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The Interplay Between Nonalcoholic Fatty Liver Disease and Atherosclerotic Heart Disease

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Nonalcoholic fatty liver disease (NAFLD), the most common form of chronic liver disease, exists in two predominant histological subtypes: nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH).[1] NASH is the clinically aggressive variant with higher risk of fibrosis progression and mortality. The leading cause of mortality in patients with NAFLD is cardiovascular disease (CVD),[2] which is linked to diagnosis of NASH and severity of hepatic fibrosis.[3] Although NAFLD is closely associated with cardiometabolic risk factors such as diabetes, obesity, hypertension, and dyslipidemia, the association between CVD and NAFLD may be independent of these risk factors. The intimate relationship between the liver and coronary heart disease likely stems from the central role the liver plays in glucose and lipid metabolism. Development of NAFLD is associated with increased production and secretion of large triglyceride-laden very low-density lipoprotein (VLDL) particles from the liver.[4] In circulation, VLDL particles are slowly metabolized and are subject to an exchange process that removes cholesteryl ester from the particle core, replacing it with triacylglycerol, which leads to the formation of highly atherogenic small dense low-density lipoprotein particles (Fig. 1).[4] Hepatic production of proinflammatory factors and vasoactive and thrombogenic molecules further contributes to CVD in patients with NAFLD. These putative biological mechanisms result in impaired endothelial function, formation of vulnerable coronary plaque, reduction in coronary artery flow reserve, and poor coronary artery collateral formation with maladaptive response to coronary artery ischemia.[5-8] Clinically, these mechanisms culminate into clinically significant cardiovascular outcomes such as myocardial infarction, stroke, and cardiovascular death.[9] This intimate relationship between dyslipidemia and NASH is highlighted in *post hoc* analysis of the PIVENS trial that demonstrated that resolution of NASH improved dyslipidemia.[10] Finally, in patients with NAFLD, treatment of dyslipidemia with statin therapy is associated with substantial risk reduction of cardiovascular events.[11]

The study by Dr. Pais and colleagues in the current issue of Hepatology builds on the published literature and further explores the relationship between early atherosclerosis and steatosis.[12] The major limitation of the study is the lack of robust assessment of histological parameters (i.e., steatosis, fibrosis, diagnosis of NASH) and cardiovascular outcomes; however, it does provide insight into systemic atherosclerosis and NAFLD. Using fatty liver index (FLI) as a surrogate for hepatic steatosis, the authors assert that steatosis was associated with carotid and coronary artery atherosclerosis as measured by carotid duplex and multidetector computed tomography. Although the association between carotid plaque, coronary artery calcification, and hepatic steatosis is not new,[13,14] the reported link between multisite atherosclerosis

Abbreviations: CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; VLDL, very low-density lipoprotein.

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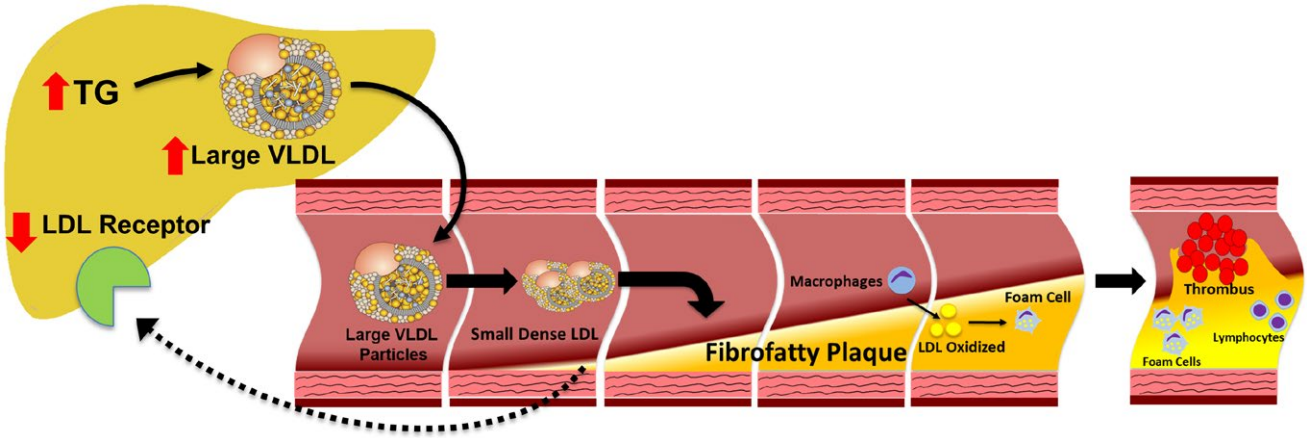

FIG. 1. Role of NAFLD in promoting atherosclerosis. LDL, low-density lipoprotein; TG, triglycerides.

is novel but intuitive. An interesting finding is the quantification of the contribution of hepatic steatosis to patients at intermediate to high risk of having a coronary heart disease event based on Framingham risk score ≥10%. Although the findings of the present study are intriguing, they need to be interpreted in the context of its limitation. First, FLI does not correlate with severity of hepatic steatosis, and therefore, the reported association between the degree of hepatic steatosis and atherosclerosis is nuanced. Due to the cross-sectional nature of the study, it is unclear how atherosclerosis disease at various sites predicts the likelihood of having a coronary heart disease–related event in the future. The clinical implications of the current study are not clear because the findings reported are not linked to clinically significant outcomes. Finally, the effect size of adding hepatic steatosis to identify patients at intermediate to high risk through Framingham risk calculation was relatively modest.

The study by Pais et al. provides valuable insight into NAFLD and early atherosclerosis and highlights key limitations within the field. It is currently unclear if the relationship between NAFLD and atherosclerosis is due to shared risk factors such as adiposopathy, insulin resistance, and dyslipidemia or if it represents an epiphenomenon. Also, the ideal tool to clinically risk-stratify cardiovascular risk in patients with NAFLD is unknown as all of the present CVD risk assessment tools do not account for NAFLD as a potential risk factor. Although the study notes that the addition of NAFLD to traditional CVD risk parameters improves risk assessment, well-designed prospective studies in patients with histologically proven NAFLD with *a priori* defined clinical outcomes are necessary to translate the published findings to clinical practice.

In conclusion, multiple studies have reported a close association between NAFLD and atherosclerosis; however, the optimal means of risk-stratifying and reducing CVD morbidity and mortality in patients with NAFLD remains unknown.

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