Metabolic-associated Fatty Liver Disease (MAFLD): A Multi-systemic Disease Beyond the Liver

Eda Kaya1 and Yusuf Yilmaz2,3

1Department of Internal Medicine, Ruhr University Bochum, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany; 2Department of Gastroenterology, School of Medicine, Marmara University, Istanbul, Turkey; 3Liver Research Unit, Institute of Gastroenterology, Marmara University, Istanbul, Turkey

Abstract

Nonalcoholic fatty liver disease (NAFLD) is a multisystemic clinical condition that presents with a wide spectrum of extrahepatic manifestations, such as obesity, type 2 diabetes mellitus, metabolic syndrome, cardiovascular diseases, chronic kidney disease, extrahepatic malignancies, cognitive disorders, and polycystic ovarian syndrome. Among NAFLD patients, the most common mortality etiology is cardiovascular disorders, followed by extrahepatic malignancies, diabetes mellitus, and liver-related complications. Furthermore, the severity of extrahepatic diseases is parallel to the severity of NAFLD. In clinical practice, awareness of the associations of concomitant diseases is of major importance for initiating prompt and timely screening and multidisciplinary management of the disease spectrum. In 2020, a consensus from 22 countries redefined the disease as metabolic (dysfunction)-associated fatty liver disease (MAFLD), which resulted in the redefinition of the corresponding population. Although the patients diagnosed with MAFLD and NAFLD mostly overlap, the MAFLD and NAFLD populations are not identical. In this review, we compared the associations of key extrahepatic diseases between NAFLD and MAFLD.

Citation of this article: Kaya E, Yilmaz Y. Metabolic-associated Fatty Liver Disease (MAFLD): A Multi-systemic Disease Beyond the Liver. J Clin Transl Hepatol 2022;10(2):329–338. doi: 10.14218/JCTH.2021.00178.

Keywords: Metabolic diseases; Fatty liver; Liver fibrosis; Diabetes mellitus, type 2; Cardiometabolic risk factors.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular disease; FIB-4, fibrosis-4 index; HCC, hepatocellular cancer; HR, hazard ratio; MAFLD, metabolic (dysfunction)-associated fatty liver disease; MRI-PDF, magnetic resonance imaging proton density fat fraction; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD Fibrosis Score; NHANES, third National Health and Nutrition Examination Surveys; OR, odds ratio; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; PNPLA3, patatin-like phospholipase domain-containing protein 3; QTC, corrected QT interval; T2DM, type 2 diabetes mellitus; TM6SF2, transmembrane 6 superfamily member 2; VCTE, vibration controlled transient elastography.

*Correspondence to: Yusuf Yilmaz, Marmara Universitesi, Gastroenteroloji Enstitusu, P.K. 53, Basibuyuk, Maltepe 34840 Istanbul, Turkey. ORCID: https://orcid.org/0000-0003-4518-5283. Tel: +90-5334403995, Fax: +90-2166886681. E-mail: dryusufyilmaz@gmail.com

Introduction

Nonalcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease worldwide, with an estimated global prevalence of 25%, placing a significant burden on the healthcare system.1 NAFLD is defined as the presence of hepatic steatosis, detected either by imaging or histology when secondary causes for hepatic fat accumulation are excluded.2 Given the close association of NAFLD with its causative drivers, such as obesity, metabolic syndrome (MS), and type 2 diabetes mellitus (T2DM), the increasing trend of these metabolic diseases is also expected to cause an increasing tendency in NAFLD incidence.3,4 As such, an international panel of experts from 22 countries proposed a change in terminology and definition that more accurately reflects the pathogenesis of the disease.5,6 The suggested terminology of metabolic (dysfunction)-associated fatty liver disease (MAFLD) is defined as hepatic steatosis entity in addition to the presence of overweight or obesity, diabetes mellitus, or evidence of metabolic dysfunction.6 The semantic modification of "NAFLD" as "MAFLD" highlights the role of metabolic factors in the disease etiology, which would hopefully facilitate understanding of the disease and patient-physician communication.7 NAFLD patients are at higher risk of not only liver-related complications but also cardiovascular and all-cause mortality. Indeed, cardiovascular disorders are the leading cause of mortality in patients with NAFLD, followed by extrahepatic malignancies and liver-related complications, indicating the multisystemic involvement in the disease.8 In addition to cardiovascular disorders, NAFLD is also associated with other extrahepatic diseases, such as MS, obesity, T2DM, chronic kidney disease (CKD), polycystic ovarian syndrome (PCOS), obstructive sleep apnea (OSA), extrahepatic malignancies, osteoporosis, and cognitive disorders (Fig. 1).9–11 As such, the possible extrahepatic involvements of NAFLD need to be screened and treated.12 However, despite increasing evidence on the strong relationship between extrahepatic diseases and NAFLD, studies on the effect of the redefinition of the patient population as "MAFLD" on the clinical reflection of extrahepatic diseases in this population are still lacking. This review will focus on the association of NAFLD with various extrahepatic diseases and discuss the influence of the semantic change to "MAFLD" in reanalyzing extrahepatic diseases in this newly defined group of patients.
Impact of redefinition on selected patients in studies

As is known, the redefinition of "NAFLD" as "MAFLD" is more than a single-letter change. Recently, this change was validated in the Third National Health and Nutrition Examination Surveys (NHANES-III 1988–1994) database, which defined hepatic steatosis according to ultrasonographic examination. It was concluded that MAFLD was able to identify patients with a high risk of disease progression more practically and accurately compared to NAFLD. This statement was concluded following a comparison of non-invasive scores including the fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), and BARD score. Accordingly, in that study, MAFLD patients were older (48.79±15.06 vs. 46.81±15.77, p<0.001), mostly male (1959 [50.42%] vs. 2014 [46.33%]),
Kaya E. et al: Extrahepatic diseases

<0.001), higher body mass index (BMI) level (31.14±6.05 vs. 29.49±6.69, p<0.001) higher proportions of T2DM (1171 [30.14%] vs. 1092 [25.12%], p<0.001) and hypertension (1405 [36.16%] vs. 1343 [30.89%], p<0.001) compared to NAFLD patients. Moreover, MAFLD patients showed higher insulin resistance, serum lipid, and transaminases.13 On the other hand, in a smaller population who underwent vibration controlled transient elastography (VCTE) examinations from 2017–2018, advanced fibrosis showed similar proportions in the MAFLD and NAFLD populations (7.5% vs. 7.4%). Moreover, the two definitions showed a high rate of agreement, with a Kappa coefficient of 0.92.14 The NHANES-III database from 1988–1994, which diagnosed hepatic steatosis with ultrasonography, showed that MAFLD and NAFLD overlapped mostly, with an agreement coefficient of 0.76.15 These data suggest that the two definitions are able to define mostly similar but not identical populations.1,4,11 When the NHANES-III 1988–1994 database was analyzed with 2015 mortality data, it was revealed that both MAFLD and NAFLD showed similar rates of overall, cardiovascular- and neoplasia-related mortality, when age and sex were adjusted (hazard ratio (HR): 1.27 (confidence interval (CI): 1.16, 1.41) vs. 1.05 (0.87, 1.28), p<0.001).16 From the NHANES-III database, 17,22 compared the association criteria. The modification of “NAFLD” to “MAFLD” emphasized the role of metabolic dysfunction and highlighted the underlying metabolic drivers for the development of the disease.23 Obesity is a well-known risk factor of NAFLD.24,25 Indeed, in the most recent decade, the prevalence of NAFLD showed a similar increasing trend, parallel to the increasing prevalence of obesity.26,27 More than 90% of morbidly obese patients who undergo bariatric surgery have NAFLD.28,29 On the other hand, lean patients with evidence of hepatic steatosis were also to no less a degree. In a recent meta-analysis by Young et al,30 “lean NAFLD” was prevalent in 11% and 25% of the general and NAFLD populations, respectively. Lean NAFLD patients presented with a more abnormal metabolic profile than healthy individuals and showed a higher prevalence of hypertension, insulin resistance, dyslipidemia, and metabolic syndrome and higher levels of inflammatory parameters.30,31 On the other hand, obese NAFLD patients showed higher levels of blood pressure, homeostatic model assessment for insulin resistance, hemoglobin A1C, alanine transaminase, and serum creatinine and albumin.31 Lean NAFLD patients also have higher levels of hemoglobin, hematocrit, and ferritin than overweight NAFLD patients.32,33,34 However, these patients also have a more favorable metabolic and histologic presentation than obese NAFLD patients.31 Notably, there are recommended ethnicity-specific BMI cutoffs to define “lean NAFLD”. The BMI cutoffs for defining lean are <25 kg/m² for Caucasians and <23 kg/m² for Asians.32 Therefore, the ethnicity of the study population should be identified when defining lean NAFLD. In general, lean NAFLD is prevalent in 5–45% of Asians and in 5–20% of Europeans.33 However, applying the proposed cutoff for Asians would lower the lean NAFLD prevalence. Therefore, accurate definition of obesity is crucial for an accurate MAFLD diagnosis. In this regard, the recent MAFLD guidelines recommend a BMI cutoff of 23 kg/m² for Asians.34 Weight reduction and dietary interventions are considered the cornerstone of NAFLD treatment, both in obese and lean patients.35,36 The beneficial effects of lifestyle modifications targeting weight reduction and exercise have been consistent and shown to be beneficial in the resolution of hepatic steatosis in both lean Asian and Caucasian NAFLD populations.37,38,39

The new definition as “MAFLD” emphasized the impor-

Genetic aspects of NAFLD and MAFLD

NAFLD progression is associated with at least five differ-
tance of metabolic dysfunction criteria or T2DM crucial for the diagnosis of the disease. In this concept, there are also patients who are classified with NAFLD but not MAFLD according to the new terminology. In the analysis performed by Angelico et al., 3.5% of the 795 NAFLD patients did not fulfill the MAFLD criteria due to not being overweight or obese and not having diabetes or metabolic dysfunction criteria. Wong et al. also reported that the lower prevalence of MAFLD than NAFLD among lean patients is due to the lack of other metabolic dysfunction criteria among lean patients. In line with these data, it appears that the new terminology would result in a non-classified group, that is, “NAFLD but not MAFLD”. However, further studies investigating the characteristics of newly defined lean MAFLD populations are needed.

T2DM accelerates disease progression, as evidenced by the higher rates of advanced fibrosis and adverse outcomes in diabetes patients with NAFLD. Moreover, the coexistence of NAFLD and T2DM is associated not only with increased liver-related mortality but also with cardiovascular and all-cause mortalities. Notably, metabolic diabetic complications, such as retinopathy, nephropathy, and polyneuropathy, more frequently occur in diabetes patients with coexisting NAFLD, independent of confounding factors.

Therefore, a first-line stratification algorithm with non-invasive diagnostic scores was recently recommended for T2DM patients with NAFLD. The FIB-4 can be easily calculated in ambulant clinical settings, and identifying patients with a FIB-4 >1.3 might be useful in the timely recognition of severe disease.

Insulin resistance also plays a major role in disease development. Traditionally, insulin resistance is the first hit of the “two-hit hypothesis”, followed by oxidative stress, lipid peroxidation, and mitochondrial dysfunction as the second hit. Although there are multiple pathways in disease development, insulin resistance constitutes a major pathway in NAFLD. Patients with insulin resistance have more severe liver histology. Further, insulin resistance is an independent risk factor for advanced fibrosis.

The new definition of MAFLD has led to an increase in its prevalence in T2DM patients. However, there are scarce data supporting the possibility that there is no significant difference in T2DM prevalence between NAFLD and MAFLD. Further studies are needed to highlight the possible impact of this terminology change. Recent MAFLD guidelines recommend that T2DM populations be screened for NAFLD. There also seems to be a bidirectional relationship between metabolic syndrome and NAFLD, as NAFLD itself is associated with MS and each of its components, namely abdominal obesity, hyperglycemia, hypertension, and dyslipidemia. In the meta-analysis performed by Ballestri et al., NAFLD was associated with incident MS in the 5-year follow-up. Similarly, another study found that patients with metabolic components were at higher risk of developing incident NAFLD. Lin et al. compared MAFLD with traditional NAFLD and found higher proportions of metabolic comorbidities in patients with MAFLD, indicating the impact of positive diagnostic criteria.

Cardiovascular diseases (CVDs)

Increasing evidence supports that CVD is a matter of debate in NAFLD. Patients with NAFLD have been reported to have a higher risk of CVD-related death than of liver-related death. A meta-analysis by Targarza et al. involving 34,600 individuals followed up for 6.9 years found an increased risk of fatal and non-fatal cardiovascular events (odds ratio [OR]: 1.64, 95% CI: 1.26–2.13). When the analysis was adjusted for the conventional cardiovascular risk factors, severe NAFLD increased the risk of a cardiovascular event (OR: 2.58, 95% CI: 1.78–3.75). Moreover, in the meta-analysis by Oni et al., NAFLD was significantly associated with increased carotid artery intimal-medial thickness, impaired flow-mediated vasodilation, increased arterial stiffness, and coronary artery calcification, which are the main indicators of subclinical atherosclerosis. This association was found to be independent of traditional risk factors and metabolic components.

The risk of cardiovascular events and mortality pertaining to NAFLD patients who were on the waiting list for liver transplantation and in the post-transplantation period. Even in primary care settings, there is an independent association between myocardial infarction and NAFLD. Advanced fibrosis is the most important prognostic factor in NAFLD. Therefore, initiating and planning therapy is of paramount importance. Among biopsy-proven NAFLD patients with incident cardiovascular events, advanced fibrosis on liver histology is an independent predictor of cardiovascular events. In a recent nationwide study from Korea, the multivariable-adjusted HRs for developing a cardiovascular event among patients with NAFLD and MAFLD were 1.09 (95% CI: 1.03–1.15) and 1.43 (95% CI: 1.41–1.45), respectively. This finding highlights that the redefinition of the disease may identify more patients with a high risk of developing cardiovascular events. Guerreiro et al. investigated 109 patients with hepatic steatosis, and 90% and 64% fulfilled the MAFLD criteria and NAFLD criteria, respectively. CVD occurred in 20% and 13%, respectively (p=0.137). These rates could be due to the inclusion of metabolic dysfunction criteria, which are associated with increased CVD rates, in the definition.

NAFLD has also been reported to be associated with cardiac arrhythmias, including atrial fibrillation (AF), prolongation of the corrected QT interval (QTc), and increased severity of ultrasonographically-defined NAFLD. After adjusting for factors associated with QTc prolongation, all types of NAFLD were associated with an increased risk of QTc prolongation in women, with ORs (95% CIs) of 1.11 (1.01–1.21) for mild, 1.61 (1.36–1.9) for moderate, and 1.31 (1.16–2.24) for severe. The corresponding ORs (95% CI) for men were 1.11 (1.01–1.21), 1.39 (1.22–1.59), and 1.87 (1.16–2.24), respectively. This significant association remained in the subgroup analysis of the diabetes and non-diabetes populations. In another retrospective analysis, the rates of nonsustained ventricular tachycardia and >30 premature ventricular complexes per hour were significantly higher in T2DM patients with an ultrasonographically-proven NAFLD compared to non-NAFLD patients with diabetes. In the adjusted analysis for age, sex, BMI, smoking, hypertension, ischemic heart disease, valvular heart disease, chronic kidney disease, chronic obstructive pulmonary disease, serum gamma-glutamyl transferase levels, medication use, and left ventricular ejection fraction, NAFLD patients had a 3.5-fold higher risk of ventricular arrhythmias compared to non-NAFLD patients.

NAFLD also appears to be associated with further structural cardiac pathologies. NAFLD was found to be significantly associated with a nearly 3-fold higher risk of cardiovascular valve stenosis and mitral annulus calcification, which are predictors of adverse cardiac outcomes. Moreover, a case-control study found that...
both hepatic steatosis and fibrosis were associated with subclinical myocardial dysfunction on fluorodeoxyglucose-positron emission tomography. NAFLD severity assessed by the FIB-4 score is also independently associated with left ventricular diastolic dysfunction, larger atrial volume, and higher all-cause mortality in patients with known heart failure. This positive association between NAFLD severity and myocardial abnormalities was also confirmed in smaller studies of biopsy-proven NAFLD.

The relation between increased cardiovascular burden and NAFLD is multifactorial. Abnormal blood glucose levels triggered by insulin resistance are a common pathophysiological condition. Another shared mechanism is endothelial dysfunction that is significantly associated with atherosclerosis. NAFLD patients have a decreased balance in proagulant metabolism, which also plays a significant role in the development of cardiovascular events. Collectively, these induce systolic and diastolic dysfunction or cardiac arrhythmias. Meanwhile, although they are significantly associated with NAFLD and NAFLD severity, genetic variants of PNPLA3 and TM6SF2 were shown to be cardioprotective. This is probably due to the strong association of those variants with lower levels of triglycerides and low density lipoproteins. Collectively, these data support the significantly higher risk of cardiovascular-related morbidity and mortality in the NAFLD population, indicating the importance of first-line screening for cardiovascular disorders independent of traditional cardiovascular risk factors in these patients. MAFLD patients also have a higher risk of developing cardiovascular events, and this issue has gained more importance.

### Extrahepatic diseases

#### CKD

There is growing evidence supporting a close relationship between NAFLD and CKD. This association could be related to a high prevalence of both diseases or an independent occurrence. Nevertheless, NAFLD and CKD share common risk factors, including abdominal obesity, insulin resistance, atherogenic dyslipidemia, and hypertension. Moreover, recent studies have consistently demonstrated that NAFLD is independently associated with a higher prevalence of CKD. However, a cross-sectional study by Akahane et al. showed that the link between NAFLD and CKD was mediated by shared risk factors rather than an independent association. Similarly, the association of NAFLD with CKD appeared to arise from increased adipose tissue-related inflammation. Therefore, a CKD-focused screening of NAFLD patients with obesity, hypertension, and hyperuricemia is recommended.

TZD is an important driving factor for both NAFLD and CKD. However, the prevalence of CKD was higher in NAFLD patients, regardless of diabetes status, than in patients without NAFLD (50% vs. 5–30%). Moreover, patients with severe liver histology were more likely to develop incident CKD. In contrast, hepatic steatosis has no adverse impact on renal function. In the meta-analysis by Musso et al., advanced fibrosis and inflammation were associated with more severe kidney dysfunction than hepatic steatosis itself. They concluded that the more severe the liver histology, the more severe the CKD. Even early kidney dysfunction was proposed to be associated with more severe liver histology in biopsy-proven NAFLD patients, highlighting the importance of early screening for the timely management of kidney disease. MAFLD patients have been found to have a higher burden of CKD. Data from NHANES-III 1988–1994 revealed that CKD is more prevalent in MAFLD patients than in NAFLD patients. This suggested that MAFLD could identify more patients with a higher risk of CKD in addition to other comorbidities.

#### Extrahepatic malignancies

Extrahepatic malignancies are one of the leading causes of mortality in NAFLD. Thus, hepatocellular cancer (HCC) surveillance is recommended in MAFLD patients with cirrhosis. The possible mechanism of carcinogenesis in NAFLD is derived from proinflammatory and procarcinogenic aspects of insulin resistance through activation of the insulin growth factor-1 axis. These induce antiapoptotic effects and adipose tissue dysfunction that increase inflammation and tumor proliferation. Gut dysbiosis was also found to be a possible contributing factor in promotion of tumorigenesis. A meta-analysis by Musso et al. found that extrahepatic malignancies were the most common cause for mortality, accounting for 28% of all deaths, followed by ischemic heart disease (25%) and liver-related diseases (13%). In a large Korean cohort, the prevalence rate of cancer was higher in the NAFLD group than in the non-NAFLD group (782.9 vs. 592.8 per 100,000 person-years; HR: 1.32; 95% CI: 1.17–1.49; p<0.001). Accordingly, the most common cancer type was HCC in the general population, colorectal carcinoma in males, and breast cancer in females.

Allen et al. recently investigated the incidence of cancer in a large community cohort within a median follow-up of 8 years and found that NAFLD patients had a 2-fold higher risk of developing cancer. The most common cancer type was HCC, followed by uterine, gastric, pancreatic, and colonic cancers. Moreover, they showed that NAFLD was more strongly associated with cancer development than obesity. In the absence of NAFLD, obesity was less strongly associated with cancer development, which indicates the possible role of NAFLD in promoting cancer development in obese patients. Unlike in obese women, NAFLD was associated with breast cancer, independent of traditional risk factors, in non-obese women.

In a recent meta-analysis of studies published between 1996 and January 2020, NAFLD was significantly associated with gastrointestinal cancers (colorectal cancer and colorectal adenoma), cholangiocarcinomas, and other cancers (including breast, gastric, pancreatic, prostate, and esophageal cancers), indicating that NAFLD is a potential influencing factor in extrahepatic diseases. A systemic review and meta-analysis suggested that NAFLD increased the risk of cholangiocarcinoma, and the increased risk was more pronounced for intrahepatic cholangiocarcinoma than for extrahepatic cholangiocarcinoma. A meta-analysis also found that NAFLD is significantly associated with extrahepatic cholangiocarcinoma but not with intrahepatic cholangiocarcinoma after excluding confounding factors. Another meta-analysis found that NAFLD increased the risk of colorectal adenoma and carcinoma. Among patients with NAFLD, the overall risk was higher for right colon tumors than for left colon tumors. Fuyugana et al. recently demonstrated that NAFLD more accurately identifies colorectal adenomas than does NAFLD. Specifically, non-obese MAFLD is an independent factor for the presence of colorectal adenomas. As such, the authors recommended colonoscopy screening in patients with MAFLD.

#### Depression and cognitive disorders

Depression and cognitive impairment have been recently shown to be associated with NAFLD; however, this rela-
tionship remains unclear. Tomeno et al.109 detected major depressive disorder in 12% of their patients with biopsy-proven NAFLD. Moreover, liver histology was more severe in patients with depression than in patients without depression, in line with the findings by Youssef et al.110 In contrast, Lee et al.111 did not identify this association. In a large population-based study, hepatitis C infection was the chronic liver disease significantly associated with depression.

In line with this, there have been attempts to compare total brain volume, gray and white matter volumes, and lateral ventricle volume between patients with and without NAFLD. The results showed a greater risk for cognitive disorders in patients with NAFLD.112 Further studies found that MAFLD patients were at higher risk for early or subtle cognitive dysfunction than healthy individuals, but this relationship was not shown to be significantly correlated with the presence of metabolic syndrome. Cognition is mainly regulated by visuospatial and executive function domains associated with the prefrontal cortex.113 Weinstein et al.114 suggested that patients at higher risk for advanced fibrosis but not MAFLD were also at higher risk for cognitive impairment development. The association between Alzheimer’s disease and NAFLD remains to be clarified. However, increasing evidence from various animal studies suggested a possible significant association,115,116 although further investigations are still needed. The underlying mechanism between these associations was suggested to be dysfunctions in lipid metabolism and insulin resistance, which have been previously proposed to trigger the development of Alzheimer’s disease.108 However, to our best knowledge, no study has compared between the impact of MAFLD and NAFLD on cognitive disorders.

PCOS

NAFLD and PCOS share several common comorbidities, such as obesity, insulin resistance, diabetes mellitus, hypertension, and metabolic syndrome.11,117 Accordingly, more than half of patients with PCOS also have NAFLD.118 A recent large population-based study found that PCOS patients were more likely to be diagnosed with NAFLD (OR: 4.3) even after adjusting for confounding factors. Thus, the risk of developing NAFLD has also been reported to increase independent of metabolic factors.119 Hyperandrogenism is another factor associated with an increased risk of MAFLD.120 In a study by Jones et al.,121 patients with hyperandrogenism showed significantly higher hepatic fat content in magnetic resonance spectroscopy examinations than did patients without hyperandrogenism and controls, even after adjusting for BMI.

Additionally, the severity of PCOS, in addition to the disease itself, appeared to be a significant factor influencing the prevalence of NAFLD. In a group of biopsy-proven NAFLD patients, women with PCOS had more severe liver histology and higher prevalence of advanced fibrosis than women without PCOS. They also had more advanced disease at a younger age.122 A FibroScan study in PCOS patients with and without NAFLD revealed that liver stiffness, as an indicator of liver fibrosis, was significantly higher among PCOS patients with NAFLD than in those without NAFLD.123 Despite the lack of exclusive studies on the MAFLD population, the common metabolic comorbidities indicate that the prevalence of PCOS may be higher in the MAFLD population.

Osteoporosis and sarcopenia

NAFLD has been shown to be associated with non-obesity-related diseases, such as osteoporosis and sarcopenia.124,125 In Chinese cohorts, bone mass density was negatively correlated with the presence of NAFLD in both sexes.126,127 Sarcopenia is also associated with severe NAFLD histology.128 As such, an increase in body muscle mass results in the resolution of NAFLD.129 The underlying pathological mechanisms seem to be associated with vitamin D deficiency, altered growth hormone/insulin-like growth factor 1 axis, and chronic inflammation.130

Hypothyroidism

Even if there is not enough evidence on cost-effectiveness of screening hypothyroid patients in terms of NAFLD, both subclinical and overt hypothyroidism are known to be associated with increased NAFLD prevalence.131,132 The relationship between hypothyroidism is both indirect and direct. Indirectly, due to association of hypothyroidism with increased visceral obesity, impaired lipid metabolism and induction of metabolic syndrome. However, increased levels of thyroid-stimulating hormone also directly affect hepatocytes and contribute to development of NAFLD.133 In biopsy-proven NAFLD cohorts, hypothyroidism was significantly more prevalent.134,135 In a population-based study conducted with USA NHANES data from 2007 to 2012, low-normal thyroid function and subclinical hypothyroidism increased the advanced fibrosis risk 1.9-fold and 2.1-fold, respectively.136

OSA

OSA plays a significant role in the development and progression of NAFLD.137 The parameters determining OSA severity, such as the apnea-hypopnea index, oxyhemoglobin desaturation index, and nocturnal oxyhemoglobin saturation, are associated with hepatic steatosis.138,139 In addition to the high prevalence of NAFLD in OSA, OSA severity was found to be an independent predictor of the presence and severity of liver fibrosis.140 The relationship between OSA and NAFLD remains controversial, owing to the confounding effects of obesity. However, the combination of early time sleepiness and OSA remains to have a significant impact in the development of NAFLD even after adjusting for visceral fat area.141 Chronic intermittent hypoxia has been suggested to play a significant role in the development of liver inflammation in OSA patients.142 Accordingly, an effective continuous positive airway pressure was proposed to be associated with improvement and even complete reversion of hepatic steatosis.143

Psoriasis

NAFLD and psoriasis co-exist frequently, with approximately half of psoriasis patients also having NAFLD.144,145 In a meta-analysis by Candia et al.,146 patients with psoriasis had a 2-fold higher risk of developing NAFLD (OR: 2.15, 95% CI: 1.57–2.94). Further, the severity of psoriasis influenced the prevalence of NAFLD. The underlying mechanism explaining the association between NAFLD and psoriasis is not fully understood; however, increased expression of pro-inflammatory cytokines, such as interleukin-6, interleukin-17 and tumor necrosis factor-alpha, is known to influence the development of insulin resistance and, finally, NAFLD.147 Both psoriasis and NAFLD are associated with MS, insulin resistance, and an increased cardiovascular risk.148 Psoriasis patients with NAFLD have a significantly higher 10-year risk of cardiovascular events (OR: 6.0, 95% CI: 3.3–11.1).149 Despite the lack of studies in biopsy-proven NAFLD patients, data suggest an increased risk of advanced
fibrosis in NAFLD patients with psoriasis.\textsuperscript{150,151} Accumulating evidence also suggests that patients with psoriasis have a higher risk of hepatic complications. Therefore, regular follow-up should be considered, especially for psoriasis patients undergoing treatment.\textsuperscript{147}

**Conclusion**

MAFLD must be evaluated as a multisystemic disease affecting many extraparenchymal organs. The disease burden extends beyond liver-related complications, underlining the importance of multidisciplinary screening and disease management. Routine screening for MAFLD is recommended in patients with obesity/overweight, T2DM, or MS. Moreover, patients with MAFLD should also be examined for CVD and cardiovascular risk. Further, treatment of dyslipidemia, T2DM, and hypertension is recommended to decrease the risk of cardiovascular and kidney diseases. Importantly, the high rate of co-existing CVD, CKD, OSA, hypothyroidism, osteoporosis, and PCOS indicates that MAFLD patients should be evaluated for these extrahepatic diseases.

**Funding**

None to declare.

**Conflict of interest**

The authors have no conflict of interests related to this publication.

**Author contributions**

Study concept and design (EK, YY), drafting of the manuscript (EK, YY), critical revision of the manuscript for important intellectual content (YY), and administrative, technical, or material support, study supervision (YY).

**References**

1. Younossi Z, Tacke F, Arrese M, Bugianesi E, et al. Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Hepatology 2019;69(6):2672–2682. doi:10.1002/hep.32051.

2. Chalasani N, Younossi Z, Lavine JE, Charbon M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of the Liver Diseases. Hepatology 2018;67(1):328–357. doi:10.1002/hep.29367.

3. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 2013;10(11):686–690. doi:10.1038/nrgastro.2013.171.

4. Kaya E, Yilmaz Y. Non-alcoholic Fatty Liver Disease: A Global Public Health Issue. In: Fantuch J, Fantuch S, editors. Obesity and Diabetes. Springer, Cham, 2020, pp. 321–333.

5. Eslam M, Sanyal AJ, George J, International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020;158(7):1999–2014.e1. doi:10.1053/j.gastro.2019.11.312.

6. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73(1):202–209. doi:10.1016/j.jhep.2020.03.039.

7. Yilmaz Y, Byrne CD, Musso G. A single-letter change in an acronym: signals, reasons, promises, challenges, and steps ahead for moving from NAFLD to MAFLD. Expert Rev Gastroenterol Hepatol 2021;15(4):345–352. doi:10.1080/17474124.2021.1866019.

8. Mantoani A, Scorreriti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of non-alcoholic fatty liver disease. Metabolism 2020;115:14170. doi:10.1016/j.metabol.2020.154170.

9. Liu SS, Ma XF, Zhao J, Du SX, Zhang J, Dong MZ, et al. Association between nonalcoholic fatty liver disease and extracardiac cancers: a systematic review and meta-analysis. Lipids Health Dis 2020;19(1):118. doi:10.1186/s12944-020-01288-6.
lines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020;14(6):889–919. doi:10.1002/hep.20094.

[36] Piazza NA, Golapi P, de Avila L, Paik JM, Shrishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 2019;71(4):793–801. doi:10.1016/j.jhep.2019.06.021.

[37] Mantovani A, Byrne CD, Bonora E, Targar G. Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis. Diabetes Care 2018;41:372–382. doi:10.2337/dc17-1902.

[38] Bernhardt P, Kratzer W, Schmidberger J, Graeter T, Cruener B, EML Study Group. Laboratory parameters in lean NAFLD: comparison of subjects with lean NAFLD with obese subjects without hepatic steatosis. BMC Res Notes 2018;11:101. doi:10.1186/s13104-018-2312-1.

[39] Hamamura V, Paly K, Eay K, Alphanumeric E, Yilmaz Y. Role of intense dietary and lifestyle interventions in the treatment of lean nonalcoholic fatty liver disease patients. Eur J Gastroenterol Hepatol 2020;32(10):1352–1357. doi:10.1097/MEG.0000000000001656.

[40] Brunner KT, Henneberg CJ, Wilechamsky RM, Long MT. Nonalcoholic fatty liver disease and obesity treatment. Curr Obes Rep 2019;8:220–228. doi:10.1007/s13679-019-00345-1.

[41] Hazehurst JM, Woods C, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and the incidence of myocardial infarction: A cohort study. J Gastroenterol Hepatol 2020;35:833–839. doi:10.1111/jgh.14856.

[42] Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol 2014;2(11):901–910. doi:10.1016/S2213-8587(14)0032-4.

[43] Kim D, Tournos A, Kim WR. Nonalcoholic Fatty Liver Disease and Meta- bolic Syndrome: Clinical Liver Dis 2018;22(1):133–140. doi:10.1016/j.cld.2017.08.010.

[44] Baltassi S, Zona S, Targar G, Ramogall M, Baldelli E, Nascimbeni F, et al. Non-alcoholic fatty liver in patients with type 2 diabetes and metabolic syndrome: an almost twofold increased range of tip type 2 diabetes and metabolic syndrome. Evid Based Med 2017;22(5):196–199. doi:10.1136/ebmed-2017-120905.

[45] Ma J, Hwang S, Pedley A, Massaro JM, Hoffmann U, Chung RT, Fujii H, Imajo K, Yoneda M, Nakahara T, Hyogo H, Takahashi H, et al. The annuity of diabetes and cardiovascular disease in patients with nonalcoholic fatty liver disease. J Gastroenterol 2018;53(2):1325–1327. doi:10.1007/s00535-018-0944-0.

[46] Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwityha P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389–397.e10. doi:10.1053/j.gastro.2015.04.043.

[47] Sunbul M, Kirik U, Ekin A, Aydin Y, Ergelen R, et al. Nonalcoholic steatohepatitis score is an independent predictor of right ventricular dysfunction in patients with biopsy-proven non-alcoholic fatty liver disease. A randomized controlled trial. J Hepatol 2019;71(4):793–801. doi:10.1016/j.jhep.2019.03.011.

[48] Pettia S, Argano C, Colomba D, Cammar D, Marco V, Cabibi D, et al. Epacardal Fat, Cardiac geometry and cardiac function in patients with non-alcoholic fatty liver disease: association with the severity of liver disease. J Hepatol 2015;62:928–933. doi:10.1016/j.jhep.2014.11.030.

[49] Song Q, Sim KH, Park JK, Lee KS, Kim Y, Kwon KH, et al. Increased visceral fat and metabolic syndrome increases the risk of cardiovascular disease. JAMA Intern Med 2018;178(5):607–616. doi:10.1001/jamainternmed.2017.7507-y.

[50] Kaya E. et al: Extrahepatic diseases.
Mantovani A, Dauriz M, Byrne CD, Lonardo A, Zoppini G, Bonora E, Kaya E, Choudhary NS, Saraf N, Kumar N, Rai R, Saigal S, Gautam D, Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural histories. Expert Rev Gastroenterol Hepatol 2019;13:385–395. doi:10.1080/17474124.2018.1580143.

Sanna C, Rosso C, Marietti M, Bugianesi E. Non-Alcoholic Fatty Liver Disease in asymptomatic adults undergoing screening colonoscopy: a systematic review. European Journal of Gastroenterology & Hepatology 2021;33(1):62–68. doi:10.1097/MEG.0000000000002017-0696-4.

Kaya E et al. Extrahepatic diseases

Association between nonalcoholic fatty liver disease and colorectal tumours. Eur J Gastroenterol Hepatol 2021;33(1):62–68. doi:10.1097/MEG.0000000000002017-0696-4.

Kaya E et al. Extrahepatic diseases

Association between nonalcoholic fatty liver disease and colorectal tumours. Eur J Gastroenterol Hepatol 2021;33(1):62–68. doi:10.1097/MEG.0000000000002017-0696-4.

Kaya E et al. Extrahepatic diseases

Association between nonalcoholic fatty liver disease and colorectal tumours. Eur J Gastroenterol Hepatol 2021;33(1):62–68. doi:10.1097/MEG.0000000000002017-0696-4.
Kaya E. et al: Extrahepatic diseases

[132] Chung GE, Kim D, Kwak MS, Yim JY, Ahmed A, Kim JS. Longitudinal change in thyroid-stimulating hormone and risk of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2021;19:848–849.e1. doi:10.1016/j.cgh.2020.02.039.

[133] Lonardo A, Ballestri S, Mantovani A, Nascimbeni F, Lugari S, Targher G. Pathogenesis of hypothyroidism-induced NAFLD: Evidence for a distinct disease entity? Dig Liver Dis 2019;51(4):462–470. doi:10.1016/j.dld.2018.12.014.

[134] Pagadala MR, Zein CO, Dasarathy S, Yerian LM, Lopez R, McCullough AJ. Prevalence of hypothyroidism in nonalcoholic fatty liver disease. Dig Dis Sci 2012;57:528–534. doi:10.1007/s10620-011-2006-2.

[135] Kim D, Kim W, Joo SK, Bae JM, Kim JH, Ahmed A. Subclinical hypothyroidism and low-normal thyroid function are associated with nonalcoholic steatohepatitis and fibrosis. Clin Gastroenterol Hepatol 2018;16:123–131. doi:10.1016/j.cgh.2017.08.014.

[136] Kim D, Yoo ER, Li AA, Fernandes CT, Tighe SP, Cholankeril G, et al. Low-normal thyroid function is associated with advanced fibrosis among adults in the United States. Clin Gastroenterol Hepatol 2018;17:2379–2381. doi:10.1016/j.cgh.2018.11.024.

[137] Messarwi OA, Loomba R, Malhotra A. Obstructive Sleep Apnea, Hypoxia, and Nonalcoholic Fatty Liver Disease. Am J Respir Crit Care Med 2019;199(7):830–841. doi:10.1164/rccm.201806-1109TR.

[138] Trzepizur W, Boursier J, Mansour Y, La Vaillant M, Chollet S, Pigeanne T, et al. Institut de Recherche en Santé Respiratoire des Pays de la Loire Sleep Cohort Group. Association between severity of obstructive sleep apnea and blood markers of liver injury. Clin Gastroenterol Hepatol 2016;14:1657–1661. doi:10.1016/j.cgh.2016.04.037.

[139] Caixmaki E, Duksal F, Altinkaya E, Acibucu F, Dogan OT, Yonem O, et al. Association Between the Severity of Nocturnal Hypoxia in Obstructive Sleep Apnea and Non-Alcoholic Fatty Liver Disease. Hepat Mon 2015;15(11):e2665. doi:10.5812/hepatmon.32655.

[140] Krolow GK, Garcia E, Schoor F, Araujo FBS, Cholankeril G, et al. Obstructive sleep apnea and severity of nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2021;33(8):1104–1109. doi:10.1097/MEG.0000000000002190.

[141] Yu JH, Ahn JH, Yoo HJ, Seo JA, Kim SG, Choi KM, et al. Obstructive sleep apnea with excessive daytime sleepiness is associated with non-alcoholic fatty liver disease regardless of visceral fat. Korean J Intern Med 2015;30:846–855. doi:10.3904/kjim.2015.30.6.846.

[142] Paschetta E, Belci P, Alisi A, Liccado D, Cutreta R, Musso G, et al. OSAS-related inflammatory mechanisms of liver injury in nonalcoholic fatty liver disease. Mediators Inflamm 2015;2015:817521. doi:10.1155/2015/817521.

[143] Buitacaovil M, Gruttad'Auria CI, Olivo M, Virdone R, Castrogiovanni A, Mazzuca E, et al. Liver steatosis and fibrosis in OSA patients after long-term CPAP treatment: A preliminary ultrasound study. Ultrasound Med Biol 2016;42:104–109. doi:10.1016/j.ultrasmedbio.2015.08.009.

[144] Miele L, Vollone S, Cefalo C, La Torre G, Di Stasi C, Vecchio FM, et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009;51:778–786. doi:10.1016/j.jhep.2009.06.008.

[145] Roberts KK, Cochet AE, Lamb PB, Brown PJ, Battafarano DF, Brunt EM, et al. The prevalence of NAFLD and NASH among patients with psoriasis in a tertiary care dermatology and rheumatology clinic. Aliment Pharmacol Ther 2015;41:293–300. doi:10.1111/apt.13042.

[146] Candia R, Ruiz A, Torres-Robles R, Chávez-Tapia N, Méndez-Sánchez N, Arrese M. Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2015;29:656–662. doi:10.1111/jdv.12847.

[147] Mantovani A, Gisondi P, Lonardo A, Targher G. Relationship between non-alcoholic fatty liver disease and psoriasis: a novel hepato-dermal axis? Int J Mol Sci 2016;17:217. doi:10.3390/ijms1702017.

[148] Lonardo A, Nascimbeni F, Maurantonio M, Marrazzo A, Rinaldi L, Adinolfi LE. Non-alcoholic fatty liver disease: Evolving paradigms. World J Gastroenterol 2017;23:6571–6592. doi:10.3748/wjg.v23.i36.6571.

[149] Romero-Pérez D, Belinchón-Romero I, Bellot P, Francés R, Marco F, Ramos-Rincón JM. Non-alcoholic fatty liver disease puts patients with psoriasis at greater cardiovascular risk. Australas J Dermatol 2019;60(4):e304–e310. doi:10.1111/jfd.13098.

[150] Gisondi P, Barba E, Girolomoni G. Non-alcoholic fatty liver disease fibrosis score in patients with psoriasis. J Eur Acad Dermatol Venereol 2015;30:282–287. doi:10.1111/jdv.13456.

[151] van der Voort EA, Koehler EM, Nijsten T, Stricker BH, Hofman A, Janssen HL, et al. Increased Prevalence of Advanced Liver Fibrosis in Patients with Psoriasis: A Cross-sectional Analysis from the Rotterdam Study, Acta Derm Venereol 2016;96(2):213–217. doi:10.2340/00015555-2161.