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Clinical Practice Guidelines

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

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ABSTRACT

Objective: To provide evidence-based recommendations regarding the diagnosis and management of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) to endocrinologists, primary care clinicians, health care professionals, and other stakeholders.
Methods: The American Association of Clinical Endocrinology conducted literature searches for relevant articles published from January 1, 2010, to November 15, 2021. A task force of medical experts developed evidence-based guideline recommendations based on a review of clinical evidence, expertise, and informal consensus, according to established American Association of Clinical Endocrinology protocol for guideline development.

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Disclaimer: The American Association of Clinical Endocrinology clinical practice guidelines include systematically developed recommendations to assist health care professionals in medical decision-making for specific clinical conditions. Most of the content herein is based on scientific evidence. In areas of uncertainty, or when clarification is required, expert opinion and professional judgement were applied.

This guideline is a working document that reflects the state of the field at the time of publication. Since rapid changes in this area are expected, periodic revisions are inevitable. We encourage health care professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision(s) by health care professionals to apply the recommendations provided in this guideline must be made in consideration of local resources and individual patient circumstances.

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steatohepatitis
weight loss
GLP-1 RA
pioglitazone

Recommendation Summary: This guideline includes 34 evidence-based clinical practice recommendations for the diagnosis and management of persons with NAFLD and/or NASH and contains 385 citations that inform the evidence base.

Conclusion: NAFLD is a major public health problem that will only worsen in the future, as it is closely linked to the epidemics of obesity and type 2 diabetes mellitus. Given this link, endocrinologists and primary care physicians are in an ideal position to identify persons at risk on to prevent the development of cirrhosis and comorbidities. While no U.S. Food and Drug Administration-approved medications to treat NAFLD are currently available, management can include lifestyle changes that promote an energy deficit leading to weight loss; consideration of weight loss medications, particularly glucagon-like peptide-1 receptor agonists; and bariatric surgery, for persons who have obesity, as well as some diabetes medications, such as pioglitazone and glucagon-like peptide-1 receptor agonists, for those with type 2 diabetes mellitus and NASH. Management should also promote cardiometabolic health and reduce the increased cardiovascular risk associated with this complex disease.

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Lay Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease affecting 25% of the global population. Despite the sizable and growing prevalence, disease awareness remains limited with <5% of persons with NAFLD being aware of their disease compared with 38% of persons with viral hepatitis. Twelve to 14% of persons with NAFLD have a more aggressive form known as nonalcoholic steatohepatitis (NASH), which can progress to advanced liver fibrosis, cirrhosis, or liver cancer. The risk of NASH is two- to threefold higher in persons with obesity and/or type 2 diabetes mellitus. NASH is among the top causes of liver cancer and the second most common indication for liver transplantation in the United States after hepatitis C. NAFLD is diagnosed by abnormal liver test results (although liver test results may be normal) and imaging studies, not related to excess alcohol use or other causes of liver disease. NASH is diagnosed by a liver biopsy; however, specialized blood tests and imaging can determine the risk of significant fibrosis. NAFLD is associated with cardiometabolic disorders: (1) obesity, (2) insulin resistance, (3) type 2 diabetes mellitus, (4) high blood pressure, and (5) atherogenic dyslipidemia, all of which increase the risk of a heart attack or stroke, the most common cause of death. The primary treatment of NAFLD is weight loss with a low-calorie diet; restriction of saturated fat, starch, and sugar; improved eating patterns (eg, Mediterranean diet and minimally processed whole foods); and exercise. Cardiometabolic benefit and reduction of liver fat can be observed with >5% weight loss. More weight loss provides increased benefits and may reverse steatohepatitis or liver fibrosis (≥10% weight loss). There are no U.S. Food and Drug Administration-approved medications for the treatment of NAFLD; however, some diabetes and antiobesity medications can be beneficial. Bariatric surgery is also effective for weight loss and reducing liver fat in persons with severe obesity.

Abbreviations

AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; ABCD, adiposity-based chronic disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; aHR, adjusted hazard ratio; BEL, best evidence level; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; CKD, chronic kidney disease; CMD, cardiometabolic disease; CPG, Clinical Practice Guidelines; CV, cardiovascular; CVD, cardiovascular disease; EBMT, Endoscopic bariatric and metabolic therapy; ELF, enhanced liver fibrosis; ESG, endoscopic sleeve gastroplasty; FDA, U.S. Food and Drug Administration; FIB-4, fibrosis-4 index; GH, growth hormone; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma; HR, hazard ratio; ^{1}H-MRS, proton magnetic resonance spectroscopy; IGB, intragastric balloon; IHTG, intrahepatic triglyceride; IR, insulin resistance; LSM, liver stiffness measurement; MACE, major adverse cardiovascular event; MetS, metabolic syndrome; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NPV, negative predictive value; OR, odds ratio; PCOS, polycystic ovary syndrome; PCP, primary care physician; PNPLA3, patatin-like phospholipase domain-containing 3; PPAR, peroxisome proliferator-activated receptor; PPV, positive predictive value; pSWE, point shear wave elastography; RCT, randomized controlled trial; RYGB, Roux-en-Y gastric bypass; SGLT2, sodium-glucose cotransporter 2; SWE, shear wave elastography; TBW, total body weight; TE, transient elastography; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; US, ultrasonography; 2DSWE, 2-dimensional shear wave elastography; VCTE, vibration-controlled transient elastography.

Structure of Clinical Practice Guideline

1. Introduction
   - Epidemiology of Adult and Pediatric NAFLD
   - Purpose
   - Scope
   - Limitations of the Literature
2. Methods
3. Summary of Recommendations: summary list of all recommendations developed for this clinical practice guideline
4. Recommendations With Evidence Base
   - Recommendation
   - Recommendation Grade, Strength of Evidence Grade, and Best Evidence Level
   - Evidence Base: summary of clinical background and highlighted studies that best support the recommendation

Introduction

Epidemiology

What Is the Magnitude of the Problem/Disease Burden in Endocrine and Primary Care Clinics?

Nonalcoholic fatty liver disease (NAFLD) is part of a multisystemic disease and is closely associated with obesity, insulin resistance (IR), type 2 diabetes mellitus (T2D), hypertension, and atherogenic dyslipidemia.[1,2] The definition of NAFLD is based on the presence of hepatic steatosis in >5% of hepatocytes in the absence of significant ongoing or recent alcohol consumption and other known causes of liver disease.[1,2] Nonalcoholic steatohepatitis (NASH), more likely to progress to advanced stages of fibrosis, is characterized by the presence of active hepatocyte injury (ballooning) and inflammation in addition to steatosis (Table 1 shows the common terms and definitions, and Table 2 shows the histologic definition of NAFLD grades and fibrosis stages).

Table 1
Relevant Definitions in NAFLD

NAFLD[a]	Nonalcoholic fatty liver disease	Term used for the broad spectrum of the disease, ranging from hepatic steatosis only to steatohepatitis (NASH) to cirrhosis, in the absence of ongoing or recent consumption of significant amounts of alcohol or the presence of other secondary causes of fatty liver disease.
NASH[a]	Nonalcoholic steatohepatitis	Presence of ≥5% hepatic steatosis with inflammation and hepatocyte injury (also known as hepatocyte ballooning), with or without evidence of liver fibrosis.
NASH cirrhosis[a]		Cirrhosis with histologic evidence of steatosis or steatohepatitis.
NAS[a]	NAFLD activity score	An unweighted composite of steatosis, lobular inflammation, and ballooning scores.
Significant alcohol consumption[a,b]	…	Defined as ingestion of >21 standard drinks per week in men and >14 standard drinks per week in women over a 2-year period preceding baseline liver histology.
FIB-4	Fibrosis-4 index	An index to estimate the risk of hepatic cirrhosis calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count. This noninvasive estimate of liver scarring is used to assess the need for biopsy. The score is calculated using a person's age, AST level, platelet count (PLT), and ALT level. FIB-4 score = age (years) × AST (U/L)/[PLT (10^9/L) × ALT ½ (U/L).
ELF	Enhanced liver fibrosis test	This blood test measures the levels of tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid and is used to estimate the rate of liver extracellular matrix metabolism reflecting the severity of liver fibrosis.
NFS	NAFLD fibrosis score	−1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × (impaired fasting glucose or DM) + 0.99 × (AST/ALT) − 0.013 × platelet (× 10^9/L) = 0.66 × albumin (g/dL) (where impaired fasting glucose/DM had a value of 1 if the participants had impaired fasting glucose and 0 if they did not)
APRI	AST-to-platelet ratio index	[AST level (IU/L)/AST (upper limit of normal AST range (IU/L) × 100] divided by platelet count (10^9/L)
^{1}H-MRS	Proton magnetic resonance spectroscopy	A technique for quantifying hepatic steatosis
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction	A technique for quantifying hepatic steatosis
VCTE	Vibration-controlled transient elastography	A technique for liver stiffness measurement that is correlated with the severity of liver fibrosis on histology.
MRE	Magnetic resonance elastography	Technology that combines MRI with low-frequency vibrations to assess liver stiffness.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DM = diabetes mellitus.
[a] Sanyal et al.[3]
[b] A standard alcoholic drink is defined as a given drink with approximately 14 g of pure alcohol (https://pubs.niaaa.nih.gov/publications/practitioner/pocketguide/pocket_guide2/htm). Accessed on December 10th, 2021.

Table 2
Features of NASH and Fibrosis Staging (Adapted and Reprinted With Permission From Younossi et al[2] and Kleiner et al[4])

Feature	Definition	Score or code
Steatosis grade	Low- to medium-power evaluation of parenchymal involvement by steatosis	<5% = 0 5%-33% = 1 (mild) 33%-66% = 2 (moderate) >66% = 3 (severe)
Lobular inflammation	Overall assessment of all inflammatory foci per ×200 field	No foci = 0 <2 foci per 200 field = 1 2-4 foci per 200 field = 2 >4 foci per 200 field = 3
Ballooning	…	None = 0 Few (or borderline) balloon cells = 1 Many cells/prominent ballooning = 2
NAS	Sum of steatosis + lobular inflammation + ballooning	0-8
Fibrosis stage	…	None = 0 Mild = perisinusoidal or periportal (stage 1) Moderate = perisinusoidal and portal/periportal (stage 2) Severe = bridging fibrosis (stage 3) Cirrhosis = stage 4

Abbreviation: NAS = nonalcoholic fatty liver disease activity score.

Globally, the overall prevalence of NAFLD is 25%, while the prevalence of the potentially progressive form of NAFLD or NASH is between 12% and 14%.[5] The highest prevalence rates for NAFLD and NASH have been reported from the Middle Eastern countries.[1] In addition, the prevalence rates are significantly higher in those with T2D and visceral obesity. In fact, among those with obesity, the prevalence of NASH is between 25% and 30%, while approximately 30% to 40% of persons with diabetes have NASH.[1,6–8] A recent study indicated that in outpatient family medicine, internal medicine, and endocrine clinics, approximately 70% of persons with T2D have NAFLD (steatosis), and approximately 15% have clinically significant liver fibrosis (stages ≥ F2),[9] consistent with other recent population-based studies in the United States.[10,11]

The prevalence of NAFLD[12] is expected to continue to increase, likely with a disproportionate increase in advanced disease.[13] Current estimates suggest that approximately 20% of persons with NASH could potentially develop significant liver disease including cirrhosis and its complications.[14] NASH is now among the top causes of hepatocellular carcinoma (HCC)[15,16] and the second most common cause of HCC in those on the waiting list for liver transplantation in the United States after hepatitis C.[17] This growth is especially worrisome for Asia, the Middle East, and

North African regions, with the highest documented prevalence of NAFLD.[18]

Despite the sizable and growing prevalence of NAFLD, disease awareness remains quite limited, with <5% of persons with NAFLD being aware of their liver disease compared with liver disease awareness in 38% of persons with viral hepatitis.[19] Furthermore, a global survey of over 2200 physicians recently highlighted the knowledge gap regarding NAFLD among providers, especially for primary care physicians (PCPs) and endocrinologists.[20] Another recent survey of 751 clinicians in the United States, including PCPs, endocrinologists, and gastroenterologists or hepatologists, found that they underestimated the prevalence of NAFLD in high-risk groups (eg, those with severe obesity or T2D) and that there was underutilization of medications with proven efficacy in NASH.[21] Finally, diagnosis and referral to specialists for management remain low among endocrinologists.[21,22] In contrast to other highly prevalent noncommunicable chronic conditions (ie, obesity, diabetes, and cardiovascular disease [CVD]), NAFLD has received little attention from a public health perspective with global health strategies characterized as inadequate and fragmented.[23] This conundrum of increasing disease burden, limited awareness, and clinical inertia exacerbates the public health challenge. This is especially relevant given the fact that the vast majority of persons with T2D, who may have underlying NAFLD, are predominantly seen by primary care clinicians and endocrinologists but remain undiagnosed and untreated. Therefore, the aim of developing this evidence-based guideline is to increase awareness about NAFLD and NASH and provide easy-to-use and practical recommendations to guide clinicians for the assessment of NAFLD in their practices.

What Is Known About the Natural History of NAFLD?

T2D is a major driver of disease progression. A prevalence study conducted across 20 countries found an alarmingly 55% prevalence of NAFLD among individuals with T2D.[6] This may be an underestimation of the real prevalence of steatosis as screening in approximately 90% of the studies was performed by liver ultrasonography (US), considered less sensitive than elastography (controlled attenuation parameter [CAP]) or magnetic resonance imaging (MRI)-based techniques for hepatic steatosis.[24] Higher estimates of NAFLD and liver fibrosis have been suggested in people with T2D based on 8 studies from 2020 and 2021 from Europe, Southeast Asia, and the United States using transient elastography (TE) and/or MRI-based techniques as screening tools for NAFLD, NASH, and fibrosis.[25]

Age (>50 years), IR, and features of metabolic syndrome (MetS) all increase the probability of NASH with a more severe fibrosis stage and cirrhosis.[5,26-28] The strong association between steatohepatitis and T2D does not establish causality, but it does demonstrate the impact of diabetes on liver due to a higher prevalence of obesity in Hispanics than in Caucasians disease severity.[29] However, the role of poor glycemic control remains unclear, with some studies suggesting that it increases the risk of fibrosis progression,[30-32] while another study did not show an increased risk.[11]

Ethnicity may be another factor in disease progression. In the United States, the prevalence of steatohepatitis in the Hispanic population with or without diabetes is the highest, with reports of approximately 20%[7,33] or higher.[5] However, when body mass index (BMI) is well matched, neither steatohepatitis nor fibrosis is worse in Hispanics than in Caucasians.[34] Additionally, although NASH may be more common in people of Hispanic descent than in Caucasians or those with African American ancestry, a meta-analysis of 34 studies comprising 368 569 participants reported that the proportion of those with significant fibrosis did not significantly differ among racial or ethnic groups.[33]

Several reports have shown that obesity and diabetes interact with genetic factors to increase the risk of cirrhosis in Hispanics, with their relative contribution being often difficult to fully untangle. Several genetic variants that modify hepatocyte triglyceride metabolism have been investigated by genome-wide association and exome sequencing. The risk variants most studied alter either lipid droplet trafficking (patatin-like phospholipase domain-containing 3 [PNPLA3]), secretion of low-density lipoprotein cholesterol (transmembrane 6 superfamily member 2), lipid signaling/metabolism (hydroxysteroid 17-beta dehydrogenase), de novo lipogenesis (GCKR), or hepatic phosphatidylinositol acyl chain remodeling (MBOAT7), among others.[35] The PNPLA3 148I→M (rs738409) is highly prevalent in Hispanics,[36] likely promoting steatosis by interfering with lipid droplet function and hepatocyte lipid turnover. The major implication is that the variant has been associated with a greater risk of NASH progression and cirrhosis.[35,37,38] It appears that the genetic variants identified amplify their impact across the spectrum of the disease in the presence of obesity, from steatosis to inflammation to cirrhosis.[39] However, there is insufficient evidence to strongly conclude that race, by itself, plays a central role in the development of hepatic fibrosis.[36,37] Therefore, at the present time, genetic testing cannot be recommended in the clinical realm for the management of patients with NASH, although this may change as more data become available about the clinical implications of different gene variants.

While the disease progression rate is relatively slow in most people, progression may be faster in some individuals with risk factors (ie, obesity and T2D),[40] and approximately one third of individuals eventually progress to NASH, of which an estimated 20% develop fibrosis with a high risk of extrahepatic complications, cirrhosis, and liver failure.[41] Development of fibrosis is a key predictor of liver-related outcomes. There is substantive evidence to support a dose-dependent effect of fibrosis on liver-related and all-cause mortality (5- to 12-fold increase in relative risk), with a greater risk of liver decompensation, HCC, liver transplantation, and death.[42,43] Excess mortality associated with NAFLD is mostly attributable to extrahepatic cancer, cirrhosis, CVD, and HCC. All NAFLD histologic stages (Table 2), including isolated steatosis with no fibrosis, are associated with a significant increase in overall mortality, which worsens with liver disease severity.[44]

Due to the increasing incidence of obesity and diabetes, the prevalence of NAFLD-HCC is on the rise. Thus, NAFLD is likely to replace hepatitis B and C viruses as the leading cause of HCC globally. Some gene variants, such as PNPLA3 or transmembrane 6 superfamily member 2, as discussed earlier, are associated with a much higher risk not only of cirrhosis but also of HCC, with both risks amplified in the presence of obesity or diabetes.[38] There is an increasing body of evidence for the association of NAFLD and cancer, which offers the underlying pathophysiology for long-time observation that diabetes is associated with a twofold higher risk of HCC[17,45] with a modest contribution from extrahepatic cancers.[46] A few earlier long-term cohort studies have found extrahepatic cancers to be the second leading cause of death after CVD,[47] especially in those with more advanced (bridging) fibrosis.[41] Hence, even though extrahepatic cancers do not pose a significant clinical burden, the increasing incidence of NAFLD-HCC calls for better cancer screening strategies in this population.

What Are the Extrahepatic Complications Relevant to Endocrinologists and Practitioners Who Care for Persons With Endocrine and Cardiometabolic Diseases?

T2D and CVD are the 2 most important extrahepatic diseases associated with NAFLD and are closely associated with visceral adiposity and IR. The relationship between NAFLD and T2D is

bidirectional, with visceral adiposity and IR being mediators in the causal pathway.[48,49] Visceral adipose tissue is known to increase de novo gluconeogenesis, and liver fat is associated with hepatic IR.[48] NAFLD, especially NASH, exacerbates hepatic and adipose tissue IR, which can contribute to the development of T2D.[50] A 2016 meta-analysis of 20 studies conducted that followed 117 020 persons for a median follow-up period of 5 years found an approximately twofold greater relative risk of developing T2D among persons with NAFLD than among those without NAFLD.[51] This finding was consistent with 2 more recent meta-analyses that reported a similar twofold increased risk of diabetes associated with having NAFLD.[52,53] A recent study estimated that there were 18.2 million people in the United States living with T2D and NAFLD, of whom 6.4 million had NASH. Health care costs for persons with T2D and NASH were estimated to be $55.8 billion over the next 20 years, to account for 65 000 transplants, 1.37 million cardiovascular (CV)-related deaths, and 812 000 liver-related deaths.[54]

With up to one third of persons with type 1 diabetes mellitus (T1D) having obesity, greater attention is being paid to their risk of developing NAFLD.[55] The pooled prevalence of NAFLD was 22% in adults with T1D based on a systematic review and meta-analysis published in 2020 (95% Confidence interval [CI], 13.9%-31.2%). The estimation differed substantially between reports given that different imaging modalities and heterogeneous populations were included.[56] In addition, several studies did not use “gold standard” diagnostic techniques, such as MRI-based techniques or a liver biopsy. In one of the few studies using liver MRI, in a predominantly nonobese population (mean BMI, 26.5 kg/m^2), the prevalence of steatosis was 8.8%, much lower than the 68% prevalence observed in persons with T2D.[57] Because NAFLD affects mostly those with IR or obesity, it is not entirely surprising that depending on the population studied, some studies have not found persons with T1D to have a higher risk of NAFLD.[56]

The relationship between NAFLD and diabetic complications remains poorly understood. Persons with steatosis and T1D have been reported to be at greater risk of developing CVD, arrhythmias, and other cardiac complications.[58-60] The presence of NAFLD has also been associated with microvascular diabetic complications, especially chronic kidney disease (CKD).[61,62] A meta-analysis including 20 cross-sectional studies with approximately 28 000 individuals reported that NAFLD was associated with a twofold increased prevalence of CKD (odds ratio [OR], 2.12; 95% CI, 1.69-2.66).[63] In the 13 longitudinal studies included in the meta-analysis, NAFLD was associated with an overall 80% increased risk of incident CKD (hazard ratio [HR], 1.79; 95% CI, 1.65-1.95). Subgroup analysis suggested that advanced hepatic fibrosis was associated with an even greater risk of CKD.[63] Similar results have been reported in a more recent meta-analysis that included 96 500 persons (one third with NAFLD) followed for a median of 5.2 years.[64] In persons with diabetic retinopathy, the relationship remains controversial, with a recent meta-analysis of 9 studies involving 7170 persons unable to find an overall association between NAFLD and diabetic retinopathy.[65] However, significant heterogeneity and apparent ethnic differences were present among studies, with some studies from Italy and India demonstrating an association between NAFLD and diabetic retinopathy, while other studies from the United States, China, Korea, or Iran did not demonstrate such an association.[65]

Women with polycystic ovary syndrome (PCOS) are at increased risk of T2D and NAFLD. A population-based retrospective study of a primary care database of 63 000 women with PCOS and nearly 121 000 age-, BMI-, and location-matched controls reported an increased incidence of NAFLD in women with PCOS (HR, 2.23; 95% CI, 1.86-2.66).[66] Recently, a retrospective study of 102 women with biopsy-confirmed NAFLD found that after adjusting for age and BMI, PCOS remained associated with severity of steatohepatitis (hepatocyte ballooning) (OR, 3.4; 95% CI, 1.1-10.6; $P = .03$) and advanced fibrosis (OR, 7.1; 95% CI, 1.3-39; $P = .02$).[67] The underlying mechanisms for the development of NAFLD in PCOS are multifactorial; however, IR is a key driver.[68] Of interest, women with PCOS and hyperandrogenism have a threefold higher prevalence of NAFLD, strongly associated with severe IR.[69,70]

Obesity, IR, and development of T2D appear to be the underlying factors associated with development of NAFLD in several endocrine conditions; the most studied include hypothyroidism, growth hormone (GH) deficiency, and hypogonadism. Most studies have been small, of poor quality, and either case reports or uncontrolled. For instance, hypothyroidism appears associated with steatosis in animal models and some human studies.[71] Although a recent meta-analysis suggested a modest association,[72] the results were not conclusive. Most studies were small and used a liver US for the diagnosis, and 7 of 13 studies were negative. A number of other caveats have been raised from this meta-analysis.[73] The definition of hypothyroidism was very broad including overt hypothyroidism, subclinical hypothyroidism, and/or levothyroxine replacement. Moreover, it was unclear how persons receiving levothyroxine replacement actually had a higher risk of NAFLD than those with hypothyroidism not receiving treatment (OR, 2.19 [95% CI, 1.41-3.43] vs 1.31 [95% CI, 1.04-1.66]). Moreover, in the 3 longitudinal studies, subclinical hypothyroidism was not independently associated with the risk of incident NAFLD over a median of 5 years (random-effects HR, 1.29 [95% CI, 0.89-1.86]; $I^2 = 83.9\%$). In the largest study using “gold standard” measurements of liver fat (proton magnetic resonance spectroscopy [^{1}H-MRS]) and liver histology in 232 middle-aged persons with T2D, only a modest relationship was observed between steatosis and low free thyroxine levels but no association with inflammation, hepatocyte injury (ballooning), or fibrosis.[74] In animal models, there are reports showing an association between low sex hormone levels and alterations in glucose and lipid metabolism and NAFLD.[75] However, in a study including 175 men with T2D examining the relationship between lower total testosterone level and hepatic steatosis using ^{1}H-MRS and liver histology, the relationship disappeared when adjusted for IR and obesity. Moreover, no relationship was observed between lower total testosterone levels and severity of liver necroinflammation or fibrosis.[76] Finally, GH deficiency has been associated with NAFLD given the broad effects of GH on glucose metabolism.[77] Panhypopituitarism has also been linked to NAFLD.[78] GH replacement has shown some benefit,[79] but studies have been usually small and uncontrolled. In a recent meta-analysis,[80] pooled analysis showed an association between low insulin-like growth factor 1 level and NAFLD, although significant heterogeneity was present among the 12 studies included. In subgroup analyses, a low insulin-like growth factor 1 level was strongly associated with obesity and IR.[80] Clearly, more studies are needed, but GH and testosterone replacement should be used with caution and following current medical guidelines given their risk of misuse and of adverse events. Thus, it is premature to recommend persons with endocrinopathies to be routinely evaluated for NAFLD, beyond the risk associated with the presence of obesity or T2D.

Given the high prevalence of NAFLD and CVD and their mutual association with MetS, it is not unexpected for the 2 conditions to coexist. Although end-stage liver disease and HCC are the most common causes of death in persons with cirrhosis, CVD and extrahepatic malignancy are the leading causes of morbidity and mortality in most individuals with less advanced disease.[60,81,82] A 2015 analysis of the Framingham Heart Study found that hepatic steatosis was strongly associated with subclinical CVD outcomes, independent of other metabolic risk factors.[83] Persons with NAFLD have increased carotid intima-media thickness compared with

those without NAFLD.[53,84] In a recent cross-sectional study of asymptomatic individuals undergoing coronary computed tomography angiography, NAFLD was consistently associated with high-risk noncalcified atherogenic plaques, indicative of a greatly increased CV risk.[85] In a longitudinal study of 603 individuals with biopsy-proven NAFLD, followed for a mean of 18.6 years, 28% of persons with NAFLD versus 21% of controls experienced a CVD event (HR, 1.54; 95% CI, 1.30-1.83).[86] The increased risk of both fatal and nonfatal CV events has been correlated in some studies with the severity of hepatic steatosis, inflammation, or fibrosis,[53,84] but this remains to be fully established. Finally, a recent meta-analysis among 10 576 383 individuals across 24 countries in nonobese persons with NAFLD aiming to remove obesity as a confounding factor found that there was still a much higher incidence rate of new-onset CVD in individuals with NAFLD (18.7 per 1000 person-years; 95% CI, 9.2-31.2).[87]

Complications other than atherosclerotic CVD may be associated with the presence of NAFLD. A meta-analysis of 9 cross-sectional and longitudinal studies in 2019 that included 364 919 individuals found a strong correlation between NAFLD and atrial fibrillation (pooled OR, 2.07; 95% CI, 1.38-3.10).[88] A cross-sectional study conducted in 2015 found a significant association between NAFLD and ventricular arrhythmias.[89] However, it must be noted that in the former study, individuals did not undergo 24-hour Holter monitoring, whereas the latter included Holter monitoring data. A 2020 meta-analysis found that other cardiac complications, such as cardiomyopathy, cardiac valvular calcification, and cardiac arrhythmias, were also more prevalent in persons with NAFLD.[84] In a meta-analysis of 12 studies including approximately 280 000 individuals, early heart failure with preserved ejection fraction was found to be more prevalent in persons with well-controlled T2D and NAFLD independent of other risk factors.[90] However, it will be difficult to establish a causal relationship between NAFLD and CVD given the tangled web of overlapping metabolic disturbances present in these individuals (ie, IR, obesity, T2D, atherogenic dyslipidemia, and visceral adiposity). Future studies are needed to establish this mechanistic link, but even if not causal, endocrinology and primary care clinicians should consider persons with NAFLD as being at high risk of CV complications.

Finally, several other complications, such as gallbladder disease,[91] obstructive sleep apnea,[87,92] colorectal neoplasm,[93] and other cancers[90] as well as sarcopenia,[94] have also been reported with increased prevalence in those with NAFLD. Of interest, persons with both NAFLD and sarcopenia have a higher risk of CVD (OR, 1.83; $P = .014$) than those without NAFLD and sarcopenia.[95] Additionally, recent data suggest that sarcopenia in NAFLD is associated with increased mortality.[96]

Purpose

Given the high prevalence of NAFLD in clinical endocrinology and primary care practice and the paucity of guidelines that address the metabolic and endocrinologic perspectives, little guidance is available for frontline practitioners who care for persons with NAFLD, most of whom are undiagnosed. The purpose of this guideline is to provide endocrinology and primary care clinicians with practical evidence-based recommendations for the diagnosis and management of NAFLD.

Scope

This guideline addresses key management questions and focuses on the metabolic and endocrinologic aspects of prevention, diagnosis, treatment, and long-term prognosis for the entire population of persons with NAFLD. Outside the scope of this guideline is an in-depth review of the epidemiology in the general population or inclusion of controversial aspects of NAFLD reserved for the liver specialist. It is meant to provide practical patient-centered guidance for endocrinologists and PCPs who often see populations at high risk of developing NASH (ie, those with obesity, MetS, and/or T2D). It also does not address interventions of a purely investigational nature; it includes only those interventions available to the practicing clinician: (1) lifestyle intervention, (2) bariatric surgery, (3) weight loss and diabetes treatment agents, and (4) any other agent with strong evidence from randomized controlled trials (RCTs) deemed as safe and effective. There are no U.S. Food and Drug Administration (FDA)-approved medications for the treatment of NASH available at the time of publication.

Limitations of the Literature

NAFLD has reached epidemic proportions fueled by the increase in the incidence of obesity and T2D, creating a need for endocrinology and primary care clinicians to become engaged in its early diagnosis and management. Although there is a rapidly growing body of literature, the field still has several knowledge gaps. For instance, while the diagnosis of hepatic steatosis by imaging is rather simple (ie, liver US or MRI-based techniques), there is a lack of robust and well-validated blood tests or imaging studies for the noninvasive diagnosis of nonalcoholic steatohepatitis (NASH). Similar limitations apply to the accurate diagnosis of hepatic fibrosis, with liver biopsy remaining the “gold standard” test for the diagnosis of NASH and for staging the severity of fibrosis. This calls for the stepwise use of noninvasive tests to minimize the need for a liver biopsy, but still, the vast majority of persons with NASH and advanced fibrosis (stages F2-F4; Table 2) remain undiagnosed in primary care and endocrinology clinics. There is also a limited understanding of the natural history of the disease and factors that modulate disease progression. In the pediatric field, there is inadequate evidence in terms of the optimal diagnostic and treatment pathways, with current care being based on early diagnosis and promotion of healthy lifestyle changes.

Regarding management, the many lifestyle studies in the field have small sample sizes, heterogeneous populations, and a short duration (none beyond 12 months). The best diet for the management of NAFLD is unclear, although weight loss in people with obesity and improved eating patterns (eg, Mediterranean diet) with modification of macronutrient composition (reduction of saturated fat, starch, and added sugars) have consistently been beneficial. There are still no FDA-approved drugs for the treatment of NASH. Limited well-designed and adequately powered RCTs to assess the effectiveness of available agents, such as those used for the treatment of diabetes (pioglitazone and glucagon-like peptide-1 receptor agonists [GLP-1 RAs]), have been published. However, these studies have not exceeded a duration of 2 to 3 years for pioglitazone[97,98] or 1.5 years for a GLP-1 RA.[99] Several RCTs with sodium-glucose cotransporter 2 (SGLT2) inhibitors have employed an open-label design with potential bias, but some RCTs have shown a reduction in the plasma aminotransferase levels and hepatic steatosis. However, there are no studies with paired biopsies to assess the effect on steatohepatitis or fibrosis.

Recognizing the aforementioned limitations, the grading of the evidence base was informed by trial design and potential generalizability, and this guideline should be viewed as breaking new ground by gathering the available information for endocrinologists and other stakeholders to guide the early diagnosis and treatment of persons with NAFLD. We anticipate that it will likely be frequently updated as the field rapidly advances in the diagnosis and management of the disease.

Methods

The American Association of Clinical Endocrinology (AACE) Clinical Practice Guidelines (CPG) Oversight Committee and AACE Board of Directors identified the necessity of this guideline on NAFLD, confirmed the extent of literature, and empaneled a task force of clinicians for its development in adherence to the 2017 AACE Protocol for Standardized Production of Clinical Practice Guidelines[100] (Supplementary Tables 1 through 4).

The AACE CPG Staff conducted comprehensive literature searches in PubMed using medical subject headings, field descriptions, and free-text terms to identify all possible studies that included human participants; were published in English between January 1, 2010, and November 15, 2021; and met inclusion criteria (Supplementary Table 5). Bibliographies of select articles were also reviewed to ensure inclusion of all possibly relevant studies. The literature searches and examination of reference lists from primary and review articles yielded 1000 studies, of which 385 citations were included to support this guideline's recommendations and provide supplementary information.

At least 2 task force authors screened the titles and abstracts of broad pools of evidence found in literature searches for each topic and submitted decisions to include or exclude each article along with rationale for exclusion. Disagreements about inclusion among reviewers were resolved by consensus with a third reviewer or the chairs. Through this process, the authors conducted a thorough appraisal of evidence based on the full scope of available literature to determine studies that best support each recommendation.

The AACE CPG Staff assigned evidence levels and study types to included studies according to established AACE evidence ratings (Supplementary Table 1) and extracted data from each full-text article into a structured table to document the authors, title, journal citation, study design and population, limitations, comparison group/controls, intervention, outcomes, and limitations. The CPG Staff assigned a grade for the quality of each article, which informed assigned grades for the confidence and strength of evidence in aggregate for each recommendation (Supplementary Tables 2, 3, and 4). In cases where the task force determined guidance to be necessary despite a lack of available supporting literature, a recommendation was developed based on expert opinion and consensus of task force authors' collective experience, knowledge, and judgment. Recommendation qualifiers and subjective factors informed the overall grade assigned for each recommendation (Supplementary Table 4). Through discussion and consensus of the full task force, the task force members confirmed recommendation grades and grades for strength of evidence. The task force chairs provided oversight throughout the entire development process.

Clinical questions provide the framework for this guideline with answers in the form of recommendations. The task force authors submitted contributions to specific clinical questions, which were integrated into the final document and discussed to achieve unanimous consensus for each of the recommendations. Semantic descriptors of "must," "should," and "may" are generally but not strictly correlated with grade A (strong), B (intermediate), and C (weak) recommendations, respectively; each semantic descriptor can be used with grade D (no conclusive evidence and/or expert opinion) recommendations. Deviations from this mapping take into consideration further decision making based on clinical expertise. The AACE followed a rigorous developmental process based on strict methodology to systematically collect and objectively evaluate and clearly summarize available scientific literature to develop trustworthy recommendations for clinical practice regarding diagnosis and management of NAFLD.

Table 3
Summary of Recommendations

2. **Diagnosis of NAFLD in adults**
Q2.1 Which adults with NAFLD should be considered at "high risk" of clinically significant fibrosis (stages F2-F4) and at risk of cirrhosis?
R2.1.1 Clinicians should consider persons with obesity and/or features of metabolic syndrome, those with prediabetes or T2D, and those with hepatic steatosis on any imaging study and/or persistently elevated plasma aminotransferase levels (over 6 months) to be "high risk" and screen for NAFLD and advanced fibrosis. **Grade B; Intermediate/High Strength of Evidence; BEL 2** **R2.1.2** Persons undergoing bariatric surgery should be evaluated for the presence and severity of NASH, and a liver biopsy should be considered at the time of bariatric surgery. Liver biopsy should be recommended if presurgical stratification suggests indeterminate or high risk of liver fibrosis. **Grade B; Intermediate Strength of Evidence; BEL 2**
Q2.2 What blood tests (eg, diagnostic panels and specific biomarkers) can be used to diagnose NAFLD with clinically significant fibrosis (stages F2-F4) in adults?
R2.2.1 Clinicians should use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred noninvasive initial test is the FIB-4. **Grade B; Intermediate Strength of Evidence; BEL 2** **R2.2.2** Clinicians should consider persons belonging to the "high-risk" groups (as defined under R2.1.1) who have an indeterminate or high FIB-4 score for further workup with an LSM (transient elastography) or ELF test, as available. **Grade B; Intermediate Strength of Evidence; BEL 2**
Q2.3 What imaging studies can be used to diagnose NAFLD with clinically significant fibrosis (stages F2-F4) in adults?
R2.3 To stage the risk of fibrosis in persons with NAFLD, clinicians should prefer the use of VCTE as best validated to identify advanced disease and predict liver-related outcomes. Alternative imaging approaches may be considered, including shear wave elastography (less well validated) and/or magnetic resonance elastography (most accurate but with a high cost and limited availability; best if ordered by liver specialist for selected cases). **Grade B; Intermediate Strength of Evidence; BEL 2**
Q2.4 Should all persons with diabetes mellitus be screened for clinically significant fibrosis (stages F2-F4) associated with NAFLD?
R2.4.1 In persons with T2D, clinicians should consider screening for clinically significant fibrosis (stages F2-F4) using the FIB-4, even if they have normal liver enzyme levels. **Grade B; High/Intermediate Strength of Evidence; BEL 2** **R2.4.2** In persons with T1D, clinicians may consider screening for NAFLD with clinically significant fibrosis (stages F2-F4) using the FIB-4, only if there are risk factors such as obesity, features of metabolic syndrome, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis on imaging. **Grade C; Intermediate/Weak Strength of Evidence; BEL 2; downgraded based on the heterogeneity of studies and moderate to high probability of bias** **R2.4.3** Clinicians should further risk stratify persons with T2D, or T1D with cardiometabolic risk factors and/or elevated plasma aminotransferase levels (>30 U/L) using the FIB-4, elastography, and/or ELF test. **Grade B; High/Intermediate Strength of Evidence; BEL 2**

Table 3 (*continued*)

Q2.5 When should an adult be referred to a gastroenterologist/hepatologist for management?

R2.5.1 Persons with persistently elevated ALT or AST levels and/or with hepatic steatosis on imaging and indeterminate risk (FIB-4, 1.3-2.67; LSM, 8-12 kPa; or ELF test, 7.7-9.8) or high risk (FIB-4, >2.67; LSM, >12 kPa; or ELF test, >9.8) based on blood tests and/or imaging (as described in R2.2.1, R2.2.2, and R2.3) should be referred to a gastroenterologist or hepatologist for further assessment, which may include a liver biopsy.
Grade B; Intermediate Strength of Evidence; BEL 2

R2.5.2 Clinicians should refer persons with clinical evidence of advanced liver disease (ascites, hepatic encephalopathy, esophageal varices, or evidence of hepatic synthetic dysfunction) to a gastroenterologist/hepatologist for further care.
Grade B; Intermediate/High Strength of Evidence; BEL 2

3. **Management of NAFLD in adults**

Q3.1 How should cardiometabolic risk and other extrahepatic complications be managed in the setting of NAFLD?

R3.1 Clinicians must manage persons with NAFLD for obesity, metabolic syndrome, prediabetes, diabetes mellitus, dyslipidemia, hypertension, and CVD based on the current standards of care.
Grade A; High/Intermediate Strength of Evidence; BEL 1

Q3.2 What lifestyle modifications (dietary intervention and exercise) should be recommended in adults with NAFLD?

R3.2.1 Clinicians should recommend lifestyle changes in persons with excess adiposity and NAFLD with a goal of at least 5%, preferably ≥10%, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, depending on individualized risk assessments. Clinicians must recommend participation in a structured weight loss program, when possible, tailored to the individual's lifestyle and personal preferences.
Grade B; Intermediate/High Strength of Evidence; BEL 1; downgraded due to small sample sizes, large heterogeneity of interventions, short duration, and few studies with liver biopsy

R3.2.2 Clinicians must recommend dietary modification in persons with NAFLD, including a reduction of macronutrient content to induce an energy deficit (with restriction of saturated fat, starch, and added sugar) and adoption of healthier eating patterns, such as the Mediterranean diet.
Grade A; Intermediate Strength of Evidence; BEL 1

R3.2.3 In persons with NAFLD, clinicians must recommend physical activity that improves body composition and cardiometabolic health. Participation in a structured exercise program should be recommended, when possible, tailored to the individual's lifestyle and personal preferences.
Grade A; Intermediate Strength of Evidence; BEL 1

Q3.3 What medications have proven to be effective for the treatment of liver disease and cardiometabolic conditions associated with NAFLD or NASH?

R3.3.1a Pioglitazone and GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH.
Grade A; High Strength of Evidence; BEL 1

R3.3.1b Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests.
Grade A; High Strength of Evidence; BEL 1

R3.3.2 To offer cardiometabolic benefit in persons with T2D and NAFLD, clinicians must consider treatment with GLP-1 RAs, pioglitazone, or SGLT2 inhibitors; however, there is no evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors.
Grade A; High Strength of Evidence; BEL 1

R3.3.3 Due to the lack of evidence of efficacy, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for the treatment of steatohepatitis (no benefit on hepatocyte necrosis or inflammation) but may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH.
Grade B; High Strength of Evidence; BEL 1; downgraded due to the use of surrogate outcome measures in many of the studies

R3.3.4 Vitamin E can be considered for the treatment of NASH in persons without T2D, but there is not enough evidence at this time to recommend for persons with T2D or advanced fibrosis.
Grade B; High Strength of Evidence; BEL 1; downgraded due to risk/benefit

R3.3.5 Other pharmacotherapies for persons with NASH cannot be recommended at the present time due to the lack of robust evidence of clinical benefit.
Grade A; High Strength of Evidence; BEL 1

Q3.4 What obesity pharmacotherapies have proven benefit for the treatment of liver disease and cardiometabolic conditions associated with NAFLD or NASH in adults?

R3.4.1 Clinicians should recommend the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH with a goal of at least 5%, preferably ≥10 %, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, when this is not effectively achieved by lifestyle modification alone.
Grade B; Intermediate Strength of Evidence; BEL 1; downgraded due to small sample sizes used in studies and short duration of trials

R3.4.2 For chronic weight management in individuals with a BMI of ≥27 kg/m^2 and NAFLD or NASH, clinicians should give preference to semaglutide 2.4 mg/week (best evidence) or liraglutide 3 mg/day.
Grade B; High/Intermediate Strength of Evidence; BEL 1; downgraded due to different formulations and doses used in the semaglutide and liraglutide NASH trials

R3.4.3 Clinicians must consider obesity pharmacotherapy (with preference to semaglutide 2.4 mg/week [best evidence] or liraglutide 3 mg/day) as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent T2D, CVD, and other end-stage manifestations of obesity.
Grade A; High/Intermediate Strength of Evidence; BEL 1

Q3.5 What is the effect of bariatric surgery on liver disease and cardiometabolic conditions associated with NAFLD or NASH in adults?

R3.5.1 Clinicians should consider bariatric surgery as an option to treat NAFLD **(Grade B; Intermediate/Weak Strength of Evidence; BEL 2**) and improve cardiometabolic health **(Grade A; High/Intermediate Strength of Evidence; BEL 2; upgraded based on the cardiometabolic and all-cause mortality benefits in all persons with or without NAFLD)** in persons with NAFLD and a BMI of ≥35 kg/m^2 (≥32.5 kg/m^2 in Asian populations), particularly if T2D is present. It should also be considered an option in those with a BMI of ≥30 to 34.9 kg/m^2 (≥27.5 to 32.4 kg/m^2 in Asian populations)
(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).

R3.5.2 For persons with NASH and compensated cirrhosis, clinicians should exercise caution in recommending bariatric surgery, which should be highly individualized if prescribed and performed at experienced centers
(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).
In persons with decompensated cirrhosis, bariatric surgery should not be recommended due to limited evidence and potential for harm
(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).

R3.5.3 Endoscopic bariatric and metabolic therapies and orally ingested devices should not be recommended in persons with NAFLD due to insufficient evidence.
Grade C; Intermediate/Weak Strength of Evidence; BEL 2; downgraded due to the quality of studies and small sample sizes

(*continued on next page*)

Table 3 (*continued*)

4. Diagnosis and management of children with NAFLD
Q4.1 Who should be screened for NAFLD and comorbidities?
R4.1.1 Children of any age and adolescents with obesity or T2D, but not T1D, should be screened for NAFLD using serum ALT. **Grade B; Intermediate/High Strength of Evidence; BEL 2**
R4.1.2 Clinicians should screen adolescent females with polycystic ovary syndrome for NAFLD using serum ALT. **Grade B; Intermediate/High Strength of Evidence; BEL 2**
R4.1.3 Clinicians should screen children and adolescents with NAFLD for prediabetes or T2D using an oral glucose tolerance test if the fasting glucose level is ≥100 mg/mL or if the glycated hemoglobin (A1c) level is in the range of prediabetes (≥5.7% to 6.4%). **Grade B; Intermediate Strength of Evidence; BEL 2**
Q4.2 What tests can be used to diagnose pediatric NAFLD?
R4.2.1 Clinicians should use plasma aminotransferases to test children at high risk of NAFLD. **Grade B; Intermediate Strength of Evidence; BEL 2**
R4.2.2 Pediatric NAFLD can be diagnosed with imaging (ultrasound or magnetic resonance imaging-proton density fat fraction) or liver biopsy, in combination with exclusion of non-NAFLD causes of hepatic steatosis such as Wilson syndrome, mitochondrial disease, and medications. **Grade B; Intermediate Strength of Evidence; BEL 2**
R4.2.3 Liver fibrosis prediction calculations and proprietary biomarkers currently available for the diagnosis of advanced fibrosis in adults should not be used in children as they either are inaccurate or require further validation. **Grade B; Intermediate Strength of Evidence; BEL 2**
Q4.3 What are the lifestyle, medical, or surgical treatment options for pediatric NAFLD, and what is the role of pharmacotherapy developed for endocrine disorders in the treatment of pediatric NAFLD?
R4.3.1 Clinicians should recommend lifestyle changes in children with NAFLD, promoting the adoption of dietary changes to create an energy deficit, with reduction in sugar consumption as first-line lifestyle modification and increased physical activity aiming for BMI optimization. **Grade B; Intermediate Strength of Evidence; BEL 1; downgraded due to the limited number of RCTs and small sample sizes**
R4.3.2 Clinicians may consider GLP-1 RAs for the treatment of pediatric obesity and T2D **(Grade D; Expert Opinion; BEL 4)**, which may also offer benefit for pediatric NAFLD, although not FDA-approved for this indication **(Grade D; Expert Opinion; BEL 4)**.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BEL = best evidence level; BMI = body mass index; CVD = cardiovascular disease; ELF = enhanced liver fibrosis; FDA = U.S. Food and Drug Administration; FIB-4 = fibrosis-4 index; GLP-1 RA = glucagon-like peptide-1 receptor agonist; LSM = liver stiffness measurement; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; Q = question; R = recommendation; SGLT2 = sodium-glucose cotransporter 2; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

Recommendations with Evidence Base

Diagnosis of NAFLD in Adults

Q2.1 Which Adults With NAFLD Should Be Considered at "High Risk" of Clinically Significant Fibrosis (Stages F2-F4) and at Risk of Cirrhosis?

Recommendation 2.1.1. Clinicians should consider persons with obesity and/or features of MetS, those with prediabetes or T2D, and those with hepatic steatosis on any imaging study and/or persistently elevated plasma aminotransferase levels (over 6 months) to be "high risk" and screen for NAFLD and advanced fibrosis.

Grade B; Intermediate/High Strength of Evidence; best evidence level (BEL) 2

Evidence Base. The diagnosis of NAFLD is based on the following: (1) presence of hepatic steatosis, in addition to (2) lack of significant alcohol consumption (defined as ongoing or recent alcohol consumption of >21 standard drinks [1 drink = 14 g of pure alcohol]/week for men and >14 standard drinks/week for women), and (3) exclusion of other liver diseases.[101] Initial evaluation in persons with suspected or incidental finding of hepatic steatosis on imaging should include investigations to exclude competing causes for hepatic steatosis and liver disease (eg, hepatitis B and C serology, antimitochondrial antibodies, antinuclear antibodies, anti–smooth muscle antibodies, serum ferritin, alpha 1 antitrypsin, and evaluation for MetS (Table 4).

In the past 20 years, it has become evident that persons with T2D have a very high prevalence of NAFLD and associated fibrosis.[5,6,9-11,52,102-104] Additionally, individuals with persistently abnormal aminotransferase levels in the absence of other causes of liver disease (eg, viral hepatitis and excessive alcohol use) are also at high risk of NAFLD and development of hepatic fibrosis (Table 5).[105,106] It is important to highlight that a landmark population-based study established that the upper limit of plasma alanine aminotransferase

Table 4
Causes of Secondary Hepatic Steatosis[101] and Laboratory Evaluation for the Secondary Causes of Liver Disease[22,a]

Causes
• Excessive alcohol consumption
• Hepatitis C (genotype 3)
• Lipodystrophy
• Acute weight loss (bariatric surgery and starvation)
• Malnutrition
• Parenteral nutrition
• Abetalipoproteinemia
• Reye syndrome
• Pregnancy associated
◦ HELLP syndrome
◦ Acute fatty liver of pregnancy
• Medications (eg, corticosteroids, mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, valproate, and antiretroviral medicines)
• Rare causes: autoimmune hepatitis, A1AT deficiency, Wilson syndrome, and other
Laboratory evaluation
• Hepatitis C
◦ HCV antibody with reflex testing HCV RNA
• Additional tests to consider:
◦ Hepatitis B: HBsAg, HBsAb, and HBcAb[b]
◦ ANA
◦ AMA
◦ ASMA
◦ Immunoglobulins
◦ Ferritin
◦ A1AT

Abbreviations: AMA = antimitochondrial antibodies; ANA = antinuclear antibodies; A1AT = alpha-1 antitrypsin; ASMA = anti–smooth muscle antibodies; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HELLP = Hemolysis, Elevated Liver enzymes and Low Platelets; RNA = ribonucleic acid.

[a] In persons at high risk of nonalcoholic fatty liver disease NAFLD (eg, type 2 diabetes mellitus, obesity, and metabolic syndrome), abdominal ultrasound is not required to diagnose hepatic steatosis, and it is reasonable to move directly to risk stratification after ruling out the secondary causes of liver disease.

[b] Not everyone should be tested for HBcAb due to high positivity and uncertain clinical significance.

Table 5
Additional Causes of Elevated Aminotransferase Levels[22,a]

- Medications, vitamins, and supplements
- Viral hepatitis (A, B, and C)
- Endocrine disorders[a] (hyper- or hypothyroidism, Cushing syndrome, hypogonadism, growth hormone deficiency, Addison's disease, and other)[b]
- Hemochromatosis
- Autoimmune hepatitis
- Primary biliary cholangitis
- Alpha-1 antitrypsin deficiency
- Budd-Chiari syndrome
- Mass lesions

[a] Causes of elevated aminotransferase levels that should be considered in the clinical evaluation of elevated aminotransferase levels in addition to the secondary causes of hepatic steatosis listed in Table 4.
[b] Steatosis in several endocrinopathies linked to associated development of obesity, insulin resistance, and/or type 2 diabetes mellitus.

(ALT) should be 30 U/L for men and 19 U/L for women.[107] Additional studies have made the American College of Gastroenterology consider a true normal ALT level to range from 29 to 33 U/L for males and 19 to 25 U/L for females.[108] This is because a level above the upper limit of normal, even in a population without identifiable risk factors, is associated with increased liver-related mortality and should be evaluated by clinicians. In this context, it is important to remember that persons with NAFLD and normal aminotransferase levels can still have significant steatohepatitis and develop advanced fibrosis or cryptogenic cirrhosis,[30,109] but the presence of high aminotransferase levels does increase the prevalence of adverse outcomes.[106]

Screening for NAFLD to prevent future cirrhosis is justified based on recent studies indicating a high prevalence of liver fibrosis (12%-21%) in persons with T2D[5,6,9-11,52,102-105,110,111] and the association of liver fibrosis with the future risk of developing complications of cirrhosis, including ascites, renal dysfunction, HCC, hepatic encephalopathy, and bacterial infections, and overall higher mortality.[43,47,112] A recent international cohort of 299 individuals with biopsy-proven NASH and compensated cirrhosis, during a median follow-up of 5 years, found that having T2D increased the risk of death (adjusted HR [aHR], 4.23; 95% CI, 1.93-9.29) and liver-related outcomes (aHR, 2.03; 95% CI, 1.005-4.11), including HCC (aHR, 5.42; 95% CI, 1.74-16.80),[46] by approximately twofold. It is well established that cirrhosis and poor outcomes are much more common in persons with diabetes.[54]

In fact, individuals with multiple components of MetS or IR, obesity, or prediabetes are also at risk of significant fibrosis and increased mortality.[5,6,9-11,52,102-104] High-risk groups for NAFLD with liver fibrosis are individuals who are 50 years or older and/or have moderate to severe obesity (BMI, >35 kg/m^2), including those seeking consultation for bariatric surgery, or T2D and/or MetS.[6,30,103,111,113-115] It should also be emphasized that the purpose of screening for NAFLD is to identify persons who are at risk of disease progression and liver fibrosis, the most important predictor of liver and overall outcomes. Screening is important because early intervention can halt or reverse disease progression. In a recent study in persons with T2D, screening for NAFLD followed by intensive lifestyle interventions or pioglitazone was cost-effective, providing further support for screening recommendations.[113,115]

Recommendation 2.1.2. Persons undergoing bariatric surgery should be evaluated for the presence and severity of NASH, and a liver biopsy should be considered at the time of bariatric surgery. Liver biopsy should be recommended if presurgical stratification suggests indeterminate or high risk of liver fibrosis.

Grade B; Intermediate Strength of Evidence; BEL 2

Evidence Base. Bariatric surgery can induce sustained weight loss, improve diabetes, and reduce CVD and cancer risks, which are common comorbidities in NAFLD.[116-121] As reported in a couple of recent meta-analyses[122,123] and discussed later (under Evidence Base for Recommendations 3.5.1-3.5.3), weight loss induced by bariatric surgery unquestionably improves steatosis, steatohepatitis, and, to a lesser extent, hepatic fibrosis. A recent meta-analysis even reported a reduction in the risk of HCC.[124] While the vast majority of persons undergoing bariatric surgery have NAFLD, only approximately 8.5% have F3 and F4 (cirrhosis) at the time of intraoperative liver biopsy[125], and 2% to 4% have unexpected cirrhosis diagnosed at the time of surgery.[126] This is in part related to presurgical screening and likely reluctance to proceed with surgery in those with known stable early or advanced cirrhosis.

Bariatric surgery should not be considered in persons with decompensated cirrhosis due to the increased postoperative mortality. The risk of complications, including postoperative complications, decompensation, and mortality, are higher in persons with cirrhosis than in those without cirrhosis. In a systematic review and meta-analysis of 18 studies that reported outcomes of bariatric surgery in persons with cirrhosis, the risks of postoperative complications, liver-related complications, and liver failure-related mortality were 22.14% (95% CI, 15.43%-29.55%), 4.62% (95% CI, 1.27%-9.30%), and 0.08% (95% CI, 0%-1.03%), respectively. In persons with cirrhosis, postoperative complications appear to be significantly lower with sleeve gastrectomy (10.08% [95% CI, 5.14%-16%]) than with Roux-en-Y gastric bypass (RYGB) (31.53% [95% CI, 18.62%-45.68%]; $P = .02$).[127]

Q2.2 What Blood Tests (eg, Diagnostic Panels and Specific Biomarkers) Can Be Used to Diagnose NAFLD With Clinically Significant Fibrosis (Stages F2-F4) in Adults?

Recommendation 2.2.1. Clinicians should use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred noninvasive initial test is the fibrosis-4 index (FIB-4).

Grade B; Intermediate Strength of Evidence; BEL 2

Evidence Base. Plasma liver aminotransferase levels can be unreliable and normal in many cases of NAFLD[128] and should not be used alone for the diagnosis of NAFLD. In a study in persons with T2D, up to 50% had NAFLD despite the so-called "normal" ALT levels (defined as <40 U/L in this study).[30] More recent studies have confirmed that the vast majority of persons with NAFLD in primary care or endocrinology clinics, even those with clinically significant fibrosis (≥F2), have a plasma aminotransferase level of <40 U/L.[9,10,102,114]

Hepatic steatosis can be diagnosed on imaging, including liver US, CAP, computed tomography, or the 2 most accurate and sensitive methods, ^{1}H-MRS and magnetic resonance imaging-proton density fat fraction (MRI-PDFF). The accuracy of liver US for the detection of moderate and severe steatosis was >80% in a meta-analysis when compared with liver histology.[129] However, this was based on data from hepatology clinics and does not represent the population with less severe disease observed in primary care or endocrinology clinics, where liver US was shown to have suboptimal sensitivity for mild-to-moderate steatosis (below a liver fat content of 12.5%) compared with ^{1}H-MRS and liver biopsy in 146 individuals.[24] Liver US is also highly operator dependent and does not inform about the severity of liver fibrosis (unless cirrhosis is present). MRI-based techniques (^{1}H-MRS and MRI-PDFF) for the diagnosis of steatosis are reserved at present largely to clinical trial research. Magnetic resonance elastography (MRE) should be ordered in selected persons primarily by liver specialists for the diagnosis of liver fibrosis,[130-133] but the test is expensive and does not replace the "gold standard" liver biopsy for the diagnosis of those with NASH.[2,134]

Most important for endocrinology and primary care clinicians is to calculate liver fibrosis scores for the diagnosis of clinically significant fibrosis, particularly using the FIB-4 (definition shown in Table 1), which has been the most validated among the many tested to this

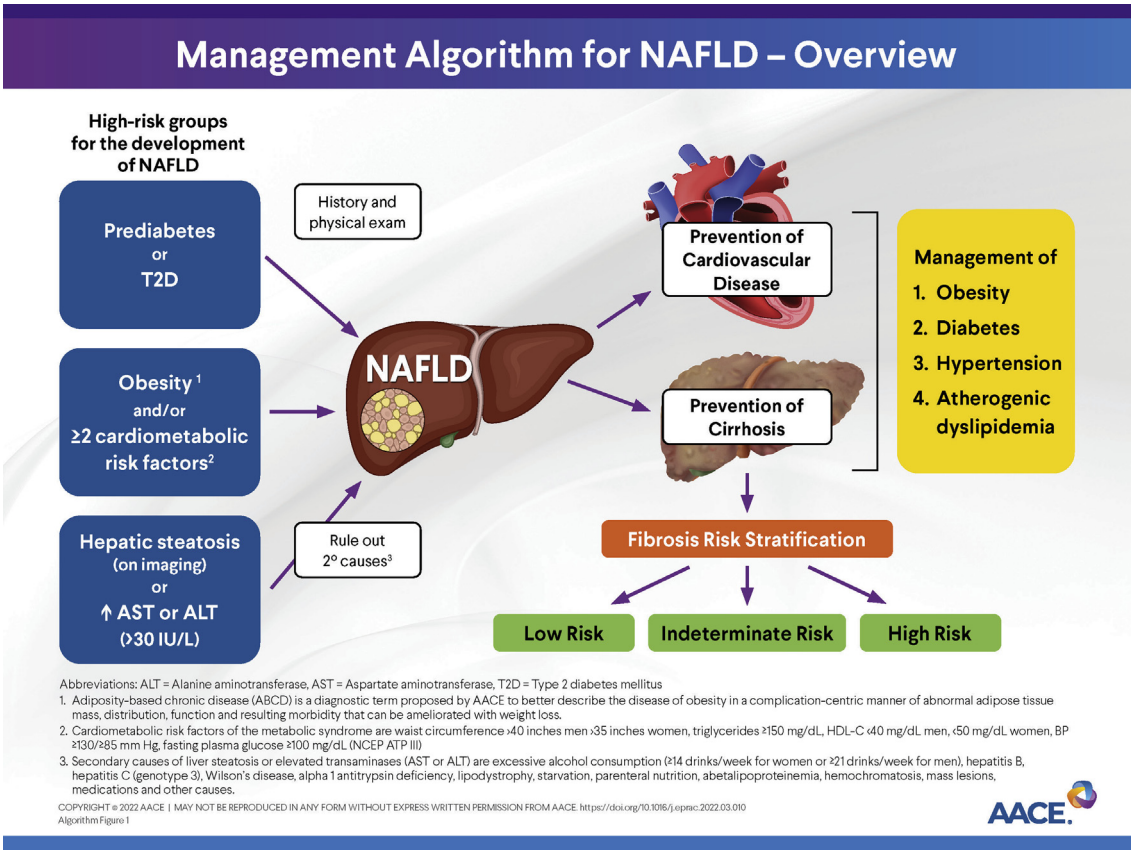
end.[43,130,135-141] The FIB-4 has strong validation in its ability to predict changes over time in hepatic fibrosis [135] and allows risk stratification of persons in terms of future liver-related morbidity and mortality, as shown in a population-based prospective survey[136] and in a recent meta-analysis of 13 longitudinal studies.[137] Of interest, the NAFLD fibrosis score (NFS), a liver score commonly used in hepatology clinics, may overestimate in the primary care setting the prevalence of advanced liver fibrosis in persons with obesity,[142] and in particular with T2D[11]; therefore, it should be avoided in this setting (noninvasive tests and screening tools shown in Table 1). Proprietary biomarkers include the FibroTest, enhanced liver fibrosis (ELF) test,[143] propeptide of type III collagen,[144-146] NIS4[141] and others.[130,134,137,147-149]

Endocrinology and primary care clinicians must be aware of the limitations of blood panels, compared with a liver biopsy (ie, the "gold standard"). Overall, panels for the diagnosis of fibrosis have a good specificity and negative predictive value (NPV) that allow the clinician to rule out advanced fibrosis and use this as a rule-out test.[130,134,137,147,148] However, they lack adequate sensitivity and positive predictive value (PPV) to establish the presence of advanced fibrosis; therefore, several individuals fall in the "indeterminate-risk" group (Algorithm Fig. 2). In this context, a multistep process must be used. For example, the area under the receiver operating characteristic curve for the FIB-4 is 0.78 to 0.80[135,147,150,151] but lower for NFS (0.72-0.75), in particular in persons with T2D.[147] Of note, their performance is dependent on the population being studied, with a better performance in hepatology clinics where more people have advanced disease than in primary care settings, where the FIB-4 and other tests have been less well characterized.

Recommendation 2.2.2. Clinicians should consider persons belonging to the "high-risk" groups (as defined under R2.1.1) who have indeterminate or high FIB-4 score for further workup with a liver stiffness measurement (LSM) (TE) or ELF test, as available.

Grade B; Intermediate Strength of Evidence; BEL 2

Evidence Base. In endocrine and primary care clinics, the initial step in persons at high risk of having NAFLD (prediabetes, T2D, obesity and/or MetS, or elevated plasma aminotransferase level) is to evaluate their risk of NAFLD. Hepatic steatosis may be assessed by means of simple noninvasive liver steatosis scores (fatty liver index, US fatty liver index, and hepatic steatosis index), although these diagnostic modalities have inherent limitations.[11,115,152] A liver US is not recommended for routine clinical diagnosis.[115] Instead, TE is preferred over liver US, where available, as it can quantify liver fat (CAP) and fibrosis (vibration-controlled transient elastography [VCTE]) for risk stratification during the same testing. In persons with a high pretest probability of NAFLD, such as the 3 at-risk groups identified in the diagnostic algorithm (Algorithm Fig. 1), it is reasonable to perform a risk stratification (FIB-4) without the need for a liver US for the diagnosis of hepatic steatosis (ie, in the 3 at-risk groups, the chance of having hepatic steatosis is very high and ≥70%).[5,9-11,52,102-104] It is important to perform a complete medical history and routine clinical chemistries that allow clinicians to rule out secondary causes of liver steatosis (Table 4) and elevated plasma aminotransferase levels (Table 5). A thorough workup should be performed to rule out competing causes for steatosis, in addition to excluding significant alcohol consumption.



Algorithm Fig. 1. Overview of management algorithm for nonalcoholic fatty liver disease (NAFLD). The assessment of persons for the risk of NAFLD and cirrhosis starts by testing the 3 major high-risk groups for the development of NAFLD, after a careful medical history and physical examination. Clinicians should also rule out secondary causes of liver steatosis. Once NAFLD is confirmed, assessment must stratify persons for the risk of liver cirrhosis and CVD and coordinate in a multidisciplinary approach (depending on disease severity) the management of obesity, diabetes, hypertension, and atherogenic dyslipidemia.

It is important to assess further for the risk of clinically significant fibrosis (stages F2-F4), which provides prognostic information on the future risk of cirrhosis and can guide treatment strategies, as well as need for referral to a hepatologist/gastroenterologist. A combination of the FIB-4 followed by VCTE (description under Q2.3) seems to be the best approach. If the FIB-4 score is >1.3, then a second level test, such as VCTE or ELF, should be performed (Algorithm Fig. 2). Using the FIB-4 as a first-line test, followed by VCTE, can help stratify persons in the "indeterminate zone" and greatly reduce the number of referrals to the specialist.[130,134,137,147,148,153] Of note, higher cutoffs for the FIB-4, in the range of 1.9 to 2.0 (rather than >1.3), have been suggested with older age (≥ 65 years) to determine advanced fibrosis.[154,155]

This combination or sequential use of tests yields a higher PPV in identifying at-risk persons with active NASH and fibrosis. In a study of 968 persons with biopsy-confirmed NAFLD, sequential testing with the FIB-4 or NFS followed by TE in those with an indeterminate score was more accurate than performing either test alone.[156] In another cross-sectional study of 3202 persons with bridging fibrosis and compensated cirrhosis, noninvasive tests alone or in combination with imaging (VCTE) reduced the need for a liver biopsy when trying to discriminate advanced fibrosis caused by NASH.[150] Persons with high or intermediate fibrosis risk should be referred to hepatology for further evaluation and consideration of a liver biopsy. Liver biopsy remains the "gold standard" for the diagnosis of NASH; however, it should not be used as a screening method to diagnose NAFLD given its multiple caveats: it is invasive, subject to interpretation errors,[157] and difficult to apply to large populations. An algorithm to screen for NAFLD and identify those at risk of clinically significant fibrosis has been proposed (Algorithm Fig. 2).

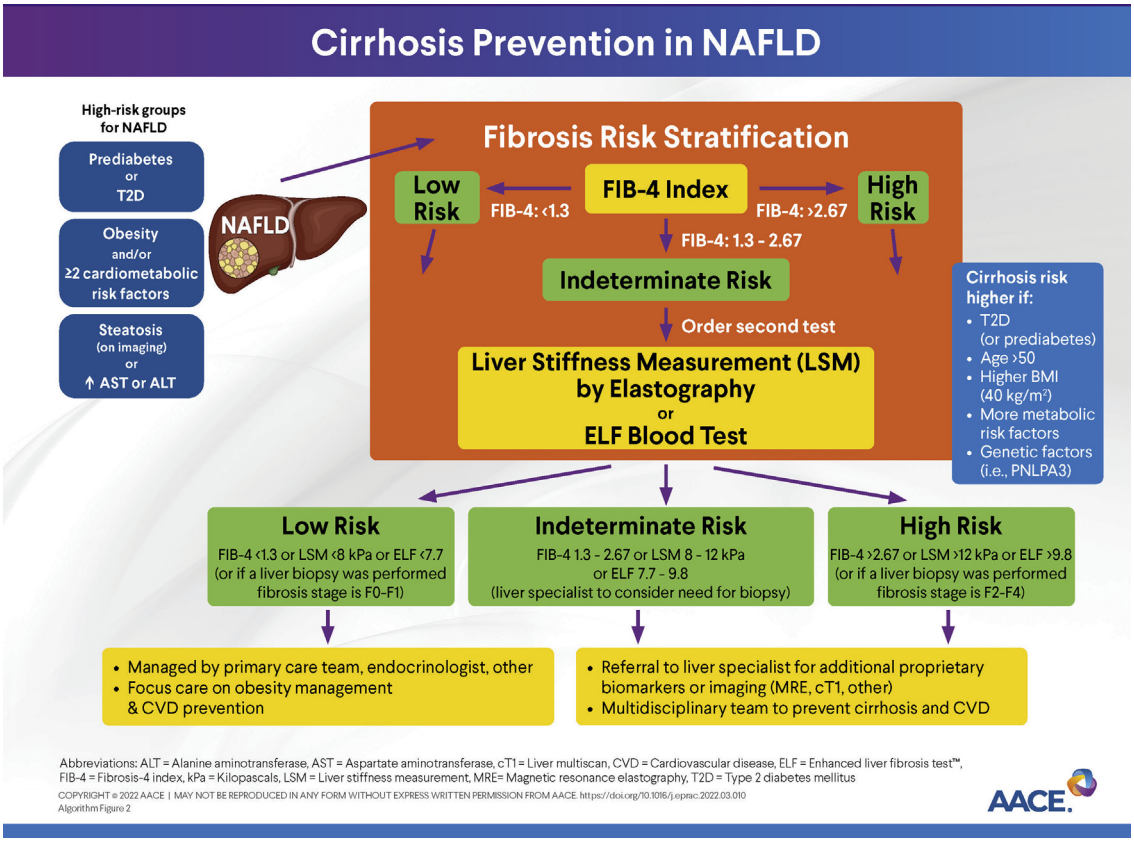
Q2.3 What Imaging Studies Can Be Used to Diagnose NAFLD With Clinically Significant Fibrosis (Stages F2-F4) in Adults?

Recommendation 2.3. To stage the risk of fibrosis in persons with NAFLD, clinicians should prefer the use of VCTE as best validated to identify advanced disease and predict liver-related outcomes. Alternative imaging approaches may be considered, including shear wave elastography (SWE) (less well validated) and/or MRE (most accurate but with a high cost and limited availability; best if ordered by a liver specialist for selected cases).

Grade B; Intermediate Strength of Evidence; BEL 2

Evidence Base. The current "gold standard" for the diagnosis of steatohepatitis is a liver biopsy. Although safe, it is an invasive procedure associated with potential adverse effects, such as pain, bleeding, and infection. In addition, it has other limitations, including reduced acceptability, intraobserver and interobserver variability, sampling variability, and cost.[157]

As mentioned earlier, VCTE (Table 1 and Algorithm Fig. 2) is the most broadly used noninvasive method for LSM and, thus, for establishing the risk of liver fibrosis[158-160] and for eventually excluding cirrhosis.[158] At a fixed sensitivity, a cutoff LSM of 6.5 kPa excluded advanced fibrosis with an NPV of 0.91, and a cutoff LSM of 12.1 kPa excluded cirrhosis with an NPV of 0.99.[158] Minor limitations of VCTE include overestimation of LSMs at higher stages of fibrosis and unsuccessful LSMs with inappropriate use of probes in



Algorithm Fig. 2. Cirrhosis prevention in nonalcoholic fatty liver disease (NAFLD). Once the presence of NAFLD is established, fibrosis risk stratification is essential. The first test recommended is the FIB-4, which often allows separation of those at low risk versus those at high risk of liver fibrosis. However, a significant proportion of persons will fall in a "gray zone" of indeterminate risk that requires additional testing to decide referral to the liver specialist. The second test recommended is LSM or, if unavailable, an ELF blood test. This should determine the risk in most individuals. Persons with a low risk of cirrhosis should be managed in primary care and/or endocrinology clinics, while those with an indeterminate to high risk of liver fibrosis merit referral to the liver specialist and a multidisciplinary approach to management.

individuals with overweight and obesity, which can be circumvented using the right probe in individuals with higher BMI.[161] With refined CAP algorithms and knowledge of steatosis prevalence and covariates, there is potential for more precise CAP-based steatosis grading.[162] Therefore, from a practical perspective for endocrinologists and PCPs, there is a growing consensus[8,22] to use TE (FibroScan) scores to assess the risk of clinically significant fibrosis and trigger early intervention to prevent cirrhosis (Algorithm Fig. 2). The best evidence comes from 2 recent studies. A European study in 450 adults who underwent TE and a liver biopsy using an LSM Youden cutoff value for clinically significant fibrosis (≥F2) of 8.2 kPa demonstrated NPVs of 78% in persons from diabetes clinics and 97% in the general population.[159] Another study in 1073 persons with NAFLD among 10 European tertiary liver centers confirmed these cutoffs, reporting that a cutoff of 8.0 kPa had a 93% sensitivity to exclude advanced fibrosis (≥F3-F4).[163] Similarly, a recent systematic review further supported the cutoff of 8.0 kPa for screening for clinically significant liver fibrosis.[164] For practical purposes then, people with an LSM of <8.0 kPa determined using TE are considered low risk for clinically significant fibrosis (≥F2) and are best managed in the nonspecialty clinics with repeat surveillance testing in 2 to 3 years. If the LSM is >12.1 kPa based on VCTE, the risk of advanced fibrosis is high, with PPVs of 76% and 88% in persons seen in diabetes and hepatology clinics, respectively, but lower in primary care populations.[159] It is recommended then to use rounded-off values of <8.0 kPa for the low-risk group, 8.0 to 12.0 for the indeterminate-risk group, and >12.0 kPa for the high-risk group for advanced liver fibrosis (Algorithm Fig. 2). A referral to a hepatologist is given for all of those in the indeterminate- to high-risk groups.

Other methods to measure liver fibrosis are also available. As discussed earlier, MRE has the best accuracy but is costly and has limited availability[130-133]; therefore, it is best ordered by the hepatologist when additional workup is needed in selected circumstances. Hepatologists also have significant experience with SWE, either 2-dimensional (2DSWE) or point (pSWE).[165-167] 2DSWE and pSWE appear to have an accuracy similar to that of TE but less than that of MRE. A recent meta-analysis of 82 studies with a total of 14 609 persons compared diagnostic methods for fibrosis staging (53 studies with VCTE, 11 with MRE, 12 with pSWE, and 4 with 2DSWE). The summary estimates of the sensitivity, specificity, and area under the curve were best for MRE, while pSWE was comparable to VCTE, and 2DSWE had somewhat lower estimates.[165] The summary estimates of the area under the curve varied for the diagnosis of significant fibrosis (≥F2) (0.85 for VCTE, 0.92 for MRE, 0.89 for pSWE, and 0.72 for 2DSWE) but were similar for the diagnosis of cirrhosis (0.89 for VCTE, 0.90 for MRE, 0.90 for pSWE, and 0.88 for 2DSWE).[165] However, pSWE and 2DSWE are newer techniques with limited evidence in terms of long-term predictive value for future liver outcomes, whereas data are already available for VCTE. Finally, newer imaging techniques are becoming available. Velacur (Sonic Incytes Medical Corp.) is a point-of-care liver assessment device based on Shear Wave Absolute Vibro-Elastography that incorporates elastography and a greater liver volume visualization.[168,169] LiverMultiScan uses multiparametric MRI to noninvasively quantify liver fat[170] and cT1 signal maps of the liver to assess disease activity (NAFLD activity score [NAS]) and potentially outcomes.[171,172] These techniques are currently being used largely in research for screening studies[5,173] or to assess primary end points in clinical trials for investigational drugs in development for the treatment of NASH. Both have received FDA-approval for use in persons with chronic liver disease and await future work to fully assess their place in the diagnostic algorithm of persons with NAFLD.

Q2.4 Should All Persons With Diabetes Mellitus Be Screened for Clinically Significant Fibrosis (Stages F2-F4) Associated With NAFLD?

Recommendation 2.4.1. In persons with T2D, clinicians should consider screening for clinically significant fibrosis (stages F2-F4) using the FIB-4, even if they have normal liver enzyme levels.

Grade B; High/Intermediate Strength of Evidence; BEL 2

Recommendation 2.4.2. In persons with T1D, clinicians may consider screening for NAFLD with clinically significant fibrosis (stages F2-F4) using the FIB-4, only if there are risk factors such as obesity, features of MetS, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis on imaging.

Grade C; Intermediate/Weak Strength of Evidence; BEL 2; downgraded based on the heterogeneity of studies and moderate to high probability of bias

Recommendation 2.4.3. Clinicians should further risk stratify persons with T2D or T1D with cardiometabolic risk factors and/or elevated plasma aminotransferase levels (>30 U/L) using the FIB-4, elastography, and/or ELF test.

Grade B; High/Intermediate Strength of Evidence; BEL 2

Evidence Base. A bidirectional relationship exists between NAFLD and T2D, whereby the presence of one increases the risk and severity of the other.[174] The rationale for universal screening is based on emerging evidence that T2D is a major risk enhancer of disease burden and disease progression to cirrhosis among individuals with NAFLD. Studies strongly suggest a relationship between NAFLD, hepatic IR and MetS, and T2D.[29,53] In prospective longitudinal studies, persons with T2D have approximately double the rate of NAFLD compared with the general population.[6,52,81] Conversely, persons with NAFLD have double the risk of developing T2D (HR, 2.2),[52] which may encourage screening for NAFLD in individuals with prediabetes.[175] Recent studies report that approximately 60% to 70% of persons with T2D have NAFLD with the majority having plasma aminotransferase levels below what is reported by most clinical laboratories to be "normal" (≥40 IU/L).[9] The global prevalence of NASH among persons with T2D based on 10 studies that included results from liver biopsies is 37.3%, although there was some selection bias among the populations included and the prevalence may be lower.[6] However, a recent study in individuals undergoing a routine colonoscopy who agreed to be screened for NAFLD, with additional cT1 MR testing (which can estimate the risk of steatohepatitis) and/or a liver biopsy if positive, gave a similar prevalence.[5] Of note, a meta-analysis suggested that persons with more "severe" NAFLD are more likely to develop T2D and the risk is even greater among those with advanced fibrosis.[52]

In a recent comprehensive analysis, the prevalence of NAFLD in persons with T1D was relatively low (≤10% with MRI-based techniques).[56,57] The pooled prevalence of NAFLD in persons with T1D determined using US studies was high (27.1%; 95% CI, 19.7%-36.3%) compared with that using the more accurate liver fat measurement with TE (2.3%; 95% CI, 0.6%-4.8%) or studies using "gold standard" MRI (8.6%; 95% CI, 2.1%-18.6%).[56,57] There is no high-quality study on the prevalence of steatohepatitis or fibrosis in persons with T1D. One study examining a database of 4641 people with T1D collected over a period of 20 years (1991-2011) found 57 persons (1.2%) with elevated plasma aminotransferase levels in whom a liver biopsy had been performed.[176] Only 20.4% had NASH, the rest had other diagnoses such as metastatic malignancy, alcoholic liver disease, hepatitis C, or hepatic glycogenosis. The presence of NAFLD is associated with the use of higher insulin doses for comparable glycemic control in both T1D and T2D populations.[57,177,178] Obesity and IR appear to be the driving factors, with significant heterogeneity among studies that makes it difficult to fully assess the impact of T1D in the development of NAFLD. Overall, screening appears justified only in persons

with obesity, MetS, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis on imaging.[152,179-183]

Although not yet established, it is likely that interventions that improve NAFLD and hepatic IR may decrease the risk of developing T2D,[52,53] as suggested with pioglitazone that reduces the progression from prediabetes to T2D by 70% to 80% in persons at risk of diabetes.[184-187] Individuals with T2D and NAFLD are also at increased risk of NASH with advanced fibrosis, particularly in those aged >50 years with T2D or obesity.[81] It also appears to accelerate the progression of liver disease in NAFLD and promote its development at younger ages.[6] Several systematic reviews and meta-analyses have shown that among persons with NAFLD and T2D, approximately 12% to 21% have advanced liver fibrosis (stages F2-F4).[6,9-11,102,110,114,188-190] A 2018 systematic review and meta-analysis found that overall, 31% (ranging from 27% to 56%) of persons with cirrhosis had diabetes mellitus, which is approximately threefold higher than that of the general U.S. population.[191]

Q2.5 When Should an Adult Be Referred to a Gastroenterologist/Hepatologist for Management?

Recommendation 2.5.1. Persons with persistently elevated ALT or aspartate aminotransferase (AST) levels and/or with hepatic steatosis on imaging and indeterminate risk (FIB-4, 1.3- 2.67; LSM, 8-12 kPa; or ELF test, 7.7-9.8) or high risk (FIB-4, >2.67; LSM, >12 kPa; or ELF test, >9.8) based on blood tests and/or imaging (as described in R2.2.1, R2.2.2, and R2.3) should be referred to a gastroenterologist or hepatologist for further assessment, which may include a liver biopsy.

Grade B; Intermediate Strength of Evidence; BEL 2

Recommendation 2.5.2. Clinicians should refer persons with clinical evidence of advanced liver disease (ascites, hepatic encephalopathy, esophageal varices, or evidence of hepatic synthetic dysfunction) to a gastroenterologist/hepatologist for further care.

Grade B; Intermediate/High Strength of Evidence; BEL 2

Evidence Base. The initial steps in managing persons with NAFLD encompass the assessment and treatment of associated cardiometabolic risks, such as visceral obesity, T2D, hypertension, and dyslipidemia.[192] Individuals with obesity and T2D are at increased risk of NAFLD enriched for NASH and advanced fibrosis.[9,10,102,110,114,188-190] While only a minority of individuals with NAFLD progress to advanced liver disease and require specialty care, their identification is often challenging. Furthermore, to optimize resource utilization, individuals who do not have advanced fibrosis could be effectively managed in the nonhepatology setting. Another challenge is that most individuals with advanced liver disease in the context of NAFLD are asymptomatic. Thus, the risk stratification of high-risk individuals or those with known NAFLD using simple clinically available tools is critical to identify those at higher risk of liver-related outcomes, including mortality, that should be seen in specialty practices, as well as those who can be managed in a primary care or endocrine practice setting.

The frequency of testing for individuals considered at low risk based on the FIB-4 (<1.3) or VCTE (<8.0 kPa) is not as well established as it is for the "high-risk" groups; however, it is prudent to consider repeat testing every 2 years for those at low risk, as 1 study showed that only a minority will progress to a higher fibrosis stage within that period of time (<20%).[41,193] In a RCT, the progression of persons with obesity and prediabetes or T2D in the placebo arm of the study over 72 weeks was 26% compared with only 7% on pioglitazone.[98] More data are clearly needed for stronger recommendations moving forward.

Several studies have reported on the feasibility of screening for NAFLD and liver fibrosis in persons with T2D in primary care settings using clinical and routine chemistries and/or TE.[9,10,102,110,114,188-190] A serial combination of 2 tests to improve screening accuracy has been used less commonly, but new data are emerging.[5,113,115,142,150,156] In a prospective longitudinal cohort study of 3012 adults, the results before and after the introduction of a 2-step care pathway were compared.[194] The implementation of this care pathway using the FIB-4 and ELF test resulted in an 88% reduction in unnecessary specialist referrals when the pathway was followed (OR, 0.12; 95% CI, 0.042-0.449; P < .0001) and a fourfold increase in the identification of individuals likely to have advanced fibrosis (OR, 4.32; 95% CI, 1.52-12.25; P = .006). However, more long-term outcome data are needed on screening strategies to prevent cirrhosis.

Additional management of persons with NAFLD depends on the stage and severity of liver disease. Fibrosis stage is an important predictor of long-term outcomes.[43,148,195] Again, the initial steps of risk stratification using the algorithms outlined in Algorithm Figures 1 and 2 should be performed by endocrinologists and in the primary care setting.[194,196-198] For persons with evidence of advanced liver disease (eg, ascites, hepatic encephalopathy, esophageal varices, hypersplenism/low platelet count, or evidence of hepatic synthetic dysfunction as characterized by a low albumin level and/or evidence of prolonged prothrombin time/international normalized ratio), assessment and management by a gastroenterologist or hepatologist may be necessary. In this context, risk assessment with additional tests, including liver biopsy, may be required. In fact, liver biopsy is important to not only exclude other coexisting causes of liver disease (eg, autoimmune hepatitis and iron overload) (Tables 4 and 5) but also firmly establish the stage of liver disease when blood tests and imaging provide conflicting results. Furthermore, liver biopsy is required for enrollment in most of the clinical trials for new pharmacologic treatment of NASH. In addition to liver biopsy, gastroenterologists or hepatologists will manage advanced liver disease, including periodic screening for HCC, large esophageal varices, and liver disease progression and timely referral to liver transplantation.

Management of NAFLD in Adults

Q3.1 How Should Cardiometabolic Risk and Other Extrahepatic Complications Be Managed in the Setting of NAFLD?

Recommendation 3.1. Clinicians must manage persons with NAFLD for obesity, MetS, prediabetes, diabetes mellitus, dyslipidemia, hypertension, and CVD based on the current standards of care.

Grade A; High/Intermediate Strength of Evidence; BEL 1

Evidence Base. There is broad consensus that screening and early intervention for obesity,[117,199,200] prediabetes,[201-205] T2D,[199,205-208] dyslipidemia,[209,210] and hypertension[211,212] are warranted because it is cost-effective and safe and allows for interventions to prevent diabetic complications and CV events. This has led to guidelines encouraging the screening for these risk factors that are commonly present in persons with obesity and T2D.[213-220] Cardiometabolic benefit from weight loss is apparent after 5% weight loss and greater with further weight loss.[207]

NAFLD and NASH are integral to the nexus of these diseases that comprise the spectrum of cardiometabolic disease (CMD).[221] At the core of CMD is IR that encompasses abnormal glucose tolerance, systemic inflammation, oxidative stress, mitochondrial dysfunction, endothelial dysfunction, and dysfunctional adipose tissue.[29,59,222] Early in CMD progression, the insulin-resistant state is largely subclinical but over time results in prediabetes and MetS, which indicate the presence of CMD and IR and mark individuals at high risk of future T2D, NAFLD, hypertension, myocardial dysfunction, dyslipidemia, CVD events, and CKD.[221,223] Obesity plays a key role in CMD because it can exacerbate IR and impel this disease progression. To accommodate the need for fat storage

under conditions of increased caloric intake, the accumulation of intracellular lipid becomes more pronounced in myocytes and hepatocytes.[29,222] Based on pathophysiology, persons with NAFLD will be at risk of other CMD manifestations, and individuals who have 1 or more CMD manifestations will be at increased risk of NAFLD, as substantiated by multiple studies employing epidemiology, prospectively and retrospectively followed cohorts, nested cases-controls, and related meta-analyses.[213-216,221,223] For example, a systematic review analyzing 86 studies with a sample size of 8 515 431 from 22 countries has documented high rates of CMD manifestations in persons with NAFLD and still higher rates in persons with NASH for obesity (51% and 82%, respectively), T2D (23% and 44%, respectively), hyperlipidemia (69% and 83%, respectively), hypertension (39% and 68%, respectively), and MetS (43% and 71%, respectively).[221] Thus, care of persons with NAFLD extends beyond the liver and must comprehensively consider the broader context of CMD.

Whether NAFLD is an independent risk factor for CVD remains controversial. Individuals with NAFLD appear to have a higher prevalence of clinical CVD than individuals without steatosis.[1,53] Moreover, CVD is the leading cause of death in NAFLD.[224] Several studies including meta-analyses have shown that NAFLD is an independent risk factor for CVD after controlling for other risk factors, that it confers an independent risk of fatal and nonfatal CV events (in both persons with and without diabetes), and that this risk becomes greater as NAFLD progresses to more severe forms of NASH.[47,224,225] However, this is somewhat controversial since other studies fail to demonstrate an independent risk of CVD and that the increased incidence of CVD events is explained by the burden of other risk factors that accompany NAFLD.[83,86,226] The limitations of most studies are the lack of adequate controls, short-term follow-up, and few reporting on CV events but rather surrogate end points such as endothelial dysfunction and carotid intima-media thickness test. Diagnosis of NAFLD has been made using different methodologies but mostly noninvasive tests such as elevated plasma aminotransferase levels or by US and rarely by “gold standard” MRI-based techniques or liver biopsy. Future prospective studies using more rigorous study designs may be required to resolve this discrepancy.

The AACE[213] and European Association for the Study of Obesity[214] have advocated for the use of adiposity-based chronic disease (ABCD) as a medical diagnostic term for obesity, and the treatment of ABCD to prevent progression to NAFLD and NASH underscores the complications-centric approach to treatment consistent with the AACE Guidelines for Comprehensive Medical Care for Patients with Obesity.[216]

A renewed emphasis has been put on increasing awareness of the need for vaccinations in persons with diabetes, chronic liver disease, and associated comorbidities. Table 6 shows the current immunization recommendations for those with chronic liver disease.[227,228]

Table 6
Immunizations for Persons With Chronic Liver Disease[227,228]

Hepatitis A vaccine
Hepatitis B vaccine
Pneumococcal polysaccharide vaccine (PPSV23)
Additional vaccines:
• Influenza vaccine
• Tdap vaccine
• Zoster vaccine
• HPV vaccine
• MMR vaccine
• Varicella vaccine
• COVID-19 vaccine

Abbreviations: HPV = human papilloma virus; MMR = measles, mumps, and rubella; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; Tdap = tetanus, diphtheria, and pertussis.

Q3.2 What Lifestyle Modifications (Dietary Intervention and Exercise) Should Be Recommended in Adults With NAFLD or NASH?

Recommendation 3.2.1. Clinicians should recommend lifestyle changes in persons with excess adiposity and NAFLD with a goal of at least 5%, preferably ≥10% weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, depending on individualized risk assessments. Clinicians must recommend participation in a structured weight loss program, when possible, tailored to the individual’s lifestyle and personal preferences.

Grade B; Intermediate/High Strength of Evidence; BEL 1; downgraded due to small sample sizes, large heterogeneity of interventions, short duration, and few studies with liver biopsy

Recommendation 3.2.2. Clinicians must recommend dietary modification in persons with NAFLD, including a reduction of macronutrient content to induce an energy deficit (with restriction of saturated fat, starch, and added sugar) and adoption of healthier eating patterns, such as the Mediterranean diet.

Grade A; Intermediate Strength of Evidence; BEL 1

Evidence Base. Lifestyle change primarily consists of nutritional therapy and physical activity and is the first-line therapy for ABCD and related complications, including NAFLD. While dietary macronutrient content and distribution is important in NAFLD, weight loss achieved through caloric deficit, irrespective of the specific dietary approach, is effective in reducing hepatic steatosis, even necroinflammation, although results are more variable for fibrosis. Several studies have reported normalization of plasma aminotransferase levels and a reduction of hepatic steatosis (most by imaging) that is proportional to the amount of weight loss.[229-237] However, fewer studies have examined the impact of weight loss on necrosis, inflammation, and fibrosis by performing liver biopsies before and after treatment. An early, small RCT (n = 31) demonstrated that persons with biopsy-proven NASH randomized to lifestyle intervention (diet, exercise, and behavioral modification) and who lost significant body weight (9.3%) showed improved steatosis and necroinflammation disease activity scores but not fibrosis.[238] Those who achieved a weight loss of ≥7%, compared with those who lost <7%, had significant improvements in steatosis, lobular inflammation, ballooning injury, and the overall NAS. In a more recent prospective cohort study of individuals (N = 261) undergoing a 52-week program of lifestyle intervention, a higher proportion of persons with ≥5% weight loss had NAS reductions and NASH resolution compared with those who lost <5% of their weight; all persons who lost ≥10% of their weight had NAS reductions, 90% had NASH resolution, and 45% had fibrosis regression.[239] The authors subsequently developed a predictive model derived from weight loss, presence of T2D, ALT normalization, age, and an NAS of ≥5 that exhibited a high predictive value for histologic improvement (eg, NASH resolution) after lifestyle intervention.[240] A 2021 meta-analysis of 43 studies involving 2809 participants (26 behavioral weight-loss programs, 9 with pharmacotherapy, 8 with surgery) found evidence of a dose-response relationship between the magnitude of weight loss and the degree of liver improvement of steatosis and resolution of NASH but not for fibrosis.[241]

Specific dietary patterns can exert benefit in persons with NAFLD, with debate as to the best dietary approach in NAFLD. However, a reduction in overall macronutrient content, and in particular saturated fat, appears to be consistent across studies. For

instance, overfeeding 1000 kcal/day of saturated fat for 3 weeks induced a greater increase in the intrahepatic triglyceride (IHTG) level than similar overfeeding of unsaturated fat or simple sugars.[242-244] The role of restricting carbohydrates in NAFLD, particularly simple sugars in food and beverages sweetened with high fructose corn syrup, has been examined in a number of studies.[245] Several recent studies have shown the value of a Mediterranean diet (ie, low in carbohydrates and saturated fat but higher in monosaturated fat) as it improves CV risk parameters and effectively reduces hepatic fat content.[229,246-252] Consistent with the aforementioned, another RCT showed that a calorie-restricted DASH diet, rich in fruit, vegetables, whole grains, and low-fat dairy and low in saturated fat and refined grains, also results in beneficial weight loss and reduced ALT levels in persons with obesity and NAFLD compared with a control diet.[253] These results have led several societies including the European Association for the Study of the Liver-European Association for the Study of Diabetes-European Association for the Study of Obesity,[254] European Society for Clinical Nutrition and Metabolism,[255] Asian Pacific Association for the Study of the Liver,[256] Latin American Association for the Study of the Liver,[257] and most recently the American Gastroenterological Association[258] to specifically recommend the Mediterranean diet for persons with NAFLD. Other approaches that have reported benefit in decreasing hepatic steatosis include high protein/lower carbohydrate intake diets with 30% protein, 40% carbohydrates, and 30% fat[259,260] and intermittent fasting and/or time-restricted feeding.[261-263] These approaches also create an energy deficit that may be helpful for some persons with NAFLD.[264]

Structured weight-loss programs and antiobesity medications are usually more successful for weight loss than the efforts of clinicians and dieticians at regular visits.[232,235] We recommend a greater use of formal weight-loss programs.[258] Bariatric surgery performed by well-established programs is another tool that should be considered in appropriate individuals with clinically significant fibrosis and obesity with comorbidities.[236]

In summary, caloric restriction within a Mediterranean diet appears to have the best evidence and likely the best chance of long-term adherence. However, comparing results across studies remains a challenge due to heterogeneity of the study designs (even within the same diets, in terms of dietary and caloric composition), small number of participants and diverse populations included, intervention duration, and end points utilized (various imaging techniques vs histology). One major limitation is that none of these studies has extended beyond 12 months, a major drawback considering NAFLD is a chronic disease.

Recommendation 3.2.3. In persons with NAFLD, clinicians must recommend physical activity that improves body composition and cardiometabolic health. Participation in a structured exercise program should be recommended, when possible, tailored to the individual's lifestyle and personal preferences.

Grade A; Intermediate Strength of Evidence; BEL 1

Evidence Base. Exercise helps maintain weight loss and may have benefits that are independent of weight loss on liver fat and histology. While most clinical studies on exercise in NAFLD have been of short duration (≤12 months) and included small numbers of participants, benefit has been fairly consistent.[230,265,266] In a 2016 meta-analysis (N = 8 studies prescribing exercise [2 with diet]; N = 433 persons with NAFLD), a reduction in the IHTG level was independent of dietary intervention but more evident with diet plus exercise than with exercise alone.[267] In another 2016 meta-analysis and meta-regression (N = 28 RCTs including persons with obesity complicated by T2D or MetS and NAFLD), physical activity reduced intrahepatic lipid and aminotransferase levels correlating with baseline BMI.[268] Subsequent controlled studies[269-273] and a 2018 meta-analysis[274] of 17 studies including 373 participants concluded that structured exercise training elicits an absolute reduction in the IHTG level of 3.31% (95% CI, −4.41% to −2.22%) that is often proportional to the magnitude of the exercise training and anthropometric improvements. The most common intervention frequency among studies was 3 times per week, for 30 to 60 minutes each session and lasting 12 weeks. However, greater intensity has not always translated into a more significant decrease in hepatic steatosis.[271,274,275]

Specific types of exercise exert different effects in persons with NAFLD. There were no significant differences between aerobic and resistance trainings, but there was more benefit with high-volume continuous training than with low-volume continuous training even with high intensity.[190] While there are more data on aerobic exercise, resistance training can improve NAFLD and may be more feasible for persons with poor cardiorespiratory fitness or an inability to participate in aerobic exercise. A 2017 meta-analysis (N = 12 studies comparing aerobic with resistance training protocols) found that resistance training improves hepatic steatosis with reduced energy requirements, compared with aerobic exercise.[276] An RCT (N = 220) of 12-month duration in people with biopsy-proven NAFLD compared 3 interventions: (1) vigorous-moderate exercise (jogging 150 minutes per week at 65%-80% of maximum heart rate for 6 months and brisk walking 150 minutes per week at 45%-55% of maximum heart rate for another 6 months), (2) moderate exercise (brisk walking 150 minutes per week for 12 months), or (3) no-exercise control group. The investigators found that both exercise groups were equally effective in reducing the IHTG content measured by ^{1}H-MRS and significantly reduced hepatic steatosis compared with those in the no-exercise controls.[275] In another RCT (N = 18 adults with obesity and hepatic steatosis) comparing energy-matched moderate-intensity exercise with high-intensity exercise, again, both modalities reduced the IHTG content to a similar extent as well as markers of hepatic inflammation.[277]

In summary, exercise has shown to consistently benefit persons with NAFLD, the challenge being long-term adoption. Benefit from increasing physical activity appears more linked to the intensity and adherence to the training program rather than the type of exercise. Of note, a decrease in hepatic steatosis with exercise is observed even in the absence of major weight loss.[265,266,269,278] Overall, a larger cardiometabolic and liver histologic benefit is observed when exercise is associated with lifestyle and dietary changes.

Q3.3 What Medications Have Proven to Be Effective for the Treatment of Liver Disease and Cardiometabolic Conditions Associated With NAFLD or NASH?

Recommendation 3.3.1. **R3.3.1a** Pioglitazone or GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH.

Grade A; High Strength of Evidence; BEL 1

R3.3.1b Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests.

Grade A; High Strength of Evidence; BEL 1

Recommendation 3.3.2. To offer cardiometabolic benefit in persons with T2D and NAFLD, clinicians must consider treatment with GLP-1 RAs, pioglitazone, or SGLT2 inhibitors; however, there is no evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors.

Grade A; High Strength of Evidence; BEL 1

Recommendation 3.3.3. Due to the lack of evidence of efficacy, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for the treatment of steatohepatitis (no benefit on hepatocyte necrosis or inflammation) but may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH.

Grade B; High Strength of Evidence; BEL 1; downgraded due to the use of surrogate outcome measures in many of the studies

Recommendation 3.3.4. Vitamin E can be considered for the treatment of NASH in persons without T2D, but there is not enough evidence at this time to recommend for persons with T2D or advanced fibrosis.

Grade B; High Strength of Evidence; BEL 1; downgraded due to risk/benefit

Recommendation 3.3.5. Other pharmacotherapies for persons with NASH cannot be recommended at the present time due to the lack of robust evidence of clinical benefit.

Grade A; High Strength of Evidence; BEL 1

Evidence Base. The rationale for pharmacologic treatment of NASH in persons with T2D (in addition to lifestyle changes) is based on the following aspects, as discussed earlier: (1) NASH has reached epidemic proportions with clinically significant fibrosis (stage ≥F2) being present in approximately 12% to 21% of individuals in T2D[9,10,102,110,114,188-190]; (2) NASH with clinically significant fibrosis is associated with an increased risk of mortality from liver-related complications[279]; (3) early diagnosis and treatment offer a window of opportunity to prevent disease progression; (4) T2D appears to accelerate progression to cirrhosis in NASH, making a dual intervention versus diabetes and NASH more cost-effective[28,147]; (5) while weight loss alone may reverse NASH, usually in proportion to the magnitude of weight loss, halting fibrosis progression is less predictable and highly variable among individuals[106]; and (6) some medications effective to treat T2D and NASH (pioglitazone and GLP-1 RAs) also reduce CVD, the leading cause of death in this population.[29,59] Taken together, it follows that adding pharmacologic therapy with agents proven to reverse NASH is warranted to prevent progression to cirrhosis more effectively.

At present, there are no FDA-approved drugs for the treatment of NASH. Therefore, treatment recommendations for persons with T2D and NASH are centered on the dual purpose of treating hyperglycemia and/or obesity and NASH, especially if clinically significant fibrosis (stage, ≥F2) is present, to prevent development of cirrhosis. As discussed, a liver biopsy is the optimal approach to confirm the diagnosis and stage of the severity of liver fibrosis. However, it is recognized that this may not be feasible or acceptable to several individuals. Therefore, in high-risk populations (ie, those with obesity and T2D), pharmacologic therapy to treat obesity or diabetes may also be considered in the presence of elevated plasma aminotransferase levels and/or FIB-4 scores of >1.3 and confirmatory imaging (ie, TE and MRE) or proprietary fibrosis biomarkers, such as the ELF test,[143] when suggestive of clinically significant liver fibrosis, if imaging not available.[134,147,148] Additional biomarkers are undergoing further evaluation in NAFLD (ie, NIS4,[141] propeptide of type III collagen,[142,144-146] and others[134]).

Two antidiabetic agents have proven to be safe and effective to reverse NASH in persons with obesity, prediabetes, or T2D: pioglitazone and GLP-1 RA (Table 7). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-γ that improves IR, primarily targeting adipose tissue and improving lipid storage/redistribution and glucose utilization.[29] It was the first diabetes agent to show efficacy in an early RCT in 55 individuals with prediabetes or diabetes and biopsy-proven NASH.[280] This was followed by positive 12- to 24-month RCTs showing histologic improvement in persons without diabetes.[97,98,281,282] A 2016 single-center study in 101 persons with obesity, and either prediabetes or T2D, confirmed its sustained benefit on glucose and lipid metabolism and NASH over 36 months of follow-up.[98] With pioglitazone treatment (45 mg), 58% of individuals achieved the primary outcome of a reduction of at least 2 points in NAS, while 51% had resolution of NASH (treatment difference of 41% and 32% vs placebo, respectively; both $P < .001$ vs placebo). There was also improvement in the mean fibrosis score ($P = .039$).[98] A 2017 meta-analysis of available pioglitazone RCTs in persons with biopsy-proven NASH noted a significant improvement versus placebo for NASH resolution (OR, 3.22; 95% CI, 2.17-4.79; $P < .001$) and for any stage of fibrosis (OR, 1.66; 95% CI, 1.12-2.47; $P = .01$), with even greater ORs for the effect on advanced fibrosis (OR, 3.15; 95% CI, 1.25-7.93; $P = .01$), with similar results for those with and without T2D.[283] A 2020 incremental cost-effectiveness ratio analysis that added a more recent 2019 study combining pioglitazone with vitamin E confirmed the aforementioned findings.[284] The side effects of pioglitazone include dose-dependent weight gain (1% with pioglitazone 15 mg/day up to 3%-5% with 45 mg/day), increased fracture risk, heart failure if used in persons with preexisting heart disease, and bladder cancer. A meta-analysis of 17 cohort or case-control studies revealed a minimal prevalence of bladder cancer compared with robust CV benefits and improvements for those with NASH (the numbers needed to treat for 1 additional case of bladder cancer ranged from 899 to 6380, while the numbers needed to benefit CVD and NASH were 4-256 and 2-12, respectively).[285]

GLP-1 RAs have become pillars of pharmacotherapy for obesity and T2D because of robust clinical benefits, including weight loss, glycemic control, and cardiometabolic improvements. The challenge of systematic reviews of GLP-1 RAs in NAFLD is the heterogeneity of populations included and study designs, with broad differences in treatment duration, primary end points, and assessment of treatment efficacy with random liver imaging modalities and rare use of liver biopsy as the "gold standard" for grading NASH. However, taken

Table 7
Medications to Treat Diabetes and Their Efficacy for the Treatment of Nonalcoholic Fatty Liver Disease

Medication	Liver fat	Disease activity (steatohepatitis/NAS)	Studies
Metformin	Unchanged	Neutral	(298-302)
Pioglitazone	Decreased	Improved[a]	(97, 98, 280-282)
Insulin	Decreased	Effect unknown	(177, 178, 306)
GLP-1 RAs (semaglutide and liraglutide)	Decreased	Improved[a]	(99, 286-288)
SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin)	Decreased	Effect unknown	(28, 294-297)
DPP-IV inhibitors (sitagliptin and vildagliptin)	Unchanged (in RCTs)	Effect unknown	(286, 303-305)

Abbreviations: DPP-IV = dipeptidyl peptidase IV; GLP-1 RAs = glucagon-like peptide11 receptor agonists; NAS = nonalcoholic fatty liver disease activity score; RCTs = randomized controlled trials; SGLT2 = sodium-glucose cotransporter 2.

[a] The effect on hepatic fibrosis of diabetes medications that improve steatohepatitis has been overall small, although some individual studies[98,281] and meta-analyses of available RCTs[283,284] report a decrease in fibrosis with pioglitazone.

together, studies agree that GLP-1 RAs normalize plasma aminotransferase levels and reduce liver fat content on imaging in individuals with NAFLD[222,286,287] (Table 7). A small (n = 52) 2016 proof-of-concept RCT suggested that liraglutide improved some features of liver histology in persons with NASH, including delaying fibrosis progression versus placebo.[288] In 2021, a phase 2 RCT compared the doses of 0.1, 0.2, and 0.4 mg of semaglutide daily with placebo in 320 persons with NASH (of whom 230 had stage F2 or F3 fibrosis). Resolution of steatohepatitis was found in 40% of those in the 0.1-mg group, 36% of those in the 0.2-mg group, 59% of those in the 0.4-mg group, and 17% of those in the placebo group ($P < .001$ for semaglutide 0.4 mg vs placebo) in the context of significant weight loss (13% in the 0.4-mg group vs 1% in the placebo group).[99] There were no significant between-group differences in the percentage of individuals with an improvement in fibrosis stage, but progression of liver fibrosis was significantly less with the highest dose of the GLP-1 RA (4.9%) versus placebo (18.8%). Of note, the semaglutide dose of 0.4 mg/day employed is equivalent to the dose of semaglutide 2.4 mg/week shown in phase 3 trials to be highly effective for weight loss in persons with obesity.[289-292]

SGLT2 inhibitors, approved for the treatment of T2D and heart failure and associated with robust cardiorenal benefits, have been considered potentially beneficial for NAFLD because of the reduced lipid burden on the liver from glycosuria creating energy deficit and weight loss.[293] Several small, open-label studies have suggested benefit in persons with T2D and NAFLD.[29,222,294] More recent RCTs have been performed showing the potential benefit of these medications in NAFLD and NASH in persons with obesity and T2D via imaging of hepatic steatosis using "gold standard" MRI-based techniques, but none yet has been performed with histologic evaluation[295-297] (Table 7). SGLT2 inhibitors may be considered as adjunctive pharmacotherapy for individuals with T2D and NAFLD as they reduce hepatic steatosis and offer significant cardiometabolic and renal protection.

Metformin is a biguanide that improves hepatic and muscular insulin sensitivity; however, in several paired-biopsy studies in persons with NASH, there was no clinical evidence of benefit on disease activity or liver fibrosis (Table 7). Early studies suggested a modest effect, largely on hepatic steatosis and associated with weight loss,[298,299] but a meta-analysis of metformin trials has shown that weighted liver histologic scores for steatosis, ballooning, and fibrosis did not significantly improve and lobular inflammation significantly worsened (weighted mean increase, 0.21; 95% CI, 0.11-0.31; $P < .0001$),[300] consistent with other systematic reviews and meta-analyses.[301,302] Early studies suggested benefit from dipeptidyl peptidase IV inhibitors, but this was not confirmed in recent RCTs.[286,303-305] Insulin may reduce hepatic steatosis, but the effect is modest, and no liver biopsy study to assess its effects on liver histology is available.[177,178,306]

Among other agents, only vitamin E showed efficacy to ameliorate steatohepatitis (but not fibrosis) in individuals without T2D and biopsy-proven NASH in a 2-year RCT.[97] Improvement in steatohepatitis has also been reported in a single-center, uncontrolled retrospective observational study in persons with advanced liver fibrosis.[307] However, the results in persons with T2D have been mixed, and vitamin E cannot be recommended with the current evidence, as benefit has been modest overall, and fibrosis has not been improved in any of the studies.[282] Controversy remains about vitamin E being associated with a modest increased risk of cardiovascular disease and of prostate cancer,[101] although not confirmed in more recent studies. Finally, a number of agents have been tested in individuals with NAFLD or NASH; however, studies have been generally uncontrolled, small, used only imaging as the primary end point, and/or been overall negative.[300,301,308,309]

Q3.4 What Obesity Pharmacotherapies Have Proven Benefit for the Treatment of Liver Disease and Cardiometabolic Conditions Associated With NAFLD or NASH in Adults?

Recommendation 3.4.1. Clinicians should recommend the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH with a goal of at least 5%, preferably ≥10%, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, when this is not effectively achieved by lifestyle modification alone.

Grade B; Intermediate Strength of Evidence; BEL 1; downgraded due to small sample sizes used in studies and short duration of trials

Recommendation 3.4.2. For chronic weight management in individuals with a BMI of ≥27 kg/m^2 and NAFLD or NASH, clinicians should give preference to semaglutide 2.4 mg/week (best evidence) or liraglutide 3 mg/day.

Grade B; High/Intermediate Strength of Evidence; BEL 1; downgraded due to different formulations and doses used in the semaglutide and liraglutide NASH trials

Evidence Base. Among persons with NASH, weight loss of >5% total body weight (TBW) can reduce hepatic steatosis, weight loss of >7% TBW can improve NASH, and weight loss of >10% TBW can result in fibrosis regression/stability.[238,239,241] Weight loss assisted by several obesity medications as an adjunct to lifestyle therapy can ameliorate NAFLD and NASH in persons who have obesity. Although this is recommended, it is acknowledged that access to these medications can be a challenge due to their high cost, lack of health insurance, and inadequate coverage by payers. Insurance plans should guarantee access to these medications to treat obesity. Medications approved for the chronic treatment of obesity include the centrally acting oral combinations phentermine/topiramate ER and naltrexone/bupropion ER, the oral lipase inhibitor orlistat, and subcutaneous GLP-1 receptor agonists liraglutide (titrated up to 3 mg daily) and semaglutide (titrated up to 2.4 mg weekly).[310] Obesity medications are approved by the FDA for chronic weight management for individuals with a BMI of ≥30 kg/m^2 or those with a BMI of 27 to 29.9 kg/m^2 and at least 1 weight-related complication. Early response to therapy is a key predictor of long-term success, and the medications should be continued if 5% weight loss has been achieved within 3 months of using the full dose of medication. The amount of weight loss anticipated from obesity medications is greater than 10% or more of body weight and is associated with cardiometabolic and T2D risk reduction, if the early 3-month efficacy threshold is achieved.[310,311] While head-to-head trials have not been performed, there is a range of efficacy for obesity medications when compared according to placebo-subtracted (included lifestyle intervention) weight loss in RCTs. When combined with a lifestyle intervention, the efficacy for weight loss ranges between 7% and 18% of baseline weight at 1 year on average. Of the medications currently approved for chronic obesity therapy, semaglutide has shown the most efficacy in achieving 10%, 15%, and even ≥20% weight loss.[289-292]

Medications for the management of obesity have not undergone rigorous testing in RCTs using liver histology (ie, paired liver biopsies) as the primary outcome in persons with NAFLD. Available data come from a 48-week pilot study (n = 52) with liraglutide and a larger study (n = 320) with semaglutide for 72 weeks,[99] as discussed earlier, and recently summarized in 2 narrative reviews.[286,287]

Weight loss associated with orlistat may also exert beneficial effects on hepatic fat content and histology in NAFLD. A recent meta-analysis including 3 RCTs and 4 single-arm trials of 330 participants with NAFLD or NASH concluded that orlistat reduced the aminotransferase levels in persons with NAFLD but failed to improve liver histology in NASH.[312] However, studies have been usually small and of short duration (up to 36 weeks) with overall modest or no liver histologic improvement. A 2009 prospective trial over 36 weeks compared 23 participants given orlistat/diet/vitamin E and 18 given diet/vitamin E.[313] The orlistat group lost a mean of 8.3% body weight compared with 6.0% in the diet plus vitamin E group (not significant). While orlistat does not appear to have drug-specific effects in steatohepatitis, improvement in insulin sensitivity and liver histology is proportional to the magnitude of weight loss. When stratified according to weight loss, persons who lost ≥9% of body weight (n = 16) showed improved liver steatosis, ballooning, and inflammation ($P < .01$) compared with those who failed to do so (n = 25).[313] A 2006 RCT studied 52 persons with NAFLD on liver US (confirmed by liver biopsy in 40 persons) from Israel.[314] There was a modest improvement in plasma aminotransferase levels and in steatosis by liver US, but histology did not change significantly in the 22 in whom the biopsy was repeated. A post hoc analysis of phase 3 trials of naltrexone/bupropion ER showed improved ALT levels linearly correlating with weight loss in responders who achieved at least 5% weight loss on average at 12 months.[315]

Recommendation 3.4.3. Clinicians must consider obesity pharmacotherapy (with preference to semaglutide 2.4 mg/week [best evidence] or liraglutide 3 mg/day) as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent T2D, CVD, and other end-stage manifestations of obesity.

Grade A; High/intermediate Strength of Evidence; BEL 1

Evidence Base. Meta-analyses of weight-loss medication RCTs suggest modest overall benefit for improving the cardiometabolic risk profile in persons with obesity.[199,310] Phentermine/topiramate ER has been shown to delay progression to T2D in those at high cardiometabolic risk (MetS or prediabetes), improve glycemic control with weight loss in T2D, and improve lipids and blood pressure with significant improvement in cardiometabolic parameters.[316-318] The indication for the reduction of CVD risk with liraglutide was substantiated in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial showing that liraglutide reduced the HR for the composite major adverse cardiovascular event (MACE) outcome by 13%.[319] A CV outcome trial has not been performed for liraglutide 3 mg in persons with obesity, although clinicians can be reassured by cardioprotection demonstrated in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial for liraglutide 1.8 mg in those with T2D.[319] Semaglutide reduces the risk of MACEs supported by findings in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes CV outcome trial that enrolled persons with T2D and established CVD and/or CKD,[320] where it significantly reduced MACE by 26% compared with placebo. Other GLP-1 RAs have reported CV and renal benefits, with a network analysis suggesting that semaglutide has the highest probability to reduce myocardial infarction and stroke events,[321] but other GLP-1 RAs have not been systematically tested with paired liver biopsies in persons with NASH.[287]

Q3.5 What Is the Effect of Bariatric Surgery on Liver Disease and Cardiometabolic Conditions Associated With NAFLD or NASH in Adults?

Recommendation 3.5.1. Clinicians should consider bariatric surgery as an option to treat NAFLD (**Grade B; Intermediate Strength of Evidence; BEL 2**) and improve cardiometabolic health (**Grade A; High/Intermediate Strength of Evidence; BEL 2; upgraded based on the cardiometabolic and all-cause mortality benefits in all persons with or without NAFLD**) in persons with NAFLD and a BMI of ≥35 kg/m^2 (≥32.5 kg/m^2 in Asian populations), particularly if T2D is present. It should also be considered an option in those with a BMI of ≥30 to 34.9 kg/m^2 (≥27.5 to 32.4 kg/m^2 in Asian populations) (**Grade B; Intermediate/Weak Strength of Evidence; BEL 2**).

Recommendation 3.5.2. For persons with NASH and compensated cirrhosis, clinicians should exercise caution in recommending bariatric surgery, which should be highly individualized if prescribed and performed at experienced centers (**Grade B; Intermediate/Weak Strength of Evidence; BEL 2**). In persons with decompensated cirrhosis, bariatric surgery should not be recommended due to limited evidence and potential for harm (**Grade B; Intermediate/Weak Strength of Evidence; BEL 2**).

Evidence Base. It is well established that bariatric surgery induces sustained weight loss with improvement of common comorbidities in NAFLD, such as hypertension, sleep apnea, atherogenic dyslipidemia, hyperglycemia with frequent resolution of diabetes, and amelioration of the risk of CVD and HCC.[116-118,120,121,322] A systematic review and meta-analysis of 32 studies of persons undergoing bariatric surgery, including 3093 liver biopsies obtained during and after bariatric surgery, reported that 66% had complete resolution of steatosis, while 50% and 76% had resolution of inflammation and ballooning, respectively. Although fibrosis improved in 40% of individuals, fibrosis worsened in approximately 12%. Of note, the overall quality of the individual studies included was low.[123] In another meta-analysis of 21 studies including 2374 persons who underwent primarily RYGB, the pooled proportion of steatosis improvement was 88%, that of NASH resolution was 59%, and that of fibrosis improvement was 30%.[122] More recently, the impact of bariatric surgery on the natural history of cirrhosis and CVD associated with NASH has been reported.[323] The investigators examined 25 828 liver biopsies performed at a U.S. health system between 2004 and 2016, where 1158 adults with obesity met enrollment criteria for bariatric surgery and had a confirmed histologic diagnosis of NASH with stage 1 to 3 liver fibrosis. The median follow-up was 7 years (interquartile range, 4-10 years). Bariatric surgery, compared with nonsurgical management, was associated with a 12.4% lower risk of incident major adverse liver outcomes (95% CI, 5.7%-19.7%), aHR of 0.12 (95% CI, 0.02-0.63; $P = .01$), and a 13.9% decrease in MACE (95% CI, 5.9%-21.9%), aHR of 0.30 (95% CI, 0.12-0.72; $P = .007$).[323]

The degree of weight loss resulting from bariatric surgery improves NAFLD as assessed by either imaging technologies or liver histology. A recent meta-analysis of 43 studies with 2809 individuals examined the outcomes of NAFLD and NASH 6 months following weight loss with either behavioral/lifestyle intervention, pharmacotherapy, or bariatric surgery and reported a weight loss-dependent improvement in ALT, AST, and hepatic steatosis assessed by imaging and/or histology; however, there was limited evidence of a dose-response relationship with changes in hepatic fibrosis.[241] There is limited information about the best surgical approach for persons with NAFLD. In recent reports from the

Oseberg study, the reduction of liver fat content at 1 year was similar with sleeve gastrectomy compared with that of RYBG,[324] although the latter was found to be superior for remission of T2D.[325] Of note, follow-up was too short to make strong conclusions. The average durability of weight loss induced by RYGB has been reported to be −21%, with 72% having more than 20% and 40% having more than 30% estimated weight loss at 10 years, compared with 11% and 4%, respectively, in nonsurgical matched controls.[116]

In a prospective study examining the impact of bariatric surgery, NASH resolution was observed in 85% after 1 year[326] and in 90.5% at 5 years and with 70% having fibrosis regression.[327] In the subset with stage 3 fibrosis (precirrhosis) at baseline (n = 19), fibrosis improved in 68% and resolved in 45% after 5 years. This study only had paired biopsies for 3 persons with cirrhosis at baseline, of which 2 remained cirrhotic at the 5-year assessment. These results make it difficult to draw firm conclusions about the role of bariatric surgery in reversing cirrhosis.[327] Caution is necessary when considering individuals for bariatric surgery who have advanced fibrosis or cirrhosis. In a retrospective study of 29 persons with cirrhosis and stage 3 fibrosis,[328] the risk of hepatic decompensation in individuals with cirrhosis and history of decompensation (presence of hepatic encephalopathy, variceal bleeding, or ascites) was very high. While bariatric surgery can be effective at reducing metabolic comorbidity in persons with cirrhosis, weight loss without adequate protein intake in such persons can be detrimental. Furthermore, the potential benefit of bariatric surgery in the context of cirrhosis with respect to histologic improvement or liver-related outcomes is unclear. While there are limited data, the safety of bariatric surgery in selected persons with cirrhosis appears to be comparable to those with less advanced fibrosis; however, persons with hepatic decompensation have a mortality of 7.68% versus 0.94% (OR, 8.78; 95% CI, 3.41-22.59; $P < .001$) in those with compensated cirrhosis.[329] Thus, individuals with advanced fibrosis need to be carefully selected, and a risk-benefit analysis should be performed. Finally, a potential benefit was suggested in a case-controlled meta-analysis of 9 studies in over 19 000 individuals following bariatric surgery that demonstrated a significant risk reduction in the incidence of HCC compared to those with no surgery.[124]

There are no prospective studies or RCTs with CV end points (ie, MACE) comparing the benefit of bariatric surgery in persons with T2D or obesity stratified for the presence or absence of NAFLD. Further studies along these lines are warranted. Nevertheless, there is ample evidence that bariatric surgery can produce profound health benefits in individuals with obesity and CMD, including persons with NAFLD, and is associated with reduced CVD and all-cause mortality.[117,118,200,330-332] Recently, a population-based matched cohort study comparing 13 679 persons who underwent bariatric surgery who were matched to 13 679 nonsurgical participants reported that bariatric surgery was associated with significantly lower all-cause, CV, and cancer mortality.[333] Finally, a recent meta-analysis that included 74 042 participants with obesity and CVD demonstrated that bariatric surgery was responsible for an approximately 43% reduction in the combined MACE outcome after adjustment for confounding variables.[334]

Recommendation 3.5.3. Endoscopic bariatric and metabolic therapies (EBMTs) should not be recommended in persons with NAFLD due to insufficient evidence.

Grade C; Intermediate/Weak Strength of Evidence; BEL 2; downgraded due to the quality of studies and small sample sizes

Evidence Base. There are limited data for the treatment of NASH with EBMT. These therapies encompass devices such as intragastric balloon (IGB), endoscopic sleeve gastroplasty (ESG), and aspiration therapy by means of a gastrostomy. Only 2 studies reported on liver histology as the primary outcome in persons with NASH.[335,336] Limited acceptance is due to limited evidence arising from uncontrolled, small (<50 participants), and short-duration (most of 6-month duration) studies.[337,338] Long-term trials[339,340] are associated with significant participant attrition from adverse events or participants being lost to follow-up. Studies have been prone to potential bias from participant selection by recruiting highly motivated individuals agreeable to substantial time commitment and/or follow-up (ie, usually, those better able to tolerate the procedure continue the study). Thus, the generalizability of these trials has been questioned. Finally, studies have reported that approximately one third of participants have adverse events ranging from gastrointestinal side effects to (less frequently) surgical leaks, infections, and occasionally serious adverse events.

In contrast to the significant evidence about the cardiometabolic and liver benefits of bariatric surgery in NAFLD, EBMT appears less efficacious and with more limited short- and long-term data. A meta-analysis of long-term data from 4 published trials with aspiration therapy (n = 373) reported a weight loss between 16% and 21%.[338] Approximately 20% of participants withdrew per year or were lost to follow-up, with only 46 and 27 participants in the meta-analysis being followed at years 3 and 4, respectively. Two studies found plasma aminotransferase levels to decrease. One prospective cohort study of 216 persons undergoing ESG reported 15% weight loss in 5 years, although no liver-specific outcomes were included.[340] Caveats were as outlined earlier: (1) missing data from 25% to 30% of participants per year of follow-up and (2) limited long-term data with only 56 participants enrolled at year 5. Within 3 to 9 months after ESG, 27% of participants had weight regain and needed concomitant antiobesity medication, and 6% required a repeat ESG, making data difficult to interpret. Finally, a meta-analysis of 18 EBMT studies in 863 participants reported an overall modest improvement in ALT, with steatosis on imaging (US or MRI) improving in 2 studies.[338] Only 2 studies examined the impact of IGB on liver histology before and after 6 months of IGB. One RCT treated 18 participants with NASH with diet plus exercise plus IGB or sham-IGB placement. Although BMI significantly decreased, there was no significant improvement in steatosis, lobular inflammation, hepatocellular ballooning, or fibrosis scores in either group after treatment. However, there was a modest improvement in the median NAS (combining steatosis, inflammation, and ballooning). More recently, a prospective cohort study examined the use of IGB in 20 participants with NASH. The mean body weight loss 6 months following IGB was 11.7% ± 7.7%. Steatohepatitis improved, but the results on fibrosis were mixed, improving by ≥1 stage in 3 participants and worsening in 5 participants.[336]

Clearly, more work is needed to establish the role of EBMT in the management of people with NASH, and current data are insufficient to support their use in this population.

Diagnosis and Management of Children With NAFLD

Epidemiology of NAFLD in the Pediatric Population: What Is the Prevalence, Spectrum of Liver Disease, and Natural History, Particularly in Those With Underlying Endocrine Conditions?

NAFLD is the most common liver disease in pediatrics in the United States,[341] coexisting with obesity, multiorgan IR, an increased risk of prediabetes/T2D, and cardiac dysfunction.[341-343] The prevalence of NAFLD varies by sex (higher in males) and race/ethnicity (higher in Hispanic, White, and Asian children than in African American children).[344] Pediatric NAFLD can occur as early as in utero and can be detected in infancy.[345-347] A meta-analysis, using liver chemistry and imaging (US or MRI) to

detect NAFLD, estimated a prevalence of 7.6% in the general pediatric population, increasing to 34.2% in children with obesity.[348]

In children with prediabetes/T2D, approximately half are estimated to have NAFLD. In a retrospective cohort study of 118 children with T2D from the United States, 42% had serum aminotransferase data available, and of those, 48% were above the normal range.[349] In another retrospective study of 57 newly diagnosed children with T2D, 88% of non-Hispanic Whites, 71% of Hispanics, and 20% of African Americans had serum ALT levels above the upper limit of normal.[350] In terms of PCOS, a prospective study of 199 adolescent females from Australia found that PCOS was an independent predictor of NAFLD (diagnosed with US) in these individuals, with an OR for NAFLD of 2.99 (95% CI, 1.01-8.82).[351]

Q4.1 Who Should Be Screened for NAFLD and for Comorbidities?

Recommendation 4.1.1. Children of any age and adolescents with obesity or T2D, but not T1D, should be screened for NAFLD using serum ALT.

Grade B; Intermediate/High Strength of Evidence; BEL 2

Recommendation 4.1.2. Clinicians should screen adolescent females with PCOS for NAFLD using serum ALT.

Grade B; Intermediate/High Strength of Evidence; BEL 2

Recommendation 4.1.3. Clinicians should screen children and adolescents with NAFLD for prediabetes or T2D using an oral glucose tolerance test if the fasting glucose level is ≥100 mg/mL or if the glycated hemoglobin (A1c) level is in the range of prediabetes (≥5.7% to 6.4%).

Grade B; Intermediate Strength of Evidence; BEL 2

Evidence Base. Children at risk of NAFLD should undergo screening. A 2019 meta-analysis revealed that the prevalence ratio of NAFLD in children with overweight/obesity is 26.1 (95% CI, 9.4-72.3).[352] Severe obesity further increases the risk.[353] PCOS is another risk factor for NAFLD.[351] Low-quality (retrospective and small sample size) studies suggest that youth with T2D are also at increased risk of NAFLD.[349,350] In contrast, children with T1D are not at increased risk and do not require screening.[354,355] In clinical practice, the serum ALT levels have traditionally been used for screening and are considered the most validated tool in pediatrics.[341,356,357]

Prediction scores developed for the diagnosis of pediatric NAFLD are inaccurate and should not be used for screening.[358] MRI-PDFF is accurate for the detection of hepatic steatosis in children[359-361] of various ethnic backgrounds[362]; however, it is not widely used as a screening tool in part due to availability and cost. In summary, the serum ALT levels remain the most validated, practical biomarker of histologic disease severity in children with NAFLD, and until better biomarkers become available, should continue to be used for screening. If normal, repeat screening can be considered on an annual basis if the risk factors persist.

Robust data regarding the natural history of pediatric NAFLD are limited. A recent analysis of histologic outcomes of children enrolled in the placebo arms of RCTs revealed that the majority of participants do not improve with lifestyle interventions alone.[356] In fact, 23% of participants have evidence of worsened fibrosis over a mean time of 1.6 years. Among predictors of progression to definite NASH and/or fibrosis were an increasing A1c level and the development of T2D. Epidemiologic data of children and adolescents with severe obesity, who are at increased risk of NAFLD, show an increased risk of CV and all-cause mortality in adulthood.[353] More pediatric NAFLD-specific studies are needed.

Q4.2 What Tests Can Be Used to Diagnose Pediatric NAFLD?

Recommendation 4.2.1. Clinicians should use plasma aminotransferases to test children at high risk of NAFLD.

Grade B; Intermediate Strength of Evidence; BEL 2

Recommendation 4.2.2. Pediatric NAFLD can be diagnosed with imaging (US or MRI-PDFF) or liver biopsy in combination with exclusion of non-NAFLD causes of hepatic steatosis such as Wilson syndrome, mitochondrial disease, and medications.

Grade B; Intermediate Strength of Evidence; BEL 2

Recommendation 4.2.3. Liver fibrosis prediction calculations and proprietary biomarkers currently available for the diagnosis of advanced fibrosis in adults should not be used in children as they either are inaccurate or require further validation.

Grade B; Intermediate Strength of Evidence; BEL 2

Evidence Base. Pediatric NAFLD diagnosis requires histologic confirmation; however, this is not always possible considering the high prevalence of the disease. The diagnosis requires exclusion of other causes of liver disease (eg, autoimmune hepatitis, viral hepatitis, Wilson disease, alpha 1 antitrypsin deficiency, hemochromatosis, celiac disease, and thyroid dysfunction), even though the most common diagnosis in children with obesity referred for suspected fatty liver disease is NAFLD.[363] Often, imaging evidence of steatosis is also sought. US is inaccurate in this context, with a low PPV for the diagnosis of fatty liver in the range of 47% to 62%.[364] In contrast, MRI-PDFF-based estimates of steatosis are more accurate and can be used for the diagnosis of NAFLD (PPV, 88%-100%).[360-362,365] However, the test is expensive, and access is often limited to tertiary academic centers; therefore, it is not recommended for routine use but should be individualized and ordered by the liver specialist. With regard to diagnosing disease severity, there are currently no noninvasive approaches to determine the presence of NASH in children. In terms of fibrosis, prediction scores developed in adults (eg, AST-to-platelet ratio, NFS, FIB-4, and AST/ALT ratio) are inaccurate in children.[366] Other biomarkers (eg, combination of cytokeratin 18 and waist circumference and microbiome signatures) have been studied with encouraging results but require further validation.[361,367] MRE has been studied in children with NAFLD and found to have a PPV for the presence of any fibrosis of 74% to 76%.[368] Other imaging approaches, such as TE, are becoming more widely available; however, pediatric-specific norms have not yet been developed for NAFLD.[369-372]

Q4.3 What Are the Lifestyle, Medical, or Surgical Treatment Options for Pediatric NAFLD, and What Is the Role of Pharmacotherapy Developed for Endocrine Disorders in the Treatment of Pediatric NAFLD?

Recommendation 4.3.1. Clinicians should recommend lifestyle changes in children with NAFLD, promoting the adoption of dietary changes to create an energy deficit, with reduction in sugar consumption as first-line lifestyle modification, and increased physical activity aiming for BMI optimization.

Grade B; Intermediate Strength of Evidence; BEL 1; downgraded due to the limited number of RCTs and small sample size

Recommendation 4.3.2. Clinicians may consider GLP-1 RAs for the treatment of pediatric obesity and T2D **(Grade D; Expert Opinion; BEL 4)**, which may also offer benefit for pediatric NAFLD, although not FDA-approved for this indication **(Grade D; Expert Opinion; BEL 4)**.

Evidence Base. The mainstay of treatment for pediatric NAFLD is dietary and physical activity modifications. A study of children

participating in the placebo arms of RCTs receiving lifestyle advice showed that dietary and physical activity recommendations lead to NASH resolution in 29% and fibrosis improvement in 34% of children over a mean of 1.6 years.[356] However, in the same timeframe, 18% of children progressed to definite NASH, and 23% had worse fibrosis.

To assess the effects of <3% of total calories from free sugars versus usual diet, an 8-week open-label, randomized (1:1) trial was performed in 40 adolescent boys with NAFLD.[373] The primary outcome was change in hepatic steatosis estimated by MRI-PDFF. The mean decrease in hepatic steatosis was significantly greater for the intervention diet group (25% to 17%) versus the usual diet group (21% to 20%). Long-term clinical outcomes remain unknown. Both aerobic and resistance exercise trainings, at vigorous or moderate-to-vigorous intensities aiming to improve cardiorespiratory fitness and muscular strength, had benefits on hepatic fat content reduction in youth.[374]

There are no FDA-approved pharmacotherapies for pediatric NAFLD. The Treatment of Nonalcoholic Fatty Liver Disease in Children and Adolescents RCT found no benefit of metformin or vitamin E in achieving a reduction in the NAS of ≥2 in children.[375] However, the secondary analyses found a significantly greater resolution of NASH with 400 IU twice a day of vitamin E daily versus placebo. The long-term efficacy and safety of vitamin E in children with NASH remain unknown. Metformin at a dose of 500 mg orally twice a day was not effective, possibly due to the underdosing effect of the drug.[375] The effects of treatment with polyunsaturated fatty acids or probiotics have not been validated with histologic analysis.[376]

Despite the mounting evidence from recent RCTs in adults indicating a favorable effect of GLP-1 RAs on NAFLD in adults,[99,286-288] similar studies in children and adolescents with NASH are lacking and greatly needed. Liraglutide appears to be safe in this population[377-379] and is effective for the treatment of pediatric T2D and obesity.[380,381] It has been approved for use in children aged 10 years and ≥12 years, respectively. However, there are no RCTs of a GLP-1 RA for the treatment of NAFLD in children and adolescents with NASH.

Bariatric surgery is an accepted treatment for youth with class II severe obesity with significant comorbid conditions and for those with class III with or without comorbid conditions (Table 8).[382,383] Adolescents who underwent RYGB had marked weight loss 5 years after surgery showing remission of diabetes and hypertension more often than adults.[384,385] A small pediatric study showed that bariatric surgery is superior to lifestyle interventions at treating NASH and NAFLD-related fibrosis.[385] The risks of surgery in adolescents in general are comparable to those in adults but with the potential for long-term nutritional complications.[384]

Table 8
BMI-for-Age Weight Status Categories in Children and Adolescents and the Corresponding Percentiles[382,383]

Weight status category	BMI percentile range
Underweight	<5th percentile
Healthy weight	5th percentile to <85th percentile
Overweight	85th to <95th percentile
Obesity class I	≥95th percentile to <120% of the 95th percentile for age and sex
Obesity class II	≥120% to <140% of the 95th percentile or BMI ≥ 35 kg/m^2
Obesity class III	≥140% of the 95th percentile or BMI ≥ 40 kg/m^2

Abbreviation: BMI = body mass index;

Future Directions

NAFLD is a growing public health problem likely affecting many of those seen by endocrinologists and primary health care professionals, as it is closely linked to the epidemics of obesity and T2D and other comorbidities. People at greatest risk of NASH and cirrhosis are those with MetS and prediabetes, T2D, or the presence of elevated plasma aminotransferase levels or steatosis on imaging. Those with NASH and cirrhosis are also at increased risk of HCC and future T2D, CVD and other comorbidities. Given the aforementioned findings, there are 3 major areas that will likely be transformed in the care of people with NAFLD in the near future:

1. Greater awareness: education of all health care providers and people with the disease about the magnitude of the problem and need for early diagnosis and treatment.
2. Diagnosis: with the development and implementation of simple, cost-effective, and accurate diagnostic tests to screen and diagnose early on large numbers of people at risk.
3. Treatment: in addition to improved lifestyle approaches and CV risk reduction strategies, greater awareness of the benefits from some currently available diabetes medications (ie, pioglitazone and GLP-1 RAs) and new drugs in development to become FDA-approved will radically change the treatment of NASH.

Greater awareness will be critical among endocrinologists as well as PCPs and all health care professionals. There is an urgent need for health care providers to educate and detect early on those at highest risk of cirrhosis and improve their early referral to liver specialists. Endocrinology and primary care clinicians are at the frontline in the battle to identify those at risk early on, as recent studies suggest that persons with NASH and clinically significant liver fibrosis (stages F2-F4) concentrate in endocrinology and primary care clinics. Endocrinology and primary care clinicians will have to incorporate calculation of the individual's liver fibrosis risk (FIB-4) as the initial step in screening for NAFLD and liver fibrosis, in the same way as we do today for ordering microalbumin or ordering an annual dilated eye examination to prevent diabetic nephropathy or retinopathy, respectively. Knowledge about the best next steps, such as the use of additional liver imaging and/or plasma biomarkers, will be mandatory, followed by fibrosis risk stratification into low, indeterminate, or high risk of developing future cirrhosis and when referral to the liver specialist will be needed in the higher risk groups.

With a growing body of evidence that NASH and clinically significant liver fibrosis are common in endocrine and primary care clinics, it is likely that this experience and a growing literature will assist in the development of the optimal use of current and novel diagnostic tests for people at risk. Future tests being developed include the use of metabolomics, proteomics, and other strategies that, when combined, will further increase diagnostic sensitivity and specificity, allowing optimization of referrals to liver specialists and more cost-effective approaches.

Lifestyle changes that lead to an energy deficit, if overweight or obesity, and improve cardiometabolic health have proven effective in NAFLD, but large, long-term controlled studies are needed. Future studies will establish if there is a particular macronutrient dietary recommendation that yields the best results in reversing steatohepatitis and/or liver fibrosis or if histologic improvement is largely dependent on the magnitude of weight loss. Future studies should also determine with more precision the threshold to reverse steatohepatitis and/or liver fibrosis. Finally, there is a lack of large, long-term controlled studies in bariatric surgery to establish the best surgical approach in NASH.

Several studies are testing a broad array of pharmaceutical agents with multiple biologic targets versus NASH. Despite many recent failures, agents that promote weight loss (ie, GLP-1 RAs such as liraglutide and semaglutide) have improved NASH. New weight-loss medications are undergoing testing in NASH, including dual GLP-1 RA/gastric inhibitory polypeptide (ie, tirzepatide) analogs and GLP-1 RA/glucagon agonists (ie, cotadutide). Another approach undergoing phase 3 testing are medications, similar to pioglitazone, that restore dysfunctional adipose in obesity to normal and reverse IR in those with or without diabetes, improving both steatohepatitis and fibrosis (ie, lanifibranor, a pan-PPAR, with PPAR-alpha, PPAR-delta, and PPAR-gamma activity). Other approaches in large phase 3 RCTs include FXR agonists (having predominantly antifibrotic activity) and thyroid hormone receptor agonists (largely improving steatohepatitis), with many other drugs being in phase 2a and 2b.

In the meantime, clinicians should become more familiar with the utilization of diabetes agents, such as pioglitazone (inexpensive generic) or the GLP-1 RAs (best evidence for semaglutide), proven to reverse steatohepatitis in controlled clinical trials of 1.5- to 3-year duration in persons with or without diabetes. Vitamin E has also shown benefit in people with NASH without diabetes. However, these agents are not FDA approved for the treatment of NASH. Future management should also include more careful control of CV risk factors, such as hypertension and atherogenic dyslipidemia, incorporating newer agents as needed to reach treatment targets.

Pediatric NAFLD is also becoming a growing concern, but there is limited awareness among the public and health care professionals about the problem. Future studies must improve the quality of the evidence in terms of the optimal diagnostic and treatment pathways and the optimal healthy lifestyle changes in children at different ages.

Conclusions

Endocrinologists and primary care clinicians are in an ideal position to identify those at risk early on to prevent the development of cirrhosis and comorbidities. Screening should involve calculation of the individual's liver fibrosis risk (FIB-4), followed by additional plasma biomarkers and/or liver imaging based on fibrosis risk stratification into low, indeterminate, or high risk of developing future cirrhosis, with referral to a liver specialist for those in the higher-risk groups. Lifestyle changes leading to an energy deficit if overweight or obese and improved cardiometabolic health are essential to reduce CVD risk. Treatment must include consideration of weight-loss medications, particularly GLP-1 RAs with proven benefit for steatohepatitis and bariatric surgery. Some diabetes medications, such as pioglitazone and GLP-1 RAs, should be preferred for those with T2D and NASH, particularly when at indeterminate or high risk of developing future cirrhosis. Management should also include careful control of CV risk factors, such as hypertension and atherogenic dyslipidemia. Pediatric NAFLD is also becoming a growing concern, but there is limited awareness among health care professionals about the problem. Inadequate evidence in terms of the optimal diagnostic and treatment pathways is a major barrier with current care being based on early diagnosis and promotion of healthy lifestyle changes. Rapid changes in diagnostic tools and in drug development promise to offer new options for endocrinologists and other health care professionals involved in the management of NAFLD.

Disclosures

The Task Force was empaneled in accordance with the AACE's Conflict of Interest (COI) Policy and approved by the AACE COI Subcommittee. All members of the expert Task Force completed the AACE's disclosure form regarding any multiplicities of interests related to commercial and direct financial relationships within the preceding 12 months with companies that develop products connected with endocrine disorders. Categories for disclosure include employment, stock or other ownership, direct financial relationships (eg, speaker or consultant), research funding, authorship or panel involvement on a guideline related to an overlapping topic, or other situations related to a perceived COI. The AACE COI Subcommittee reviewed these disclosures against an AACE-approved list of affected companies for this guideline and reached consensus regarding members who could serve on the Task Force in the nonconflicted majority, those who could serve in the conflicted minority with management strategy, and those who were disqualified from serving on the Task Force. The AACE Clinical Practice Guidelines Oversight Committee reviewed and approved the AACE COI Subcommittee's decisions regarding manageable COI and empanelment. The members of this Task Force were reminded to update potential disclosures if new potential conflicts arose during their appointments and verify currency of disclosures. The AACE made every effort to minimize the potential for conflicts of interest that could influence the recommendations of this clinical practice guideline.

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Panel Composition

The Task Force was empaneled in accordance with the AACE's COI Policy and Diversity, Equity, and Inclusion Policy. This evidence-based clinical practice guideline was developed by a multidisciplinary group of credentialed medical professionals in the fields of endocrinology and hepatology. The members of the task force included current AACE members in good standing and 2 AASLD representatives.

Review Process

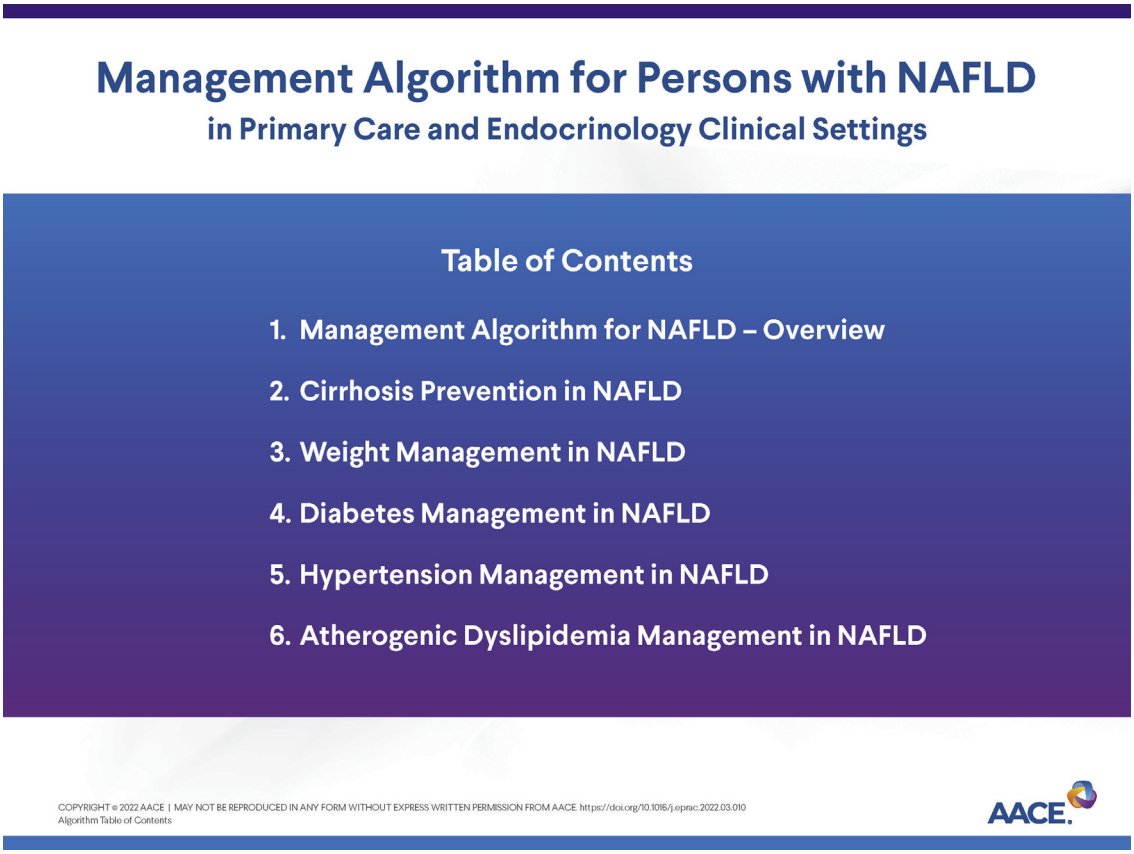
Drafts of this guideline were reviewed and approved by the writing task force, AACE CPG Oversight Committee, AACE Board of Directors, and peer reviewers for *Endocrine Practice*.

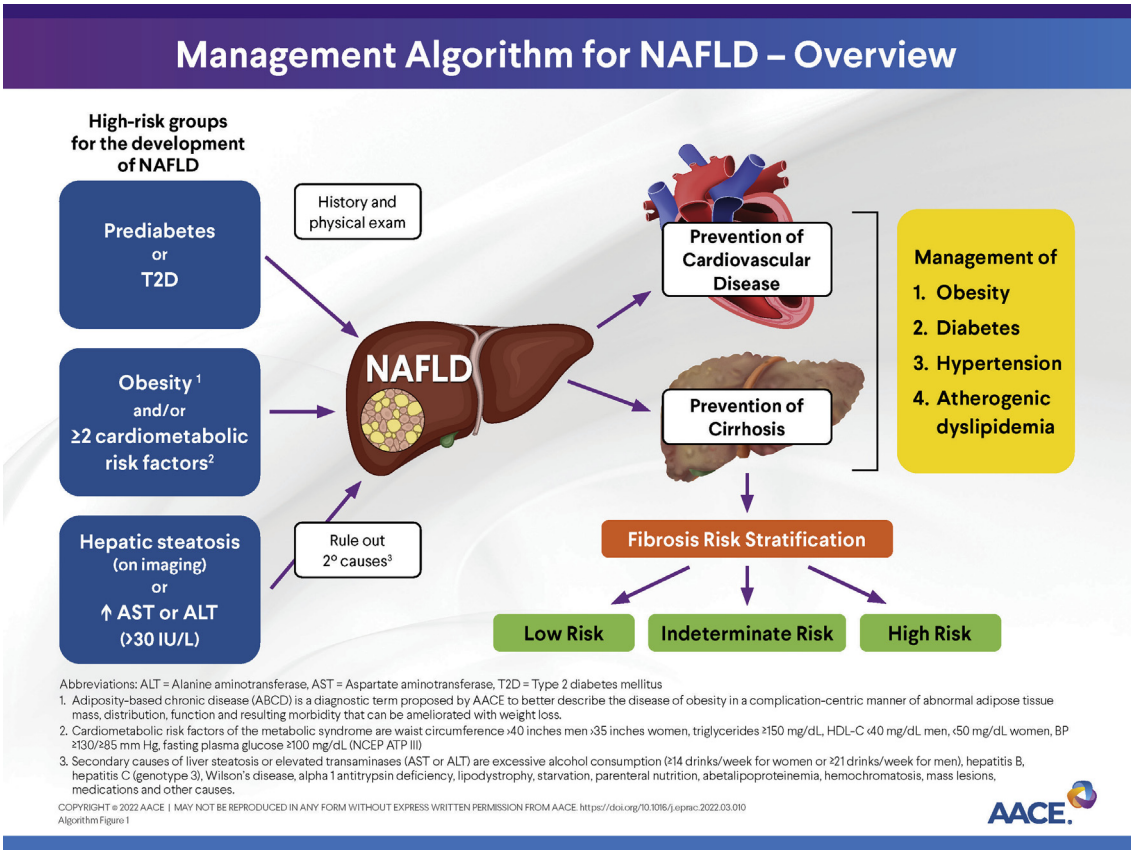
Updating Policy

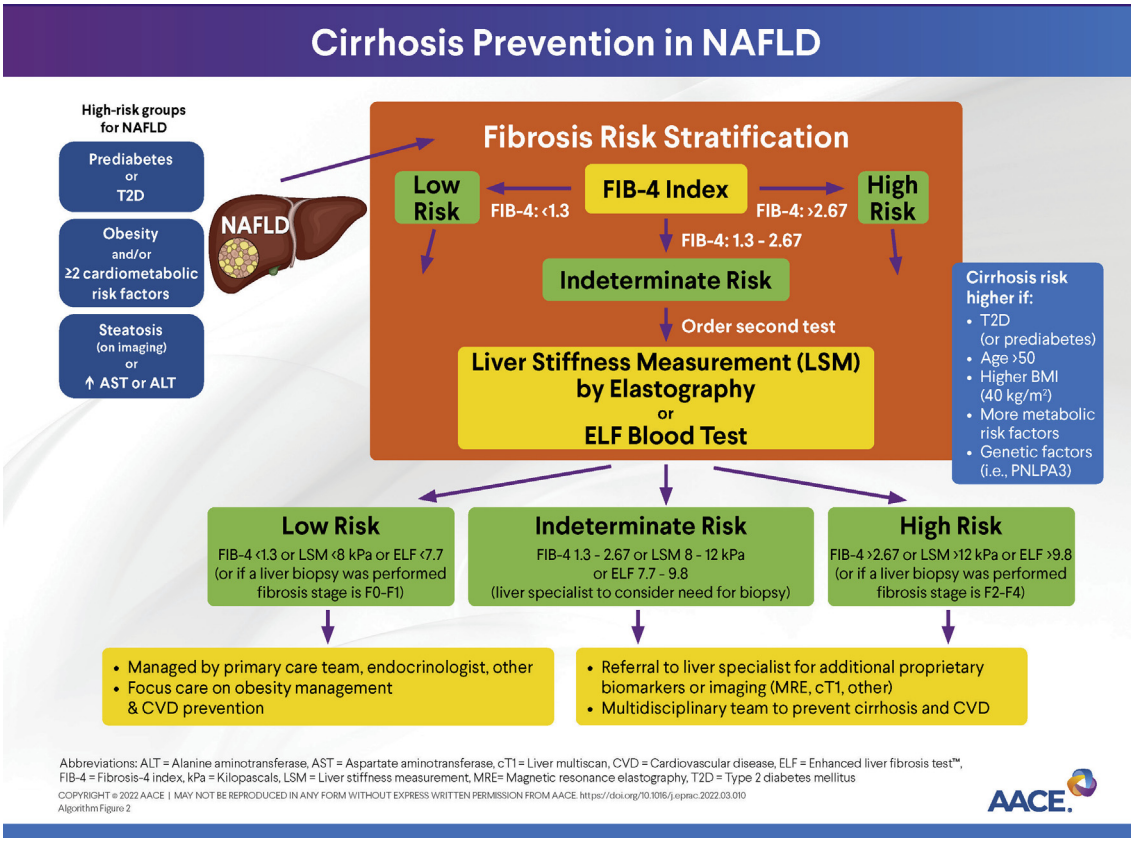
The AACE reviews and updates or retires its evidence-based guidelines every 3 to 5 years or after significant scientific developments or change in public policy as determined by the AACE executive leadership, AACE CPG Oversight Committee, and relevant AACE Disease-State Network.

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Management Algorithm for Persons with
NAFLD
in Primary Care and Endocrinology Clinical Settings
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Algorithm Title Page
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Management Algorithm for Persons with NAFLD
in Primary Care and Endocrinology Clinical Settings
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5. Hypertension Management in NAFLD
6. Atherogenic Dyslipidemia Management in NAFLD
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Management Algorithm for NAFLD – Overview
High-risk groups for the development of NAFLD
Prediabetes or T2D
Obesity [1] and/or ≥2 cardiometabolic risk factors[2]
Hepatic steatosis (on imaging) or ↑ AST or ALT (>30 IU/L)
History and physical exam
Rule out 2° causes[3]
NAFLD
Prevention of Cardiovascular Disease
Prevention of Cirrhosis
Management of
1. Obesity
2. Diabetes
3. Hypertension
4. Atherogenic dyslipidemia
Fibrosis Risk Stratification
Low Risk
Indeterminate Risk
High Risk
Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T2D = Type 2 diabetes mellitus
1. Adiposity-based chronic disease (ABCD) is a diagnostic term proposed by AACE to better describe the disease of obesity in a complication-centric manner of abnormal adipose tissue mass, distribution, function and resulting morbidity that can be ameliorated with weight loss.
2. Cardiometabolic risk factors of the metabolic syndrome are waist circumference >40 inches men >35 inches women, triglycerides ≥150 mg/dL, HDL-C <40 mg/dL men, <50 mg/dL women, BP ≥130/≥85 mm Hg, fasting plasma glucose ≥100 mg/dL (NCEP ATP III)
3. Secondary causes of liver steatosis or elevated transaminases (AST or ALT) are excessive alcohol consumption (≥14 drinks/week for women or ≥21 drinks/week for men), hepatitis B, hepatitis C (genotype 3), Wilson's disease, alpha 1 antitrypsin deficiency, lipodystrophy, starvation, parenteral nutrition, abetalipoproteinemia, hemochromatosis, mass lesions, medications and other causes.
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Algorithm Figure 1
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Cirrhosis Prevention in NAFLD
High-risk groups for NAFLD
Prediabetes or T2D
Obesity and/or ≥2 cardiometabolic risk factors
Steatosis (on imaging) or ↑ AST or ALT
NAFLD
Fibrosis Risk Stratification
Low Risk
FIB-4 Index
High Risk
FIB-4: <1.3
FIB-4: >2.67
FIB-4: 1.3 - 2.67
Indeterminate Risk
Order second test
Liver Stiffness Measurement (LSM) by Elastography
or
ELF Blood Test
Cirrhosis risk higher if:
• T2D (or prediabetes)
• Age >50
• Higher BMI (40 kg/m²)
• More metabolic risk factors
• Genetic factors (i.e., PNLPA3)
Low Risk
FIB-4 <1.3 or LSM <8 kPa or ELF <7.7 (or if a liver biopsy was performed fibrosis stage is F0-F1)
Indeterminate Risk
FIB-4 1.3 - 2.67 or LSM 8 - 12 kPa or ELF 7.7 - 9.8 (liver specialist to consider need for biopsy)
High Risk
FIB-4 >2.67 or LSM >12 kPa or ELF >9.8 (or if a liver biopsy was performed fibrosis stage is F2-F4)
• Managed by primary care team, endocrinologist, other
• Focus care on obesity management & CVD prevention
• Referral to liver specialist for additional proprietary biomarkers or imaging (MRE, cT1, other)
• Multidisciplinary team to prevent cirrhosis and CVD
Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, cT1 = Liver multiscan, CVD = Cardiovascular disease, ELF = Enhanced liver fibrosis test™, FIB-4 = Fibrosis-4 index, kPa = Kilopascals, LSM = Liver stiffness measurement, MRE= Magnetic resonance elastography, T2D = Type 2 diabetes mellitus
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Algorithm Figure 2
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Weight Management in NAFLD

Fibrosis Risk Stratification

	Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	High Risk FIB-4: >2.67 LSM >12 kPa ELF >9.8
General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[2]	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liragluitde 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH.[3,4]	GLP-1 RA preferred for NASH.[3,4]
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.

Abbreviations: GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HCC = Hepatocellular carcinoma, NASH = Nonalcoholic steatohepatitis
1. Persons with confirmed cirrhosis based on biopsy or high likelihood based on LSM >13.6kPa from vibration controlled transient elastography (FibroScan®), ELF ≥9.8 or >5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM >20 kPa or platelet count of <150,000/mm^3.
2. These goals should only be taken as a broad guidance. NAFLD/NASH may also improve by changes in macronutrient content, exercise and other factors beyond magnitude of weight loss. All high-quality studies available limited to a maximum of 12 month duration.
3. No high-quality evidence for pharmacotherapy in persons with NASH cirrhosis. Treatment should be individualized and used with caution only by liver specialists.
4. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

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Algorithm Figure 3

Diabetes Management in NAFLD

Fibrosis Risk Stratification

	Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	High Risk[1] FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize glycemic control using preferred agents that reverse steatohepatitis, whenever possible. Prefer GLP-1 RA and SGLT2i in CVD. Prefer SGLT2i in CKD and HF.		
Dietary recommendations	Glycemic load reduction via emphasis on whole food carbohydrates (vegetables, legumes, fruit) versus sugar/processed carbohydrates.		
Individualize A1c target	≤6.5% for persons without concurrent serious illness and at low hypoglycemic risk (>6.5% otherwise).		In advanced cirrhosis[1], caution with risk of hypoglycemia and avoid oral agents[2]
Preferred diabetes pharmacotherapy	Consider agents that reduce liver fat (pioglitazone, GLP-1 RA, SGLT2i).	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No evidence that SGLT2i improve steatohepatitis.	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No efficacy data in cirrhosis.
Metformin, sulfonylurea, DPP-4i, acarbose and insulin	May continue but limited benefit on liver histology in NAFLD.	May continue but limited benefit on liver histology in NAFLD.	May continue (F2-F3) but avoid oral agents if advanced cirrhosis present. Cannot avoid insulin in patients with advanced liver cirrhosis – often only option

Abbreviations: CKD = Chronic kidney disease, CVD = Cardiovascular disease, DPP-4i = Dipeptidyl peptidase 4, GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HF = Heart failure, NASH = Nonalcoholic steatohepatitis, SGLT2i = Sodium-glucose cotransporter-2 inhibitors.
1. Advanced cirrhosis is defined as persons with cirrhosis based on biopsy and Child class B or C with clinical evidence of comorbidities (varices, portal hypertension, ascites, etc.).
2. Limited data on oral diabetes medications and GLP-1 RA in persons with cirrhosis. Avoid metformin, GLP-1 RA appear safe, insulin preferred. Avoid oral agents in advanced cirrhosis.
3. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

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Algorithm Figure 4

Hypertension Management in NAFLD

Fibrosis Risk Stratification

	 Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	 Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	 High Risk[1] FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize BP control and improve cardiovascular health using preferred agents, whenever possible. Assess every 3 months and intensify therapy until goal achieved.		
Goal (individualize)[2,3,4]	Systolic < 130 mm Hg / Diastolic < 80 mm Hg	Systolic < 130 mm Hg / Diastolic < 80 mm Hg	Systolic < 130 mm Hg / Diastolic < 80 mm Hg; individualize if decompensated cirrhosis
Dietary recommendations	In addition to general dietary recommendations, reduce sodium & increase high potassium foods (e.g., DASH diet).		
Pharmacotherapy for hypertension[5]	First-line therapy: ACEIs and ARBs.	First-line therapy: ACEIs and ARBs.	Same but avoid ACEI or ARB if decompensated cirrhosis.
Intensification of therapy	Second agent: CCB, BB[6] or thiazide diuretic (as additional agents as needed).		Same but individualize if decompensated cirrhosis. Use diuretics with caution (risk of excessive diuresis).
Additional options	Additional BP medication choices: alpha blockers, central agents, vasodilators, aldosterone antagonist.		Same but individualize if decompensated cirrhosis.

Abbreviations: ACEIs = Angiotensin-converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, BB = beta blockers, CCB = calcium channel blockers.
1. Advanced cirrhosis defined as persons with cirrhosis based on biopsy and Child class B or C and clinical evidence of comorbidities (varices, portal hypertension, ascitis, etc.).
2. AACE recommends that BP control be individualized, but that a target of <130/80 mm Hg is appropriate for most persons.
3. Less-stringent goals may be considered for frail persons with complicated comorbidities or those who have adverse medication effects.
4. A more intensive goal (e.g., <120/80 mm Hg) should be considered for some persons if this target can be reached safely without adverse effects from medication.
5. If initial BP > 150/100 mm Hg start with dual therapy. (ACEI or ARB + CCB, BB or thiazide diuretic).
6. Prefer weight neutral beta-blockers: carvedilol, nebivolol.

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Algorithm Figure 5

AACE.

Atherogenic Dyslipidemia Management in NAFLD

Lipid risk levels are similar in the presence of NAFLD or NASH

General goal	Early intensive management of dyslipidemia needed to reduce cardiovascular risk. Intensify therapy until lipid goal is reached.		
Dietary recommendations	Increase fiber intake (>25 g/d), prioritize vegetables, fruits whole grains, nuts, reduce saturated fat & added sugars (e.g., Mediterranean diet).		
Lipid risk levels	**High CV Risk[1]** ≥2 risk factors and 10-year risk 10-20% Diabetes or CKD ≥3 with no other risk factors	**Very high CV Risk[1]** Established CVD or 10-year risk >20% Diabetes with >1 risk factor, CKD ≥3, HeFH	**Extreme CV Risk[1]** Progressive CVD CVD + diabetes or CKD ≥3 or HeFH FHx premature CVD (<55 yrs male <65 yrs female)
LDL-C goal (mg/dL)	<100	<70	<55
Non-HDL-C goal (mg/dL)	<130	<100	<80
Triglycerides goal (mg/dL)	<150	<150	<150
Apo B goal (mg/dL)	<90	<80	<70
First line pharmacotherapy: Statins	Use a moderate-to-high intensity statin[2], unless contraindicated. Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C).		
If LDL-C not at goal[3]: Intensify statin therapy	Use higher dose or higher potency statin.		
If LDL-C not at goal (or statin intolerant)[4]: add 2nd agent, then add 3rd agent	Ezetemibe, PCSK9 inhibitor, bempedoic acid, colesevelam, inclisiran.		
If triglycerides > 500 mg/dL	Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone).[5]		
If TG 135-499 mg/dL on max statin dose	Emphasize diet (as above).	Add icosapent ethyl.[6]	Add icosapent ethyl.[6]

Adapted from Handelsman Y, et al. Endocr Pract. 2020;26:1196-1224.

Abbreviations: CKD = Chronic kidney disease, CVD = cardiovascular disease, FA = Fatty acids, HeFH = Heterozygous familial hypercholesterolemia, HTN = Hypertension, Rx = Prescription
1. Major risk factors: age >40, DM, HTN, FHx of early CVD, low HDL C, elevated LDL, Smoking, CKD 3,4
2. High intensity statin therapy: rosuvastatin 20, 40 mg/d, atorvastatin 40, 80 mg/d.
3. Other lipid modifying agents should be used in combination with maximally tolerated statins if goals not reached: ezetimibe, PCSK9 inhibitor, bempedoic acid, colesevelam, or inclisiran.
4. Assess adequacy and tolerance of therapy with focused laboratory evaluations and patient follow up.
5. Niacin may lower triglycerides but does not reduce CVD and worsens insulin resistance. It may promote hyperglycemia in a population at high-risk of diabetes.
6. Icosapent ethyl 4g/d is recommended as an adjunct to maximally tolerated statin therapy to reduce risk of cardiovascular disease in high-risk persons.

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Algorithm Figure 6

AACE.

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