



Association of Metabolic Dysfunction-Associated Fatty Liver Disease with Cognitive Impairment and All-Cause Dementia: A Comprehensive Review

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Cite this article as: Kaya E, Yilmaz Y. Association of metabolic dysfunction-associated fatty liver disease with cognitive impairment and all-cause dementia: A comprehensive review. *Turk J Gastroenterol.* 2024;35(2):76-82.

ABSTRACT

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a significant public health concern, affecting one-third of the global population and posing a risk for progressive liver disease. MAFLD is characterized by hepatic steatosis and impaired metabolic status, which not only impact the liver but also other systems of the human body, making it a multisystemic disorder. Emerging evidence suggests that MAFLD and its associated pathological pathways may contribute to cognitive impairment, potentially through neuroinflammation and neurodegeneration. Studies have detected cognitive impairment in patients with MAFLD using magnetic resonance imaging, which revealed decreased brain volume and cerebral perfusion, in addition to self-reported cognitive tests. While numerous studies have demonstrated an association between MAFLD and cognitive impairment, the relationship between MAFLD and all-cause dementia remains controversial. However, the shared pathological pathways between MAFLD and dementia, such as systemic inflammation, insulin resistance, gut dysbiosis, hyperammonemia, and vascular dysfunction, indicate the possibility of a common prevention strategy for both diseases. In this review, we provide a summary of the current evidence regarding the association between cognitive impairment, all-cause dementia, and MAFLD.

Keywords: Cognitive dysfunction, dementia, insulin resistance, liver fibrosis, metabolic dysfunction-associated fatty liver disease

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by the presence of hepatic steatosis, diagnosed either through imaging or biopsy, after excluding secondary factors contributing to hepatic fat infiltration. It poses a significant public health concern, affecting approximately 30% of the global population and having the potential to progress to advanced liver disease.¹ In 2020, a new definition, metabolic dysfunction-associated fatty liver disease (MAFLD), was proposed as an alternative to NAFLD.² MAFLD is defined by the presence of hepatic steatosis along with criteria such as diabetes mellitus (DM), overweight/obesity, or metabolic dysfunction.^{3,4} While MAFLD and NAFLD represent similar, although not identical, diseases, approximately 90% of the patient population falls under both definitions.⁵ Therefore, in this review, we have made a deliberate effort to avoid using NAFLD and MAFLD interchangeably and present the data separately. In the definition of MAFLD, the primary clinical measurement has been identified as disease severity, encompassing inflammation and fibrosis stages. However, this has

sparked a discussion. The main criticism revolves around the potential to impede awareness of nonalcoholic steatohepatitis, a key endpoint in clinical trials and a crucial factor in drug development.^{6,7} In 2023, Rinella et al recommended the term “metabolic dysfunction-associated steatotic liver disease” (MASLD) after conducting 4 Delphi surveys and 2 face-to-face meetings. The updated terminology defines MASLD as the presence of hepatic steatosis along with at least 1 of the 5 cardiometabolic risk factors. This adjustment ensures the preservation of endpoints from previous clinical trials. Additionally, a new category, MetALD, was introduced to classify patients with MASLD who also exhibit significant alcohol consumption.⁸ Due to the novelty of the terminology and lack of studies investigating the cognitive status of the patients identified as having MASLD, our review was unable to include data on the cognitive status of MASLD patients.

With a reported prevalence of 40%, MAFLD is the most common chronic liver disease globally.⁹ Projected studies indicate that fatty liver prevalence will continue to rise

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Received: December 1, 2023 Revision Requested: December 11, 2023 Last Revision Received: December 12, 2023 Accepted: December 15, 2023 Publication Date: February 1, 2024

DOI: 10.5152/tjg.2024.23629

due to the increasing rates of DM and obesity epidemics.^{10,11} Despite primarily manifesting as a liver disease, MAFLD is extensively documented as a multisystemic disorder. Consequently, MAFLD and its associated conditions are under intense scrutiny in industrialized nations. Accumulating evidence highlights the strong association between MAFLD and cardiovascular disorders, DM, metabolic syndrome, obesity, chronic kidney disease, and extra-hepatic malignancies, among others.¹² Recently, MAFLD has emerged as a potential risk factor for the development of cognitive impairment and dementia, attributable to shared risk factors.¹³ In this review, our objective is to provide a comprehensive summary of the current clinical data and elucidate the common pathophysiological mechanisms representing the relationship between these 2 conditions.

EVIDENCE FOR COGNITIVE IMPAIRMENT IN PATIENTS WITH FATTY LIVER DISEASE

Accumulating evidence indicates a strong association between MAFLD and decreased cognitive function across various domains. Studies based on patient-reported outcomes have shown that patients with NAFLD, without evidence of cirrhosis, experience higher rates of fatigue, memory loss, and concentration problems.^{14,15}

One study conducted by Cushman et al¹⁶ prospectively investigated 30 000 adults aged over 45 years using repetitive tests that assessed word list learning and recall, as well as verbal fluency. The NAFLD was defined based on the fatty liver index, including body mass index, waist circumference, gamma-glutamyl transferase, and triglycerides. The study found that the presence of NAFLD was associated with a two-fold increased risk of cognitive impairment. After adjusting for cardiovascular, stroke, and metabolic risk factors, the risk increased to 2.95-fold.¹⁶

In another study, middle-aged and elderly patients (n = 1651) were followed up for 4 years and assessed using a mini-mental test adapted according to education level. Nearly half of the population in this study had NAFLD,

as defined by ultrasonography. After the 4-year follow-up, 17.7% of patients with NAFLD and 11.7% of patients without NAFLD showed evidence of significantly impaired cognitive performance ($P < .001$).¹⁷

A systematic review by Georg et al¹⁸ identified the cognitive domains that were most affected by NAFLD, including general cognition, mental speed, attention and psychomotor speed, as well as ideas, abstraction, figural creations, and mental flexibility.

Not only MAFLD itself, but metabolic disturbances, including DM, have been shown to be associated with cognitive impairment. In a prospective study conducted with 62 obese adults (41 patients with prediabetes and 21 patients with newly diagnosed type 2 DM), the patients' memory function was evaluated. The contribution of NAFLD and insulin resistance, defined by Homeostasis Model Assessment-Insulin Resistance, to cognitive decline in the memory domain was found to be significant.¹⁹ Another study using data from the National Health and Nutrition Examination Survey (NHANES) 2011-2014 showed that patients with both NAFLD and type 2 DM performed significantly worse in tasks combining processing speed, sustained attention, and working memory compared to those without type 2 DM.²⁰ Additionally, patients with both type 2 DM and NAFLD were reported to have worse fine motor performance. However, it should be noted that they were also less physically active, which is known to be significantly associated with fine motor performance.²¹ Consistent with this evidence, current knowledge indicates that patients with MAFLD experience more severe cognitive impairment compared to those with NAFLD but not MAFLD. In this study, the authors investigated NHANES-III data. Cognitive performance was evaluated using the serial digit learning test (SDLT), the simple reaction time test (SRTT), and the symbol digit substitution test (SDST). The SDLT assessed learning ability, short-term memory, and concentration; the SRTT assessed visual-motor speed and response time; and the SDST assessed processing speed and visual attention. In their analysis, MAFLD patients had significantly lower scores for the SRTT, indicating lower visual-motor speed and response time, after adjusting for sex, age, ethnicity, education level, and history of stroke (odds ratio [OR] = 1.47; 95% CI 1.14-1.89). Moreover, the high likelihood of fibrosis among MAFLD patients was found to be associated with poorer performance on the SRTT and SDST. In fact, the presence of prediabetes among MAFLD patients resulted in a twice worse SRTT performance, while type 2 DM led to a 3-fold worse performance (OR = 2.01; 95% CI 1.37-2.96; OR = 2.87; 95% CI 1.44-5.74, respectively).¹³

Main Points

- The accumulating evidence shows a significant relationship between metabolic dysfunction-associated fatty liver disease (MAFLD) and cognitive impairment.
- The relationship is possibly due to shared metabolic factors such as systemic inflammation, hyperammonemia, insulin resistance, gut dysbiosis, and vascular dysfunction.
- The association of MAFLD with all-cause dementia remains controversial.

Not only have patient-reported studies demonstrated a correlation between decreased cognitive performance and NAFLD, but imaging studies have also supported this finding. In a comparative study, patients with NAFLD exhibited worse results on the Montreal Cognitive Assessment test, which serves as an indicator of cognitive performance, as well as decreased brain tissue volume in magnetic resonance imaging (MRI) compared to those without NAFLD.²² Furthermore, in a cross-sectional study conducted with 766 individuals from the Offspring cohort of the Framingham Study, NAFLD was found to be associated with decreased brain volume in MRI after adjusting for age, sex, and metabolic risk factors, suggesting a potential link between NAFLD and brain aging.²³ In a study by VanWagner et al, it was indeed observed that brain volume was significantly lower among individuals with NAFLD. However, after adjusting for adipose tissue volume and body mass index, this relationship did not remain significant. Lower cerebral perfusion, as a marker of early brain damage, was significantly more common among patients with NAFLD after adjusting for cardio-metabolic factors.²⁴ Conflicting results have also been reported. In another study conducted among hypertensive and diabetic patients, the presence of hepatic steatosis was not associated with cognitive impairment or brain volume. However, it is worth noting that in this study, the diagnosis of hepatic steatosis was defined using the Dallas steatosis index rather than imaging methods utilized in other studies, which might lead to misclassification of the patients.²⁵

The positive correlation between the presence of MAFLD and decreased cognitive performance notwithstanding, there are similar trends in the severity of liver disease and cognitive impairment. It has been shown that MAFLD patients with higher fibrosis scores perform worse in cognitive tests.^{13,26} In a study by Weinstein et al,²⁶ however, the authors did not find a significant association between NAFLD and cognitive impairment. Nevertheless, among patients with NAFLD, a higher NAFLD fibrosis score, which indicates a higher probability of advanced fibrosis, was associated with poorer cognitive outcomes, independent of confounding factors.²⁶ However, a study that used liver biopsy to diagnose NAFLD found no significant relationship between liver fibrosis stage and the severity of cognitive status. In this study, evidence of hepatic inflammation was linked to poorer cognitive status, as defined by the mini-mental state examination.²⁷ In addition to cognitive impairment, depression was found to be a strong predictor of MAFLD due to the effect of chronic inflammation on the gut-brain axis. However, the

association of depression with the severity of liver disease was not proven.²⁸ Therefore, the current evidence points to a strong association between impaired cognitive status and liver disease itself, as well as its severity. However, there is a need for future research to address this issue.

PRESENCE OF DEMENTIA IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE AND ITS RELATIONSHIP TO DISEASE SEVERITY

Despite the existence of shared pathways in the pathophysiological development of MAFLD and dementia, the clinical data regarding the relationship between these 2 conditions remains limited and controversial. Table 1²⁹⁻³⁷ provides a summary of the current studies examining the association between fatty liver disease and dementia. In 2 nationwide Korean studies, a significant correlation was observed between incident dementia and the presence of NAFLD. In the study conducted by Jeong et al, data from 608 994 adults aged ≥ 60 years, obtained from the Korean National Health Insurance Service database, were analyzed. An elevated fatty liver index, serving as an indicator of NAFLD, was found to be associated with an increased risk of dementia (hazard ratio [HR]: 1.05; 95% CI 1.02-1.08; $P = .001$). Additionally, their study demonstrated a significant inclination toward the development of Alzheimer's dementia rather than vascular dementia.²⁹ Likewise, in a nationwide study conducted with the Korean population, Kim et al³⁰ discovered a positive correlation between NAFLD, as determined by the hepatic steatosis index, and dementia. Furthermore, they identified that female and non-obese patients were at higher risk for dementia.³⁰ Similarly, in a cross-sectional, population-based study conducted in China, the authors observed a significant association between NAFLD patients with moderate to severe ultrasonographically defined hepatic steatosis and the presence of dementia. These patients had a twice higher risk of all-cause dementia and a 2.65-fold increased risk of vascular dementia compared to patients with mild steatosis. Interleukin 6 was identified as a major factor contributing to the relationship between NAFLD and vascular dementia. However, limitations of this study include the absence of a healthy control group and the evaluation of severity based on steatosis grade, which is a crucial prognostic determinant of NAFLD.³¹ In contrast, among patients with vascular dementia, nearly half of them exhibited ultrasonographically defined NAFLD, with the severity of steatosis grade being associated with more severe neurological profiles.³² In a population-based Swedish study, a total of 2898 patients with NAFLD and matched controls, aged 65 years and older, were included from the national database. The study reported a 5-year

Table 1. Summary of Articles Investigating the Relationship Between Fatty Liver Disease and Dementia

| Author | Year | Diagnosis of Hepatic Steatosis | Type of Dementia | Diagnosis of Dementia | Population | Follow-up Time | Result |
|-----------------------------|------|--|---|---|---|----------------|--|
| Jeong et al ²⁹ | 2022 | Fatty liver index | Vascular dementia and Alzheimer's disease | ICD-10 codes or presence of dementia associated medication use | 608 994 adults aged ≥60 years from Korean National Health Insurance Service database | 11 years | Higher fatty liver disease is associated with higher risk of incident dementia. |
| Kim et al ³⁰ | 2022 | Hepatic steatosis index | NA | ICD-10 codes | 4 031 948 adults aged 40-69 years from Korean National Health Insurance Service database | 9.5 years | NAFLD patients defined by hepatic steatosis index are under higher risk for dementia development. |
| Wang et al ³¹ | 2022 | Ultrasonography | All-cause dementia | ICD-10 codes | 5129 Chinese participants from rural regions aged ≥60 years | NA | Moderate to severe NAFLD was significantly associated with dementia, particularly with vascular dementia. |
| Moretti et al ³² | 2022 | Ultrasonography | Vascular dementia | CT/MRI | 285 patients from a tertiary care center | NA | Patients with NAFLD and vascular dementia had worse neuropsychological outcomes and a worse metabolic profile. |
| Shang et al ³³ | 2022 | ICD-10 codes | All-cause dementia | ICD-10 codes | 2898 patients with NAFLD and 28 357 matched controls from Swedish cause of death register 2016 | 5.5 years | NAFLD and coexistence of cardiometabolic risk factors increased the risk for dementia. |
| Wang et al ³⁴ | 2022 | Noninvasive tests, liver biopsy and ICD-10 codes | All-cause dementia and cognitive impairment | ICD-10 codes | Meta-analysis 891 562 individuals from 6 countries | 3-9.5 years | NAFLD is associated with increased risk for cognitive impairment but not with all-cause dementia. |
| Xiao et al ³⁵ | 2022 | Fatty liver index, ultrasonography, Fibroscan | All-cause dementia and cognitive impairment | <i>Diagnostic and Statistical Manual of Mental Disorders, Third Edition</i> | 3975 participants from Rotterdam study | 15.5 years | NAFLD is a protective factor against development of dementia. |
| Labenz et al ³⁶ | 2021 | ICD-10 codes | All-cause dementia | ICD-10 codes | A population-based German study consisted of 22 317 patients with NAFLD were matched to 22 317 patients without NAFLD | 10 years | NAFLD and development of dementia are not associated. |
| Shang et al ³⁷ | 2020 | Liver biopsy | All-cause dementia | ICD-10 | 656 NAFLD patients underwent liver biopsy and 6436 matched controls | 19.7 years | NAFLD and dementia are not associated. However, increased fibrosis stage may be predictor of dementia. |

CT, computed tomography; MRI, magnetic resonance imaging; NA, not applicable; NAFLD, nonalcoholic fatty liver disease.

cumulative incidence rate of 3.6% for dementia in patients with NAFLD, compared to 2% in those without NAFLD. Furthermore, when NAFLD patients had heart disease and stroke as cardiometabolic risk factors, the risk of developing dementia was doubled (HR = 2.00; 95%

CI 1.52-2.62).³³ Currently, there are no studies specifically conducted with the MAFLD population investigating this aspect. However, considering that the cardiometabolic profile of MAFLD patients is known to be more severe compared to NAFLD, it can be speculated that there may

be a higher risk for dementia in individuals with MAFLD in the future.^{2,38}

Despite these studies, there was no significant association between dementia and NAFLD. A meta-analysis including recent data from 891562 individuals in 6 countries did find a relationship between NAFLD and cognitive impairment. However, there was no significant association between NAFLD and all-cause dementia (OR = 1.03; 95% CI 0.97-1.09). Interestingly, NAFLD was associated with a decreased risk of vascular dementia compared to Alzheimer's disease (OR = 0.88; 95% CI 0.79-0.98). It is important to note that the analysis was limited due to a scarcity of studies on this topic.³⁴ The results of the Rotterdam study were consistent with these findings. Neither NAFLD nor fibrosis stage increased the incidence of dementia or worsened cognitive status. In fact, a higher fatty liver index was associated with a lower occurrence of dementia (HR = 0.48; 95% CI 0.24-0.94).³⁵ It is known that hepatic steatosis and even fibrosis can be reversed with significant weight loss.³⁷ Therefore, these findings can be explained by the tendency to lose weight due to dementia.³⁹ A previous population-based German study also reported similar results.³⁶ However, even though NAFLD itself is not associated with dementia, a more severe fibrosis stage was found to predict dementia, indicating a positive correlation. Further analysis revealed that fibrosis stage increased the hazard ratio for non-Alzheimer dementia rather than Alzheimer's dementia, suggesting an association between fibrosis stage and a worsened cardiovascular risk profile.³⁸

As it is known, all components of metabolic syndrome (hypertension, obesity, insulin resistance, and dyslipidemia) have been linked to systemic inflammation, atherosclerosis, and ultimately, inflammation-induced neurodegeneration.⁴⁰ In light of this knowledge, while the relationship between MAFLD and dementia remains controversial, metabolic syndrome has been proven to be a leading cause of dementia, particularly vascular dementia.⁴¹ In fact, individual components of metabolic syndrome have also been shown to increase the risk of dementia. Therefore, it is recommended to evaluate patients for cognitive impairment if 1 or 2 components of metabolic syndrome are present in their medical history.⁴² The Westernized diet has been proposed to cause systemic inflammation and alterations in the gut-brain axis.⁴³ For this reason, the Mediterranean diet has been suggested as a helpful approach for the prevention of both MAFLD and cognitive decline, as diet and lifestyle

are considered modifiable factors for the prevention of both MAFLD and dementia.^{43,44}

MECHANISMS LINKING METABOLIC (DYSFUNCTION) ASSOCIATED FATTY LIVER DISEASE AND COGNITIVE IMPAIRMENT

The accumulating evidence supports the relationship between MAFLD and cognitive impairment. Although the relationship between MAFLD and dementia remains controversial, there are common pathways that contribute to the development of both diseases over a prolonged period of time.³⁵ These common pathways include systemic inflammation, insulin resistance, vascular dysfunction, gut dysbiosis, and hyperammonemia.⁴⁵

Systemic inflammation, starting from the liver and causing neuroinflammation, triggers the development of Alzheimer's dementia due to shared inflammatory pathways. In a mouse model, decreased expression of low-density lipoprotein receptor-related protein 1, which plays a significant role in β -amyloid clearance, has been observed.⁴⁶ In another diet-induced mouse model, changes in lipid homeostasis resulted in increased expression of Tnfa, Cox2, p21, and Nox2, leading to increased oxidative stress and brain inflammation. Mice fed a NAFLD diet showed decreased cerebral perfusion and increased cognitive impairment.⁴⁷ Moreover, aging itself is proposed to result in alterations in the balance of pro-inflammatory and anti-inflammatory cytokines, which is described as the inflamm-aging theory.⁴⁸ Finally, chronic inflammation triggered by the activation of the nuclear factor-kappa B pathway and continuous secretion of pro-inflammatory cytokines contribute to the development of NAFLD and cognitive impairment.⁴⁹

Insulin signaling pathways, such as the IGF-1/IGF-1 receptor-induced phosphoinositide 3-kinase/Akt signaling pathway, are involved in axon development and synaptic formation, ultimately contributing to neuronal plasticity and memory formation. Therefore, insulin resistance triggers neuronal damage and cognitive impairment.⁵⁰ Furthermore, the association between insulin resistance and vascular injury is well established. Vascular injury and atherosclerosis have been speculated to be key factors in the development of vascular dementia.²³ Indeed, dementia is more prevalent among patients with type 2 diabetes mellitus. Therefore, the regulation of blood glucose levels and the management of diabetes could be considered common therapeutic targets for both MAFLD and dementia.⁵¹ Similarly, hypertension and atherosclerosis

are other shared targets in the management of MAFLD and dementia. These vascular complications have been shown to alter total cerebral blood flow and microcirculation, leading to cognitive impairment in patients with NAFLD.²⁴

The gut microbiota has been identified as playing a crucial role in the communication between the gut and the brain. Changes in the microbiota can lead to an increase in insulin resistance and intestinal permeability, ultimately resulting in chronic inflammation.⁵² In fact, the use of probiotics is recommended as a therapeutic option in the management of MAFLD and even for patients with psychiatric disorders such as depression.⁵² Furthermore, certain products of bacterial metabolism, such as endotoxins and ammonia, can induce neuroinflammation. Hyperammonemia, caused by dysbiosis and decreased liver metabolism, makes the blood-brain barrier more susceptible and leads to hepatic encephalopathy and cognitive impairment.⁵³

CONCLUSION

Both MAFLD and dementia are currently recognized as significant issues in the industrialized world, primarily due to changes in diet and an aging population. While there are conflicting results, accumulating evidence suggests that MAFLD is associated with cognitive impairment, likely through shared pathological pathways. Timely detection and management of metabolic comorbidities might be beneficial in the prevention of dementia.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.K., Y.Y.; Design – E.K., Y.Y.; Supervision – E.K., Y.Y.; Resource – E.K., Y.Y.; Materials – E.K., Y.Y.; Data Collection and/or Processing – E.K., Y.Y.; Analysis and/or Interpretation – E.K., Y.Y.; Literature Search – E.K., Y.Y.; Writing – E.K., Y.Y.; Critical Review – E.K., Y.Y.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

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