Cardiovascular Risk in NAFLD: An Intimate Relationship?

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Abbreviations

HCC	Hepatocellular carcinoma
HOMA	Homeostatic model assessment of insulin resistance
kPa	Kilopascal
LFC	Liver fat content
MACE	Major adverse cardiovascular events
MRI-PDFF	Magnetic resonance imaging-based proton density fat fraction
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
OR	Odds ratio
2D-SWE	2-Dimensional shear wave elastography

Nonalcoholic fatty liver disease (NAFLD) is an umbrella definition that designates a wide spectrum of histological liver changes ranging from uncomplicated simple steatosis (nonalcoholic fatty liver disease [NAFLD]) to nonalcoholic steatohepatitis, (NASH) with or without fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), which are closely and mutually interrelated with the metabolic syndrome, in the absence of significant alcohol consumption and other competing causes of chronic liver disease [1]. The development and the progression of the entire histopathological spectrum of NAFLD is affected by several physiological and pathological modifiers, notably including age, sex, ethnicity, abdominal obesity, and diabetes [2]. The natural course of NAFLD is typically characterized by an increased risk

of developing liver-related complications and extrahepatic diseases. Indeed, the presence of NAFLD-related cirrhosis is predominantly more conducive to liver-related complications, i.e., hepatic decompensation (ascites or upper gastrointestinal bleeding secondary to portal hypertension or hepatic encephalopathy) or HCC, whereas the presence of histological “bridging” liver fibrosis is more closely associated with an increased risk of developing major vascular events (myocardial infarction, heart failure requiring hospitalization, angina, aneurysm dissection, cardiac arrest, and ischemic or hemorrhagic stroke) and extrahepatic cancers [3]. Of the three key histological elementary lesions of NAFLD/NASH [1], the amount of liver fat content (LFC) and the severity of liver fibrosis can be accurately assessed with several noninvasive imaging techniques, including magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) and shear wave elastography (SWE), respectively [4, 5].

With explosive global epidemiological growth, excess expenditures owing to hepatic and extrahepatic complications/manifestations and increasing clinical importance owing to the decline of other competing causes of transmissible chronic liver disease, the public health alarm raised by NAFLD is fully justified. Of importance, the thresholds of body mass index or waist circumference, which are the two most commonly used anthropometric parameters to define obesity, should be ethnospecific given that, for example, Asian and Caribbean populations develop metabolic complications at lower levels of obesity than do populations of European ethnicity [6].

Atherosclerosis, a word of ancient Greek etymology, literally meaning “accumulation of fat and thickening,” is a chronic inflammatory disease affecting arteries and eventually culminating, in a subset of individuals, into clinically manifest complications, which are collectively termed major adverse cardiovascular events (MACE). Before the development of MACE, atherosclerosis may be silent and often insidious, termed as subclinical atherosclerosis. A consistent line of research has exhaustively proven that NAFLD, as detected by imaging or by histology, is strongly associated with an increased risk of both subclinical atherosclerosis

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and MACE [7]. In fact, two systematic reviews and meta-analyses have recently estimated that the excess cardiovascular risk associated with imaging-defined or biopsy-proven NAFLD is 40–370% (Table 1).

Although NAFLD and atherosclerosis are strongly associated, is there a causal relationship? We have recently postulated the existence of two conceptually and biologically distinct pathways [7]. The first, longer pathway would lead from uncomplicated simple steatosis to subclinical atherosclerotic burden via traditional and non-traditional cardiovascular risk factors including chronic kidney disease, type 2 diabetes, hypertension, dyslipidemia, hyperuricemia, chronic inflammation, or expanded adipose tissue in the epicardial region. The second, shorter pathway would more directly link fibrosing NASH to enhanced risk of MACE via increased hepatic production of multiple pro-thrombotic mediators such as hypoxia-inducible factor, vascular endothelial growth factor, and intercellular adhesion molecule-1, fetuin-A, interleukin-6, and the lipidomic commonalities shared by NAFLD and unstable atherosclerotic plaques of coronary arteries. This theoretical paradigm accounts for the finding that fibrosing NASH is more strongly associated with clinically manifest cardiovascular disease than is simple steatosis [7].

On this background of evidence, Shao et al., in a paper published in this issue of *Digestive Diseases and Sciences* reported that subclinical atherosclerosis, defined by increased carotid intima-media thickness or an increased prevalence of carotid atherosclerotic plaques, is strongly associated with increasing liver stiffness measurement and advancing age in patients with NAFLD. Nevertheless, in obese patients with NAFLD, but not in those who are non-obese, increased LFC $\geq 10\%$ (as measured with MRI-PDFF) was an additional independent predictor of subclinical

atherosclerosis [8]. In particular, in this cross-sectional study, the authors enrolled 543 consecutive Chinese adult individuals with NAFLD (mean age 42 years, 67.6% men), who were stratified by either the presence or absence of obesity using a body mass index cut-off value of 25 kg/m², this cut-off being in accord to the widely accepted definition of obesity in Asian populations. MRI-PDFF was performed using a 3.0-Tesla scanner for quantifying LFC, whereas 2D-SWE was used to measure liver stiffness, a surrogate index of fibrosis. Once these 543 patients with NAFLD were classified according to obesity status, no significant differences were found in carotid intima-media thickness, carotid atherosclerotic plaques (defined as a focal thickening of intima-media > 0.5 mm or 50% of surrounding intima-media into the arterial lumen, or a focal thickening > 1.5 mm), the Framingham Risk Score or the atherosclerosis index, calculated as the ratio of total cholesterol to high-density lipoprotein-cholesterol: TC/HDL-C. Specifically, the authors found that in non-obese patients ($n=240$), each 10-year increase in age and liver fibrosis at 2D-SWE (defined as liver stiffness > 6.1 kPa) were independently associated with increased carotid intima-media thickness (adjusted odds ratio [OR] = 9.68; $P < 0.001$ and OR = 4.42; $P = 0.004$, respectively) even after adjusting for established risk factors and potential confounding factors. Conversely, in obese patients ($n=303$) the independent predictors of increased carotid intima-media thickness were older age, liver stiffness > 6.1 kPa and LFC $\geq 10\%$ (adjusted OR = 2.02; $P < 0.001$; OR = 2.18; $P = 0.039$ and OR = 2.29; $P = 0.021$, respectively). In non-obese patients, only hypertriglyceridemia (> 1.7 mmol/l) was independently associated with an increased prevalence of carotid atherosclerotic plaques (adjusted OR = 2.42; $P = 0.033$), whereas in the subgroup

Table 1 Meta-analytic quantification of the excess of risk of subclinical atherosclerosis and major adverse cardiovascular events (MACE) in individuals with imaging-defined or biopsy-proven NAFLD compared to NAFLD-free control subjects

Reference	Study population	Markers/patients	Odds ratio (95% confidence intervals)
Markers of subclinical atherosclerosis			
Zhou YY et al. Hepatol Commun. 2018;2:376–392	85,395 individuals (28.9% with NAFLD)	Carotid artery intima-media thickness/plaques	1.74 (1.47–2.06)
		Arterial stiffness	1.56 (1.24–1.96)
		Coronary artery calcification	1.40 (1.22–1.60)
		Endothelial dysfunction	3.73 (0.99–14.09)
MACE ^a			
Targher G et al. J Hepatol. 2016;65:589–600	34,043 individuals (36.3% with NAFLD)	All NAFLD patients	1.64 (1.26–2.13)
		Patients with “more severe” NAFLD ^b	2.58 (1.78–3.75)

^aFatal and/or non-fatal cardiovascular events were defined as the presence of cardiovascular death, non-fatal CVD events (i.e., myocardial infarction, angina, ischemic stroke or coronary revascularization procedures), or both

^bDefined by the presence of either NAFLD on imaging techniques *plus* either elevated serum gamma-glutamyltransferase concentrations or high NAFLD fibrosis score or high F-18 fluorodeoxyglucose uptake on positron emission tomography, or by increasing fibrosis stage on liver biopsy

of obese patients, only advancing age and LFC $\geq 10\%$ were independent predictors of carotid atherosclerotic plaques (adjusted OR = 1.77; $P = 0.002$ and OR = 2.83; $P = 0.019$, respectively). Notably, body mass index, waist circumference, homeostatic model assessment (HOMA)-estimated insulin resistance, hypercholesterolemia, and hyperuricemia were not independently associated with increased carotid intima-media thickness or increased prevalence of carotid atherosclerotic plaques in non-obese or in obese patients with NAFLD.

Among the major strengths of this cross-sectional study is that patients were recruited at a single university center on Chinese individuals with NAFLD who were consecutively observed over a 4-year period. LFC was measured with MRI-PDFF and liver stiffness with 2D-SW which are deemed to be accurate imaging techniques for diagnosing and staging liver steatosis and fibrosis [4, 5]. Nevertheless, the study lacks an adequate group of control individuals without NAFLD and its cross-sectional design limits establishing temporality or causality of the observed associations.

In another cross-sectional study involving 1509 consecutive Chinese patients with NAFLD, the same authors have recently reported that the predictors of liver steatosis and fibrosis severity differed significantly among lean, overweight and obese individuals with NAFLD. Increased waist circumference was strongly associated with disease severity in all NAFLD patients, whereas body mass index and serum uric acid levels *plus* HOMA-estimated insulin resistance were additional significant predictors in those who were either overweight or obese [9]. Collectively, these two observational studies support the assertion that, in both clinical practice and in the research arena, patients with NAFLD should be stratified at least by their anthropometric features, i.e., body mass index and waist circumference [8, 9].

In conclusion, the cross-sectional study by Shao et al. [8] supports important contributions of age and obesity as potential modifiers of the risk of subclinical atherosclerosis among individuals with NAFLD. The findings of this study also suggest that individuals with NAFLD might benefit from screening and surveillance of early atherosclerosis, which would facilitate the cardiovascular risk stratification of these patients and appropriate interventions in the long term. Despite its indisputable points of strength, which include the relatively large number of individuals recruited and the diagnostic accuracy of imaging techniques used for staging liver steatosis and fibrosis, the study appears to have neglected two important clinical modifiers of NAFLD epidemiology, i.e., sex and ethnicity [2, 10]; for which additional

research is indeed needed. Moreover, further mechanistic studies are also needed to better explore the biological mechanisms linking liver steatosis and fibrosis with increased risk of cardiovascular disease, assessed as markers of subclinical atherosclerosis and, more importantly, development of MACE over time. Finally, proof-of-concept studies should also address the question of whether reversal of hepatic steatosis is accompanied by a parallel decrease in overall cardiovascular risk.

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