Nonalcoholic Fatty Liver Disease
Management & Treatment Options
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No Disclosures
Objectives

1. Definition and Epidemiology of NAFLD
2. Clinical Features and Diagnosis of NAFLD
3. Non-pharmacologic and Pharmacologic Management of NAFLD
Non-Alcoholic Fatty Liver Disease (NAFLD)

- Alcohol-like liver disease in individuals who do not consume **significant** amount of alcohol
  
  (♂ : >21 drinks/week) ~2 year time, ≥3 drinks/d
  
  (♀ : >14 drinks/week) ~2 year time, ≥2 drinks/d

*Neuschwander-Tetri BA, Caldwell SH. Hepatology 2003;37:1202-1219*
Definition of NALFD

- Evidence of hepatic steatosis (imaging/histology)
- Lack of secondary causes of hepatic fat accumulation:
  - significant alcohol consumption
  - long term use of a steatogenic medication
  - monogenic hereditary disorders
NAFLD is a spectrum of liver disease

NAFLD

NAFL
Steatosis*

NASH
Inflammation

Fibrosis

Cirrhosis

* ≥5% of hepatocytes

AASLD PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 1, 2018
Steatohepatitis (NASH)

- Histologic spectrum of liver damage
  - Steatosis +
  - Lobular inflammation +
  - Cellular injury (ballooning) predominantly centrilobular (zone 3) +
  - Mallory-Dink bodies

Neuschwander-Tetri BA, Caldwell SH. Hepatology 2003;37:1202-1219
Histologic Spectrum of NAFLD

A normal liver, B macrosvesicular steatosis, C steatohepatitis, D pericellular fibrosis, E cirrhosis.

Banini, B & Sanyal, A. Am J Gastroenterol 2017; 112:821–824
NAFLD is linked to obesity

How Common NAFLD in US?

- ~40% of US population (~100 million)
  - Simple steatosis (NAFL): 14-34%
  - NASH: 1.5-6%

- Most common cause of ↑ALT in general population
  - Obesity: 80%, Dyslipidemia: 44%, DM: 44%
Prevalence of NAFLD in High-Risk Populations

- **Type 2 Diabetes**
  - NAFL: 12%
  - NASH: 87%
  - Advanced fibrosis: 20%

- **Morbidly Obese Gastric Bypass Patients**
  - NAFL: 30-90%
  - NASH: 33-42%
  - Advanced fibrosis (F3-F4): 14%

Prognostic Implications of NASH + Fibrosis

- More consistent and rapid progression to cirrhosis than just steatosis

Steatosis (NAFL) → Cirrhosis
- > 10 years
  - 3%

NASH + Fibrosis → Cirrhosis
- 5-10 years
  - 30%

Mortality in Patients With NAFLD

- Patients with NAFLD (N = 420) matched by age and sex to general population in Minnesota, followed for 7.6 ± 4.0 yrs


Top 3 Causes of Death in NAFLD, %

- Malignancy: 28%
- Ischemic heart disease: 25%
- Liver disease: 13%

Survival at 10 Yrs
- General population: 87%
- Patients with NAFLD: 77%

Log-rank $P < .005$

Yrs

Survival (%)

0 20 40 60 80 100

General population
Patients with NAFLD

N = 420 (1980-2000)
53 Died (12.6%)

$P = .03$
Conditions Associated with NAFLD

- **Insulin resistance**
  - DM, HTN, dyslipidemia, obesity

- **Dietary abnormalities**
  - CHO excess, starvation, TPN

- **Drugs**
  - Tamoxifen, steroids, amiodarone, estrogen, CCB, zidovudine, valproate, tetracycline

- **Toxins**
  - Amanita phalloides, volatile hydrocarbons

- **Altered small bowel anatomy**
  - Short gut, SB diverticula

- **Metabolic diseases**
  - Wilson disease, hemochromatosis, Abetalipoproteinemia, Weber-Christian syndrome, hypothyroidism

- **Infections**
  - HCV-3, AIDS, bacterial overgrowth, bacillus cereus
Pathogenesis of NASH

Insulin Resistance

Steatosis + Metabolic Dysregulation

ER stress

Intestinal dysbiosis
Bacterial translocation
Portal endotoxin

Oxidative stress

Mitochondrial injury

Stellate cell activation

Fibrosis

Ferritin

↑FFA + ↑Insulin
↑Cytokines

Impairment in insulin-mediated suppression of lipolysis

↑Proinflammatory mediator

↑visceral adipose tissue

↑FFA flux to liver

Integrating factors:

- ↑visceral adipose tissue
- ↑FFA + ↑Insulin + ↑Cytokines

Consequences:

- Steatosis + Metabolic Dysregulation
- ER stress
- Oxidative stress
- Mitochondrial injury
- Stellate cell activation
- Fibrosis → Cirrhosis → HCC

Apoptosis
Cell death
Clinical Features & Diagnosis

NAFLD
Clinical Features of NAFLD

- **Symptoms**
  - Fatigue
  - Fullness in the RUQ

- **Signs**
  - *Abdominal obesity* (50%-90%)
  - Hepatomegaly
  - ↑Dorsocervical fat (28%)
  - *Acanthosis nigricans*
  - Features of metabolic syndrome (66%)
  - Stigmata of chronic liver disease
Clinical Conditions Commonly Encountered in Patients with NAFLD

- Cardiovascular morbidity and mortality 25-43%
- Malignancy 19-28%: Esophageal, adenoma, CRC, HCC
- Infection 5-11%
- Sleep abnormalities: ↑ risk of OSA, abnormal sleep pattern
- Psychiatric disorders: ↑ depression and anxiety disorders
- Chronic fatigue and pain syndrome: ↑ fatigue, malaise, lethargy, narcotic intake
- Coagulopathy: ↑ prothrombotic state (↑ TF, VII)
- Metabolic: Hypothyroidism, hypopituitarism, hypogonadism, PCOS, hyperuricemia, hyperferritinemia, vit D deficiency, osteoporosis
What to do when suspect NASH?

Other conditions that cause fatty liver

- Excessive alcohol consumption
- Malnutrition

Other liver diseases

- Hepatitis B or C (HBsAg, HBcAb, anti-HCV)
- α1-Antitrypsin deficiency (α1-antitrypsin level)
- Wilson disease (ceruloplasmin)
- Medications
- Parenteral nutrition
- Autoimmune (ANA, ASMA, LKM)
- Lysosomal acid lipase deficiency
- Hemochromatosis (ferritin/TIBC/iron)

Noninvasive Diagnosis of Fibrosis

Serologic Markers
- Simple
  - AST/ALT ratio
  - APRI
  - FIB-4 index
  - NAFLD fibrosis score
- Complex
  - NASH FibroSURE
  - ELF
  - HA

Imaging
- Elastography
  - VCTE
  - MR Elastography
  - ARFI

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ALT, alanine transaminase; AST, aspartate aminotransferase.

APRI, AST-to-platelet ratio index; ARFI, acoustic radiation force impulse; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 score; HA, hyaluronic acid; MR, magnetic resonance; VCTE, vibration-controlled transient elastography.
Fibrosis-4 (FIB-4) Calculator

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

\[
\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\sqrt[2]{\text{Platelet Count (10^9/L)} \times \text{ALT (U/L)}}
\]

Interpretation:

Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.
NAFLD Fibrosis Score

**NAFLD fibrosis score**

Online calculator


- **Age** (years)
- **BMI** (kg/m²)
- **IGF/diabetes**
- **AST**
- **ALT**
- **Platelets** (x10⁹/l)
- **Albumin** (g/l)

**Score**: 1.223

- **< -1.455**: predictor of absence of significant fibrosis (F0-F2 fibrosis)
- **≤ -1.455 to ≤ 0.675**: indeterminate score
- **> 0.675**: predictor of presence of significant fibrosis (F3-F4 fibrosis)

**AUROC of 0.85**
FibroScan-Hepatic Elastography

- Vibration-controlled transient elastography-liver shear wave speed and equivalent stiffness through pulse-echo ultrasonic acquisition
- Rapid, noninvasive, and can be performed easily at the bedside
- Can serve as a surrogate for degree of fibrosis
- Provide estimate of degree of steatosis (CAP)

Vuppalanchi and Sanyal, Clinical Gastro and Hep, Nov 2014
Imaging

Hyperechoic liver parenchyma
Vascular blurring

↓Hepatic attenuation
Liver is dark in comparison to spleen

Zakim and Boyer’s Hepatology, 6th edition 2012
Imaging
Don’t differentiate NAFL from NASH

Sensitivity 85%-95%
PV 62%

Sensitivity
PPV 76%

Zakim and Boyer’s Hepatology, 6th edition 2012
Potential Approach to Evaluating Fibrosis in Adult Patients With NAFLD

NAFLD fibrosis score + VCTE

NAFLD fibrosis score < -1.455 and LSM < 7.9 kPa
- No advanced fibrosis
  - Consider repeating every 2-3 yrs

Discordant results

Perform liver biopsy

NAFLD fibrosis score > 0.676 and LSM ≥ 9.6 kPa
- Advanced fibrosis
  - Screen for cirrhosis complications
  - EGD every 2-3 yrs
  - US every 6 mos

Predictors of Fibrosis on Liver Biopsy in Patients With NAFLD

- Age > 50 years
- Obesity
- Diabetes
- AST/ALT > 1

Non-pharmacologic & pharmacologic Management

NAFLD
Non-pharmacologic and Pharmacologic Management of NAFLD

• Lifestyle intervention

• Medication

• Surgery
Percentage of Weight Loss Associated With Histological Improvement in NAFLD

- Analysis of data from 4 randomized studies
  - Weight loss ≥ 10%
  - Weight loss ≥ 7%
  - Weight loss ≥ 5%
  - Weight loss ≥ 3%

- Fibrosis regression
  - (45% of pts)
- NASH resolution
  - (64% to 90% of pts)*
- Ballooning/inflammation
  - (41% to 100% of pts)*
- Steatosis
  - (35% to 100% of pts)*

*Depending on degree of weight loss.

Hypocaloric diet
Deficit ~500-1000cal/day

10% Reduction in Body Weight ~6 months

**PRE**
- Bridging fibrosis (stage 3)

**POST**
- Zone 3 perivenular perisinusoidal/pericellular fibrosis, focal (stage 1a)
Exercise and Weight Loss in Treatment of NAFLD/NASH

- Hypocaloric diet (-ve 500-1,000 kcal/d) and moderate-intensity exercise is likely to provide sustaining weight loss over time.

- Weight loss ≥3%-5% of body weight improve steatosis, 7%-10% is needed to improve the majority of the histopathological features of NASH, including fibrosis.

- Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown.
Rationale for the Therapeutics for NASH

Insulin sensitizers

Insulin Resistance

Impairment in insulin-mediated suppression of lipolysis

↑FFA + ↑Insulin
↑Cytokines

Steatosis + Metabolic Dysregulation

ER stress

Inflammatory signaling

Oxidative stress

Antioxidants

Mitochondrial injury

Apoptosis
Cell death

Stellate cell activation

Fibrosis
Pharmacologic Approach to the Management of NASH

- **Metformin**: is not recommended for treating NASH in adult patients.
- **Rosiglitazone**: is no longer available in most countries, and its prescribing remains severely restricted in the US because of controversial findings of an increase in coronary events.
- **UCDA**: is not recommended for the treatment of NAFLD or NASH.
- **Omega-3 fatty acids**: should not be used as a specific treatment of NAFLD or NASH, but may be considered to treat hypertriglyceridemia in patients with NAFLD.
What about Vitamin E?
PIVENS: Histologic Improvement at Wk 96 With Vitamin E vs Pioglitazone

Histologic improvement: ≥ 1-point improvement in hepatocellular ballooning score, no increase in fibrosis score, and either a decrease in NAS to ≤ 3 or a ≤ 2-point decrease in NAS plus ≥ 1-point decrease in either the lobular inflammation or steatosis score.

Vitamin E 800 IU/day: 43% improvement, NNT = 4.2

Placebo: 19% improvement

Pioglitazone 30 mg/day: 34% improvement, NNT = 6.9

P = .001

P = .04

PIVENS: No Significant Improvement in Fibrosis at Wk 96 for Vitamin E or Pioglitazone

- Vitamin E 800 IU/day: Δ grade -0.3
- Placebo: Δ grade -0.1
- Pioglitazone 30 mg/day: Δ grade -0.4

P = .19
P = .1

Pts With Change in Fibrosis Score (%)
Worsened
Improved

Vitamin E and Pioglitazone: AASLD guidelines 2018

- **Vitamin E**: 800U/day improves liver histology in non-diabetic adults with biopsy-proven NASH, however it is not recommended in NASH diabetic patients, NAFLD without liver biopsy, NASH cirrhosis or cryptogenic cirrhosis.

- **Pioglitazone**: improves liver histology in patients with and without T2DM with biopsy-proven NASH. Risks and benefits should be discussed with each patient before starting therapy.
FLINT: Obeticholic Acid in Noncirrhotic Patients With NASH

- Double-blind, placebo-controlled, randomized, multicenter phase IIb trial

Primary Endpoint: Wk 72 Improvement in NAS ≥ 2 Points With No Worsening of Fibrosis

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<thead>
<tr>
<th>Treatment</th>
<th>Wk 72 Improvement in NAS ≥ 2 Points With No Worsening of Fibrosis</th>
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<tbody>
<tr>
<td>Obeticholic acid 25 mg PO QD (n = 141)</td>
<td>45% (50/110)</td>
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<tr>
<td>Placebo (n = 142)</td>
<td>21% (23/109)</td>
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P = .0002

Wk 72 Improvement in Fibrosis

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<tr>
<td>Obeticholic acid 25 mg PO QD (n = 141)</td>
<td>35% (36/102)</td>
</tr>
<tr>
<td>Placebo (n = 142)</td>
<td>19% (19/98)</td>
</tr>
</tbody>
</table>

P = .004

Pts with NASH or borderline NASH confirmed by entry biopsy, NAS ≥ 4 (individual scores each ≥ 1), no cirrhosis (N = 283)

Changes in Enzymes and Body Weight

• **Obeticholic acid**: Not recommended till further safety and efficacy data become available in patients with NASH

• **Elafibranor**: (a dual PPARα/δ agonist) 120 mg/day, in phase 2 study showed improvement in NASH without fibrosis worsening over a 12-month study period. There was a mild, reversible increase in serum creatinine.

Ratziu V et al. Elafibranor, Gastroenterology 2016;150:1147-1159
Bariatric Surgery in NASH

- 12 studies between 2004 – 2007 evaluating liver histology following bariatric surgery
  - 431 patients with NASH
- All studies report improvements in
  - Steatosis
  - Ballooning
  - Inflammation
- Mixed results of improvement in fibrosis
- Resolution of NASH in 75-100% of patients

Pillai and Rinella, Clinics in Liver Disease 2009
Bariatric Surgery and NASH

- Foregut bariatric surgery is not contraindicated in eligible obese patients with NAFLD or NASH without cirrhosis but it is premature to consider it as an established option to treat NASH (AASLD guidelines 2018)
Summary

- NAFLD is the hepatic manifestation of the metabolic syndrome
- NAFLD is the most common cause of persistent abnormal liver transaminases in North America
- The prevalence varies among different risk groups (2.8-46%)
- NAFLD consist of a spectrum of NAFL, NASH, NASH+fibrosis, NASH+cirrhosis
- Oxidative stress is a key mechanism in the genesis of NASH
- Exercise & Weight loss affords the greatest impact on NAFLD
- Vitamin E, Pioglitazone, Liraglutide and Obeticholic acid have shown some promises in treatment of patients with NASH
- Surgical interventions are significantly more effective than lifestyle / pharmacological therapy in promoting weight loss, improvement in NASH in selected population
Thank you