI. To assess the incremental utility of the logarithmic transformed Agatston score in relation to LA and VAT, the above multivariable analyses were repeated as a second analysis. Similar models were also examined for the dichotomized CAC or AAC, defined by Agatston score > 100 because the frequency of coronary heart disease is generally low if the Agatston score is less than 100 (20). All computations were performed by SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Study sample characteristics are presented in Table 1. Overall, the mean age was 59 years and 65% were women; 48% (n=1386) of study individuals had CAC and 66% (n=1898) of individuals had AAC. On average, participants with the presence of artery calcification had more adverse risk factor profiles as compared to participants with the absence of artery calcification (Table 1).

Age-sex-adjusted correlation coefficients of log CAC and log AAC with cardiometabolic risk factors are displayed in Table 2. We observed correlations of log CAC or log AAC to most cardiometabolic risk factors tested including log LA, VAT, systolic BP, triglycerides, fasting plasma glucose, and HDL-C. Abdominal SAT did not significantly correlate to log CAC or log AAC ($p > 0.05$).

For CAC, log LA and VAT were modeled as continuous variables (Table 3). Per 1-standard deviation (SD) decrement in log LA, we observed associations with CAC in the age-sex-adjusted ($p < 0.003$) and multivariable-adjusted models ($p < 0.01$). The association persisted with additional adjustment for VAT ($p < 0.04$) or body mass index (BMI) ($p < 0.03$). Conversely, per 1-SD increment in abdominal VAT, we observed association with CAC in the age-sex-adjusted models ($p < 0.0001$) but not in the multivariable-adjusted models ($p < 0.09$). For AAC, significant associations were observed in the age-sex-adjusted models with log LA ($p < 0.005$) and VAT ($p < 0.0001$), but not in the multivariable-adjusted models. Finally, we did not observe significant interactions between LA and gender for CAC ($p = 0.79$) or AAC ($p = 0.16$), interactions between VAT and gender for CAC ($p = 0.18$) or AAC ($p = 0.35$), and interactions between LA and VAT for CAC ($p = 0.18$) or AAC ($p = 0.24$).

Discussion

Principal Findings

Low log LA (i.e. high levels of fatty liver) was associated with CAC. This association persisted after adjustment for traditional CVD risk factors and VAT or BMI. For AAC, the association with log LA or VAT was diminished upon multivariable adjustment. The findings suggest that fatty liver is associated with coronary artery atherosclerotic calcification after accounting for VAT or BMI in African Americans.

In the Context of the Current Literature

Although the association between atherosclerotic calcification and fatty liver has been observed (11–13), not all prior findings have been consistent. In the Multi-ethnic Study of Atherosclerosis (MESA), 398 participants underwent multi-detector computerized tomography to detect fatty liver; no associations were observed with CAC after adjustment for multiple cardiovascular risk factors (21). In contrast, several clinical and population studies observed associations of fatty liver with CAC (11–13; 22). However, these studies have relatively small sample sizes ($n = 29$ to 300), which may not be able to detect small but significant association between fatty liver and atherosclerotic burden. In the present study, we extend these previously-observed clinical findings (11–13; 22) by evaluating the joint associations of fatty liver and abdominal VAT with CAC in a large, well-characterized sample of African Americans from the Jackson Heart Study. We additionally adjusted for traditional CVD risk factors and abdominal VAT or BMI. Taken together, our findings suggest that fatty liver is a correlate of CAC above and beyond traditional risk factors and measures of generalized and central adiposity.

Potential Mechanisms

Although fatty liver is an independent risk factor for cardiometabolic risk factors (6; 10), the mechanisms behind this association remain unclear. Several potential explanations exist, including hepatic insulin resistance (23), endothelial dysfunction (24), low-grade inflammation (25) and lipotoxicity due to abnormal portal free fatty acid metabolism (26). In addition, it is possible that different pathways including patterns of proteins and adipokines associated with cardiometabolic abnormalities could explain the differential influence of abdominal VAT and fatty liver on metabolic profiles that lead to CAC. Indeed, C-reactive protein, leptin, interleukin-6 and adiponectin are associated with visceral adiposity (27),

whereas α_2 -Heremans-Schmid glycoprotein/fetuin-A (AHSG) and circulating retinol-binding protein 4 (RBP4) are produced in the liver and highly associated with hepatic insulin resistance and fat accumulation in the liver (28; 29). Therefore, abnormal fat accumulation in the liver may cause atherosclerosis.

Implications for Future Research

African Americans have a lower prevalence of hepatic steatosis (24% in blacks as compared to 33% in whites) (30) but experience greater cardiovascular mortality rates and greater risk for early mortality compared to other ethnic groups (31). This paradox may not be explained only by differences in amounts of VAT or fatty liver but also partially by varied associations of obesity with cardiometabolic risk factors in African Americans compared to European Americans (32). Despite of a lower prevalence of hepatic steatosis in African Americans (30), our results indicate that increased amounts of fatty liver increase the risk for CVD events above and beyond abdominal obesity and burden of CVD risk factors in African Americans. Whether such individuals should be screened in the setting of their fatty liver evaluation should be the topic of subsequent studies.

Strengths and Limitations

The strengths of the present study include our large, well-characterized African American cohort with a wealth of metabolic traits and covariates measured. Some limitations warrant mention. Our findings are cross-sectional and derived from an observational study; neither temporality nor causality can be inferred. CT is a relatively insensitive measure of fatty liver compared to hepatic triglyceride content measured by proton magnetic resonance spectroscopy (17), which may bias our results toward the null and underestimate the relative strength of the association between fatty liver and atherosclerotic calcification. In addition, although our findings have demonstrated the associations between fatty liver and coronary atherosclerosis in African Americans, the clinical implications of fatty liver on coronary atherosclerosis are questionable. Further investigations are also warranted to examine the relationship between fatty liver and coronary atherosclerosis in the longitudinal settings.

Conclusions

Fatty liver is associated with coronary atherosclerotic calcification in African Americans, which is independent of abdominal VAT or BMI. Further investigations to uncover the clinical implications of fatty liver on coronary atherosclerosis in obesity are warranted.

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- Fatty liver and abdominal visceral fat (VAT) are metabolically connected.
- We examine whether fatty liver is a risk factor for coronary calcification.
- We have found that fatty liver is associated with coronary calcification in African Americans.
- This association is independent of abdominal VAT or body mass index.

Table 1
Characteristics of Study Participants Who Underwent Assessment of CT Exam (Mean ± SE)

	CAC (Score>0)			AAC (Score>0)		
	Absent (n=1496)	Present (n=1384)	p	Absent (n=984)	Present (n=1896)	p
Covariates						
Age (years)	55±10	66±10	0.0001	52±9	63±10	0.0002
Women %	69.2	60.1	0.0001	68.5	62.9	0.003
Smoking %	4.9	8.7	0.0001	2.7	8.8	0.0001
Alcohol Drinker	5.7	8.2	0.009	5.3	7.7	0.02
Fat-related						
Log LA (HU)	4.07±0.0	4.05±0.0	0.002	4.07±0.0	4.06±0.0	0.05
VAT (cm ³)	760±9.7	907±10.1	0.0001	726±12.0	885±8.6	0.0001
BMI (kg/m ²)	31.8±0.2	31.5±0.2	0.27	32.1±0.2	31.5±0.1	0.02
Hepatic Steatosis%	22.1	29.2	0.0001	22.5	27.0	0.009
Obesity %	55.0	54.9	0.52	57.1	53.8	0.02
BP-related						
SBP (mm Hg)	124±0.5	131±0.5	0.0001	122±0.6	130±0.5	0.0001
DBP (mm Hg)	78±0.3	76±0.2	0.0001	79±0.3	76±0.2	0.0001
HTN%	63.0	82.9	0.0001	58.6	79.8	0.0001
HTN Med %	53.6	74.9	0.0001	49.0	71.6	0.0001
Glucose-related						
Fasting Glu (mg/dl)	102.2±1.0	110.0±1.1	0.0001	101.5±1.2	108.2±1.0	0.0001
DM %	15.7	37.6	0.0001	14.4	32.3	0.0001
DM Med %	11.2	26.3	0.0001	10.3	22.7	0.0001
Lipid-related						
Log TRG	4.4±0.1	4.6±0.1	0.0001	4.4±0.1	4.6±0.1	0.0001
HDL-C (mg/dl)	55.2±0.5	53.7±0.5	0.02	55.3±0.5	54.1±0.4	0.07
Lipid-lowering Med %	17.0	38.5	0.0001	14.2	34.2	0.0001

		CAC (Score>0)		AAC (Score>0)	
		Absent (n=1496)	Present (n=1384)	Absent (n=984)	Present (n=1896)
		<i>p</i>		<i>p</i>	
Syndrome-related					
MetS %		48.4	70.3	44.1	66.6
		0.0001		0.0001	
				0.0001	

Table 2

Age-Sex-adjusted Correlation Coefficients of Coronary and Abdominal Aortic Artery Calcium Score with Risk Factors

	Log CAC Score	<i>p</i>	Log AAC Score	<i>p</i>
Log LA (HU)	−0.06	<i>0.004</i>	−0.07	<i>0.002</i>
VAT	0.08	<i>0.0001</i>	0.10	<i>0.0001</i>
SAT	0.02	<i>0.40</i>	−0.00	<i>0.99</i>
BMI	0.06	<i>0.01</i>	0.04	<i>0.11</i>
Systolic BP	0.06	<i>0.004</i>	0.10	<i>0.0001</i>
Diastolic BP	−0.03	<i>0.14</i>	−0.01	<i>0.59</i>
Fasting Glucose	0.09	<i>0.0001</i>	0.10	<i>0.0001</i>
Total Cholesterol	−0.01	<i>0.61</i>	0.04	<i>0.04</i>
Log TRG	0.11	<i>0.0001</i>	0.12	<i>0.0001</i>
HDL-C	−0.07	<i>0.0008</i>	−0.08	<i>0.0002</i>

CAC: coronary artery calcium; AAC: abdominal aortic artery calcium; VAT: visceral adipose tissue; LA: liver attenuation in Hounsfield Units; SAT: subcutaneous adipose tissue; BMI: body mass index; BP: blood pressure; TRG: triglyceride; HDL-C: high-density lipoprotein cholesterol.

Table 3

Associations[#] of VAT and LA with Artery Calcification

	Age- Sex- adjusted	p	MV- adjusted	p	MV+ VAT or Log LA adjusted	p	MV+BMI adjusted	p	p for VAT & LA interaction
CAC									
Log LA	0.84(0.7–0.9)	0.003	0.89(0.8–0.9)	0.01	0.90(0.8–0.9)	0.04	0.89(0.8–0.9)	0.03	0.18
VAT	1.27(1.2–1.4)	0.0001	1.10(0.9–1.2)	0.09	1.07(0.9–1.2)	0.24	1.06(0.9–1.2)	0.33	
AAC									
Log LA	0.88(0.8–0.9)	0.005	0.91(0.8–1.0)	0.10	0.92(0.8–1.1)	0.14	0.92(0.8–1.1)	0.12	0.24
VAT	1.29(1.2–1.4)	0.0001	1.07(0.9–1.2)	0.28	1.05(0.9–1.2)	0.50	1.10(0.9–1.3)	0.19	

[#]Data represents odds ratio and 95% confidence intervals of the presence of artery calcification (CAC/AAC). All fat measurements are standardized to a mean of 0 and standard deviation of 1.
MV: adjusted for age, sex, smoking and alcohol status, diabetes, systolic blood pressure, total cholesterol and HDLC and treatments for hypertension, diabetes and dyslipidemia.
CAC: coronary artery calcium; AAC: abdominal aortic calcium; VAT: visceral adipose tissue; LA: liver attenuation in Hounsfield Units; BMI: body mass index.