

Extrahepatic Manifestations of Nonalcoholic Fatty Liver Disease

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Published online: 28 March 2016
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Abstract Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide with an increased prevalence of metabolic, macro-, and microvascular complications. The primary causes of mortality in NAFLD are cardiovascular disease (CVD), malignancy, and liver disease. NAFLD is a multisystem disease that affects a variety of extrahepatic organ systems. The main focus of this review is to summarize the reported extrahepatic associations, which include CVD, chronic kidney disease, obstructive sleep apnea, osteoporosis, psoriasis, colorectal cancer, iron overload, and various endocrinopathies (e.g., type 2 diabetes mellitus, thyroid dysfunction, and polycystic ovarian syndrome). Due to the systemic manifestations of NAFLD, patients require a multidisciplinary assessment and may benefit from more rigorous surveillance and early treatment interventions to decrease mortality related to malignancy or cardiometabolic diseases.

Keywords Nonalcoholic fatty liver disease (NAFLD) · Nonalcoholic steatohepatitis (NASH) · Cardiovascular disease (CVD) · Diabetes · Kidney disease · Sleep apnea · Thyroid disease · Bone disease · Sex hormones · Iron overload

This article is part of the Topical Collection on *Fatty Liver Disease*

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a global disease and the most common cause of chronic liver disease worldwide [1]. The prevalence of NAFLD is approximately 30 % and parallels the continual rise of the obesity epidemic [2]. NAFLD is often referred to as the “hepatic manifestation” of the metabolic syndrome (MetS), and risk markers for underlying NAFLD include type 2 diabetes (T2DM), obesity, and dyslipidemia [3•]. NAFLD prevalence approaches 90 % among patients with dyslipidemia, 70 % among diabetics, and is greater than 91 % in patients undergoing bariatric surgery [4, 5, 6•]. However, NAFLD is also detected among persons who do not have T2DM or MetS and there is now convincing evidence suggesting that NAFLD may precede the development of T2DM and MetS [3•, 7•]. Thus, the conventional theory that NAFLD represents the hepatic manifestation of the MetS may be outdated as data accumulates indicating that NAFLD may in fact be a pathogenic determinant of the MetS [8•].

NAFLD represents a disease spectrum that ranges from isolated hepatic steatosis to steatosis with inflammation and hepatocyte injury (e.g., nonalcoholic steatohepatitis (NASH)). NASH is a frequent cause of cirrhosis and hepatocellular carcinoma and is projected to become the most common indication for liver transplantation in the USA in the coming decade [9]. Overall, morbidity and mortality among NASH patients are significantly higher when compared to the general population [10]. Cardiovascular disease and malignancy followed by liver-related mortality are the most common causes of death among patients with NAFLD [10]. Some estimates suggest that NASH increases the risk of liver-related mortality by fivefold to tenfold, primarily dependent on the degree of hepatic fibrosis present [11, 12].

Over the past decade, mounting data support the notion that NAFLD is a multisystem disease effecting a variety of extra-hepatic organ systems [7•]. Considerable evidence now supports a strong link between NAFLD and the development of important cardiometabolic complications, mainly cardiovascular diseases (CVD), T2DM, and more recently chronic kidney disease (CKD) [3•, 7•]. In addition, NAFLD has been linked to colorectal cancer, obstructive sleep apnea (OSA), polycystic ovarian syndrome (PCOS), osteoporosis, psoriasis, hypothyroidism, and iron overload. This narrative review will briefly evaluate the current literature, proposed pathogenesis, and clinical implications of these associations among persons with NAFLD.

NAFLD and Type 2 Diabetes Mellitus

The link between NAFLD and T2DM is bidirectional and intricate. Once established, T2DM may promote progression to NASH, cirrhosis, and is itself an independent risk factor for hepatocellular carcinoma (HCC) [3•]. Insulin resistance is a central *risk marker* for underlying NAFLD, and a *risk factor* for disease progression. In fact, based on proton magnetic resonance spectroscopy (¹H-MRS), all constituents of the MetS correlate with liver fat content [13] and increased liver fat is associated with future or worsening of current metabolic disease [14]. Although steatosis rises in parallel with obesity, these associations remain significant even when controlled for body mass index (BMI) [13]. The fatty liver is resistant to insulin, which normally acts to suppress hepatic glucose production. This in turn results in hyperglycemia and hyperinsulinemia [15]. Therefore, both reduced insulin clearance and hepatic insulin resistance contribute to fasting hyperinsulinemia among NAFLD patients.

NAFLD Among Patients with T2DM

Since NAFLD is strongly associated with systemic insulin resistance, patients with T2DM and NAFLD commonly have poor glycemic control compared to those with T2DM without NAFLD [3•, 16, 17]. In addition, among patients with T2DM, the presence of NAFLD increases risk of all-cause mortality by 2.2-fold compared with those without NAFLD [18]. Finally, NAFLD is independently associated with microvascular diabetic complications including CKD and retinopathy in both type 1 and type 2 diabetes [19–21]. The clinical implications are that in patients with coexisting T2DM and NAFLD careful surveillance for macro- and microvascular complications are needed in order to prevent disease progression. Of note, the majority (~85 %) of patients with T2DM and NAFLD have normal liver enzymes [3•, 16, 17]. Therefore, even in the presence of normal liver enzymes, a

histological diagnosis should still be pursued in this high-risk group if there is a suspicion for advanced liver disease based on noninvasive markers (e.g., transient elastography and/or noninvasive clinical fibrosis scores) [22, 23, 24•].

NAFLD and Incident T2DM

Not only is NAFLD prevalent among patients with established T2DM, but there is also an established relationship between NAFLD and incident T2DM that has been replicated among different ethnic populations and is independent of common risk factors for T2DM [25–27]. Two large meta-analyses have confirmed the association between NAFLD, as assessed by liver enzymes, and incident T2DM [28, 29]. Similar results have been found in prospective studies using liver ultrasonography to diagnosis NAFLD [30–34]. However, all of these studies were performed in Asian populations and adjustment for potential confounders was frequently inconsistent (for example, fully adjusted models excluded family history of T2DM, fasting glucose and fasting insulin levels) [3•]. Only one study has prospectively assessed biopsy-proven NAFLD and risk for incident T2DM [35]. Among 129 patients with biopsy-proven NAFLD, 78 % developed either T2DM (58 %) or impaired glucose tolerance (20 %) during the 13.7-year follow-up. Importantly, compared to those with simple steatosis NASH patients had a threefold higher risk of developing T2DM [35].

NAFLD and Cardiovascular Disease

Patients with NAFLD have numerous established risk factors for cardiovascular disease (CVD) including insulin resistance, hypertension, atherogenic dyslipidemia, and obesity [22, 23]. They also have an increased prevalence of CKD, which is another established risk factor for CVD [36]. Furthermore, NAFLD is associated with many non-traditional and emerging CVD risk factors including increased serum levels of uric acid [37], pro-inflammatory markers such as C-reactive protein and IL-6 [38], and pro-coagulant factors including fibrinogen, von Willebrand factor and plasminogen activator inhibitor-1 [39]. NAFLD is also associated with lower plasma levels of adiponectin, a protein with anti-atherogenic and anti-diabetic properties [40]. Thus, it is not surprising that CVD is the leading cause of death among patients with NAFLD [10, 12].

NAFLD and Atherosclerosis

Growing evidence suggests that NAFLD is a risk marker, and perhaps an independent risk factor, for atherosclerosis. NAFLD has been associated with a higher prevalence of unstable coronary plaques [41], impaired endothelial function [42], and subclinical atherosclerosis as measured by carotid

intima media thickness [43] and coronary artery calcification (CAC) [44, 45]. Due to these strong subclinical associations, it is not unexpected that clinical ischemic heart disease is highly prevalent among patients with NAFLD when compared to those without steatosis [46–48]. Several prospective, population-based cohort studies have utilized serum levels of liver enzymes or other markers of NAFLD (e.g., fatty liver index) to diagnose NAFLD and to monitor the natural history of the disease. These studies have shown that in both men and women, mildly increased liver enzymes are independent predictors of future ischemic cardiovascular events [29, 49].

NAFLD and Myocardial Structure and Function

NAFLD has also been independently associated with changes in cardiac structure and function. Small studies have found that NAFLD is associated with altered cardiac energy metabolism [50], myocardial insulin resistance [51], impaired diastolic function, and abnormal left ventricular (LV) structure [52]. In a recent large, population-based study of middle-aged asymptomatic adults, CT-diagnosed NAFLD was associated with both sub-clinical cardiac remodeling as well as systolic and diastolic dysfunction independent of traditional heart failure (HF) risk factors including hypertension, dyslipidemia, diabetes, and obesity [53]. In addition, serum γ -glutamyltransferase (GGT), which is a possible marker of underlying NAFLD but is also found in coronary plaque and thus is a marker of atherosclerosis, has been independently associated with an increased risk of incident HF [54–56]. Thus, NAFLD may play a pathogenic role in the development of clinical HF, particularly HF with preserved ejection fraction. Finally, NAFLD has been independently associated with an increased risk of dysrhythmia [57], including atrial fibrillation [58], prolonged QTc interval [59] (a strong predictor of sudden cardiac death), and cardiac autonomic dysfunction [60].

NAFLD and CVD Events

To date, there are over 20 published studies assessing the relationship between NAFLD diagnosed on biopsy or imaging and the risk of developing fatal and nonfatal CVD events both in patients with and without T2DM (see Byrne et al. [7•] *Table 2* for a comprehensive summary). Most of these studies support the notion that CVD is detrimental among NAFLD patients. In contrast, based on data from the NHANES 1988–94 database, ultrasound-diagnosed NAFLD was not shown to predict the risk of all-cause or cardiovascular-specific mortality over a 14-year period among US adults [46, 47]. However, the latest analyses of the same NHANES-III database demonstrated that NAFLD with advanced hepatic fibrosis (defined by noninvasive scoring systems) was independently associated with a 70 % increased risk of all-cause mortality, and that this increase in mortality was almost entirely due to CVD

causes after correcting for multiple cardiac risk factors [61]. This supports the concept that fibrosis stage is the most important predictor of both overall and disease-specific mortality among persons with NAFLD [12]. Finally, among liver transplant recipients, NASH has been independently associated with an increased risk of post-operative CVD events when compared to recipients transplanted for alcohol-induced cirrhosis [62], and NASH has also been associated with an increased risk of CVD-related mortality compared to other indications for liver transplantation [63, 64]. Although there is considerable heterogeneity among the aforementioned studies, and many lack a histological diagnosis of NAFLD, the large body of available literature supports the notion that NAFLD is in fact an independent contributor to the development of CVD. Thus, integrating this knowledge of the complex interplay between NAFLD and cardiac disease is paramount in the clinical approach of both the patient with NAFLD and the patient with CVD.

NAFLD and Chronic Kidney Disease

The possible link between NAFLD and CKD has recently drawn considerable scientific attention [19, 20, 65, 66]. Experimental and epidemiological data suggest that the presence of NAFLD can accelerate the development and progression of CKD independent of traditional risk factors and also that CKD itself may contribute to liver disease progression in NAFLD, though this is less substantiated [67•]. A recent meta-analysis demonstrated that NAFLD is associated with an approximately twofold increased risk of both prevalent (odds ratios (OR)=2.12) and incident (hazard ratio (HR)=1.79) CKD [67•]. Notably, both advanced fibrosis and NASH were associated with a higher prevalence (OR=5.20 for advanced fibrosis, OR=2.53 for NASH) and incidence (HR=2.12 for NASH, HR=3.29 for advanced fibrosis) of CKD than simple steatosis [67•]. These findings were unaffected by diabetes status and after adjustment for other important CKD risk factors. In addition, NAFLD severity was positively correlated with CKD stages. Thus, consideration should be given to screening individuals with NAFLD for CKD even in the absence of other risk factors for the disease. Further studies are needed to determine whether better treatment of NAFLD may help to prevent future CKD.

Potential pathophysiologic mechanisms linking NAFLD and CKD include, but are not limited to, upregulation of the renin-angiotensin system (RAS) and impaired anti-oxidant defense [66, 68]. A surplus of dietary fructose may also contribute to NAFLD and CKD [69, 70]. In animal studies, NAFLD may promote renal injury through lipoprotein dysmetabolism and altered secretion of syndecan-1, insulin-like growth factor-1, fetuin-A and fibroblast growth factor-21 [66, 68]. Finally, CKD may exacerbate both NAFLD and associated metabolic disorders through altered intestinal

microbiota and barrier function, alterations in glucocorticoid metabolism, and the accrual of uremic toxic metabolites [66].

NAFLD and Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is an obesity-related condition characterized by repetitive events of upper airway occlusion during sleep, leading to repeated oxyhemoglobin desaturations termed chronic intermittent hypoxia (CIH) [71]. CIH induces oxidative stress and, consequently, promotes insulin resistance, systemic and vascular inflammation, endothelial dysfunction, and cardiovascular morbidity and mortality [72]. Studies in mice and humans have suggested that OSA also leads to liver injury [73–75]. In morbidly obese subjects referred for bariatric surgery, CIH contributes to the severity of liver fibrosis and necroinflammation independent of obesity [76]. An emerging body of evidence suggests that the development of NAFLD is closely associated with OSA in both children and adults [74, 76–81]. However, since obesity is a common co-morbid condition in both NAFLD and OSA, the true independent contribution of CIH for the development of NAFLD and subsequent CVD is difficult to discern. In a recently published study of 226 subjects referred for suspicion of OSA, including nonobese subjects, Minville et al. [81] demonstrate a dose-response relationship between the severity of nocturnal CIH and liver injury (as measured by noninvasive blood tests: SteatoTest, NashTest, and FibroTest) among obese subjects ($BMI > 37.8 \text{ kg/m}^2$). This finding was not replicated in lean subjects with OSA. In addition, the authors demonstrate that in the setting of OSA, severe hepatic steatosis and borderline or possible NASH were associated with higher CVD risk as demonstrated by elevated blood pressure and more severe endothelial dysfunction [81]. These findings suggest that associated or pre-existing obesity is required for nocturnal hypoxemia to transition from isolated hepatic steatosis to a more progressive NASH phenotype and may play a causal role in the development of endothelial dysfunction and future CVD among patients with OSA. Finally, a recent meta-analysis of 18 cross-sectional studies that included over 2000 subjects found that OSA is associated with an increased risk of NAFLD (OR 2.99), NASH (OR 2.37), and advanced fibrosis (OR 2.30) independent of sex, age and BMI [82].

The clinical implication for this association is that in obese patients with NAFLD, screening for underlying OSA and treatment of OSA with continuous positive airway pressure (CPAP) may impact future CVD outcomes. One recommended method for screening individuals with NAFLD for OSA includes a two-step approach: (1) administer an Epworth Sleepiness Scale questionnaire and (2) among those with high-risk scores, perform nocturnal monitoring [82]. However, screening questionnaires for OSA have somewhat poor sensitivity/specificity and have not been specifically

validated among NAFLD patients [83]. In addition, among obese patients with OSA, an investigation into possible underlying NAFLD and monitoring for disease progression should be considered.

NAFLD and Osteoporosis

Metabolic bone disease is common in patients with chronic liver disease [84] and multiple studies among both children and adults have demonstrated that NAFLD patients have lower bone mineral density (BMD) than their non-NAFLD counterparts [85]. There are potentially major clinical implications to these findings, including a potential for increased risk of osteoporotic fractures recently reported among a large population-based study in China [86]. Notably, in this study, the prevalence of osteoporotic fractures was only increased among Chinese men with NAFLD (3.6 vs. 1.7 %, $p < 0.005$). There was no significant difference among Chinese women (3.4 vs. 2.6 %, $p = 0.14$). On multivariate regression analysis, NAFLD was associated with a ~2.5-fold increased odds of osteoporotic fractures among Chinese men, independent of multiple potential confounders, including use of oral steroids or osteoporosis drugs, MetS components, estimated glomerular filtration rate, and physical activity levels. However, this study had several limitations, mainly that the ascertainment of osteoporotic fracture was based on self-report and not measurements of bone mineral density, thus the authors could not identify asymptomatic osteoporotic fractures. The potential contribution of NAFLD to development of osteoporosis warrants further study.

NAFLD and Endocrinopathies

Hypothyroidism

Hormones synthesized in the thyroid gland play an important role in the regulation of diverse metabolic processes. Furthermore, disturbances in thyroid hormone concentrations may promote hyperlipidemia and obesity, thus potentially contributing to the development of NAFLD [87]. A recent systematic review found 11 studies assessing the relationship between NAFLD and hypothyroidism from 2003 to 2013 including 12,924 participants collectively [88]. Importantly, five studies used liver biopsy to diagnose NAFLD. The prevalence of hypothyroidism ranged between 15.2 and 36.3 % among patients with NAFLD and/or NASH. In one small study, biopsy-proven NASH was associated with hypothyroidism, independent of age and MetS components [89]. This association has since been confirmed in a larger study of over 2000 subjects with either overt or subclinical hypothyroidism, including a subpopulation with normal thyroid stimulating hormone (TSH) levels [87]. Clinically, future studies are needed

to assess whether or not thyroid replacement therapy in patients with NAFLD/NASH and hypothyroidism will improve disease progression and outcomes.

Polycystic Ovarian Syndrome

Hyperandrogenism commonly manifests in reproductive-aged women as a condition known as PCOS, which is typically also accompanied by polycystic appearing ovaries and oligomenorrhea [90]. Like NAFLD, PCOS is strongly associated with CVD risk factors as 70 % of these women have insulin resistance, 60 % are obese, and up to half of PCOS women also have hepatic steatosis on imaging independent of BMI [90]. A recent meta-analysis that included 7 studies from 6 different countries found that patients with PCOS had a 3.93-fold increased odds of co-existing NAFLD (95 % CI 2.17–7.11), independent of co-existing MetS features [91]. However, the prevalence of NAFLD among women with PCOS varied in different countries ranging from 32.9 % among Chinese women with PCOS to 73.3 % among Brazilian women [91]. PCOS women with NAFLD have been shown to have a higher prevalence of the MetS (and its individual traits) and more insulin resistance compared to PCOS women without NAFLD; however, no significant differences have been found in circulating levels of total testosterone or dehydroepiandrosterone sulfate (DHEAS) [91, 92]. It is important to note the young age of PCOS women in these studies and the fairly advanced stage of biopsy-proven NASH raising concern for significant risk of long-term liver-related complications among PCOS patients. Therefore, careful monitoring and evaluation for the presence of NAFLD among women with PCOS is of utmost importance. Unfortunately, the optimal method of screening in this population is currently unknown. Since serum liver enzymes alone lack adequate sensitivity and specificity for the detection of NAFLD [23], we believe that liver ultrasonography combined with transient elastography and noninvasive fibrosis scoring systems (e.g., NAFLD fibrosis score) may be useful to help identify those at greater risk of NASH and fibrosis among women with PCOS in whom liver biopsy should then be considered [24•].

NAFLD and Colorectal Cancer

Colorectal cancer is the third most common cancer worldwide and there are approximately 1.2 million new cases detected each year [93]. In epidemiological studies, MetS and its individual components have been associated with an increased risk of colorectal adenoma and/or cancer [94]. However, studies investigating the link between NAFLD and colorectal adenoma and/or cancer have reported conflicting findings. In a recent meta-analysis which included a total of 6263 subjects across 5 studies (4 cross-sectional, 1 retrospective cohort), NAFLD was significantly associated with colorectal adenoma

(pooled odds ratio (OR) 1.74, 95 % confidence interval (CI) 1.53–1.97) [95]. The association was more significant in Asian populations (pooled OR = 1.77, 95 % CI 1.52–2.05, $n=3$ studies), compared to European/North American populations (pooled OR = 1.42, 95 % CI 0.75–2.67, $n=2$ studies) and strongest among patients with NASH ($n=2$ studies, pooled OR 2.54, 95 % CI 1.07–6.03). There was no reported association between NAFLD or NASH and colorectal cancer; however, the colorectal cancer detection rate among this screening population was small and therefore there was little statistical power to detect such an association. In addition, overall follow-up time was small (e.g., <10 years) and none of the included studies were prospectively designed. Therefore a true causal relationship between NAFLD/NASH and colorectal adenoma and/or cancer cannot be confirmed. Further research is needed to confirm the associated risk of colorectal cancer (or advanced adenomas) among various NAFLD populations and ethnic backgrounds.

NAFLD and Psoriasis

Psoriasis is an immune-mediated, chronic, inflammatory disease with an estimated worldwide prevalence of 2–3 % [96]. Psoriasis is a multisystem disease with a high prevalence of coexisting MetS particularly among patients aged ≥ 40 years [96, 97]. Furthermore, the relationship between psoriasis and MetS is independent of obesity and directly correlated to the severity of psoriasis [97]. Since both NAFLD and psoriasis are related to the MetS, it is not surprising that the prevalence of NAFLD may be increased among patients with psoriasis compared to those without psoriasis. In one large prospective population-based cohort study of 2292 participants aged 55 or greater, 118 (5.1 %) had psoriasis. NAFLD prevalence was higher among those with psoriasis (46.2 vs. 33.3 %) even after adjustment for cigarette and alcohol use, MetS components and alanine aminotransferase level [98]. Patients with NAFLD and psoriasis may also be at an increased risk for severe liver fibrosis [99]. In a small study of 109 clinic patients with psoriasis, the overall prevalence of biopsy-proven NASH was 22 % [100]. Interestingly, the presence of NAFLD among patients with psoriasis may also be linked to psoriasis severity [99, 101]. However, it is currently unknown if incident psoriasis is increased among patients with NAFLD or NASH. Future epidemiologic studies assessing whether there is a causal relationship between NAFLD and psoriasis are needed. Given the current observational data that NAFLD is highly prevalent in patients with psoriasis, heightened clinical awareness for underlying NAFLD in this population may be warranted.

NAFLD and Iron Overload

Approximately one third of NAFLD patients have excess iron stores. The association of fatty liver with moderate

Table 1 Proposed screening strategy for extrahepatic manifestations among patients with the NAFLD spectrum

Proposed screening strategy based on current evidence	
Established risk	
Type 2 diabetes	Yearly HbA1c and fasting glucose Assess historical risk factors: • Family history of T2DM • History of gestational DM [111]
Cardiovascular diseases • Dyslipidemia • Atherosclerosis • Dysrhythmia • Heart failure	Yearly fasting lipid profile ^a Annual blood pressure screening • If hypertensive, measure blood pressure at every clinical visit ^b Measure waist circumference Assess historical ASCVD risk factors: • Smoking history • Diabetes history • Family history of premature CVD (males <50, females <60) Calculate 10-year and lifetime ASCVD risk using AHA/ACC risk calculator [112] • If age 40–79 and 10-year risk >7.5 %, consider statin for primary prevention [112, 113] • If 10-year risk <7.5 %, consider other factors that may influence lifetime risk ^c Heightened clinical awareness for signs/symptoms of dysrhythmia (e.g., presyncope, palpitations) or impaired function (e.g., dyspnea, chest pain)
Chronic kidney disease	Yearly urine microalbumin and urinary albumin/creatinine ratio Yearly eGFR
Obstructive sleep apnea	Assess and document standard risk factors: • Smoking • BMI • Neck circumference • Alcohol and sedative use Heightened clinical awareness for symptoms of OSA (e.g., daytime somnolence) Administer Epworth sleepiness scale questionnaire; if high-risk refer for sleep study [82]
Endocrinopathies • Hypothyroidism • PCOS	Yearly serum thyroid function tests Lower threshold for ovarian ultrasound and serum androgens in females of reproductive age with irregular menstruation, infertility, hirsutism, etc. NOTE: In women with documented PCOS, consider liver ultrasound +/- transient elastography to assess for underlying NAFLD/NASH
Emerging risk	
Osteoporosis	Standard of care NOTE: Screen (DEXA scan) in patients undergoing transplant assessment to prevent peri-/post-operative fracture [114]
Colorectal cancer	Standard of care screening according to national guidelines [115]
Psoriasis	In patients with documented psoriasis, a heightened clinical awareness for possible underlying NAFLD is warranted
Iron overload	Serum ferritin and transferrin saturation to identify dysmetabolic iron overload syndrome versus hemochromatosis

ACC American College of Cardiology, AHA American Heart Association, ASCVD atherosclerotic cardiovascular disease, BMI body mass index, CAD coronary artery disease, CAC coronary calcium score, CVD cardiovascular disease, ASCVD atherosclerotic cardiovascular disease, eGFR estimated glomerular filtration rate, HbA1c glycosylated hemoglobin, HTN hypertension, HF heart failure, NAFLD nonalcoholic fatty liver disease, NASH nonalcoholic steatohepatitis, PCOS polycystic ovarian syndrome, OSA obstructive sleep apnea

^a For ASCVD risk alone, sample does not need to be fasting and can be completed every 5 years among those individuals at average ASCVD risk. Fasting lipid profile is required for triglyceride assessment in order to assess overall metabolic risk among NAFLD patients. Yearly fasting lipid panel is recommended in all liver transplant recipients

^b Consider ambulatory blood pressure monitoring among those with an elevated single blood pressure reading

^c Factors that influence lifetime risk of ASCVD include extreme elevation of a single traditional ASCVD risk factor (e.g., heavy smoker, hypertensive urgency, familial hyperlipidemia, poorly controlled blood glucose, strong family history of CVD) and evidence of subclinical vascular disease (e.g., abnormal coronary calcium score, abnormal carotid intima media thickness, etc.)

histological iron deposition (hemosiderosis) and increased serum ferritin with normal serum transferrin saturation is referred to as the dysmetabolic iron overload syndrome

(DIOS) [102]. Compared to hemochromatosis, the magnitude of hyperferritinemia in patients with NAFLD and/or the MetS overestimates the degree of iron overload detected on

histology [103]. Among patients with NAFLD, a serum ferritin $>1.5\times$ the upper limit of normal is associated with hepatic iron deposition, underlying NASH, and worsened histologic activity [104]. Furthermore, elevated serum ferritin is independently associated with higher NAFLD activity score (NAS), even among patients without hepatic iron deposition [104]. Although serum levels of ferritin correlate with more severe liver fibrosis, serum ferritin levels alone have a low level of diagnostic accuracy for the presence or severity of liver fibrosis in patients with NAFLD (AUROC <0.60) [105]. Distinct histological features in patients with NAFLD are associated with specific patterns of hepatic iron deposition. For example, the presence of iron in the reticuloendothelial system (versus hepatocellular deposition) among patients with NAFLD is associated with more advanced histological features, including NASH and fibrosis [106], and sinusoidal iron deposition is associated with the development of HCC in NASH [107]. Small studies have suggested that iron removal may improve insulin sensitivity among patients with NAFLD [108, 109]. However, a recent prospective 6-month randomized, controlled trial of 74 NAFLD subjects (33 phlebotomy and 41 control) failed to demonstrate an effect of phlebotomy on hepatic steatosis, liver injury, or insulin resistance [110]. In addition, in contrast to patients with hemochromatosis, those with NAFLD have impaired iron mobilization from storage sites and may therefore develop anemia in response to phlebotomy treatment [110]. Thus, serial phlebotomy to lower ferritin in NAFLD patients is not currently recommended, unless associated with documented iron overload.

Conclusions

The clinical burden of NAFLD extends beyond liver-related mortality to cardiovascular diseases, chronic kidney disease, obstructive sleep apnea, osteoporosis, psoriasis, colorectal cancer, iron overload, and various endocrinopathies. Based on current evidence, heightened awareness and screening for these conditions, particularly CVD, CKD, OSA, hypothyroidism, and PCOS is warranted (Table 1). Awareness of these increased risks among patients with NAFLD should lead practitioners to emphasize lifestyle modifications (i.e., physical activity, weight loss, smoking cessation) and pharmaceutical treatments (i.e., insulin sensitizers, lipid-lowering agents) to impact these extrahepatic manifestations of NAFLD. The current evidence and reported associations between NAFLD and many extrahepatic manifestations of disease are primarily observational with short follow-up periods. Future studies are needed that collect detailed cardiometabolic risk profiles at baseline and follow subjects over time in order to fully evaluate the incremental impact of NAFLD on micro- and macrovascular complications of this systemic disease. Importantly, the influence of treatment for NAFLD on the

risks and outcomes of extrahepatic disease should be considered in clinical trials going forward.

Acknowledgments The authors thank Donald Lloyd-Jones, MD, MSc, FAHA, FACC, for his expert review of the cardiovascular and chronic kidney disease screening and treatment recommendations for patients with NAFLD.

Compliance with Ethical Standards

Conflict of Interest LBVW and MER declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Funding Research reported in this publication was supported, in part, by the National Institutes of Health's National Center for Advancing Translational Sciences, Grant Number KL2TR001424.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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