

Myocardial steatosis and its association with obesity and regional ventricular dysfunction: Evaluated by magnetic resonance tagging and ^1H spectroscopy in healthy African Americans

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ABSTRACT

Background: Cardiac steatosis is common in patients with diabetes or obesity, and cardiac steatosis may result in cardiomyopathy. However, factors associated with cardiac steatosis have not been reported in healthy individuals without diabetes and hypertension. The objectives of this study were to explore factors associated with myocardial triglyceride levels, and to examine the association between myocardial triglyceride and regional left ventricular (LV) function in healthy African Americans (AAs).

Methods: Between November 2010 and June 2012, 92 healthy AAs aged 21 years or older, without clinical evidence of cardiac dysfunction, coronary artery disease, diabetes, or hypertension from Baltimore, Maryland, were enrolled in an observational proton magnetic resonance spectroscopy and imaging study investigating factors associated with cardiac steatosis, and the relationships between cardiac steatosis and LV volumes and LV function.

Results: Among the participants, all had a low Framingham risk; 31 had a normal BMI, 23 were overweight and 38 were obese. The median myocardial triglyceride content was 0.5% (IQR: 0.3–1.0%). Among the factors investigated, BMI ($R^2 = 0.43$, $p = <0.0001$) was independently associated with myocardial triglyceride. Overall, myocardial triglyceride was not associated with LV EF/structure, but may be associated with regional LV function.

Conclusions: In healthy AA adults, obesity is associated with cardiac steatosis. In contrast to studies in patients with diabetes suggesting a link between cardiac steatosis and LV dysfunction, this study found no relationship between cardiac steatosis and left ventricular volumes or EF, though there is some evidence suggesting that cardiac steatosis may be associated with LV regional function in healthy AA women.

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1. Introduction

Free fatty acids are well recognized as the major source of energy for the myocardium. Under normal conditions, the majority of free fatty acids undergo rapid oxidation and little is stored. Under conditions of excess fatty acids, however, they are stored as triglycerides [1] and result in the development of cardiac steatosis. Cardiac steatosis is common in patients with diabetes, and is associated with lipoapoptosis [2–9]. Furthermore, animal model studies suggest that cardiac steatosis may result in cardiac dysfunction, and eventually cardiomyopathy [8,9].

However, the exact mechanisms responsible for the development of cardiac steatosis and the factors associated with cardiac steatosis in humans are not fully understood. Although cardiac steatosis was recognized by clinicians 60 years ago [6], *in vivo* human studies have only become possible with the use of magnetic resonance spectroscopy (MRS) [6,10–12]. Most of these studies were performed in patients with diabetes and/or obesity and no studies to date have focused on cardiac steatosis in otherwise healthy individuals or in African Americans (AAs),

The objectives of this study were (1) to explore demographic, physical, and laboratory factors that are independently associated with myocardial triglyceride contents, and (2) to examine whether myocardial triglyceride content is associated with regional and global left ventricular dysfunction in healthy AAs using noninvasive magnetic resonance (MR) modalities.

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2. Methods

2.1. Study participants

Between November 2010 and June 2012, as part of a cohort study of heart disease in AAs conducted in Baltimore, 109 AA study participants from the city of Baltimore, Maryland, were enrolled in an observational follow-up study investigating factors associated with cardiac steatosis. Cardiac steatosis was measured as myocardial triglyceride content, as indexed by the ratio of the signal of myocardial triglyceride to the signal of myocardial water.

Inclusion criteria were age ≥ 21 years and AA race. Exclusion criteria were (1) any evidence of ischemic heart disease as indicated by clinical history, previous hospitalization for myocardial infarction, angina pectoris, or ECG or echocardiographic evidence of previous ischemic-induced myocardial damage, (2) any symptoms believed to be related to cardiovascular disease, (3) a positive urine test for illegal drugs, (4) HIV infection, (5) pregnancy, and (6) history of MRI-related claustrophobia. Seventeen of these had diabetes or hypertension and were excluded from further analyses.

Interviews regarding sociodemographics, medical history, and behaviors were conducted; urine tests for illegal drugs were performed to exclude those with drug abuse, and HIV infection was determined by ELISA and confirmed by Western blot test. Clinical examinations, blood pressure (BP) measurement, MR myocardial imaging and proton magnetic resonance spectroscopy (^1H MRS) were performed; and laboratory tests, including lipid profiles, leptin and high-sensitivity C-reactive protein (hsCRP) levels were obtained.

The Johns Hopkins Medicine Institutional Review Board approved the study protocol and consent form, and all study participants provided written informed consent. All procedures used in this study were in accordance with institutional guidelines. Although the overall investigation is a cohort study, the data presented herein are cross-sectional only.

2.2. Main procedures

2.2.1. Myocardial and hepatic imaging and spectroscopy

All studies were performed on a 3.0-T MR scanner (Trio Tim; Siemens, Erlangen, Germany). To measure left ventricular (LV) volumes and ejection fraction, the heart was imaged in both long and short-axis orientation, using retrospectively gated steady state free precession cine images.

Myocardial ^1H MRS spectra were obtained with electrocardiogram gating during early systole, with navigator gating to enable free-breathing using a single voxel point-resolved spectroscopy sequence. The spectroscopic volume (6- to 8-mL voxel) was positioned within the interventricular septum. One spectrum was recorded with water suppression (32 averages), and another spectrum (eight averages) was recorded without water suppression (Fig. 1). Measurement of hepatic triglyceride content was performed using the same sequence with the MRS voxel placed in the right hepatic lobe. Eight averages of water suppressed as well as eight averages of no water suppressed spectrum were acquired with breath holding.

The distributions of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were assessed by an axial single-shot fast spin echo sequence (slice thickness = 10 mm). Three contiguous transverse images were acquired at the level of the fifth lumbar vertebrae during one breath hold.

To assess regional myocardial function, myocardial MR-tagged images were obtained in the short-axis plane at the mid-LV level. A retrospectively ECG-gated, segmented k-space fast low-angle shot (FLASH) pulse sequence was used (TR/TE: 4.6/2.22 ms,

10° flip angle, 10 mm thickness; 256×125 , 360 mm field of view, 25 ms temporal resolution, 25–35 frames per R–R interval).

2.3. MRI data analysis

Cardiac functional and structural measurements including LV EF, cardiac output, volumes, and mass were using commercially available software (MASS®, Medis, the Netherlands). Tagged ventricular magnetic resonance images were analyzed by HARP MRI (Diagnosoft, Inc., Palo Alto, California) [13]. The average peak midwall circumferential strain (Ecc, in percentage) in the systolic phase was determined in all myocardial segments at the basal, mid and apical levels as previously described [14]. The value of Ecc is normally negative during the contraction of the ventricle as it corresponds to relative circumferential shortening. Less negative Ecc (or positive Ecc) indicates diminished regional LV shortening. Tagged images were analyzed by a single reader who was blinded to the participants' demographics and steatosis results.

Java-based MR software (jMRUI v.3.0 software; A. van den Boogaart, Katholieke Universiteit Leuven, Leuven, Belgium) [15] was used to process spectral data and the reader was also blinded to the participants' characteristics and LV function results. The areas under the resonance frequency estimates of lipids at 0.9 and 1.3 parts-per-million (ppm) were summed to quantify myocardial triglycerides content and related to water in unsuppressed spectra. Myocardial fat fraction was expressed as the ratio of fat to water and reported as a percentage.

Visceral and subcutaneous adipose tissue was identified by selecting the region of interest and thresholding the pixel signal intensity using MASS software. Adipose tissue volumes were quantified by converting the number of pixels to square centimeters and multiplied by the thickness of slices. The total volume of VAT and SAT was calculated by totaling the volumes of the individual slices.

2.4. Statistical analysis

Statistical analysis was performed with SAS (SAS 9.3, SAS Institute, Cary, NC). All continuous parameters were summarized by medians and interquartile ranges (IQRs), and all categorical parameters were summarized as proportions. To compare between-group (normal weight, overweight, and obesity) differences in demographic and clinical characteristics, lipid profiles, and other factors, the non-parametric Wilcoxon test was used for continuous variables and the Fisher's exact test was employed for categorical variables.

Since the distribution of myocardial triglyceride content was considerably skewed, square-root-transformed myocardial triglyceride content was used as the outcome variable in the regression analyses. Since the ordinary least-squares regression model minimizes the sum of all the residuals and thus is sensitive to outliers, a robust regression model with the least trimmed squares (LTS) estimation method was used to provide robust results in the presence of outliers [16]. The Framingham risk score was calculated to estimate the CAD risk [17]. Univariate robust regression models were first fitted to evaluate the crude association between myocardial triglyceride content and each of the factors—including age, sex, total serum cholesterol, HDL-cholesterol, LDL-cholesterol, serum triglycerides, hsCRP, leptin, cigarette smoking, alcohol use, glucose level, systolic BP, diastolic BP, body mass index (BMI), and Framingham risk score, individually. Those factors that were significant at the $P < 0.10$ level in the univariate models were put into the multivariate models to identify the ones independently associated with the presence of cardiac steatosis. Those variables that ceased to make significant contributions to the models based on these criteria were deleted in a stagewise manner and a new model was refitted. This process of eliminating, refitting, and verifying continued until all of the variables included were statistically significant, yielding a final model. To examine

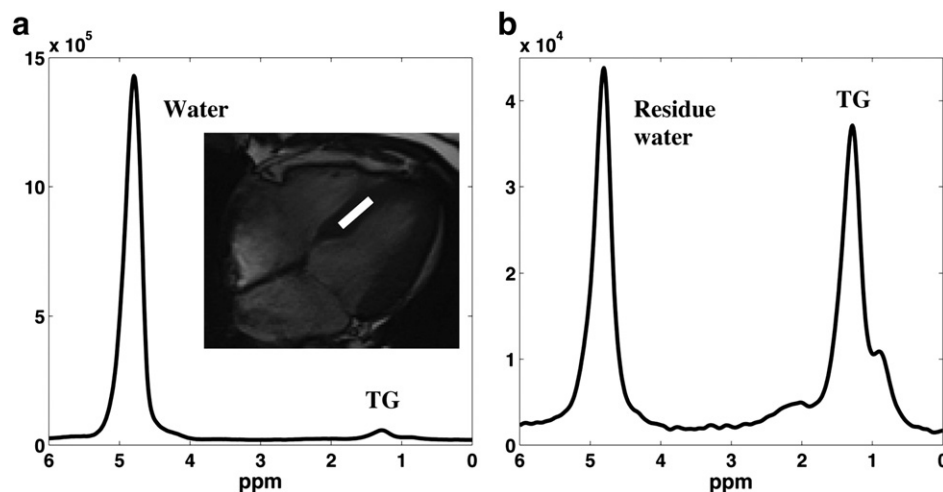


Fig. 1. Proton MR spectroscopic image of septal myocardial fat. (a) Nonwater-suppressed spectrum of interventricular septal fat. MR image (inset) shows voxel positioning (white rectangle) in the septum. (b) Water-suppressed spectrum of the same subject; TG: triglyceride peaks at 0.9 and 1.3 ppm. Amplitude is expressed in arbitrary units.

whether cardiac steatosis influences regional/global LV function/structure a univariate robust regression model was first fitted for each LV parameter and then multivariate robust regression analysis was performed for each parameter, adjusting for potential confounding factors. To account for the correlation among the 6 regional strains (Ecc), which were obtained from the same person, a generalized estimating (GEE) model was used to examine whether elevated myocardial triglyceride content is associated with regional left ventricular function. The p-values reported are two-sided. A p-value <0.05 indicated statistical significance.

3. Results

Among the 109 study participants, 17 with hypertension and/or diabetes were excluded from the analyses (8 with hypertension, 7 with diabetes, and 2 with both hypertension and diabetes). Thus, 92 without hypertension or diabetes were included in this study.

3.1. General characteristics

The median age (with IQR) was 37 (27–44) years. Thirty-eight (41.3%) were males. Sixty-two percent were cigarette smokers, and 50% consumed alcohol. According to the Framingham risk score algorithm, all the study participants had low risk of coronary artery disease (CAD). The median BMI was 27.7 (22.5–34.3) kg/m². Among these 92, 31 (33.7%) were of normal weight (18.5 ≤ BMI < 25), 23 (25.0%) were overweight (25 ≤ BMI < 30), and 38 (41.3%) were obese (BMI ≥ 30). The median myocardial triglyceride content was 0.5 (IQR: 0.3–1.0). The distribution of myocardial triglyceride content was highly skewed (Fig. 2).

The general, laboratory and clinical characteristics of the study participants by sex are presented in Table 1. The median myocardial triglyceride contents for men, and women were 0.4% (IQR: 0.3–0.8), and 0.7 (IQR: 0.4–1.1), respectively. The median myocardial triglyceride content for those with normal weight (BMI < 25 kg/m²), overweight (25 kg/m² ≤ BMI < 30 kg/m²), and obesity (BMI ≥ 30 kg/m²), were 0.4% (IQR: 0.3–0.5), 0.6% (IQR: 0.4–0.8), and 0.9 (IQR: 0.5–1.2), respectively (Fig. 3).

3.2. Factors associated with myocardial triglyceride levels

According to univariate robust regression analyses, factors positively associated with myocardial triglyceride content at the 0.10 level included BMI, waist circumference, waist/hip ratio, hsCRP, hsCRP > 2 mg/dL, leptin, fasting glucose, hepatic triglyceride, subcutaneous fat, and visceral fat. Male sex and serum high-density lipoprotein

cholesterol were negatively associated with myocardial triglyceride content. According to univariate analyses, visceral fat and BMI explained 45% and 43% of variation in myocardial triglycerides, respectively (Figs. 4 and 5). The final robust regression model indicated that serum high-density lipoprotein cholesterol, hepatic triglyceride, and visceral fat were independently associated with myocardial triglyceride content (Table 2). These three factors explained 49% of variation in myocardial triglycerides (final model, Table 2). However, BMI alone explained 43% of variation in myocardial triglycerides (alternative model, Table 2).

3.3. Associations between LV volumes, EF, and myocardial triglyceride content

By univariate robust regression analyses, there was a significant negative association of myocardial triglyceride content with end-diastolic volume index ($R^2 = 0.08$, $p = 0.002$), LV end-systolic volume ($R^2 = 0.06$, $p = 0.02$), and end-systolic volume index ($R^2 = 0.09$, $p = 0.002$). There was a positive association between myocardial triglyceride content and LV EF ($R^2 = 0.04$, $p = 0.04$). However, after controlling for age, sex, BMI, serum vitamin D and serum leptin, myocardial triglyceride content was not significantly associated with any above-mentioned parameters (Table 3).

3.4. Associations between regional LV function and myocardial triglyceride content

Of the 92 participants, data for regional myocardial circumferential strain for each left ventricular wall segment (anterior, anteroseptal, inferior, inferoseptal, inferolateral, and anterolateral) were available from 74 participants. For male participants, myocardial triglyceride content was not univariately or multivariately associated with regional strain. However, for female participants, myocardial triglyceride content was independently associated with regional strain. The significant association was not observed in all participants (Table 4).

4. Discussion

4.1. Major findings

To our best knowledge, this is the largest study to explore factors that are independently associated with myocardial triglyceride content, and to investigate whether myocardial triglyceride content is associated with cardiac volumes and EF in healthy AAs without hypertension and/or diabetes. The most important findings of this study are (1) cardiac stenosis is associated with obesity, measured by BMI or by visceral fat, and (2) elevated myocardial triglyceride content was associated with regional LV dysfunction in women.

4.2. Myocardial triglyceride and cardiac steatosis

Although the feasibility of obtaining ¹H MRS spectra of human myocardial triglycerides was demonstrated in 1994 [10], no human studies were published until 2003 [2]. That landmark study included 15 healthy study subjects and demonstrated that triglyceride was detectable in those who were very lean, and that myocardial triglyceride was linearly associated with BMI (though not significantly so, probably due to a small sample size). Actually, the general characteristics of this study population (median age: 39, 46.7% male, median BMI: 27, median systolic BP: 126 mm Hg, and diastolic BP: 80 mm Hg) in [2] were quite similar to those in our study (median age: 37, 41.3% male, median BMI: 27.7, median systolic BP: 113 mm Hg, and diastolic BP: 65 mm Hg) with the exception that AAs constituted the study population in this report. In our study, myocardial triglyceride was also detectable in the three leanest subjects, and was 0.37, 0.28, and 0.26, for those with BMIs of 17.9, 17.3, and 17.7, respectively.

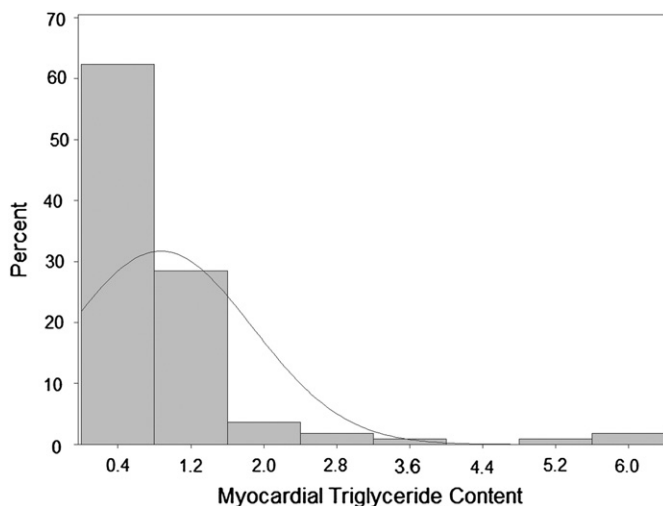


Fig. 2. Distribution of myocardial triglyceride content. The histogram of myocardial triglyceride content with a superimposed normal curve, indicating that the distribution of myocardial triglyceride content was highly skewed.

Table 1
Characteristics of 92 healthy African American study participants in Baltimore, Maryland*

Characteristic	Total (N = 92)	Male (N = 38)	Female (N = 54)	p-value
Age (year)	37 (27–44)	34 (26–42)	37 (28–47)	0.52
Cigarette smoking (%)	62.0	81.6	48.2	0.001
Years of cigarette smoking	5 (0–15)	12 (2–20)	0 (0–10)	0.001
Alcohol use (%)	50.0	65.8	38.9	0.01
Years of alcohol use	0 (0–11)	5 (0–15)	0 (0–5)	0.016
BMI (kg/m ²)	27.7 (22.5–34.3)	24.8 (21.3–29.5)	30.7 (25.6–37.8)	0.0005
Waist circumference (cm)	93 (81–102)	89 (81–97)	97 (80–105)	0.09
Waist/hip ratio	0.85 (0.81–0.91)	0.89 (0.84–0.92)	0.83 (0.80–0.88)	0.024
hsCRP ≥ 2 mg/dL (%)	38.0	21.1	50.0	0.005
hsCRP (mg/dL)	1.2 (0.4–3.5)	0.6 (0.2–1.5)	2.2 (0.6–4.8)	0.43
Systolic BP (mm Hg)	113 (105–124)	117 (107–126)	111 (105–120)	0.18
Diastolic BP (mm Hg)	65 (59–74)	64 (60–73)	66 (58–75)	0.98
Glucose (mg/dL)	81 (77–89)	80 (77–90)	82 (78–89)	0.56
Vitamin D (serum 25(OH)D) (ng/mL)	12.6 (9.0–17.2)	13.3 (9.0–17.0)	12.0 (9.0–17.2)	0.98
Leptin (ng/mL)	10.6 (3.9–37.0)	3.4 (2.7–4.7)	36 (12–52)	<0.0001
Total cholesterol (mg/dL)	168 (148–191)	161 (147–186)	172 (149–198)	0.39
LDL-C (mg/dL)	94 (77–114)	87 (72–102)	100 (79–119)	0.09
HDL-C (mg/dL)	58 (49–64)	54 (45–64)	59 (51–64)	0.28
Triglycerides (mg/dL)	70 (56–102)	70 (56–115)	70 (56–98)	0.63
Framingham risk score	2 (1–3)	3 (2–4)	1 (1–2)	<0.0001
Framingham score <10.0 (%)	100.0	100.0	100.0	1.00
Hepatic triglycerides (%)	1.3 (0.7–4.6)	1.0 (0.4–1.5)	2.1 (0.9–5.4)	0.008
Myocardial triglycerides (%)	0.5 (0.3–1.0)	0.4 (0.3–0.8)	0.7 (0.4–1.1)	0.023
Subcutaneous fat (mL)	796 (476–1295)	441 (253–733)	1105 (730–1420)	<0.0001
Visceral fat (mL)	402 (294–582)	348 (267–458)	473 (337–650)	0.001
LV end-diastolic volume (mL)	153 (134–174)	172 (156–194)	143 (122–160)	<0.0001
LV end-systolic volume (mL)	70 (57–82)	79 (72–88)	62 (51–71)	<0.0001
LV stroke volume (mL)	83 (74–99)	92 (81–110)	80 (71–90)	0.0005
Cardiac output (mL)	5.8 (5.0–6.8)	5.8 (5.1–6.8)	5.6 (4.7–6.7)	0.09
Ejection fraction (%)	55 (52–59)	54 (51–58)	56 (52–62)	0.03
LV mass (gm)	118 (91–134)	134 (122–148)	102 (84–118)	<0.0001
LV mass to volume ratio	0.75 (0.67–0.81)	0.77 (0.71–0.84)	0.70 (0.64–0.77)	0.0008
LV end-diastolic volume index (mL/m ²)	88 (74–91)	90 (84–97)	76 (69–81)	<0.0001
LV end-systolic volume index (mL/m ²)	38 (31–41)	41 (39–44)	33 (29–39)	<0.0001
LV stroke volume index (mL/m ²)	44 (40–51)	48 (44–54)	42 (39–47)	0.0002
Cardiac index (mL/m ²)	3.1 (2.7–3.4)	3.1 (2.7–3.6)	3.1 (2.6–3.4)	0.23
LV mass index (g/m ²)	61 (53–68)	69 (65–76)	54 (47–61)	<0.0001
Heart rate (beats per minute)	64 (58–72)	60 (58–69)	66 (58–74)	0.12

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; glucose, fasting glucose; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BSA, body surface area; Framingham score, Framingham risk score.

* Median (interquartile range) for continuous variables, proportion (%) for categorical variables.

4.3. Factors associated with myocardial triglyceride and cardiac steatosis

According to our univariate analysis, myocardial triglyceride had outliers and was highly skewed (Fig. 2). Thus, the conventional

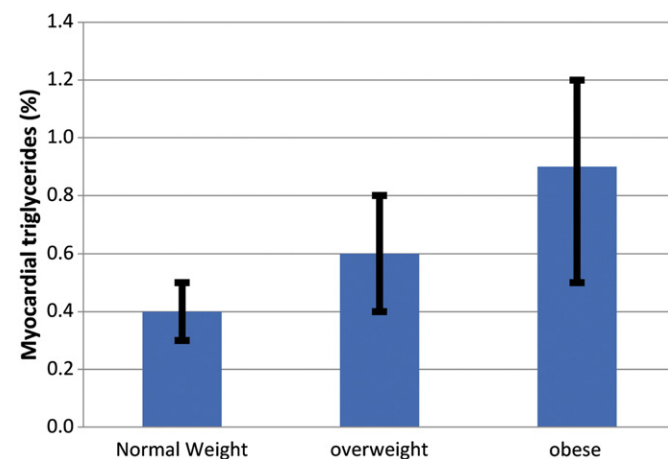


Fig. 3. Myocardial triglyceride levels by obesity status. The median myocardial triglyceride levels with interquartile ranges (error bars) by obesity status (normal weight: BMI 18–<25, overweight: BMI 25.1–<30, and obese: BMI ≥ 30).

regression analysis (including correlation analysis) may not be adequate for analyzing the data. We used square-root transformed myocardial triglyceride and robust regression analysis to explore factors that

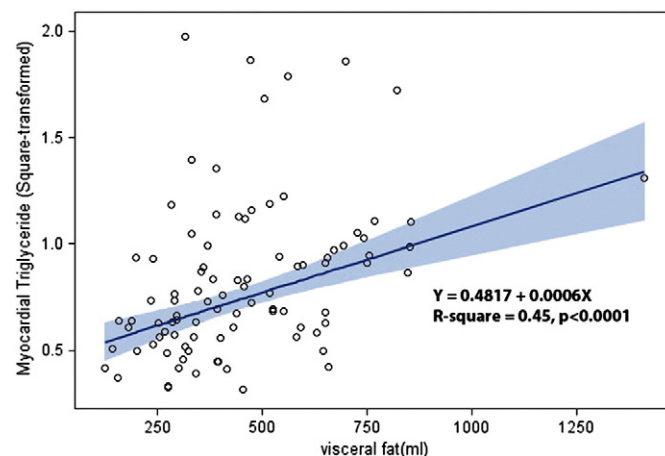


Fig. 4. The relationship between myocardial triglyceride content (square-root transformed) and visceral fat. Univariate robust regression with the LTS estimator was run to investigate the relationship between myocardial triglyceride and visceral triglyceride. Robust regression $R^2 = 0.45$. Y is myocardial triglyceride (square-root transformed), while X is visceral triglyceride.

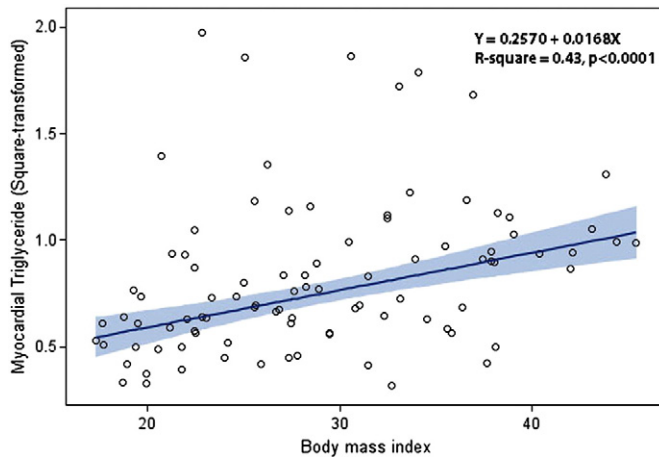


Fig. 5. The relationship between myocardial triglyceride content (square-root transformed) and BMI. Univariate robust regression with the LTS estimator was run to investigate the relationship between myocardial triglyceride and BMI. Robust regression $R^2 = 0.43$. Y is myocardial triglyceride (square-root transformed), while X is BMI.

were associated with (square-root transformed) myocardial triglyceride.

In the univariate analyses including all study participants, we found that leptin was significantly associated with myocardial triglyceride. As one of the most important adipose-derived hormones, plasma leptin was strongly associated with abdominal fat, increased in proportion to body fat mass and thus is considered a good indicator of adiposity [18,19]. hsCRP was also univariately associated with myocardial triglyceride. This finding is in accordance with a recent publication [20], suggesting that inflammation contributes to the development of cardiac steatosis. Univariate analysis also indicated that BMI was significantly associated with myocardial triglyceride. This finding is also consistent with previous reports in other populations [2,21]. Our analysis showed that female gender was univariately associated with elevated myocardial triglyceride content, however, the association disappeared in

multivariate analysis since female participants (median BMI: 30.7, median visceral fat: 473 mL) in this study were significantly more obese than their male counterparts (median BMI: 24.8, median visceral fat: 348 mL). This study also showed that HDL-cholesterol was negatively associated with myocardial triglyceride. This finding is consistent with a recent report, indicating that pericardial and periaortic lipid negatively correlated with HDL-cholesterol [21]. Finally, univariate analyses also showed that hepatic, subcutaneous, and visceral fat were all associated with myocardial triglyceride content.

The results of the final robust regression model including all study participants indicated that MRI-measured visceral fat, MRS-measured hepatic fat and HDL were independently associated with myocardial triglyceride content. Myocardial fat was not previously reported to be associated with visceral fat in healthy people. This association was identified in obese Caucasian men [22], however, the alleged association was based on simple correlation analyses and was not adjusted for potential confounding factors [22]. Hepatic fat was associated with myocardial fat, however, hepatic fat only explained less than 25% of variation in myocardial fat, suggesting that hepatic steatosis and cardiac steatosis may have different responsible mechanisms. This cross-sectional study cannot conclude which factor occurred first.

Although the above-mentioned three factors were identified with the use of a statistical model, this model may have only theoretical implications since an important clinical question and relevance is the issue of whether it is necessary to perform cardiac MR spectroscopy to learn whether myocardial triglycerides are elevated. Practically speaking, the contribution of these factors is relatively minor when compared to BMI. This alternative model in Table 2 showed that BMI explained 43% of variation in myocardial triglyceride, while the three factors in the final model only explained 6% more variation in myocardial triglyceride than BMI alone. Therefore, this study suggests that a simple marker, BMI may be appropriate to identify high risk individuals for intervention/prevention.

4.4. Cardiac steatosis and LV volumes and EF

Univariate analysis suggested that there were potentially negative associations between myocardial triglyceride content and LV volumes

Table 2

Demographic, laboratory, and clinical factors in relation to myocardial triglyceride (square-root transformed), robust regression analysis with LTS estimation.

Variable	Myocardial triglyceride content (square-root transformed)				Final model, $R^2 = 0.49$		Alternative model, $R^2 = 0.43$	
	Univariate analysis			Regression estimate (SE)	p-value	Regression estimate (SE)	p-value	Regression estimate (SE)
	Regression estimate (SE)	R^2	p-value					
Age (year)	0.0032 (0.0026)	0.04	0.22					
Male sex	−0.1264 (0.0553)	0.05	0.02					
Cigarette smoking	−0.0163 (0.0578)	0.00	0.78					
Years of cigarette smoking	0.0011 (0.0026)	0.01	0.68					
Alcohol use	−0.0364 (0.0562)	0.01	0.52					
Years of alcohol use	0.0005 (0.0027)	0.01	0.84					
Leptin (ng/mL)	0.0038 (0.0012)	0.24	0.001					
hsCRP (mg/dL)	0.0134 (0.0056)	0.21	0.017					
hsCRP > 2 mg/dL	0.1567 (0.0523)	0.28	0.003					
Systolic BP (mm Hg)	0.0018 (0.0024)	0.04	0.45					
Diastolic BP (mm Hg)	0.0014 (0.0032)	0.08	0.65					
Fasting glucose (mg/dL)	0.0105 (0.0035)	0.18	0.003					
BMI (kg/m ²)	0.0168 (0.0031)	0.43	<0.0001					0.0168 (0.0031)
Waist circumference (cm)	0.0073 (0.0016)	0.35	<0.0001					<0.0001
Waist/hip ratio	1.3838 (0.3830)	0.13	0.0003					
Total cholesterol (mg/dL)	−0.0008 (0.0008)	0.07	0.31					
LDL-C (mg/dL)	0.0003 (0.0009)	0.00	0.78					
HDL-C (mg/dL)	−0.0040 (0.0017)	0.08	0.02	0.0032 (0.0014)	0.026			
Triglycerides (mg/dL)	0.0002 (0.0007)	0.02	0.74					
Framingham score	0.0014 (0.0178)	0.00	0.94					
Hepatic triglyceride (%)	0.0359 (0.0066)	0.24	<0.0001	0.0102 (0.0049)	0.036			
Subcutaneous fat (mL)	0.0002 (0.0000)	0.33	0.0003					
Visceral fat (mL)	0.0006 (0.0001)	0.45	<0.001	0.0004 (0.0001)	0.0005			

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Framingham score, Framingham risk score.

Table 3

Association between LV structure/function and myocardial triglyceride, robust regression analysis.

Outcome variables	Myocardial triglyceride content (%)				
	Univariate analysis			Multivariate analysis*	
	regression estimate (SE)	R ²	p-value	regression estimate (SE)*	p-value
LV end-diastolic volume (mL)	−8.23 (4.11)	0.04	0.05	−5.28 (3.25)	0.10
LV end-systolic volume (mL)	−5.42 (2.26)	0.06	0.009	−3.69 (1.97)	0.06
LV stroke volume (mL)	−1.47 (2.52)	0.003	0.56	−1.75 (2.20)	0.43
Cardiac output (mL)	0.11 (0.17)	0.005	0.50	0.02 (0.15)	0.88
LV ejection fraction (%)	1.60 (0.77)	0.03	0.04	0.85 (0.78)	0.28
LV mass (g)	−2.29 (3.85)	0.004	0.55	−2.42 (2.53)	0.34
LV mass/volume ratio (%)	0.02 (0.01)	0.02	0.21	0.02 (0.01)	0.25
LV end-diastolic volume index (mL/m ²)	−5.05 (1.62)	0.08	0.002	−2.05 (1.43)	0.15
LV end-systolic volume index (mL/m ²)	−3.28 (1.05)	0.09	0.002	−1.57 (0.94)	0.10
LV stroke volume index (mL/m ²)	−1.31 (1.02)	0.01	0.20	−0.48 (1.04)	0.65
Cardiac index (mL/m ²)	0.07 (0.07)	0.007	0.35	0.07 (0.07)	0.35
LV mass index (g/m ²)	−1.66 (1.55)	0.01	0.28	−0.38 (1.14)	0.74

* Adjusted for age, sex, BMI, and leptin.

and a positive association with EF. Despite the fact that the above-mentioned associations diminished after further adjustments for potential confounding factors, a larger study is needed to further explore the relationships between cardiac steatosis and LV volumes and EF.

4.5. Cardiac steatosis and regional LV function

As discussed above, this study did not observe significant associations between myocardial triglyceride content and LV function or structure. The lack of the associations may be due to the fact that all study participants were cardiovascularly healthy. To explore whether elevated myocardial triglyceride content adversely influences LV function, we assessed the associations between myocardial triglyceride content and regional LV strains. Since we were not interested in identifying which wall segment(s) demonstrated an association between peak strain myocardial triglyceride content, and since all strains within the same person are highly correlated to each other, a GEE model was used to assess the relationship between myocardial triglyceride content and peak strain. A statistically significant association between myocardial triglyceride content and peak strain in women suggests that excess myocardial triglyceride may be associated with regional LV

dysfunction. Nevertheless, a significant association was not observed in men. A possible interpretation of lack of association between myocardial triglyceride content and regional LV function in men is that the myocardial triglyceride levels in women (median with IQR: 0.7 (0.4–1.1)) were significantly higher than those in men (median with IQR: 0.4 (0.3–0.8), $p = 0.02$, Wilcoxon rank-sum test) and a possible effect of a lower myocardial triglyceride content on regional LV function is difficult to identify without a large sample.

This study found that vitamin D levels were independently associated with peak strain in women, implying that high levels of vitamin D are associated with better regional LV function. In animal studies, evidence suggests that vitamin D deficiency is associated with increased cardiac contractility, hypertrophy, and fibrosis [22]. However, a possible impact of vitamin D levels on regional function in human has never been reported.

4.6. Potential mechanisms

The exact mechanism by which cardiac steatosis develops is not fully understood. Excess triglyceride is stored primarily in the adipocytes [9,23]. During triglyceride deposition, adipocytes may secrete a

Table 4

Association between midwall peak circumferential strain (Ecc) of the left ventricular segments and myocardial triglyceride, generalized estimating equation (GEE) analysis (N = 74).

Variable	Outcome variable: midwall peak circumferential strain (Ecc)					
	Univariate model		Initial model*		Final model	
	Regression estimate (SE)	p-value	Regression estimate (SE)	p-value	Regression estimate (SE)	p-value
<i>Males</i>						
Age (year)	−0.038 (0.028)	0.18	−0.036 (0.027)	0.19		
BMI (kg/m ²)	−0.100 (0.052)	0.05	−0.108 (0.074)	0.15		
Serum 25(OH)D (ng/mL)	−0.004 (0.038)	0.92	0.039 (0.039)	0.32		
Leptin (ng/mL)	−0.082 (0.041)	0.04	0.030 (0.062)	0.62		
Myocardial triglycerides (%)	−0.486 (0.447)	0.28	−0.231 (0.387)	0.55		
<i>Females</i>						
Age (year)	−0.014 (0.026)	0.59	0.001 (0.032)	0.97		
BMI (kg/m ²)	0.023 (0.053)	0.66	−0.033 (0.091)	0.72		
Serum 25(OH)D (ng/mL)	−0.055 (0.033)	0.10	−0.071 (0.030)	0.02	−0.061 (0.029)	0.039
Leptin (ng/mL)	0.013 (0.014)	0.34	0.023 (0.028)	0.41		
Myocardial triglycerides (%)	0.465 (0.309)	0.13	0.660 (0.267)	0.01	0.535 (0.272)	0.049
<i>All</i>						
Age (year)	−0.028 (0.022)	0.20	−0.011 (0.024)	0.64		
BMI (kg/m ²)	−0.053 (0.036)	0.14	−0.030 (0.060)	0.61		
Serum 25(OH)D (ng/mL)	−0.037 (0.026)	0.16	−0.031 (0.029)	0.28		
Leptin (ng/mL)	−0.017 (0.011)	0.14	−0.008 (0.019)	0.67		
Myocardial triglycerides (%)	−0.078 (0.295)	0.79	0.010 (0.258)	0.67		

Abbreviations: BMI, body mass index (kg/m²); serum 25(OH)D = 25-hydroxyvitamin D.

* Adjusted for age, sex, BMI, serum 25-hydroxyvitamin D, and serum leptin.

signal limiting triglyceride accumulation in nonadipocytes [9]. When adipocytes can no longer store triglycerides, nonadipocytes are then exposed to high levels of triglycerides, and develop steatosis, and lipopoptosis, leading to cardiac dysfunction and cardiomyopathy [9,22,24].

4.7. Study limitations

This study has several limitations. First, because all the study participants were AAs, the results may not be generalized to other race/ethnic groups without caution. Second, the data presented here are cross-sectional and causality cannot be inferred. The relationships between changes in myocardial triglyceride and LV function will be investigated when follow-up studies are completed. Third, due to the nature of a cross-sectional design, some hidden confounding factors, such as socioeconomic status, were not adjusted for.

5. Conclusions

This study's findings of myocardial triglyceride accumulation, associated factors, and relation to LV parameters in healthy AAs have important potential implications. Myocardial triglyceride accumulation occurs in this group and is related to other measures of fat accumulation. Despite the fact that there did not appear to be a negative association between myocardial triglyceride and global left ventricular function parameters in healthy AAs, this investigation revealed that a higher myocardial triglyceride level appeared to be associated with worse regional LV function in cardiovascularly healthy women. A large study is needed to explore this association in men.

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