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Increased severity of liver fat content and liver fibrosis in non-alcoholic fatty liver disease correlate with epicardial fat volume in type 2 diabetes: A prospective study

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Abstract

Objectives—To determine whether severity of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis quantitatively assessed in individuals with diabetes mellitus (DM)-2 correlate with increased coronary heart disease (CHD) risk using non-invasive markers.

Methods—We conducted a single-centre, prospective, cross-sectional study in 100 consecutive diabetic individuals without known CHD recruited between March 2013 and September 2014. History, physical examination, serum markers, cardiac computed tomography (CT), magnetic resonance (MR) imaging-estimated proton density fat fraction (PDFF) and MR elastography (MRE) were obtained for 95 participants. Written informed consent was provided. Institutional review board approved this study. Spearman rank correlation was performed to assess for

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Rohit Loomba MD MHSc.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in the following:

Doycheva I, Cui J, Nguyen P, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. *Aliment Pharmacol Ther.* 2016;43(1):83–95.

Methodology

- Prospective
- Cross-sectional study
- Performed at one institution

correlations. Multiple linear regression model determined independent predictors of epicardial adipose tissue (EAT) volume.

Results—A p value < 0.05 determined statistical significance. The EAT volume was higher in the NAFLD group, defined as MR-imaging PDFF $\geq 5\%$, compared to the non-NAFLD group (126.5 ml (IQR 80.9) versus 85.4 ml (IQR 44.7), $p=0.002$). MR imaging-PDFF correlated with EAT ($r=0.42$, $p < 0.0001$). MR imaging-PDFF and liver fibrosis were independently associated with EAT.

Conclusions—Higher liver fat content and liver fibrosis may portend worse cardiovascular risk in diabetics.

Keywords

Non-alcoholic fatty liver disease; Liver fibrosis; Magnetic resonance imaging; Coronary disease; Multidetector computed tomography

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a growing epidemic that is closely linked to metabolic syndrome and insulin resistance with a prevalence of 69–87 % in the setting of diabetes [1]. A growing body of evidence supports the association between NAFLD and increased cardiovascular risk independent of traditional risk factors, including those shared with metabolic syndrome [2]. In diabetics, prior studies have demonstrated that NAFLD is independently associated with cardiovascular disease prevalence, significant coronary artery stenosis and cardiovascular events [3–7]. Therefore, diagnosis of NAFLD in diabetic individuals may warrant aggressive cardiovascular risk factor modification and targeted therapy for NAFLD [1].

The utility of imaging-based markers of subclinical cardiovascular disease, coronary artery calcium (CAC), a robust tool in the assessment of cardiovascular risk, and more recently epicardial adipose tissue (EAT) in individuals with NAFLD and liver fibrosis has yet to be fully elucidated [4, 5, 8–13]. Recently, epicardial fat thickness was shown to be independently associated with severity of liver fibrosis on biopsy specimens [14]. In those with type 2 diabetes mellitus (DM-2), evidence supporting an association between NAFLD and CAC is scant and conflicting [6, 15, 16]. Epicardial adipose tissue (EAT) is a fat depot that is emerging as a novel marker of subclinical cardiovascular disease, and, like CAC score, it can be derived from non-contrast cardiac computed tomography (CT). Several studies have demonstrated that EAT provides incremental prognostic information over and above CAC and traditional risk factors for the prediction of major adverse cardiac events [17, 18]. EAT is unique to other fat depots in the body in that it may exert proatherogenic effects on the coronary arteries through local inflammatory mediators and infiltration of inflammatory cells [19–24]. Additionally, EAT seems to be higher in cardiac CT angiography-classified noncalcified or mixed plaques as opposed to no plaque or calcified plaques [25]. Whereas CAC is present in advanced stages of existing arterial plaque, EAT may be involved in plaque development and therefore may potentially be an earlier marker

of cardiovascular risk, particularly in an asymptomatic population with no or little CAC [26].

Although EAT has been shown to be associated with CAC in diabetic individuals [27–31], the relationship between NAFLD and EAT to our knowledge has yet to be investigated in the setting of DM-2. It remains unclear whether imaging-based biomarkers improve upon traditional risk factors for assessment of cardiac heart disease (CHD) risk in diabetic individuals with NAFLD. Further, whether severity of NAFLD and liver fibrosis in diabetic individuals correlates with a graded increase in cardiovascular risk has not been evaluated. Magnetic resonance (MR) imaging-estimated proton density fat fraction (PDFF) enables objective and accurate estimation of NAFLD severity [32–36]. The purpose of this study was: (1) to determine whether severity of NAFLD and liver fibrosis quantitatively-assessed in individuals with diabetes mellitus (DM)-2 correlate with increased coronary heart disease (CHD) risk using non-invasive markers and (2) to determine whether NAFLD and liver fibrosis are associated with EAT independent of traditional risk factors.

Materials and methods

Study design

To this end, we conducted a single-centre, prospective, cross-sectional study in 100 consecutive diabetic individuals without known CHD who were recruited through newspaper advertisements and from primary-care clinics in the greater San Diego area between March 2013 and September 2014. Of the 195 individuals screened, 95 were excluded due to at least one of the following criteria: prior history of heart attack, coronary artery stent placement, chest pain requiring hospital visit, stroke, diagnosis of congestive heart failure, evidence of chronic liver disease as determined by presence of hepatitis B surface antigen or hepatitis C antibody; history or imaging evidence of other chronic liver disease; history of medications associated with development of NAFLD, such as tamoxifen, amiodarone or methotrexate; severe end-organ damage due to diabetes mellitus; alcohol consumption > 30 g per day within the preceding 10 years or > 10 g per day in the prior year as determined by the Alcohol Use Disorders Identification Test (AUDIT) questionnaire, positive HIV test, pregnancy or contraindication to MRI. A feasibility study on screening for NAFLD and hepatic fibrosis using MR imaging-PDFF and MR elastography (MRE), respectively, on the 100 diabetic individuals included in this study was previously published [37].

Participants underwent a research visit performed at the University of California San Diego (UCSD) Clinical and Translational Research Institute for medical history, physical examination, anthropometric measurements and biochemical and serological markers in fasting state including evaluation for metabolic syndrome, insulin resistance and Framingham Risk Score (FRS). Participants completed the AUDIT questionnaire to assess for excessive alcohol consumption. Within 30 days of the research visit, individuals subsequently underwent cardiac CT for CAC score and epicardial fat volume analysis, MR-imaging PDFF for evaluation of NAFLD and MRE for evaluation of liver fibrosis. This study was conducted at the University of California San Diego and was approved by the

institutional review board. All participants provided written informed consent upon enrolment.

MRI-PDFF and MRE

MRI was performed using a 3T research scanner (GE Signa EXCITE HDxt, GE Healthcare, Waukesha, WI, USA). Participants were asked to fast for at least 4 h prior to the scan. Scan was performed in the supine position using a torso phased array coil positioned over the abdomen. The technique for MR-imaging PDFF and MRE have been previously described, and imaging analysis was performed by trained analysts with at least a bachelor's degree and 6 months' experience under the supervision of a radiology investigator (C.S.) [32, 38]. The MR-imaging PDFF technique utilises a low-flip angle, gradient echo sequence to acquire multiple echoes in which fat and water protons are in and out of phase. Data from echoes at multiple echo times were post processed offline using a custom plug-in algorithm on open-source software (Osirix; Osirix Foundation, Geneva, Switzerland) to create MR imaging-PDFF maps. The data are passed through a fitting algorithm to estimate the fat and water proton densities and T2* in each pixel using non-linear least-squares fitting. PDFF is the ratio of fat proton density to total proton density calculated from regions of interest (ROIs) on liver parenchyma on PDFF maps. NAFLD was defined as MR-imaging PDFF $\geq 5\%$ [39].

For MRE, an acoustic passive driver was fitted around the body wall over the liver and connected to an acoustic active driver that delivered continuous vibrations at 60 Hz to produce shear waves in the liver. 2D gradient-recalled echo MRE pulse sequence was repeated at four non-contiguous slices through the widest transverse dimension of the liver during breath-hold. Wave images depicting shear waves in the liver were processed on the scanner using direct inversion algorithm to generate elastograms depicting stiffness in units of kiloPascals (kPa). Using a custom software package, average per pixel liver stiffness was calculated by drawing ROIs on each of the four slices. Advanced fibrosis was defined as ≥ 3.6 kPa based upon previously published studies [35, 40].

Cardiac CT and CAC

Non-contrast cardiac prospective electrocardiogram-triggered volumetric CT was performed utilising a 320-slice CT scanner (Aquilion One, Toshiba Medical Systems, Otawara, Japan). Medications for heart rate control or vasodilation were not administered prior to scan. Scan length spanned the carina to below the level of the heart and was performed during a breath-hold at end inspiration. Scan collimation was 320×0.5 mm, and the field of view was 220 mm. Radiation dose parameters were 120 kVp and tube current ranging from 40 mA to 580 mA (± 10) determined by SUREExposure 3D scanner software. Rotation time was 0.35 s. Reconstruction slice thickness was 3 mm using a filter convolution of 5. CAC was quantified with the Agatston scoring method, previously described, by a fellowship-trained cardiac radiologist using independent post-processing software (Vital Images, Inc., Minnetonka, MN, USA) [41].

Epicardial fat volume analysis

EAT was calculated utilising independent semi-automated volume analysis software (GE Health Care, Waukesha, WI, USA). The pericardium was traced from three slices, or 9 mm,

above the level of the left main coronary artery ostium to the bottom of the pericardium by a fellowship-trained cardiac radiologist. Manual tracings were performed on the most superior image, the most inferior image and select images of the volume. Automated software tracings on other images were interpolated and manually corrected. In regions where pericardial thickening or fluid was present, the visceral pericardium was traced as shown in Fig. 1. To calculate the epicardial fat, pixels between -30 to -190 Hounsfield units (HU) were included in the volume of EAT [42] extending no more than 4 HU beyond the range with an adjustable sliding axis, as the software does not allow exact HU range determination.

Covariates

Demographic data acquired during the research visit included age, sex, race, body mass index (BMI) and waist circumference. Hypertension was defined as blood pressure ≥ 130 systolic or ≥ 85 mm Hg diastolic or use of antihypertensive medication. Metabolic syndrome was defined according to the American Heart Association and the National Heart, Lung, and Blood Institute criteria with three of the five following criteria met: hypertension, fasting glucose ≥ 100 mg/dl or receiving therapy for hyperglycaemia; hypertriglyceridaemia ≥ 150 mg/dl or receiving therapy for hypertriglyceridaemia; high-density lipoprotein cholesterol (HDL-C) < 50 mg/dl in women and < 40 mg/dl in men or receiving therapy for reduced HDL-C; waist circumference ≥ 102 cm in men and ≥ 88 cm in women or ≥ 90 cm in Asian men and ≥ 80 cm in Asian women, duration of diabetes, diabetic complications (diabetic retinopathy, neuropathy or nephropathy), current treatment of diabetes, antilipemic therapy and current therapy with vitamin E [43]. Insulin resistance was assessed with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in the fasting state according to the following formula: $[\text{glucose (mg/dl)} \times \text{insulin (mIU/ml)}] / 405$. Adipose tissue insulin resistance (Adipo-IR) was also calculated in the fasting state according to the following formula: $\text{free fatty acids (mmol/L)} \times \text{insulin (mIU/ml)}$.

Statistical analysis

Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC, USA). For statistical analysis, both CAC and EAT were log-transformed when evaluated as continuous variables as previously described [18]. Participants were categorised as having NALFD or no NALFD and as having CAC equal to zero or greater than zero. Chi-square test was used to assess for differences between the dichotomised groups for all categorical variables except for presence of advanced fibrosis, for which Fisher's exact test was used. Spearman rank correlation was performed to assess for correlations between MR imaging-PDFF, CAC and EAT with and without age adjustment in the entire study population and by sex. Spearman rank correlation was also performed for EAT and multiple variables, including MR imaging-PDFF, MRE, LDL-C, HDL-C, triglycerides, BMI, age and biomarkers of glucose intolerance and insulin resistance for CAC=0 and CAC>0. Multiple linear regression model was subsequently performed to determine independent predictors of EAT volume including covariates that were significantly correlated with EAT in univariate analysis. A p value < 0.05 determined statistical significance.

Results

Baseline demographics

Of the 100 individuals enrolled, five were excluded due to incomplete imaging evaluation. Baseline characteristics of the study population are shown in Table 1. The mean age of the study population was 59.2 ± 11.0 years; 53.7 % were male, 56.8% were White and 19.0% were Hispanic. The mean BMI of the entire study population was 30.9 ± 6.6 kg/m². The median glycated haemoglobin (HbA1c) was 7.0 % (interquartile rank (IQR) 1.6 %), and 68.4 % had metabolic syndrome.

Analysis of characteristics associated with NAFLD

Baseline characteristics of individuals with NAFLD and without NAFLD are shown in Table 1. Of the 95 participants, 62 (65.3 %) had NAFLD with median MR imaging-PDFF of 12.3 % (IQR 9.3) compared to 2.6 % (IQR 1.6) in the group without NAFLD. Although the presence of fibrosis as determined by MRE was not significantly different, the FIB-4 was significantly lower in the NAFLD group [0.90 (IQR 0.65) vs. 1.19 (IQR 0.64), $p=0.0087$].

The NAFLD group was significantly younger than the non-NAFLD group (32 years vs. 19 years, $p=0.0282$), but there were no significant differences in sex or ethnicity. The NAFLD group had a significantly higher BMI (32.7 ± 5.4 vs. 27.6 ± 7.4 , $p=0.0010$) and was more likely to have metabolic syndrome (83.9 % vs. 39.4 %, $p<0.0001$). Alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) were significantly higher in those with NAFLD (30.0 U/L, $p=0.0003$ and 28.0 U/L, $p=0.0236$, respectively). In the NAFLD group, HDL-C was lower (49.0 mg/dl (IQR 19.0) vs. 61.0 mg/dl (IQR 31.0), $p=0.0358$), while triglyceride level was significantly higher [162.5 mg/dl (IQR 83.0) vs. 92.0 mg/dl (IQR 58.0), $p<0.0001$].

Although the HbA1c did not differ significantly between the NAFLD and non-NAFLD groups, the NAFLD group demonstrated a higher fasting glucose [132.0 (IQR 61.0) vs. 106.0 (IQR 52.5), $p=0.0327$]. Further, surrogates of insulin resistance were significantly worse in the NAFLD group, including fasting insulin [17.0 (IQR 20.0) vs. 11.5 (IQR 14.0), $p=0.0453$, HOMA-IR [5.8 (IQR 5.5) vs. 3.3 (IQR 3.6), $p=0.0029$] and adipon-IR [9.1 (IQR 11.5) vs. 5.3 (IQR 8.4), $p=0.0091$].

The EAT volume was significantly higher in the NAFLD group compared to the non-NAFLD group (126.5 ml (IQR 80.9) vs. 85.4 ml (IQR 44.7), $p=0.002$). Figure 2 shows representative cardiac CT slices showing epicardial adipose tissue and corresponding MR imaging-PDFF maps in two individuals with high and low epicardial fat. Framingham Risk Score was lower in individuals with NAFLD compared to those without NAFLD ($p=0.0453$). However, neither the absolute CAC nor the prevalence of CAC>0 was significantly different between the two groups.

Analysis by prevalence of CAC

Comparison between individuals with CAC=0 and those with CAC>0 is depicted in Tables 2, 3 and 4. Of the study population, 62.1 % had CAC>0. Compared to participants with a

CAC of 0, those with CAC>0 were older (63.0 ± 9.0 years vs. 52.9 ± 11.3 years, $p<0.0001$) with a higher prevalence of males (64.4 % vs. 57.6 %, $p=0.0073$). Anthropometric parameters and prevalence of metabolic syndrome were not statistically different by CAC. There was a trend toward greater prevalence of hypertension among those with CAC>0 (74.6 % vs. 55.6 %, $p=0.0551$). Liver enzymes and lipid panel were not significantly different except for lower total cholesterol in the CAC>0 cohort (170.0 ± 34.2 vs. 188.8 ± 32.2 , $p=0.0094$). Among surrogate variables of glycaemia and insulin resistance, only HbA1c was significantly higher in the CAC>0 cohort [7.1 % (IQR 1.6 %) vs. 6.5 % (IQR 1.3), $p=0.0196$].

EAT was higher in the CAC>0 subgroup (112.7 ml vs. 90.4 ml, $p=0.0203$). Neither MR imaging-PDFF nor the prevalence of NAFLD determined by MR imaging-PDFF differed between the groups. Advanced fibrosis as determined by MRE was slightly higher in individuals with CAC>0 compared to CAC=0 (2.6 (IQR 0.9) vs. 2.4 (IQR 0.5), $p=0.0319$). The NAFLD fibrosis score and FIB-4 were higher in the CAC>0 than those with CAC of 0.

Correlation of covariates with EAT and multivariable analysis

MR imaging-PDFF demonstrated a positive correlation with EAT ($r=0.42$, $p<0.0001$), which was higher after adjustment for age ($r=0.50036$, $p<0.0001$). This association was higher in men than in women ($r=0.49575$, $p=0.0002$ vs. $r=0.36730$, $p=0.0142$), and even higher after adjustment for age ($r=0.62320$, $p=0.0001$ vs. $r=0.41311$, $p=0.0059$). Extent of advanced fibrosis as determined by MRE was also positively correlated with EAT ($r=0.31$, $p<0.01$). MR imaging-PDFF did not correlate with CAC ($r=-0.11$, $p=0.28$). Similarly, EAT did not correlate with CAC ($r=0.17354$, $p=0.0926$). EAT ($r=0.21$, $p<0.04$) and CAC ($r=0.49$, $p<0.0001$) were significantly correlated with FRS. Scatter plots and Spearman rank correlations among EAT, MR imaging-PDFF and CAC are depicted in Fig. 3.

Among traditional CHD risk factors, only HDL-C, triglycerides, BMI and age were correlated with EAT. Biomarkers of insulin resistance and hyperglycaemia including HbA1c, glucose level, insulin level and HOMA-IR were not correlated with EAT. Age ($r=0.2553$, $p=0.0125$) and BMI ($r=0.3473$, $p=0.0006$) were correlated with EAT. Also, liver fibrosis determined by MRE was significantly correlated with EAT in the overall population ($r=0.3105$, $p=0.0025$) and in those with CAC>0 ($r=0.3642$, $p=0.0049$), but not in those with CAC=0.

Multivariable linear regression model including MRIPDFF, HDL-C, triglycerides, BMI, age and MRE showed that MR imaging-PDFF, BMI, age and MRE remained significantly associated with EAT.

Discussion

This is the first study to demonstrate a positive correlation between EAT and NAFLD severity, even in milder forms, in an asymptomatic diabetic population. Further, NAFLD and liver fibrosis were associated with EAT in diabetics independent of traditional cardiovascular risk factors including biomarkers of insulin resistance and hyperglycaemia. Hence, among asymptomatic patients with type 2 diabetes, liver fat content may portend a worse

cardiovascular risk in those who have higher liver fat content than those with lower liver fat content.

Our study further supports prior studies that have demonstrated an association between NAFLD and cardiovascular disease prevalence and incident cardiovascular events in the type 2 diabetic population [4, 5]. Few studies have investigated the association between NAFLD and EAT. A recent study in non-diabetic men showed that epicardial fat increased with increasing amounts of liver fat determined by MR spectroscopy [44]. Additional studies have suggested similar findings in different study populations although not conclusively in mild forms of NAFLD [29, 30]. Our study suggests that NAFLD severity may in part determine cardiovascular risk in diabetic individuals. If so, identification of even mild forms of NAFLD in diabetic individuals may warrant treatment and aggressive cardiovascular risk factor modification to reduce cardiovascular risk.

MRE, a surrogate of liver fibrosis, was significantly correlated with EAT. Further, MRE was independently associated with EAT in the overall study population and in those with CAC>0, but not CAC=0. Given that hepatic fibrosis or cirrhosis may be an end-stage sequelae of hepatic steatosis, it is not surprising that extent of liver fibrosis determined by MRE in addition to MR imaging-PDFF are associated with EAT [45]. That MRE is independently associated with EAT only in the CAC>0 subgroup also suggests that hepatic fibrosis is associated with later stages of coronary atherosclerotic plaque. Further, these findings suggest that the natural history of hepatic steatosis may be age related in that hepatic steatosis may decline while hepatic fibrosis increases with age. Interestingly, diabetic individuals with NAFLD were significantly younger than those without NAFLD, perhaps due to the non NAFLD group including those on either end of the spectrum of NAFLD: minimal to no hepatic steatosis and those with advanced hepatic fibrosis or cirrhosis. Previously, a longitudinal study demonstrated that alanine aminotransferase (ALT), a surrogate marker of liver function, decreases with advancing age, possibly indicating loss of functional liver parenchyma in the aging population [46]. Previous studies on the natural history of fatty liver support the hypothesis that the natural history of NAFLD is age related and that hepatic steatosis and liver fibrosis may even be inversely related [47, 48]. Further longitudinal studies are needed to further elucidate the natural history of NAFLD and development of hepatic fibrosis.

Despite a positive correlation with EAT, MR imaging-PDFF was not significantly correlated with CAC and MR imaging-PDFF was not higher in CAC>0. This paradox may in part be attributed to the hypothesis that EAT is involved in the early stages of atherogenesis while CAC can be found in advanced forms of plaque. Although diabetes is considered a CHD equivalent, 36 of the 95 asymptomatic individuals in our study had CAC=0 and were significantly younger than the CAC>0 subgroup. Therefore, plaque, if present, in our study population may be earlier on the spectrum of plaque progression, supported by analysis of the Heinz Nixdorff Recall Study population [18, 49]. For this reason, EAT may represent an earlier and improved marker of subclinical cardiovascular risk in an asymptomatic diabetic population.

Limitations of our study include a small sample size and lack of longitudinal data and outcomes. Based on our findings, further studies are warranted in larger, multi-ethnic populations to confirm the correlation between severity of NAFLD as determined by MR imaging-PDFF and EAT in diabetic individuals. Additionally, longitudinal studies to determine whether EAT prognosticates cardiovascular events and mortality in diabetic individuals according to the severity of NAFLD are needed. Such studies would help elucidate whether EAT adds incremental prognostic value to traditional risk factors particularly in those with little to no coronary artery calcium and whether NAFLD is a poor prognostic indicator in diabetic individuals. Further, studies to determine if cardiovascular risk factor modification and treatment of NAFLD impact outcomes are warranted.

In asymptomatic type 2 diabetic individuals, EAT volume was significantly higher in those with NAFLD compared to those without NAFLD. Given that MR imaging-PDFF and extent of liver fibrosis determined by MRE were independently associated with EAT in diabetics, liver fat content and fibrosis may increase cardiovascular risk, and therefore, identification of even mild forms of NAFLD in diabetic individuals may warrant treatment and aggressive risk factor modification to reduce cardiovascular risk.

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Abbreviations

CAC	Coronary artery calcium
CHD	Coronary heart disease
CT	Computed tomography
DM	Diabetes mellitus
EAT	Epicardial adipose tissue
MR	Magnetic resonance
MRE	Magnetic resonance elastography

NAFLD	Non-alcoholic fatty liver disease
PDFF	Proton density fat fraction

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Key Points

- EAT volume is higher in diabetic individuals with NAFLD.
- Liver fat content is positively correlated with EAT.
- Liver fat content and liver fibrosis were independently associated with EAT.
- Higher liver fat content and fibrosis may adversely affect cardiovascular risk.

Fig. 1.
Representative cardiac CT slices demonstrating tracings of pericardium in asymptomatic diabetic individuals without (a) and with (b) pericardial fluid or thickening depicted by yellow arrows

Fig. 2.

Representative cardiac CT slice showing epicardial adipose tissue and corresponding MR imaging-proton density fat fraction (PDFF) map in asymptomatic diabetic individuals with a calcium score of 0. **(a)** A 53-year-old female with EAT volume of 48 mL, and MR imaging-PDFF of 1.6 %. **(b)** A 59-year-old female with EAT volume of 229 mL, and MR imaging-PDFF of 23.0 %. Minimum 0–50 % on scale

Fig. 3.

Scatter plot and Spearman rank correlations for coronary artery calcium score, epicardial fat, MR elastography (MRE) and MR imaging-proton density fat fraction (MRI-PDFF) in asymptomatic diabetic individuals. Solid red line indicates line of best fit by using least squares method. Dotted red line shows 95 % prediction limits

Baseline demographic, anthropometric, clinical, biochemical and imaging characteristics of subjects, categorised by presence of non-alcoholic fatty liver disease (NAFLD)

Table 1

	Overall (n=95)	NAFLD (MRI-PDFF ≥ 5 %) (n=62)	No NAFLD (MRI-PDFF <5 %) (n=33)	p value
Demographic				
Male	51 (53.7 %)	32 (51.6 %)	19 (57.6 %)	0.56
Age (years)	59.2 ± 11.0	57.4 ± 11.1	62.6 ± 10.3	0.03
White	54 (56.8 %)	34 (54.8 %)	20 (60.6 %)	0.59
Hispanic	18 (19.0 %)	14 (22.6 %)	4 (12.1 %)	0.22
Anthropometric				
Height (cm)	168.7 ± 10.3	167.8 ± 10.6	170.4 ± 9.6	0.24
Weight (kg)	88.6 ± 24.8	92.5 ± 20.0	81.3 ± 31.0	0.07
BMI (kg/m ²)	30.9 ± 6.6	32.7 ± 5.4	27.6 ± 7.4	0.001
Clinical				
Hypertension	64 (67.4 %)	40 (64.5 %)	24 (72.3 %)	0.42
Metabolic syndrome	65 (68.4 %)	52 (83.9 %)	13 (39.4 %)	<.001
Biochemical				
AST (U/L)	21.0 (10.0)	21.5 (12.0)	20.0 (10.0)	0.28
ALT (U/L)	25.0 (16.0)	30.0 (23.0)	19.0 (12.0)	<.001
GGT (U/L)	25.0 (18.0)	28.0 (19.0)	22.0 (11.0)	0.02
Alkaline phosphatase (U/L)	73.0 (31.0)	72.5 (23.0)	77.0 (43.0)	0.54
Total cholesterol (mg/dl)	177.1 ± 34.5	179.5 ± 33.6	172.7 ± 36.4	0.36
HDL-C (mg/dl)	52.0 (23.0)	49.0 (19.0)	61.0 (31.0)	0.04
LDL-C (mg/dl)	89.0 (48.0)	89.5 (44.0)	88.0 (46.0)	0.61
Triglycerides (mg/dl)	131.0 (89.0)	162.5 (83.0)	92.0 (58.0)	<.001
Platelet (1,000/mm ³)	254.6 ± 71.4	259.5 ± 73.4	245.5 ± 67.6	0.36
HbA1C (%)	7.0 (1.6)	7.1 (1.7)	6.9 (1.3)	0.26
Ferritin (ng/ml)	86.0 (149.0)	90.0 (159.0)	69.0 (124.0)	0.19
Fasting glucose (mg/dl)	121.0 (49.0)	132.0 (61.0)	106.0 (52.5)	0.03
Fasting insulin (μIU/ml)	16.0 (19.0)	17.0 (20.0)	11.5 (14.0)	<.05
HOMA-IR	5.1 (5.8)	5.8 (5.5)	3.3 (3.6)	0.003

	Overall (n=95)	NAFLD (MRI-PDFF 5 %) (n=62)	No NAFLD (MRI-PDFF <5 %) (n=33)	p value
FFA, (mg/dl)	0.54 ± 0.23	0.55 ± 0.21	0.52 ± 0.27	0.47
Adipo-IR	8.0 (10.9)	9.1 (11.5)	5.3 (8.4)	0.009
Imaging				
MRI-PDFF (%)	8.2 (10.2)	12.3 (9.3)	2.6 (1.6)	<0.001
MRE (Kpa)	2.6 (0.7)	2.7 (0.7)	2.4 (0.4)	0.17
EAT (cm ³)	100.8 (73.6)	126.5 (80.9)	85.4 (44.7)	<0.001
CAC (Agatston units)	14.0 (480.0)	10.0 (401.0)	52.0 (546.0)	0.26
CAC > 0	59 (62.1 %)	36 (58.1 %)	23 (69.7 %)	0.27
Advanced Fibrosis (MRE 3.6)	7 (7.5 %)	5 (8.2 %)	2 (6.3 %)	1.00
Fibrosis scores				
Framingham Risk Score	5.0 (11.0)	4.0 (10.0)	10.0 (14.0)	0.05
NAFLD fibrosis score	-0.81 ± 1.25	-0.88 ± 1.33	-0.66 ± 1.08	0.42
FIB-4	1.00 (0.66)	0.90 (0.65)	1.19 (0.64)	0.009
APRI	0.22 (0.15)	0.22 (0.15)	0.21 (0.11)	0.71

Mean (± SD) is presented above for normally distributed variables with associated *p* values from t-test, median (interquartile range) for non-normally distributed variables with associated *p* values from Wilcoxon-Mann-Whitney U test. Categorical variables presented as N (%), with *p* values from chi-square or Fisher's exact test. Significant *p* values (>0.05) are in bold

Adipo-IR adipose tissue insulin resistance, *ALT* alanine aminotransferase, *APRI* AST-to-platelet ratio index, *AST* aspartate aminotransferase, *BMI* body mass index, *CAC* coronary artery calcium score, *DM* diabetes mellitus, *EAT* epicardial adipose tissue, *FFA* free fatty acids, *FIB-4* Fibrosis-4, *GGT* gamma-glutamyl transpeptidase, *HbA1c* haemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *LDL-C* low-density lipoprotein cholesterol, *MRE* magnetic resonance elastography, *MRI-PDFF* magnetic resonance imaging estimated proton density fat fraction

Baseline demographic, anthropometric, clinical, biochemical and imaging characteristics of subjects, categorised by presence of coronary artery calcium (CAC)

Table 2

	Overall (n=95)	(CAC > 0) (n=59)	(CAC = 0) (n=36)	p value
Demographic				
Male	51 (53.7 %)	38 (64.4 %)	13 (36.1 %)	0.007
Age (years)	59.2 ± 11.0	63.0 ± 9.0	52.9 ± 11.3	<.001
White	54 (56.8 %)	38 (64.4 %)	16 (44.4 %)	0.057
Hispanic	18 (19.0 %)	9 (15.3 %)	9 (25.0 %)	0.24
Anthropometric				
Height (cm)	168.7 ± 10.3	170.0 ± 10.4	166.7 ± 9.8	0.13
Weight (kg)	88.6 ± 24.8	89.8 ± 26.3	86.7 ± 22.3	0.56
BMI (kg/m ²)	30.9 ± 6.6	30.8 ± 6.8	31.0 ± 6.3	0.89
Clinical				
Hypertension	64 (67.4 %)	44 (74.6 %)	20 (55.6 %)	0.055
Metabolic syndrome	65 (68.4 %)	41 (69.5 %)	24 (66.7 %)	0.77
Biochemical				
AST (U/L)	21.0 (10.0)	22.0 (10.0)	20.5 (11.5)	0.88
ALT (U/L)	25.0 (16.0)	26.0 (16.0)	22.5 (21.0)	0.89
GGT (U/L)	25.0 (18.0)	25.5 (15.0)	25.0 (21.0)	0.79
Alkaline phosphatase (U/L)	73.0 (31.0)	72.0 (31.0)	74.0 (33.0)	0.75
Total cholesterol (mg/dl)	177.1 ± 34.5	170.0 ± 34.2	188.8 ± 32.2	0.009
HDL-C (mg/dl)	52.0 (23.0)	51.0 (21.0)	58.0 (28.5)	0.075
LDL-C (mg/dl)	89.0 (48.0)	88.0 (46.0)	100.5 (44.0)	0.20
Triglycerides (mg/dl)	131.0 (89.0)	127.0 (87.0)	145.0 (90.0)	0.50
Platelet (1,000/mm ³)	254.6 ± 71.4	237.1 ± 67.4	283.4 ± 69.3	0.002
HbA1C (%)	7.0 (1.6)	7.1 (1.6)	6.5 (1.3)	0.020
Ferritin (ng/ml)	86.0 (149.0)	93.5 (155.0)	76.0 (123.0)	0.38
Fasting glucose (mg/dl)	121.0 (49.0)	132.0 (59.0)	109.5 (34.0)	0.28
Fasting insulin (µU/ml)	16.0 (19.0)	17.0 (27.0)	14.5 (12.0)	0.26
HOMA-IR	5.1 (5.8)	5.8 (7.5)	4.2 (4.1)	0.16

	Overall (n=95)	(CAC > 0) (n=59)	(CAC = 0) (n=36)	p value
FFA, (mg/dl)	0.54 ± 0.23	0.57 ± 0.26	0.50 ± 0.18	0.14
Adipo-IR	8.0 (10.9)	8.8 (16.2)	7.5 (6.8)	0.26
Imaging				
MRI-PDFF (%)	8.2 (10.2)	6.8 (11.0)	8.7 (9.6)	0.46
MRE (Kpa)	2.6 (0.7)	2.6 (0.9)	2.4 (0.5)	0.032
EAT (cm ³)	100.8 (73.6)	112.7 (80.0)	90.4 (62.2)	0.020
CAC (Agatston units)	14.0 (480.0)	301.0 (771.0)	0 (0)	<.001
NAFLD	62 (65.3 %)	36 (61.0 %)	26 (72.2 %)	0.27
Advanced Fibrosis (MRE 3.6)	7 (7.5 %)	6 (10.3 %)	1 (2.9 %)	0.25
Fibrosis scores				
Framingham Risk Score	5.0 (11.0)	10.0 (13.0)	2.0 (7.0)	<.001
NAFLD fibrosis score	-0.81 ± 1.25	-0.43 ± 1.17	-1.43 ± 1.13	<.001
FIB-4	1.00 (0.66)	1.25 (0.69)	0.85 (0.35)	<.001
APRI	0.22 (0.15)	0.23 (0.15)	0.20 (0.11)	0.052

Mean (± SD) is presented above for normally distributed variables with associated *p* values from t-test, median (interquartile range) for non-normally distributed variables with associated *p* values from Wilcoxon-Mann-Whitney U test. Categorical variables presented as N (%), with *p* values from chi-square or Fisher's exact test.

Adipo-IR adipose tissue insulin resistance, *ALT* alanine aminotransferase, *APRI* AST-to-platelet ratio index, *AST* aspartate aminotransferase, *BMI* body mass index, *CAC* coronary artery calcium score, *DM* diabetes mellitus, *EAT* epicardial adipose tissue, *FFA* free fatty acids, *FIB-4* Fibrosis-4, *GGT* gamma-glutamyl transpeptidase, *HbA1C* haemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *LDL-C* low-density lipoprotein cholesterol, *MRE* magnetic resonance elastography, *MRI-PDFF* magnetic resonance imaging estimated proton density fat fraction

Table 3

Spearman rank correlations between epicardial adipose tissue (EAT) and covariates for the overall study population, individuals with coronary artery calcium (CAC)=0 and individuals with CAC>0

Variable	Overall (n=95)		CAC=0 (n=36)		CAC>0 (n=59)	
	r_s	<i>p</i> value	r_s	<i>p</i> value	r_s	<i>p</i> value
CAC	0.1735	0.0926	---	---	---	---
MR-PDFF	0.4218	<0.0001	0.4096	0.0131	0.4745	0.0001
Cholesterol	-0.1799	0.0811	-0.1409	0.4124	-0.1216	0.3588
LDL-C	-0.1855	0.0719	-0.0924	0.5920	-0.1823	0.1670
HDL-C	-0.2992	0.0032	-0.2623	0.1222	-0.2694	0.0391
Triglycerides	0.3954	<0.0001	0.3308	0.0487	0.4757	0.0001
HbA1c	-0.0382	0.7135	0.1572	0.3599	-0.2200	0.0943
Glucose	0.0282	0.7884	0.2289	0.1793	-0.0799	0.5546
Insulin	0.1654	0.1193	0.1014	0.5682	0.1578	0.2454
HOMA-IR	0.2087	0.0510	0.1505	0.3955	0.1856	0.1791
MRE	0.3105	0.0025	0.1418	0.4167	0.3642	0.0049
BMI	0.3473	0.0006	0.3057	0.0698	0.3863	0.0025
Age	0.2553	0.0125	0.2351	0.1675	0.1604	0.2249

MR-PDFF magnetic resonance imaging-estimated proton density fat fraction, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high density lipoprotein cholesterol, *HbA1c* glycosylated haemoglobin A1c, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *MRE* magnetic resonance elastography *BMI*: body mass index

Table 4

Multivariable linear regression model among covariates significantly correlated with epicardial adipose tissue (EAT)

Variable	All diabetics (n=93)				CAC=0 (n=35)				CAC > 0 (n=58)			
	Estimate	SE	t	p value	Estimate	SE	t	p value	Estimate	SE	t	p value
Intercept	-125.16	46.68	-2.68	0.0088	-162.37	79.99	-2.03	0.0520	-97.05	70.29	-1.38	0.1734
MRI-PDFF	2.38	0.67	3.58	0.0006	3.87	1.34	2.89	0.0073	1.94	0.81	2.40	0.0202
HDL	0.18	0.26	0.70	0.4855	0.53	0.34	1.56	0.1312	-0.05	0.53	-0.09	0.9300
TG	0.09	0.06	1.48	0.1417	0.04	0.09	0.40	0.6941	0.13	0.09	1.51	0.1366
MRE	13.39	6.48	2.07	0.0418	1.45	20.05	0.07	0.9428	14.46	7.31	1.98	0.0534
BMI	1.92	0.80	2.40	0.0183	2.96	1.31	2.26	0.0318	1.57	1.03	1.52	0.1346
Age	1.64	0.45	3.62	0.0005	1.65	0.72	2.30	0.0289	1.53	0.72	2.14	0.0373

MRE magnetic resonance elastography, MRI-PDFF magnetic resonance imaging-estimated proton density fat fraction, HDL high density lipoprotein, TG triglycerides, BMI body mass index