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Nonalcoholic Fatty Liver Disease, Cardiovascular Risk, and Carotid Inflammation

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Nonalcoholic fatty liver disease (NAFLD) is defined by excessive triglycerides (TGs) accumulation in the liver (>5% of hepatocytes histologically) in the absence of alcohol excess.[1] The NAFLD ranges from simple steatosis to steatohepatitis and cirrhosis.[1] The NAFLD and nonalcoholic steatohepatitis (NASH) are now the number one cause of liver disease in Western countries.[2] The prevalence of NAFLD is increasing but is underreported, and the epidemiology and demographic characteristics vary worldwide.[2] The prevalence is increasing because of the rising occurrence of obesity and type 2 diabetes (T2DM)[1]; in fact, NAFLD is considered as the hepatic manifestation of metabolic syndrome (MetS).[3] Nonalcoholic fatty liver disease is present in 10% to 24% of the general population in various countries,[2] while the prevalence of NAFLD in obesity is 30% to 100% and in T2DM is 10% to 75%.[4] The morbidity and mortality from liver causes are increased in patients with NAFLD/NASH but is even stronger for cardiovascular disease (CVD).[5] The association of NAFLD with carotid atherosclerosis[6] and the increased risk of CVD in those with NAFLD and T2DM[7] shed light on the association between NAFLD and CVD.

Atherosclerosis risk factors, such as hypertension, dyslipidemia, obesity, and insulin resistance (IR), frequently accompany NAFLD.[7] However, the exact mechanisms involved remain unclear. Nowadays, 2 main factors are considered to contribute to the enhanced risk of CVD in persons with NAFLD, the lipoproteins synthesized by the liver and the increased visceral and ectopic adipose tissue promoting an inflammatory state. In obesity or IR conditions, excessive visceral adiposity increases the availability of free fatty acids (FFAs); this leads to enhanced hepatic production of very low-density lipoprotein (VLDL) and circulating TG levels.[8]

When evaluating patients with MetS, with and without steatohepatitis, those with NAFLD had increased circulating TG levels, higher VLDL mass, and VLDL number of particles.[9,10] Atypical VLDL particles, enriched with TG, are also more atherogenic[8]; these particles have inhibitory effects on endothelial relaxation and are efficiently lipolyzed by lipoprotein lipase,[11] thus leading to the formation of smaller lipoproteins with atherogenic potential that can be further processed by hepatic lipase.[12] Patients with NAFLD also had higher small dense low-density lipoprotein (sdLDL) concentration, associated with increased cholesterol ester transfer protein (CETP) concentration and hepatic lipase activity[13] beyond IR; these factors contribute to a more atherogenic profile linked to increased CVD risk. Although the association between IR and increased LDL-cholesterol (LDL-C) levels is not typical, elevated sdLDL levels with lower large LDL concentrations are related to IR and increased adiposity.[14] In contrast to large buoyant LDL, sdLDL particles are taken up more easily by arterial tissue and have greater oxidative and glycation susceptibility, suggesting a link with atherogenesis.[15,16] Patients with high levels of sdLDL particles have an approximately 3- to 7-fold increased risk of developing coronary heart disease, independent of LDL-C concentration.[17]

Growing evidence suggests that the pathogenesis of NAFLD involves oxidative stress and inflammation.[18] Patients with NAFLD present increased circulating concentrations of C-reactive protein (CRP) and FFA as well as reduced levels of adiponectin, independent of IR.[19] In addition, high-sensitivity CRP (hsCRP) levels correlate with other inflammatory markers such as tumor necrosis factor α and with soluble cellular adhesion molecules such as vascular cell adhesion molecule 1 and intercellular adhesion molecule 1.[19]

Inflammation plays a key role in the initiation, progression, and rupture of atherosclerotic plaques.[20] Furthermore, the inflammatory component of vulnerable plaques triggers events suggesting the need for research to understand the combined

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role of inflammation and IR in the progression from subclinical to clinical atherosclerosis.[21]

Recent studies have shown that patients with NAFLD have significantly greater cIMT than age- and sex-matched patients without NAFLD, independent of the classical risk factors.[22] Moreover, cIMT, assessed by ultrasound examination, is associated with the severity of liver histopathology among patients with NAFLD.[22] It is of interest that statins may exert beneficial effects on cIMT and NAFLD.[23-25]

Nontraditional risk factors, as surrogate markers of cIMT, should also be considered, such as the recently proposed hsCRP–adiponectin ratio, a potential predictor of atherosclerosis progression.[26] In controls and patients with MetS, the hsCRP–adiponectin ratio was associated with circulating levels of matrix metalloproteinases (MMPs), enzymes that are associated with vulnerable plaques and IR conditions.[27,28] Elevated serum MMP concentrations have been reported to be independently associated with carotid artery plaque instability and high cIMT value.[29] Matrix metalloproteinases are activated in inflammatory states and IR[28] and have also been proposed as surrogate markers of the severity of carotid artery disease. More recently, positron emission tomography with[18] F-fluorodeoxyglucose has been considered as a marker for active inflammation in atherosclerotic plaques in patients with NAFLD.[30] It is important to decide whether further recommendations with regard to carotid atherosclerosis screening should be implemented in patients with NAFLD.

Declaration of Conflicting Interests

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