Nonalcoholic Fatty Liver Disease

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No Disclosures

1. The speaker/planner Lauren Myers, MMSc, PA-C have no relevant financial relationships to disclose.

2. The speaker/planner Atif Zaman, MD MPH have no relevant financial relationships to disclose.
Objectives

- Prevalence of NAFLD
- Differentiate the nomenclature of NAFL vs NAFLD vs NASH
- Identifying NAFLD
- Discuss the use non-invasive tests/biomarkers vs. liver biopsy
- Discuss available treatments for NAFLD/NASH
Epidemic of Nonalcoholic Fatty Liver Disease

- NAFLD cases are forecasted +21% from 83.1 million (2015) to 100.9 million (2030)
- NASH cases are forecasted +63% from 16.52 million to 27 million (2030)
- Overall NAFLD prevalence among adult population (≥15 years) projected at 33.5% in 2030
Racial and Ethnic disparities in the prevalence of NAFLD

- Systematic review of literature and meta-analysis of 34 studies (n=368,569)
- Steatosis to NASH
- 1 in 6 occurrence of NAFLD in population studies, 1 in 2 with NAFLD in high risk studies (DM and obesity)
- *NAFLD and NASH were highest in Hispanics and lowest in Blacks when compared to Whites*
- Proportion of advanced fibrosis (F3/F4) did not differ significantly among groups
- Data was too limited to see racial differences in NAFLD-related prognosis

Rich et al, Abstract #57, AASLD 2017
Rich et al, Clin Gastro Hep, 2017
NAFLD

NAFL

(Nonalcoholic Fatty Liver)
≥5% Steatosis

NASH

(Nonalcoholic Steatohepatitis)
≥5% Steatosis + ballooning of hepatocytes + necroinflammation
NASH is a biopsy-proven diagnosis!

Fibrosis

Fibrosis with risk of progression to cirrhosis
NAFLD as a Complex Disease Trait: Genetic and Environmental Modifiers

Genes
- PNPLA3
- TM6SF2
- GCKR
- SOD2
- MBOAT7

Environment
- Sedentary lifestyle
- Snacking, fast food
- Saturated fats
- Trans fats
- Processed red meat

Diagram:
- Normal
- Steatosis
- NASH
- Cirrhosis
NAFLD Disease Progression

Histological Subtypes\cite{1,2}

- NAFLD
  - Isolated steatosis
  - Steatosis with mild inflammation
  - NASH
- Fibrosis
  - Cirrhosis

Change in Fibrosis\cite{3,4}

- Regression: 18\%-22\%
- Stable: 40\%-43\%
- Progression: 34\%-42\%

\*N = 108 pts with NAFL/NASH and median 6.6 yrs follow-up (data from serial biopsies).

Hepatic fibrosis drives mortality

Dulai et al, Hepatology 2017
Fibrosis progression risks

• Increasing age
• Obesity
• Type 2 Diabetes

Prevalence of Advanced Fibrosis Among Patients with Type 2 Diabetes in Primary Care

- Prospective study enrolled 100 consecutive diabetic patients

- Assessed feasibility in a primary care setting of screening diabetics for NAFLD and advanced fibrosis by using non-invasive MRI-PDFF and MRE

- 26% of those with NAFLD had elevated ALT

- 7.1% of patients with diabetes had advanced fibrosis (F3 & F4)

- 1/100 diagnosed with HCC

MRI-PDFF=magnetic resonance imaging-proton density fat fraction; MRE=magnetic resonance elastography
Doycheva et al. Aliment Pharmacol Ther 2016;43:83-95
How do we find those at risk?

25% to 35% of general population has NAFLD

Only a minority will ever progress beyond NAFL

An important paradox exists:
A substantial proportion of the population has NAFLD but only a minority progresses to advanced liver disease or morbidity/mortality

No current guidelines on the routine screening for NAFLD in primary care, diabetes or obesity clinics

However

Maintain a high index of suspicion for NAFLD in Type 2 Diabetics
Evaluation for NAFLD

Hepatic Steatosis on imaging with normal liver chemistries

• Assess for metabolic syndrome risks
• Assess for other causes of hepatic steatosis such as significant alcohol consumption or medications

Hepatic Steatosis on imaging with abnormal liver chemistries

• Assess for significant alcohol consumption
• Assess for other causes hepatic steatosis
• Rule out co-existing causes of liver disease (Wilson’s, hemochromatosis, AIH, DILI, A1AT, viral hepatitis)

Chalasani, et al. Hepatology 2018
Diagnosis of NAFLD

1. Evidence of hepatic steatosis by imaging
2. No significant alcohol consumption
3. No competing etiologies for hepatic steatosis
4. No coexisting causes of chronic liver disease

Chalasani, et al. Hepatology 2018
NAFLD Associations

- Obesity
- Hypertension
- Hyperlipidemia
- Type 2 DM
- Polycystic Ovarian Syndrome
- Obstructive Sleep Apnea
- Psoriasis
- Hypothyroid/Hypogonadism
- Colorectal Cancer
- Osteoporosis

Metabolic Syndrome

Chalasani, et al. Hepatology 2018
Excluding the “A” in NAFLD

Significant Alcohol Consumption:

> 21 standard alcoholic drinks a week for men

> 14 standard alcoholic drinks a week for women

(standard drink 14 grams alcohol)
AASLD Guidance on Non-invasive Tools

Noninvasive Tools

- **NAFLD Fibrosis Score (NFS)**: Based on 6 readily available variables and is calculated using a published formula.
- **FIB-4 Index**: Noninvasive scoring system based on several routine laboratory tests that help to estimate the amount of liver fibrosis.
- **ELF Test**: An algorithm combining specific serum markers. Approved for commercial use in Europe but not available for clinical use in the US.
- **VCTE (Fibroscan)**: Assesses liver stiffness via measurement of shear wave velocity. Approved by the FDA in 2013 for use in adults and children with liver disease.
- **MRE**: Stiffness measurement through modified phase-contrast pulse sequence using magnetic resonance technology.

AASLD Guidance Statements

- NFS or FIB-4 Index are clinically useful tools for identifying NAFLD patients with higher likelihood of having bridging fibrosis (F3) or cirrhosis (F4).
- Vibration controlled transient elastography (VCTE) or Magnetic resonance elastography (MRE) are clinically useful tools for identifying advanced fibrosis in patients with NAFLD.

**No current noninvasive marker to distinguish NAFL from NASH**

Chalasani, et al. Hepatology 2018
Non-invasive fibrosis scores in NAFLD change with age

<table>
<thead>
<tr>
<th>FIB-4 Score</th>
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<tbody>
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<td>Age</td>
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<td>Platelet count</td>
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<table>
<thead>
<tr>
<th>NAFLD Fibrosis Score (NFS)</th>
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<tbody>
<tr>
<td>Age</td>
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<td>Platelet count</td>
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<td>BMI</td>
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<td>Albumin</td>
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<td>Impaired fasting glucose/DM?</td>
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- Scores were previously developed and validated in those aged 35-65 to identify or exclude the presence of advanced fibrosis (F3/F4)
- HOWEVER, specificity falls in those aged ≥ 65 (FIB-4 35%, NFS 20%) increasing false positive rate with greater indeterminate-risk
- Noted significant age-related fall in serum ALT levels, independent of fibrosis

McPherson, et al Gastro 2017
Non-invasive fibrosis scores in NAFLD change with age

• New derived lower cutoffs for both FIB-4 and NFS for patients aged ≥65 years

• Increased specificity to 70% for identifying advanced fibrosis with both scores, decreased number of patients with indeterminate score

• Those aged ≤35 it is recommended for alternative fibrosis assessment

<table>
<thead>
<tr>
<th>Test</th>
<th>Lower Cutoff (excludes F3/F4)</th>
<th>Indeterminate score (further assessment)</th>
<th>Upper Cutoff (suggestive F3/F4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIB-4 (35-65)</td>
<td>&lt;1.3</td>
<td>1.3 - 2.67</td>
<td>&gt;2.67</td>
</tr>
<tr>
<td>NFS (35-65)</td>
<td>&lt;-1.455</td>
<td>-1.455 to 0.676</td>
<td>&gt;0.676</td>
</tr>
<tr>
<td>FIB-4 (≥65)</td>
<td>&lt;2.0</td>
<td>2.0 - 2.67</td>
<td>&gt;2.67</td>
</tr>
<tr>
<td>NFS (≥65)</td>
<td>&lt;0.12</td>
<td>0.12-0.676</td>
<td>&gt;0.676</td>
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McPherson, et al Gastro 2017
Consider liver biopsy in NAFLD patients with an increased risk of advanced fibrosis

Consider liver biopsy if there are competing etiologies of hepatic steatosis or cannot exclude additional chronic liver disease
Treatments

Weight reduction and targeting metabolic syndrome risk factors

<table>
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<tr>
<td>≥10% of body weight loss associated with improvement in NASH (including portal inflammation and fibrosis)</td>
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<tr>
<td>≥5% of body weight loss stabilized or improved fibrosis in 94% of cases</td>
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<tr>
<td>3-5% body weight loss improves hepatic steatosis</td>
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Exercise alone may prevent or reduce hepatic steatosis but currently has unknown impacts on liver histology

Treatments

• Bariatric surgery may be considered but is not yet recommended to specifically treat NASH
• Statin therapy may be used in NAFL/NASH but should not be used in decompensated cirrhotics
• Pharmacological treatments should be reserved for those with biopsy-proven NASH with fibrosis
• Vitamin E and pioglitazone are not recommended in the absence of biopsy-proven NASH

Chalasani, et al. Hepatology 2018
Targeting Pathophysiological Processes of NAFLD

Normal Liver
- Targets related to insulin resistance and/or lipid metabolism

NAFL
- Targets related to lipotoxicity and oxidative stress

NASH
- Targets related to inflammation and immune activation

Cirrhosis
- Targets related to cell death (apoptosis and necrosis)
- Targets related to fibrogenesis and collagen turnover

**PPARγ:** Pioglitazone, Liraglutide, Semaglutide
**GLP-1:** Liraglutide, Semaglutide
**ACC:** GS-0976, PF-05221304
**SCD1:** Aramchol
**SGLT1/2:** BMS-986036
**FGF21:** MGL-3196
**THR-β:** Vitamin E

**PPARα/δ:** Elafibranor, IVA337
**PPARα/δ/γ:** Saroglitazar, MSDC-0602K, OCA, GS-9674, LCN-452, LMB-763
**mTOT:** FXR:
**FXR:** TGR5:
**TGR5:** TGR5:
**ASBT:** Volixibat
**FGF19:** NGM282

**CCR2/5:** Cenicriviroc
**AOC3:** BI 1467335
**TLR4:** JKB-121

**ASK1:** Selonsertib
**Caspases:** Emricasan
**LOXL2:** Simtuzumab
**Galectin:** GR-MD-02

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