Comorbidities and Nonalcoholic Fatty Liver Disease: The Chicken, the Egg, or Both?

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Improvement in NAFLD may lead to improvement of metabolic syndrome, cardiovascular disease, and malignancy and vice versa.

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Nonalcoholic fatty liver disease (NALFD) is now the most common chronic liver disease in the developed world and affects about 25% to 30% of adults in the US and 30% of veterans who receive care in the VHA system (Figure 1). Comprised of a spectrum of disease severity, NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis ([NASH] steatosis with hepatocyte inflammation, necrosis, and fibrosis). Patients with NALFD have significantly increased mortality because of both hepatic (such as cirrhosis and hepatocellular carcinoma [HCC]) and extrahepatic complications (such as metabolic syndrome [MetS], cardiovascular disease [CVD], and malignancy). In this article, we will focus on the extrahepatic manifestations of NAFLD and its impact on diagnosis and management.

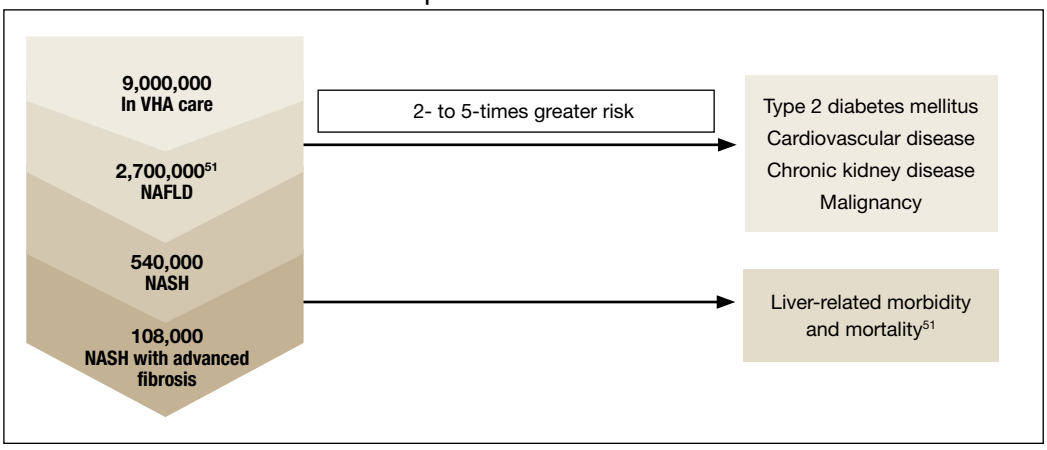
NAFLD is significantly associated with the presence of MetS, so much so that it has been considered the hepatic manifestation of MetS. NAFLD also is strongly associated with type 2 diabetes mellitus (T2DM), CVD, chronic kidney disease (CKD), and obstructive sleep apnea (OSA) (Figure 2). Although these associations may result from shared risk factors, strong evidence suggests that for some of the factors at least, there is bidirectional influence on the natural history of the other comorbid conditions (Table). This means that the management of NAFLD can help improve the management of comorbidities and vice versa. This is important, as the primary cause of mortality in patients with NAFLD, particularly in those without advanced fibrosis or cirrhosis, is related to CVD and extrahepatic malignancy and not from liver disease.

OBESITY/VISCERAL ADIPOSITY

Obesity (body mass index [BMI] > 30) prevalence in the US has almost doubled over the past 30 years and continues to climb.[1] Obesity affects 41% of veterans in the Veterans Health Administration and is the most common risk factor for NAFLD.[2] NAFLD is 4 times more prevalent in obese patients, thus, it is not surprising that 80% to 90% of patients evaluated in bariatric centers have NAFLD, reported in 2 large series.[3,4] Increased BMI and waist circumference predict the presence of NASH and advanced fibrosis.[5]

While obesity is a hallmark for NAFLD, particularly in the US, it is important to note that up to 20% of Americans with normal BMI have NAFLD, based on findings of steatosis on ultrasound.[6] These patients with lean NAFLD are often underdiagnosed. In addition to the patient's BMI, it is important to recognize that in NAFLD, the distribution and type of fat deposition is more important than just BMI. Visceral fat refers to fat accumulation within the abdominal cavity and is key to the pathogenesis of NAFLD. Visceral fat, compared with subcutaneous fat, is metabolically active and can deliver an overabundance of free fatty acids to the liver as well as secrete proinflammatory mediators in the setting of insulin resistance. Visceral fat stores can predict increased hepatic fat content, inflammation, and fibrosis.[5] Thus, it is important to recognize that those patients with relatively more visceral fat are more prone to NAFLD. The best clinical indicator of

FIGURE 1 NAFLD in the VHA: Population-Based Estimates



Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; VHA, Veterans Health Administration.

visceral adiposity is abdominal obesity, indicated by waist circumference > 40 inches in men and > 35 inches in women.

METABOLIC SYNDROME

Hepatic fat deposition can be associated with or precede MetS. MetS is defined as having at least 3 of the following characteristics: abdominal obesity, elevated triglycerides (TGs) (≥ 150 mg/dL), reduced high-density lipoprotein cholesterol (< 40 mg/dL in men or < 50 mg/dL in women), elevated blood pressure (BP) (systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg), or elevated fasting glucose (≥ 110 mg/dL). Population studies have found that 50% of patients with MetS have NAFLD, and liver fat content is strongly correlated with the number of MetS features present in an individual.[5,7] In addition to this association, NAFLD also promotes the development of MetS. Increased energy intake relative to energy expenditure will facilitate ectopic fat accumulation in the liver, which then increases hepatic gluconeogenesis and drives the pathogenesis of insulin resistance.[8] Therefore, the presence of NAFLD is both a marker and a promotor of insulin resistance and its complications.

TYPE 2 DIABETES MELLITUS

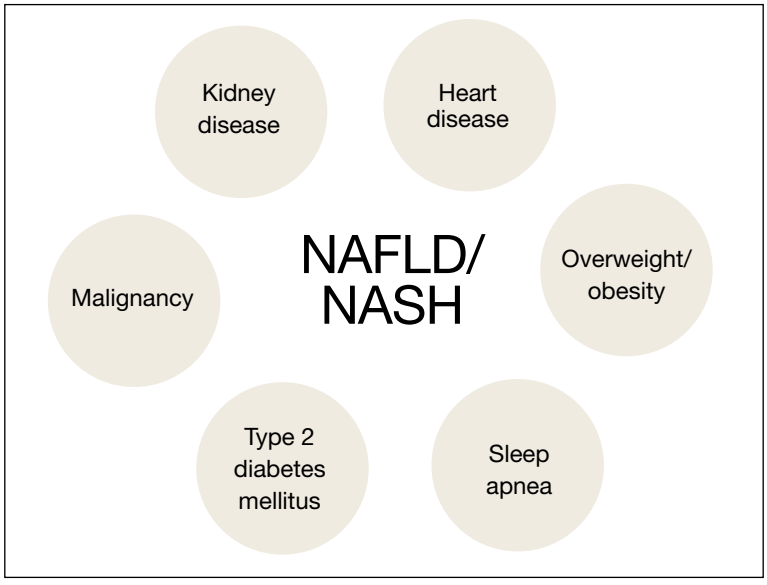
At 70% to 75%, the prevalence of NAFLD in patients with T2DM is more than twice as high as that in the general US adult population. Conversely, about 23% of patients with NAFLD also have T2DM.[9]

Influence of NAFLD on T2DM

Patients with ultrasound-based evidence of NAFLD are 2 to 5 times more likely to develop T2DM after adjusting for lifestyle and metabolic risk factors in multiple epidemiologic studies.[10,11] The severity of hepatic fat content measured by ultrasound also is associated with an increasing risk of T2DM incidence over the next 5 years (normal, 7%; mild, 9.8%; moderate-severe, 17.8%; $P < .001$).[12] In another study, 58% of patients with biopsy-proven NAFLD developed T2DM after a mean follow-up of 13.7 years.[13] Those who were found to have NASH had a 3-fold higher risk of developing T2DM than did those with simple steatosis. This finding was confirmed in another study where T2DM incidence was 2 times higher in patients predicted to have advanced fibrosis compared with those who did not.[14]

Because liver steatosis interferes with insulin-induced glycogen production and suppression of gluconeogenesis, hepatic fat content predicts the insulin dose required for adequate glucose control in patients with diabetes mellitus (DM) and NAFLD.[15] Higher levels of insulin are required in patients with DM and NAFLD compared with those without NAFLD.[5] Furthermore, patients with DM and NAFLD have increased complications, including both retinopathy and CKD.[5] It is thus not surprising that a population-based study of more than 330 patients with T2DM found that the presence of NAFLD was associated with a 2-fold increase in all-cause mortality over a mean follow-up period of 11 years.[16]

FIGURE 2 NAFLD: A Multisystem Disease



Abbreviations: NAFLD, Nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Additionally, a 10-year cohort study found that resolution of ultrasound-based NAFLD in patients without baseline T2DM, was associated with a reduced T2DM incidence (multivariate odds ratio [OR] 0.27, 95% CI, 0.12-0.61) after controlling for factors such as age, BMI, and impaired fasting glucose.[11,17]

Given this close relationship between T2DM and NAFLD, both the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of Liver Diseases (EASL) guidelines recommend that patients found to have NAFLD should be screened for the presence of impaired fasting glucose/T2DM by testing hemoglobin A_{1c} or fasting glucose levels.[18,19] Recognizing the role that NAFLD can play in patients with DM also is important, as improving hepatic steatosis may also improve DM.

Influence of DM on NAFLD

Patients with T2DM and NAFLD are at increased risk of progressive liver disease and have increased rates of NASH, cirrhosis, and HCC. In a paired-biopsy study, the development of T2DM was the strongest predictor of progression of NASH and hepatic fibrosis.[20] This fibrosis progression can easily go undetected, as NASH can be present even with normal aminotransferases. This increased risk of fibrosis progression in the setting of comorbid T2DM is clinically important, as it is the severity of fibrosis that predicts all-cause and liver-related mortality in patients with NAFLD/NASH.[21,22] In fact, the prevalence of biopsy-proven NASH in overweight/obese patients with DM with normal liver aminotransferases (defined as aspartate aminotransferase and alanine aminotransferase < 40 U/L) was found to be 58%.[23] Because chronic liver disease, including NAFLD, is underrecognized in the "healthy population" used to establish normal aminotransferase levels, more recent AASLD and ACG guidelines now define normal aminotransferase levels as < 35 U/L for males and < 25 U/L for females.[24] These stricter cutoffs are based on populations with normal BMI and negative testing for chronic liver diseases.[24] The lower cutoffs may improve recognition of progressive liver disease in NAFLD and NASH patients.

Medications used in the treatment of T2DM, such as metformin, pioglitazone, and liraglutide, have been studied in patients with biopsy-proven NASH. The initial data showing histologic improvement in NAFLD patients taking metformin was more likely related to the associated weight loss in the treatment group. In a study by Loomba and colleagues the improvement in the NAFLD activity score was only seen in patients who lost ≥ 5% of their total body weight.[25] Pioglitazone is a PPAR-γ agonist that helps regulate glucose and lipid metabolism as well as inflammation. Pioglitazone helps adipose tissue, hepatocytes, and muscle cells restore insulin sensitivity. A recent trial in 100 patients with prediabetes or T2DM as well as NASH showed that 36 weeks of pioglitazone treatment was associated with significant improvements in steatosis, inflammation, and most important, in stage of fibrosis compared with that of placebo.[26]

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide, have effects on lipid and glucose metabolism as well. They can lower glucose levels by increasing insulin secretion, reducing glucagon concentration, suppressing appetite (resulting in weight loss), and increasing sensitivity to insulin in hepatocytes and adipocytes. Liraglutide has been studied in patients with NASH both with and without DM, and results of the largest study to date show that it is

associated with significant improvement in hepatic inflammation compared with that of placebo.[27] Additional phase 3 clinical trials are currently underway.

Current AASLD guidelines do not recommend routine screening for NAFLD, even among high-risk patients, such as patients with DM.[18] This is due to the widespread prevalence of NAFLD, the unclear utility of diagnostic tests, and limited efficacy of available treatment. Lifestyle modification to achieve weight loss remains the backbone of management, and rates of successful adherence are low.[28] Contrary to this, EASL guidelines state that NAFLD screening with ultrasound even in patients with normal liver enzymes should be performed in high-risk patients with T2DM.[19]

Once detected, T2DM should be diligently treated in patients with NAFLD, and pioglitazone may be considered in patients with biopsy-proven NASH per AASLD guidelines.[18] Pioglitazone has been studied in patients with biopsy-proven NASH both with and without DM and has been associated with significant resolution of NASH, as well as improvement in histologic changes of NASH and improvement in fibrosis.[29,30] Because of potential medication AEs, including a mean weight gain of 2.5 kg to 4.7 kg in trials of 12- to 36-months' duration, as well as potential bone loss in women, discussions about the risks and benefits of treatment should occur prior to treatment initiation.[18] Additionally, pioglitazone is not safe in the setting of left ventricular heart failure. Future studies may point to the utility of other DM medications, such as GLP-receptor agonists.

CARDIOVASCULAR DISEASE

Given the association between features of MetS and NAFLD, it is not surprising that the primary cause of death in patients with NAFLD is related to CVD.[21,22,31] However, it is increasingly recognized that NAFLD predicts CVD independently of the traditional risk factors associated with MetS. The increase in cardiovascular risk in the setting of NAFLD can be partly explained by the increased hepatic de novo lipogenesis that is associated with increased production of highly atherogenic small dense low-density lipoproteins (sd-LDL) independent of BMI and presence of insulin resistance.[32]

TABLE NAFLD Comorbidities Prevalence and Risks

Comorbidities	NAFLD Prevalence/ Risk	Progression of Liver Disease/ Complication	Progression of Comorbidity From NAFLD
Obesity	60%-90%	Strong risk	N/A
Type 2 diabetes mellitus	70%	Strong risk	Strong risk
Metabolic syndrome	53%	Strong risk	Strong risk
Obstructive sleep apnea	2- to 3-times risk	Moderate risk	—
Chronic kidney disease	Unknown	—	Impacts risk

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

Additionally, increased intracellular free fatty acids can activate proinflammatory cytokine production by hepatocytes in addition to the increase in systemic inflammatory mediators and oxidative stress associated with NASH.

A recent meta-analysis of 27 studies confirmed the association between NAFLD and many subclinical features of CVD, including increases in coronary-artery calcium score, carotid artery intimal media thickness, and arterial wall stiffness, as well as impaired flow-mediated vasodilation after controlling for classic CVD risk factors.[33] The risk of subclinical carotid and coronary atherosclerosis progression was higher in NAFLD patients with evidence of advanced fibrosis using noninvasive measures. Additionally, NAFLD was associated with increased severity of coronary artery disease in > 600 patients undergoing cardiac angiograms.[34] Conversely, the regression of NAFLD on ultrasound was associated with a decreased risk of carotid atherosclerosis progression.[35]

Multiple epidemiologic studies have found an increased incidence of clinically overt CVD in patients with NAFLD after controlling for confounders. The largest updated meta-analysis, which included more than 34,000 patients with 2,600 CVD outcomes over a median of 6.9 years found that the presence of NAFLD (based on imaging or biopsy) was associated with an odds ratio (OR) of 1.64 (95% CI, 1.26-2.13) for fatal and nonfatal incident CVD.[36] In the same meta-analysis, patients with NASH, with or without fibrosis, were at an

KEY POINTS

- Obesity is the most common risk factor for NAFLD: 70% to 90% of obese patients have NAFLD, but up to 20% of Americans with normal BMI have NAFLD. Visceral fat, even with normal BMI, is metabolically active and is associated with hepatic steatosis.
- NAFLD can be associated with or precede MetS.
- Patients with NAFLD are up to 5 times more likely to develop T2DM after controlling for other risk factors. Hepatic steatosis is associated with increased insulin requirements, and the presence of NAFLD is associated with a 2-fold increase in all-cause mortality in patients with DM. Improving hepatic steatosis can improve diabetic control.
- Patients with T2DM in addition to NAFLD are at increased risk of progressive liver disease and have increased rates of NASH, cirrhosis, and hepatocellular carcinoma.
- Patients found to have NAFLD should be annually screened for the presence of impaired fasting glucose/T2DM by testing hemoglobin A_{1C} or fasting glucose levels. Once detected, T2DM should be rigorously treated in patients with NAFLD, and pioglitazone may be considered in patients with biopsy-proven NASH.
- The primary cause of death in patients with NAFLD is related to CVD. NAFLD predicts CVD independently of the traditional risk factors associated with MetS. Cardiovascular risk assessment should be performed when patients are diagnosed with NAFLD, and risk factors should be diligently modified. Statins are safe in the setting of NAFLD/NASH and should be used to manage cardiovascular risk if they are otherwise indicated.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type 2 DM.

even higher risk, with an OR of 2.58 (95% CI, 1.78-3.75).

Initial studies of statin medications for the treatment of NASH using surrogate endpoints like improvement in aminotransferases or imaging, suggested a potential liver-related benefit. However, there was no histologic improvement in the single study comparing 12 months of simvastatin therapy with placebo in patients with NASH.[37] Although it is unclear whether statin use will directly improve NAFLD, there is no evidence to suggest that statin use should be avoided in patients with elevated CVD risk.[38] Treatment with atorvastatin has been shown to be associated with a greater reduction in cardiovascular events in patients with NAFLD compared with that of patients without NAFLD.[39]

The strong association between CVD and NAFLD has important clinical implications that may influence the decision to initiate treatment for primary prevention, including lipid-lowering, antihypertensive, or antiplatelet therapies. The clinical algorithms currently used to help risk stratify patients and determine appropriate preventative strategies, the Framingham risk equation or the systemic coronary risk evaluation, do not incorporate NAFLD as a potential risk factor for CVD. Additional studies are needed to determine whether adding NAFLD to the assessment will improve the predictive accuracy of future CVD events. Nevertheless, European clinical guidelines recommend performing a CVD risk assessment for patients with NAFLD.[19]

CHRONIC KIDNEY DISEASE

The prevalence of CKD, defined as estimated glomerular filtration rate (GFR) < 60 mL/min/1.72 m^2, abnormal albuminuria, or proteinuria, is significantly increased in patients with NAFLD. Several epidemiologic studies have shown the prevalence of CKD in NAFLD patients ranges from 20% to 55% compared with 5% to 30% among patients without NAFLD.[40] Overall, patients with NAFLD have a 2-fold increased risk of prevalent (OR 2.12; 95% CI, 1.69-2.66) or incident (hazard ratio 1.79; 95% CI, 1.65-1.95) CKD, even after adjusting for T2DM, visceral fat, and insulin resistance.[40] There is an additional 2-fold increase in CKD risk in patients with NASH and advanced fibrosis compared with those with NASH and mild/no fibrosis. Additionally, advancing NASH fibrosis stage is independently associated with worsening stage of CKD.[41]

Data regarding the exact mechanism of kidney pathology in the setting of NAFLD is lacking. The accelerated atherogenesis in NAFLD likely contributes to renal damage. Another potential mechanism to explain the association between NASH and CKD involves the increased activation of the angiotensin-aldosterone system (RAAS) seen in NASH, which leads to increased hepatic fibrogenesis as well as kidney damage.[42]

Similar to the previously listed comorbidities, there is evidence that improvement in NAFLD can lead to improvements in renal disease. A prospective study of NASH patients undergoing 52 weeks of lifestyle modification found that the patients who had improvements in histologic NASH endpoints also had improvement in renal function.[43]

There are currently no specific recommendations on screening for CKD in professional

guidelines, but many experts propose monitoring for CKD yearly with serum creatinine and urinalysis and referring to nephrology if needed. Given the association between NASH and activation of the RAAS pathway that is associated with worsening hepatic fibrosis, RAAS-inhibitors should be a first-line agent in the treatment of hypertension in patients with NAFLD.

OBSTRUCTIVE SLEEP APNEA

OSA is characterized by repeated pharyngeal collapse during sleep, which leads to chronic intermittent hypoxia and is associated with increased metabolic and cardiovascular morbidity and mortality. The cycle of intermittent hypoxia and reoxygenation in OSA results in inflammation and oxidative stress. Multiple studies have supported a link between NAFLD and OSA.

Hepatic fat content on ultrasound was increased in patients with OSA independent of BMI. There also has been evidence of a positive association between the severity of chronic intermittent hypoxia and increased hepatic fibrosis based on liver elastography.[44] A meta-analysis using histologic NAFLD diagnosis showed that the presence of OSA was associated with a higher risk of fibrosis compared with that of patients with NAFLD without OSA (OR 2.6; 95% CI, 1.3-5.2).[45]

Based on animal models, hypoxia can drive fat accumulation and inflammation in the liver via multiple different pathways. Hypoxia can increase fasting glucose and systemic TG levels and induce hepatic lipogenesis by altering gene expression.[45] Hypoxia also can increase oxidative stress and reduce β-oxidation, which leads to the production of lipotoxic lipids. These hypoxia-induced changes are typically more pronounced in subjects with obesity compared with that in subjects without obesity. Despite multiple adverse metabolic effects of OSA-induced hypoxia in the setting of NAFLD, preliminary, short-term studies have failed to find an association with OSA treatment with continuous positive airway pressure and improvement in NAFLD.[45] Perhaps larger, long-term prospective trials will clarify this question.

MALIGNANCY

Extrahepatic malignancy (colon, esophagus, stomach, pancreas, kidney, and breast) is the second most common cause of death in patients with NAFLD.[21,22] The primary association between NAFLD and malignancy is found in the colon. Most large population-based studies have been performed in East Asia and have found that NAFLD is associated with a 1.5 to 1.7-fold increased risk for colonic adenomas and a 1.9 to 3.1-fold increased risk of colorectal cancer.[46-49] Using magnetic resonance spectroscopy and liver biopsy to diagnose NAFLD and NASH, respectively, Wong and colleagues found that NASH, but not simple steatosis, is associated with a higher risk of advanced colorectal neoplasia (OR 5.34; 95% CI, 1.9-14.8), after adjusting for age, gender, BMI, family history, smoking, and T2DM.[50]

Data showing a definitive causative role of NAFLD in the development of colorectal cancer are lacking, but the presence of increased insulin levels has many potential effects on carcinogenesis in general, including stimulation of cell proliferation and apoptosis. Currently, there are no recommended changes to the standard colorectal cancer screening recommendations specifically for patients with NAFLD.

CONCLUSION

NAFLD is a multisystem disease that is associated with increased liver-related and all-cause mortality. Data on the close association between NAFLD and several extrahepatic complications, including MetS, T2DM, CVD, CKD, and malignancy are well established. There also is growing evidence of a bidirectional relationship between some of these diagnoses, whereas NAFLD is not only a consequence, but also a cause of MetS, T2DM, and CKD independent of other typical risk factors.

Given the multiple comorbidities associated with NAFLD and its potential to influence the severity of these diagnoses, management of these complex patients requires diligence and a multidisciplinary approach. In order to engage in early recognition and intervention to prevent potential morbidity and mortality, regular screening and surveillance for the development of NAFLD in patients with metabolic risk factors can be considered, and careful screening for metabolic complications in patients with established NAFLD is important.

Author disclosures

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