

## Extrahepatic Manifestations of Nonalcoholic Fatty Liver Disease

Andrew A. Li<sup>1</sup>, Aijaz Ahmed<sup>2</sup>, and Donghee Kim<sup>2</sup>

<sup>1</sup>Department of Medicine and <sup>2</sup>Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and encompasses a spectrum of pathology from simple steatosis to inflammation and significant fibrosis that leads to cirrhosis. NAFLD and its comorbid conditions extend well beyond the liver. It is a multisystemic clinical disease entity with extrahepatic manifestations such as cardiovascular disease, type 2 diabetes, chronic kidney disease, hypothyroidism, polycystic ovarian syndrome, and psoriasis. Indeed, the most common causes of mortality in subjects with NAFLD are cardiovascular disease, followed by malignancies and then liver-related complications as a distant third. This review focuses on several of the key extrahepatic manifestations of NAFLD and areas for future investigation. Clinicians should learn to screen and initiate treatment for these extrahepatic manifestations in a prompt and timely fashion before they progress to end-organ damage. (**Gut Liver 2020;14:168-178**)

**Key Words:** Nonalcoholic steatohepatitis; Cardiovascular disease; Metabolic syndrome

### INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined by the presence of hepatic steatosis in the absence of other causes for hepatic fat accumulation, most commonly significant alcohol use, medications and other causes of chronic liver disease. NAFLD encompasses a spectrum of liver disease ranging from isolated hepatic steatosis characterized by intrahepatic triglyceride accumulation (nonalcoholic fatty liver, NAFL), steatosis with inflammation and hepatocyte injury (nonalcoholic steatohepatitis, NASH), NASH with fibrosis that can progress to end-stage liver disease (NASH-related cirrhosis), and potentially hepatocellular carcinoma. NAFLD has become increasingly common, with estimates of prevalence in the United States ranging from

10% to 46%<sup>1-3</sup> and worldwide up to 25%.<sup>1,4</sup> Its rise in prevalence has closely paralleled with metabolic syndrome and individual components of metabolic syndrome such as central obesity, dyslipidemia, and type 2 diabetes mellitus (T2DM).<sup>5</sup> Although NAFLD is sometimes perceived as the hepatic manifestation of the metabolic syndrome, there is now a growing body of evidence that NAFLD may, in fact, be a key driver in metabolic syndrome. The hepatic involvement is just one component of a multi-organ manifestation of NAFLD, with effects on the cardiovascular, renal, and endocrine systems, as well as the risk of extrahepatic malignancies. In fact, the leading cause of mortality in patients with NAFLD is cardiovascular disease, followed by extrahepatic malignancies, and then liver-related mortality.<sup>6,7</sup> Therefore, physicians and patients should be aware of the multisystemic involvement of NAFLD without a clear pattern or order of clinical presentation. Therefore, a high level of clinical suspicion based on a patient risk profile is the most prudent approach. Widespread screening for NAFLD is not recommended at this time. This review will focus on the association between NAFLD and metabolic syndrome and the extrahepatic manifestations of NAFLD (Table 1).

### METABOLIC SYNDROME

The metabolic syndrome is typically defined by the presence of at least three of following risk factors: central obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein cholesterol. The metabolic syndrome is highly prevalent in subjects with NAFLD. The prevalence of metabolic syndrome increased with increasing body mass index (BMI), from 18% in nonobese NAFLD to 67% in obese-NAFLD in 304 subjects with NAFLD.<sup>8</sup> Eighty-eight percent of subjects with NASH had metabolic syndrome (vs 53% of subjects with NAFL).<sup>8</sup> The presence of metabolic syndrome carried a high risk of NASH and severe fibrosis among subjects

Correspondence to: Donghee Kim

Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94304, USA  
Tel: +1-650-497-9261, Fax: +1-650-498-5692, E-mail: dhkimmd@stanford.edu

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**Table 1.** Key Extrahepatic Manifestations of NAFLD

Extrahepatic manifestation	Key finding
Metabolic syndrome	Increasing prevalence of metabolic syndrome with progression of NAFLD, NASH, and severe fibrosis (18%–88%) Presence of metabolic syndrome associated with higher overall mortality in NAFLD
Visceral adiposity	Visceral adiposity carries a higher risk than subcutaneous adiposity for NAFLD
Type 2 diabetes	Insulin resistance is a common pathogenic mechanism for both type 2 diabetes and NAFLD, and more "severe" NAFLD is more likely to have incident diabetes Presence of type 2 diabetes in NAFLD increases mortality by 2.2-fold, and NAFLD increases the risk of microvascular diabetic complications
Cardiovascular disease	Cardiovascular disease is the primary cause of mortality in NAFLD, with multiple associations with cardiovascular disease events and subclinical markers More "severe" forms of NAFLD associated with higher risk of cardiovascular disease events and mortality
Chronic kidney disease	More "severe" NAFLD increases the likelihood of renal impairment, and improvement in hepatic disease may also improve renal function
Hypothyroidism	Subclinical and overt hypothyroidism link with NAFLD
Psoriasis	High prevalence of concurrent NAFLD and NASH in psoriasis
Polycystic ovarian syndrome	Polycystic ovarian syndrome and NAFLD share common risk factors in obesity and insulin resistance

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

with NAFLD after correction for sex, age, and BMI.<sup>8</sup> A recent study from the NASH Clinical Research Network reported that metabolic syndrome had a 40% increased risk of histology-confirmed NASH.<sup>9</sup> In an analysis using the National Health and Nutrition Examination and Survey (NHANES) III, the metabolic syndrome was independently associated with increased risk of overall mortality among subjects with NAFLD, although obesity was not associated with an increased risk of all-cause mortality in subjects with NAFLD.<sup>10</sup>

There may be a bidirectional relationship as well, with a study of approximately 1,000 participants of the Framingham Heart Study identifying that those with NAFLD at baseline were at higher risk to develop subsequent hypertension and T2DM than those without NAFLD, and those with elements of the metabolic syndrome were more likely to develop incident NAFLD.<sup>11</sup> Kwon *et al.*<sup>12</sup> showed that NAFLD was associated with a risk of having components of metabolic syndrome, and the association was stronger for nonobese NAFLD than for obese NAFLD. A meta-analysis reported that NAFLD, as diagnosed by either liver enzymes or ultrasonography, significantly increased the risk of incident metabolic syndrome during a 5-year follow-up period.<sup>13</sup> In a pooled population of 81,411, NAFLD was associated with increased risk of incident metabolic syndrome with a relative risk of 1.80 for alanine aminotransferase (last vs first quartile or quintile), 1.98 for gamma-glutamyltransferase, and 3.22 for ultrasonography.<sup>13</sup>

## VISCERAL ADIPOSITY

The prevalence of NAFL on biopsy in patients undergoing bariatric surgery for morbid obesity ranges up to 90%; NASH

was seen in 30% to 50%, and up to 5% had cirrhosis.<sup>14–17</sup> In addition, visceral adiposity appears to confer a higher risk for NAFLD compared to subcutaneous fat deposition. A longitudinal study of approximately 2,000 subjects identified that larger areas of visceral adipose tissue (VAT) at baseline was associated with higher incident NAFLD, with a hazard ratio (HR) of 2.23 in the highest quintile after adjusting for other factors, whereas an association with subcutaneous adipose tissue was nonexistent.<sup>18</sup> In contrast, higher areas of subcutaneous adipose tissue were longitudinally associated with regression of NAFLD.<sup>18</sup> Increases in VAT area over time also correlate higher likelihood of incident NAFLD, while a decrease in VAT over time was correlated with the likelihood of regressed NAFLD.<sup>19</sup> Within NAFLD, VAT area also predicts the likelihood of NAFL, NASH, and NAFLD with fibrosis, with higher areas of VAT associated with more advanced liver disease.<sup>20</sup> In summary, these data indicate that certain types of body fat are risk factors for NAFLD, whereas other types could reduce the risk for NAFLD. Visceral obesity is most likely an important target for future interventions in the treatment of NAFLD and advanced fibrosis.

## TYPE 2 DIABETES

NAFLD and T2DM share common pathogenic pathways including obesity and insulin resistance. NAFLD is insulin resistant and therefore does not adequately suppress hepatic glucose production, and patients with both T2DM and NAFLD often have poor glycemic control, as compared to those with only T2DM without NAFLD.<sup>21,22</sup> A recent meta-analysis in a pooled population of 296,439 subjects determined that NAFLD significantly increased the risk of incident T2DM with a pooled HR

of 2.22 (95% confidence intervals [CI], 1.84 to 2.60).<sup>23</sup> Subjects with more “severe” NAFLD were also more likely to develop incident diabetes.<sup>23</sup> However, there are likely complex bidirectional links between the two diseases. Approximately 75% of subjects with T2DM have concurrent NAFLD, and the diagnosis of NAFLD in subjects with T2DM increases the risk of all-cause mortality by 2.2-fold.<sup>24</sup> Microvascular diabetic complications are also seen at higher rates in T2DM patients with concurrent NAFLD as compared to those without, with higher rates of both diabetic nephropathy and retinopathy.<sup>25-27</sup> T2DM also appears to exert effects on the progression of NAFLD, with incident T2DM being the most predictive factor for progression of NAFLD to NASH and advanced fibrosis.<sup>28</sup>

## CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is the leading cause of mortality in patients with NAFLD. Classical CVD risk factors such as hypertension, dyslipidemia, insulin resistance, smoking, and central obesity, share a strong overlap with both the metabolic syndrome and risk factors for NAFLD.<sup>8</sup> These shared risk factors, many encapsulated by the metabolic syndrome, intimately link CVD and NAFLD, but there is growing evidence that the presence of NAFLD confers additional risk of premature CVD. This has potentially important clinical implications for risk factor reduction and screening. Additional shared risk factors between NAFLD and CVD are also emerging, along with altered levels of interleukin 6, adiponectin, tumor necrosis factor alpha, vitamin D, fibrinogen, plasminogen, vascular adhesion molecules, and C-reactive protein, with many of these being liver-synthesized proteins (Table 2).<sup>25,29-51</sup>

A large body of evidence links NAFLD with atherosclerotic plaque formation and subclinical markers of CVD.<sup>52</sup> Several cross-sectional studies linked NAFLD with increased carotid in-

tima-media thickness, a well-validated tool for assessing atherosclerosis in asymptomatic patients that independently predicts CVD events.<sup>53-55</sup> A meta-analysis including approximately 3,500 subjects also reported that NAFLD based on ultrasonography is significantly associated with carotid intima-media thickness and carotid plaques.<sup>56</sup> Presence of NAFLD is also independently associated in a dose-dependent manner with higher cardio-ankle vascular indices, a score which represents the stiffness of whole arterial segments from the aorta to the ankle that is closely associated with coronary atherosclerosis, cardiac function, hypertension, stroke.<sup>57</sup> Other case-control studies have also demonstrated an association of NAFLD with increase arterial wall stiffness,<sup>58,59</sup> altered endothelium-dependent flow-mediated vasodilation.<sup>29,60</sup> Large cross-sectional studies have also established the association between ultrasonography-defined NAFLD and coronary artery calcification independent of classical coronary risk factors.<sup>61-63</sup> These three studies include more than 20,000 subjects and used computed tomography-based coronary artery calcium scores<sup>61,63</sup> or coronary angiography<sup>64</sup> to determine coronary artery calcification. In a longitudinal study, NAFLD has also been shown to play an important role in the initial development of coronary artery calcification without any at baseline calcification.<sup>65</sup>

In terms of CVD events, epidemiological associations point to an association between NAFLD and the risk of cardiovascular events. In a study of 17,350 subjects without known liver disease or significant alcohol consumption, ultrasonographically-detected NAFLD was associated with an elevated 10-year risk of CVD as estimated using the Framingham risk score (FRS), independent of classical risk factors and other components of the metabolic syndrome.<sup>66</sup> NAFLD had an odds ratio (OR) of 1.35 (95% CI, 1.10 to 1.65) of higher 10-year risk of CVD with FRS >20 % in a multivariate model after for controlling for age, gender, BMI, waist circumference, and individual components

**Table 2.** Pathophysiologic Mechanism Linking NAFLD and Cardiovascular Disease

Pathophysiologic mechanism	References
Insulin resistance and type 2 diabetes	21,29-31
Obesity	14,15,17,20,21,32-34
Hypertension	5,8
Dyslipidemia	5,8,35
Increased: LDL, triglycerides, VLDL	
Decreased: HDL	
Proinflammatory mediators	
Increased: C-reactive protein, interleukin-6, tumor necrosis factor $\alpha$ , reactive oxygen species	36-41
Decreased: adiponectin	36,42-45
Altered coagulation and fibrinolysis	
Increased: fibrinogen, von Willebrand factor, plasminogen activator inhibitor	46,47

NAFLD, nonalcoholic fatty liver disease; LDL, low-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

of the metabolic syndrome. A recent meta-analysis including a pooled population of 34,043 adults showed that NAFLD significantly increased the risk of fatal and/or non-fatal CVD events during a median 6.9 years follow-up period, with a random effect OR of 1.64 (95% CI, 1.26 to 3.75).<sup>67</sup> More severe NAFLD was also more likely to develop fatal and nonfatal CVD events (OR, 2.58; 95% CI, 1.78 to 3.75).<sup>67</sup> Regarding mortality, an analysis of the NHANES III in the United States, with a mean follow-up period of 15 years for NAFLD as defined by noninvasive scoring systems demonstrated increased mortality from CVD in subjects with advanced fibrosis.<sup>7</sup> Indeed, another cohort study also supported the notion that more advanced fibrosis in NASH is associated with higher risk of CVD-related mortality and liver-related disease.<sup>68</sup> A multinational study of 458 patients with biopsy-confirmed NAFLD with bridging fibrosis or cirrhosis reported that patients with NAFLD cirrhosis have predominantly liver-related events, whereas those with bridging fibrosis have predominantly non-hepatic cancers and CVD events.<sup>69</sup>

Taken together, subjects with NAFLD are at high risk for CVD, including carotid and coronary atherosclerosis beyond what is explained by classical cardiovascular risk factors, visceral adiposity, and metabolic syndrome. Subjects with NAFLD should undergo careful cardiovascular surveillance. Moreover, those with the more severe forms of NAFLD need particular attention to ameliorate their high risk of CVD mortality.

## CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD), defined as decreased estimated glomerular filtration rate less than 60 mL/min/1.73 m<sup>2</sup>, abnormal albuminuria or overt proteinuria, is observed at high rates in subjects with NAFLD diagnosed by imaging or biopsy, ranging from approximately 20% to 50% in those with NAFLD compared to 5% to 25% in those without,<sup>25-27,70-79</sup> which in most studies was independent of common risk factors for CKD such as hypertension, T2DM, and other renal risk factors. A meta-analysis totaling nearly 64,000 subjects demonstrated that NAFLD, as diagnosed by either noninvasive scoring systems, imaging, or histology, was associated with an approximately 2-fold increase in both prevalent (OR, 2.12; 95% CI, 1.69 to 2.66) and incident CKD (HR, 1.79; 95% CI, 1.65 to 1.95).<sup>80</sup> There additionally appears to be a greater degree of renal impairment with histological severity of NASH.<sup>26</sup> Indeed, a meta-analysis mentioned earlier demonstrated that NASH was associated with a higher prevalence (OR, 2.53; 95% CI, 1.58 to 4.05) and incidence (HR, 2.12; 95% CI, 1.42 to 3.17) of CKD than NAFLD.<sup>80</sup> Additionally, advanced fibrosis was associated with a higher prevalence (OR, 5.20; 95% CI, 3.14 to 8.61) and incidence (HR, 3.29; 95% CI, 2.30 to 4.71) of CKD than non-advanced fibrosis.<sup>80</sup> More intriguingly, there is evidence that in patients with biopsy-proven NASH being treated with lifestyle modification over a year, improvement in NASH and histological findings were indepen-

dently associated with improvement in renal function.<sup>81</sup> Emerging mechanistic links between NAFLD and CKD include altered regulation of angiotensin-converting enzyme 2, impaired antioxidant defense mediated by nuclear factor erythroid 2-related factor-2, lipoprotein dysmetabolism, altered intestinal barrier integrity, and microbiome disturbances.<sup>82</sup> Although the mechanism of renal injury is postulated to be mediated primarily through atherogenesis, the absence of renal biopsies in studies examining NAFLD and CKD makes this an open question. These findings suggest that the strong association between NAFLD and CKD, including a relationship that appears to correspond with the severity of NAFLD, warrants clinical consideration in that improvement of NAFLD may also improve CKD, and that management of CKD and its sequelae should be incorporated in the care of patients with NAFLD.

## HYPOTHYROIDISM

The thyroid gland plays an integral part in maintaining metabolic homeostasis, with effects on obesity, dyslipidemia, and therefore may be linked with NAFLD.<sup>83</sup> Chung *et al.*<sup>83</sup> determined that subclinical hypothyroidism was related to NAFLD in a dose-dependent manner. A cross-sectional study of 2,324 cases with hypothyroidism with age- and sex-matched controls demonstrated a higher prevalence of NAFLD with both increased thyroid-stimulating hormone (TSH) and decreased free thyroxine (T4), including with subclinical hypothyroidism and overt hypothyroidism.<sup>83</sup> Multivariate analysis showed that subclinical and overt hypothyroidism are closely associated with NAFLD independent of the metabolic risk factors.<sup>83</sup> A study using biopsy-proven NAFLD cohorts identified a higher prevalence (21% vs 9.5%) of hypothyroidism versus controls matched for age, sex, ethnicity, BMI, and metabolic syndrome components.<sup>84</sup> A cross-sectional study of 425 subjects with biopsy-proven NAFLD determined that the prevalence of NASH and advanced fibrosis were significantly higher in subjects with low thyroid function (TSH  $\geq$ 2.5 mIU/L) versus strict-normal (TSH, 0.4 to 2.5 mIU/L) thyroid function (52.4% vs 37.2% for NASH, 21.0% vs 10.6% for advanced fibrosis,  $p < 0.01$ ).<sup>85</sup> Multivariate analyses showed that "low thyroid function" was significantly associated with NASH (OR, 1.61; 95% CI, 1.04 to 2.50) and advanced fibrosis (OR, 2.23; 95% CI, 1.18 to 4.23).<sup>85</sup> The effects of plasma TSH within the euthyroid range on histological damage associated with NAFLD, found that low-normal thyroid function (TSH, 2.5 to 4.5) may also produce negative health effects similar to overt and subclinical hypothyroidism.<sup>85</sup> Subclinical hypothyroidism, even in the range of upper normal TSH levels, was correlated to NAFLD in a dose-dependent manner.<sup>85</sup> This Asian study was confirmed by another study based on U.S. NHANES 2007 to 2012. The prevalence of advanced fibrosis was significantly higher in subjects with low-normal thyroid function and subclinical hypothyroidism than those with strict-normal thy-

roid function.<sup>86</sup> In this study, multivariate analysis showed that “low-normal” thyroid function and subclinical hypothyroidism were significantly associated with a 1.9-fold increase (OR, 1.94; 95% CI, 1.10 to 3.44) and 2.1-fold increase (OR, 2.05; 95% CI, 1.01 to 4.16) in the risk for advanced fibrosis, respectively (p for trend=0.005).<sup>86</sup> A recent study hypothesized that thyroid hormone receptor may activate hepatic stellate cells, suggesting the potential role of thyroid hormone signaling in hepatic fibrogenesis.<sup>87</sup> Currently, an orally administered, small-molecule liver-directed thyroid hormone receptor b agonist (MGL-3196) is under development for the treatment of NASH and hyperlipidemia.<sup>88,89</sup> This hypothesis remains an area of open investigation, and further studies are warranted to elucidate the exact role of thyroid dysfunction in the progression to NASH and related advanced fibrosis.

### POLYCYSTIC OVARIAN SYNDROME

Polycystic ovarian syndrome (PCOS) is characterized by hyperandrogenism, polycystic appearing ovaries, and oligomenorrhea or amenorrhea and occurs in 5% to 18% of women.<sup>90</sup> The prevalence of NAFLD within the PCOS population is estimated to be 15% to 55% depending on the diagnostic criteria and population.<sup>91</sup> Conversely, a small study of female patients at a liver clinic identified a prevalence of 71% for PCOS amongst reproductive-aged women with NAFLD, and those with PCOS had a high prevalence of NASH.<sup>92</sup> Indeed, several meta-analyses have demonstrated that in women with PCOS, there is a higher risk of co-existing NAFLD compared to matched controls with estimates ranging from 2.2-fold to 3.9-fold, independent of features of the metabolic syndrome.<sup>93-95</sup> Like NAFLD, PCOS is associated with T2DM and insulin resistance, with approximately 50% to 80% of women with PCOS exhibiting the latter.<sup>96</sup> Insulin resistance may directly contribute to the pathogenesis of PCOS. Interestingly, multiple studies have now shown that women with PCOS and hepatic steatosis have increased levels of insulin resistance compared to women with PCOS without steatosis.<sup>97,98</sup> In women with PCOS, elevated alanine aminotransferase levels were also associated with insulin resistance as measured by euglycemic hyperinsulinemic clamp measures whereas it is similar to healthy controls in those with normal alanine aminotransferase.<sup>99</sup> Similarly, approximately 60% of women with PCOS are also obese, and 50% have metabolic syndrome.<sup>91</sup> However, a recent study reported that women with PCOS had a higher prevalence of NAFLD than those without in nonobese population.<sup>100</sup> Hyperandrogenism was a risk factor for nonobese NAFLD irrespective of age, obesity, lipid profile, insulin resistance or glycemic status, suggesting an independent contribution of hyperandrogenism to NAFLD in nonobese women with PCOS.<sup>100</sup> What is clear from the data is that there are several common shared risk factors for both PCOS and NAFLD. Thus, careful evaluation for comorbid NAFLD and PCOS is warranted, especially in light

of data suggesting higher rates of NASH in this population.<sup>92</sup>

### PSORIASIS

Psoriasis is a chronic inflammatory disease with an estimated prevalence of 2% to 3%<sup>101</sup> and has been observed to have a higher prevalence in subjects with coexisting metabolic and/or obesity.<sup>101-103</sup> NAFLD is also observed at a higher prevalence in subjects with psoriasis. One study of 129 subjects with psoriasis or psoriatic arthritis found that NAFLD occurs in approximately 47% of subjects with psoriasis, and 22% of subjects with psoriasis also had biopsy-proven NASH.<sup>104</sup> Other studies have similarly observed this association and moreover demonstrated an adjusted OR of 1.7 for ultrasonographically-identified NAFLD in elderly subjects (age >55 years) with psoriasis as compared to those without, independent of alcohol consumption, smoking status, and presence of the metabolic syndrome.<sup>105</sup> Interestingly, NAFLD was also associated with severity of psoriasis independent of age, gender, BMI, duration of psoriasis, and alcohol consumption.<sup>106</sup> Psoriasis-associated NAFLD was more likely to have higher estimated liver fibrosis based on noninvasive scoring systems.<sup>107</sup> Whether psoriasis and NAFLD are caused by common underlying mechanisms, or if one affects the incidence of the other remains undefined. Notably, there exists evidence suggesting that patients with psoriasis, metabolic syndrome, and NAFLD treated with etanercept, a tumor necrosis factor  $\alpha$  inhibitor, as compared to those treated with psoralen-ultraviolet A had reductions in aspartate transaminase/alanine transaminase ratio, C-reactive protein serum levels, increased insulin sensitivity.<sup>108</sup> Prospective studies are still needed to determine the impact of biologic treatments on NAFLD in psoriasis.<sup>109</sup>

### TREATMENT

Currently, in the absence of approved effective pharmacologic treatment for NAFLD, the treatment of choice for NAFLD is weight loss with lifestyle modification. The same treatment strategy may be applied for extrahepatic manifestations, with lifestyle modification being a key component of treatment strategy in the control of blood glucose, blood pressure, hyperlipidemia, cardiovascular disease, and other risk factors.<sup>110,111</sup> In addition, clinicians should have a higher index of suspicion for common extrahepatic manifestations in patients with NAFLD. A proposed screening strategy for the more common extrahepatic has been proposed by VanWagner and Rinella,<sup>112</sup> which includes monitoring hemoglobin A1c, fasting glucose, blood pressure, lipid profile, urine microalbumin and albumin/creatinine ratio, estimated glomerular filtration rate, thyroid function tests, and ovarian ultrasound and/or serum androgens.

#### 1. Weight loss

According to the American Association for the Study of Liver



Disease practice guideline, loss of at least 3% to 5% of body weight may improve NAFLD, but a greater weight loss of up to 10% may be necessary to improve the degree of hepatic necroinflammation.<sup>113</sup> By the same token, sustained weight reduction by 5% to 7% may be sufficient to lower the risk of T2DM.<sup>114</sup> Recent intervention trials have shown a remarkable reduction in the risk of T2DM (of 42% to 67%) with weight reduction compared with control groups, even when the weight reduction was overall modest.<sup>114,115</sup> Weight loss is associated with improvement in cellular insulin signal transduction, peripheral insulin sensitivity, and insulin secretory responses.<sup>115</sup> Patients with patatin-like phospholipase domain-containing protein 3 (PNPLA3) NAFLD appear to be more sensitive to the beneficial effects of lifestyle modification on hepatic steatosis.<sup>116</sup> Two European studies showed that weight loss decreases intrahepatic triglyceride concentration<sup>117</sup> and liver enzymes<sup>118</sup> even more in subjects with homozygous GG than in those with homozygous CC. The pathophysiology of this finding is still unknown—the differences in insulin sensitivity between two alleles and the effect on abdominal obesity, which may modulate the effect of PNPLA3 G allele on liver damage, may provide the explanations.<sup>117,118</sup>

## 2. Diet

Several dietary strategies have potentially positive effects on NAFLD, metabolic syndrome, and CVD. Reduction in the total calorie consumption is a crucial aspect of lifestyle modification, though at this time there is no consensus recommendation for dietary interventions to treat NAFLD, metabolic syndrome, and CVD. Daily caloric intake varies according to ethnicity, sex, BMI, and comorbidities. To achieve the optimal caloric reduction, estimation of individual energy requirements and prescription of an energy deficit of 500 kcal/day or 30% of baseline is generally recommended.<sup>119</sup> In addition to the reduction of the total caloric intake, a change in the composition of the diet may be important in the treatment of NAFLD and comorbid metabolic syndrome and/or CVD. Subjects with NAFLD tend to consume more soft drinks and meat, and less fish rich in omega-3 fatty acids.<sup>120</sup> Recent systematic reviews have reported that restriction of dietary carbohydrate (e.g., simple carbohydrate and high glycemic carbohydrate) and fat (e.g., total and saturated fat) can lower the liver enzymes and/or reduce the grade of steatosis in subjects with NAFLD.<sup>121</sup> To the extent that high fructose is associated with NAFLD and advanced histology,<sup>122</sup> limiting fructose consumption may be beneficial.

## 3. Physical activity

Increased physical activity is thought to have a beneficial effect on NAFLD and comorbid conditions including metabolic syndrome and CVD by reducing visceral fat. Several studies have suggested that a reduction in hepatic fat was secondary to a reduction in visceral fat. Thus, the relationship between hepatic fat content and physical activity disappears when accounting

for intra-abdominal obesity,<sup>123-125</sup> although conflicting data exist.<sup>126-128</sup> In a large cross-sectional study, an inverse association between total and leisure-time physical activities and the prevalence of NAFLD was observed, independent of visceral adiposity and insulin resistance.<sup>129</sup> A recent prospective cohort study from our group demonstrated a lower risk of incident NAFLD in 4 years of follow-up based on physical activity level at baseline.<sup>130</sup> Furthermore, sustained or increased physical activity had a preventive effect on incident NAFLD, independent of visceral adiposity and insulin resistance.<sup>130</sup> In summary, increased physical activity is an important component of lifestyle modification in patients with NAFLD and comorbid extrahepatic manifestations, irrespective of visceral obesity or insulin resistance. However, there is no consensus regarding the most effective exercise regimen, such as duration and type of activities.

## CONCLUSION

Based on current evidence, the clinical burden of NAFLD extends well beyond liver-related morbidity and mortality. NAFLD can be associated with extrahepatic complications including CVD, CKD, T2DM, hypothyroidism, PCOS, psoriasis, and metabolic syndrome. Though the majority of evidence to date is observational and retrospective, these associations have important clinical significance in screening, risk factor modification, and potential therapeutics. For example, weight loss, smoking cessation, and dietary changes have the potential to affect the progression of NAFLD and its extrahepatic comorbid complications, but future studies will be needed to better understand the pathophysiology and to potentially alter the natural history of these conditions.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ORCID

Andrew A. Li <https://orcid.org/0000-0002-1295-8115>  
 Aijaz Ahmed <https://orcid.org/0000-0002-3609-8586>  
 Donghee Kim <https://orcid.org/0000-0003-1919-6800>

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