# 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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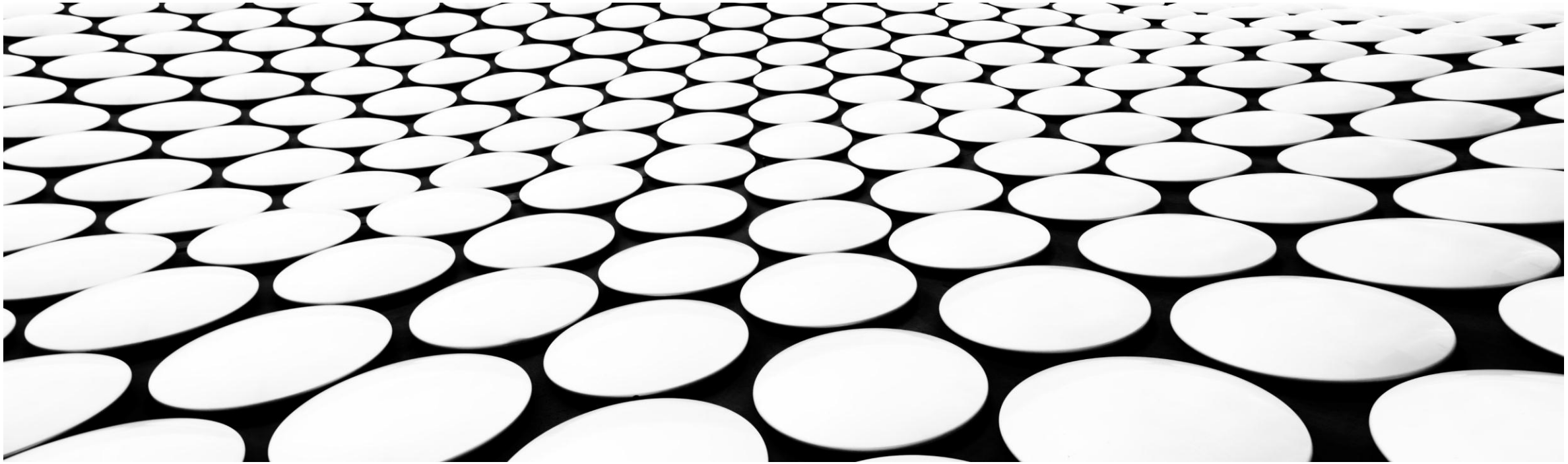


# INTRODUCTION

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

NAFLD is part of a multisystemic disease and is closely associated with obesity, insulin resistance (IR), type 2 diabetes mellitus, hypertension, and atherogenic dyslipidemia.

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.

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**
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. |

**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<br>5%-33% = 1 (mild)<br>33%-66% = 2 (moderate)<br>>66% = 3 (severe) |
| Lobular inflammation | Overall assessment of all inflammatory foci per ×200 field | No foci = 0<br><2 foci per 200 field = 1<br>2-4 foci per 200 field = 2<br>>4 foci per 200 field = 3 |
| Ballooning | … | None = 0<br>Few (or borderline) balloon cells = 1<br>Many cells/prominent ballooning = 2 |
| NAS | Sum of steatosis + lobular inflammation + ballooning | 0-8 |
| Fibrosis stage | … | None = 0<br>Mild = perisinusoidal or periportal (stage 1)<br>Moderate = perisinusoidal and portal/periportal (stage 2)<br>Severe = bridging fibrosis (stage 3)<br>Cirrhosis = stage 4 |

Abbreviation: NAS = nonalcoholic fatty liver disease activity score.

# INTRODUCTION

overall prevalence of NAFLD: 25%

the prevalence of the potentially progressive form of NAFLD or NASH is between 12% and 14%.

The highest prevalence rates for NAFLD and NASH: Middle Eastern countries.

The prevalence rates are significantly higher in those with T2D and visceral obesity.

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).

# INTRODUCTION

NASH is now among the top causes of HCC and the second most common cause of HCC in those on the waiting list for liver transplantation in the United States after hepatitis C.

# INTRODUCTION

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.

A recent survey found that physicians 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.

Finally, diagnosis and referral to specialists for management remain low among endocrinologists. 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.

# INTRODUCTION

- What Is Known About the Natural History of NAFLD?

T2D is a major driver of disease progression.

There is an alarmingly 55% prevalence of NAFLD among individuals with T2D. 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 or MRI-based techniques for hepatic steatosis.

Age (>50 years), IR, and features of metabolic syndrome all increase the probability of NASH with a more severe fibrosis stage and cirrhosis.

Excess mortality associated with NAFLD is mostly attributable to extrahepatic cancer, cirrhosis, CVD, and HCC. All NAFLD histologic stages, including isolated steatosis with no fibrosis, are associated with a significant increase in overall mortality, which worsens with liver disease severity.

# INTRODUCTION

- What Are the Extrahepatic Complications Relevant to Endocrinologists and Practitioners Who Care for Persons With Endocrine and Cardiometabolic Diseases?
- T2D:
  - The relationship between NAFLD and T2D is bidirectional , with visceral adiposity and IR being mediators in the causal pathway. Visceral adipose tissue is known to increase de novo gluconeogenesis, and liver fat is associated with hepatic IR. NAFLD, especially NASH, exacerbates hepatic and adipose tissue IR, which can contribute to the development of T2D.
- Diabetes Complications:
  - The relationship between NAFLD and diabetic complications remains poorly understood
  - NAFLD has been associated with microvascular diabetic complications, especially CKD.
  - In persons with diabetic retinopathy, the relationship remains **controversial**
- PCO
  - Women with PCOS are at increased risk of T2D and NAFLD.
  - PCOS is associated with severity of steatohepatitis (hepatocyte ballooning) and advanced fibrosis.

- 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.

- CVD
  - 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.
  - strong correlation between NAFLD and AF, ventricular arrhythmias, cardiomyopathy, cardiac valvular calcification, and cardiac arrhythmias, early HFpEF
  - However, it is difficult to establish a causal relationship between NAFLD and CVD

- Finally, several other complications, such as gallbladder disease, OSA, colorectal neoplasm, and other cancers as well as sarcopenia, have also been reported with increased prevalence in those with NAFLD.

# INTRODUCTION

- 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.

# RECOMMENDATIONS

## 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 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; best evidence level (BEL) 2

**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

**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.

- It is important to highlight that a landmark population-based study established that **the upper limit of plasma ALT should be 30 U/L for men and 19 U/L for women**. Additional studies have made the **ACG consider a true normal ALT level to range from 29 to 33 U/L for males and 19 to 25 U/L for females.**

- 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, but the presence of high aminotransferase levels does increase the prevalence of adverse outcomes.

High-risk groups for NAFLD with liver fibrosis are individuals who are ≥ 50 years and/or have moderate to severe obesity (BMI ≥35 kg/m2), including those seeking consultation for bariatric surgery, or T2D and/or MetS.

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.

# RECOMMENDATIONS

- 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

Bariatric surgery can induce sustained weight loss, improve diabetes, and reduce CVD and cancer risks, which are common comorbidities in NAFLD.

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.

Bariatric surgery should not be considered in persons with decompensated cirrhosis due to the increased postoperative mortality.

In persons with cirrhosis, postoperative complications appear to be significantly lower with sleeve gastrectomy than with Roux-en-Y gastric bypass (RYGB).

# RECOMMENDATIONS

## 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

- 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

Plasma liver aminotransferase levels can be unreliable and normal in many cases of NAFLD and should not be used alone for the diagnosis of NAFLD.

Hepatic steatosis can be diagnosed on imaging, including liver US, CAP, CT, or the 2 most accurate and sensitive methods, 1H-MRS and 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. 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 1H-MRS and liver biopsy in 146 individuals.

Liver US is also highly operator dependent and does not inform about the severity of liver fibrosis (unless cirrhosis is present).

MRI-based techniques (1H-MRS and MRI-PDFF) for the diagnosis of steatosis are reserved at present largely to clinical trial research.

MRE should be ordered in selected persons primarily by liver specialists for the diagnosis of liver fibrosis, but the test is expensive and does not replace the “gold standard” liver biopsy for the diagnosis of those with NASH.

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, which has been the most validated among the many tested to this end.

The FIB-4 has strong validation in its ability to **predict changes over time** in hepatic fibrosis and allows risk stratification of persons in terms of future liver-related morbidity and mortality.

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, and in particular withT2D; therefore, it **should be avoided in this setting**.

Proprietary biomarkers include the FibroTest, enhanced liver fibrosis (ELF) test, propeptide of type III collagen, NIS4 and others.

Endocrinologists must be aware of the limitations of blood panels, compared with a liver biopsy. 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.** 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.

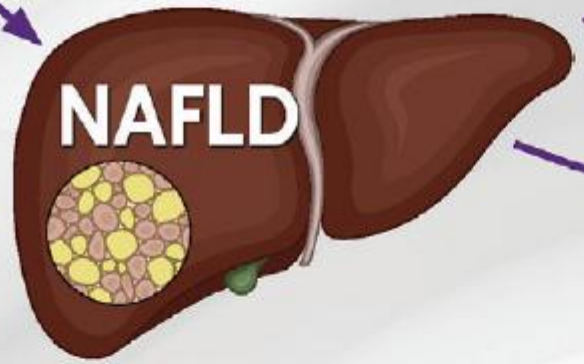
In this context, a multistep process must be used.

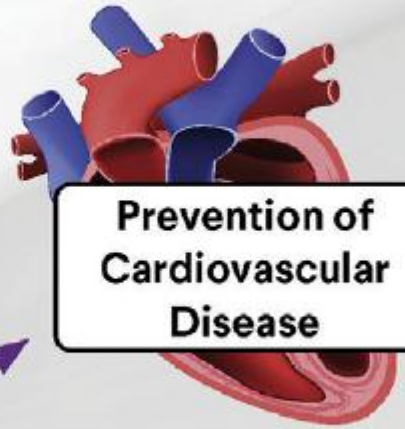
**High-risk groups for the development of NAFLD**

- Prediabetes or T2D
- Obesity [1] and/or ≥2 cardiometabolic risk factors[2]
- Hepatic steatosis (on imaging) or ↑ AST or ALT (>30 IU/L)

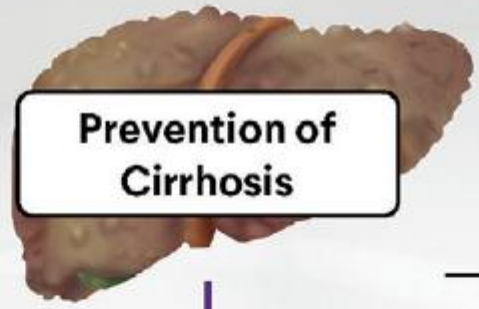
History and physical exam

Rule out 2° causes[3]



Prevention of Cardiovascular Disease



Prevention of Cirrhosis

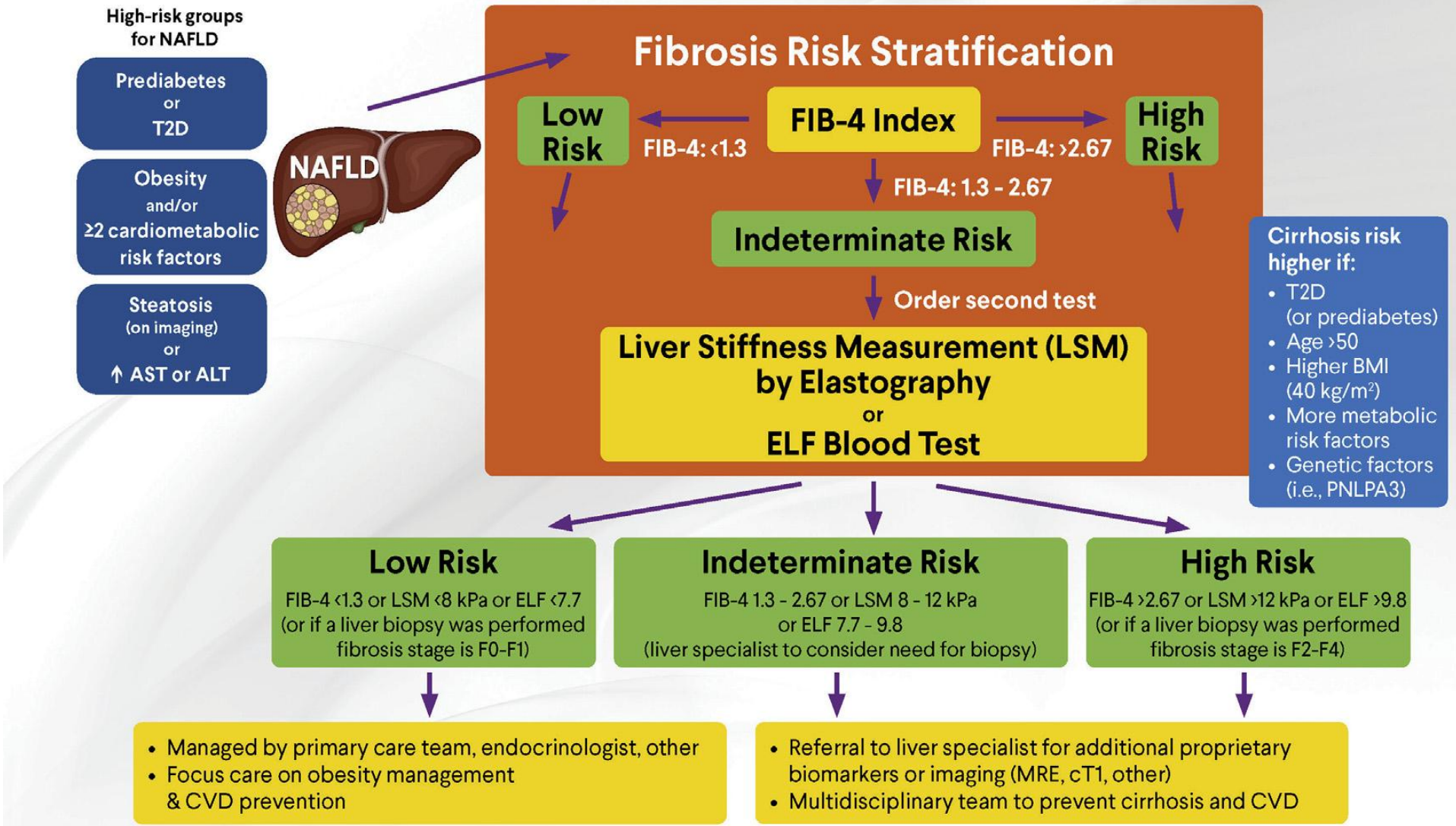
**Management of**

1. Obesity
2. Diabetes
3. Hypertension
4. Atherogenic dyslipidemia

**Fibrosis Risk Stratification**

- Low Risk
- Indeterminate Risk
- High Risk

# Cirrhosis Prevention in NAFLD




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



Algorithm Figure 2

AACE.

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.

**A liver US is not recommended for routine clinical diagnosis**. 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.

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. 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.

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.

# RECOMMENDATIONS

## 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

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.

As mentioned earlier, **VCTE** is the most broadly used noninvasive method for LSM and, thus, for establishing the risk of liver fibrosis and for eventually excluding cirrhosis. 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**.

Minor limitations of VCTE include **overestimation of LSMs at higher stages of fibrosis** and **unsuccessful LSMs with inappropriate use of probes in individuals with overweight and obesity**, which can be circumvented using the right probe in individuals with higher BMI.

a recent systematic review supported the cutoff of 8.0 kPa for screening for clinically significant liver fibrosis. 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. 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 highrisk group for advanced liver fibrosis. 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:

MRE: the best accuracy but is costly, limited availability; it is best ordered by the hepatologist in selected circumstances.

SWE: good experience among hepatologists (either 2-dimensional (2DSWE) or point (pSWE)), have an accuracy similar to that of TE but less than that of MRE; A recent 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; newer techniques with limited evidence in terms of long-term predictive value for future liver outcomes in comparison to 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.

**LiverMultiScan uses multiparametric MRI** to noninvasively quantify liver fat and cT1 signal maps of the liver to assess disease activity (NAFLD activity score [NAS]) and potentially outcomes. These techniques are currently being used largely in **research** for screening studies 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.

# RECOMMENDATIONS

## 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 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

- 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

# RECOMMENDATIONS

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

- Recommendation 2.5.1. 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 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

In a prospective longitudinal cohort study of 3012 adults, the results before and after the introduction of a 2-step care pathway were compared. 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; P¼.006). However, more long-term outcome data are needed on screening strategies to prevent cirrhosis.

# RECOMMENDATIONS

## 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, 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

**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. Moreover, CVD is the leading cause of death in NAFLD.

Future prospective studies using more rigorous study designs may be required to resolve this controversy.

The AACE and European Association for the Study of Obesity 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

# 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.

 https://doi.org/10.1016/j.eprac.2022.03.010

Algorithm Figure 3

AACE.

# 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.

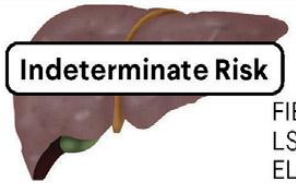


Algorithm Figure 4

AACE.

# 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.

 https://doi.org/10.1016/j.eprac.2022.03.010

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]<br>≥2 risk factors and 10-year risk 10-20%<br>Diabetes or CKD ≥3<br>with no other risk factors | **Very high CV Risk**[1]<br>Established CVD<br>or 10-year risk ›20%<br>Diabetes with ›1 risk factor, CKD ≥3, HeFH | **Extreme CV Risk**[1]<br>Progressive CVD<br>CVD + diabetes or CKD ≥3 or HeFH<br>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.



Algorithm Figure 6

AACE.

- 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.

**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.

# RECOMMENDATIONS

## 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

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.

A 2021 meta-analysis 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.

Specific dietary patterns can exert benefit in persons with NAFLD, with debate as to the best dietary approach in NAFLD.

The results of different studies have led several societies to specifically recommend the Mediterranean diet for persons with NAFLD.

# RECOMMENDATIONS

- 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

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.

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.

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.

# RECOMMENDATIONS

## 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 GLP1RAs, 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

# RECOMMENDATIONS

- 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

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:

primarily targeting adipose tissue and improving lipid storage/redistribution and glucose utilization

histologic improvement in persons without diabetes

With pioglitazone treatment (45mg), 58% of individuals achieved the primary outcome of a reduction of at least 2 points in NAS, while 51% had resolution of NASH.

improvement in the mean fibrosis score.

significant improvement for NASH resolution and for any stage of fibrosis, with even greater ORs for the effect on advanced fibrosis

The side effects of pioglitazone include dose-dependent weight gain, increased fracture risk, heart failure if used in persons with preexisting heart disease, and bladder cancer.

GLP-1 Ras:

normalize plasma aminotransferase levels

reduce liver fat content on imaging in individuals with NAFLD

liraglutide improved some features of liver histology in persons with NASH including delaying fibrosis progression

semaglutide caused resolution of steatohepatitis in 36-59% patients in the context of significant weight loss.

**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.

SGLT2 inhibitors:

have been considered potentially beneficial for NAFLD because of the reduced lipid burden on the liver from glycosuria creating energy deficit and weight loss.

Several small, open-label studies have suggested benefit in persons with T2D and NAFLD.

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.

# RECOMMENDATIONS

## 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/m2 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

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 3mg daily) and semaglutide (titrated up to 2.4 mg weekly).

Obesity medications are approved by the FDA for chronic weight management for individuals with a BMI of 30 kg/m2 or those with a BMI of 27 to 29.9 kg/m2 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

Of the medications currently approved for chronic obesity therapy, semaglutide has shown the most efficacy in achieving weight loss.

# RECOMMENDATIONS

- 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

# RECOMMENDATIONS

## 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/m2 (32.5 kg/m2 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/m2 (**27.5 to 32.4 kg/m2 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).

The degree of weight loss resulting from bariatric surgery improves NAFLD as assessed by either imaging technologies or liver histology.

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, although the latter was found to be superior for remission of T2D. Of note, follow-up was too short to make strong conclusions.

# RECOMMENDATIONS

- 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

EBMT: include intragastric balloon (IGB), endoscopic sleeve gastroplasty (ESG), and aspiration therapy by means of a gastrostomy.

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.

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.

# RECOMMENDATIONS

## 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

# RECOMMENDATIONS

## 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).