Non-Alcoholic Fatty Liver Disease: The Emerging Burden in Cardiometabolic and Renal Diseases

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As the number of individuals with non-alcoholic fatty liver disease (NAFLD) has increased, the influence of NAFLD on other metabolic diseases has been highlighted. Accumulating epidemiologic evidence indicates that NAFLD not only affects the liver but also increases the risk of extra-hepatic diseases such as type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, hypertension, cardiovascular or cerebrovascular diseases, and chronic kidney disease. Non-alcoholic steatohepatitis, an advanced type of NAFLD, can aggravate these inter-organ relationships and lead to poorer outcomes. NAFLD induces insulin resistance and exacerbates systemic chronic inflammation and oxidative stress, which leads to organ dysfunction in extra-hepatic tissues. Although more research is needed to identify the pathophysiological mechanisms and causal relationship between NAFLD and cardiometabolic and renal diseases, screening for heart, brain, and kidney diseases, risk assessment for diabetes, and a multidisciplinary approach for managing these patients should be highly encouraged.

Keywords: Arrhythmias, cardiac; Atherosclerosis; Diabetes mellitus; Hypertension; Insulin resistance; Metabolism; Non-alcoholic fatty liver disease; Obesity; Renal insufficiency; Stroke

INTRODUCTION

As the prevalence and incidence of obesity has dramatically increased worldwide, it has had a great impact on the development of obesity-related diseases, including type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), which is considered a global health threat to both individuals and societies. The substantial burden of obesity is not only limited to Western nations, but is also occurring in many Asian countries [1-3]. Recently, non-alcoholic fatty liver disease (NAFLD) has been recognized as the hepatic manifestation of metabolic syndrome [4] and established as a major leading cause of chronic liver disease [5]. Over the past two decades, the reported number of patients with NAFLD has increased, while the number of individuals with hepatitis B virus, hepatitis C virus, or alcohol-related liver disease remained stable [6]. The prevalence of NAFLD in Asia has been reported from 15% to 45% [3], and a quarter of the total Asian population is affected by this disease on average [7]. This high rate is similar to the global NAFLD prevalence [5].

NAFLD is characterized as the presence of more than 5% of lipid accumulation in the hepatocytes, excluding other liver disease etiologies (virus, autoimmune, alcohol, drugs, and genetics) [5]. NAFLD can progress to an advanced form, non-alcoholic steatohepatitis (NASH), which is defined by histological findings of hepatic steatosis with hepatocyte damage/inflammation [5]. Both NAFLD and NASH can further develop into liver fibrosis, cirrhosis, and eventually hepatocellular carcinoma (HCC). Although the reported incidence of HCC from NAFLD is rare, the number of patients with NAFLD-related
HCC or liver transplantation are continuously increasing, which might suggest a significant role of NAFLD in these end-stage hepatic complications [8,9].

NAFLD has been regarded as the hepatic phenotype of metabolic impairment [4], indicating one aspect of multisystem disease. In addition to obesity, aging and sarcopenia are also known to be crucial risk factors for NAFLD or NASH [10-12]. As aging gradually induces sarcopenia, which is linked to frailty, leading to the development of cardiometabolic and renal diseases as well as NAFLD or NASH, NAFLD can confer significant risks of morbidity and mortality in elderly patients in particular. The current review outlines the recent epidemiologic evidence of the extrahepatic complications of NAFLD and highlights the clinical relevance of NAFLD.

ASSOCIATION AND PROGRESSION TO CARDIOMETABOLIC AND RENAL DISEASES

Prediabetes and type 2 diabetes mellitus in NAFLD Traditionally, T2DM has been a well-known risk factor for NAFLD [12]. Although insulin resistance is common for both NAFLD and T2DM [13], several studies support that NAFLD per se can increase the risk of T2DM as well as prediabetes [14-17]. Furthermore, the degree of hepatic steatosis is positively associated with future T2DM risk in a dose-dependent manner [14,16]. In a large and healthy cohort study, individuals with NAFLD had a 2-fold higher risk for T2DM and the risk for T2DM was elevated up to 4-fold with an increase in hepatic fibrosis [16]. Even among the non-obese population, the impact of NAFLD on the incidence of impaired fasting glucose (IFG) and T2DM was strong [17]. Moreover, this association remained significant regardless of insulin resistance, obesity, and age [14], suggesting the direct role of NAFLD in the pathogenesis of T2DM. Although the incident risk for T2DM in NAFLD was not as high as that of IFG, the presence of NAFLD had an additive effect on future T2DM risk among subjects with IFG [15]. The severity of NAFLD, NASH, significant hepatic fibrosis, and HCC are all highly linked with diabetes; thus, modalities for screening diabetes should be implemented for individuals diagnosed with NAFLD [18].

Metabolic syndrome and dyslipidemia in NAFLD NAFLD is considered a strong predictor for metabolic syndrome and vice versa. Dyslipidemia can be involved in the development of NAFLD and also occurs as a complication of NAFLD [19]. Currently, 20% to 80% of NAFLD patients have dyslipidemia, mainly characterized as high triglyceride and low high-density lipoprotein cholesterol (HDL-C) [19]. Although the reported findings regarding low density lipoprotein cholesterol (LDL-C) levels are controversial, an increase or no difference in LDL-C levels or a higher proportion of small dense LDL were demonstrated across several studies [20-22]. Among the components of the lipid parameters, elevated non-HDL-C is the most frequently observed in the NASH population (low HDL-C in 63%, high triglyceride in 46%, high non-HDL-C in 73%, and high LDL-C in 16%) [23]. An 11-year follow-up study showed that NAFLD increased the incidence of metabolic syndrome by 50%; however, only two components of metabolic syndrome, waist circumference and triglyceride levels, had significant associations after multivariable regression analyses [24]. This evidence might support the possible role of NAFLD in the development of abdominal obesity and excessive levels of very low density lipoprotein (VLDL), which are essential components of insulin resistance, an underlying pathophysiology of metabolic syndrome. Both hepatic overproduction of VLDL and impaired lipoprotein clearance contribute to dyslipidemia in NAFLD [22]. According to the previous cross-sectional study, which revealed a strong association among liver fat contents, LDL particle size, and apolipoprotein B/A-I levels, atherogenic dyslipidemia might be driven from liver fat itself, independent of obesity [25]. Although the severity of NASH was not associated with abnormal lipoprotein profiles in this cohort [25], another study demonstrated that NASH can promote LDL-C oxidation [19].

Hypertension and atherosclerosis in NAFLD Prospective studies demonstrated that the incidence of hypertension increases in NAFLD and its rate is gradually elevated according to the degree of NAFLD [26-28]. The odds ratio (OR) of incident hypertension in individuals with NAFLD compared to those with normal livers ranges from 1.1 to 2.1, according to previous studies [26,27,29]. Moreover, among NAFLD individuals without incident hypertension, blood pressure tends to increase, and high-normal systolic blood pressure (130 to 139 mm Hg) is more prevalent [29]. In addition, dysregulated flow-mediated vasodilatation, increased thickness of intima-media, and plaques in carotid arteries, which are well-established surrogate markers for subclinical atherosclerosis, are exhibited in patients with NAFLD [20]. The carotid artery intima-medial thickness is increased in a
Cardiovascular disease in NAFLD

Given the strong association between NAFLD and diabetes, dyslipidemia, hypertension, and atherosclerosis, which are all established risk factors for CVD, it is not surprising that NAFLD subjects have a higher prevalence and incidence of CVD. In particular, CVD accounts for the most common cause of mortality in individuals with NAFLD [36], larger than the number of liver-related deaths [37]. The estimated 10-year CVD risk score is increased in individuals with NAFLD, and multivariable regression analyses demonstrate up to a 3.4-fold increase in CVD risk among advanced stages of hepatic steatosis [38]. In a meta-analysis analyzing 16 observational studies of 34,043 adults followed for 6.9 years, patients with NAFLD had a higher risk of fatal and non-fatal CVD events (OR, 1.64; 95% confidence interval [CI], 1.26 to 2.13) [39]. Furthermore, severe NAFLD, defined either by liver histology or by a combination of radiological imaging evidence and one of three components (high levels of serum γ-glutamyltransferase or NAFLD fibrosis score or high hepatic 18F-fluoro-2-deoxyglucose uptake on positron emission tomography), greatly increase the total incident CVD (OR, 2.58; 95% CI, 1.78 to 3.75) and fatal CVD events (OR, 3.28; 95% CI, 2.26 to 4.77) [39]. Metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and insulin resistance can contribute to the pathophysiologic progression of CVD in individuals with NAFLD. Beyond these traditional CVD risk factors, hyperuricemia, hypoadiponectinemia, and vitamin D deficiency are also involved in the association between NAFLD and CVD [40]. Of note, NAFLD and NASH per se could be regarded as emerging risk factors for CVD. The overall consensus states that screening for CVD is mandatory in all people, including adolescents and children with NAFLD [18].

Cardiac structure, function, and energy metabolism in NAFLD

Several limited case-control studies with a small number of participants provided consistent evidence that there are significant changes in cardiac structure, function, and energy metabolism in individuals with NAFLD who did not have a previous history of heart disease. Among subjects who did not have hypertension and diabetes, NAFLD was linked to early alterations in echocardiographic parameters that reflect diastolic function and geometry in the left ventricle of the heart, while no significant difference was found in systolic heart function [41,42]. In terms of myocardial metabolic abnormalities, individuals with hepatic steatosis show a reduction in myocardial energy metabolism assessed by 31P-magnetic resonance spectroscopy both in young and non-diabetic men [43] and in patients with T2DM [44]. Among patients with T2DM, those with NAFLD have impairment in myocardial perfusion and glucose uptake, but no difference in cardiac fatty acid metabolism as measured by positron emission tomography [44]. Insulin-resistant condition converts preference in the energy substrate utilization of the myocardium, which might induce oxidative stress, and subsequent hyperinsulinemia accelerates the growth of cardiomyocytes. Furthermore, the dysregulation in the energy metabolism of the myocardium can impair left ventricular contractility, resulting in an aggravation of fibrosis [45], which might lead to diastolic dysfunction.

Arrhythmias in NAFLD

Accumulating evidence strengthens the idea that NAFLD is an emerging risk factor for cardiac arrhythmias [46,47]. Among various types of arrhythmia, atrial fibrillation, QT prolongation, ventricular arrhythmias, and conduction defects are frequently reported in patients with NAFLD. In a prospective Finnish cohort of middle-aged adults, ultrasonographically defined NAFLD was an independent predictor of atrial fibrillation (OR, 1.88; 95% CI, 1.03 to 3.45) [48]. A recent cross-sectional study of a general population revealed that the mean QT interval increases according to the degree of steatosis in the liver (2.55 ms vs. 6.59 ms vs. 12.13 ms for mild, moderate, and se-
NAFLD beyond the liver

Alveolar septa

vere steatosis, respectively), and subjects with NAFLD had a 1.87-fold increased risk for QT prolongation [46]. The prevalence of ventricular arrhythmia detected by 24-hour Holter monitoring, including non-sustained ventricular tachycardia and frequent premature ventricular complex (>30 times per hour) was higher in individuals with NAFLD among the T2DM population (27.3% vs. 9.8%) [47]. In this cross-sectional study, NAFLD was associated with a 3-fold increased risk of ventricular arrhythmia after adjusting for history of other underlying cardiac diseases and metabolic covariates [47].

**Stroke in NAFLD**

While ischemic stroke is generally included as a composite endpoint of CVD that is significantly linked to NAFLD based on the previous section, few studies have investigated the direct association between stroke and NAFLD. A case-control study from Canada reported a 3.3-fold higher prevalence for ischemic stroke in patients with elevated alanine aminotransferase, a biomarker for NAFLD [49]. Although confounding factors such as diabetes or obesity are not fully adjusted, patients with biochemically defined NAFLD had more severe forms of stroke and worse functional outcomes compared to those without NAFLD in a prospective cohort of acute ischemic stroke patients [50]. Recently, a propensity-score matched case-control study from Korea revealed a strong association of ischemic stroke risk with liver fibrosis assessed by transient elastography (FibroScan; EchoSens, Paris, France), with the OR for ischemic stroke at 1.80 (95% CI, 1.46 to 2.23) per 1 kPa increase in liver stiffness, but not with liver steatosis per se [51]. This result might indicate the importance of liver fibrosis or NASH on the risk of ischemic stroke. Further prospective research is needed to confirm the complex link between stroke and the severity of NAFLD.

**Albuminuria and chronic kidney disease in NAFLD**

Although chronic kidney disease (CKD) is traditionally recognized as a complication of diabetes, obesity, and CVD, recent studies have clearly demonstrated the possibility that NAFLD directly affects kidney outcomes [52-55]. The prevalence of CKD in NAFLD patients ranged from 20% to 55%, an approximately 2-fold increase, compared to those without NAFLD (5% to 30%) [52]. A meta-analysis with individual participant data shows consistent findings that the presence and severity of NAFLD are associated with an increased risk and severity of CKD [55]. The NAFLD group had 2.1-fold and 1.8-fold increased risk of prevalent and incident CKD, respectively, and these risks were potentiated when they had NASH (hazard ratios [HRs] of 2.5 and 2.1 for prevalent and incident CKD, respectively) compared to those with simple steatosis [55]. Advanced fibrosis is 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 [55]. In addition, albuminuria is more prevalent in patients with NAFLD [53,54], and the impairment in kidney function is significantly associated with the severity of NASH histology [54]; thus, the presence of NAFLD and the severity of fibrosis can predict the development of CKD regardless of other risk factors. Further studies are warranted to investigate whether improvement in NAFLD can attenuate CKD progression, and efforts are needed for the early screening of renal function and albuminuria in NAFLD patients.

**Mortality in NAFLD**

The impact of NAFLD on overall mortality apparently differs according to its severity. In a community-based cohort study, the overall survival of NAFLD patients was lower than expected in the general population (standardized mortality ratio, 1.34; 95% CI, 1.01 to 1.76) [36]. Among NAFLD's causes of death, CVD was the most common (15.5% to 25%), followed by extrahepatic malignancies, and then liver-related diseases [36,37]. In the spectrum of NAFLD, simple steatosis is not associated with increased mortality [37,56], whereas NASH or advanced fibrosis, as defined by either biopsy or noninvasive fibrosis panels, showed approximately 1.14-fold and 1.66-fold to 1.85-fold increased risk for overall mortality in Swedish [37] and United States studies, respectively [56]. In addition, this decline in survival seen in advanced fibrosis or NASH is almost certainly from cardiovascular causes [56].

**POSSIBLE MECHANISM LINKING NAFLD TO CARDIOMETABOLIC AND RENAL DISEASES**

NAFLD shares a common denominator with cardiometabolic diseases and kidney diseases, such as insulin resistance, oxidative stress, and systemic inflammation. It has been reported that visceral adipose tissue and fat accumulation in the liver alter signals in lipid and glucose metabolism, resulting in inflammation and cellular injury in the liver and other organs [57]. Accelerated free fatty acid flux to the portal circulation induces oxidative stress and accumulated advanced glycation...
end-products promote vascular and renal damage [58]. In addition, endothelial dysfunction, hemodynamic alteration, and atherogenic dyslipidemia mediate prothrombotic and profibrogenic factors, stimulating organ dysfunction [31,33-35]. Recent emerging evidence has indicated that the intestinal microbiota and its dysbiosis can both affect the progression of NAFLD [59] and CVD [60] through chronic inflammation in the immune cells and insulin resistance [52]. Moreover, interorgan communications between the liver and affected organs may exist, which should be further investigated in future research (Fig. 1).

CONCLUSIONS

NAFLD is presently regarded as an emerging risk factor and essential phenotype of chronic metabolic disorder beyond benign liver disease. Accumulating evidence indicates that the presence and severity of NAFLD are strongly associated with the increased prevalence and incidence of other metabolic diseases, including diabetes, hypertension, atherosclerosis, CVD, diastolic heart dysfunction, arrhythmia, and CKD, which have considerable impacts on global healthcare. Taken together, individuals with NAFLD should be screened for these extra-hepatic disorders and early effective intervention on their lifestyle and the future development of a pharmacologic approach to treat NAFLD or NASH is necessary to further prevent future complications.

CONFLICTS OF INTEREST

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

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