Arteriosclerosis, Thrombosis, and Vascular Biology

AHA SCIENTIFIC STATEMENT

Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association

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ABSTRACT: Nonalcoholic fatty liver disease (NAFLD) is an increasingly common condition that is believed to affect >25% of adults worldwide. Unless specific testing is done to identify NAFLD, the condition is typically silent until advanced and potentially irreversible liver impairment occurs. For this reason, the majority of patients with NAFLD are unaware of having this serious condition. Hepatic complications from NAFLD include nonalcoholic steatohepatitis, hepatic cirrhosis, and hepatocellular carcinoma. In addition to these serious complications, NAFLD is a risk factor for atherosclerotic cardiovascular disease, which is the principal cause of death in patients with NAFLD. Accordingly, the purpose of this scientific statement is to review the underlying risk factors and pathophysiology of NAFLD, the associations with atherosclerotic cardiovascular disease, diagnostic and screening strategies, and potential interventions.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ diabetes mellitus ■ hepatocytes ■ hypertriglyceridemia ■ insulin resistance ■ metabolic syndrome ■ nonalcoholic fatty liver disease ■ triglycerides

Nonalcoholic fatty liver (NAFL) disease (NAFLD) is a common disorder that is estimated to affect >25% of adults worldwide and more than half of patients with type 2 diabetes, with large variations between regions and by ethnicity.[1] The prevalence in 2016 to 2018 was lowest in Africa (13.5%); intermediate in the United States (24%), Europe (23%), and East Asia (27%); and highest in Mexico, Central and South America (31%), the Middle East (32%), and South Asia (33%),[1,2] but these results may underestimate the true prevalence.

In the United States, the prevalence of NAFLD varies by race and ethnicity. Hispanic individuals have the highest prevalence rates, followed by White and Black individuals (21%, 12.5%, and 11.6%, respectively).[3,4] Risk among Hispanic people is not uniformly distributed among subgroups. For example, in MESA (Multi-Ethnic Study of Atherosclerosis), NAFLD prevalence among those of Mexican origin was 33%, but it was only 16% and 18% among those of Dominican and Puerto Rican origin, respectively.[5] This demonstrates that even within specific ethnic groups, it is not possible to generalize about the prevalence and incidence of NAFLD. Both NAFLD and nonalcoholic steatohepatitis (NASH), a subset of NAFLD associated with histological inflammation and cell injury, may be about twice as prevalent among men compared with women.[6] A common trend among all groups is a progressive increase in the incidence of NAFLD in adults and children in proportion to rising rates of obesity, the metabolic syndrome, and type 2 diabetes, which may lead to a global prevalence of NAFLD >35% within the next decade.

Accurate prevalence rates for NASH are difficult to approximate because diagnosis currently requires a liver biopsy for histology. In 1 study, among patients with NAFLD diagnosed by ultrasonography, biopsy-proven NASH was demonstrated in 19.4% of Hispanic and 9.8% of White patients (P=0.03).[7] Among liver transplant donors, NASH prevalence rates vary from 1.4% to 15%.[8–10] The estimated prevalence of NASH is 3% to 6%,[11] with potentially higher

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rates among populations with the highest prevalence of NAFLD. Risk factors for NASH include type 2 diabetes, dyslipidemia, and obesity, all of which are prevalent. The prevalence of NASH in type 2 diabetes may exceed 37%.[12] In a recently published study, 664 asymptomatic middle-aged American men and women with a mean body mass index (BMI) of 30.5 kg/m^2 (15% with type 2 diabetes) referred for colonoscopy were assessed for hepatic steatosis and liver stiffness by magnetic resonance and ultrasound imaging. Patients with abnormal imaging parameters were offered liver biopsy. The prevalence of NAFLD in this cohort was 38%, and biopsy-confirmed NASH was identified in 14%.[13]

The underdiagnosis of NAFLD is a primary barrier to optimal medical management and interferes with assessments of disease prevalence and complications. Contributors include a lack of awareness of NAFLD among patients and health care professionals, the initially asymptomatic nature of the condition, and a lack of standardized diagnostic tools. Measurements of hepatic aminotransferase levels in plasma and liver ultrasonography are commonly used screening tools but lack sensitivity for diagnosis and monitoring of NAFLD.

NAFLD is associated with visceral adiposity, atherogenic dyslipidemia (low high-density lipoprotein cholesterol, elevated triglycerides/remnant lipoproteins, and small dense low-density lipoprotein [LDL]), and insulin resistance with or without hyperglycemia. Although a portion of the risk of cardiovascular complications from NAFLD is attributable to these comorbidities, a diagnosis of NAFLD is associated with greater risk than the sum of these individual components.[14] Although 10% to 25% of patients with NAFLD may be complicated by NASH, which can lead to cirrhosis, hepatocellular carcinoma, and liver failure, the leading cause of mortality in patients with NAFLD is cardiovascular disease (CVD). Hence, the identification of NAFLD is an important aspect of CVD prevention and treatment that necessitates increased awareness among clinicians. The purpose of this scientific statement is to succinctly highlight the pathophysiology, association with CVD, diagnostic strategies, and potential interventions for NAFLD. An informational handout about NAFLD was also developed for patient education. It is available as Supplemental Material.

TERMINOLOGY

Although there are some differences in definitions between organizations, it is important to define the terminology for NAFLD. Hepatic steatosis refers to ectopic deposition of triglycerides in the liver. Alcohol-associated liver disease is associated with liver injury and characterized by hepatic steatosis that is attributable to excess alcohol intake. Many patients with NAFLD consume modest amounts of alcohol, which may contribute to the development of hepatic steatosis in this scenario, but alcohol consumption is not the underlying basis for the disorder. NAFLD is characterized by a spectrum of conditions that range from early stages of hepatic steatosis to more advanced stages such as NASH and hepatic cirrhosis. NAFLD is defined as the presence of hepatic steatosis (identified by imaging or liver biopsy) in the absence of excess alcohol intake or other causes of secondary or monogenic hepatic steatosis.[15] NAFL is typically defined as the histological finding of ≥5% fat content in the absence of hepatocellular injury (eg, ballooning, fibrosis). NASH is defined as ≥5% fat content in association with histological evidence of hepatocellular inflammation and cell death (eg, ballooning), as well as varying degrees of fibrosis, with stages 0 to 4 defined on the basis of the presence and extent of fibrosis.[15]

Recently, an international consensus panel proposed a change in the nomenclature of NAFLD to metabolic-associated fatty liver disease.[16] Among the reasons provided to support the name change was that the diagnosis of NAFLD requires the exclusion of excess alcohol intake and other chronic liver diseases. Given the high prevalence of NAFLD in the population, the likelihood of NAFLD coexisting with another liver disease is significant. To address this issue, an international expert consensus statement has proposed that positive criteria be used for the diagnosis of metabolic-associated fatty liver disease.[17] These criteria require the presence of hepatic steatosis in addition to 1 of the following: overweight/obesity, type 2 diabetes, or evidence of metabolic dysregulation. Because the change in nomenclature is new and has not yet been universally adopted,[18] we continue to use the term NAFLD for this scientific statement.

RISK FACTORS FOR NAFLD

There is overlap among risk factors for the metabolic syndrome and NAFLD, but patients can develop the metabolic syndrome without NAFLD and vice versa. Moreover, although a condition such as type 2 diabetes is associated with increased risk of NAFLD, the association is bidirectional, which means a diagnosis of NAFLD in a nondiabetic patient is associated with increased risk of incident type 2 diabetes. These interactions are related to the contribution of visceral adiposity and insulin resistance to the pathogenesis of NAFLD and type 2 diabetes. A summary of risk factors, including medications, is shown in Table 1.

Lifestyle and Acquired Conditions

Lifestyle plays an important role in the development and treatment of NAFLD.[19] Dietary factors that aggravate hypertriglyceridemia, hyperglycemia (fasting and postprandial), insulin resistance, and weight gain are associated with increased risk for the development of NAFLD. Increased carbohydrate intake, particularly in the form of

Table 1. Risk Factors for NAFLD

Metabolic/endocrine
Insulin resistance
Impaired glucose tolerance and diabetes
Hypertriglyceridemia, particularly with imbalance between hepatic triglyceride production and clearance
Visceral adiposity
Metabolic syndrome
Polycystic ovarian syndrome
Chronic kidney disease
Lipodystrophy
Hypobetalipoproteinemia (attributable to defects in apoB)
Lysosomal acid lipase deficiency
Defects in mitochondrial fatty acid oxidation (congenital and acquired)
Drugs
Alcohol
Amiodarone
Aspirin (eg, Reye syndrome)
Corticosteroids
Lomitapide
Mipomersen
Nonsteroidal anti-inflammatory drugs
Reverse transcriptase inhibitors
Tamoxifen
Tetracycline
Valproic acid
Genetic factors
Family history of NAFLD
Variants in several genes
GCKR
MBOAT7
PNPLA3
TM6SF2
HSD17B13

apoB indicates apolipoprotein B; and NAFLD, nonalcoholic fatty liver disease.

simple sugars, can aggravate hypertriglyceridemia and hyperglycemia in many patients, but there are important exceptions. Dietary fructose intake is associated with reduced glycemic index compared with glucose, but it is more likely to aggravate insulin resistance and hypertriglyceridemia. In addition, among patients with severe hypertriglyceridemia (plasma triglycerides >500 mg/dL), weight reduction is likely to reduce triglyceride levels. Reduced dietary fat intake may reduce triglyceride levels, especially if very severely elevated. However, increased carbohydrate intake may also increase triglyceride levels in some individuals in the 500- to 1000-mg/dL range. Weight gain is a multifactorial condition that aggravates multiple risk factors for NAFLD, including increased triglyceride production, insulin resistance, hyperglycemia, and hypertriglyceridemia. Although obesity is common among patients with NAFLD, ≈10% to 20% of Americans and Europeans with NAFLD are lean by BMI criteria.[2] Physical inactivity favors weight gain and insulin resistance, which contribute to development of NAFLD.

Type 2 Diabetes

Type 2 diabetes and impaired glucose tolerance are important risk factors for the development of NAFLD and NASH.[20] Type 2 diabetes is associated with insulin resistance, hyperglycemia, hypertriglyceridemia, increased free fatty acid flux from adipose tissue to the liver, and increased visceral adiposity, all of which are associated with increased risk of NAFLD and NASH. Not all glucose-lowering interventions are associated with improvement in hepatic steatosis, whereas treatment with medications that augment insulin sensitivity is associated with improvement.

Dyslipidemia

Hypertriglyceridemia is associated with insulin resistance, impaired glucose tolerance, type 2 diabetes, visceral adiposity, obesity, and the metabolic syndrome, all of which are associated with increased risk of NAFLD. As described in the section on pathophysiology, the plasma triglyceride concentration may be less important than the balance between rates of triglyceride synthesis, very-low-density lipoprotein (VLDL) secretion, free fatty acid flux, hydrolysis of triglycerides in hepatocyte lipid droplets, and intrahepatic fatty acid oxidation. If triglyceride production exceeds the rates of clearance/secretion, ectopic deposition of excess triglycerides in the liver will be favored.

Metabolic Syndrome

We do not yet have a universal consensus on defining the metabolic syndrome, but visceral adiposity and insulin resistance are key underlying features of the condition. In the United States, the diagnosis of the metabolic syndrome is based on the presence of 3 or more of the following: increased waist circumference (men >40 in, women >35 in), hyperglycemia (fasting plasma glucose ≥100 mg/dL), hypertriglyceridemia (fasting triglycerides ≥150 mg/dL), low high-density lipoprotein cholesterol (men <40 mg/dL, women <50 mg/dL), and elevated blood pressure (≥130/85 mm Hg). The association of the metabolic syndrome with insulin resistance, hyperglycemia, visceral adiposity, and hypertriglyceridemia contributes to increased risk of NAFLD, but it is also possible that the presence of NAFLD negatively affects features of the metabolic syndrome. Metabolic syndrome is also associated with increased risk of hepatic steatohepatitis and fibrosis.[21]

Lipodystrophy

Lipodystrophy can be congenital or acquired and is characterized by diminished adipose tissue, either total or partial. The inability to store fat in adipose tissue depots is associated with severe insulin resistance and ectopic triglyceride deposition, including in the liver, which frequently demonstrates features of NASH and NAFLD in both total and partial forms of lipodystrophy.[22]

Chronic Kidney Disease

A high prevalence of chronic kidney disease exists among patients with NASH. Both NASH and chronic kidney disease are associated with visceral obesity, type 2 diabetes, metabolic syndrome, and insulin resistance.[23] The severity of NASH histology is associated with decreased kidney function independently of insulin resistance and other components of the metabolic syndrome,[24] although the presence of type 2 diabetes has been shown to predict renal dysfunction in patients with NASH.[25] Moreover, a meta-analysis showed that the presence and severity of NAFLD were associated with increased risk and severity of chronic kidney disease.[26] Mechanisms proposed to account for how NAFLD might potentiate renal injury include lipoprotein dysmetabolism and altered hepatic secretion of fibroblast growth factor-21, fetuin-A, insulin-like growth factor-1, and syndecan-1. Conversely, chronic kidney disease may mutually aggravate NAFLD and associated metabolic disturbances through altered intestinal barrier function and microbiota composition, accumulation of uremic toxic metabolites, and alterations in prereceptor glucocorticoid metabolism.[27]

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome is characterized by chronic anovulation and hyperandrogenism and is strongly associated with obesity and insulin resistance, which are 2 key features of NASH. NAFLD and polycystic ovarian syndrome are direct manifestations of insulin resistance. About 25% to 40% of patients with polycystic ovarian syndrome have evidence of NASH.[28,29] A systematic review and meta-analysis demonstrated that patients with polycystic ovarian syndrome have increased prevalence of NAFLD with an odds ratio of 2.5 and that the presence of NAFLD is associated with high serum androgen levels, obesity, and insulin resistance.[30]

PATHOGENESIS OF NAFLD

The initial stages of hepatic steatosis involve ectopic accumulation of triglycerides in the liver. Several sources of fatty acids are used for hepatic synthesis of ectopically deposited triglycerides, but the majority are typically derived from increased flux of free fatty acids resulting from excess hydrolysis of adipose tissue triglycerides attributable to unsuppressed hormone-sensitive lipase in the setting of insulin resistance. There also are contributions from increased intrahepatic de novo fatty acid synthesis from excess carbohydrates, as well as uptake from plasma of dietary derived chylomicrons and hepatically synthesized VLDL. Hepatic triglyceride assembly is generally coordinated with VLDL synthesis and secretion, with intrahepatic triglycerides stored in intracellular lipid droplets. Hepatic steatosis occurs when there is an imbalance between hepatic lipid storage and lipid clearance, thereby favoring excessive triglyceride storage in hepatocyte lipid droplets. Factors that may contribute to this imbalance include (1) deviations in the relative size of the intrahepatic pool of fatty acids, (2) rates of triglyceride and apolipoprotein B (apoB) synthesis, (3) rates of lipolysis of lipid droplet triglycerides, and (4) rates of fatty acid β-oxidation. The formation of microvesicular (small) and macrovesicular (large) lipid droplets is a bidirectional process that can be diminished or reversed by interventions that reduce fatty acid uptake and de novo synthesis, decrease triglyceride synthesis, increase lipolysis, increase fatty acid oxidation, or increase VLDL production and secretion.

It has been challenging to predict which patients will progress from NAFL to NASH and cirrhosis. Among those patients who develop progressive disease, there is additional heterogeneity in the tempo of the disease, with some patients experiencing rapid progression from steatohepatitis to fibrosis and cirrhosis and, in some cases, hepatocellular carcinoma. The rapidity of progress is best predicted by the extent of fibrosis observed on the initial liver biopsy. Other patients with NAFL may have an indolent course of progression over many years. It is important to emphasize that although lack of progression from NAFL to NASH is associated with the best prognosis for liver outcomes, uncomplicated NAFL is nonetheless associated with increased risk of CVD.

PREDISPOSING GENETIC FACTORS

Because the majority of patients with NAFL appear not to be at risk of progression to NASH and cirrhosis, there is great interest in identifying genetic factors that may augment the risk of NAFL and more advanced forms of NAFLD. One notable risk factor for NAFL and progression to all stages of NAFLD that was identified more than a decade ago is a variant in the gene encoding patatin-like phospholipase domain containing protein 3 (*PNPLA3*).[31] The prevalence of NAFLD in various countries around the world is associated with the local prevalence of *PNPLA3* genetic variants.[2] Polymorphisms in additional genes that are associated with increased risk of NAFLD include glucokinase regulatory protein (*GCKR*), membrane bound O-acyltransferase domain containing 7 (*MBOAT7*), and

Table 2. Summary of Studies That Evaluated the Association Between NAFLD and ASCVD Risk

Reference	NAFLD diagnosis	Patients, n	Type of study	Impact of NAFLD on CVD outcomes or ASCVD compared with control subjects after adjustment for risk factor covariates
Jepsen et al,[34] 2003	Ultrasound	1804	Retrospective	OR, 2.1 for CVD mortality
Targher et al,[35] 2007	Ultrasound	2839	Cross-sectional	OR, 1.49 for CAD, PAD, and cerebrovascular disease in type 2 diabetes
Hamaguchi et al,[36] 2007	Ultrasound	1637	Prospective	HR, 4.1 for nonfatal CVD events
Santos et al,[37] 2007	Ultrasound	505	Cross-sectional	OR, 1.73 for coronary calcification
Haring et al,[38] 2009	Ultrasound	4160	Prospective	HR, 6.22 for all-cause and CVD mortality
Assy et al,[39] 2010	CT	61	Cross-sectional	OR, 2.03 for coronary calcification
Chen et al,[40] 2010	Ultrasound/CT	295	Cross-sectional	OR, 2.46 for CAC >100
Wong et al,[41] 2011	Ultrasound	612	Prospective	OR, 2.31 for significant coronary artery disease (>50% obstruction)
Targher et al,[42] 2012	Ultrasound	343	Cross-sectional	OR, 7.6 for CAD, PAD, and cerebrovascular disease in type 1 diabetes
Kim et al,[43] 2012	Ultrasound	4023	Cross-sectional	OR, 1.32 for CAC >10
Zhou et al,[44] 2012	Ultrasound	3543	Prospective	OR, 3.0 for CVD mortality
Stepanova and Younossi,[45] 2012	Ultrasound	20 050	Prospective	OR, 1.23 for CVD events
Ekstedt et al,[46] 2015	Liver biopsy	229	Retrospective	HR, 1.55 for CVD mortality
Mellinger et al,[47] 2015	CT	3014	Cross-sectional	OR, 1.20 for CAC score >90th percentile for age
Mantovani et al,[48] 2016	Ultrasound	286	Retrospective	OR, 6.73 for incident cardiovascular events in type 1 diabetes
Pais et al,[49] 2016	Fatty Liver Index	5671	Retrospective	NAFLD severity correlates with CIMT and carotid plaque severity
Yoshitaka et al,[50] 2017	Ultrasound	1647	Prospective	HR, 10.4 in nonoverweight, 3.1 in overweight for incident cardiovascular events
Mahfood Hadad et al,[51] 2017	Ultrasound	25 837 (11 studies)	Meta-analysis	RR, 1.77 for incident CVD, 1.43 for cardiovascular mortality
Zhou et al,[52] 2018	Ultrasound/CT	8346 (6 studies)	Meta-analysis	OR, 2.20 for incident CVD in patients with diabetes
Kapuria et al,[53] 2018	Ultrasound/CT	42 410 (12 studies)	Meta-analysis	OR, 1.64 for higher CAC scores
Sinn et al,[54] 2019	Ultrasound	111 492	Retrospective	HR, 1.54 for myocardial infarction
Pais et al,[55] 2019	Fatty Liver Index	2554	Retrospective	NAFLD correlated with CIMT, CAC, and carotid plaque

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CIMT, carotid intima-media thickness; CT, computed tomography; CVD, cardiovascular disease; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PAD, peripheral artery disease; and RR, relative risk.

transmembrane 6 superfamily member 2 (*TM6SF2*).[32] Polymorphisms in 17β-hydroxysteroid dehydrogenase type 13 (*HSD17B13*) are associated with protection from NASH, and this protection is independent of liver triglycerides.[32,33] It is plausible that the majority of individuals with progressive NAFLD may have pathogenic polymorphisms in 1 (or more) of these genes or possibly polygenic risk, but more systematic studies of the associations of gene variants with increased or decreased risk of NAFLD are needed to verify this possibility.

NAFLD AND ATHEROSCLEROTIC CVD RISK

NAFLD is an underappreciated and independent risk factor for atherosclerotic CVD (ASCVD) even after adjustment for ASCVD risk factor covariates in a large number of investigations (Table 2).[34–55] Subclinical CVD and many other cardiovascular risk factors are increased among patients with NAFLD/NASH.[56–58] Risk factors for ASCVD are also increased by NAFLD; severity of NAFLD is associated with a higher incidence of ASCVD risk factors such as diabetes and hypertension.[59] The underlying risk factors for NAFLD such as dyslipidemia and dysregulation of glucose homeostasis contribute to the increased ASCVD risk in NAFLD, but the predilection for ectopic fat deposition in the liver and other tissues seems to be associated with heightened risk of ASCVD beyond the risk attributable to traditional risk factors. In addition to the aforementioned factors, NAFLD is associated with endothelial dysfunction, heightened systemic inflammatory tone,[60,61] and ectopic fat deposition in other organs (eg, pancreas, skeletal muscle, and epicardium). Increased epicardial fat pad volume correlates highly with heightened intramyocardial inflammation, endothelial dysfunction, and accelerated atherogenesis.[62] Although the results of a previous meta-analysis suggested that NAFLD was associated with all-cause mortality and not CVD mortality[63] and results of a recent analysis demonstrated that fibrosis stages F3 and F4 were associated with increased liver complications and total mortality,[64] ASCVD is the principal cause of death in patients with NAFLD.[65]

NAFLD is a consequence of profound systemic disturbances in lipid metabolism.[66] In the setting of insulin resistance, there is metabolic dysregulation of visceral adipose tissue. Within adipocytes, hormone-sensitive lipase is no longer appropriately inhibited by insulin, resulting in increased lipolysis of adipocyte triglycerides and circulating levels of free fatty acids.[67] As the flux of fatty acids to the liver increases, fatty acids can

be disposed of through a variety of pathways: (1) Fatty acids can be transported into mitochondria and consumed via β-oxidation; (2) they can be reassimilated into triglycerides, packaged into VLDL particles, and secreted into the circulation; (3) glycerol and odd chain fatty acids arising from triglycerides can be diverted to gluconeogenesis; and (4) if these systems are overwhelmed, excess triglyceride can form cytosolic fat droplets, leading to the development of NAFLD. The propensity for increased liver fat deposition is exacerbated by augmented de novo hepatic lipogenesis induced by insulin resistance.[68]

NAFLD IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION AND CORONARY ARTERY BYPASS GRAFT SURGERY

Patients with NAFLD who undergo coronary angiography have an increased likelihood of having percutaneous coronary interventions or meeting criteria for coronary artery bypass graft surgery. Patients with NAFLD undergoing coronary artery bypass graft surgery have increased systemic markers of inflammation compared with individuals without NAFLD. Fatal and nonfatal outcomes after coronary artery bypass graft surgery may be increased in the context of NAFLD.[69,70]

HYPOBETALIPOPROTEINEMIA AND NAFLD

Hypobetalipoproteinemia is an uncommon condition associated with low plasma levels of LDL-C <50 mg/dL, often a consequence of truncation pathogenic variants in the gene encoding apoB.[71] This results in interference with hepatic synthesis of VLDL attributable to abnormal apoB folding and triglyceride accrual during MTP (microsomal transfer protein)–mediated VLDL assembly. Consequently, excess triglycerides in proportion to apoB can in turn lead to ectopic triglyceride deposition and hepatic steatosis. Although this form of NAFLD is mechanistically distinct from more typical NAFLD resulting from insulin resistance and features of the metabolic syndrome, it is unknown whether NAFLD that occurs in association with hypobetalipoproteinemia has a more benign course. Moreover, variants in *TM6SF2* also result in reduced hepatic VLDL secretion but are associated with increased risk of NAFLD.[32] Treatment with the lipid-lowering drugs mipomersen (an antisense molecule that blocks apoB mRNA) and lomitapide (an inhibitor of MTP) recapitulates defects in VLDL synthesis and development of NAFLD similar to hypobetalipoproteinemia[72] and has not been documented to cause NASH in the short-term follow-up, but the long-term risk of NASH is unknown.

Loss-of-function variants in the gene for proprotein convertase subtilisin/kexin type 9 (*PCSK9)* also cause hypobetalipoproteinemia but through a different mechanism resulting from increased LDLR activity and increased hepatic clearance of LDL particles from plasma.[73] This form of hypobetalipoproteinemia is not associated with hepatic steatosis.

Familial combined hypobetalipoproteinemia is a rare disorder that is associated with low levels of VLDL, LDL, and high-density lipoprotein particles in plasma that are a consequence of homozygous or compound heterozygous loss-of-function pathogenic variants in the gene for angiopoietin like 3 (*ANGPTL3)*.[74] Production of VLDL may be normal in this condition, but extrahepatic clearance of triglyceride-rich lipoproteins is accelerated as a consequence of increased activity of lipoprotein lipase and endothelial lipase, as well as decreased levels of apo CIII. The association between this condition and risk of NAFLD is undefined.

SAFETY OF STATINS IN NAFLD

Statins have an essential role in primary and secondary prevention of ASCVD. Although statin treatment is associated with a low risk of hepatic transaminase elevations, it is well documented that statins can be used safely and are not contraindicated in patients with NAFLD who have normal liver function.[75,76] Results from post hoc analyses of data from statin trials suggested that cardiovascular outcomes may improve more in patients with mildly to moderately elevated aminotransferase levels (possibly resulting from NAFLD) compared with individuals with normal liver tests, in association with improved aminotransferase levels in the majority of individuals.[77–79]

STRATEGIES FOR SCREENING FOR NAFLD AND NASH

A common misconception is that confirmation of normal plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on routine laboratory testing is sufficient to exclude a diagnosis of NAFLD, but many patients with NAFLD have aminotransferase levels in the normal range, although frequently approaching the upper limit of normal. Moreover, hepatic ultrasonography is a relatively insensitive tool for identification of hepatic steatosis. As a consequence, many patients with NAFLD are undiagnosed or may be misdiagnosed as not having NAFLD. In some cases, patients may not be identified as having NAFLD until after they have progressed to NASH with cirrhosis or end-stage liver disease. Several strategies for identification of patients with increased risk or extant NAFLD have been developed. Because the definitive diagnosis of NAFLD is established on the basis of histological findings from liver biopsy, which is often

unavailable, additional strategies have been developed to facilitate a tentative nonhistological diagnosis of NAFLD and to determine which patients warrant liver biopsy.

Patients with elevated plasma activities of ALT and AST warrant evaluation for causes of aminotransferase elevations and consideration of assessment for hepatic steatosis, particularly when risk factors for NAFLD are present. Patients with normal ALT and AST levels can be considered for evaluation for hepatic steatosis when multiple risk factors are present, particularly type 2 diabetes. The NAFLD fibrosis score is a tool for predicting the presence of fibrosis that is calculated with an online formula using readily available clinical data consisting of age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio.[80] The area under the receiver-operating characteristic curve for predicting advanced fibrosis is 0.85. Similarly, a simpler fibrosis-4 index score calculated from age, AST, ALT, and platelet count also predicted the presence or absence of advanced fibrosis, but the area under the receiver-operating characteristic curve was less robust than that of the NAFLD fibrosis score.[81]

Options for imaging studies include hepatic ultrasonography, computed tomography (CT) imaging, and magnetic resonance imaging (MRI), as summarized below. Advantages of ultrasonography include the relatively low cost, but the disadvantage is the relative insensitivity for identification of hepatic steatosis. If ultrasonography identifies hepatic steatosis in the absence of excess alcohol intake or causes of secondary or monogenic hepatic steatosis, a presumptive diagnosis of NAFLD can be made. CT imaging has greater sensitivity for detection of hepatic steatosis but has higher cost compared with ultrasonography and has the downside of exposure to ionizing radiation. MRI and magnetic resonance spectroscopy are excellent but expensive noninvasive tools for the detection and quantification of hepatic steatosis that have been used in many clinical trials but are more difficult to obtain for clinical use. Although these imaging studies are useful for identifying the presence and severity of hepatic steatosis, their utility for identifying fibrosis and steatohepatitis is limited.

Vibration-controlled transient elastography (ie, FibroScan) is an ultrasound-based method for noninvasive assessment of elasticity of the liver (ie, liver stiffness measurement) that is approved by the US Food and Drug Administration (FDA) for assessing liver disease in children and adults.[82] This imaging modality is becoming more readily available for clinical use and is efficacious for assessing steatosis and estimating the extent of fibrosis. In 1 study, the area under the receiver-operating characteristic curve for detection of advanced fibrosis was 0.93. In many centers, this imaging study is performed and interpreted by hepatologists. Magnetic resonance elastography is an additional tool to assess hepatic fibrosis.

Liver biopsy is the definitive test for diagnosis of more advanced stages of NAFLD that include hepatic steatosis, NASH, and cirrhosis, but it is an expensive procedure that is associated with risk of morbidity and very low risk of death.[83] Liver biopsy is not required in many patients but may be considered when the risk of advanced NASH is sufficiently elevated to warrant liver biopsy or when liver biopsy is required to exclude other causes of liver disease. Consultation with a hepatologist is warranted. Elevated NAFLD risk scores such as the NAFLD fibrosis score and fibrosis-4 index score and evidence of fibrosis by liver stiffness measurement are potential indications for liver biopsy. The enhanced liver fibrosis score is based on plasma extracellular matrix protein biomarkers, has a high negative predictive value, and has been recommended by the National Institute for Health and Care Excellence NAFLD guidelines as a potential additional tool for identifying patients who may benefit from liver biopsy.[84,85] The presence of the metabolic syndrome or type 2 diabetes may lower the threshold for consideration of liver biopsy.

American Heart Association.

Summary of Diagnostic Imaging Tools: Pros, Cons, Sensitivity, and Specificity

1. Hepatic ultrasonography. Ultrasound is frequently used as the imaging modality of choice for detecting and evaluating NAFLD because it is noninvasive, does not expose the patient to radiation, and is relatively inexpensive.[86,87] Hepatic steatosis is detectable by ultrasound when >20% of hepatocytes contain lipid droplets.[88] The utility of ultrasound for assessment of NAFLD is limited because it is nonquantitative, subjective, less accurate for detecting mild disease/more accurate for moderate to severe disease, and unreliable for detecting fibrosis.[89] Ultrasound for detecting moderate to severe hepatic steatosis has a sensitivity and specificity of 79.7% and 86.2%, respectively.[90]
2. Vibration-controlled transient elastography (FibroScan). The Controlled Attenuated Parameter score is derived from the vibration-controlled transient elastography signal and is a convenient office-based measurement that accompanies the liver stiffness measurement. This measurement discriminates 4 grades of steatosis: S0, 0% to 10%; S1, 11% to 33%; S2, 34% to 66%; and S3, >67%. According to biopsy comparisons in a characteristic study,[82] the Controlled Attenuated Parameter score identified patients with steatosis with area under receiver-operating characteristic curves of 0.87 (95% CI, 0.82–0.92) for S≥S1, 0.77 (95% CI, 0.71–0.82) for S≥S2, and 0.70 (95% CI, 0.64–0.75) for S=S3.
3. CT. When unenhanced CT imaging is used to identify steatosis, the severity of steatosis correlates with the magnitude of attenuation

measured in Hounsfield units.[91] The greater the steatosis is, the greater the attenuation is. Hence, CT imaging provides a more quantitative assessment of the degree of steatosis. However, like ultrasonography, it provides more precise diagnostic information in the presence of moderate to severe steatosis, with less sensitivity for detecting mild steatosis. Unenhanced CT has a sensitivity and specificity of 82% and 100%, respectively.[88] Because of its cost, need for ionizing radiation, and low sensitivity for detection of mild steatosis, it is not a favored imaging modality for assessing NAFLD.

4. MRI. MRI is currently the preferred imaging modality for quantitatively assessing NAFLD. It can reliably assess mild steatosis as well as moderate to severe grades. In 2 comparative studies, MRI significantly outperformed both ultrasound and CT imaging for detecting hepatic steatosis.[92,93] MRI demonstrated a clear capacity to distinguish histological grades of steatosis, whereas ultrasound and CT did not.[93] The sensitivity and specificity of MRI for hepatic steatosis are 76.7% to 90.0% and 87.1% to 81%, respectively.

POTENTIAL INTERVENTIONS FOR NAFLD

This section briefly reviews the efficacy of various interventions, but treatment recommendations are beyond the scope of this scientific statement. There are 3 overlapping goals of treatment of patients with NAFLD. The first is to preserve liver function and to prevent progression to end-stage liver disease and hepatocellular carcinoma. The second is to prevent and treat metabolic complications such as diabetes, dyslipidemia, and the metabolic syndrome. The third but primary goal for many patients is to prevent cardiovascular complications. Fortunately, there are similarities in therapeutic strategies for achieving each of these goals.

Lifestyle Modification

The mainstay of treatment for both NAFLD and NASH is lifestyle modification, with a focus on sustainably reducing adiposity, improving insulin sensitivity, and reducing cardiometabolic risk factors associated with the metabolic syndrome. Thus, lifestyle modification, including regular exercise and heart-healthy dietary habits, is the cornerstone of intervention for NAFLD and NASH. The amount of fat in the liver is reduced dramatically after a 10% reduction in body weight, and improvements can be seen with as little as 5% reduction in body weight.[94] Patients with NAFLD should aim for a 5% to 10% reduction in body weight for appreciable results, but this can be a challenging goal for many patients.

Dietary Modification

Beyond the benefit attributable to significant weight loss in ameliorating NASH (ie, ≥10% body weight reduction), some specific dietary recommendations may exert independent effects in reducing NASH beyond weight loss. Hypocaloric diets, whether low carbohydrate or low fat, reduce intrahepatocellular lipid content, although the former results in faster (eg, within 2 days) and more pronounced effects even in an isocaloric context. Restriction of high-fructose corn syrup intake to <20 g/d has been shown to improve NASH even in the absence of weight loss.[95] Sucrose-sweetened beverages are a significant source of fructose intake for many individuals. Consumption of a Mediterranean-like diet with a pattern of dietary consumption limited to 8 to 12 hours during the day and restriction of food before bedtime may be most advantageous in formulating dietary recommendations for NASH.[51] Mediterranean-style dietary habits have been shown to reduce hepatic fat and to improve insulin sensitivity independently of exercise and weight loss.[96] This is a particularly important consideration given the difficulty that many patients have achieving sustainable weight loss.[97] Currently, the Mediterranean diet is the only specific dietary pattern recommended by the European Association for the Study of the Liver/European Association for the Study of Diabetes/European Association for the Study of Obesity clinical practice guidelines for the treatment of NAFLD and NASH.[98] Fructose intake should be minimized because it aggravates weight gain, stimulates intrahepatic triglyceride accumulation, and has been associated with worsening fibrosis and progression to NASH among patients with NAFLD.[99,100] Restriction of dietary fat intake may lower plasma triglyceride levels, particularly when the triglyceride concentration is severely elevated >800 to 1000 mg/dL, but increased carbohydrate intake may increase triglyceride levels in some individuals with triglycerides in the range of 500 to 1000 mg/dL. Consultation with a dietitian can be invaluable to educate patients and to facilitate optimization of dietary habits.

Alcohol Avoidance

Excess alcohol consumption is an independent risk factor for hepatic steatosis. Ethanol exerts a number of metabolic alterations in the liver, predisposing hepatocytes to excess fatty acid and triglyceride production; it also reduces fatty acid β-oxidation and VLDL secretion. Hepatic alcohol dehydrogenase converts alcohol to acetaldehyde. The acetaldehyde is metabolized to acetate by acetaldehyde dehydrogenase. Both of these reactions convert NAD to NADH, thereby increasing the cytosolic redox potential of the cell. This results in reduced gluconeogenesis and diminished flux of acetyl coenzyme A (through the citric acid cycle), and the

excess acetyl coenzyme A is diverted to ketone body and fatty acid biosynthesis.[101,102] Excess ethanol reduces the availability of peroxisomal proliferator-activated receptor (PPAR)-α, a nuclear transcription factor inhibited by acetaldehyde.[102,103] PPAR-α is responsible for regulating mitochondrial fatty acid transport and β-oxidation. In the setting of impaired PPAR-α signaling, fatty acids and triglycerides accumulate in the hepatocyte cytosol secondary to impaired oxidative metabolism and reduced capacity for VLDL production and secretion. The excess triglycerides accumulate intracellularly as lipid droplets, potentiating steatosis resulting from insulin resistance or other pathogeneses.

Excessive alcohol intake, defined as >2 drinks daily (eg, 24 oz beer, 8 oz wine, or 2 oz spirits) is reported by ≈8% of the adult population in the United States and is associated with increased risk of alcohol-associated liver disease and cirrhosis. Whereas moderate drinking (ie, 1–2 drinks daily) may reduce the risk of NASH and CVD in the general population, studies indicate that any alcohol consumed with established NASH enhances disease progression and therefore should be completely avoided.[104,105]

Exercise

Exercise is another essential lifestyle intervention for management of NAFLD that decreases hepatic steatosis, increases free fatty acid uptake in myocytes, and increases insulin sensitivity independently of weight loss.[97,106]

Weight Loss

The effect of weight loss on NASH has been examined in several prospective trials. In 1 study of 293 obese (mean BMI, 31.3 kg/m^2) Cuban subjects (approximately two-thirds with the metabolic syndrome and one-third with diabetes) with histologically documented NASH, 12 months of lifestyle intervention (ie, low-fat hypocaloric diet that provided 750 kcal/d less than daily energy requirements) resulted in a mean 4.6-kg weight loss and resolution of NASH in 25%. An important point is that among obese patients who reduced body weight by at least 10%, repeat liver biopsy demonstrated resolution of NASH in 90% and improvement in fibrosis and portal inflammation; lower body weight loss (eg, 5%) correlated with only an ≈40% improvement in NASH resolution.[94] Another 12-month study conducted in 154 Korean individuals with NASH also observed >90% resolution of liver fat assessed by magnetic resonance spectroscopy in patients sustaining ≥10% body weight reduction (mean weight loss, 5.6 kg) after a low-fat, low-glycemic diet combined with 20 to 30 minutes of physical activity daily.[107] Finally, in a more recent 18-month weight loss study in 278 men and women (mean BMI, 30.8 kg/m^2), a Mediterranean diet was superior to a low-fat diet in reducing hepatic fat assessed by MRI, despite more modest weight loss (mean, ≈3 kg).[108] Taken together, these findings show that a weight reduction of ≥10% achieved by reduced energy intake (Mediterranean diet versus low fat diet) and enhanced energy expenditure can have a dramatic effect in reversing NASH over a relatively short time frame.

Sustained weight reduction is difficult for many patients to achieve through lifestyle modification alone. FDA-approved weight-lowering medications such as phentermine, phentermine+topiramate, bupropion+naltrexone, high-dose liraglutide, high-dose semaglutide, and orlistat may be appropriate and efficacious for achievement of sustained weight loss in some patients with BMI >30 kg/m^2 (or BMI >27 kg/m^2 in association with comorbid conditions),[109] but the role of these agents in the management of NAFLD and NASH is currently undefined. The efficacy of liraglutide and semaglutide for treatment of NAFLD is reviewed below.

The most efficacious intervention for achieving sustained major median weight loss of 21% to 30% is bariatric surgery (eg, Roux-en-Y gastric bypass, sleeve gastrectomy, and other procedures),[110] which is associated with multiple health benefits that include remission of type 2 diabetes and improved dyslipidemia,[111] decreased risk of ASCVD events,[112] and amelioration of NAFLD and NASH.[113–116] Hence, bariatric surgery is a consideration for selected patients with BMI >35 kg/m^2 and NAFLD or NASH.

Medications

Pioglitazone

A systematic review of glucose-lowering drugs used to treat NASH showed that compared with placebo, pioglitazone improved liver function, reduced liver fat, and decreased NASH despite increasing body weight.[117,118] The evidence for other thiazolidinediones is more limited.[60] Pioglitazone has a beneficial effect on NASH in people with and without diabetes, although it appears to have a more robust effect in those with diabetes.[119] The heterogeneity in response may relate to genetic[120] or other factors.[121]

Liraglutide

The glucagon-like peptide 1 receptor agonist liraglutide is highly efficacious for treatment of type 2 diabetes and has proven cardiovascular benefit.[122] In the LEAN trial (Liraglutide Safety and Efficacy in Patients With Non-Alcoholic Steatohepatitis), 52 overweight patients with biopsy-proven NASH were randomized to treatment with liraglutide 1.8 mg SC daily or placebo for 48 weeks. Compared with placebo, liraglutide significantly resolved NASH in about one-third of patients

(39% versus 9%; *P*=0.019) and reduced progression of fibrosis (9% versus 36%; *P*=0.04).[123] However, confirmatory studies using liraglutide are needed, as is determining the extent to which improvement in NASH may be attributable to mechanisms beyond weight loss. In contrast, other diabetes therapies (eg, dipeptidyl peptidase inhibitors and inhibitors of the sodium-glucose transport protein 2) either have exhibited no favorable effects on NASH or have been insufficiently evaluated to date, despite modest, albeit significant, weight loss in association with sodium-glucose transport protein 2 inhibitor treatment.[124,125]

Semaglutide

This glucagon-like peptide 1 receptor agonist was tested in a randomized placebo-controlled 72-week study of 320 patients with biopsy-proven NASH with liver fibrosis stages 1 to 3.[126] Although semaglutide is used to treat diabetes at a dose of 0.25, 0.5, or 1 mg SC weekly, the drug was administered in this trial at doses of 0.1, 0.2, or 0.4 mg SC or corresponding placebo daily. This corresponds to total weekly doses of 0.7, 1.4, or 2.8 mg. Resolution of NASH with no worsening of fibrosis occurred in 40% treated with 0.1 mg daily, 36% with 0.2 mg daily, 59% with 0.4 mg daily, and 17% with placebo (*P*<0.001 for semaglutide 0.4 mg versus placebo), but there were no differences in rates of improvement of fibrosis stage. Placebo-corrected weight loss was 12% in the semaglutide 0.4 mg daily group. It is notable that the results of another study demonstrated 12.4% placebo-corrected weight loss in 1961 adult nondiabetic patients with BMI ≥30 kg/m^2 or BMI >27 kg/m^2 with comorbid conditions who were treated with semaglutide 2.4 mg SC weekly for 68 weeks.[127]

Metformin

Metformin is a first-line therapy for patients with type 2 diabetes. It has a mild insulin-sensitizing effect that may relate in part to suppression of hepatic gluconeogenesis and mild weight reduction that accompanies its use. Metformin has been shown to result in modest biochemical improvement in patients with NAFLD not responding to lifestyle interventions.[128] It also improves liver histology and ALT levels in about one-third of patients with NASH, likely attributable in part to weight loss.[129] In an open-label study, the combination of rosiglitazone and metformin conferred greater benefit in patients with NASH than rosiglitazone alone.[130] Despite the results from these studies, the quality of evidence supporting the use of metformin in NASH is low,[131] and its use to treat NASH and NAFLD is not currently recommended.

Lipid-Lowering Agents

Studies evaluating lipid-lowering lowering therapies on NASH (eg, statins, ezetimibe, fibrates, omega-3 fatty acids) have generally been negative or have yielded inconsistent results. Data on NAFLD and NASH are lacking for other therapies with proven CVD benefit (eg, proprotein convertase subtilisin/kexin type 9 inhibitors, icosapent ethyl).[125,132,133]

Leptin in Lipodystrophy

Because of the rarity of the condition, large controlled studies are unlikely to be performed in patients with lipodystrophy. However, in a study of 27 patients with lipodystrophy and hypoleptinemia, 86% met criteria for NASH at baseline, whereas only 33% had NASH after leptin treatment for ≈2 years. Significant improvements were observed in steatosis grade, mean NAFLD activity scores, and metabolic profiles, and fibrosis did not progress.[134] Similar results were observed in a smaller study,[135] suggesting that leptin is an effective therapy for NASH in patients with hypoleptinemia and lipodystrophy.

Pharmacological Intervention Specifically for NAFLD/NASH

Although a number of medications have shown promise for treating NAFLD/NASH, none are yet approved by the FDA. A large number of prospective randomized clinical trials are underway to test the safety and efficacy of these drugs for regressing steatosis and preventing fibrosis and progression to hepatic cirrhosis. Currently, any drug prescribed for treatment of NAFLD/NASH must be considered off-label.

Vitamin E

In patients with biopsy-proven NASH, serum levels of antioxidants, including α-tocopherol (vitamin E), are significantly reduced.[136] At least some histological injury in NASH is attributable to oxidative damage incurred by the intracellular generation of reactive oxygen species.[83] These findings provided the conceptual justification for testing whether vitamin E provides benefit for patients with established NASH. The TONIC trial (Treatment of NAFLD in Children) evaluated the efficacy of vitamin E 800 IU daily compared with placebo over 96 weeks of treatment in children and adolescents with NASH.[137] Compared with placebo, vitamin E did not reduce serum levels of ALT; however, it did significantly reduce hepatocellular ballooning and NAFLD activity score and increase the percentage of patients who resolved NASH (58% versus 28%; *P*=0.006). In the PIVENS trial (Pioglitazone Versus Vitamin E Versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis), compared with placebo, vitamin E therapy dosed at 800 IU daily reduced both serum ALT and AST levels and reduced hepatic steatosis and lobular inflammation in adults with biopsy-proven NASH.[138] Fibrosis, however, was not improved. Given these findings, therapy with vitamin E 800 IU can be considered

for some patients with biopsy-proven NASH who are not diabetic and have not yet progressed to cirrhosis.[83] It is important to note that treatment with vitamin E 400 IU daily compared with placebo for 7 to 12 years was associated with increased risk of prostate cancer in healthy men (hazard ratio, 1.17),[139] suggesting that treatment with vitamin E may not be appropriate for men with a diagnosis of or high risk for prostate cancer. The results of several randomized placebo-controlled clinical trials have shown that vitamin E supplementation does not prevent cardiovascular events and may increase the risk of heart failure.[140]

Farnesoid X Receptor Agonists

The farnesoid X receptor (FXR) is a nuclear transcription factor that, when activated, suppresses expression of cholesterol 7-α-hydroxylase, the enzyme that regulates the rate-limiting step for bile acid biosynthesis from cholesterol. In addition, FXR affects hepatocyte triglyceride metabolism by inhibiting lipogenesis and activating mitochondrial β-oxidation and intracellular triglyceride clearance.[141] Bile acids are naturally occurring ligands for FXR. Treatment with cholic acid in patients with lipodystrophy and hepatic steatosis did not reduce hepatic triglyceride content, perhaps because cholic acid was not a potent FXR agonist.[142] Obeticholic acid (6α-ethyl-chenodeoxycholic acid) is a derivative of chenodeoxycholic acid that has high affinity for FXR.[143] In the FLINT trial (Farnesoid X Nuclear Receptor Ligand Obeticholic Acid for Non-Cirrhotic, Non-Alcoholic Steatohepatitis), compared with placebo in patients with biopsy-proven NASH, obeticholic acid significantly improved serum ALT levels, steatosis, hepatocellular ballooning, fibrosis, and lobular inflammation.[144] Clinical trials with this agent continue, but the FDA determined that the benefit of obeticholic acid based on surrogate histopathologic end points remains uncertain and did not sufficiently outweigh potential risks to support accelerated approval of the treatment for patients with fibrosis attributable to NASH.

Other Experimental Agents

1. Pentoxifylline. Tumor necrosis factor-α is a master regulator of cytokine biosynthesis and inflammation.[145] Tumor necrosis factor-α secreted by macrophages promotes hepatocyte injury and caspase-induced apoptosis.[146] Treatment with pentoxifylline, an inhibitor of tumor necrosis factor-α production, for 1 year improved steatosis and lobular inflammation and showed a nonsignificant trend for improving fibrosis in patients with NASH.[147] In a meta-analysis of 5 trials, pentoxifylline significantly reduced levels of ALT, AST, and tumor necrosis factor-α; NAFLD activity score; and lobular inflammation, with nonsignificant trends for improving ballooning and severity of steatosis compared with placebo.[148] In addition to reducing inflammatory cytokine expression, pentoxifylline reduced oxidative stress secondary to scavenging oxygen free radicals and prevention of formation of fatty acid peroxides, which correlated with improvements in fibrosis and lobular inflammation.[149]
2. Emricasan. Caspase-driven apoptosis and inflammation are important contributors to progressive hepatic injury in NAFLD/NASH. Emricasan is a pan-caspase inhibitor. Emricasan treatment reduced serum levels of aminotransferase, caspases 3 and 7, and cleaved cytokeratin 18 in patients with NASH[150] but failed to improve liver histology in a placebo-controlled trial of 318 patients treated for 72 weeks.[151]
3. Cenicriviroc. Activation of C-motif chemokine receptor 2 by monocyte chemoattractant protein-1 on the surface of monocytes stimulates monocyte recruitment and potentiates hepatic inflammation and phagocytosis of cellular debris.[152] Activation of C-C chemokine receptor 5 expressed on the surface of hepatic stellate cells potentiates fibrosis and hepatocyte regeneration.[153] Cenicriviroc antagonizes both C-motif chemokine receptor 2 and C-C chemokine receptor 5, which was hoped to inhibit hepatic inflammation and fibrosis, but the drug lacks efficacy and is unlikely to have clinical utility.[154,155]
4. Elafibranor. Elafibranor is a dual PPAR-α/δ agonist that was expected to improve NASH/NAFLD because of (1) PPAR- α–mediated regulation of hepatic fatty acid metabolism and triglyceride biosynthesis, (2) improved lipoprotein lipase–mediated hydrolysis of VLDL triglycerides in blood,[156] and (3) PPAR-δ–mediated antagonism of hepatocyte insulin resistance and lipotoxicity.[157] Despite promising phase 1 and 2 data,[158] a phase 3 trial (RESOLVE-IT [Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis]) in 1070 patients with stage 2 or 3 NASH was terminated early because the drug failed to meet the primary end point in an interim analysis.
5. Lanifibranor. This drug is a PPAR-α/δ/γ agonist that was evaluated in a phase 2b study of 247 patients with active NASH who were randomized 1:1:1 to receive daily lanifibranor 1200 or 800 mg or placebo for 24 weeks.[159] Treatment with lanifibranor 1200 or 800 mg compared with placebo was associated with increased resolution of NASH without worsening of fibrosis (49%, 39%, and 22%, respectively), more frequent improvement in fibrosis stage by at least 1 without worsening of NASH (48%, 34%, and 29%, respectively), and increased resolution of NASH with improvement in fibrosis stage by least 1 (35%, 25%, and 9%, respectively).[159] Phase 3 testing in a 72-week

study in a cohort of adults with NASH and fibrosis score of 2 or 3 treated with lanifibranor 800 or 1200 mg daily compared with placebo is planned (NATiV3 [NASH Lanifibranor Phase 3 Trial]).[160]

6. Arachidyl amido cholanoic acid is a novel fatty acid–bile acid conjugate that downregulates stearoyl-CoA desaturase 1 activity in the liver.[161] Stearoyl-CoA desaturase 1 is the rate-limiting enzyme in conversion of saturated fatty acids to monounsaturated fatty acids. Preclinical data from animal models demonstrated decreased hepatic steatosis, inflammation, and fibrosis. Phase 2b data from the ARREST trial (Aramachol for Resolution of Steatohepatitis) conducted in 247 subjects with hemoglobin A1c >6.6%, BMI of 25 to 40 kg/m^2, NAFLD activity score ≥4, and hepatic fat ≥5.5% on magnetic resonance spectroscopy treated with arachidyl amido cholanoic acid for 52 weeks showed a trend for decreased hepatic fat and higher rates of NASH resolution without worsening of fibrosis (P=0.051). The ARMOR study (Aramchol in Subjects With NASH) is a phase 3 randomized placebo-controlled trial that will evaluate the efficacy and safety of arachidyl amido cholanoic acid 300 mg twice daily compared with placebo (2:1) in adults with NASH and fibrosis stages 2 to 3 who have prediabetes or type 2 diabetes and BMI of 25 to 40 kg/m^2.[162] Arachidyl amido cholanoic acid was granted fast-track designation status by the FDA for development for the treatment of NASH.

SUMMARY AND CONCLUSIONS

NAFLD and NASH are increasingly common conditions that are underdiagnosed and underappreciated as risk factors for ASCVD morbidity and mortality. Improved diagnostic strategies for identification of NAFLD and NASH are needed, but existing modalities such as ultrasound-based vibration-controlled transient elastography (FibroScan) assessment of hepatic elasticity and steatosis are useful for disease staging and longitudinal monitoring. A major gap exists in the treatment for NAFLD and NASH. Lifestyle modification that includes 5% to 10% weight loss, increased physical activity, and dietary modification is a key intervention, but further studies are needed to define optimal treatment strategies for the prevention of both hepatic and cardiovascular complications from NAFLD. Many experimental drugs with targeted mechanisms of action are in development, but toxicity has been an impediment for many. It is hoped that with increased awareness of NAFLD, better access to reliable imaging tools for screening and monitoring for NAFLD, and proven tools for the treatment of NAFLD, the rising tide of NASH and more advanced hepatic disease can be reversed and adverse ASCVD outcomes prevented.

KEY TAKE-HOME MESSAGES FOR HEALTH CARE PROFESSIONALS

1. NAFLD is common, occurring in >25% of individuals worldwide, with rates increasing everywhere in association with rising rates of obesity and the metabolic syndrome.
2. Most patients with NAFLD are undiagnosed. Measurements of AST and ALT are not useful for diagnosing NAFLD and NASH because of poor sensitivity and specificity. AST and ALT levels can be normal, even among patients with NASH. Liver biopsy is the gold standard for diagnosis of NAFLD and NASH, but the procedure is expensive and has increased risk of complications. Noninvasive diagnostic options such as vibration-controlled transient elastography (FibroScan) are available but are underused.
3. Most patients with hepatic steatosis do not progress to develop NASH, cirrhosis, or hepatocellular carcinoma, but a subgroup will. It is difficult to identify which patients will have progression of disease, so imaging studies, possibly in combination with liver biopsy, are essential for monitoring disease severity and progression. Routine hepatic ultrasonography is useful if it demonstrates hepatic steatosis, but it cannot quantify the extent of steatosis, nor can it rule out hepatic steatosis because of insensitivity of the technique.
4. NAFLD occurs in association with insulin resistance, with or without diabetes, obesity (especially visceral adiposity), metabolic syndrome, and dyslipidemia consisting of hypertriglyceridemia, increased free fatty acids, low high-density lipoprotein cholesterol, and small dense LDL. Genetic factors (monogenic or polygenic) modulate the risk of development of NAFLD and progression to NASH.
5. NASH is an increasingly common cause of end-stage liver disease.
6. NASH is a contributor to and marker for increased ASCVD risk. Many risk factors for NAFLD are also risk factors for ASCVD. A component of the increased risk of ASCVD in NAFLD is attributable to individual risk factors, but the presence of NAFLD is associated with increased ASCVD risk compared with individuals who have the same ASCVD risk factors without NAFLD.
7. NAFLD can be considered a risk enhancer when ASCVD risk is assessed in patients.
8. Lifestyle intervention is the key therapeutic intervention for patients with NAFLD. Dietary modification, increased physical activity, weight loss, and

alcohol avoidance are strongly encouraged. Weight loss of 5% to 10% of body weight can reverse hepatic steatosis and stabilize or diminish NASH in many patients, but this goal is frequently difficult to achieve. Improved insulin sensitivity, reduced hyperglycemia, and triglyceride lowering are additional goals of treatment.

9. Glucagon-like peptide 1 receptor agonists may modestly improve NAFLD in association with improved glycemia, weight loss, and reduced risk of major adverse cardiovascular events.
10. Novel experimental drug therapies that target various steps in the pathogenesis of NAFLD are in development, but most have modest efficacy, and toxicity has been a limiting factor for some agents.
11. An informational handout about NAFLD is available for patient education (Supplemental Figure 1).

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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