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TOPIC HIGHLIGHT

2016 Nonalcoholic Fatty Liver Disease: Global view

Nonalcoholic fatty liver disease as a multi-systemic disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. NAFLD includes a wide spectrum of liver conditions ranging from simple steatosis to nonalcoholic steatohepatitis and advanced hepatic fibrosis. NAFLD has been recognized as a hepatic manifestation of metabolic syndrome linked with insulin resistance. NAFLD should be considered not only a liver specific disease but also an early mediator of systemic diseases. Therefore, NAFLD is usually associated with cardiovascular disease, chronic kidney disease, type 2 diabetes, obesity, and dyslipidemia. NAFLD is highly prevalent in the general population and is associated with increased cardiovascular morbidity and mortality. The underlying mechanisms and pathogenesis of NAFLD with regard to other medical disorders are not yet fully understood. This review focuses on pathogenesis of NAFLD and its relation with other systemic diseases.

Key words: Nonalcoholic fatty liver disease; Obesity; Insulin resistance; Cardiovascular effect; Multi-systemic disease

Core tip: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. NAFLD has been recognized as a hepatic manifestation of metabolic syndrome linked with insulin resistance. NAFLD should be considered not only a liver specific disease but also an early mediator of systemic diseases. Therefore, NAFLD is usually associated with cardiovascular disease, chronic kidney disease, type 2 diabetes, obesity, and dyslipidemia. This review focuses on the pathogenesis of NAFLD and its relation with other systemic diseases.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of diseases from simple steatosis, nonalcoholic steatohepatitis, to liver cirrhosis[1]. The overall prevalence of NAFLD varies between 20% and 50% in Western countries, and it is accepted as the most common type of chronic liver disease[2,3]. Fatty liver and NAFLD occur in all age groups, and its prevalence increases with increases in body weight. Fatty liver is found in 10%-15% of normal weight individuals and 70% of obese subjects[4]. The distribution of excess fat is important, as increased visceral fat increases the risk of hepatic steatosis both in lean and overweight individuals[5].

NAFLD is closely related to obesity, type 2 diabetes mellitus, and dyslipidemia, with a prevalence ranging from 50% to 90% in these patient subgroups[6-8]. Most patients have "simple steatosis" or non-alcoholic fatty liver (NAFL) without inflammation, tissue damage, or fibrosis. However, in a subgroup of patients, nonalcoholic steatohepatitis (NASH), fibrosis, and/or cirrhosis may develop. Progression is more likely in the setting of diabetes, insulin resistance (IR), and other preexisting conditions[4]. The fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD[9]. Biopsy is the gold standard technique for the detection of liver fibrosis, but it may have some disadvantages, such as insufficient sampling, high cost, processing site pain, and intraobserver and interobserver variability[10,11]. It should be reserved for patients with ultrasound-proven fatty liver who have risk factors for NASH or elevated liver enzymes without definitive diagnosis[12]. Consequently, patients with NAFLD who are diagnosed with advanced fibrosis or cirrhosis should be included in surveillance programs that utilize ultrasonography and endoscopy. In addition, recent data have shown that advanced fibrosis in NAFLD predicted not only liver-related mortality but also increased mortality due to cardiovascular events[9,13]. Furthermore, NASH was associated with more metabolic abnormalities compared with NAFL[14], and the increasing severity of NASH was shown to affect adversely renal function[15]. There is some debate about whether NAFL without inflammation is associated with kidney related events. This review focuses on the pathogenesis of NAFLD and its relation with other systemic diseases.

DEFINITION AND PATHOGENESIS

The hallmark histologic feature of NAFLD is the accumulation of fat in the form of triglycerides in hepatocytes without signs of secondary hepatic fat accumulation due to alcohol consumption, steatogenic medication, or hereditary disorders[16]. In 1999, Matteoni *et al*[5] presented the first diagnostic criteria to categorize NAFLD into four different subtypes: NAFLD type 1 with fatty liver alone; type 2 with fatty liver plus lobular inflammation; type 3 with fatty liver plus ballooning degeneration; and type 4 with fat accumulation, ballooning degeneration, and either Mallory-Denk bodies or fibrosis. They revealed that cirrhosis developed in 21%-28% of patients whose liver biopsies displayed NAFLD type 3 or 4, whereas only 4% of patients with NAFLD type 1 and none of those with type 2 developed cirrhosis after a mean follow-up of 10 years. There was a trend for increased liver-related mortality in patients with subtypes 3 and 4 compared with subtypes 1 and 2. Today, subtypes 3 and 4 are considered as NASH[17].

Hepatic lipid content is regulated by balancing hepatic lipid uptake, synthesis, oxidation, and export. Most of the triglycerides are re-esterified fatty acids that come from adipose tissue lipolysis into the liver. Adipose tissue IR is present in the majority of patients with NAFLD, whether they are obese or not[18], and adipose tissue lipolysis provides approximately 60% of the fatty acids used for hepatic triglyceride synthesis. The rest of the hepatic fatty acids come from *de novo* lipogenesis within the liver (25%) and dietary intake (15%)[19]. Excess hepatic fat results in increased very low-density lipoprotein (VLDL) secretion and some of the serum lipid abnormalities noted in metabolic syndrome and NAFLD, including hypertriglyceridemia, decreased high-density lipoprotein (HDL), and higher low-density lipoprotein (LDL)[20]. However, the increased export of triglycerides as VLDL is unable to compensate for the increase in intra-hepatic triglycerides. The high serum glucose and insulin associated with IR further impair liver lipid metabolism by increasing the activity of carbohydrate response element-binding protein (ChREBP) and sterol regulatory-element binding protein 1c (SREBP-1c), the master regulator of hepatic *de novo* lipogenesis[21]. Net lipid accumulation, specifically buildup of the triglyceride precursor diacylglycerol, leads to activation of a serine kinase cascade. This, in turn, inhibits insulin signaling, leading to IR in the liver[22,23].

IR has a strong association with both hepatic steatosis and NASH[18]. In 1998, Day *et al*[24] presented a "two hit" hypothesis to describe the pathogenesis of NAFLD whereby IR contributes to steatosis (first hit), which sensitizes the liver to oxidative stress (second hit) resulting in inflammation, fibrosis, and necrosis[24,25]. Additional theories, such as the multiple-hit hypothesis, suggest other factors, including adipokines and mitochondrial dysfunction, may also contribute to NAFLD[26]. At present, the precise factors leading to inflammation remain unclear, with various metabolites, cytokines, inflammatory cells, and dysregulated processes, such as oxidative stress and autophagy, having been implicated[27]. Elevated fatty acid β-oxidation as a result of increased lipolysis of adipose tissue in NAFLD patients increases reactive oxygen species and activates oxidative stress[28]. The hepatic lipid accumulation and intracellular stresses activate the transcription and release of pro-inflammatory factors, such as

interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and C-reactive protein[29,30]. A sedentary lifestyle in conjunction with excessive energy intake promotes obesity and dysfunction of white adipose tissue. White adipose tissue secretes more TNF-α and IL-6 and reduces the secretion of adiponectin[30]. Elevated circulating levels of pro-inflammatory cytokines and reduced levels of anti-inflammatory factors cause a chronic low-grade inflammatory state that is recognized as an important pathogenic mechanism of NAFLD. Among clinical associations, diabetes and metabolic syndrome, advanced age, Hispanic ethnicity, female sex, and obesity are all related to more aggressive liver histology but without a clear distinction of cause and effect[31].

On genetic basis, a lot of single nucleotide polymorphism (SNP) have been identified by genome-wide association studies (GWAS)[32]. Romeo *et al*[33], was the first to report that the rs738409 C>G SNP in the Patatin-like phospholipase domain-containing 3 (PNPLA3) gene, which encodes an isoleucine to methionine variant at protein position 148 (I148M), was strongly associated with increased liver fat content. Since then, several other pieces of evidence have highlighted the role of PNPLA3 in the development and progression of NAFLD. Furthermore, transmembrane 6 superfamily member 2 (TM6SF2) E167K variant is currently emerging as another relevant contributor both for NAFLD pathogenesis and cardiovascular outcomes. Recently, Goffredo *et al*[34] revealed that rs58542926 SNP in the TM6SF2 gene was associated with pediatric NAFLD but may confer protection against cardiovascular risk. As of today, the PNPLA3 gene variant is the most validated susceptibility factor for steatosis, NASH, fibrosis, and hepatocellular carcinoma (HCC), despite a number of other genetic variants contributing to liver damage.

The gastrointestinal tract contains the largest number of bacteria in the human body and serves a variety of physiologic functions, including an active role in glucose and lipid metabolism. The commensal organisms that populate the human gut are dominated by four main phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*. Since the liver and intestine are connected anatomically and *via* the hepatic portal system, the gut microbiota and their metabolic products may influence hepatic pathology[35]. The liver is exposed to metabolites originating from intestinal bacteria (such as ethanol and other volatile organic compounds) or the bacteria themselves[36]. The liver acts as a barrier between the gut and the systemic circulation by removing toxins. When Kupffer cells, the specialized macrophages in the hepatic sinusoids, are impaired, or when the gut mucosal barrier is damaged by inflammation or portal hypertension (HTN), a metabolic endotoxinemia may be developed. The high endotoxin level activates Kupffer cells and hepatic stellate cells. Bacteria can also produce lipopolysaccharides, which bind to Toll-like receptor 4 and activate the production of proinflammatory cytokines, subsequently resulting in inflammation[37]. These events may contribute to the pathogenesis of obesity and NAFLD[38,39]. Furthermore, probiotics may modulate gut microbiota, reduce inflammation, increase epithelial barrier function, and increase antibacterial substance production[36]. Current data with probiotic treatment should be considered with caution since related studies were conducted with small group sizes without dietary control. The use of probiotics for NAFLD is not recommended at this moment[40]. The standard treatment of patients with NAFLD has been accepted as weight loss through diet and exercise.

CARDIOVASCULAR DISEASES AND NAFLD

One of the most important mortality and morbidity reasons of NAFLD are cardiovascular events. Multiple pathogenetic conditions contribute to the development of cardiovascular diseases (CVD). Firstly, high levels of LDL have been identified as the most important culprit. The molecular mechanism responsible for the high levels of LDL, oxidized LDL, and their receptors have been clarified, and strategies against high LDL levels have been established using effective cholesterol-lowering drugs, such as statins. Impaired glucose tolerance, HTN, and lipid disorders, including hypertriglyceridemia and low levels of HDL, were recognized as weaker risk factors for CVD compared with high level of LDL. However, the coexistence of multiple risk factors apart from LDL is considered as important as hypercholesterolemia. Such disorders are commonly found in obesity and NAFLD but not in all NAFLD patients. The distribution of excess fat is important in NAFLD patients, as increased visceral fat increases the risk of hepatic steatosis both in lean and overweight individuals[5]. Visceral fat accumulation contributes to the development and/or worsening of various disorders, such as glucose intolerance, hyperlipidemia[41], HTN[42], cardiac dysfunction[43], and sleep apnea syndrome[44]. Even in mildly obese individuals, visceral adiposity is related to a cluster of risk factors and coronary artery disease (CAD)[45]. Recent results from the Framingham Heart study revealed that there was a significant association between NAFLD and subclinical CVD outcomes, independently of many metabolic diseases[46]. Nevertheless, it is not clear if this increased CVD risk is conferred by the presence of several CVD risk factors associated to the metabolic syndrome, which are common in patients with NAFLD, or if NAFLD might be itself a mediator of atherosclerosis.

One of the earliest manifestations of atherosclerosis is the presence of endothelial dysfunction, occurring even in the absence of angiographic evidence of disease. Brachial artery flow-mediated dilation (FMD)

is the most often noninvasive test used for assessing endothelial function as the result of endothelial release of nitric oxide[47]. An impaired FMD was found in a wide variety of CV and metabolic diseases associated to chronic low-grade inflammation, oxidative stress, and metabolic abnormalities[48,49]. Moreover, FMD predicted future CV events in patients with[50] and in those without CVDs[51]. Recently, some studies revealed that NAFLD might affect endothelial function independently from other CVD risk factors, thus suggesting that CVD risk of patients with NAFLD could not be explained entirely by conventional CVD risk factors[52,53]. Increased carotid intima-media thickness (CIMT) is a marker of early generalized atherosclerosis and is associated with increased risk of myocardial infarction, cerebrovascular accident, and peripheral vascular disease[54]. An increasing number of studies, predominantly involving Western population, indicates that the presence of NAFLD is associated with higher CIMT, indicating increased cardiovascular risk[55,56]. Thakur *et al*[57] showed that thicker CIMT and a higher prevalence of atherosclerotic plaques and endothelial dysfunction were observed in patients with NAFLD as compared to those without NAFLD in the Indian population. The presence of NAFLD was independently associated with higher CIMT and impaired FMD, even after taking into account adiposity, blood pressure, lipid levels, and the presence of metabolic syndrome.

Expansion of dysfunctional visceral adipose tissue along with infiltration of mononuclear cells (MNCs) lead to initiation and propagation of inflammatory pathways contributing to IR. Increased expression of inflammatory mediators like inhibitor of kappa light polypeptide gene enhancer in B cells-kinase beta, protein-kinase C-beta 2, suppressor of cytokine signalling-3, and nuclear factor kappa B has been indicated in MNCs from obese subjects[58]. These inflammatory mediators disturb insulin signaling by inhibiting the phosphorylation of insulin receptor (INSR) beta subunit and reducing INSR activity[58]. Increased hydrolysis of adipose tissue triglycerides and flux of free fatty acids to liver result in hepatic steatosis. This coupled with chronic low grade inflammation may progress to steatohepatitis. However, injured liver itself may contribute to systemic inflammation as indicated by increased transcription of proinflammatory genes[59]. Increased production of proinflammatory cytokines by the liver may not only contribute to the progression of liver injury but also induce the proatherogenic effect. Elevated levels of CRP have been observed in patients with NAFLD as compared to controls, with the levels being higher in those with steatohepatitis than in those with simple steatosis[56]. Additionally, chronic inflammatory state in patients with NAFLD is associated with increased expression of biomarkers of endothelial dysfunction. Elevated levels of sICAM-1 have been consistently associated with endothelial dysfunction[60]. In a recent study, patients with NAFLD were observed to have elevated levels of sICAM-1, plasminogen activator inhibitor-1, and soluble CD40 ligand as compared to controls[61]. Uric acid was regulated by a decrease in CPS 1 (a ligase enzyme located in the mitochondria), and it was shown to erect pro-inflammatory and pro-oxidant effects both on adipose tissue and vascular smooth muscles[62,63]. Uric acid may also contribute to IR by inducing local adipose tissue inflammation, which may cause a reduction in the production of adiponectin[64]. Another link may be adiponectin between NAFLD and atherosclerosis[65]. Adiponectin is an adipocyte-specific protein that is abundantly present in the plasma. Since its discovery, numerous experimental and clinical studies have demonstrated that adiponectin has anti-atherogenic, anti-diabetic, and anti-inflammatory properties. Some studies demonstrated the presence of lower adiponectin levels in patients with NASH diagnosed by liver biopsy compared with body mass index-matched controls, or subjects with simple fatty liver, and that in patients with NASH, hypoadiponectinemia correlated with necroinflammatory changes of the liver independent of IR[66,67]. Furthermore, it is well known that adiponectin suppressed (1) tumor necrosis factor alpha-induced expression of adhesion molecules in vascular endothelial cells by inhibiting the nuclear translocation of NF-κB[68]; (2) growth factor-induced proliferation of smooth muscle cells by inhibiting mitogen activated protein kinase pathways[69]; and (3) foam cell transformation of macrophages by suppression of class A scavenger receptor expression[70]. These data suggested that adiponectin provided protection against the development of atherosclerosis. Some clinical studies supported that theory. One of them showed significantly lower plasma concentrations of adiponectin in patients with acute myocardial infarction and unstable angina pectoris compared to those in patients with stable angina pectoris and control subjects[71]. Among patients with CAD, plasma adiponectin levels are lower in subjects with complex coronary lesions associated with plaque vulnerability[72].

Some studies revealed an association between NAFLD and arterial stiffness[73,74]. Arterial stiffness has been shown to be an independent indicator of symptomatic CVD and events as well as a measure of vascular health[75,76]. Arterial stiffness was assessed by carotid-femoral pulse wave velocity (PWV), brachial-ankle pulse wave velocity, or arterial stiffness index. Carotide-femoral PWV has been considered the non-invasive gold standard measure of arterial stiffness. Two studies reported the association of NAFLD with carotid-femoral PWV. In both studies, NAFLD independently increased the carotide-femoral PWV[77,78]. Similarly, in a study of non-hypertensive, non-diabetic individuals without metabolic syndrome, Kim *et al*[79] reported that NAFLD independently predicted increased brachial-ankle PWV. The mechanism underlying the relationship between NAFLD and arterial stiffness is not completely understood. Studies have shown that insulin-resistant states are associated with decreased endothelium-

dependent vasodilation and arterial compliance may be a partially nitric oxide-dependent process[80]. In addition, insulin has been shown to induce vascular smooth muscle proliferation and migration in cell culture[81]. Of interest, recent evidence indicates that TGF-β changes in adventitial collagen may play a role in arterial stiffening[82]. Furthermore, pro-fibrogenic markers, such as endothelin 1 and insulin like growth factor-1, can lead to arterial stiffening[83].

Studies in patients with metabolic syndrome (MetS) have consistently shown increased left ventricular (LV) mass index and diastolic function impairment when compared with controls, which are in the main secondary to the effects of IR, obesity, and HTN on cardiac structure and function[84,85]. Some studies have focused specifically on NAFLD subjects, and the finding of abnormal LV geometry and diastolic dysfunction has been similarly reported[86,87]. Additionally, Kim *et al*[88] found that NAFLD was associated with LV diastolic dysfunction independently of traditional risk factors. Multiple mechanisms may contribute to LV dysfunction in NAFLD, including lipotoxicity associated with cardiac steatosis and lipoapoptosis, alterations in fatty acid metabolism, overproduction of cardio-inhibitory cytokines, upregulation of some neurohormones (especially angiotensin Ⅱ), myocardial fibrosis and chronic overload with LV dilatation and hypertrophy, and increased oxygen consumption[89-91]. IR may represent a link between NAFLD and LV dysfunction. Elevated insulin levels in patients with IR stimulate myocyte growth and interstitial fibrosis. Insulin also causes sodium retention and activates the sympathetic nervous system, which can affect cardiac performance[90,91]. Moreover, alterations in myocardial metabolism, including progressive increases in fatty acid turnover, may impair LV contractility[89]. Finally, chronic sodium retention increases blood pressure levels, which in turn cause myocardial tissue damage, myocardial fibrosis, and impairment of the LV function in response to LV pressure overload[92]. The other possible explanation is that increased aortic stiffness may also increase afterload, which induces myocardial structural changes of the left ventricle and impairs LV diastolic function[73]. Recently, Nakamori *et al*[93] revealed that patients with fatty liver showed decreased myocardial perfusion reserve (MPR) compared to patients without fatty liver. Altered MPR may indicate an early alteration in myocardial tissue and vascular properties in patients with fatty liver. The presence and severity of fatty liver on computed tomography (CT) were closely associated with reduced MPR, independent of classical risk factors. Based on this study, it may be speculated that patients with NAFLD might be prone to subendocardial ischemia in cases of hemodynamic compromise.

Another issue that needs to be discussed is the increase in prothrombotic activity in patients with NAFLD. Platelets producing vasoactive and prothrombotic factors like IL-1β and CD40L play an important role in atherothrombosis[94]. Mean platelet volume (MPV), a simple and inexpensive test, is commonly used to measure platelet size and is also a marker of platelet activity[94]. MPV has been associated with CVD risk factors like diabetes[95], HTN[96], and dyslipidemia[97]. MPV is also associated with acute myocardial infarction[98], arterial and venous thrombosis[99], and ischemic strokes[100]. Recently, Madan *et al*[101] published a meta-analysis suggesting that MPV is significantly higher in patients with NAFLD, indicating the presence of increased platelet activity in such patients. The pathophysiological mechanism for increased platelet volume observed in NAFLD is not yet clearly understood; however, a plausible explanation might be that NAFLD is a chronic inflammatory condition, with increases in various inflammatory mediators, like IL-1, IL-6, and TNF-α[102]. Platelets have been known to respond to these inflammatory mediators by alteration in size measured as MPV[99]. Obesity and the MetS are known to be associated with an increased risk of thromboembolic events[103]. An increase in plasminogen activator inhibitor 1 (PAI-1), fibrinogen, factor Ⅷ, and von Willebrand factor and a decrease in antithrombin Ⅲ are most frequently reported. Recently, Verrijken *et al*[83] showed that NAFLD and NASH independently contributed to the prothrombotic state in obesity by increasing PAI-1, whereas other prothrombotic factors were unaffected by liver status. Large epidemiological studies have shown that elevated plasma level of PAI-1 is a predictor of myocardial infarction[104]. PAI-1 levels are related to the severity of vessel wall damage and are good predictors of subsequent development of a first acute myocardial infarction[105]. It may be hypothesized that the increase in PAI-1 levels by the steatotic and inflamed liver, at least in part, explains the observed link between NAFLD and increased cardiovascular risk.

There is some debate about the association between NAFLD and coronary artery calcification (CAC). Because the CAC score indicates the presence and extent of coronary atherosclerosis, it is not surprising that many studies have reported that a high CAC score is a marker for an increased risk of coronary events[106]. Thus, a CAC score of zero is associated with a very low risk of subsequent coronary events[106], whereas an elevated CAC score is related to a stepwise increase in the risk of subsequent coronary events[106,107]. Several prior studies have demonstrated an increased burden of CAC among individuals with NAFLD independent of traditional risk factors and measures of abdominal adiposity[108,109], whereas others have not[110,111]. However, many of these studies that find a positive correlation included ethnically homogeneous populations of either Africans or Eastern Asians (Taiwan, Korea, Japan). In a sub-study of the Multi-Ethnic Study of Atherosclerosis, 398 participants underwent multi-detector CT to detect liver fat, and no associations were observed with CAC after adjustment for CVD risk factors in a multi-ethnic population[110].

The QT interval represents the duration of electrical depolarization and repolarization of the ventricle. A prolonged QT interval reflects a lengthening of this vulnerable period and increases the risk of malignant arrhythmias[112]. Extreme prolongation of the QT interval is also associated with sudden cardiac death. Moreover, the duration of the QT interval, even within a reference range, is a predictor for cardiovascular death in the general population[113,114]. The QT interval has been shown to be related to cardiac and metabolic disorders, including HTN, diabetes, obesity, and CAD[114,115]. In a recent report of 400 patients with type 2 diabetes, the presence of NAFLD was associated with QT prolongation after adjustment for established confounders[116]. Furthermore, Hung *et al*[117] showed that the severity of NAFLD was associated with prolonged QTc intervals and higher risk for QTc prolongation in the general population with or without diabetes. Their findings suggest that NAFLD-associated QT prolongation might be a link to adverse cardiovascular outcomes among these patients. Recently, two important studies revealed that NAFLD is strongly associated with an increased incidence of atrial fibrillation (AF) in patients with type 2 diabetes even after adjustment for important clinical risk factors for AF[118] and independently associated with the risk of AF in the general population[119]. Increased systemic inflammation and autonomic dysfunction may play a role in the development of AF in patients with NAFLD. Additionally, preliminary studies indicate that there is a strong relationship between NAFLD and early LV diastolic dysfunction in both non-diabetic and type 2 diabetic individuals[73,86]. It is likely that LV diastolic dysfunction plays a role in AF pathogenesis either by increasing pressure that can affect stretch receptors in pulmonary veins triggers and other areas of the atria or by inducing direct structural changes in atrial myocardium[120,121]. It may be thought that the increased incidence of AF may cause an increase in cardiovascular morbidity and mortality in patients with NAFLD.

HTN AND NAFLD

Compared with those with normal blood pressure (BP), prehypertension (PHT) increases the risk of HTN by two to six-fold over 4 years[122]. PHT is also associated with increased risk of mortality and other major cardiovascular events, such as myocardial infarction, stroke, and congestive heart failure[123,124]. Recent studies suggest an independent association between NAFLD and HTN[125,126], and when present among hypertensive patients, NAFLD is associated with CVD complications, such as LV hypertrophy, ventricular dysfunction, and cardiovascular dysautonomia[127-129]. The mechanisms by which BP becomes elevated in the presence of NAFLD and in the absence of MetS are still unclear. However, it is likely that the common pathway between these two pathologies is IR. IR is a major factor in the development of NAFLD[124] and has been implicated in the development of both PHT and HTN independent of other cardiometabolic risk factors[130]. IR is also a proven risk factor of CVD by inducing dyslipidemia and secreting proinflammatory cytokines, such as TNF-α and IL-6, accelerating the arteriosclerosis[131,132]. Under these effects of IR, arterial vascular elasticity and luminal width may be able to decrease to raise BP. In addition, sympathetic activation provoked by IR likely contributed to the development of hypertension. Previous studies showed that IR could raise BP through the sympathetic excitation[133,134]. Elevated insulin level related to IR was reported to induce sympathetic overactivity by direct and indirect action on the central nervous system, and the enhanced uptake of noradrenaline in the arterial wall by hyperinsulinemia increased the vascular sympathetic tone[135]. Accordingly, elevated sympathetic activation related to IR could play a significant role in the development of HTN of NAFLD patients.

OBSTRUCTIVE SLEEP APNEA AND NAFLD

Robust scientific data indicate that obstructive sleep apnea (OSA) is strongly related to NAFLD independently of traditional risk factors[136-138]. Recently, a meta-analysis by Sookoian and Pirola showed that patients with OSA have greater transaminase values and a higher prevalence of NAFLD and liver fibrosis compared to individuals without OSA[133]. Intermittent hypoxia (IH) is a key mediator of OSA and leads to various alterations in biological homeostasis[139]. It activates the sympathetic nervous system *via* the carotid body chemoreceptors, which in turn leads to fat degradation (lipolysis) from adipose tissue. Free fatty acids (FFA) compose the triglycerides, which are transported to different organs to serve as fuel. However, FFA can lead to steatosis and organ inflammation, such as in the setting of NAFLD. At the same time, IH activates hypoxia inducible factors 1 and 2 (HIF-1 and HIF-2 respectively), which leads to decreased lipid metabolism in the liver, increased hepatic fat synthesis, upregulated liver inflammation, and fibrosis. In addition, Vgontzas *et al* included the production of inflammatory cytokines, which led to oxidative stress in patients with chronic sleep apnea, and it may be a possible mechanism contributing to the pathogenesis of NAFLD. This process may not only increase IR seen in patients with NAFLD but also may accelerate the process of liver fibrosis leading to the progression to steatohepatitis, cirrhosis, and its complications[140,141].

CHRONIC KIDNEY DISEASE AND NAFLD

To date, there is uncertainty whether NAFLD poses an independent risk for chronic kidney disease (CKD) (defined as decreased estimated glomerular

filtration rate (GFR) and/or proteinuria) above and beyond known risk factors for CKD. The complex and intertwined interactions among NAFLD, abdominal obesity, and IR make it extremely difficult to dissect out the specific role of the liver and the underlying mechanisms responsible for the association between NAFLD and the risk of developing CKD. NAFLD may contribute to the development and progression of CKD by atherogenic dyslipidemia, systemic/hepatic IR, dysglycemia (increased hepatic glucose production), activation of renin-angiotensin system, and the systemic release of numerous potentially pathogenic mediators (proinflammatory biomarkers and procoagulant and profibrogenic factors)[142]. Choudhary *et al*[143] showed that presence of NAFLD does not adversely affect renal function. In contrast, Machado *et al*[15] found that NASH, particularly lobular inflammation and advanced fibrosis, was associated with mild decreases in e-GFR, suggesting a common inflammatory link between liver and renal lesion in morbid obese patients. Additionally, a recently published a meta-analysis by Musso *et al*[144] revealed that the presence and severity of NAFLD are associated with an increased risk and severity of CKD. The main results of their analysis are the following: (1) NAFLD was associated with an increased prevalence and incidence of CKD; (2) liver disease severity in NAFLD was associated with an increased risk and severity of CKD; and (3) these associations remained statistically significant in diabetic and non-diabetic individuals as well as in studies adjusting for traditional risk factors for CKD and were independent of whole body/abdominal obesity and IR. Finally, large-scale prospective studies are needed to draw firm conclusions about any independent hepatic contribution to the increased risk of CKD observed in patients with NAFLD.

CONCLUSION

To date, growing evidence links NAFLD to CVD and CKD. Dyslipidemia, IR, increased production of proinflammatory cytokines, low adiponectin, high PAI-1, prehypertension, and hyperglycemia are main factors that lead to NAFLD, further aggravate the course of NAFLD, and accelerate the progress of atherosclerosis and the development of CVD. The key questions are whether NAFLD plays a direct role in CVD pathogenesis and whether an inflamed liver (NASH) adds to the CVD risk above the effect of steatosis alone. Therefore, further prospective studies are needed to detect whether NAFLD poses an independent risk for CVD above and beyond known metabolic risk factors. Additional well-conducted large scale studies are also needed to crystallize whether treatment of NAFLD will ultimately prevent or slow the development and progression of CVD and CKD.

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