Extra-Hepatic Manifestations of Nonalcoholic Fatty Liver Disease: A Review

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Nonalcoholic fatty liver disease (NAFLD) is now the leading cause of chronic liver disease worldwide with a strong association with metabolic syndrome. NAFLD is truly a systemic disease and is associated with a plethora of extra-hepatic manifestations or comorbidities. These are either related to secondary effects of associated obesity or from pathophysiological effects of insulin resistance in NAFLD. Three most common causes of increased morbidity and mortality associated with NAFLD are cardiovascular disease, liver disease, and cancer. In this narrative review, we will discuss comprehensively on cardiovascular disease, type 2 diabetes mellitus, and chronic kidney disease and will also highlight on malignancy especially colorectal cancer, pulmonary disorders including obstructive sleep apnea, endocrine disorders such as hypothyroidism and polycystic ovarian syndrome, dermatological disorders especially psoriasis, and hematological associations including iron overload and susceptibility to thrombosis. In addition to focusing on pathogenesis of these extrahepatic manifestations, we will highlight their clinical implications for physicians in routine clinical practice. Further, there remains an unmet need for safe and effective therapies and examining their benefits on these extra-hepatic manifestations among patients with NAFLD. (J CLIN EXP HEPATOL 2020;10:81–87)

During the past few decades, the prevalence of nonalcoholic fatty liver disease (NAFLD) has significantly increased in parallel with increasing obesity, and it is now the leading cause of chronic liver disease in the United States and worldwide.^{1,2} The prevalence of NAFLD is higher among patients with dyslipidemia and type 2 diabetes mellitus (T2DM) compared with the general population^{3,4}; additionally, there is evidence that NAFLD might have a role in the development of T2DM and metabolic syndrome (MetS) rather than just being one of its manifestations.⁵ It should be recognized that most of the studies have defined NAFLD based on ultrasound and/or computed tomography (CT) scan which can miss mild steatosis, and these patients may have been included in the healthy population without NAFLD.

The pathogenesis of occurrence of liver inflammation and fibrosis in patients with NAFLD is not completely understood. Other than insulin resistance, iron abnormalities have been thought to be one of the triggering factors. However, studies have not favored iron overload and hemochromatosis gene (HFE) gene mutations as major factors in the pathogenesis of nonalcoholic steatohepatitis (NASH) in Asian Indians.

NAFLD encompasses a wide spectrum of disease including nonalcoholic fatty liver (NAFL) and NASH which is characterized by liver inflammation with potential to progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma. In 80% of patients, NAFLD is histologically characterized as NAFL and NASH is present in 20% of patients.⁶ The mortality among patients with NAFLD is higher compared with general population with most common causes of death being cardiovascular events, malignancy, and liver-related mortality.⁷ Studies demonstrate that the degree of liver fibrosis among patients with NASH is independently associated with mortality, liver transplantation, and liver-related outcomes.⁸

There is growing evidence to support that NAFLD is a multisystem disease, and it involves extra-hepatic organ systems (Figure 1).⁹ To date, most of the studies have evaluated the association of NAFLD with cardiovascular disease (CVD), T2DM, and chronic kidney disease (CKD). Studies have also suggested association of NAFLD with colorectal cancer, obstructive sleep apnea (OSA), polycystic ovarian syndrome (PCOS), and hypothyroidism. In this

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Abbreviation: CKD: chronic kidney disease; CT: computed tomography; CVD: cardiovascular disease; MetS: metabolic syndrome; NAFL: nonalcoholic fatty liver; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; OSA: obstructive sleep apnea; PCOS: polycystic ovarian syndrome; T2DM: type 2 diabetes mellitus

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Adapted from Adams et al. *Gut* 2017.

Figure 1 Nonalcoholic fatty liver disease (NAFLD): a multisystem disease. Reported associations between NAFLD and various human diseases.

review, we briefly discuss the current literature regarding the pathogenesis and clinical implications of these associations among patients with NAFLD.

NAFLD AND CARDIOVASCULAR DISEASE

There is a strong association between NAFLD and atherosclerosis, as NAFLD patients have numerous established risk factors for CVD including insulin resistance, dyslipidemia, and obesity.¹⁰ Further, risk for CKD is increased in NAFLD, which in itself is a risk factor for development of CVD. In addition to these established risk factors, insulin resistance and MetS in NAFLD is associated with other nontraditional risk factors for atherosclerosis such as elevated serum uric acid level, proinflammatory markers including C-reactive protein, interleukin-6, leptin, tumor necrosis factor- α , circulating free fatty acids, and decreased levels of antiinflammatory hormone adiponectin.^{5,11,12} In addition, other markers of atherosclerosis are increased in NAFLD patients independent of MetS with carotid atherosclerotic plaques and rupture,¹³ endothelial dysfunction,¹⁴ increased carotid intimal thickness,¹⁵ and increased coronary artery calcification.¹⁶ These pathological changes along with physiological abnormalities of

impaired myocardial perfusion result in structural changes in the myocardium with increased remodeling and with increased myocardial fat content, impaired ventricular relaxation, aortic valvular sclerosis, and arterial stiffness.¹⁷ All these changes result in impaired myocardial energy metabolism as assessed on magnetic resonance spectroscopic examination, resulting in diastolic dysfunction and heart failure.¹⁸ Additionally, NAFLD is independently associated with risk for ventricular arrhythmias including atrial fibrillation, prolongation of QT interval, cardiac autonomic dysfunction, and sudden cardiac death.^{19,20}

Patients with NAFLD are at an increased risk of CVD. One study from National Health and Nutrition Examination Survey-III database demonstrated that patients with advanced hepatic fibrosis from NAFLD had a 70% increased risk of all-cause mortality, and even after adjusting for multiple cardiac risk factors, the mortality was found to be almost entirely due to CVD.²¹ Another study found the 10-year risk of acute coronary events in patients with NAFLD to be 4-fold higher compared with controls.²² In other studies, patients with biopsy/imaging-proven NAFLD with or without T2DM are associated with increased risk of CVD.^{23,24} Degree of fibrosis in NAFLD patients predicts the long-term outcomes with risk for extra-hepatic

morbidity and mortality. The risk for cardiac events and mortality also remains among transplant patients while they are waiting for receiving the organ and during the post-transplant period.^{25,26} Given the higher incidence and mortality due to NAFLD in CVD patients, screening should be considered in intermediate, and higher risk patients should be referred to cardiologist for evaluation. However, the data are still limited in terms of appropriate screening modalities. Patients with NASH cirrhosis undergoing liver transplantation evaluation should be screened for significant coronary artery disease (CAD). Screening modalities include stress echocardiography and CT coronary angiography. Conventional angiography is reserved for patients with combination of risk factors for CAD.

NAFLD AND TYPE 2 DIABETES MELLITUS

The relation between NAFLD and T2DM is complex and bidirectional. Prevalence of NAFLD among patients with T2DM is increased with varying rates of 10–75% among different series. The risk varies depending upon degree and control of diabetes and presence and severity of other components of MetS. On the other hand, among NAFLD subjects, the prevalence of T2DM varies between 18 and 33% depending on the severity of NAFLD. For example, the prevalence of T2DM was 7% among patients without NAFLD, 9.8% with mild NAFLD, and 17.8% in subjects with moderate to severe NAFLD.^{27,28} T2DM is also associated with progression of NAFLD to steatohepatitis, cirrhosis, and hepatocellular carcinoma.²⁹ NAFLD is also associated with microvascular complications of T2DM including retinopathy and CKD.³⁰ Further, the incidence for new-onset T2DM is about 2–3 folds increased among NAFLD patients as assessed in two different large meta-analyses.^{31,32} The risk is increased irrespective of the modality for NAFLD diagnosis, biochemical, imaging, or histological. Further, alanine aminotransferase and gamma glutamyl transpeptidase levels were independent predictors for incident T2DM.^{31,32} One prospective study assessed the incidence of T2DM in biopsy proven NAFLD and found that among 129 patients, a total of 58% developed T2DM and 20% developed impaired glucose tolerance during a follow-up period of 13.7 years. Patients with NASH had a 3-fold higher risk of developing T2DM compared with simple fibrosis.²⁷ Based on these data, it is recommended to screen NAFLD patients (a) without T2DM for annual assessment of hemoglobin A1C and (b) with established T2DM for annual retinal examination and microalbuminuria with urinary albumin to creatinine ratio.

NAFLD AND CHRONIC KIDNEY DISEASE

The relationship between NAFLD and CKD is still unclear. Studies suggest that the presence of NAFLD may accelerate

the development and progression of CKD independent of the traditional risk factors.^{33,34} Impaired antioxidant mechanism, upregulation of the renin-angiotensin system, and dietary factors potentially mediate the development of CKD among NAFLD patients.³⁵ Additionally, CKD is associated with alterations in gut microbiota and increased gut permeability which may lead to progression of NAFLD.³⁵ A recent meta-analysis evaluated the risk of CKD with NAFLD and found that NAFLD was associated with an increased prevalence (odds ratio [OR] 2.12, 95% confidence interval [CI] 1.69–2.66) and incidence (hazard ratio [HR] 1.79, 95% CI 1.65–1.95) of CKD. NASH was associated with a higher prevalence (OR 2.53, 95% CI 1.58–4.05) and incidence (HR 2.12, 95% CI 1.42–3.17) of CKD than simple steatosis. Further, the NAFLD spectrum and severity was associated with higher and worst CKD stage in this meta-analysis. These findings were independent of T2DM and other traditional risk factors.³³ However, another study did not find such an association.³⁶ Nevertheless, because of the higher risk of CKD in NAFLD subjects, it is recommended to protect kidneys with cautious and judicious use of nephrotoxic drugs and regularly screening their renal function. The increased risk of CKD in NAFLD patients probably accounts for NASH cirrhosis as the leading and most rapidly growing indication for simultaneous liver kidney transplantation.³⁷ Recipients of liver transplant alone for NASH cirrhosis also remain at risk for poorer renal function with risk of CKD during the posttransplant follow-up.^{38,39} Although studies have suggested that NAFLD may accelerate progression of CKD, screening for NAFLD in CKD patients is not routinely performed, and there is no specific guideline for screening NAFLD in CKD patients. Further studies are required to determine the approach and the clinical management of NAFLD in CKD patients.

NAFLD AND OBSTRUCTIVE SLEEP APNEA

Obesity among patients with MetS and NAFLD leads to upper airway collapse with airway edema leading to chronic intermittent hypoxia, which further leads to worsening of insulin resistance and risk for NAFLD.^{40,41} Several studies have suggested that OSA leads to liver injury and further worsening of NAFLD.^{42,43} The association of OSA and NAFLD is observed among both children and adults.^{43,44} A meta-analysis showed that the patients with OSA were at increased risk of NAFLD, NASH, and advanced fibrosis irrespective of the age, sex, and body mass index.⁴⁵ In another meta-analysis, OSA increased advanced spectrum from NAFLD with 2–3 folds increased risk of NAFLD and of advanced disease. This risk was present after controlling for traditional risk factors including patient's age, gender, degree of obesity, and body mass index.⁴⁵ Based on these data, it is recommended to screen obese patients with NAFLD for possible OSA and patients

with established OSA for underlying NAFLD. Another pulmonary issue in NAFLD patients is hyper responsive airways with asthma because of increased levels of leptin and generalized proinflammatory state in NAFLD.³⁸

NAFLD AND OSTEOPOROSIS

Chronic liver disease patients are at higher risk of developing metabolic bone disease; however, the relationship between osteoporosis and NAFLD is still poorly understood. A study among both children and adults suggested that patients with NAFLD had low bone mineral density compared with patients without NAFLD.⁴⁶ A large population-based study in China studied the prevalence of osteoporotic fractures and found that Chinese men with NAFLD had higher incidence compared with men without NAFLD (3.6% *vs.* 1.5%, $P < 0.005$). The increased risk was not seen among Chinese women. On multivariate regression analysis, the risk remained elevated among Chinese men independent of multiple potential confounders.⁴⁷ It should be noted that this assessment was based on self-report by the patients and not based on bone density evaluation. Screening guidelines for osteoporosis among NAFLD patients are as for any other patient. Clearly, further studies are warranted to explore and validate this association.

NAFLD AND COLORECTAL CANCER

Insulin resistance with hyperinsulinemia and proinflammatory state with oxidative stress mediate cellular proliferation and risk for malignancy. The risk is particularly observed for colorectal cancer, the third most common cancer worldwide with approximately 1.2 million cases diagnosed annually.⁴⁸ The incidence of colorectal cancer and adenoma is increased among patients with MetS; however, studies evaluating increased risk for colorectal cancer in patients with NAFLD have shown conflicting results.⁴⁹ In a meta-analysis of 5 studies on over 6000 patients, NAFLD was associated with about 2-folds risk of colorectal adenoma, the risk was highest among Asian population and among patients with NASH.⁵⁰ Despite having an increased risk, there was no association established between NAFLD and NASH with colorectal cancer. However, this analysis was limited with retrospective studies and short follow-up period of about 10 years. Hence, further large prospective studies are needed to establish the association between NAFLD and colorectal cancer. NAFLD patients are screened for colorectal adenoma or cancer as per current guidelines for any other patient. Other sites for increased cancer risk among NAFLD patients are breast, endometrium, prostate, kidneys, and esophagus. Specifically, in the esophagus, the risk is increased for gastroesophageal reflux with potential for Barrett's esophagus and subsequent adenocarcinoma of the esophagus.³⁸

NAFLD AND HYPOTHYROIDISM

Thyroid hormone is an important regulator of metabolic processes in the body. Additionally, hypothyroidism is associated with dyslipidemia and obesity, which in turn promote the progression of NAFLD.⁵¹ A systematic review of 11 studies with 12,924 participants found that the prevalence of hypothyroidism in NAFLD is 15.2–36.3%, and the prevalence was higher in NASH patients compared with those without NASH.⁵² On the other hand, prevalence of NAFLD was higher among patients with primary hypothyroidism including patients with subclinical disorder with upper normal thyroid stimulating hormone (TSH) levels. It is recommended to screen NAFLD patients annually for TSH levels.⁵¹ Further studies are needed to assess if there is any causal relationship between NAFLD and hypothyroidism and if thyroid replacement therapy has any impact on course of progression of liver disease.

NAFLD AND POLYCYSTIC OVARIAN SYNDROME

PCOS is a syndrome that affects women of reproductive age and manifests as hyper androgenism, cystic appearing ovaries, and oligomenorrhea. Like NAFLD, patients with PCOS have insulin resistance and obesity and are at higher risk of CVD. Additionally, up to 50% of patients with PCOS have hepatic steatosis.⁵³ One meta-analysis including 7 studies found that patients with PCOS had almost 4-fold increased prevalence of co-existing NAFLD.⁵⁴ PCOS women with NAFLD have a higher prevalence of MetS and more insulin resistance compared with patients without NAFLD, with no significant difference between the serum levels of androgenic hormones.^{54,55} Given the current evidence, careful screening and evaluation for NAFLD among PCOS patients is important given these patients are generally young and have high risk of developing long-term liver-related complications.

NAFLD AND SKIN MANIFESTATIONS

Patients with autoimmune chronic inflammatory skin disorder of psoriasis have higher prevalence of MetS and NAFLD. This association is directly proportional to severity of psoriasis.^{56,57} Whether incident psoriasis is higher among NAFLD patients remains unclear. It remains unclear whether this association is truly with psoriasis or because of drugs used to treat psoriasis, especially methotrexate. Other dermatologic issues in these patients due to underlying insulin resistance are acanthosis nigricans, keratosis, and hirsutism.³⁸ Further, obesity in these patients results in reduced skin barrier function with dysfunctional sweat and sebaceous gland activity. Further, obesity has mechanical impact leading to

Table 1 Principal Meta-analyses Examining Association Between Nonalcoholic Fatty Liver Disease and Various Comorbidities.

Comorbidities	Study	Type	Odds ratio (95% CI)
Cardiovascular disease	Zhou <i>et al.</i> , 2018	Meta-analysis	2.20 (1.67–2.90)
Incident type 2 diabetes	Marrison <i>et al.</i> , 2019	Meta-analysis	2.17 (1.77, 2.65)
Chronic kidney disease	Mantovani <i>et al.</i> , 2018	Meta-analysis	1.37 (1.20–1.53)
Obstructive sleep apnea	Musso, 2013	Meta-analysis	2.37 (1.59–3.51)
Colorectal cancer	Huafeng, 2014	Meta-analysis	1.74 (1.53–1.97)
Hypothyroidism	Mantovani, 2018	Meta-analysis	1.42 (1.15–1.77)
Psoriasis	Candia, 2015	Meta-analysis	2.15 (1.57–2.94)

CI: confidence interval.

higher prevalence of varicose veins with resultant effects of lymphedema, varicose ulcers, cellulitis, and fasciitis³⁸

NAFLD AND HEMATOLOGICAL DISORDERS

NAFLD is associated with increased ferritin levels, iron overload, and hepatic iron deposition. The degree and severity of iron overload in NAFLD patients is associated with degree of liver fibrosis and with risk for hepatocellular carcinoma^{58,59}. Although the body of evidence suggesting the association of increased ferritin level and liver injury in NAFLD is reasonably strong, few studies have found no clear association.^{60,61} In one of these studies, serum ferritin concentration did not predict fibrosis stage >1 in NAFLD patients, although the proportion of patients with fibrosis stage >1 in this cohort was relatively small.⁶⁰ Further, therapeutic phlebotomy in one study among NAFLD patients reduced the iron indices significantly, but without any effect on insulin resistance or hepatic histology.⁶² Additionally, these patients may develop anemia in response to phlebotomy in contrast to experience of phlebotomy among primary hemochromatosis patients. Proinflammatory activity with elevated levels of plasminogen activator inhibitor-I among NAFLD patients results in low level activation of the coagulation cascade, resulting in increased risk of thrombophilia and vascular thrombosis.⁵ Among patients with cirrhosis, NASH etiology is the leading cause for portal venous thrombosis. Further, transplant recipients for NASH cirrhosis compared with those without pretransplant portal venous thrombosis have higher risk for poorer post-transplant graft and patient survival.⁶³

During the past decade, it has become clear there is an increased risk of CVD, T2DM, and CKD among NAFLD patients (Table 1), with risk for mortality from causes other than liver related, especially from malignancy and cardiovascular causes. Physicians and patients with NAFLD (particularly with fibrosis/NASH) should be aware of these increased risks while managing patients with NAFLD. When appropriate, patients may benefit from appropriate pharmaceutical therapies including lipid lowering agent

and insulin sensitizers which will help to limit progression of NAFLD and decrease risk for extrahepatic manifestations. Further studies with longer follow-up are needed that collect detailed cardiometabolic risk profiles of these patients at baseline and over course of follow-up period for evaluating the impact of NAFLD as a systemic disease. Additionally, clinical trials examining the effect of treatment of NAFLD on risks and outcomes of its extrahepatic manifestations are warranted.

AUTHOR CONTRIBUTIONS

Raseen Tariq wrote the paper, Page Axley edited the paper, and Ashwani Singal edited, revised, and contributed with conceptual development.

CONFLICTS OF INTEREST

The authors have none to declare.

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