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Editorial

Does nonalcoholic fatty liver disease predispose patients to carotid arteriosclerosis and ischemic stroke?

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See Article on Page 483

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, affecting around 25% of the general population. Recently, the term NAFLD has been changed to metabolic dysfunction-associated fatty liver disease (MAFLD), as it is associated with obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome in lean and non-diabetic individuals.[1,2] The spectrum of NAFLD ranges from simple hepatic steatosis and nonalcoholic steatohepatitis (NASH) to cirrhosis and hepatocellular carcinoma. In addition to NASH-related liver outcomes, NAFLD also increases the risk of atherosclerotic cardiovascular disease (ASCVD) and extra-hepatic tumor.[1,2] ASCVD is the leading cause of death in patients with NAFLD/NASH, with higher mortality than general population. NAFLD is considered to be independently associated with increased risk of incident myocardial infarction, heart failure, and atrial fibrillation in healthy adults after comprehensive control of metabolic risk factors. Meanwhile, there is a potential synergistic increase of coronary heart disease risk in NAFLD patients with dyslipidemia and T2DM.[2-4] However, the relationship of NAFLD with carotid arteriosclerosis (CAS) and stroke still remains controversial and inconsistent, and the impact of NAFLD on the outcomes of stroke is seldom reported.

It is well-known that CAS is a major and potentially preventable cause of cerebrovascular disease, especially ischemic stroke. Carotid intima media thickness (CIMT) is a widely used marker for the evaluation of subclinical CAS and prediction of ASCVD, with higher values representing endothelial dysfunction. Kumari et al.[5] reported that the CIMT levels were higher in patients with NAFLD compared to healthy controls, and also higher in patients with NASH than in those with simple hepatic steatosis. Furthermore, a Japanese study demonstrated that advanced liver fibrosis was significantly

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and independently associated with high-risk CIMT in biopsy-proven NAFLD patients.[6] PNPLA3 GG genotype was associated with higher severity of CAS in younger patients with NAFLD.[7] Moreover, a longitudinal cohort study conducted in diabetic patients suggested that steatosis-related fibrosis was independently associated with the progression of CAS.[8] However, a recent cross-sectional study found that NAFLD was associated with CIMT only in patients with metabolic syndrome, while advanced fibrosis evaluated via transient elastography was not associated with CIMT in NAFLD.[9]

In this issue of the journal, Tang et al.[10] conducted a systematic review with meta-analysis of 64 studies between 1998 to 2019 across multiple countries, illustrating an up-to-date comprehensive assessment of the association of NAFLD with CAS and stroke, with further subgroup analyses based on NAFLD severity and diagnostic modalities. The results demonstrated that a stepwise increment of hepatic steatosis can significantly increase the odds of incident CAS and stroke in patients with NAFLD. Among 7,951 individuals with NAFLD, the pooled prevalence of CAS was 35.02% (95% confidence interval [CI], 27.36% to 43.53%), which was twice that of non-NAFLD controls, and it also varied from region to region, ranging from 19.21% (95% CI, 12.58% to 28.21%) in the Middle East to 44.72% (95% CI, 31.02% to 59.28%) in Europe. Compared to non-NAFLD controls, patients with NAFLD diagnosed by liver biopsy (odds ratio [OR], 4.42; 95% CI, 2.29 to 8.54; P=0.02), ultrasound (OR, 3.32; 95% CI, 2.41 to 4.57; P<0.01), and computed tomography scan (OR, 1.18; 95% CI, 1.01 to 1.39; P=0.04) all had significantly higher odds of developing CAS. Patients with NAFLD were found to have significantly greater CIMT compared to those without NAFLD, and the histological severity of NAFLD was also associated with the mean CIMT. However, the existence of hyperlipidemia and diabetes did not significantly increase the risk of CAS or stroke in patients with NAFLD. Regarding the contradictory results, the first possible explanation might be the insufficient sensitivity of ultrasound for the diagnosis of NAFLD, although ultrasound remains the first choice of non-invasive tool for fatty liver in clinical practice. Secondly, the presence of metabolic risk factors and related therapeutic drugs cannot be completely excluded in NAFLD patients, and they may have been non-significant due to the insufficient statistical power arising from the limited sample size in the risk factor analysis. Finally, age is likely to be an important determinant of CAS development in NAFLD, and long course of fatty liver may be required to develop higher CIMT and incident cerebrovascular disease.

As the most common serious manifestation of ASCVD, stroke is the second-leading cause of death worldwide.[11] Results from the Korean Genome and Epidemiology Study demonstrated that the risk of stroke incidence gradually increased with the degree of fatty liver index, a non-invasive predictor for NAFLD in both lean and overweight/obese adults.[12] Similarly, a meta-analysis of 18 observational studies found that NAFLD was associated with increased risk of stroke, but there was insufficient evidence to support the proposed relationship between the stage of fibrosis and an increased risk of stroke.[13] In this issue of the meta-analysis, Tang et al.[10] reported that the pooled prevalence of stroke was 5.04% (95% CI, 2.74% to 9.09%) among 25,839 individuals with NAFLD, while ischemic stroke and hemorrhagic stroke was 6.05% (95% CI, 2.93% to 12.07%) and 2.22% (95% CI, 0.22% to 18.77%), respectively. Compared to non-NAFLD controls, patients with NAFLD were found to have significantly higher odds of developing ischemic stroke (OR, 2.05; 95% CI, 1.05 to 3.98; P=0.04), whereas hemorrhagic stroke was not the case. The results also showed that the pathologic severity of NAFLD was positively associated with the high odds of developing stroke.

The pathological link between NAFLD and ASCVD risk included the common metabolic risk factors and adipokines disturbance they share, and the increased insulin resistance, oxidative stress, and systemic inflammation originated from NAFLD/NASH, increased platelet activity, endothelial dysfunction, and subsequent enhanced development of arteriosclerosis (Fig. 1).[2-4,14] NAFLD is thus a contributor to increased ASCVD risk, and MAFLD may define patients with higher risk for ASCVD due to the underlying obesity, visceral adiposity, atherogenic dyslipidemia, and T2DM.[1,3]

Particularly, NAFLD appeared to increase the risk for ischemic stroke instead of hemorrhagic stroke, and the severity of NAFLD was positively associated with a higher risk of fu-

Abbreviations:

ASCVD, atherosclerotic cardiovascular disease; CAS, carotid arteriosclerosis; CI, confidence interval; CIMT, carotid intima media thickness; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; T2DM, type 2 diabetes mellitus

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ture ischemic stroke, independent of classic metabolic risk factors.[15] In addition, Baik et al.[16] found that liver fibrosis stage but not steatosis degree, assessed via transient elastography, was an independent predictor of all-cause and cardiovascular mortality during long-term follow-up in patients with ischemic stroke. The potential causal effect of NAFLD on ischemic stroke might be confined to the large artery arteriosclerosis and small vessel occlusion subtypes rather than cardioembolic stroke subtypes, which prompts the heterogeneity of the association.[17] Moreover, the REGARDS Study declared that advanced liver fibrosis might be associated with a higher risk of ischemic stroke in women, but not in men, suggesting the existence of gender difference.[18] A prospective study exploring the impact of NAFLD on the outcome of acute ischemic stroke showed that the National Institutes of Health Stroke Scale score and the modified Rankin scale score were significantly higher in ischemic stroke patients with NAFLD than in those without NAFLD.[19] Similarly, a retrospective study of 306 patients with ischemic stroke demonstrated that NAFLD patients experienced more severe stroke and were at higher risk for neurological deterioration during hospitalization, but had no difference in functional outcomes.[20]

However, the article by Tang et al.[10] had some limitations. Firstly, the studies included in the meta-analysis were mostly retrospective, making the research subject to the inherent limitations of the study design, such as selection bias. Therefore, prospective studies with large samples may be required to provide sufficient and reliable evidence for a causal relationship of NAFLD with CAS and stroke. Secondly, magnetic resonance imaging and liver biopsy may serve as more accurate modalities for the diagnosis of NAFLD and the assessment of its severity. However, in this meta-analysis, the most frequently used modality in the assessment of NAFLD severity was ultrasound; therefore, grading diagnosis of NAFLD was limited to ultrasound findings to maintain homogeneity, despite its less desirable sensitivity and specificity. Lastly, Tang et al.[10] were unable to assess the effects of fibrosis stage on CIMT or stroke, due to the lack of granularity in the reported data. Further studies are needed to uncover the causal relationship between NASH, fibrosis stage, and CAS, stroke, and explore the prognosis of stroke in patients with NAFLD, especially in those with fibrotic NASH. Meanwhile, well-designed prospective cohort studies that fully take account of the specific population, type of stroke, confounding risk fac-

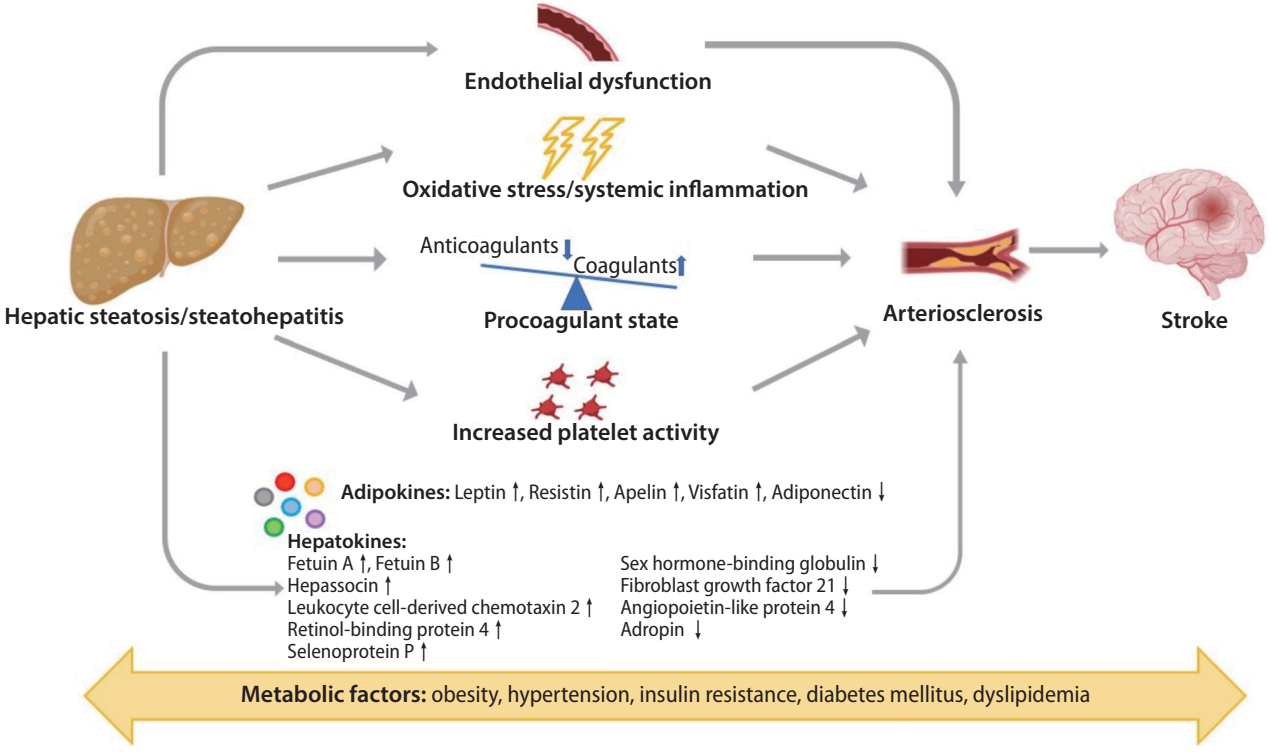

Figure 1. The potential pathologic physiology of the relationship between non-alcoholic fatty liver disease and stroke.

tors, and specific intervention are warranted to reveal and clarify the causal relationship of NAFLD with stroke and the appropriate treatment strategy to reduce the morbidity and mortality of ASCVD in patients with NAFLD.

In summary, NAFLD might be associated with the increased prevalence and severity of CIMT and ischemic stroke. Therefore, the identification of NAFLD is an important aspect of stroke prevention and treatment, and requires increased awareness among clinicians. Since NAFLD patients are at high risk for ASCVD morbidity and mortality, they should undergo regular check-ups of cardiometabolic risk factors and CIMT measurement, and be assessed for ASCVD risk with time-specific thresholds for intervention according to the current guidelines.[3] A better understanding of the evidence-based management of NAFLD, with focus on lifestyle modification, statins, aspirin, and newer diabetes drugs, will help reduce ASCVD risk.

Authors' contribution

Qian Jin: manuscript writing; Rui-Xu Yang: manuscription revision; Jian-Gao Fan: critical revision and supervision

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Conflicts of Interest

The authors have no conflicts to disclose.

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