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Liver Stiffness Severity is Associated With Increased Cardiovascular Risk in Patients With Type 2 Diabetes

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death among patients with nonalcoholic fatty liver disease (NAFLD) and is strongly associated with type II diabetes mellitus (DMII) [1]. Accurately assessing CVD risk in NAFLD patients is critical to improving clinical outcomes [1]. Utilization of liver stiffness measurements to non-invasively assess for liver fibrosis is broadening and magnetic resonance elastography (MRE) is the most accurate modality in NAFLD [2]. However, the association between fibrosis severity on MRE and the degree of CVD risk is unknown. The aim of this study was

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AUTHOR CONTRIBUTIONS

Neeraj Mangla: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, approved final submission.

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Cyrielle Caussy: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, approved final submission.

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Ricki Bettencourt: data collection, data analysis, critical revision of the manuscript, approved final submission

Lisa Richards: critical revision of the manuscript, approved final submission

Rohit Loomba: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, obtained funding, study supervision, approved final submission

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to determine if MRE-assessed liver fibrosis stage is associated with CVD risk determined by Framingham risk score (FRS) and coronary artery calcium (CAC).

METHODS

This was a secondary analysis of a single-center, cross-sectional study of 96 DMII adults prospectively recruited in the greater San Diego area between March 2013 and September 2014 with institutional review board approval [3]. All participants were greater than 21 years old and previously diagnosed with DMII [4]. Participants with known CVD, non-NAFLD chronic liver disease, steatogenic medications, severe end-organ damage due to DMII, excessive alcohol use, HIV, and pregnancy were excluded. A research study visit included a detailed medical history, anthropometric measurements, validated alcohol use questionnaires, fasting laboratory measurements, cardiac CT for CAC, magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF) and MRE evaluation.

Patients were categorized according to severity of fibrosis: no fibrosis was defined as MRE<2.5 kPa, mild fibrosis MRE 2.5–3.62 kPa, and advanced fibrosis MRE>3.62 kPa [2]. CAC was defined as 0 (10-year low ASCVD risk of less than 5%), 1–300 (10-year intermediate ASCVD risk of greater than 7.5%), and greater than 300 (10-year severe ASCVD risk of greater than 13.1%) [5]. FRS low risk was defined as less than 10%, intermediate risk as 10–20%, and high risk as 20% or higher [6]. The association between fibrosis severity and cardiovascular risk was assessed among the entire cohort and among patients with MRI-PDFF ≥ 5% using Kruskal-Wallis test and logistic regression.

RESULTS

Among 96 patients, 63 had NAFLD (MRI-PDFF ≥ 5%). The median (IQR) age and BMI was 62 (13) years and 30 (8.8) kg/m^2, respectively. 54.2% were male, 55.2% were non-Hispanic white and 19.8% were Hispanic. The median glycated hemoglobin (HbA1c) was 7.1% and 69.8% had metabolic syndrome (Table 1). The median age for advanced fibrosis, mild fibrosis and no fibrosis were 69.5, 62, and 60 years (p = 0.04), respectively. Prevalence of statin use in advanced fibrosis, mild fibrosis, and no fibrosis were 100%, 55.8%, 44.7%, respectively (p=0.029). There were no significant differences in gender, ethnicity, BMI, hypertension, anti-hypertensive drugs use, total cholesterol, or metabolic syndrome by fibrosis group.

Median (IQR) CAC increased with greater fibrosis and was 824 (1029) in the advanced fibrosis group, 14 (373) in mild fibrosis and 1 (480) in no fibrosis (p=0.009). Median FRS was 13% in advanced liver fibrosis, 6% in mild fibrosis, and 3% in no fibrosis (p=0.104) (Figure 1a). Similarly, in NAFLD patients only, median (IQR) CAC was 522 (1336) in advanced fibrosis, 10 (264) in mild fibrosis and 0 (250) in no fibrosis (p=0.041).

Five patients with low to intermediate FRS (less than 20%) had advanced fibrosis. The median CAC was 904 and 80% (N=4) had CAC scores of greater than 300. Patients with advanced fibrosis had increased odds of CAC>300 compared to those without advanced fibrosis (OR 14 [95% CI 1.47–133.24 p=0.02]). Similarly, NAFLD patients with advanced

fibrosis had greater odds of CAC>300; OR: 11.72 (95% CI 1.11–123.96 p=0.04) (Figure 1b).

DISCUSSION

In a well-phenotyped cohort of asymptomatic patients with type 2 DM, in which 66% had NAFLD, increased liver fibrosis assessed by MRE is associated with higher cardiovascular risk. This is the first study to demonstrate that advanced fibrosis on MRE is associated with a significantly increased CAC. Also, our findings support prior studies suggesting that NAFLD may be an independent risk factor for CVD risk [7] and provides additional evidence that the severity of fibrosis may be associated with CVD risk [1].

This study was limited by the lack of longitudinal data and clinical outcomes. Furthermore, the sample size precluded extensive multivariable analysis to adjust for potential confounders. Although patients did not receive liver biopsy, MRE is the most accurate non-invasive marker of liver fibrosis and MRI-PDFF may be more accurate than liver biopsy for quantifying hepatic steatosis. In summary, increased fibrosis severity on MRE is associated with higher CVD risk and aggressive mitigation of cardiovascular risk should be pursued in DMII patients with advanced fibrosis.

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Abbreviations:

NAFLD	nonalcoholic fatty liver disease
MRI-PDFF	magnetic resonance imaging proton density fat fraction
MRE	magnetic resonance elastography
CVD	cardiovascular disease
CAC	coronary artery calcium
FRS	Framingham risk score

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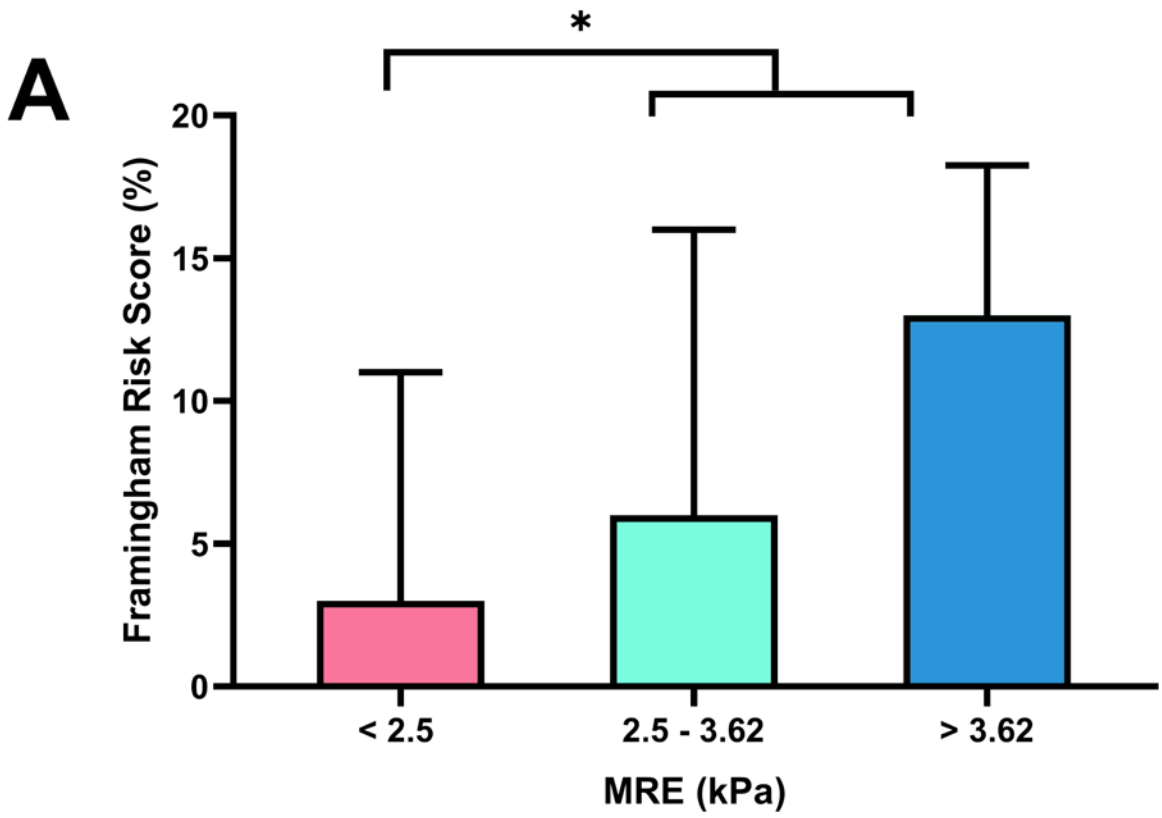

Figure 1A. Higher liver stiffness on MRE is associated with elevated cardiovascular risk in asymptomatic diabetic individuals.

The association between MRE fibrosis stage and FRS median with interquartile range. FRS increases with worse fibrosis stage (p=0.14). *Median FRS in any fibrosis was significantly higher than median FRS in no fibrosis (p=0.041).

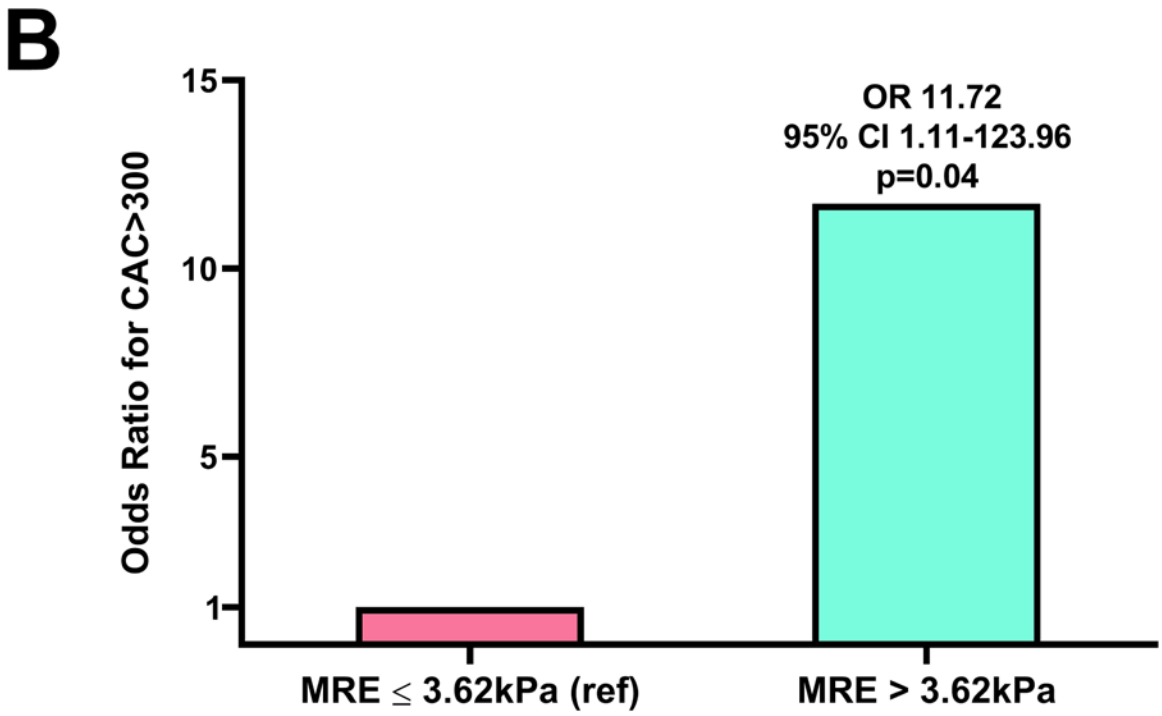

Figure 1B. Odds ratio of CAC>300 in NAFLD patients with low to intermediate FRS – Elevated Cardiac Risk in NAFLD patients with Advanced Fibrosis with low to intermediate risk on Framingham Risk Score compared to mild or no fibrosis.

Table 1.

Descriptive characteristics of type 2 diabetic patients categorized by MRE assessed fibrosis stage.

	Overall	MRE<2.5	MRE 2.5–3.62	MRE>3.62	p-value
Total	N=96	N=43	N=47	N=6	
Demographic					
Male (%)	52 (54.2)	20 (46.5)	28 (59.6)	4 (66.7)	0.415
Age (years)	62 (13)	60 (13)	62 (13)	69.5 (11)	**0.04**
White (%)	53 (55.2)	23 (53.5)	25 (53.2)	5 (83.3)	0.393
Hispanic (%)	19 (19.8)	8 (18.6)	10 (21.3)	1 (16.7)	0.918
Anthropometric					
Height (cm)	168.3 (16.3)	168 (14.5)	169 (18)	172.5 (17.6)	0.781
Weight (kg)	85.8 (24.6)	82 (26)	87 (20.5)	91.6 (20.3)	0.145
BMI (kg/m^2)	30 (8.8)	28.5 (7.1)	31 (8)	34.1 (13.1)	0.161
Clinical					
Hypertension (%)	63 (65.6)	27 (62.8)	30 (63.8)	6 (100)	0.220
Anti-Hypertensive Use (%)	55 (57.3)	20 (46.5)	30 (63.8)	5 (83.3)	0.121
Metabolic Syndrome (%)	67 (69.8)	26 (60.5)	36 (76.6)	5 (83.3)	0.221
Statin Use (%)	51 (53.1)	24 (55.8)	21 (44.7)	6 (100)	**0.029**
Biochemical					
AST (U/L)	24 (16)	21 (12)	27 (18)	34 (15)	0.237
ALT(U/L)	21 (10.5)	19 (11)	21 (11)	36.5 (18)	**0.039**
GGT (U/L)	26 (18)	27 (22)	25 (10)	50 (36)	0.492
Alkaline Phosphatase (U/L)	73 (30)	67 (30)	76 (29)	67.5 (24)	0.059
Total Cholesterol (md/dl)	176 (46)	178 (43)	175 (43)	146.5 (29)	0.077
HDL-C (mg/dl)	53 (23)	60 (25)	48 (20)	57.5 (19)	**0.044**
LDL-C (mg/dl)	88.5 (46)	92 (36)	88 (43)	65 (14)	0.072
Triglycerides(mg/dl)	136 (89)	115 (102)	143 (76)	108 (66)	0.430
Platelet ($10^3/\mu l$)	242.5 (94)	257 (92)	237 (101)	182.5 (128)	**0.022**
HbA1C (%)	7.1 (1.6)	6.7 (1.2)	7.2 (2.3)	6.7 (1.2)	0.347
Ferritin (ng/ml)	83 (139)	72 (88)	102.5 (177)	110 (133)	0.490
Fasting Glucose (mg/dl)	124 (49)	118.5 (39)	130 (58)	132 (46)	0.915
Fasting Insulin (U/L)	16.5 (19)	14 (14)	17 (15)	45 (114)	0.053
MRI-PDFF (%)	8 (9.9)	6.3 (10.2)	8.8 (10.1)	7.1 (8.5)	0.460
HOMA-IR	5.2 (5.9)	4.3 (6)	5.8 (5.1)	9.1 (14.7)	0.083
Fibrosis Scores					
NAFLD fibrosis Score	−0.8 (1.7)	−1 (1.6)	−0.7 (1.8)	0.8 (0.9)	**0.002**
FIB-4	1 (0.7)	0.9 (0.7)	1 (0.6)	2 (2.1)	**0.002**
APRI	0.2 (0.2)	0.2 (0.1)	0.2 (0.2)	0.6 (0.2)	**0.004**

Median and interquartile range (IQR) values are provided. Categorical variables presented as N (%). BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, Alk P: Alkaline Phosphatase, GGT: Gamma-Glutamyl Transferase, HbA1c: glycated

hemoglobin, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, MRI-PDFF: Magnetic Resonance Imaging Proton Density Fat Fraction, HOMA: Homeostasis Model Assessment, FIB-4: Fibrosis 4 Index, APRI: AST to Platelet Ratio Index. All numbers are median (iqr) or N (%).P-values from Kruskal-Wallis or Fisher's Exact Test as appropriate. Metabolic syndrome definition: Grundy SM, Cleeman JI, Daniels SR et al. (2005) Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112:2735–2752.