CURRENT GUIDELINES AND REVIEW ON NASH

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Fatty Liver Disease

- Nonalcoholic fatty liver disease (NAFLD)
  - **Nonalcoholic Fatty Liver (NAFL)**
  - **Nonalcoholic Steatohepatitis (NASH)**
    - 3rd leading cause of cirrhosis
    - 2nd most common indication for liver transplantation
NAFL versus NASH

• **NAFL**
  • Hepatic steatosis
    • Excess fat accumulation in the liver can progress to steatohepatitis
    • No causes of secondary hepatic fat accumulation (alcohol, medications, or hereditary disorders)

• **NASH**
  • Steatohepatitis defined by histology
    • *Hepatocyte injury*
    • *Inflammation*
    • *Fibrosis*
  • Multiple etiologies
  • Most common cause of fibrosis/cirrhosis with unexplained increased ALT levels
  • Insulin resistance and metabolic syndrome (obesity, DM, hyperlipidemia)
NATURAL HISTORY OF NASH

Isolated Fatty Liver:
1. None to very minimal progression to fibrosis and to cirrhosis
2. No increased risk of death compared with the general population

1. Increased risk of death compared with general population.
   In order: 1- Cardiovascular / 2- Malignancy / 3- Liver related
2. NASH with fibrosis leads to worse prognosis
   Fibrosis progression a/w DM, severe IR weight gain > 5kg, rising ALT, AST

HCC: ~7.2%
  over 6.5 years

Decompensation: ~19-45%
  over 7-10 years

NAFL

Adverse lifestyle habits can lead to non-alcoholic fatty liver (NAFL) with isolated steatosis, defined as an abnormal accumulation of fat in the hepatocytes.

NASH

~20-25%

In people with NASH, liver homeostasis is impaired due to an accumulation of toxic lipids. Certain gut bacteria-derived products can also penetrate in the liver, where they activate immune responses. This contributes to local inflammation of hepatic tissue. This pathological environment provokes hepatocytes damage and leads to a state called ballooning. Steatosis, inflammation and ballooning are the three lesions that define NASH histologically.

NASH Cirrhosis

~11% over 15 years, but significant variability

Hepatocyte suffering, apoptosis and inflammation leads to the release of signaling molecules that contribute to hepatic stellate cells activation. As a result of this activation, hepatic stellate cells secrete collagen fibers that form scar tissue, leading to hepatic fibrosis. NASH can evolve to cirrhosis (fibrosis stage F4) or hepatocellular carcinoma.
PREVALENCE OF NAFLD

NAFLD prevalence in the general population has been estimated in several studies using different methodologies. In a meta-analysis conducted over 22 countries, worldwide prevalence of NAFLD was estimated at 25.2%⁷.

31.8%  
Middle Eastern countries

30.5%  
South America

27.4%  
Asia

24.1%  
North America

23.7%  
Europe

13.5%  
Africa

25.2%  
Worldwide

Meta-analysis, 86 studies included with a sample size of 8,515,431 adults from 22 countries²

34%  
United States

Analysis of NHANES database, including 12,317 individuals⁸
PREVALENCE OF NASH

The exact prevalence of NASH in an adult population remains difficult to assess due to a lack of cost-effective and widely available minimally-invasive diagnostic test, and to the absence of specific symptoms before end-stages.

1,5–6.45%
Worldwide

Meta-analysis, 86 studies included with a sample size of 8,515,431 adults from 22 countries.

The prevalence of NASH is expected to increase by 63% between 2015 and 2030 in relation to the worldwide increase of diabetes and obesity.\textsuperscript{13}

12.2%
United States

Prospective study enrolling 328 patients in Texas. age range: 28–70, mean age: 54.6 years.\textsuperscript{9}
PREVALENCE OF NAFLD BY ETHNICITY IN THE UNITED STATES

58.3% Hispanics
44.6% Caucasian
35.1% African American

Prospective study enrolling 328 patients in Texas, age range: 28-70, mean age: 54.6 years.
Prevalence by ethnicity in the US

- **NAFLD** prevalence (Williams 2011)
  - Hispanics: 58.3%
  - Caucasians: 44.6%
  - Afro-Americans: 35.1%

- **NASH** prevalence (Williams 2011)
  - Hispanics: 19.4%
  - Caucasians: 9.8%
PREVALENCE OF NAFLD/NASH AMONG PATIENTS WITH TYPE 2 DIABETES*

NAFLD: 65% to 70%\textsuperscript{14}
NASH: 25-30%\textsuperscript{15}

TRENDS IN TYPE 2 DIABETES: +55% increase of adults with diabetes worldwide by 2035 (592 million individuals affected in 2035 vs. 382 million in 2013)\textsuperscript{16}

* The above estimations of NAFLD/NASH prevalence are based on data found in the cited reviews. The existing data vary depending on the study design (diagnostic tools used, characteristics of the population - e.g. age, BMI, bariatric surgery, hospitalization, state...).
PREVALENCE OF NAFLD/NASH AMONG PATIENTS WITH OBESITY*

NAFLD: 70% or more\textsuperscript{17}

NASH: 25-30\%\textsuperscript{15}

TRENDS IN OBESITY: 47\% of adults affected by obesity in US population by 2030\textsuperscript{18} vs. 39.8\% in 2015-2016\textsuperscript{19}

* The above estimations of NAFLD/NASH prevalence are based on data found in the cited reviews. The existing data vary depending on the study design (diagnostic tools used, characteristics of the population - e.g. age, BMI, bariatric surgery, hospitalization, state…).
Risk factors associated with NAFLD

- Well-established risk factors
  - Obesity
  - Type 2 diabetes
  - Dyslipidemia
  - Metabolic syndrome
  - Polycystic ovary syndrome
  - Genetic variation related to PNPLA3

- Emerging conditions that are associated with NAFLD
  - Hypothyroidism
  - Obstructive sleep apnea
  - Hypopituitarism
  - Hypogonadism
  - Pancreatoduodenal resection
  - Psoriasis
Risk factors for NASH among NAFL patients

• **Main risks factors**
  • Obesity
  • Older age
  • Female sex
  • DM
  • Hypertension

• **Other factors**
  • High AST/ALT
  • Low platelet count
  • Elevated C-peptide level
  • Ultrasound steatosis score
NAFLD & mortality 3 main causes of death

- **Cardiovascular disease (38%)**
- All cause malignancy (19%)
- Liver-related death (9%)
- Infections (8%)
NAFLD progression Non-Diabetic and Diabetic Patients

Non-Diabetic

10-20% NAFLD → 10-15% NASH → 3% Cirrhosis → 14% HCC → 21% Liver Transplant

13% Mortality

Diabetic

40% NAFLD → 20-25% NASH → 5% Cirrhosis → 14% HCC → 42% Liver Transplant

25% 85% Mortality
Pathogenesis

- Not fully understood
- **Insulin resistance** as a key mechanism leading to hepatic steatosis
- Additional **oxidative injury** is needed to manifest the necroinflammatory component of steatohepatitis
- Potential oxidative stressors:
  - Hepatic iron
  - Leptin
  - Antioxidant deficiencies
  - Intestinal bacteria
Clinical Manifestations

- Most **asymptomatic**
  - Fatigue
  - Malaise
  - Vague right upper abdominal discomfort
- Physical findings
  - Hepatomegaly (highly variable presentation)
  - Stigmata of chronic liver disease (palmar erythema, spider angioma, ascites)
Laboratory findings

- Mild to moderate elevations in AST and ALT
  - 2-5x the upper limit of normal
- **AST: ALT ratio** less than 1
- Degree of elevation does not predict degree of inflammation/fibrosis
- Alkaline phosphatase
  - 2-3x ULN
- Serum albumin and bilirubin normal, abnormal in cirrhosis
- Elevated serum ferritin or transferrin saturations
  - Serum ferritin 1.5x ULN in NAFLD higher disease activity score
Radiographic findings

- **Ultrasound**
  - Hyperechoic texture or bright liver from diffuse fatty infiltration
  - Sensitivity 85% and specificity 94%
  - Decreased sensitivity with patients who are morbidly obese

- Decreased hepatic attenuation on **CT**
  - Sensitivity 33-50% is poor for hepatic steatosis, specificity 83-100%

- Increased fatty signal on **MRI**
  - Sensitivity 88%, Low specificity 63%
Diagnosis

The diagnosis of NAFLD requires all of the following:

- Demonstration of hepatic steatosis by imaging or biopsy
- Exclusion of significant alcohol consumption
- Exclusion of other causes of hepatic steatosis
- Absence of coexisting chronic liver disease
Rule out other disorders

- Significant alcohol use, starvation, medication use, pregnancy-related steatosis
- **Obtain the following tests in all patients:**
  - Anti-hepatitis C virus antibody
  - Hepatitis A IgG
  - Hepatitis B surface antigen, surface antibody, and core antibody
  - Plasma iron, ferritin, and total iron binding capacity
  - Serum gammaglobulin level, ANA, anti-smooth muscle antibody, and anti-liver/kidney microsomal antibody-1
- Consider based on history, symptoms, and family history:
  - Wilson disease, thyroid disease, celiac disease, alpha-1 antitrypsin deficiency, HELLP, Budd-Chiari syndrome
Radiographic examinations for diagnosis

- **First line is ultrasound imaging**
- Consider a radiographic diagnosis sufficient for NAFLD diagnosis if all of the following are met:
  - Radiographic imaging shows fatty infiltration
  - Other causes for the patient’s liver disease have been excluded
  - No signs of symptoms of cirrhosis
  - The patient is not high risk for fibrosis or cirrhosis
Vibration controlled transient elastography

- Used to **grade fibrosis** based on liver stiffness and grade hepatic steatosis
- **Advantages**: High accuracy, rapid results, reproducible, easy to learn
- **Disadvantages**: cost, limited recognition of intermediate stages of fibrosis, blind selection of measurement data, restricted value in obese patients or ascites
- Shear wave elastography (SWE) and strain elastography (shear waves propagate faster in fibrotic tissue)
- Velocity of shear wave m/s proportional to kilopascal (kPA)
Transient Elastography

Castera Transient Elastography Breakpoints

2.5  |  7.0  |  9.5  |  12.5  |  75kPa

Metavir  |  F0-F1  |  F2  |  F3  |  F4

Absent or mild fibrosis  |  Significant fibrosis  |  Severe fibrosis  |  Cirrhosis

Shear Wave Speed Measurement

Ultrasound Echo  |  Ultrasound Pulse

Pulse Echo Ultrasound
Role of liver biopsy

- **Gold standard for diagnosing NAFLD**, diagnosis and staging, prognosis, ≥11 portal tracts should be represented to get accurate assessment of fibrosis
- Limitations: high cost, potential complications, sampling/reading error
- **Unclear** diagnosis then liver biopsy is indicated
- **Obtain biopsy if the patient:**
  - Has peripheral stigmata of chronic liver disease (cirrhosis)
  - Has splenomegaly (cirrhosis)
  - Has cytopenias (cirrhosis)
  - Serum ferritin > 1.5 x ULN (suggestive of NASH and advanced fibrosis)
  - Is > 45 years of age with associated obesity or diabetes (increased risk for advanced fibrosis)
**Histologic findings**

- Histologic diagnosis of NASH requires:
  - Steatosis > 5%
  - Lobular inflammation
  - Hepatocellular ballooning

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**Nonalcoholic steatohepatitis liver biopsy**

Liver biopsy showing steatosis, hepatocyte balloon degeneration, mixed acute and chronic inflammation, and pericellular fibrosis.

*Courtesy of Marshall M. Kaplan, MD.*

**Mallory-Denk bodies in alcoholic hepatitis**

High power view of a liver biopsy in alcoholic hepatitis shows macrovesicular fat and Mallory-Denk bodies (arrows), which are eosinophilic accumulations of intracellular material. Similar changes can occur in nonalcoholic steatohepatitis.

*Courtesy of Robert Odze, MD.*
Screening

• AASLD does not recommend screening given the uncertainty about which diagnostic test to use
• High index of suspicion for NAFLD/NASH in type 2 diabetes
  • Identify those at low or high risk for advanced fibrosis
  • NAFLD fibrosis score (NFS)
  • Fibrosis-4 index (FIB-4)
  • Vibration controlled transient elastography (VCTE)
Management

• All patients
  • Abstain from alcohol
    • Avoid heavy alcohol use >14 drinks per week or > 4 drinks on a given day for men and > 7 drinks per week or > 3 drinks on a given day in women
  • Immunizations
    • Hepatitis A, Hepatitis B, pneumococcal, influenza
  • Modify risk factors for CV disease
    • Optimization of blood glucose control
    • Lipid-lowering therapy
    • Control hypertension
• Weight loss
  • For all patients with NAFLD with BMI > 25
  • For patients that do not meet weight loss goals in 6 months, discuss bariatric surgery
Treatment

**Drug therapy:**

- **Metformin** is not recommended
  - Improves serum aminotransferases, but does not improve liver histology
- **Pioglitazone** (moderate NAFLD benefit, weight gain)
  - Improves liver histology in patients with and without type 2 DM with biopsy-proven NASH
  - Do not use to treat NAFLD without biopsy-proven NASH
- **GLP1 receptor agonists** (mild NAFLD benefit, weight loss)
  - Not recommended at this time to specifically treat liver disease patients with NAFLD or NASH
  - Liraglutide improves biopsy evidence of NASH
Vitamin E

• Vitamin E 800 IU/day
  • Nondiabetic adults with biopsy-proven NASH, fibrosis stage > 2
  • Improves liver histology, not fibrosis
  • Not recommended to treat NASH in:
    • Diabetic patients
    • NAFLD without liver biopsy
    • NASH cirrhosis
    • Cryptogenic cirrhosis
    • Personal or family history of prostate cancer
Statin use in NAFLD and NASH

- Statins can be used to treat dyslipidemia
- Avoid statin use in patients with decompensated cirrhosis
- Patients are not at higher risk for serious liver injury from statins
Aspirin use in NAFLD

• Recent cohort study of over 360 patients with NAFLD, daily aspirin use was associated with lower baseline risk of NASH and fibrosis

• Promising results, need future trials to understand the hepatoprotective effects of aspirin
When to refer

- **Referral to hepatologist** for patients with NAFLD and any of the following features:
  - Aminotransferases that remain elevated despite loss of > 5% body fat (to evaluate for other etiologies of liver disease)
  - Clinical features of advanced liver disease (ascites, splenomegaly, jaundice)
  - Steatohepatitis on liver biopsy
  - Advanced fibrosis (fibrosis stage > 3F) on a noninvasive liver assessment

- **Liver transplant referral:**
  - Cirrhosis and have complications (ascites, variceal bleeding)
  - MELD score > 10
Current Research

- **FLINT STUDY** *(Obeticholic acid in NASH patients without cirrhosis)* – FXR agonist
- **GOLDEN-505 Study** *(Elafibranor in NASH Patients without cirrhosis)* – PPARα/δ Agonist regulate lipid metabolism in liver and glucose homeostasis
- **Study 1491** *(Selonsertib ± Simtuzumab in NASH patients without cirrhosis):* apoptosis signal-regulating kinase 1 inhibitor, ASK1 pathway activated in NASH, inhibition improves steatosis, inflammation, fibrosis
- **CENTAUR Study** *(Cenicrivoroc for treatment of NASH):* activation of CCR Type 2/5 Antagonist promotes recruitment and migration of monocytes to the liver
References