Obesity: Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

May 2020
Defining NAFLD

NAFLD is the presence of hepatic steatosis on either imaging or liver histology, or increased echogenicity and coarsened echotexture on liver ultrasound.¹⁻³

• >5% of hepatocytes showing steatosis¹,²
• In individuals who consume little/no alcohol¹,²
• With no other secondary cause for hepatic steatosis (eg, alcohol, steatogenic drugs, autoimmune causes, viral hepatitis)¹,²
• USFLI >30 (in the absence of heavy alcohol use and other known liver disease)³

Defining NAFLD: NAFL and NASH

NAFLD can be broadly subdivided into NAFL and NASH\(^1,2\)

- **NAFL** is a nonprogressive form of NAFLD\(^3\)
  - Hepatic steatosis without hepatocellular injury (hepatocyte ballooning)
  - Minimal risk of progression to cirrhosis and liver failure

- **NASH** is a progressive form of NAFLD\(^3\)
  - Hepatic steatosis and inflammation with hepatocyte ballooning, with or without fibrosis
  - Substantial risk of progression to liver fibrosis, cirrhosis, and/or mortality from liver dysfunction

Prevalence of NAFLD

- NAFLD is the most common liver disease worldwide\(^1,2\)
  - 2nd leading indication for liver transplantation\(^2\)
  - 3rd leading cause of HCC in US\(^2\)
- In Western countries, affects up to 30% of general population\(^3-6\)
  - 3% to 5% of global population\(^7\)
  - >10% of patients with NAFLD have advanced fibrosis\(^4\)
  - 2% to 5% have substantial liver injury\(^5\)
  - 1% to 2% will progress to NASH cirrhosis\(^5\)
- In 2013, NASH was the second leading indication for liver transplantation in the US, accounting for 15.8% of waitlist registrants (170% increase from 2004).\(^8,9\)
- Increased risk in patients with metabolic syndrome, obesity, T2D\(^3,10\)

Symptoms of NAFLD

- Early stage NAFLD usually is asymptomatic or “silent.”¹
- Patients with more advanced disease (NASH) may experience:¹
  - Fatigue, malaise
  - Pain in the upper right abdomen
- Symptoms of cirrhosis due to NASH progression:²-³
  - Worsening fatigue
  - Ascites (swelling in the belly)
  - Jaundice
  - Enlarged liver and/or spleen, or breasts (men)
  - Red palms
  - Internal bleeding (patients may notice bruising or bleeding)

Clinical Burden of NAFLD

- NAFLD is a multisystem disease\textsuperscript{1}
  - Affects extra-hepatic organs and regulatory pathways
- Burden is not confined to liver-related morbidity/mortality\textsuperscript{1}
  - Increased risk of T2D, CVD, metabolic syndrome, liver fibrosis, and CKD\textsuperscript{2}
- NAFLD increases mortality risk\textsuperscript{3}
  - Majority of deaths among patients with NAFLD are attributable to CVD\textsuperscript{1,3,4}
  - Significantly greater overall mortality in patients with advanced fibrosis\textsuperscript{3}

Pathophysiology of NAFLD

• NAFLD pathophysiology is complex and not well understood.¹
• NAFLD is considered a hepatic manifestation of the metabolic syndrome.¹
• Adiposity-based chronic disease/obesity predisposes patients to NAFLD.¹⁻⁴
• Insulin resistance is the major mechanism in NAFLD/NASH development and progression.⁵
• Also involved: adipokines, inflammation, lipid metabolism dysfunction, oxidative stress, pro-coagulant status, proinflammatory cytokines.⁶
• Increasing evidence links NAFLD and CKD.⁷

Screening for NAFLD

- Screening for NAFLD is recommended for patients with:¹⁻²
  - Insulin resistance, metabolic syndrome, and/or obesity
  - Abnormal liver enzymes (ie, increased ALT, AST, or γGT)
  - Incidental discovery of steatosis
  - Persistently high serum ferritin/increased iron saturation

- Exclude competing etiologies (eg, chronic viral hepatitis, hemochromatosis, autoimmune liver disease)¹⁻²

- Rule out significant fibrosis (≥F2) using surrogate markers (NFS, FIB-4, ELF, or FibroTest®)¹⁻²
  - Refer patients for transient elastography if ≥F2 cannot be ruled out.¹

- If ≥F2 is confirmed, final diagnosis of disease severity by liver biopsy (gold standard).¹⁻²

Diagnosis of NAFLD via Conventional Imaging: Ultrasonography

Ultrasound is the recommended first-line imaging modality to diagnose hepatic lipid accumulation in clinical practice.¹

**Benefits²**

- Most commonly used modality, due to limitations of other noninvasive tests
- Widely available
- Safe and well tolerated
- Can be performed on all scanners

**Limitations¹,²**

- Lacks sensitivity to detect liver fat content at 5%
- Limited sensitivity if <30% of hepatocytes are steatotic
- Qualitatively interpreted; findings may be influenced by factors other than presence/degree of hepatic steatosis
- Limited accuracy, repeatability, reproducibility, especially in individuals with obesity

To detect hepatic steatosis, quantitative ultrasound may be superior to conventional ultrasound.²

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Diagnosis of NAFLD via Liver Biopsy

Ultrasound is the recommended first-line imaging modality to diagnose hepatic lipid accumulation in clinical practice.1

Benefits
• Confirms/excludes NAFLD diagnosis, especially in setting of competing etiologies or in patients with atypical clinical features2,3
• Distinguishes between NAFL, NAFL with inflammation, and NASH2
• Provides information on disease severity, inflammatory activity, and fibrosis stage2

Limitations
• Invasive and expensive1
• Sampling error4
• Intraobserver and interobserver variability in interpretation4
• Adverse effects include pain, infection, bleeding/hemorrhage, and death (rare)1,4

To facilitate risk stratification, there is a compelling need for non-invasive assessments that detect the presence of hepatic steatosis and NASH and identify fibrosis stage.1

Diagnosis of NAFLD via Conventional Imaging: CT and CAP

• **Computed Tomography**
  • Rarely used to diagnose NAFLD\(^1\)
  • Typically an incidental finding on abdominal CT performed for another indication\(^1\)
  • Density of liver to spleen ratio is typically used to detect hepatic steatosis\(^1\)
  • Due to ionizing radiation exposure, not recommended to assess hepatic steatosis\(^1\)

• **Controlled Attenuation Parameter**
  • Available on newer FibroScan machines as an adjunct to liver stiffness measurement by VCTE\(^1\)
  • May be used to detect hepatic steatosis and fibrosis; does not provide reliable quantitative estimate of liver fat content\(^1,2\)

Quantifying NAFLD Liver Fat and Fibrosis with Novel Imaging Modalities

Liver stiffness/elasticity can be used as a surrogate for fibrosis; ideally, imaging methods would evaluate the entire liver.\(^1\)

**MRS** (gold standard to quantify hepatic TG content)\(^1\)
- Can yield an accurate NAFLD diagnosis if liver fat content is ≥5%\(^1\)
- Can quantify liver fat content beyond the presence of HS\(^1\)
- Time-consuming; requires special expertise\(^1\)
- Affords only minimal spatial coverage; high sampling error risk\(^1\)
- Equipment is not universally available\(^1\)

**MRI-PDFF** (MRI without spectroscopy):
- Provides image of liver to identify exact region of interest, and accurate estimate of liver fat content\(^1\)
- Preferred vs CAP to grade steatosis\(^2\)

NASH Progression and Presentation

- An estimated one-third of patients with NAFLD will progress to NASH; prevalence may be higher because liver biopsy is needed to confirm diagnosis.¹,²

- NASH is asymptomatic³
  - Linked to key features of the metabolic syndrome: obesity, dyslipidemia, and glucose intolerance
  - Histologically indistinguishable from alcoholic hepatitis

- Whereas NAFLD can be diagnosed with imaging, NASH requires liver biopsy to identify the presence and location of inflammation, hepatocyte ballooning, Mallory-Denk bodies, and early fibrosis.⁴

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NASH Disease Progression: Hepatocellular Carcinoma

• NASH-related HCC is the fastest growing indication for liver transplant in HCC candidates.
  • As hepatitis C prevalence declines, there is likely to be an increase in HCC owing to NASH, due to obesity and T2D epidemics.

• Annual HCC incidence in patients with NASH-related cirrhosis ranges from 2.6%-12.8%.
  • Patients may progress to HCC in the absence of cirrhosis.

• Segmental liver resection or transplantation are the only curative therapeutic options for NASH-related HCC.

Risk Factors for Progression from NAFLD to NASH

- T2D\(^1,2\)
- Obesity\(^1,2\)
- Older age\(^1,2\)
- Liver fibrosis\(^2\)
  - Can occur with NAFLD, but progression is slower than with NASH
  - Reduced survival if fibrosis occurs with hepatocyte ballooning, portal inflammation

Identification of patients at risk for progression may prompt the use of proven therapies.\(^2\)

2. Neuschwander-Tetri BA. *BMC Medicine*. 2017;15:45. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2D, type 2 diabetes.
NAFLD Prevention and Treatment: Lifestyle Modifications

- Lifestyle intervention and modification—exercise, diet, and weight loss—is the cornerstone of NAFLD prevention and treatment.\(^1\)\(^-\)\(^3\)

- Maintaining physical activity >150 min/week, or otherwise increasing activity level by >60 min/week, has been shown to reduce serum aminotransferases.\(^1\)

- Optimal diets: Low-carbohydrate, low-fat, low-glycemic-index, Mediterranean\(^2\),\(^4\)
  - Mediterranean has shown significant improvement in steatosis vs high-fat, low-carbohydrate diet, despite similar weight loss\(^1\)
  - Long-term calorie-restricted diet is associated hepatic fat mobilization and CV risk improvement\(^1\)

- Weight loss can reduce liver fat, inflammation, fibrosis, and scarring.\(^1\),\(^5\)
  - To improve steatosis: Weight loss ≥3%-5% of baseline body weight\(^1\)
  - To improve histopathologic features of NASH, including fibrosis: Weight loss 7%-10% of baseline body weight\(^1\)
  - Rapid weight loss via fasting can worsen NAFLD\(^5\)
  - Patients with BMI≥35 kg/m\(^2\) and NAFLD should be considered for bariatric surgery\(^6\)

Treating NAFLD

• There are currently no FDA-approved pharmaceutical interventions for NAFLD or NASH.1

• Treatment is focused on addressing associated/coexisting conditions (dyslipidemia, obesity, T2D) to control glycemia, lipids, and liver function.1,2

• Pharmaceuticals to treat liver disease should generally be limited to patients with confirmed NASH.3
  • Treatment options: TZDs (pioglitazone), GLP-1 RA (liraglutide), antioxidants (vitamin E)3-5
  • In a phase 4 clinical trial, the SGLT2i empagliflozin reduced hepatic fat in patients with T2D.6

• Statins are safe but underutilized for patients with NAFLD or NASH.2,7
  • May reduce liver enzymes and substantially reduces CVD morbidity/mortality in patients with NAFLD/NASH7
  • Provide a protective effect on steatosis, steatohepatitis, and fibrosis7

Available and Potential Future Therapies for Various Stages of NAFLD

Hepatic steatosis → Hepatitis → Fibrosis → HCC

- **Oxidative stress**: Anthocyanins, Pro- and prebiotics
- **Inflammation**: Anthocyanins, Cenicriviroc*, Dual PPAR agonists*, FXR ligands*, Pro- and prebiotics, SGLT2i
- **Apoptosis**: Anthocyanins, Pro- and prebiotics, Selonsertib*

Lifestyle modifications

1. Jeznach-Steinhagen A, et al. Medicina (Kaunas). 2019;55(5):166. ACCi, acetyl-CoA carboxylase inhibitors; DPP4i, dipeptidyl peptidase 4 inhibitor; FXR, farnesoid X receptor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular cancer; NAFLD, nonalcoholic fatty liver disease; PPAR, peroxisome proliferator-activated receptors; SGLT2i, sodium-glucose cotransporter 2 inhibitor; VAP1i, vascular adhesion protein-1 inhibitors.
# Pharmacologic Treatments Used for NAFLD and/or NASH in Patients With T2D

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Thank You

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