Does non-alcoholic fatty liver disease predispose patients to carotid arteriosclerosis and ischemic stroke?

Qian Jin¹*, Rui-Xu Yang¹*, Jian-Gao Fan¹,²

1. Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

2. Shanghai Key Lab of Pediatric Gastroenterology and Nutrition, Shanghai 200092, China

Correspondence author: Prof. Jian-Gao Fan, Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine; Shanghai Key Lab of Pediatric Gastroenterology and Nutrition, Shanghai 200092, China.

Email: fanjiangao@xinhuamed.com.cn

* Qian Jin and Rui-Xu Yang contributed equally to this work

Heading title: NAFLD and atherosclerotic cerebrovascular risk

Key words: non-alcoholic fatty liver disease, carotid intima media thickness, carotid arteriosclerosis, ischemic stroke, cardiovascular disease

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, affecting around 25% of the general population. Recently, the term NAFLD is 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, non-alcoholic steatohepatitis (NASH) to cirrhosis and hepatocellular carcinoma. In addition to
NASH related liver outcomes, NAFLD does increase the risk for atherosclerotic cardiovascular disease (ASCVD) and extra-hepatic tumor\textsuperscript{1,2}. ASCVD is the leading cause of death in patients with NAFLD/NASH, with excess mortality than general population. NAFLD is regarded 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\textsuperscript{2-4}. However, the relationship of NAFLD with carotid arteriosclerosis (CAS) and stroke is still controversial and inconsistent, and the impact of NAFLD on the outcomes of the 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\textsuperscript{5} reported that the CIMT levels were higher in patients with NAFLD compared with healthy controls, and higher in patients with NASH than those in simple hepatic steatosis. Further, a Japanese study demonstrated that advanced liver fibrosis was significantly and independently associated with high-risk CIMT in biopsy-proven NAFLD patients\textsuperscript{6}. PNPLA3 GG genotype was associated with higher severity of CAS in younger patients with NAFLD\textsuperscript{7}. Moreover, a longitudinal cohort conducted in diabetic patients suggested that steatosis related fibrosis was independently associated with the progression of CAS\textsuperscript{8}. However, a recent cross-sectional study found that NAFLD was associated with CIMT only occurred in patients with metabolic syndrome, and 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\%), twice as which among non-NAFLD controls, and 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 CT scan (OR: 1.18; 95\%CI: 1.01 to 1.39; \(p=0.04\)) had all significantly higher odds of developing CAS. Patients with NAFLD were found to have a significantly greater CIMT than those without NAFLD, and the histological severity of NAFLD was also associated with mean CIMT. However, the existence of hyperlipidemia and diabetes did not significantly increase the risk of CAS or stroke in patients with NAFLD. For the contradictory results, the first possible explanations might be the insufficient sensitivity of ultrasound for the diagnosis of NAFLD, although ultrasound remains the first choice of noninvasive 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 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. 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 noninvasive predictor for NAFLD in both lean and overweight/obese adults. 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. In this issue of the meta-analysis, Tang et al. 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). 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.

Particularly, NAFLD appear to increase the risk for ischemic stroke instead of hemorrhagic stroke, and the severity of NAFLD was positively associated with a higher risk of future ischemic stroke, independent of classic metabolic risk factors. In addition, Baik et al. 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. Moreover, the REGARDS Study declared that advanced liver fibrosis might be associated with a higher risk of ischemic stroke in women but not men, suggesting the existence of gender difference. 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 was significantly higher in ischemic stroke patients with NAFLD than those without NAFLD. Similarly, a retrospective study of 306 patients with ischemic stroke demonstrated that those with NAFLD experienced more severe stroke and were at higher risk for neurological deterioration during hospitalization but had no difference in functional outcomes.
However, the article by Tang et al\textsuperscript{10} has some limitations. Firstly, the studies included in the meta-analysis were mostly retrospective and were subject to inherent limitations of study design, such as selection bias. So prospective studies with large samples may be essential 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 a more accurate modality for diagnosis of NAFLD and assessment its severity. However, in this meta-analysis, the most frequently used modality in the assessment of NAFLD severity was ultrasound, the grading diagnosis of NAFLD was thus limited to ultrasound findings to maintain homogeneity, despite its less desirable sensitivity and specificity. Lastly, they were unable to assess the effects of stage of fibrosis on CIMT or stroke due to lack of granularity in the reported data. Further studies need to uncover the causal relationship between NASH, fibrosis stage and CAS, stroke, and explore the prognosis of stroke in patients with NAFLD, especially in patients with fibrotic NASH. Meanwhile, well-designed prospective cohort studies that take fully account of specific population, type of stroke, confounding risk factors, and specific intervention are warranted to reveal and clarify the causal relationship of NAFLD with stroke and the appropriate treatment strategy, so as to the reduction of 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. Hence, the identification of NAFLD is an important aspect of stroke prevention and treatment that necessitates increased awareness among clinicians. Because NAFLD patients are at high risk for ASCVD morbidity and mortality, they should get regular
cardiometabolic risk factors and CIMT measurement, and be assessed for ASCVD risk with timely specific thresholds for intervention according to current guidelines. A better understanding of the evidence-based management of NAFLD will help to reduce ASCVD risk with focus on lifestyle modification, statins, aspirin and newer diabetes drugs.

Acknowledgments

Jian-Gao Fan received the grant from the National Key Research and Development Program of China (2021YFC2700802), the National Natural Science Foundation of China (81873565 and 82170593), and the Clinical Research Unit, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (17CSK04). Rui-Xu Yang received the grant from the National Natural Science Foundation of China (81900507).

Authors’ contributions

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

Conflict of interest statement

All authors declare that they have no conflict of interest.

References

1. Zeng J, Fan JG. From NAFLD to MAFLD: Not just a change in the name. Hepatobiliary


9. Tan EC, Tai MS, Chan WK, Mahadeva S. Association between non-alcoholic fatty liver disease evaluated by transient elastography with extracranial carotid atherosclerosis in a


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