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Increasing Liver Fat is Associated with Incident Cardiovascular Risk Factors

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Introduction:

Non-alcoholic fatty liver disease (NAFLD) is associated with increased liver and cardiovascular disease (CVD)-related morbidity and mortality. In cross-sectional analyses, NAFLD clusters with several cardiometabolic traits including obesity (1) (2), hypertension (3), diabetes (1), and dyslipidemia (3). However, liver fat is dynamic and changes over time. Aside from limited prior studies evaluating diet or exercise interventions, little is known about the association between changes in liver fat and the incidence of CVD risk factors. Additionally, previous studies often have limited follow-up, evaluate only select populations, such as individuals with obesity (4, 5) or diabetes (6–8), and may not account for changes in weight or body mass index (BMI). The aim of the present study was to examine, in a longitudinal cohort, the natural history of liver fat change and the association with the incidence of multiple CVD risk factors.

Methods:

Study participants (n=808) were drawn from the Framingham Heart Study Third Generation cohort who participated in a substudy with two serial computed tomography (CT) scans performed 6 years apart. CT-derived liver fat attenuation was measured in Hounsfield Units and standardized to a radiographic phantom to create liver phantom ratios (LPR). We

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Author Contributions:

Study concept and design (KTB, EJB, MTL); acquisition of data (UH); analysis and interpretation of data (KTB, AP, JMM, UH, EJB, MTL); drafting of the manuscript (KTB); critical revision of the manuscript for important intellectual content (AP, JMM, UH, EJB, MTL); statistical analysis (AP, JMM); obtained funding (EJB, MTL); administrative, technical, or material support (UH); study supervision (MTL).

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performed multivariable-adjusted logistic regression models to measure the association between changes in liver fat and the incidence of multiple CVD risk factors, accounting for baseline demographics and risk factors. We excluded participants with the outcome of interest at baseline so the sample size varied (Table). The first model adjusted for age, sex, baseline LPR, smoking, drinks per week, and baseline continuous CVD risk factors, hypertension, diabetes, impaired fasting glucose, hypercholesterolemia, low HDL, and hypertriglyceridemia, as well as treatment variables. The second model additionally adjusted for baseline BMI and change in BMI, to examine whether changing BMI drives any or all associations.

Results:

The baseline prevalence of NAFLD in our sample (mean age 45 ± 6 years, 46.9% women) was 14%, which increased to 24% at follow-up. Increasing liver fat was associated with the incidence of multiple CVD risk factors. Each standard deviation increase in liver fat was associated with incident impaired fasting glucose (OR 1.51; 95% CI: 1.22–1.87), incident diabetes (OR 1.66, 95% CI: 1.25–2.21), and incident metabolic syndrome (OR 1.76, 95% CI: 1.36–2.26) (Table). After accounting for baseline and change in BMI, increasing liver fat remained associated with incident diabetes (OR 1.68, 95% CI: 1.23, 2.30) and metabolic syndrome (OR 1.55, 95% CI 1.19, 2.03). Each standard deviation increase in liver fat was also associated with low HDL in the first model, but once baseline and change in BMI were accounted for, this association was no longer significant.

Discussion:

In our longitudinal, observational cohort study, we observed a general increase in liver fat, along with BMI, over the 6.2-year follow-up period, as well as the incidence of several CVD risk factors. Even after accounting for increasing BMI over the follow-up period, an adverse progression of liver fat remained significantly associated with incident diabetes and metabolic syndrome.

Our study has a number of important clinical implications worth noting. Whereas clinically we often characterize patients as having NAFLD or not, those that have increasing fat over time may be at increased CVD risk. Additionally, the associations between increasing liver fat and incident diabetes and metabolic syndrome remained after accounting for change in BMI and other covariates. Clinically, weight change or BMI change may not correlate well with changes in liver fat or with changes to an individual’s cardiometabolic risk. Additional studies are needed to determine if tools to quantify liver fat provide additional insights to cardiometabolic risk over changes in BMI.

The strengths of our study include the moderate sample size and follow-up period, allowing us to study the natural history of liver fat change in relation to multiple CVD risk factors. Limitations include the observational nature of the study, though this allows for examination of the course of disease. Participants were not tested for the viral hepatitis, though we expect the population prevalence to be low. We did not account for changes in diet or physical activity over the follow up period which also may have influenced CVD risk. Additionally,

CT imaging is not able to distinguish those with simple steatosis versus nonalcoholic steatohepatitis or hepatic fibrosis, though CT is a noninvasive, but reliable, method of quantifying changes in liver fat attenuation over time. In conclusion, increasing liver fat over 6.2 years is associated with the development of diabetes and metabolic syndrome after accounting for changes in generalized adiposity.

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List of Abbreviations:

BMI	body mass index
CI	confidence interval
CT	Computed tomography
CVD	cardiovascular disease
HDL	high density lipoprotein
LPR	liver phantom ratio
MR	magnetic resonance
MV	multivariable
NAFLD	non-alcoholic liver disease
OR	odds ratio

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Table:

Multivariable-Adjusted Logistic Regression Models for the Risk of Incident Cardiovascular Disease Risk Factors with Increasing Liver Fat

	Number of participants	Model	OR (95% Confidence Interval)	p value
Hypertension[‡]	654	MV[†]	1.22 (0.96, 1.55)	0.11
		MV + BMI + ΔBMI[†]	1.06 (0.81, 1.38)	0.69
Diabetes[‡]	788	MV	1.66 (1.25, 2.21)	<0.001
		MV + BMI + ΔBMI	1.68 (1.23, 2.30)	0.001
Impaired Fasting Glucose[‡]	585	MV	1.51 (1.22, 1.87)	<0.001
		MV + BMI + ΔBMI	1.28 (1.00, 1.63)	0.05
Hypercholesterolemia[‡]	661	MV	1.13 (0.93, 1.37)	0.23
		MV + BMI + ΔBMI	1.05 (0.84, 1.31)	0.68
Low HDL[‡]	565	MV	1.38 (1.01, 1.88)	0.04
		MV + BMI + ΔBMI	1.25 (0.88, 1.76)	0.21
Hypertriglyceridemia[‡]	574	MV	1.14 (0.92, 1.43)	0.23
		MV + BMI + ΔBMI	1.04 (0.81, 1.34)	0.74
Metabolic Syndrome[‡]	608	MV	1.76 (1.36, 2.26)	<0.001
		MV + BMI + ΔBMI	1.55 (1.19, 2.03)	0.001

MV, multivariable; BMI, body mass index; HDL, high density lipoprotein.

[†]MV model adjusts for baseline age, sex, baseline smoking status (former, current, never), baseline drinks per week, baseline liver phantom ratio, and baseline continuous outcome variables (baseline SBP and DBP for hypertension, baseline glucose for diabetes and impaired fasting glucose, baseline total cholesterol for hypercholesterolemia, baseline HDL for low HDL, baseline log triglycerides for hypertriglyceridemia and baseline waist circumference, log triglycerides, HDL, glucose, SBP and DBP for the metabolic syndrome). The MV+ BMI + ΔBMI was additionally adjusted for baseline BMI and change in BMI.

[‡]Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or treatment with antihypertensive medication. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or use of hypoglycemic medications including insulin. Impaired fasting glucose was defined as fasting glucose 100 to 125 mg/dL in the absence of hypoglycemic medications. Hypercholesterolemia was defined as a total cholesterol ≥ 240 mg/dL or use of lipid-lowering medication. Low HDL cholesterol was defined as < 50mg/dL for women or < 40 mg/dL for men. Hypertriglyceridemia was defined as triglycerides ≥ 150 mg/dL or lipid treatment. Metabolic syndrome was defined as present if a participant had three or more of the following characteristics: abdominal obesity, defined as waist circumference greater > 35 inches for women or 40 inches for men, triglycerides ≥ 150 mg/dL, HDL cholesterol < 50 mg/dL for women and < 40 mg/dL for men, a systolic blood pressure ≥ 130 mm Hg or a diastolic blood pressure ≥ 85 mm Hg, or a fasting glucose ≥ 110 mg/dL.