Non-alcoholic Fatty Liver Disease (NAFLD)

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Outline

- Definitions and Epidemiology
- Role of Primary Care Providers
- Diagnosis
- When to refer to specialist
- Treatment





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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DEFINITIONS AND EPIDEMIOLOGY

NAFLD vs. NASH

- Nonalcoholic fatty liver disease (NAFLD): Broad spectrum of liver disease, ranging from hepatic steatosis to steatohepatitis to cirrhosis
 - In the absence of significant alcohol consumption or presence of secondary causes of fatty liver disease
- Nonalcoholic steatohepatitis (NASH): Presence of > 5% or more of hepatic steatosis with inflammation and hepatocyte injury, with or without evidence of fibrosis







Stages of Hepatic Fibrosis





F4

Cirrhosis

F0 F1 F2 No fibrosis Perisinusoidal Perisinusoidal fibrosis with portal/periportal fibrosis F3 Bridging fibrosis

https://www.clearvuehealth.com/questions/what-is-nash-fibrosis/

Major Risk Factors

- Obesity/Metabolic syndrome
 - 25-30% prevalence of NASH
- Type 2 Diabetes/Insulin resistance
 - 55% prevalence of NAFLD
 - 30-40% prevalence of NASH





Co-morbidities

- Hepatic
 - Cirrhosis
 - Hepatocellular carcinoma
- Extra-hepatic
 - Cardiovascular disease
 - Major cause of morbidity and mortality
 - Hypertension
 - Non-hepatic cancer





ROLE OF PRIMARY CARE PROVIDERS

Despite the increasing prevalence of NAFLD and potential for increased morbidity and mortality...

- It is estimated that < 5% of persons with NAFLD are aware of their liver disease
- Studies have shown that there is a knowledge gap regarding NAFLD among endocrinologists and PCPs, resulting in
 - Underestimation of prevalence of NAFLD in high risk groups
 - Underutilization of medications with proven efficacy in NASH
 - Underdiagnosis and low referral rates to gastroenterologists and hepatologists for management





Role of Primary Care Providers

- Screen patients who are at high risk of clinically significant fibrosis and cirrhosis
- Manage cardiometabolic risk factors
- Recommend lifestyle modifications
- Initiate appropriate medical therapy with proven efficacy
- Identify patients that should be referred to a gastroenterologist or hepatologist for management





DIAGNOSIS

Who should be screened?

- Obesity and/features of metabolic syndrome
- Pre-diabetes or Type 2 Diabetes
- Hepatic steatosis on imaging study
- Persistently elevation plasma aminotransferase levels (> 6 months)
- Persons undergoing bariatric surgery





Diagnosis

- Liver biopsy
- Biomarkers
 - Liver enzymes
 - FIB-4 Index
- Imaging
 - Abdominal Ultrasound
 - Elastography





Liver Biopsy

- **Gold Standard** for diagnosis of NASH
 - Allows direct visualization of liver parenchyma
 - Liver fibrosis stage indicating severity of fibrosis
- Limitations
 - Invasive and costly
 - Many more non-invasive strategies have been developed





Liver Transaminases

- ALT is higher in patients with T2DM and NAFLD
 - However, this has limited accuracy as liver enzymes can be normal in patients with NAFLD

	Sensitivity	Specificity
NASH		
ALT 1x ULN	75%	47%
ALT 0.5x ULN	100%	11%
Fibrosis		
ALT 1x ULN	64%	47%
ALT 0.5x ULN	93%	10%

- Limitations:
 - Does not reflect the severity or stage of the disease
 - Does not confirm the diagnosis





Fibrosis-4 (FIB-4) Index

- Preferred initial noninvasive test
- Components: age, AST, ALT, and platelet count
 - Score > 2.67 = High risk for advanced fibrosis
 - Score < 1.3 = Advanced fibrosis is excluded
 - Score of 1.3-2.67 = Indeterminate
- Patient's with an indeterminate or high risk score should be considered for further evaluation with imaging







Please fill out required fields.

https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis

Fibrosis-4: A simple fibrosis marker FIB-4 includes Age, AST, ALT and platelet count



Fig. 2. Clinical use of FIB-4 to screen for NAFLD-related liver fibrosis in patients with T2D. https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis.

Abdominal Ultrasound

- 4-point qualitative scoring system to grade severity of NAFLD
 - Normal, mild, moderate, and severe
- Benefits:
 - Commonly available, affordable, and easy to use
 - Accuracy > 80%
 - Effective in patients with DM
- Limitations:
 - Operator-dependent technique
 - Unable to quantify amount of steatosis present, provide information on staging of NALFD-related fibrosis, cannot detect mild hepatic steatosis (<30% steatosis)
 - Sensitivity reduced by presence of severe obesity





Vibration controlled transient elastography (TE)

- Considered the preferred imaging study in recent AACE guidelines
- Uses ultrasound-based device that measures shear wave velocity as a surrogate of liver stiffness (more stiff = more fibrotic)
- Examples: Fibroscan





Steatosis – Vibration controlled transient elastography (TE)

- Benefits:
 - Includes two probes (M and XL) depending on body habitus
 - High accuracy for detecting both steatosis and fibrosis when compared to liver biopsy
 - Well studied in patients with DM
- Limitations:
 - Less widely available
 - May produce unreliable results in cases of acute hepatic inflammation, congestion, cholestasis, ascites, or portal vein thrombosis
 - Contraindicated in pregnancy and intracardiac devices
 - Limited results in patients with Obesity





WHEN TO REFER?

When should a patient be referred to a liver specialist?

- Persistent elevation in ALT or AST
- Hepatic steatosis on imaging
- Indeterminate or high risk FIB-4 score
- Clinical evidence of advanced liver disease (ascites, hepatic encephalopathy, esophageal varices, or evidence of hepatic synthetic dysfunction)





TREATMENT

Weight Loss!!

- Goal of at least 5%, but preferably 10% weight loss
 - More weight loss = greater liver histologic and cardiometabolic benefit
- Dietary modification: calorie reduction and restriction of saturated fat, starch, and added sugars
 - Adopt healthy eating patterns such as the Mediterranean diet
- Increase physical activity
- Consider bariatric surgery
 - Not recommended in patients with cirrhosis





Pharmacotherapy – Patients with T2DM

- **Pioglitazone** and **GLP-1 receptor agonists** have shown efficacy in treatment of steatohepatitis (NASH)
- SGLT-2 inhibitors do not provide benefit for treatment of steatohepatitis, but may offer cardiometabolic benefit
- Other diabetes medications (metformin, acarbose, insulin, DPP4 inhibitors) have no benefit on treatment of steatohepatitis, but can be continued if needed for treatment of hyperglycemia





Pharmacotherapy – Obesity

- Use as adjunctive to lifestyle modification to achieve weight loss goal
- Semaglutide 2.4 mg weekly has best evidence
 - Can also consider Liraglutide 3 mg/day





SUMMARY

Management Algorithm for NAFLD – Overview



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)
- Secondary causes of liver steatosis or elevated transaminases (AST or ALT) are excessive alcohol consumption (214 drinks/week for women or 221 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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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 convisiont e 2022 AACE | MAY NOT 85 8890000000 IN ANY FORM WITHOUT DURIESS WIIITTEN PERVISION PROM AACE. https://doi.org/10.1016/j.opnic.2022.03.010 Algorithm Figure 2







Weight Management in NAFLD

	Fibrosis Risk Stratification			
	Low Risk FIB-4: 1.3 LSM 48 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 incre	ease daily movement. Stress reduction th	rough 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,24	GLP-1 RA preferred for NASH,34	
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 x13.6kPa from vibration controlled transient elastography (FibroScan®), ELF 29.8 or x5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM >20 kPa or platelet count of d50,000/mm².

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 steatchepatitis and fibrosis.

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Diabetes Management in NAFLD

Fibrosis Risk Stratification

	Low Risk FIB-4: 4.3 LSM (8 kPa ELF (7.7	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-1RA 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-1RA 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-1RA = 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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Questions?