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An Overview on Non-Alcoholic Fatty Liver Disease and Cardiovascular Diseases

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries and affects approximately 25% of the adult population. Since NAFLD is frequently associated with further metabolic comorbidities such as obesity, type 2 diabetes mellitus, or dyslipidemia, it is generally considered as the hepatic manifestation of the metabolic syndrome. In addition to its potential to cause liver-related morbidity and mortality, NAFLD is also associated with subclinical and clinical cardiovascular disease (CVD). Growing evidence indicates that patients with NAFLD are at substantial risk for the development of hypertension, coronary heart disease, cardiomyopathy, and cardiac arrhythmias, which clinically result in increased cardiovascular morbidity and mortality. The natural history of NAFLD is variable and the vast majority of patients will not progress from simple steatosis to fibrosis and end stage liver disease. However, patients with progressive forms of NAFLD, including non-alcoholic steatohepatitis (NASH) and/or advanced fibrosis, as well as NAFLD patients with concomitant types 2 diabetes are at highest risk for CVD.

Keywords: Cardiovascular diseases**,** non-alcoholic steatohepatitis, Non-alcoholic fatty liver disease.

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1. Introduction

NAFLD is associated with cardiovascular disease (CVD), and the 2 disorders share several cardiometabolic risk factors [1]. In some, the liver is particularly involved in the pathophysiology of the metabolic syndrome (MetS), and the subsequent development of CVD and other complications, whereas in others, NAFLD is a manifestation of end-organ damage due to MetS [2]. Given the high burden of CVD, the relationship between NAFLD and cardiovascular events has generated significant interest from a standpoint of CVD prevention [3]. The American Association for the Study of Liver Diseases (AASLD) does not recommend routine screening for NAFLD even in high-risk groups due to uncertainties in diagnostic work up and limited treatment options [4]. However, the European Association for the Study of the Liver recommends screening obese, MetS, and high CVD-risk patients for NAFLD with liver enzymes and/or ultrasound because of its prognostic implications [5] in spite of limited benefit in outcomes. The CardioMetabolic Heath Alliance has advocated for more comprehensive screening in the community to improve prevention of MetS [5]. Such screening should focus on measurable biomarkers such as blood pressure, lipids, body mass index (BMI), and waist circumference. An important part of MetS screening is an assessment of abdominal obesity, but unfortunately, technology for measuring abdominal obesity is limited.

2. Nonalcoholic Fatty Liver Disease Increasing Risk of Cardiovascular Disease

2.1. Pathophysiological Mechanisms

There are likely multiple underlying mechanisms by which NAFLD increases the risk of CVD (Central Illustration). A comprehensive review by Francque et al. [6] summarizes these mechanisms and their potential clinical impact. One of early steps in process of developing atherosclerosis is endothelial dysfunction. Increased levels of asymmetric dimethyl arginine, which is an endogenous antagonist of nitric oxide synthase, are typically observed in NAFLD patients [6]. Elevated serum homocysteine levels are often seen in NAFLD, primarily due to changes in methionine metabolism, which disrupts the production and catabolism of homocysteine in the liver [7]. Hyperhomocysteinemia is associated with increased intrahepatic vascular resistance, impairs nitric oxide formation. Furthermore, elevated homocysteine levels because oxidative stress, enhances platelet activation. Last, circulating markers of systemic inflammation (interleukin 6, high sensitivity C-reactive protein, interleukin 1β, tumor necrosis factor [TNF]-α, chemokine [C-C motif] ligand 3, soluble intracellular adhesion molecule 1, and macrophage phenotype 1/2 ratio [M1/M2]) often increased in patients with NAFLD [6].

Obesity plays a direct role in M1/M2 Kupffer cell imbalance and secretion of proinflammatory cytokines [8].

Systemic inflammation increases endothelial dysfunction, alters vascular tone, and enhances vascular plaque formation. These mechanisms are supported by the clinical findings in a study of NAFLD patients that found significantly reduced flow-mediated vasodilation, compared with age- and sex-matched control subjects (although BMI matching was not performed) [9]. The liver plays a vital role in lipid metabolism via lipogenesis, lipid breakdown, and the uptake and secretion of serum lipoproteins [10]. NAFLD alters serum lipid profiles, causing abnormally elevated triglyceride (TG), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) levels, as well as abnormally decreased high-density lipoprotein (HDL) levels [11]. Patients with obesity, type 2 diabetes mellitus (DM), and MetS have oversecretion of VLDL due to high plasma free fatty acid levels and high liver fat content [8]. Elevated serum VLDL and LDL concentration has been linked to hepatic lobular inflammation, independent of steatosis [12]. Further investigation of lipoprotein subclasses reveals that patients with NASH have significantly smaller LDL particle size and peak diameter, higher particle concentration of LDL, higher levels of LDL-IVb, and decreased levels of HDL2b, suggesting a mechanism for potentially higher risk of CVD in individuals with more severe NAFLD [13].

This altered serum lipoproteins composition is likely to contribute to the increased risk for CVD. NAFLD is very closely associated with insulin resistance, which is a risk factor for CVD. Obesity and excess free fatty acids not only lead to muscle insulin resistance but also induce hepatic insulin resistance and reduce insulin clearance [8]. The mechanism by which NAFLD is associated with hepatic insulin resistance is believed to be due to increased hepatic diacylglycerol, which activates protein kinase C, resulting in decreased insulin signaling [14]. Fatty acid accumulation in the liver, primarily from adipose tissue lipolysis, also leads to a suppression of endogenous liver glucose production, further stimulating insulin resistance [15]. Saturated fatty acids, in particular, produce intrahepatic oxidative stress, which further impairs hepatic insulin signaling [16]. Importantly, the relationship between NAFLD and CVD appears to be in addition to risk conferred by DM, as the prevalence of CVD in patients with DM and NAFLD is increased compared with the risk in individuals with DM without NAFLD [17]. This association with NAFLD and CVD, independent of multiple cardiometabolic risk factors including DM. In Danish National Death Registry, mortality was similar between diabetic and nondiabetic individuals with NAFLD [18].

Currently, as evidenced in the data it is difficult to distinguish clear independence of association of NAFLD and CVD given the prevalence of NAFLD in individuals with DM, which approaches nearly 70% to 75%. Additional factors that influence atherogenesis and plaque instability in NAFLD have been identified. In the early stages of NAFLD preceding fibrosis, centrozonal arteries and microvessels develop, suggesting active angiogenesis [19]. Increased serum levels of vascular endothelial growth factor (VEGF) and increased hepatic expression of VEGF and VEGF receptor-2 have been demonstrated in NAFLD patients [20]. Although the theorized association between VEGF and atherogenesis and plaque instability would be suspected of contributing to CVD, the clinical significance remains limited [21]. Patients with NAFLD may also be at increased risk for atherosclerosis due to an increase in prothrombotic factors [22]. Finally, intestinal dysbiosis contributes to both NAFLD and CVD via secretion of bile acids, trimethylamine, and short-chain fatty acids [23]. The role of genetic factors linking NAFLD and CVD has yet to be defined, but much has documented [24].

Two missense genetic variants have been identified by genome-wide association studies of NAFLD: patatin-like phospholipase domain containing protein 3 (PNPLA3) and transmembrane 6 superfamily member 2. PNPLA3 modulates morphology and physiology of lipid droplets and appears to be related to TG metabolism [25]. Carriers of this mutation have shown to increased atherosclerosis [26], but paradoxically lower serum TG levels [27]. Transmembrane 6 superfamily member 2 is the other protein with genetic variants that have been studied and modulates secretion of TG and cholesterol in liver via VLDL excretion [28]. Carriers of this mutation are at risk for NAFLD due to increased retention of TG and lipids in liver but may experience some degree of cardioprotection with subsequently reduced levels of serum TG, LDL cholesterol, and total cholesterol [29]. Structural changes that occur early in NAFLD can impose effects on heart left ventricular remodeling, increased mass, and diastolic dysfunction. Increased portal pressure occurs in NAFLD due to changes in sinusoidal morphology, reduction in sinusoidal flow, and increased intrahepatic resistance, particularly as disease severity progresses with increased fibrosis. NAFLD causes an increased body surface area, further increases left ventricular filling pressures, cardiac output, and volume overload [30].

3. Increased Risk of CVD in NAFLD Patients

3.1. Cardiovascular events

Whether NAFLD is an independent risk factor for cardiovascular mortality and other cardiovascular events has been studied but remains controversial. In a systematic review and meta-analysis of 11 prospective studies, Fraser et al. [31] found that an elevated serum GGT level was an independent predictor of cardiovascular events in both men and women. However, GGT level is a poor surrogate marker for NAFLD. The question remains whether NAFLD independently contributes to cardiovascular mortality and morbidity. Patients with NAFLD had a higher risk of fatal and/or nonfatal CVD events than those without NAFLD. However, when the analysis was restricted to studies with CVD mortality as the primary outcome, the association between NAFLD and fatal CVD events was not statistically significant.Severe NAFLD was defined as the presence of hepatic steatosis on imaging plus elevated serum GGT level, high NAFLD fibrosis score, high hepatic FDG uptake on positron emission tomography, or increasing fibrosis stage on liver histology. CVD events were defined as myocardial infarction, angina, stroke, transient ischemic attack, CVD death, coronary or peripheral revascularization, symptomatic peripheral vascular disease, clinically driven angiography demonstrating >50% stenosis of epicardial coronaries, or composite endpoints.

3.2. Atherosclerotic disease

Atherosclerosis, the main contributor to coronary artery disease (CAD), has been linked to fatty liver disease, and recently, there have been a number of studies quantifying this relationship. Carotid intima-media thickness (CIMT) and coronary artery calcification (CAC) have been the 2 main

studied measures of atherosclerosis. Studies have shown that NAFLD is independently associated with increased CIMT [32] and CAC [33]. Compared with patients who do not have any steatosis, patients with NAFLD have been shown to have impaired flow-mediated vasodilation, increased CIMT, and increased carotid atherosclerotic plaques independent of metabolic syndrome characteristics [34]. In addition to subclinical atherosclerosis, patients with NAFLD are at increased risk of clinically significant atherosclerosis requiring percutaneous coronary intervention [35]. While NAFLD patients are at increased risk of CAD, they may additionally have worse outcomes if they should experience acute coronary syndrome.

3.3. Risk for cardiomyopathy

Cardiac structural changes appear to occur in patients with NAFLD, as well. NAFLD has also been shown to be independently associated with valvular heart disease, specifically aortic valve sclerosis (AVS) and mitral annulus calcification (MAC). Patients with NAFLD also experience changes in epicardial fat distribution. Not only is epicardial adipose tissue (EAT) independently associated with NAFLD, but increasing steatosis grades correlate with increasing thickness of EAT [36]. Furthermore, those with NAFLD and thicker EAT (>3.18 mm) are at increased risk for coronary calcification (CAC score >0) [37].

3.4. Cardiac arrhythmias

There is growing evidence that NAFLD patients are at increased risk for cardiac arrhythmias, specifically atrial fibrillation, QTc prolongation, and ventricular arrhythmias [38]. Given the multiple shared risk factors, an association of NAFLD with arrhythmias may not be unexpected. This association was independent of age, sex, BMI, smoking, hypertension, ischemic heart disease, valvular heart disease, chronic kidney disease, chronic obstructive pulmonary disease, serum GGT levels, medication use, and left ventricular ejection fraction. In aggregate, these studies offer significant evidence for an association between NAFLD and arrhythmias, independent of overlapping comorbidities and other risk factors, although the specific mechanisms remain unclear. NAFLD results in proinflammatory and pro-oxidative states, which may alter the electrophysiological myocardial substrate [39]. As previously discussed, NAFLD can cause changes to the myocardial structure via valvular calcifications, diastolic dysfunction, or left ventricular hypertrophy. These myocardial changes are significant risks for arrhythmias. Last, NAFLD has been shown to be associated with autonomic dysfunction [40], which is another risk factor for arrhythmias.

4. Primary & Secondary Prevention of CVD in NAFLD

4.1. Primary prevention

Primary prevention of NAFLD overlaps with cardiovascular prevention. Lifestyle modifications including weight loss, improved dietary patterns, and increased physical activity are the essential components of prevention. The American College of Cardiology and the American Heart Association have specific recommendations on lifestyle management to reduce the risk of CVD [41]. A healthy dietary pattern should focus on vegetables, fruits, and whole grains, and also include low-fat dairy, fish, legumes, nontropical vegetable oils, and nuts. Sodium, sweets, sugar-sweetened beverages, and red meats should be limited. Physical activity should entail at least 2.5 h of moderate-intensity exercise or 75 min of vigorous-intensity exercise per week. Achieving and maintaining an optimal body weight is important. The prevalence of NAFLD was studied in participants performing varying degrees of physical activity [42]. NAFLD prevalence was lower with higher levels of reported physical activity (45% in low activity group, 38% in the moderate activity group, and 30% in the high activity group). An important component of primary prevention is cardiovascular risk assessment. The Framingham Risk Score (FRS) is a validated measure of CV risk within the general population as well as in individuals with NAFLD [43]. Importantly, degree of liver fibrosis does seem to play an important role in cardiovascular risk. The FRS was shown to correlate with degree of fibrosis, as measured by the NAFLD fibrosis score, with higher fibrosis scores correlating with a higher risk of CVD, as calculated by the FRS [44]. This correlates with data seen in the meta-analysis by Wu et al. [3], in which individuals with NASH were found to be at higher risk of CVD. The FRS should be routinely included in patients with NAFLD without DM by clinicians to risk-stratify patients and guide treatment of risk factors.

4.2. Secondary prevention

Lifestyle modification remains an essential aspect of treatment for those with NAFLD. Although the AASLD states that there is insufficient evidence to make a recommendation on nonheavy alcohol consumption in NAFLD patients, there is emerging evidence that even a small amount of alcohol is harmful to NAFLD patients [45]. Modest alcohol consumption has also been associated with less improvement in steatosis based on liver biopsy [46]. It is probable that the risk of light alcohol consumption in NAFLD patients would outweigh the benefit of the well-known cardiovascular benefit [47]. The significant benefit of statins in reducing the risk of CVD is well-established, but concerns regarding adverse effects of muscle symptoms and increased transaminases are a factor leading to underutilization in patients with NAFLD. Although the role of statins in hepatotoxicity is now considered a “myth” [48], these medications continue to be underprescribed in patients with liver disease [49]. Severe cases of drug-induced liver injury occurring 3 to 4 months after initiation of therapy have been reported, but are rare (1.2 of 100,000 users) [50], and the overall incidence of liver failure in patients on statins has not significantly different from that in general population [51]. Several large randomized controlled trials did not find any difference in the incidence of persistently elevated liver function tests between statin and placebo therapy [52].

Demonstrated that those patients with NAFLD who have elevated liver enzymes at baseline are not at increased risk for statin-induced hepatotoxicity. Therefore, routine monitoring of liver biochemistries while on statin therapy is no longer recommended [53]. In addition to these histological benefits of statins in patients with NAFLD, statins have also been shown to have clinical benefits in this patient population [54]. These findings were also replicated in the primary prevention ATTEMPT (Assessing the Treatment Effect in Metabolic syndrome without perceptible diabeTes) study of patients with NAFLD on atorvastatin 30 mg/day [55]. The major statin guidelines have yet to address specific NAFLD population [56], but it may be reasonable to consider an

approach similar to those with DM. Management of patients with nonalcoholic fatty liver disease (NAFLD) to reduce risk of cardiovascular disease (CVD) has yet to be defined. This potential therapeutic approach is formulated to target the pathophysiological mechanisms that associate NAFLD and CVD. ARB = angiotensin II receptor blockers; CHF = congestive heart failure; GLP = glucagon-like peptide; NASH = nonalcoholic steatohepatitis.

The cardiovascular benefits of aspirin have also been well-established. There is limited data on the use of aspirin in NAFLD patients. Similarly to statins, aspirin is thought to be effective against NAFLD by inhibiting the production of TNF-α and stimulating the expression of endothelial nitric oxide synthase and VEGF, resulting in antioxidant activity [57]. Liver injury from aspirin is rare, although adult cases of Reye syndrome have been reported [58]. Insulin resistance plays an important role in NAFLD, which is why insulin-sensitizing agents have been studied as possible therapies. Metformin improves insulin sensitivity, reduces hepatic gluconeogenesis, and in theory, should improve NAFLD [59]. However, metformin has had limited clinical efficacy for NAFLD, as it has been shown to reduce liver enzyme levels, but not improve liver histology [60]. Another insulin sensitizer that has been studied is the peroxisome proliferator-activated receptor (PPAR)-α agonist pioglitazone. Its effects on patients with DM has been established. It has been shown to reduce the risk of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with type 2 DM with evidence of macrovascular disease [61] and to reduce the composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death among patients with insulin resistance or pre-DM [62].

Pioglitazone's effect on insulin sensitivity appears to have benefit in patients with NAFLD as well. In patients with NASH and impaired glucose tolerance or type 2 DM, pioglitazone has been shown to decrease hepatic fat content; increase hepatic insulin sensitivity; decrease serum ALT levels; and improve fibrosis, steatosis, inflammation, and ballooning necrosis [63]. In patients with NASH without DM, pioglitazone has been demonstrated to reduce steatosis, inflammation, and hepatocellular ballooning [64]. In larger meta-analyses of patients with NASH and with or without DM, pioglitazone was associated with improvement in steatosis and fibrosis, and NASH resolution [65]. While more robust confirmatory clinical outcomes studies are needed, the benefits of pioglitazone in patients with NAFLD appears significant. However, the risk of this drug, especially with regards to congestive heart failure, fluid retention, and weight gain, is a potential clinical concern [66]. Last, there is strong evidence that glucagon-like peptide (GLP)-1 analogues reduce weight in obese diabetic patients, and they may be of benefit in patients with NAFLD. However, this benefit was not independent of weight loss.

Liraglutide also appears to be beneficial from a cardiovascular standpoint. Liraglutide has been shown to improve glycemic control; reduce total cholesterol, LDL, and TG; reduce systolic blood pressure; and decrease the incidence of nonfatal myocardial infarction, nonfatal stroke, heart failure admissions, and death due to any cardiovascular cause [67]. GLP-1 analogues offer hope for reducing steatosis as well as for improving cardiovascular outcomes in patients with DM and NAFLD. Because the renin-angiotensin-aldosterone system plays a regulatory role in insulin sensitivity, the effects of angiotensin II receptor blockers (ARBs) on NAFLD have been studied in a limited number of clinical trials [68]. Both of these trials have demonstrated a significant decrease in serum liver enzyme levels. In a small study, Yokohama et al. [69] found that patients with NAFLD and hypertension treated with losartan (50 mg/day) had improved hepatic necroinflammation and reduction of hepatic fibrosis. A larger, well-designed randomized controlled trial is still needed to better evaluate the effects of ARBs on patients with NAFLD. Targeting oxidative stress has also theorized as a potential therapy for hepatic injury.

In the study by Sanyal et al. [64], compared with placebo, vitamin E was associated with a significant improvement in NASH but not in improvement of fibrosis. The meta-analysis by Said et al. [65], which incorporated the Sanyal et al. [64] study, also demonstrated significant improvements in steatosis, lobular inflammation, and ballooning, but not fibrosis. Although vitamin E is thought to potentially improve NASH, long-term use of this supplement has had no significant benefit in preventing major cardiovascular events [70]. Bariatric surgery is an extremely effective treatment for obesity, as well as NAFLD. It can lead to a significant improvement in liver histology and transaminases [71], as well as disappearance in NASH and reduction in fibrosis [71]. Bariatric surgery was also shown to lead to a significant reduction or resolution in CVD risk factors. In a systematic review of 73 studies with 19,543 bariatric surgery patients, post-operative improvement of DM was reached in 73% of patients, of hyperlipidemia in 65% of patients, and of hypertension in 63% of patients [72]. The presumed primary mechanism by which this surgery results in such improvement is by weight loss [73].

5. Future Directions

Although the treatment options for NAFLD may seem limited, there is optimism that future innovative safe and effective options for management will be available. A number of medications have emerged that target the pathophysiological mechanisms of NAFLD.

5.1. Obeticholic acid

Farnesoid X receptors (FXRs) are nuclear receptors that, when activated, increase insulin sensitivity, decrease hepatic gluconeogenesis, and protect against cholestasis-induced liver injury [74]. Obeticholic acid is a bile acid derivative that can bind FXRs and take advantage of this pathway. A multicenter, double-blind, placebo-controlled, randomized phase IIb trial of patients with NASH found that patients on obeticholic acid had improvement in their liver histology at 18 months compared with placebo [74]. One drawback for this medication was that it was associated with higher levels of total serum cholesterol and LDL, and a decrease in HDL level. In secondary analysis, the role of statin use on changes in LDL was assessed [75]. Statin use from baseline through the treatment period did not prevent the LDL increase while on obeticholic acid. The addition of a statin during the treatment period resulted in a decrease in LDL, but not as significant as the placebo group. The clinical significance of these LDL changes has yet to be determined.

5.2. Elafibranor

PPAR-αand PPAR-δ are nuclear receptors that activate anti-inflammatory changes in the liver [76].

Elafibranor is a dual PPAR-α/δ agonist that, in addition to improving insulin sensitivity, glucose homeostasis, and lipid metabolism, also reduces hepatic inflammation. In a multicenter, randomized, placebo-controlled phase IIb trial, elafibranor was shown to be effective in resolving NASH without worsening fibrosis in patients with moderate to severe NASH [77]. This medication is also undergoing a large phase 3 clinical trial (RESOLVE-IT [Phase 3 Study to Evaluate the Efficacy and Safety of Elfibranor Versus Placebo in Patients with Nonalcoholic Steatohepatitis (NASH) in patients with NASH and fibrosis.

5.3. Cenicriviroc

Cenicriviroc is an antagonist of C-C motif chemokine receptor (CCR) types 2 and 5, which promote anti-inflammatory and antifibrotic effects in the liver [76]. This medication has been studied with the goal of reducing hepatic fibrosis. A randomized, double-blind, phase IIb study found that this medication resulted in a significant improvement in fibrosis without worsening NASH after the first year [78] and second year [79] of treatment.

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