Review Article

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Comorbidities and Metabolic Derangement of NAFLD

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Nonalcoholic fatty liver disease (NAFLD) is an increasingly common cause of chronic liver disease worldwide and is becoming a major public health problem. NAFLD has been recognized as a hepatic manifestation of metabolic syndrome linked with insulin resistance. Growing evidence supports that NAFLD is associated with systemic diseases such as cardiovascular disease (CVD), chronic kidney disease (CKD), type 2 diabetes, obesity, and metabolic syndrome. The majority of deaths in patients with NAFLD come from cardiovascular disease. These findings are strongly attributed to nonalcoholic steatohepatitis (NASH) rather than simple steatosis. NAFLD should be considered not only a liver specific disease but also an early mediator of systemic disease. The underlying mechanisms and pathogenesis of NAFLD with regard to other medical disorders are not yet fully understood. Further investigation is needed for future therapeutic strategies for NAFLD. This review focuses on the relationship between NAFLD and various comorbid diseases and metabolic derangement.

Key Words: Comorbidities, Non alcoholic fatty liver disease, Metabolic syndrome

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) includes a wide spectrum of liver conditions ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and advanced hepatic fibrosis [1]. The incidence of nonalcoholic fatty liver disease in adults and children is rapidly increasing due to ongoing epidemics of obesity and type 2 diabetes in Western and, more recently, in Asian populations [2-5]. Prevalence estimates for NAFLD range from 17% to 33% in general populations in Western countries and a high prevalence of NAFLD has been reported especially among patients with diabetes, estimated at 34-74% [6]. NAFLD is expected to soon become the most important contributor to the need for liver transplantation [7].

As a commonly encountered chronic liver disease [8], NAFLD has important clinical implications because it increases all-cause mortality in patients compared to the general population of the same age and sex [9]. NAFLD has the potential to progress to cirrhosis or hepatocellular carcinoma and carries an increased risk of liver-related morbidity and mortality [10,11]. A recent meta-analysis revealed that NAFLD diagnosed by either imaging or histology was associated with an increased risk of all-cause mortality (odds ratio [OR] 1.57, 95% confidence intervals [CI] 1.18-2.10) [12]. Interestingly, the main causes of mortality among patients with NAFLD were malignancy (28%) and CVD (25%). Liver-related mortality was the third cause of death in patients with NAFLD [12]. In addition to liver-related disease, NAFLD is associated with extrahepatic manifestations. Cumulative evidence suggests that NAFLD is linked to obesity, type 2 diabetes, dyslipidemia, and also predicts the clustering of risk factors for CVD [4,13-17]. NAFLD shares com-

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mon features with metabolic syndrome [18] and a growing body of evidence suggests that NAFLD is not only a surrogate marker of metabolic syndrome but also an independent risk factor for CVD, CKD and type 2 diabetes [19]. This review focuses on the recent clinical evidence supporting the association between NAFLD and extrahepatic comorbidities, including metabolic syndrome, CVD, and CKD.

NAFLD AND METABOLIC SYNDROME

Metabolic syndrome is a prevalent condition among patients with NAFLD. Approximately 90% of patients with NAFLD have more than one component of metabolic syndrome and about one-third of patients meet the criteria of metabolic syndrome [16]. The pathophysiology of NAFLD includes the intrahepatic accumulation of fat in the form of triglycerides, in which insulin resistance is believed to play an important role by facilitating the transport of free fatty acid into the liver from visceral fat stores or peripheral lipolysis [20]. A large body of studies reveals that several metabolic conditions, such as obesity, insulin resistance, diabetes mellitus, dyslipidemia, and hypertension are strongly associated with NAFLD [4,16,21].

The prevalence of NAFLD is high among patients with type 2 diabetes [21] and the incidence of type 2 diabetes is increased in patients with NAFLD (adjusted OR 3.51, 95% CI 2.28-5.41)[12]. Moreover, diabetes comorbid with NAFLD is associated with more severe hepatic inflammation, fibrosis and increased overall mortality compared to patients without NAFLD (hazard ratio [HR] 2.2, 95% CI 1.1-4.2) [22]. It is reported that approximately 50% of patients with hyperlipidemia have ultrasonographic evidence of NAFLD [23]. A recent large community-based study of 9,162 subjects without diabetes revealed that ApoB/AI ratio was closely associated with the prevalence of NAFLD independent of obesity and other metabolic components [24]. According to a recent prospective study of 22,090 Korean men, incident hypertension was significantly higher in patients with NAFLD compared to patients without NAFLD (45% vs. 32%) and the incidence rate was correlated with the severity of ultrasonography diagnosed NAFLD [25]. Metabolic syndrome represents a chronic inflammatory state that links insulin resistance, endothelial dysfunction, and CVD, and has also been reported in NAFLD [26,27]. Elevated C-reactive protein levels and inflammation markers have been reported in NAFLD reflecting a subclinical inflammation state related to insulin resistance that has also been related to metabolic syndrome [26-28]. All of these findings suggest that NAFLD is closely associated with metabolic syndrome and it is now widely accepted that NAFLD is a hepatic manifestation of metabolic syndrome [14,18].

NAFLD AND CARDIOVASCULAR DISEASE

Studies on the natural history of NAFLD have suggested that NAFLD is associated with increased risk of overall mortality and cardiovascular events compared to the general population. Importantly, CVD was a leading cause of death in subjects with NAFLD [10,11,29,30]. Considering that NAFLD shares many common risk factors with CVD, it can be predicted that CVD is closely implicated in NAFLD patient mortality [31]. To date, a large number of epidemiologic studies have supported this finding [10,11,29,30,32-36]. A recent meta-analysis of 40 cohort studies reported that NAFLD has increased overall mortality (OR 1.57, 95% CI 1.18-2.10) compared to the general population with higher rates of mortality in NASH compared with simple steatosis and with incident CVD and cardiovascular mortality increased in biopsy-proven or ultrasonography diagnosed NAFLD (OR 2.05, 95% CI 1.81-2.31; OR 2.16, 95% CI 1.88-2.49, respectively) [12]. In addition, Targher *et al.* reported that type 2 diabetic patients with NAFLD had a higher prevalence of CVD such as coronary artery disease (23.0% vs. 15.5%), cerebrovascular disease (17.2% vs. 10.2%), and peripheral vascular disease (12.8% vs. 7.0%) than subjects without NAFLD independent of traditional CVD risk factors and metabolic syndrome component [37-39]. Similar findings were reported in a study of patients with type 1 diabetes [40]. Another recent meta-analysis also suggests NAFLD is associated with increased CVD and is a strong independent predictor of CVD (OR 1.88, 95% CI 1.68-2.01) [41].

Cumulative data on subclinical markers of atherosclerosis have supported the association between NAFLD and the risk of cardiovascular events. Subjects with NAFLD have increased prevalence of subclinical atherosclerosis, exhibit-

ing an increase in carotid artery intima media thickness [42-46], a decrease in brachial artery endothelial flow mediated vasodilation as a marker of endothelial dysfunction [47], higher prevalence of vulnerable coronary plaques and coronary atherosclerosis [48-51], and increased arterial stiffness [52-54]. A prospective study of 1,225 Chinese showed that arterial stiffness determined by measurement of brachial-ankle pulse wave velocity is more increased in NAFLD compared to subjects without NAFLD independent of cardiovascular risk factors [55]. In addition, patients with NAFLD showed impaired left ventricular diastolic dysfunction, alteration in energy metabolism, and disturbance of cardiac rhythm compared to subjects without NAFLD [56].

In addition to macrovascular changes, NAFLD is also associated with microvascular complications, such as nephropathy, retinopathy, and neuropathy. Accumulating evidence has demonstrated that NAFLD is associated with increased prevalence and incidence of CKD, defined as presence of microalbuminuria, overt proteinuria or an estimated glomerular filtration rate (GFR) <60 ml/min/1.73 m2, in both non-diabetic and diabetic individuals [57]. Unlike the acceptance of the adverse effects of NAFLD on CKD, there remains controversy about the effect of NAFLD on retinopathy or neuropathy. A study of 2,103 patients with type 2 diabetes revealed that NAFLD is associated with an increased prevalence of proliferative / laser-treated retinopathy (OR 1.75, 95% CI 1.1-3.7) [58]. Similar findings were reported in patients with type 1 diabetes. NAFLD was associated with prevalent retinopathy (OR 3.31, 95% CI 1.4-7.6) in patients with type 1 diabetes [59]. A hospital based Chinese study of 1,217 patients with type 2 diabetes suggested that NAFLD was negatively associated with diabetic retinopathy, peripheral neuropathy, and nephropathy [60]. Another hospital based study of 929 Korean patients with type 2 diabetes reported that the prevalence of diabetic retinopathy was significantly lower in patients with NAFLD than those without NAFLD (33.0% vs. 70.2%, $p < 0.001$), and no difference was found in the prevalence of diabetic neuropathy [61]. However, in the both of the studies, patients with NAFLD were significantly younger and had a shorter duration of diabetes. Because NAFLD was diagnosed by ultrasonography, simple steatosis may not have been differentiated from steatohepatitis. Further, these studies include only Asian patients. Considering all this, there is the potential for selection bias in these studies. Further prospective studies are necessary to define the role of NAFLD on microvascular complications.

NAFLD AND CHRONIC KIDNEY DISEASE

Recently, several studies have reported that metabolic syndrome and insulin resistance are associated with an increased incidence of microalbuminuria and chronic kidney disease (CKD) [62-67]. CKD and NAFLD were linked to the same cluster of cardiometabolic risk factors including metabolic syndrome and its individual components [18,68-70]. Interrelations between NAFLD, insulin resistance, and metabolic syndrome raise the possibility that NAFLD can predict the development and progression of CKD [71-74]. Due to study population heterogeneity, and differences in NAFLD diagnostic modality, NAFLD severity reporting, and CKD definition used, the reported prevalence and incidence of CKD are largely discordant. However, most of the recent large population based and hospital based studies show that the prevalence and incidence of CKD was significantly higher in subjects with NAFLD [9,58,59,67,73-79]. According to a recent meta-analysis, NAFLD was associated with an increased prevalence (OR 2.12, 95% CI 1.69-2.66) and incidence (HR 1.79, 95% CI 1.65-1.95) of CKD and nonalcoholic steatohepatitis (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 independent of potential confounding factors including age, smoking, obesity, hypertension, and metabolic syndrome components [80].

The prevalence of CKD ranges from 16.1% to 31.7% in subjects with liver biopsy-proven or ultrasonography diagnosed NAFLD compared to 3.7%-21.6% for control [9,75-77]. The prevalence of CKD in patients with diabetes and comorbid NAFLD ranges from 12.7% to 54.4% compared to 4.5% to 24.2% in patients without NAFLD [58,59,67,78,79]. Two large prospective studies enrolling ultrasonography diagnosed NAFLD patients demonstrated that NAFLD was associated with the development of CKD independent of potential confounders [73,74]. In a cohort study of 8329 healthy Asian men with normal baseline kid-

ney function and no proteinuria, NAFLD was associated with incident CKD (crude relative risk [RR], 2.18, 95% CI 1.75-2.71) and this relationship remained significant after adjustment for age, GFR, triglyceride, and high-density lipoprotein cholesterol (adjusted RR 1.55, 95% CI 1.23-1.95) [73]. In another cohort study of 1,760 outpatients with type 2 diabetes, ultrasonography diagnosed NAFLD was associated with incident CKD (HR 1.69, 95% CI 1.3-2.6). After adjustments for multiple potential confounders, the association was not attenuated (HR 1.49, 95% CI 1.1-2.2) [74]. The effect of NAFLD on renal dysfunction was also observed in patients with organ transplantation. 5-year loss of kidney graft and mortality was increased in patients with NASH related transplantation compared to transplantation for other causes of cirrhosis (HR 2.30, 95% CI 1.10-5.10; HR 2.20, 95% CI 1.02-5.79, respectively). NASH could be a risk factor for more rapid and severe renal impairment following liver transplantation [81].

CONCLUSION

The prevalence of NAFLD is continuously growing worldwide and NAFLD is becoming a pandemic disease in concert with the ongoing epidemics of obesity, diabetes, and metabolic syndrome. NAFLD has a potential to progress to cirrhosis or hepatocellular carcinoma and has an increased risk of liver-related morbidity and mortality. However, morbidity and mortality is not confined to the liver. Patients with NAFLD have increased cardiovascular mortality. As a liver manifestation of metabolic syndrome, NAFLD is strongly linked to the cluster of cardiometabolic risk factors including metabolic syndrome and its individual components, and insulin resistance has an essential role in the pathogenesis of NAFLD. Growing evidence suggests that NAFLD is associated with metabolic derangement and other systemic morbidities. Furthermore, recently NAFLD has been recognized as an independent risk factor for metabolic syndrome, type 2 diabetes mellitus, CVD, and CKD and the severity of NAFLD is associated with disease manifestations. However, there remains a lack of studies specifying the severity of NAFLD due to the invasiveness of liver biopsy, and its unsuitableness as a screening tool for a population-based epidemiological study. More detailed prospective studies are needed. NAFLD deserves particular attention given that NAFLD could be a risk factor for the development of metabolic syndrome, CVD, and CKD.

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