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Prevalent Cardiovascular Disease Events and T1 Mapping Defined Hepatic Fibrosis:

Long and Benjamin: Cardiovascular Disease Events and Hepatic Fibrosis

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Non-alcoholic fatty liver disease and cardiovascular disease

Non-alcoholic fatty liver disease (NAFLD), is defined by the presence of hepatic steatosis in at least 5% of hepatocytes in the absence of secondary causes such as viral hepatitis, steatogenic medications, or moderate-to-heavy alcohol consumption.¹ NAFLD, the leading cause of chronic liver disease in the United States, represents a spectrum of histologic findings including simple steatosis, lobular inflammation, and hepatic fibrosis, which can progress to end-stage liver disease.² In addition to the risk for advanced liver disease, patients are at increased risk for cardiovascular disease (CVD), which remains the leading cause of death in NAFLD.³

Numerous possible underlying mechanisms may contribute to the increased CVD risk in NAFLD. First, worsened insulin resistance,^{3,4} possibly from decreased insulin clearance and hyperinsulinemia,⁵ results in increased free fatty acid release from adipose tissue. Patients with NAFLD have increased fatty acid transport receptors in the liver, which results in increased uptake of plasma free fatty acids.⁶ There is also an increase in triglyceride synthesis in the liver (de novo lipogenesis) in NAFLD, possibly from hepatic insulin resistance and an inability of insulin to suppress gluconeogenesis. Ultimately, increased fatty acid uptake and increased triglyceride synthesis results in an accumulation of hepatic triglycerides, further worsening fatty liver.⁶ The liver secretes triglycerides into the blood as very low density lipoproteins (VLDL). Triglyceride-rich VLDLs are broken down in the periphery to triglycerides and intermediate-density and low-density lipoproteins. In NAFLD, there is an increase in hepatic VLDL secretion and accumulation of triglycerides and low

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density lipoproteins in the blood which increases the risk for atherosclerosis.⁷ Second, excess free fatty acids induce inflammatory mediators and oxidative stress in hepatocytes, which may result in metabolic lipotoxicity⁸ and endothelial dysfunction.^{9, 10} Finally, NAFLD is associated with decreased glucagon-like peptide 1 (GLP-1) hormone receptor levels and reduced uptake of GLP-1, which normally plays an important role in glucose metabolism and is protective against CVD. However, the specific underlying mechanisms linking NAFLD with CVD are not fully understood, and the degree to which NAFLD independently contributes to CVD is unknown.¹¹

Non-invasive assessment of hepatic fat and fibrosis

One limitation to our knowledge on the connection between NAFLD and CVD stems from the fact that the majority of NAFLD research has focused on hepatic steatosis instead of the more pathologically relevant phenotypes of steatohepatitis and hepatic fibrosis. Individuals with more advanced NAFLD, particularly hepatic fibrosis, are at highest risk for liver-related¹² and CVD-related death,¹³ and overall mortality.¹⁴ Although the gold-standard for the diagnosis of NAFLD is liver biopsy, it is unethical and impractical to perform on a large scale and liver biopsy may be inaccurate because of significant sampling variability.¹⁵ NAFLD is typically diagnosed using abdominal imaging, such as ultrasonography, computed tomography (CT), or magnetic resonance spectroscopy (MRS), to characterize the presence and degree of hepatic steatosis. The diagnosis of more advanced NAFLD is challenging since traditional liver imaging techniques are insensitive to hepatic fibrosis, particularly mild or moderate fibrosis.¹⁶

Recently, several noninvasive tools to detect and quantify hepatic fibrosis have become available. A number of blood-based diagnostic tools that correlate with hepatic fibrosis have been developed, such as the NAFLD fibrosis score,¹⁷ the Enhanced Liver Fibrosis panel,¹⁸ and fibrosis-specific biomarkers.¹⁹ However, most of these models were derived in hospital-based samples, which have higher disease prevalence than the general population, and most biomarkers have limited usefulness clinically and in population-based studies.^{20, 21}

Of potential promise for the non-invasive detection of hepatic fibrosis are vibration-controlled transient elastography (VCTE) and MRI-based elastography (MRE) protocols.^{22, 23} VCTE is a point-of-care device that uses modified ultrasound probes to deliver pulse waves to the liver to simultaneously estimate liver fat attenuation and a fibrosis-surrogate, liver stiffness.²⁴ Whereas VCTE has lower sensitivity and specificity for hepatic fibrosis compared to MRE,^{25, 26} because of ease of use, VCTE is a clinically attractive option¹⁹ and is starting to be studied on a large scale.²⁴ However, VCTE only evaluates a portion of the liver and it can be technically challenging, especially in patients with obesity.²⁶ MRE uses a modified phase contrast pulse sequence to image pulse waves as they propagate through the liver.²⁷ MRE is a validated, highly accurate method for detecting hepatic fibrosis that some argue should replace liver biopsy as the gold standard because it measures hepatic fibrosis in the entire liver, and it has higher inter-reader agreement than observed with histopathology.²⁸ However, issues with cost, technical scalability, and the time required to complete the examinations have limited the wide-scale adoption of MRE in clinical practice.²⁷

Magnetic resonance T1 mapping for hepatic fibrosis

Newer MRI-based imaging techniques are emerging for the assessment of hepatic fat and fibrosis. T1 mapping of the liver can now be accomplished with a single breath-hold and, as a result, interest has increased in T1 mapping as a potential modality to diagnosis hepatic fibrosis.^{29, 30} Multiparametric MRI techniques that combine T1 mapping to evaluate hepatic fibrosis, T2* mapping to quantify hepatic iron content, along with MRS to quantify hepatic fat have shown promise in studies with paired liver biopsy;³¹ however, larger validation studies are needed. Other modalities of interest include T1 decay corrected for iron content using the Liver Multiscan platform (Perspectum Diagnostics, Oxford, UK), which was recently shown to be predictive of short-term clinical outcomes in patients with chronic liver disease.³¹ Also, MRI techniques that utilize a hepatocyte-specific gadolinium contrast agent show high sensitivity and specificity for hepatic fibrosis.³² Large prospective and comparison studies are needed for validation and to distinguish between the various tools for the non-invasive assessment of hepatic fibrosis.

Magnetic resonance T1 mapping for hepatic fibrosis in a population-based study

In this issue of *Circulation: Cardiovascular Imaging*, Ostovaneh et al.,³³ evaluated the cross-sectional association of a history of CVD events and CT-derived measures of cardiac structure and function with hepatic fibrosis, as measured by pre- and post-contrast MRI T1 mapping of the liver, among participants of the Multi-Ethnic Study of atherosclerosis (MESA) study. In this multi-ethnic cohort study of over 2,000 individuals (mean age 68.7±9.1 years, 46% men), the authors demonstrated that a prior history of CVD events was associated with hepatic fibrosis as measured by pre-contrast T1 time, but not extracellular volume fraction (ECV) measures after multivariable adjustment. ECV was only available in 59% of the sample (1234/2087) which, at least in part, may explain the discrepancy in findings. Additional adjustment for coronary artery calcium score or left ventricular mass and volume attenuated the results; however, a history of CVD events remained associated with pre-contrast T1 time, indicating that atherosclerosis did not completely explain the relations between CVD and hepatic fibrosis. In the specific event analyses, a history of coronary heart disease was associated with pre-contrast T1 time, a history of heart failure was associated with hepatic fibrosis as measured by post-contrast ECV, and a history of atrial fibrillation was associated with both hepatic fibrosis measures. Additionally, myocardial fibrosis was associated with both MRI-based indices of hepatic fibrosis and a higher left ventricular ejection fraction and reduced left ventricular circumferential strain were associated with pre-contrast T1 time hepatic fibrosis.

As acknowledged by the authors the study has a number of limitations. The overall prevalence of CVD was relatively low since 895 participants died before they reached the MESA year 10 examination when liver MRI was performed. The primary analysis focused on the 153 of 2087 participants (7.3%) with a history of overall CVD, but the pathogenesis underlying the component CVD events is heterogeneous. The authors examined a composite history of 3 events: 1.2% (n=25) with heart failure, 3.7% (n=78) with atrial fibrillation, and

3.7% (n=78) with coronary heart disease. The analyses of the component prevalent events are potentially limited for several reasons including, they had low power, adjusting for multiple confounders with small numbers is problematic, and the authors did not account for multiple testing. In addition, the authors included participants with only one lobe of the liver covered in the pre- and/or post-contrast T1 maps. However, hepatic fat and fibrosis can be segmental within the liver; it is possible that misclassification of hepatic fibrosis occurred if the T1 maps did not include images of the entire liver.³⁴ In addition, the study was cross-sectional, observational, and adjusted for a limited set of confounders. Hence, the authors cannot determine temporality, i.e. did CVD contribute to liver fibrosis, did liver fibrosis contribute to CVD, or was the association due to residual confounding or intermediate mechanisms.

Whereas the Ostovaneh et al.³³ should be viewed as providing very preliminary evidence regarding the association between liver fibrosis and CVD, the study makes worthwhile contributions to the literature. The authors demonstrated the feasibility of performing T1 mapping of the liver in the context of a multi-center longitudinal cohort study of CVD. Few large cohorts have imaging measures of hepatic fibrosis available; this study represents an important advance in the study of NAFLD since most prior work has focused on the study of hepatic steatosis and not fibrosis. Interestingly, CT-derived liver fat attenuation at the baseline MESA examination was not associated with either measure of hepatic fibrosis at the year 10 MESA examination, which provides additional evidence that CT-derived hepatic steatosis may not be a suitable surrogate for advanced NAFLD phenotypes.

Future Directions

Clinicians, who not infrequently receive reports of incidentally detected NAFLD by various imaging modalities, are uncertain about what clinical steps are indicated to address the finding. It is important for clinicians to remember that advanced NAFLD may be present, even if liver biochemical tests are normal. In particular, patients over the age of 60 years or who have underlying diabetes are at particularly high risk for hepatic fibrosis.¹ Patients with clinical or laboratory measures suggestive of advanced NAFLD should be referred for risk stratification, ideally with advanced imaging, to stage liver fibrosis.

Ostovaneh et al.³³ have demonstrated that CVD events and measures of cardiac structure and function are cross-sectionally related to T1 mapping derived indices of hepatic fibrosis. Longitudinal studies are needed to determine if hepatic fibrosis is associated with incident coronary heart disease, heart failure, and atrial fibrillation after adjustment for important confounders. Future studies correlating mapping findings to liver biopsy samples from patients with proven hepatic fibrosis would be helpful to validate T1 mapping as a sensitive and specific imaging biomarker for hepatic fibrosis. Comparison studies utilizing various MRI- and other imaging-based techniques also are needed to determine the advantages and disadvantages of various non-invasive protocols to measure hepatic fibrosis. Because myocardial fibrosis and hepatic fibrosis are correlated, future studies that explore the relations between hepatic fibrosis and CVD should account for myocardial fibrosis or systemic inflammatory or fibrotic processes to help elucidate the mechanisms that drive the association between the liver and cardiovascular systems.

Ostovaneh et al.³³ have demonstrated that hepatic fibrosis can be measured in a cohort study; additional cohort studies should consider similar techniques to define hepatic fibrosis so that we can learn more about this important NAFLD phenotype. If hepatic steatohepatitis and hepatic fibrosis are associated with incident CVD outcomes, clinicians and public health experts must determine how to prevent the onset and progression of NAFLD.

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