Management of Dyslipidemia as a Cardiovascular Risk Factor in Individuals with Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most frequent cause of liver disease in the United States and is associated with an increased risk of cardiovascular disease (CVD) and cardiovascular (CV) mortality, independent of traditional cardiovascular risk factors. CVD is one of the most common causes of death among individuals with NAFLD and management of NAFLD must extend beyond liver disease to include CVD risk modification. Clinicians should assess CVD risk with the Framingham Risk Score (FRS) and screen for CVD risk factors including dyslipidemia, diabetes mellitus (DM), hypertension, tobacco use and the metabolic syndrome (MetS). CVD risk factors, particularly dyslipidemia, require aggressive medical management to reduce the high risk of CVD events and death in individuals with NAFLD.

Keywords

Dyslipidemia; Nonalcoholic fatty liver disease; Cardiovascular disease

Background

NAFLD impacts 30–40% of Americans.[1] Nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD, impacts 2–12% of Americans.[2] NASH can lead to the development of cirrhosis and it is predicted that by 2020, NASH cirrhosis will be the leading indication for liver transplantation in the United States.[3]

While NASH can result in end stage liver disease, steatosis and NASH are associated with an increased risk of CVD events and death both independently and by their frequent association with the MetS, insulin resistance and dyslipidemia.[4] A meta-analysis assessing the natural history of NAFD found that while NASH was associated with increased liver-

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related mortality when compared to steatosis, there was no difference in the risk of CVD-related death between NASH and steatosis.[4] Currently, CVD is the leading cause of death in individuals with NAFLD.[5] Modification of CVD risk factors, particularly dyslipidemia, is necessary to decrease CVD morbidity and mortality in individuals with NAFLD. In this review, we will address the need for CVD risk stratification and outline methods for CVD risk management in individuals with NAFLD. While the breadth of data on CVD risk management in NAFLD is expanding, limitations remain. Where data are unavailable for NAFLD specifically, we have drawn from the CVD literature in the general population and in individuals with other CVD risk factors.

Dyslipidemia in NAFLD

Dyslipidemia is frequent in individuals with NAFLD. A substudy from the Multi-Ethnic Study of Atherosclerosis (MEAS) assessed the relationship between radiographically diagnosed NAFLD and dyslipidemia.[6] NAFLD was independently associated with elevated triglyceride levels, increased low-density lipoprotein (LDL) particle concentration, decreased LDL particle size and decreased high-density lipoprotein (HDL) levels after controlling for insulin resistance. These findings have been replicated in individuals with NAFLD from other community cohorts and in individuals with NAFLD and DM.[7, 8] In addition, non-HDL-cholesterol (non-HDL-C) is increased in individuals with NASH.[9] Non-HDL-C is a measure of all atherogenic lipoproteins including very-low density lipoproteins (VLDL), LDL, intermediate-density lipoproteins (IDL) and Lipoprotein a (Lp(a)).[10] Non-HDL-C is calculated from a standard lipid panel (Non-HDL-C= Total cholesterol–HDL) and guidelines cite non-HDL-C<150mg/dL as a secondary target for lipid lowering therapy.[11, 12]

Cardiovascular Disease and NAFLD

CVD events are a frequent cause of morbidity and mortality in individuals with NAFLD. (Table 1) Three community-based studies have demonstrated that individuals with radiographically diagnosed NAFLD have an increased risk of CVD events and mortality compared to individuals without NAFLD.[13–15] Hamaguchi et al. assessed 1637 subjects in a community-based cohort from Japan for NAFLD by ultrasonography.[16] Nineteen percent of the cohort was found to have NAFLD. Cardiovascular events occurred in 5.2% of NAFLD subjects and 1.0% of non-NAFLD individuals over 5 years. (p<0.01) This difference remained statistically significant after adjustment for the MetS. Adams et al. found a high incidence of CV mortality in a US-based cohort.[14] Four hundred twenty individuals with NAFLD were followed for a median of 7.6 years. Individuals with NAFLD had significantly increased mortality when compared to the general population with a standardized mortality ratio of 1.34 (95% CI: 1.003–1.76). Targher et al. found that CVD events and mortality were also more common among diabetic individuals with NAFLD than diabetics without NAFLD [OR: 1.87 (95% CI: 1.2–2.60)].[13]

Histologically defined NAFLD is also associated with an increased CVD risk. Soderberg et al. performed liver biopsies in 256 subjects, 118 of whom had NAFLD which were blindly scored for steatosis and NASH.[17] Individuals with NAFLD (both steatosis and NASH) had a 69% increased mortality compared with the overall population. Ekstedt et al. also found that

individuals with NASH had increased mortality compared to the general population, a difference not seen in those with only steatosis.[18] Again, CVD was the most common cause of death among individuals with NASH. Thus, individuals with both radiographically and histologically defined NAFLD are at increased risk for CVD and mortality.

Cardiovascular Risk Stratification in NAFLD

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 cardiovascular risk in the general population. Incorporating age, gender, cholesterol, HDL, smoking status and hypertension, the FRS predicts an individual's 10-year risk of myocardial infarction or CVD death. Further, 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.[19]

The MetS is frequent in individuals with NAFLD and associated with increased CVD and all-cause mortality.[20, 21] Therefore, assessment for the MetS is an important component of CVD risk stratification. Several definitions for MetS exist.[22] The MetS as defined by the National Cholesterol Education Program (NCEP) requires the presence three or more of the following components:

1. Elevated triglycerides (150mg/dL)

2. Low HDL (<40mg/dl in men, <50mg/dl in women)

3. Elevated fasting glucose (110mg/dL)

4. Hypertension (130/85 mm Hg or on anti-hypertensive medication)

5. Abdominal obesity (waist circumference >102cm in men, >88cm in women)

In addition to evaluation for the MetS, individuals should be evaluated for other CVD risk factors including DM which can be diagnosed using fasting glucose or glycosylated hemoglobin (HbA1C).[23]

Cardiac stress testing, carotid artery intima-media thickness (CIMT) assessment and coronary artery calcium (CAC) score can also add in CVD risk stratification. These modalities can be used to detect subclinical atherosclerotic disease and to predict future CV events.[23–25] Individuals with NAFLD and elevated CVD risk have been found to have increased mean CIMT levels and elevated CAC scores suggesting the utility of these tests for risk stratification in individuals with NAFLD.[26–28]

Management of Dyslipidemia and Cardiovascular Disease Risk in NAFLD

Lifestyle modification, encompassing weight loss and increased physical activity, is the cornerstone of dyslipidemia management in NAFLD. However, for groups with elevated 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 outline treatment goals. (Figure 1)[12] These guidelines were not specifically designed to address dyslipidemia in individuals with NAFLD. However, they can be safely applied to individuals with NAFLD.

Dietary Modification

Little data are available for the preferred diet for individuals with NAFLD. Two small studies have suggested that diets low in carbohydrates may result in a reduction in intrahepatic triglyceride concentration and an improvement in histologically defined NAFLD.[29, 30] Low carbohydrate diets have a beneficial effect on serum lipid levels.[31] For LDL lowering, the NCEP recommends a diet low in saturated fat (<7% of total calories) and cholesterol (<200mg/day). Plant sterols and stanols as well as increased intake of soluble fiber can also be used for dietary lipid lowering.[12]

Recently, a large randomized controlled trial found that subjects who consumed a Mediterranean diet had a reduction in the incidence of cardiac events compared to those receiving only advice on low fat diets.[32] Limited data exist on the benefit of the Mediterranean diet in NAFLD. A trial of 12 subjects with biopsy-proven NAFLD assessed the impact of a Mediterranean diet on hepatic steatosis as assessed by magnetic resonance spectroscopy (MRS).[33] Subjects undertook, in random order, 6 weeks of a low fat, high carbohydrate diet and a Mediterranean diet, separated by a 6 week wash out period. MRS steatosis decreased significantly in the group receiving the Mediterranean diet compared to the low fat, high carbohydrate diet (39% reduction vs. 7% reduction, p=0.012), with no difference in weight loss between groups. This study suggests that in individuals with NAFLD the Mediterranean diet may have benefits beyond the management of dyslipidemia. However, further studies are needed before this diet can be routinely recommended.

Fructose consumption, present in processed foods and beverages, is associated with NAFLD development.[34] The impact of fructose avoidance has yet to be rigorously evaluated but individuals should be advised to limit fructose consumption. The United States Dietary Guidelines for 2010 classifies fructose as an "added sugar" and recommends limiting added sugars to 3 or less servings per day for persons on <2,000 calorie per day diets and 5 servings per day for those on 2,000 calorie diets.

Exercise

Regular exercise is associated with decreased triglycerides and LDL and increased HDL levels.[35, 36] The NCEP recommends at least 30 minutes of moderate activity most days of the week as part of dyslipidemia management.[12] Exercise is independently associated with a reduction in aminotransferase levels and hepatic triglyceride content. Sixty minutes per week of aerobic exercise decreases aminotransferase levels in subjects with NAFLD.[37] A trial of subjects with NAFLD randomized to no exercise or three 30–45 minute cycling sessions weekly found that the cycling group had a significant decrease in hepatic triglyceride content and visceral adipose content without a change in overall body weight.[38] Individuals with NAFLD should be advised to participate in regular, aerobic exercise.

Cigarette Smoking and Alcohol Use

Cigarette smoking is associated with increased CVD and all-cause mortality. The American College of Cardiology recommends that individuals who use tobacco receive counseling regarding smoking cessation and, if needed, referral to tobacco cessation support programs.[23] Moderate alcohol intake, defined as one unit of alcohol daily for women and 2

units daily for men, may increase HDL and apolipoprotein AI levels and decreased risk.[12] Therefore, moderate alcohol use maybe helpful in reducing CVD risk.

Several studies have suggested that mild to moderate alcohol use may be protective against NAFLD development.[39, 40] However, no data exist to determine the impact of alcohol use on existing NAFLD or NASH or on the impact of alcohol use on CVD risk in individuals with NAFLD. Therefore, it is premature to recommend regular alcohol use in individuals with NAFLD.

Obstructive Sleep Apnea (OSA)

OSA is characterized by periods of apnea during sleep resulting in oxygen desaturation. Chronically, OSA increases the risk of the MetS, CVD and sudden death while treatment of OSA improves the MetS and decreases CVD mortality.[41–44][45, 46]

Several studies suggest a relationship between OSA and NAFLD. Animal models have demonstrated that mice exposed to chronic intermittent hypoxia are more likely to develop steatosis and hepatic inflammation.[47, 48] In humans, several studies have demonstrated a relationship between OSA and NAFLD. A study of subjects with OSA and NASH found that the oxygen desaturation index, a measure of OSA severity, was directly correlated with NASH activity score and fibrosis stage even after adjustment for insulin resistance and obesity.[49] Additionally, a prospective study of individuals with radiographically defined NAFLD and OSA found that the initiation of continuous positive airway pressure (CPAP) lead to an improvement in radiographic steatosis.[50] Thus, a potential link between NAFLD and OSA may exist and requires further evaluation. It would be premature to suggest that OSA treatment will improve NAFLD. However, because treatment of OSA does improve the MetS and CVD risk, screening for OSA should be considered in individuals with NAFLD.

Diabetes Mellitus (DM)

DM is associated with an increased risk of CVD. As 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.[51] In addition, specific treatments of DM including metformin may decrease CVD events.[52].

Lipid Lowering Medications

HMG-CoA Reductase Inhibitors

Treatment of dyslipidemia should not be withheld in individuals with NAFLD. HMG-CoA reductase inhibitors or "statins" have a well established role in the primary and secondary prevention of CVD and individuals with NAFLD can benefit from risk reduction.[12] A post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study demonstrated not only that statins are safe in individuals with abnormal liver function

tests presumably due to NAFLD but that individuals with NAFLD who received statins had a significant reduction in cardiovascular events when compared to those with NAFLD not on statins (10% vs. 30%, p<0.0001).[53] Thus, statins significantly reduce cardiovascular events in individuals with NAFLD and should be used for individuals who require lipid lowering therapy.

Early data suggest that statins may also have a specific role in the treatment of NAFLD although this requires confirmation before it can be widely applied.[54] A retrospective trial of statin use in 68 individuals with histologically defined NAFLD found that those who used statins had a reduction in steatosis, despite a higher mean BMI and prevalence of DM, than those not on statins.[55] In addition, the rate of fibrosis development was unexpectedly low in individuals on statin therapy. In individuals with radiographically defined NAFLD, atorvastatin has been shown in several studies to be associated with NAFLD regression.[54, 56, 57] However, a randomized controlled trial of simvastatin in NASH therapy did not result in any histologic benefit.[58] Thus, the impact of statin therapy on NAFLD remains uncertain. Importantly, however, statin hepatotoxicity was not reported in any study, reinforcing that statins are safe in individuals with NAFLD.

In addition to the role of statins in management of dyslipidemia, statins may also play a role in the prevention of hepatocellular carcinoma (HCC).[59] Using a community-based cohort of individuals with DM, a nested case-control study found that a significantly fewer cases (individuals with HCC) were prescribed statins when compared to controls, suggesting a preventive role for statins in HCC development. While this study was not designed to assess HCC prevention in those with NAFLD, its finding may be applicable to those with NAFLD.

Statin hepatotoxicity

Concern for hepatotoxicity associated with statins has led to reluctance on the part of clinicians to treat dyslipidemia in individuals with NALFD.[60] However, the incidence of statin-induced hepatotoxicity in those with NAFLD is vanishingly low and not greater than that experienced in the general population.[61–64] Chalasani et al. evaluated the incidence of aminotransferase elevations in individuals with baseline elevations in aminotransferases (presumably secondary to NAFLD) on statins, and individuals with elevated liver enzymes who did not receive statins[64] When compared to those with elevated liver enzymes not receiving statins, individuals with elevated baseline liver enzymes on statins did not have a higher incidence of either mild-moderate elevations (4.7% vs. 6.4%, P = 0.2) or severe elevations (0.6% vs. 0.4%, P = 0.6). These findings have been replicated in a randomized controlled trial of high dose pravastatin in individuals with chronic liver disease, predominantly from NAFLD.[65]

Omega-3 Fatty Acids

If additional lipid lowering therapy is needed beyond statins, omega-3 fatty acids can be safely given in individuals with NAFLD. Omega-3 fatty acids reduce serum triglycerides by reducing VLDL secretion from hepatocytes. Omega-3 fatty acids in doses of 3–4 grams daily are associated with a decrease in triglycerides (−25–35%) and a small increase in HDL levels (1–3%).[66, 67] Early studies suggest that omega-3 fatty acids may improve

aminotransferase levels and radiographic steatosis in individuals with NAFLD and dyslipidemia and thus, are attractive for dyslipidemia management in individuals with NASH.[68–70]

Fibrates

Fibrates act to lower serum triglycerides while simultaneously increasing HDL. While fibrates reduce cardiovascular mortality among individuals with elevated triglycerides they do not decrease cardiovascular mortality among individuals with normal triglyceride levels. Statins carry a risk of muscle toxicity. When statins are taken in combination with fibrates the risk is increased. This risk can be reduced by using hydrophilic statins (i.e. pravastatin, rosuvasatin, fluvastatin and atorvastatin) which have less muscle penetration than hydrophilic statins, when combination therapy with fibrates is needed.[71, 72]

Fenofibrate has been studied in individuals with NAFLD.[73] In a trial of 16 individuals with biopsy-proven NAFLD, fenofibrate 200mg daily for 48 weeks decreased triglyceride, glucose, gamma-glutamyl transpeptidase and alkaline phosphatase levels. In addition, a decrease in hepatocyte ballooning was seen. However, there was no significant change in steatosis grade, NASH activity score, lobular inflammation or fibrosis. However, a second trial of using clofibrate did not demonstrate a change in aminotransferase levels or histology.[74] No hepatotoxicity was reported from fibrates in any of the above trials. Therefore, while fibrates have not been shown to consistently improve NAFLD histologically, they do offer an effective treatment for hypertriglyceridemia and can be used safely in individuals with NAFLD.

Niacin

Niacin (nicotinic acid) lowers lipids by inhibiting the hepatic production of lipoproteins. Niacin lowers triglyceride levels and is associated with reduced cardiovascular mortality.[75] However, niacin should be used with caution in DM as it can worsen glucose intolerance. As glucose intolerance may be associated with the development and progression of NAFLD, it should not be first line therapy for hypertriglyceridemia.

Lipid Treatment Goals

LDL targets designed to reduce CVD risk have been established by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III). These guidelines provide individualized LDL goals based on the assessment of an individual's CVD risk factors (Figure 1).

Fatty Liver and Newly Approved Lipid Lowering Agents

Statins are effective LDL lowering agents; however, in an important subset of individuals, statins cannot lower LDL to goal treatment levels. Therefore, the search for medications to improve LDL lowering is ongoing. Two new lipid lowering agents have recently been approved. Mipomersen, an anti-sense oligonucleotide binds to and degrades hepatic apoB mRNA, decreasing circulating LDL levels. Mipomersen is effective at LDL lowering in individuals with hyperlipidemia, homozygous familial hypercholesterolemia (HFH) and

statin intolerance.[76–78] However, 11–33% of subjects receiving mipomersen developed elevations in aminotransferase levels >3 times the upper limit of normal (ULN). Of the 14 individuals who developed elevations in aminotransferase levels, steatosis assessed by MRS was found in 12. Two of these individuals underwent liver biopsy. Both patients were found to have NASH, one without fibrosis and one with stage 1 fibrosis. These findings suggest an association between mipomersen use and fatty liver.

A second mechanism for lipoprotein reduction is through microsomal triglyceride transferase protein (MTTP) inhibition. MTTP catalyzes the formation of apoB containing proteins in the liver. Lomitapide, an MTTP inhibitor, has been shown in individuals with hypercholesterolemia and HFH to lower LDL levels. However, like mipomersen, lomitapide is associated with frequent elevations in aminotransferase levels and radiographic steatosis.[79, 80] As a result, lomitapide is approved for HFH but comes with a black box warning for hepatotoxicity. Thus, while mipomersen and lomitapide are beneficial in lowering LDL levels, they are associated with hepatotoxicity, possible NASH development and cannot currently be recommended for lipid lowering therapy in individuals with NAFLD.

Future Directions

NAFLD is a rising epidemic in the United States and is associated with cardiovascular mortality. Many individuals with NAFLD will die from CVD prior to the development of end stage liver disease. Thus, the careful management of CVD risk factors including dyslipidemia in individuals with NAFLD is essential to reduce CVD-related mortality. Gastroenterologists and hepatologists should play an active role in comprehensive CVD risk assessment including screening for dyslipidemia, DM, the MetS, cigarette smoking and alcohol use. Management of CVD risk factors should be grounded in counseling of lifestyle modification including weight loss, dietary changes and increased physical activity. When needed, this should be accompanied by lipid lowering medication with treatment goals set by the NCEP. Comprehensive evaluation and aggressive management of CVD risk factors in individuals with NAFLD could significantly decrease CVD events and deaths.

Acknowledgments

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
CVD	Cardiovascular disease
CV	Cardiovascular
NASH	Nonalcoholic steatohepatitis
MetS	Metabolic syndrome

| **HDL** | High-density lipoprotein |
Non-HDL-C	Non-HDL-cholesterol
VLDL	Very-low density lipoproteins
LDL	Low-density lipoproteins
IDL	Intermediate-density lipoproteins
Lp (a)	Lipoprotein a FRS: Framingham Risk Score (FRS)
hs-CRP	High sensitivity C-reactive protein
HbA1C	Glycosylated hemoglobin

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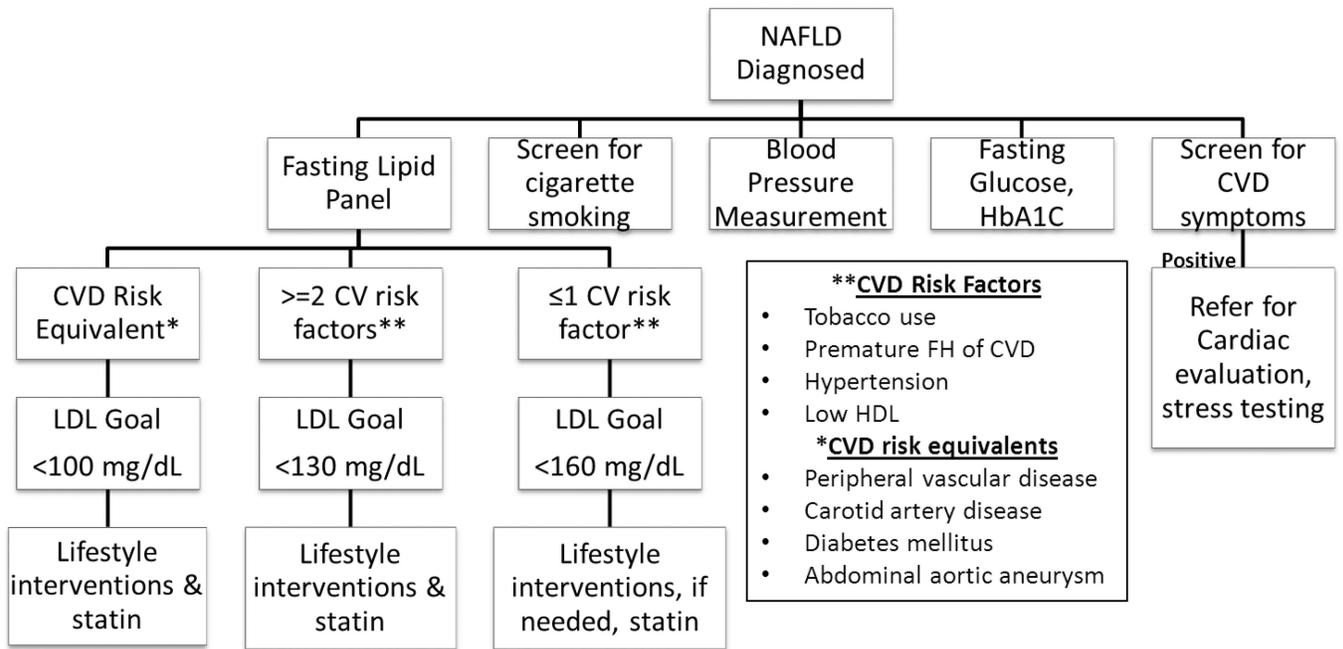
Figure 1.

Cardiovascular Risk Assessment in NAFLD

*Adapted from the National Cholesterol Education Program ATP III Guidelines

NAFLD: non-alcoholic fatty liver disease, HbA1C: glycosylated hemoglobin, CVD: cardiovascular disease, LDL: low density lipoprotein, FH family history, HDL: high density lipoprotein

Table 1

Studies of Cardiovascular Risk in NAFLD

Author	Cohort	Number of subjects	Modality of NAFLD Diagnosis	Follow-up (years)	Risk or Incidence of CVD Events	Comments
Hamaguchi et al[16]	Japanese community cohort	1637	Ultrasound	5	CVD Events NAFLD 5.2% Non-NAFLD 1.0%, p<0.001	Independent of MetS and CV risk factors
Targher et al[13]	United States Diabetic Cohort	2103	Ultrasound	6.5	Increased fatal and non-fatal CVD events OR 1.87 (1.2–2.6)	Independent of MetS and CV risk factors, DM
Haring et al[81]	German community cohort	4160	Ultrasound	7.3	Increased CVD mortality in men with NAFLD HR 6.22 (1.22–31.62)	Independent of CV risk factors No difference seen in women
Adams et al[14]	United States community based cohort	420	Ultrasound	7.6	Percentage of Deaths from CVD Events: 25%	
Soderberg et al[17]	Swedish tertiary care cohort	118	Biopsy	24	Increased total mortality in NAFLD, mainly CVD-related SMR 1.69 (1.24–2.25)	Matched controls
Ekstedt et al[18]	Swedish tertiary care cohort	129	Biopsy	13.7	Increased mortality, primarily CVD in NASH pts RR 1.38 P=0.006	Matched controls
Schwimmer et al[82]	Children at autopsy	817	Biopsy	NA	Increased coronary and aortic atherosclerosis in NAFLD OR 1.8 (p<0.001)	Independent of obesity
Dam-Larsen et al.[83]	Danish population based cohort	170	Biopsy	20.4	Percentage of Deaths from CVD Events: 38%	Only Steatosis included
Rafiq et al.[84]	US tertiary referral based cohort	173	Biopsy	18.5	Percentage of Deaths from CVD Events: 12.7%	

CVD: cardiovascular disease, NAFLD: non-alcoholic fatty liver disease, MetS: metabolic syndrome, NASH: non-alcoholic steatohepatitis, OR: odds ratio, SMR: standardized mortality ratio, HR: hazard ratio, RR: risk ratio