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MINIREVIEWS

Non-alcoholic fatty liver disease and cardiovascular risk

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease associated with insulin resistance and metabolic syndrome. The spectrum of disease ranges from simple steatosis to steatohepatitis and progression to cirrhosis. Compelling evidence over the past several years has substantiated a significant link between NAFLD and cardiovascular disease ranging from coronary artery disease to subclinical carotid atherosclerosis. Close follow up, treatment of risk factors for NAFLD, and cardiovascular risk stratification are necessary to predict morbidity and mortality in this subset of patients.

Key words: Non-alcoholic fatty liver disease; Cardiovascular risk; Outcomes; Coronary artery disease; Steatosis

Core tip: Non-alcoholic fatty liver disease (NAFLD) is often associated with insulin resistance and is strongly associated with type 2 diabetes mellitus and obesity. In addition to being at risk for nonalcoholic steatohepatitis, cirrhosis and its complications, NAFLD patients are also at higher risk of cardiovascular diseases (CVD), including coronary heart disease and stroke. NAFLD confers increased cardiovascular disease risk independent of traditional cardiovascular risk factors and metabolic syndrome. Close followup of patients with NAFLD may be indicated to prevent major vascular events. Risk stratification scores are needed that address both the risk for advanced liver disease and CVD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the upcoming leading cause of chronic liver disease in the United States and its prevalence is increasing world-

wide. It is a spectrum of liver diseases that ranges from simple steatosis to a progressive form of liver disease called nonalcoholic steatohepatitis (NASH)[1]. It may progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma in some individuals. NAFLD is often associated with insulin resistance and is strongly associated with type 2 diabetes mellitus and obesity. NAFLD patients are at risk of progressing to NASH and ultimately cirrhosis; they are also at higher risk of cardiovascular diseases (CVD), including coronary heart disease and stroke[2]. NAFLD confers increased cardiovascular disease risk independent of traditional cardiovascular risk factors and metabolic syndrome (MetS). In this review, we have discussed the association of NAFLD with cardiovascular disease, the likely mechanisms underlying this association, proper risk assessment of patients with NAFLD for cardiovascular diseases, and treatment options for modification of CVD morbidity and mortality in patients with NAFLD.

EPIDEMIOLOGY OF CVD IN NAFLD

Adverse CVD events in NAFLD subjects compared with the general population are described through a description of several recent epidemiological studies (Table 1). The diagnosis of NAFLD can be based either on histology or imaging studies. Abnormal liver enzymes are used as biochemical surrogates of NAFLD in several recent studies. The prospective cohort study by Dunn *et al*[3], using data from the Third National Health and Nutrition Examination Survey (NHANES Ⅲ), showed that subjects with NAFLD identified based on elevated alanine aminotransferase (ALT) had a higher mortality from CVD. After adjusting for cardiovascular risk factors, several large population studies have shown an association between an elevated ALT and increased cardiovascular mortality[4,5]. Elevated GGT has also been reported as a marker of NAFLD in described prospective studies. A meta-analysis of ten pooled studies confirmed the independent association between elevated GGT and adverse CV events[6].

Liver imaging may be a more reliable method for diagnosing NAFLD. In three large population studies, ultrasound imaging suggestive of NAFLD was independently associated with cardiovascular events[7-9]. Although these studies did show that NAFLD may be a predictor of CVD, ultrasound may not be as sensitive for a diagnosis of NAFLD and therefore this was a major limitation for these studies. Hepatic fat concentration as measured by MRI has been used for diagnosis of NAFLD. Quantity of liver fat has been reported to be predictive of metabolic syndrome and CVD risk. In a recent study Loomba *et al*[10] quantified liver fat in patients with NAFLD and controls using a magnetic resonance imaging and measuring proton-density-fat-fraction (MRI-PDFF). In patients with NAFLD high proton-density-fat-fraction on MRI was a predictor of metabolic syndrome and increased cardiovascular risk[10].

Liver biopsy is considered to be the gold standard for diagnosis of NAFLD and some studies have shown that patients with biopsy-proven NAFLD have higher total mortality rates compared to the general population. Söderberg *et al*[11] reported increased mortality from cardiovascular disease in patients with biopsy proven NASH. Forty-three percent of patients had NASH at initial biopsy. The median follow up in their study was 28 years. Overall survival was reduced in subjects with NASH compared to the general population due to increased mortality by cardiovascular disease. Importantly in this study, only subjects with NASH had significantly reduced survival[9-11].

MECHANISM (PATHOGENESIS)

Several mechanisms have been postulated for development of accelerated atherosclerosis in patients with NAFLD, including genetic predisposition, insulin resistance and atherogenic dyslipidemia, oxidative stress, chronic inflammation, reduced levels of the adiponectin and altered production of pro and anticoagulant factors[12]. All these mechanisms are present at the same time. NAFLD, regardless of its stage, is strongly associated with hepatic and adipose tissue insulin resistance (IR). In fact, liver fat content can be used as an independent predictor of insulin resistance. These mechanisms work synergistically[13].

NAFLD, especially in its necroinflammatory form (NASH), may cause atherogenic dyslipidemia[14]. In addition there is an increase of pro-coagulant factors like fibrinogen, plasminogen activator inhibitor-1 and tumor growth factor, which all increase the risk of atherosclerosis[15]. NAFLD is considered to have chronic sub-clinical inflammation and associated with many inflammatory markers. Increased vascular risk has been linked to increased levels of inflammatory cytokines and markers such as IL-6, TNF, CRP, and fibrinogen. Oxidative stress may also play a role. This stress is thought to trigger changes in endothelial function leading to formation and deposition of oxidized LDL in the sub-intimal space[16].

Visceral adipose tissue is also thought to play a role in NAFLD. Visceral fat is metabolically active and secretes several hormones that help regulate inflammation; tissue distribution is affected by an alteration in cellular free fatty acid transport. These alterations are possibly caused by hyperinsulinemia and ultimately divert accumulated triglycerides away from adipose tissue and towards other metabolic organs such as the liver[17,18].

Nonalcoholic fatty liver disease, abdominal obesity, and insulin resistance all play a role in increased cardiovascular risk, though the exact causal relationship is still unclear. Hepatic necroinflammation, as seen in NASH, is an atherogenic mechanism that may explain why patients with NASH have greater CV risk than patients with simple steatosis. In the liver, a signal of hepatic necroinflammation is elevated liver enzymes which may

Table 1 Recent epidemiological studies evaluating cardiovascular risk in non-alcoholic fatty liver disease

Ref.	Study characteristics	Years of follow-up	Diagnosis of NAFLD	Study outcomes	Main findings
Ekstedt *et al*[30] (2015)	Retrospective cohort study *n* = 229 Swedish patients with NAFLD and elevated liver enzymes (49% NASH); mean age 49 yr, 66% men	26.4 (mean)	Histology	*n* = 96 total deaths, 41 CVD related deaths	Increased rates of all-cause, liver-related and CVD mortality with NAFLD compared with general control population. Fibrosis stage on histology significantly predicted the risk of all-cause, liver-related and CVD mortality
Ekstedt *et al*[31] (2006)	Cohort study 129 consecutively enrolled patients diagnosed with biopsy-proven NAFLD were reevaluated. Survival and causes of death were compared with a matched reference population. Living NAFLD patients were offered repeat liver biopsy and clinical and biochemical investigation	13.7 (mean)	Histology	Mortality was not increased in patients with steatosis. Survival of patients with nonalcoholic steatohepatitis (NASH) was reduced. These subjects more often died from cardiovascular and liver-related causes. At follow-up, 69 of 88 patients had diabetes or impaired glucose tolerance. Progression of liver fibrosis occurred in 41%. These subjects more often had a weight gain exceeding 5 kg, they were more insulin resistant, and they exhibited more pronounced hepatic fatty infiltration at follow-up	Increased total mortality which was primarily CV related (only in NASH patients but not in simple steatosis) compared with matched reference population
Soderberg *et al*[11] (2010)	Retrospective cohort study 256 subjects (61% men, mean age of 45 ± 12 yr) This study was undertaken to determine the frequency of NAFLD in a cohort of subjects who underwent liver biopsy from 1980 to 1984 because of elevated liver enzymes, and to assess mortality among subjects with NAFLD in comparison with the general Swedish population. Liver biopsies were blindly scored for NAFLD and NASH	24 yr (mean)	Histology	During the follow-up period, 113 (44%) of the total population and 47 (40%) of the 118 subjects diagnosed with NAFLD died. Of the 113 deaths, 37 were of cardiovascular disease and 16 of liver diseases. NAFLD exhibited a 69% increased mortality, subjects with bland steatosis, a 55% increase, and subjects with NASH, 86%	Increased total mortality in NAFLD was predominantly CV related, compared with matched reference population
Pickhardt *et al*[32] (2014)	Retrospective cohort study United States adults undergoing abdominal CT selected among 4412 consecutive adults scanned with CT for clinical reasons over a 12-mo period: 282 NAFLD patients and 786 non-steatotic controls after exclusion of those with known liver diseases or < 1 yr of follow-up; mean 51 yr, 46% men	7.5 (mean)	Unenhanced CT	Non-fatal CVD events (myocardial infarction, stroke, TIA or coronary bypass or stent); *n* = 73 CVD events	NAFLD was not independently associated with non-fatal CVD events
Zeb *et al*[12] (2016)	Prospective cohort study *n* = 4119 United States participants aged 45-84 yr (mean 62 yr, 45% men) who were free of CVD and known liver diseases at baseline	7.6 (mean)	Unenhanced CT	All-cause mortality and no-fatal CVD events (myocardial infarction, resuscitated cardiac arrest, angina, or coronary revascularization procedures), *n* = 253 deaths and 209 non-fatal CVD events	NAFLD was independently associated with a composite endpoint inclusive of all-cause death and non-fatal CVD events

Kim *et al*[33] (2013)	Population-based cohort *n* = 11154 Unites States adults; mean age 43 yr, 48% men	14.5 (median)	Ultrasound	All-cause and CVD mortality *n* = 1795 total deaths (673 CVD deaths)	NAFLD was not associated with increased all-cause and CVD mortality in the whole cohort however NAFLD with advanced fibrosis (defined by the NAFLD fibrosis score) was independently associated with increased all-cause and CVD mortality
Emre *et al*[34] (2015)	Retrospective cohort study *n* = 186 Turkish, non-diabetic patients undergoing PCI for ST-elevation MI; patients with known liver disease were excluded; mean age 58 yr, 78% men	In-hospital cardiac events	Ultrasound	In-hospital CVD events (MI, acute heart failure, cardiac arrest), *n* = 32 CVD events and *n* = 8 CVD deaths	Moderate-severe NAFLD was independently associated with increased in-hospital CVD events but not with increased CVD death

NAFLD: Non-alcoholic fatty liver disease; CT: Computed tomography; CAC: Coronary artery calcification; CIMT: Carotid intima-media thickness; CP: Carotid plaque; DM: Diabetes mellitus; NASH: Nonalcoholic steatohepatitis.

serve as a marker for those at increased risk of CVD[19]. Patients with NASH are also noted in several studies to have a greatly increased carotid-artery intimal medial thickness which further supports the necroinflammation hypothesis.

Further research is required to uncover other specific mechanisms by which nonalcoholic fatty liver disease and nonalcoholic steatohepatitis may contribute to the development and progression of cardiovascular disease[20].

EVIDENCE FOR CORONARY ARTERY DISEASE IN NAFLD

Atherosclerosis is the main trigger of overall vascular disease and different methods are used to detect it in its subclinical stage. Endothelial dysfunction is the first stage of subclinical atherosclerosis. Carotid intima-media thickness (CIMT) and the presence of carotid plaques are important markers of vascular disease. Other markers of atherosclerosis are coronary artery calcification (CAC), as determined by multi-slice CT scan. CAC represents the atherosclerotic burden in arterial beds and is known to correlate strongly with the presence of coronary artery disease (CAD) and increased risk of poor cardiovascular outcomes.

Several studies have demonstrated the association of coronary artery calcium score (CACS) with NAFLD (Table 2). A recent, large, population-based study reported a strong relationship between NAFLD and CAC. Importantly, this association was independent of the traditional risk factors for coronary artery disease[21]. Assy *et al*[21] described that the presence of NAFLD was associated with increased prevalence of non-calcified coronary plaques, independent of metabolic syndrome, in a case-controlled study. Another study showed a significant association in NAFLD patients and the appearance of vulnernable plaques on coronary artery imaging[22,23].

Though definitions of "significant" coronary artery disease may vary from study to study, a strong correlation exists between NAFLD and the prevalence of CAD as determined by coronary angiography.

STUDIES EVALUATING SUBCLINICAL ATHEROSCLEROSIS IN NAFLD

Measuring carotid intima-media thickness (CIMT) by ultrasound is a widely accepted screening tool for the prediction of cardiovascular disease in patients with NAFLD who may be asymptomatic. Several studies show an association between NAFLD and carotid disease, some independently and other weakly after adjusting for metabolic syndrome. There seems to be a correlation histologically in severity of NAFLD when compared to increasing CIMT.

There is also evidence to support the association of NAFLD with subclinical atherosclerosis independent of traditional risk factors and metabolic syndrome. In a recent comprehensive systematic review there was strong evidence that NAFLD is associated with subclinical atherosclerosis[24]. The presence of NAFLD was associated with the increased severity of CIMT, coronary calcification, endothelial dysfunction and arterial stiffness. These were independent of traditional risk factors and metabolic syndrome.

CARDIOVASCULAR RISK ASSESSMENT IN PATIENTS WITH NAFLD

All patients with NAFLD should be evaluated for CVD disease risk; this assessment can be repeated every 1-2 years. Patients should be evaluated for traditional CVD risk factors including obesity, diabetes, dyslipidemia and hypertension. Fasting glucose or glycosylated hemoglobin level should be done on the initial visit to diagnose DM. MetS is frequent in individuals with NAFLD and is associated with increased CVD and all-cause mortality. Therefore, assessment for the MetS is an important component of CV risk stratification. The MetS as defined by the National Cholesterol Education

Table 2 Studies evaluating coronary artery disease and carotid disease in non-alcoholic fatty liver disease

Ref.	Study characteristics	Modality to assess CV risk	Diagnosis of NAFLD Ultrasound	Main findings
Sinn *et al*[16] (2016)	Retrospective cohort study - 8020 men (average age, 49.2 yr) without carotid atherosclerosis at baseline and with proven NAFLD	CIMT on carotid ultrasound		NAFLD was associated with an increased risk of subclinical carotid atherosclerosis development. This association was explained by metabolic factors that could be potential mediators of the effect of NAFLD. Markers of liver fibrosis also were associated with subclinical carotid atherosclerosis development
Pais *et al*[35] (2016)	Longitudinal cohort study - 1871 subjects (mean age 53 yr; 65% males). Half of cohort had steatosis while half did not	CIMT on carotid ultrasound	Fatty Liver Index	Steatosis occurred in 12% and CP in 23% of patients. C-IMT increased in patients with steatosis occurrence whereas it did not change in those that stayed free of steatosis. Steatosis at baseline predicted CP occurrence independent of age, sex, type-2 diabetes, tobacco use, hsCRP, hypertension and C-IMT
Park *et al*[36] (2016)	Longitudinal cohort study - 1732 subjects underwent serial CAC evaluation. Half the cohort had NAFLD and half did not	Calcium scoring CT to assess CAC	Ultrasound	More subjects with NAFLD than without showed CAC development or progression. In subjects without calcification at baseline, NAFLD significantly affected the development of calcification after adjusting for traditional metabolic risk factors. The severity of NAFLD was dose-dependently associated with the development of CAC
Kim *et al*[15] (2012)	Retrospective chart review- 4 023 subjects (mean age, 56.9 ± 9.4 yr; 60.7% males) without known liver disease or a history of ischemic heart disease	Calcium scoring CT to assess CAC	Ultrasound	Patients with NAFLD are at increased risk for coronary atherosclerosis independent of classical coronary risk factors, including visceral adiposity. These data suggest that NAFLD might be an independent risk factor for coronary artery disease
Fracanzani *et al*[20] (2016)	Longitudinal cohort study - 125 NAFLD patients and 250 age and gender matched Controls at baseline and 10 yr later were followed. Incidence of cardiovascular and cerebral events was recorded	CIMT on carotid ultrasound	Ultrasound	Major cardiovascular events were observed in 19% of NAFLD patients, with an estimated cumulative risk significantly higher in NAFLD than in Controls. Presence of plaques and of steatosis were the strongest predictors for cardiovascular events. Grade of steatosis, ALT and GGT levels were higher in NAFLD patients who developed cardiovascular events. CIMT value after 10 years was significantly higher in NAFLD than in Controls. NAFLD should be included among risk factors for cardiovascular damage and underline the utility to evaluate, once it is diagnosed, the presence of atherosclerotic lesions
Nahandi *et al*[17] (2014)	Case control study - 151 patients in three groups: group I including 49 patients with NAFLD and DM; group II including 50 non-diabetic NAFLD patients; and the control including 52 normal subjects as group III	CIMT on carotid ultrasound	Ultrasound	There is a significant association between the presence of NAFLD and atherosclerosis, but this association was independent of DM. The grade of NAFLD and elevated liver function tests had no effect on severity of atherosclerosis

NAFLD: Non-alcoholic fatty liver disease; CT: Computed tomography; CAC: Coronary artery calcification; CIMT: Carotid intima-media thickness; CP: Carotid plaque; DM: Diabetes mellitus.

Program (NCEP) requires the presence of 3 or more of the following components: (1) increased triglyceride levels (≥ 150 mg/dL); (2) low HDL level (< 40 mg/dL in men, < 50 mg/dL in women); (3) increased fasting glucose level (≥ 110 mg/dL); (4) hypertension (≥ 130/85 mm Hg or on antihypertensive medication); and (5) abdominal obesity (waist circumference: > 102 cm in men, > 88 cm in women).

Several different methods are used in the general population to estimate CVD risk including the Framingham Risk Score (FRS). The FRS is a validated measure of CV risk in the general population. The FRS predicts an individual's 10-year risk of myocardial infarction or CV death and incorporates age, sex, cholesterol, HDL, smoking status, and hypertension. Furthermore, the FRS has been validated as a predictor of CVD in NAFLD and should be used to risk-stratify individuals and guide treatment of risk factors including dyslipidemia. Recently, the American Heart Association recommended a new cardiovascular assessment tool for prediction of atherosclerotic cardiovascular disease. This score incorporates the usual risk factors for CVD but needs to be validated in patients with NAFLD[25].

ASSESSMENT OF DYSLIPIDEMIA IN NAFLD

Dyslipidemia is frequent in individuals with NAFLD. The dyslipidemia in NAFLD is characterized by increased

serum triglycerides, increased small, dense low-density lipoprotein (LDL non-type A) particles, and low high-density lipoprotein (HDL) cholesterol. Recently, the value of non-HDL-C has been demonstrated in predicting coronary heart disease. Non-HDL-C is superior in predicting incidence of cardiovascular events and cardiac death in NAFLD patients compared to the traditional marker low-density lipoprotein[25]. The Adult Treatment Panel III of the National Cholesterol Education Program has added non-HDL-C to its recommended screening algorithm for assessing cardiovascular disease risk.

Non-HDL-C is a calculated value derived by subtracting HDL cholesterol from the total cholesterol (TC) level, both available on traditional lipid panels, and requires no additional cost. In addition, because it is derived from TC and HDL levels, which are not impacted by fasting, non-HDL-C does not require fasting for accuracy.

Because patients with NAFLD have a high prevalence of cardiovascular disease, the use of non-HDL-C provides an important value in cardiovascular risk stratification and as a target for lipid-lowering therapy.

Non-HDL-C levels are increased in patients with NASH compared with those with steatosis, particularly in those persons who are not receiving lipid-lowering medications.

MANAGEMENT OF CARDIOVASCULAR DISEASE RISK IN NAFLD

All patients with NAFLD, irrespective of their body weight, should be advised lifestyle modifications in the form of regular exercise. Those who are overweight or obese are advised weight reduction. Regular exercise has been shown to improve the insulin sensitivity even without weight reduction. An exercise regimen should aim to achieve a target heart rate of 60%-70% of maximal heart rate through exercises such as brisk walking, jogging, or other aerobic exercises for at least 30 min, 5 d per week. Initial weight reduction in patients who are overweight or obese should be 10% of the body weight to be achieved in 6-8 mo. Overall, these overweight and obese patients need to create a negative balance by consuming fewer calories and burning more calories through regular exercise.

TREATMENT OF DYSLIPIDEMIA

Lifestyle modification, encompassing weight loss and increased physical activity, is the cornerstone of dyslipidemia management in NAFLD. However, for groups with increased CVD risk, lifestyle modification should be accompanied by lipid-lowering therapy. Guidelines set forth by the NCEP Adult Treatment Panel Ⅲ provide guidance on which groups should be targeted for lipid-lowering therapy and outlines treatment goals[26]. These guidelines were not designed specifically to address dyslipidemia in individuals with NAFLD; however, they can be applied safely to individuals with NAFLD.

In this context, the most attractive group of lipid-lowering agents for cardiovascular protection are the statins. In addition to a major effect in lowering LDL, they have modest effects on increasing HDL and lowering serum triglycerides, as well as non- cholesterol-lowering effects on vascular endothelium by inducing endothelial nitric oxide synthase.

Statin hepatotoxicity has not been shown to be of increased risk in NAFLD. The Liver Expert Panel stated in a report in 2014 that statins can be safely used in NAFLD and NASH, and routine liver enzyme monitoring need not be done. Statins can be safely used in patients with decompensated liver disease. There is always concern for using high dose statins in patients with elevated liver enzymes; in such circumstances adding ezetimibe has a synergistic effect with statins[26,27].

Ezetimibe is less effective as a single agent to lower serum cholesterol and does not have the same vascular protective effects as statins. Ezetemibe is also useful when patients experience partially dose-dependent statin adverse effects such as myopathy.

Evidence that cholesterol lowering with statins reduces cardiovascular risk comes from the Greek Atorvastatin and Coronary Heart Disease Evaluation study, in which atorvastatin reduced the incidence of new cardiovascular events to a greater extent in patients with NAFLD (assumed by raised liver enzymes) than among those with normal liver enzymes[28]. Patients without serum cholesterol elevation benefited as well, and there was a 40% reduction in serum triglyceride.

Triglyceride elevations are also a risk factor for cardiovascular disease, albeit less so than cholesterol. Attempts to reduce raised serum triglyceride levels center around weight reduction, improving insulin resistance (physical activity) and diabetic control, with use of polyunsaturated fatty acids (fish oil) as the first-line pharmacologic approach. Ezetimibe, has been compared with placebo for the treatment of NASH in the MOZART randomized clinical trial. In secondary analysis of the MOZART trial, FRS and CAC score improved in a greater proportion of patients with ezetimibe but did not reach statistical significance[29].

TREATMENT OF DIABETES MELLITUS

DM is associated with an increased risk of CVD. Because DM is highly prevalent among individuals with NAFLD, comprehensive management is essential for CVD risk reduction. A detailed discussion of the management of DM in individuals with NAFLD is beyond the scope of this review. However, primary and secondary prevention of CVD events in individuals with DM should focus on multifactorial risk reduction, including treatment of hypertension and dyslipidemia. In addition, specific treatments of DM, including metformin, may decrease CVD events.

CONCLUSION

In the past several years, compelling evidence has

substantiated a strong link between NAFLD and increased risk of cardiovascular disease in individuals with or without coexisting metabolic syndrome. NAFLD is now recognized as a risk factor for poor cardiovascular outcomes including mortality and morbidity from major vascular events. As a whole, NAFLD patients may benefit from more careful surveillance and early treatment interventions. However, despite evidence linking increased cardiovascular risk with NAFLD, there is still uncertainty regarding the prognostic role of NAFLD in risk stratification for CHD. Additional, large follow-up studies are needed to establish whether adding NAFLD to the currently available risk scoring systems will improve cardiovascular disease risk prediction. Furthermore, the question of whether the prognostic value of NAFLD in the development and progression of cardiovascular disease only applies to NASH or also is associated with simple steatosis remains unresolved. Finally, more research is needed to understand the pathophysiology linking NAFLD with cardiovascular disease and to better elucidate whether genetic traits in NAFLD carry the same cardiovascular risk as metabolic syndrome-associate NAFLD.

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