

## Associations between nonalcoholic fatty liver disease and ischemic stroke

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### Abstract

Nonalcoholic fatty liver disease (NAFLD) is the commonest chronic liver disease and affects a considerable proportion of the general population. NAFLD is independently associated with increased risk for cardiovascular events, particularly coronary heart disease. Importantly, even though NAFLD is more prevalent in patients with major cardiovascular risk factors (*e.g.*, type 2 diabetes mellitus, obesity and hypertension), the association between NAFLD and cardiovascular disease appears to be independent of these risk factors. However, NAFLD also appears to increase the risk for ischemic stroke, a leading cause of mortality and long-term disability worldwide. It also appears that nonalcoholic steatohepatitis is more strongly related to the risk of ischemic stroke than isolated hepatic steatosis. Moreover, emerging data suggest that patients with NAFLD experience more severe ischemic stroke and have more unfavorable prognosis after an acute ischemic stroke in terms of functional dependency and short- and long-term mortality. These associations have major public health implications, since ischemic stroke is the second leading cause of death worldwide and an important cause of long-term disability. The aim of the present review is to summarize the current knowledge regarding the relationship between NAFLD and ischemic stroke incidence, severity and outcome. Given these associations, it might be useful to evaluate patients with acute ischemic stroke for the presence of NAFLD and to manage those with NAFLD more aggressively.

**Key words:** Nonalcoholic fatty liver disease; Ischemic stroke; Risk; Incidence; Severity; Outcome; Functional dependency

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**Core tip:** Accumulating data suggest that nonalcoholic

fatty liver disease (NAFLD) is independently associated with increased risk for ischemic stroke, a leading cause of mortality and long-term disability worldwide. Moreover, emerging evidence shows that patients with NAFLD experience more severe ischemic stroke and have more unfavorable prognosis after an acute ischemic stroke in terms of functional dependency and short- and long-term mortality.

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most frequent chronic liver disease, affects approximately 25% of the general population and is the leading cause of abnormal liver function tests<sup>[1,2]</sup>. Moreover, the prevalence of NAFLD is even higher in elderly subjects and in patients with type 2 diabetes mellitus (T2DM), obesity, hypertension and/or metabolic syndrome<sup>[2,3]</sup>. Nonalcoholic steatohepatitis (NASH), a more advanced form of NAFLD, is present in up to 10% of adults<sup>[4]</sup>. NAFLD can progress to cirrhosis, hepatocellular cancer or liver failure, and is a major cause of liver transplantation<sup>[3,5]</sup>.

Several studies showed that NAFLD is a risk factor for cardiovascular disease (CVD)<sup>[6,7]</sup>. Importantly, even though NAFLD is more prevalent in patients with major cardiovascular risk factors (*e.g.*, T2DM, obesity and hypertension), the association between NAFLD and CVD appears to be independent of these risk factors (Figure 1)<sup>[6,7]</sup>.

In this context, accumulating data suggest that NAFLD is also associated with increased incidence of ischemic stroke. Moreover, emerging evidence suggests that NAFLD might also be related with more severe stroke and with worse outcome of patients with acute ischemic stroke. These associations have major public health implications, since ischemic stroke is the second leading cause of death worldwide and an important cause of long-term disability<sup>[8,9]</sup>. The aim of the present review is to summarize the current knowledge regarding the relationship between NAFLD and ischemic stroke incidence, severity and outcome.

## NAFLD AND INCIDENCE OF ISCHEMIC STROKE

Several studies reported that elevated aminotransferase and g-glutamyltransferase (gGT) levels, which are mostly due to NAFLD, are associated with

increased incidence of ischemic stroke (Table 1). In a small case-control study in 103 patients with acute ischemic stroke and 200 controls, alanine or aspartate aminotransferase levels were independently associated with increased odds ratio for ischemic stroke<sup>[10]</sup>. In a larger prospective study in 6997 men without established CVD or T2DM, gGT levels, a more specific marker of NAFLD, was independently associated with higher risk of ischemic stroke, even in subjects at low- or moderate cardiovascular risk<sup>[11]</sup>. In EUROSTROKE, a nested-case control study performed in 3 European countries (Finland, Netherlands and United Kingdom), the association between gGT levels and ischemic stroke risk appeared to be stronger in patients without T2DM<sup>[12]</sup>. Importantly, gGT appears to play a role in atherogenesis<sup>[13]</sup>. Indeed, gGT has been isolated from atheromatic plaques, macrophages and foam cells<sup>[14]</sup> and appears to contribute to atherosclerosis by inducing oxidative stress<sup>[15]</sup>. It was shown that gGT promotes oxidation of low-density lipoprotein and that it plays a crucial role in the catabolism of glutathione and the release of reactive oxygen species<sup>[16,17]</sup>. In a recent cross-sectional study, NAFLD diagnosed with ultrasonography was associated with increased prevalence of lacunar infarcts in non-obese subjects but not in obese patients<sup>[18]</sup>. In contrast, in another recent case-cohort study in 572 patients with incident ischemic stroke and 1017 controls, NAFLD defined as fatty liver index > 60 was associated with lower risk in men but there was no association in women<sup>[19]</sup>. In a meta-analysis of 9 case-control and cohort studies, NAFLD was independently associated with 2.3 times higher risk for ischemic stroke (95%CI: 1.84-2.93)<sup>[20]</sup>. The strength of this association was comparable in Caucasian and Asian patients<sup>[20]</sup>. Importantly, this association was independent of traditional cardiovascular risk factors, including dyslipidemia, obesity and T2DM<sup>[20]</sup>.

It appears that NASH is more strongly related to the risk of ischemic stroke than isolated hepatic steatosis. Indeed, in a case-control study in 295 patients with acute ischemic stroke and 1942 subjects who underwent a health check-up, the degree of liver fibrosis, evaluated with transient elastography, was independently associated with increased stroke risk<sup>[21]</sup>. In contrast, isolated steatosis was not related with the risk of stroke<sup>[21]</sup>.

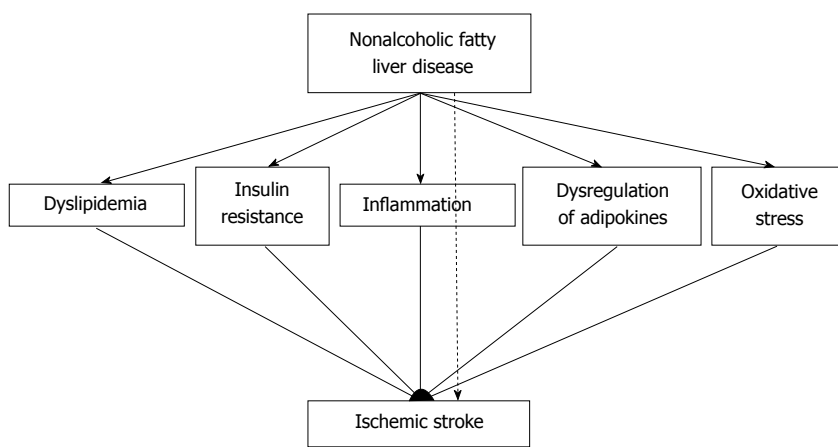
## NAFLD AND SEVERITY AND OUTCOME OF ISCHEMIC STROKE

There are very few data regarding the impact of NAFLD on the severity and outcome of ischemic stroke (Table 1). In an early prospective study in 200 patients admitted with acute ischemic stroke, NAFLD (defined as elevated aminotransferase levels in the absence of other causes) was present in 42.5% of patients<sup>[22]</sup>. Patien-

**Table 1 Major studies that evaluated the association between nonalcoholic fatty liver disease and ischemic stroke**

Ref.	Design	Mean age (yr)	Follow-up	Outcome
[7]	Prospective observational study in 1637 healthy Japanese men/women	47.8	2 yr	Higher incidence of CVD including stroke in patients with NAFLD compared with controls
[22]	Prospective study in 242 patients admitted with acute stroke	66	2 yr	Increased risk of acute stroke, more severe stroke and worse outcome in patients with NAFLD
[11]	Prospective study in 6997 men with no history of CVD or diabetes mellitus	40-59	24 yr	Association between gGT and higher incidence of fatal, major stroke events and total CVD mortality
[10]	Cross sectional study in adults with suspected acute stroke	20-27	Not applicable	Elevated ALP and ALT levels independently associated with higher risk of acute stroke
[12]	Case-control study using data from 3 European cohort studies in 13177 subjects	40-60	3-8 yr	Elevated gGT levels associated with higher risk of stroke
[21]	Case-control study in 295 patients with acute stroke and 1942 healthy subjects	60	Not applicable	Liver fibrosis was associated with higher incidence of ischemic stroke
[20]	Meta analysis of 9 studies that examined relation of NAFLD and stroke	Not reported	Not applicable	Higher risk of ischemic stroke and hemorrhagic stroke in patients with NAFLD
[23]	Retrospective study in 306 patients with confirmed brainstem infarctions	65	Not applicable	Higher incidence of brainstem infarctions in patients with NAFLD
[24]	Study in 415 patients admitted with acute ischemic stroke	78.8	Duration of hospitalization	NAFLD was not associated with stroke severity at admission or outcome during hospitalization
[19]	Case-cohort study in 572 patients with stroke and 1017 controls	> 45	5.8 yr	Fatty liver index associated with increased risk for ischemic stroke in women and with lower risk in women
[20]	Cross-sectional study in 1277 subjects who underwent brain magnetic resonance imaging and abdominal ultrasound during check-up	> 40 yr	Not applicable	NAFLD diagnosed with ultrasonography was associated with increased prevalence of lacunar infarcts in non-obese subjects but not in obese patients

CVD: Cardiovascular disease; gGT: G-glutamyltransferase; ALP: Alkaline phosphatase; ALT; Alanine aminotransferase; NAFLD: Nonalcoholic fatty liver disease.



**Figure 1 Mechanisms underpinning the association between nonalcoholic fatty liver disease and ischemic stroke (broken line suggests the independent association between nonalcoholic fatty liver disease and ischemic stroke).**

ts with NAFLD had more severe stroke at admission and worse functional outcome at discharge<sup>[22]</sup>. However, patients with NAFLD were more obese, had higher prevalence of T2DM and had higher low-density lipoprotein cholesterol and triglyceride levels than patients without NAFLD; these differences were not adjusted for in the comparisons of stroke severity and outcome between the 2 groups<sup>[22]</sup>. In a more recent retrospective study in 306 patients with brainstem infarction, a similar prevalence of NAFLD (defined as elevated aminotransferase levels in the absence of other causes) was reported (42.5%)<sup>[23]</sup>. Patients with NAFLD

had more severe stroke at admission and higher risk for neurological deterioration during hospitalization, independently of other risk factors<sup>[23]</sup>. In contrast, in a prospective study in 415 consecutive patients with acute ischemic stroke, stroke severity at admission, functional outcome at discharge and in-hospital mortality did not differ between patients with NAFLD (defined as elevated aminotransferase levels without another apparent cause) and those without NAFLD after adjustment for other cardiovascular risk factors<sup>[24]</sup>. However, only 32 patients (7.7% of the study population) had NAFLD<sup>[24]</sup>. Therefore, this study might have lacked the power to

identify an association between NAFLD and stroke severity and outcome<sup>[24]</sup>.

## CONCLUSION

Accumulating data suggest that NAFLD is independently associated with increased risk for ischemic stroke. Moreover, it appears that patients with NAFLD experience more severe stroke and have more adverse functional outcome than patients without NAFLD. Therefore, it might be useful to evaluate patients with acute ischemic stroke for the presence of NAFLD and to manage those with NAFLD more aggressively. It remains to be established whether management of NAFLD will also reduce the risk and improve the outcome of ischemic stroke.

## REFERENCES

- 1 **Armstrong MJ**, Houlihan DD, Bentham L, Shaw JC, Cramb R, Olliff S, Gill PS, Neuberger JM, Lilford RJ, Newsome PN. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. *J Hepatol* 2012; **56**: 234-240 [PMID: 21703178 DOI: 10.1016/j.jhep.2011.03.020]
- 2 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]
- 3 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**: 2005-2023 [PMID: 22488764 DOI: 10.1002/hep.25762]
- 4 **Caballería L**, Pera G, Arteaga I, Rodríguez L, Alumà A, Morillas RM, de la Ossa N, Díaz A, Expósito C, Miranda D, Sánchez C, Prats RM, Urquiza M, Salgado A, Alemany M, Martínez A, Majeed I, Fabrellas N, Graupera I, Planas R, Ojanguren I, Serra M, Torán P, Caballería J, Ginès P. High Prevalence of Liver Fibrosis Among European Adults With Unknown Liver Disease: A Population-Based Study. *Clin Gastroenterol Hepatol* 2018; **16**: 1138-1145.e5 [PMID: 29452268 DOI: 10.1016/j.cgh.2017.12.048]
- 5 **Bhala N**, Angulo P, van der Poorten D, Lee E, Hui JM, Saracco G, Adams LA, Charatcharoenwitthaya P, Topping JH, Bugianesi E, Day CP, George J. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. *Hepatology* 2011; **54**: 1208-1216 [PMID: 21688282 DOI: 10.1002/hep.24491]
- 6 **Targher G**, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, Arcaro G. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care* 2007; **30**: 2119-2121 [PMID: 17519430 DOI: 10.2337/dc07-0349]
- 7 **Hamaguchi M**, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, Kawahito Y, Yoshida N, Suetsugu A, Kato T, Okuda J, Ida K, Yoshikawa T. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. *World J Gastroenterol* 2007; **13**: 1579-1584 [PMID: 17461452 DOI: 10.3748/wjg.v13.i10.1579]
- 8 **Mendis S**, Puska P, Norrving B, editors. *Globes Atlas on cardiovascular disease prevention and control*. Geneva: World Health Organization, 2011
- 9 **Menken M**, Munsat TL, Toole JF. The global burden of disease study: implications for neurology. *Arch Neurol* 2000; **57**: 418-420 [PMID: 10714674 DOI: 10.1001/archneur.57.3.418]
- 10 **Ying I**, Saposnik G, Vermeulen MJ, Leung A, Ray JG. Non-alcoholic fatty liver disease and acute ischemic stroke. *Epidemiology* 2011; **22**: 129-130 [PMID: 21150361 DOI: 10.1097/EDE.0b013e3181feb50a]
- 11 **Wannamethee SG**, Lennon L, Shaper AG. The value of gamma-glutamyltransferase in cardiovascular risk prediction in men without diagnosed cardiovascular disease or diabetes. *Atherosclerosis* 2008; **201**: 168-175 [PMID: 18378241 DOI: 10.1016/j.atherosclerosis.2008.01.019]
- 12 **Bots ML**, Salonen JT, Elwood PC, Nikitin Y, Freire de Concalves A, Inzitari D, Sivenius J, Trichopoulos A, Tuomilehto J, Koudstaal PJ, Grobbee DE. Gamma-glutamyltransferase and risk of stroke: the EUROSTROKE project. *J Epidemiol Community Health* 2002; **56** Suppl 1: i25-i29 [PMID: 11815641 DOI: 10.1136/jech.56.suppl\_1.i25]
- 13 **Emdin M**, Passino C, Franzini M, Paolicchi A, Pompella A. gamma-glutamyltransferase and pathogenesis of cardiovascular diseases. *Future Cardiol* 2007; **3**: 263-270 [PMID: 19804218 DOI: 10.2217/14796678.3.3.263]
- 14 **Franzini M**, Corti A, Martinelli B, Del Corso A, Emdin M, Parenti GF, Glauber M, Pompella A, Paolicchi A. Gamma-glutamyltransferase activity in human atherosclerotic plaques-biochemical similarities with the circulating enzyme. *Atherosclerosis* 2009; **202**: 119-127 [PMID: 18486136 DOI: 10.1016/j.atherosclerosis.2008.03.023]
- 15 **Koenig G**, Seneff S. Gamma-Glutamyltransferase: A Predictive Biomarker of Cellular Antioxidant Inadequacy and Disease Risk. *Dis Markers* 2015; **2015**: 818570 [PMID: 26543300 DOI: 10.1155/2015/818570]
- 16 **Paolicchi A**, Minotti G, Tonarelli P, Tongiani R, De Cesare D, Mezzetti A, Dominici S, Compoti M, Pompella A. Gamma-glutamyl transpeptidase-dependent iron reduction and LDL oxidation--a potential mechanism in atherosclerosis. *J Investig Med* 1999; **47**: 151-160 [PMID: 10198571]
- 17 **Stark AA**, Zeiger E, Pagano DA. Glutathione metabolism by gamma-glutamyltranspeptidase leads to lipid peroxidation: characterization of the system and relevance to hepatocarcinogenesis. *Carcinogenesis* 1993; **14**: 183-189 [PMID: 8094645 DOI: 10.1093/carcin/14.2.183]
- 18 **Kwak MS**, Kim KW, Seo H, Chung GE, Yim JY, Kim D. Non-obese fatty liver disease is associated with lacunar infarct. *Liver Int* 2018; **38**: 1292-1299 [PMID: 29220869 DOI: 10.1111/liv.13663]
- 19 **Alexander KS**, Zakai NA, Lidofsky SD, Callas PW, Judd SE, Tracy RP, Cushman M. Non-alcoholic fatty liver disease, liver biomarkers and stroke risk: The Reasons for Geographic and Racial Differences in Stroke cohort. *PLoS One* 2018; **13**: e0194153 [PMID: 29529073 DOI: 10.1371/journal.pone.0194153]
- 20 **Hu J**, Xu Y, He Z, Zhang H, Lian X, Zhu T, Liang C, Li J. Increased risk of cerebrovascular accident related to non-alcoholic fatty liver disease: a meta-analysis. *Oncotarget* 2017; **9**: 2752-2760 [PMID: 29416808 DOI: 10.18632/oncotarget.22755]
- 21 **Kim SU**, Song D, Heo JH, Yoo J, Kim BK, Park JY, Kim DY, Ahn SH, Kim KJ, Han KH, Kim YD. Liver fibrosis assessed with transient elastography is an independent risk factor for ischemic stroke. *Atherosclerosis* 2017; **260**: 156-162 [PMID: 28222857 DOI: 10.1016/j.atherosclerosis.2017.02.005]
- 22 **Abdeldyem SM**, Goda T, Khodeir SA, Abou Saif S, Abd-Elsalam S. Nonalcoholic fatty liver disease in patients with acute ischemic stroke is associated with more severe stroke and worse outcome. *J Clin Lipidol* 2017; **11**: 915-919 [PMID: 28579247 DOI: 10.1016/j.jacl.2017.04.115]
- 23 **Li H**, Hu B, Wei L, Zhou L, Zhang L, Lin Y, Qin B, Dai Y, Lu Z. Non-alcoholic fatty liver disease is associated with stroke severity and progression of brainstem infarctions. *Eur J Neurol* 2018; **25**: 577-e34 [PMID: 29281159 DOI: 10.1111/ene.13556]
- 24 **Tziomalos K**, Giampatzis V, Bouziana SD, Spanou M, Pap-

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adopoulos M, Pavlidis A, Kostaki S, Bozikas A, Savopoulos C, Hatzitolios AI. Association between nonalcoholic fatty liver disease

and acute ischemic stroke severity and outcome. *World J Hepatol* 2013; 5: 621-626 [PMID: 24303090 DOI: 10.4254/wjh.v5.i11.621]

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