NAFLD in the Primary Care and Diabetes Settings

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Disclosures:

• None
NAFLD: What is It?

• Non-alcoholic fatty liver disease

  • Presence of fatty infiltrates in the liver (>5% steatosis)
    • Imaging or biopsy

  • Exclude other causes of hepatic fat accumulation*
<table>
<thead>
<tr>
<th>TABLE 1. Common Causes of Secondary HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovesicular steatosis</td>
</tr>
<tr>
<td>- Excessive alcohol consumption</td>
</tr>
<tr>
<td>- Hepatitis C (genotype 3)</td>
</tr>
<tr>
<td>- WD</td>
</tr>
<tr>
<td>- Lipodystrophy</td>
</tr>
<tr>
<td>- Starvation</td>
</tr>
<tr>
<td>- Parenteral nutrition</td>
</tr>
<tr>
<td>- Abetalipoproteinemia</td>
</tr>
<tr>
<td>- Medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)</td>
</tr>
<tr>
<td>Microvesicular steatosis</td>
</tr>
<tr>
<td>- Reye’s syndrome</td>
</tr>
<tr>
<td>- Medications (valproate, antiretroviral medicines)</td>
</tr>
<tr>
<td>- Acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>- HELLP syndrome</td>
</tr>
<tr>
<td>- Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman’s disease)</td>
</tr>
</tbody>
</table>
More Definitions

• **NAFLD:**
  • Includes entire spectrum of fatty liver disease

• **NAFL vs NASH:**
  • **NAFL:**
    • “Fatty liver”
    • No evidence of hepatocellular injury (hepatocyte ballooning, fibrosis)
  • **NASH:**
    • Non-alcoholic steatohepatitis
    • Presence of inflammation and hepatocyte injury (ballooning) +/-fibrosis

**NAFL**

Nonalcoholic fatty liver (NAFL) (~70%-75% of individuals with NAFLD)

- **A** Steatosis alone (isolated hepatic steatosis)
- **B** Steatosis with mild lobular inflammation

**NASH**

Nonalcoholic steatohepatitis (NASH) (~25%-30% of individuals with NAFLD)

- **C** Steatosis with lobular inflammation and cellular ballooning (inset)
- **D** Fibrosis

**Disease progression**

Risk factors for disease progression:
- Diabetes
- Insulin resistance
- Hypertension
- Weight gain >5 kg
- Increasing ALT, AST; AST:ALT >1
NAFL NASH

Nonalcoholic fatty liver disease (NAFLD)

Nonalcoholic steatohepatitis (NASH)
(-25% to 30% of individuals with NAFLD)

A. Steatosis alone (isolated fat droplets)

B. Steatosis with mild lobular inflammation

C. Steatosis with lobular inflammation and cellular ballooning (inset)

D. Fibrosis

Disease progression

Risk factors for disease progression:
- Diabetes
- Insulin resistance
- Hypertension
- Weight gain >5 kg
- Increasing ALT, AST; AST:ALT >1
Stages of Fibrosis

- Metavir
  - F0-F1: Absent or mild fibrosis
  - F2: Significant fibrosis
  - F3: Severe fibrosis
  - F4: Cirrhosis
NAFLD: Beyond definitions

“NAFLD is a disease of over-nutrition.”

• NASH is strongly associated w/ obesity & the MetS.
  • >80% of NASH patients are overweight/obese
  • 72% of NASH patients have dyslipidemia
  • 44% of NASH patients have type-2 diabetes mellitus.

• NAFLD → independent predictor of insulin resistance in non-obese patients.

“Hepatic correlate of the metabolic syndrome”

Metabolic Syndrome

Table 1
Diagnosing criteria for metabolic syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Categorical Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>Ethnicity-specific definitions</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>$\geq 100$ mg/dL and/or drug treatment of elevated glucose</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>$\geq 150$ mg/dL and/or drug treatment for elevated triglycerides</td>
</tr>
<tr>
<td>Reduced HDL cholesterol</td>
<td>$&lt;40$ mg/dL in men; $&lt;50$ mg/dL in women</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Systolic $\geq 130$ and/or diastolic $\geq 85$ mm Hg</td>
</tr>
</tbody>
</table>

Definition of MS: meeting at least 3 of the 5 criteria. Ethnicity specific definitions of elevated waist circumference: (1) Caucasian: 102 cm or greater in men and 88 cm or greater in women (2) Asian: 90 cm or greater in men and 80 cm or greater in women (3) Middle East, Mediterranean, African: 94 cm or greater in men and 80 cm or greater in women (4) Ethnic Central and South American: 90 cm or greater in men and 80 cm or greater in women.

Pathophysiology of NAFLD

Starts with precursors to visceral fat accumulation

Two-hit hypothesis
1. Steatosis = “excess fat in liver”
2. Lipotoxicity/oxidative stress = “triggers of liver inflammation”

Pathophysiology of NAFLD

• Starts with precursors to visceral fat accumulation

• Two-hit hypothesis
  1. Steatosis = “excess fat in liver”
  2. Lipotoxicity/oxidative stress = “triggers of liver inflammation”

What about DM and NAFLD?

• Common mechanisms for NAFLD, DM and MetS
  • Visceral obesity → Common denominator

• Type-II diabetes prevalence in NAFLD:*
  • NAFL: 22.5% have DM-II
  • NASH: 43.6% have DM-II

  ~45% or more of DM-II have NAFLD

• Improvement in NAFLD is associated with reduced incidence in DM-II

IR and hepatic fat have a linear relationship

Insulin Resistance

NAFLD

Fat Uptake (Liver)

Lipolysis (Peripheral)
Epidemiology of NAFLD in North America

## Epidemiology of NAFLD in North America

<table>
<thead>
<tr>
<th>Region</th>
<th>N</th>
<th>Prevalence (%)</th>
<th>95% Cl (%)</th>
<th>$I^2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>2</td>
<td>13.48</td>
<td>(5.69-28.69)</td>
<td>84.37</td>
</tr>
<tr>
<td>Asia</td>
<td>14</td>
<td>27.37</td>
<td>(23.29-31.88)</td>
<td>99.17</td>
</tr>
<tr>
<td>Europe</td>
<td>11</td>
<td>23.71</td>
<td>(16.12-33.45)</td>
<td>98.78</td>
</tr>
<tr>
<td>Middle East</td>
<td>3</td>
<td>31.79</td>
<td>(13.48-58.23)</td>
<td>99.14</td>
</tr>
<tr>
<td>North America</td>
<td>13</td>
<td>24.13</td>
<td>(19.73-29.15)</td>
<td>99.19</td>
</tr>
<tr>
<td>South America</td>
<td>2</td>
<td>30.45</td>
<td>(22.74-39.44)</td>
<td>69.10</td>
</tr>
<tr>
<td>Overall</td>
<td>45</td>
<td>25.24</td>
<td>(22.1-28.65)</td>
<td>99.07</td>
</tr>
</tbody>
</table>

Study sources in **Supporting Table A** (imaging as a diagnosis technique for all studies included).
NAFLD Prevalence

• 24-30% of the US population

45-76% of diabetic and obese patients

• >90% of patients undergoing bariatric surgery

Prevalance of NASH (US)

- NASH estimates:
  - 5-6% of the US population
  - NASH-related cirrhosis → 2nd indication for liver transplants in the US.

NASH Cirrhosis: 1 in 50 US adults
HCC: 1-2% per year

NAFLD in AI/ANs:

NAFLD in AI/ANs:

Figure 3. Percent distribution of body weight status for adults aged 18 years and over, by race and ethnicity: United States, 2004–2008

NOTE: Estimates are age adjusted using the projected 2000 U.S. population as the standard population. Estimates are based on household interviews of a sample of the civilian, noninstitutionalized population.

Figure 4. Percentage of adults aged 18 years and over who have ever been diagnosed with diabetes, and percentage of adults aged 18 years and over who have ever been diagnosed with heart disease, by race and ethnicity: United States, 2004–2008

NOTE: Estimates are age adjusted using the projected 2000 U.S. population as the standard population. Estimates are based on household interviews of a sample of the civilian, noninstitutionalized population.
NAFLD in AI/ANs:

- **PNPLA3**
  - Gene involved in regulation of TRG and retinol metabolism

- **I148M polymorphism**
  - Most prevalent in Hispanic populations.
  - More prevalent in Asian and AI/AN pops**
  - Strong association w/ hepatic steatosis, steatohepatitis, fibrosis, and cancer.
  - Promotes liver damage caused by alcohol-induced fatty liver disease and chronic hepatitis C.
NAFLD: Implications

<table>
<thead>
<tr>
<th>Population</th>
<th>Outcome</th>
<th>Incidence Rate Per 1,000 Person-Years*</th>
<th>Number of Studies</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>CVD-specific mortality</td>
<td>4.79</td>
<td>6</td>
<td>(3.43-6.7)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>HCC</td>
<td>0.44</td>
<td>3</td>
<td>(0.29-0.66)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Liver-specific mortality</td>
<td>0.77</td>
<td>7</td>
<td>(0.33-1.77)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Overall mortality</td>
<td>15.44</td>
<td>7</td>
<td>(11.73-20.34)</td>
</tr>
<tr>
<td>NASH</td>
<td>Advanced fibrosis</td>
<td>67.95</td>
<td>3</td>
<td>(46.84-98.56)</td>
</tr>
<tr>
<td>NASH</td>
<td>HCC</td>
<td>5.29</td>
<td>1</td>
<td>(0.75-37.56)</td>
</tr>
<tr>
<td>NASH</td>
<td>Liver-specific mortality</td>
<td>11.77</td>
<td>3</td>
<td>(7.1-19.53)</td>
</tr>
<tr>
<td>NASH</td>
<td>Overall mortality</td>
<td>25.56</td>
<td>2</td>
<td>(6.29-103.8)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Liver-specific mortality</td>
<td>1.94</td>
<td>5</td>
<td>(1.28-2.92)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Overall mortality</td>
<td>1.05</td>
<td>5</td>
<td>(0.7-1.56)</td>
</tr>
<tr>
<td>NASH</td>
<td>Liver-specific mortality</td>
<td>64.6</td>
<td>3</td>
<td>(35.43-117.8)</td>
</tr>
<tr>
<td>NASH</td>
<td>Overall mortality</td>
<td>2.56</td>
<td>2</td>
<td>(0.63-10.39)</td>
</tr>
</tbody>
</table>

- **NAFL** → Typical morbidity & mortality (CVD, cancer)
- **NASH** → liver-related M&M, cirrhosis, HCC + CVD

NAFL: Nonalcoholic fatty liver disease (NAFLD)
- Nonalcoholic fatty liver (NAFL) (~70%-75% of individuals with NAFLD)
  - Steatosis alone (isolated hepatic steatosis) (A)
  - Steatosis with mild lobular inflammation (B)

NASH: Nonalcoholic steatohepatitis (NASH) (~25%-30% of individuals with NAFLD)
- Steatosis with lobular inflammation and cellular ballooning (inset) (C)

Less likely to Progress to Cirrhosis

Can Progress to Cirrhosis

Disease progression:
- Risk factors for disease progression:
  - Diabetes
  - Insulin resistance
  - Hypertension
  - Weight gain >5 kg
  - Increasing ALT, AST; AST:ALT >1

NASH fibrosis: Progresses one stage every decade
NAFLD and Children

• NASH in children is strongly associated with obesity.

• Childhood obesity → increased risk of HCC in adulthood (Denmark)

Diagnosing NAFLD:

• The goal is to not only identify NAFLD but also identify who may be at high risk for complications related to NAFLD
Typical situation:

• Transaminases are drawn as part of an “LFT Panel”
• AST, ALT are mildly elevated
• RUQ Ultrasound is done → steatosis.
• Other causes to elevated AST/ALT are ruled out
  • Viral hepatitis
  • Autoimmune
  • Alcohol
  • Etc

Now what?
Think NAFLD in everybody

• 25% of adults in the US have it

• Think NASH if there are risk factors for it
Think NAFLD in persons with DM-II

- Persons with NAFLD:
  - 45-50% of persons with DM-II had NAFLD
  - NAFLD increases the incident risk of developing DM

### Table 2
Baseline prevalence and 3-year incidence of diabetes mellitus in subjects with and without non-alcoholic fatty liver disease (NAFLD)

<table>
<thead>
<tr>
<th>Subject description</th>
<th>Number of prevalent cases</th>
<th>Number disease-free</th>
<th>Prevalence per 1000 population (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD (n = 926)</td>
<td>308</td>
<td>618</td>
<td>332.6 (302.3–364.0)</td>
<td>2.15 (1.80–2.57)</td>
</tr>
<tr>
<td>Non NAFLD (n = 1954)</td>
<td>368</td>
<td>1586</td>
<td>188.3 (171.2–206.4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Number of incident cases</th>
<th>Number disease-free</th>
<th>Person-time of follow-up (years)</th>
<th>Incidence per 1000 PY of follow-up (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD (n = 543)</td>
<td>106</td>
<td>437</td>
<td>1666.4</td>
<td>63.6 (52.1–76.9)</td>
<td>1.92 (1.49–2.47)</td>
</tr>
<tr>
<td>Non-NAFLD (n = 1314)</td>
<td>138</td>
<td>1176</td>
<td>4060.6</td>
<td>34.0 (28.6–40.2)</td>
<td></td>
</tr>
<tr>
<td>NAFLD† (n = 528)</td>
<td>104</td>
<td>424</td>
<td>1620.2</td>
<td>64.2 (52.5–77.8)</td>
<td>1.95 (1.51–2.52)</td>
</tr>
<tr>
<td>Non-NAFLD† (n = 1314)</td>
<td>138</td>
<td>1176</td>
<td>4060.6</td>
<td>34.0 (28.6–40.2)</td>
<td></td>
</tr>
</tbody>
</table>

†After exclusion of subjects who started alcohol consumption above the safe-limit.
CI, confidence interval; HR, hazards ratio; OR, odds ratio; PY, person years.

But also think about NASH:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted (Univariate)</th>
<th></th>
<th></th>
<th></th>
<th>Adjusted (Multivariate)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P Value</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.07</td>
<td>1.05, 1.09</td>
<td>&lt;0.0001</td>
<td>1.04</td>
<td>1.01, 1.07</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (M)</td>
<td>0.42</td>
<td>0.28, 0.64</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>0.71</td>
<td>0.34, 1.40</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (continuous)</td>
<td>1.10</td>
<td>1.06, 1.14</td>
<td>&lt;0.0001</td>
<td>1.10</td>
<td>1.04, 1.16</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>2.69</td>
<td>1.74, 4.25</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (categories)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal (reference)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overweight</td>
<td>2.35</td>
<td>0.78, 10.2</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>obese</td>
<td>5.70</td>
<td>1.96, 23.95</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference (continuous)</td>
<td>1.01</td>
<td>0.99, 1.02</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central obesity</td>
<td>1.22</td>
<td>0.80, 1.87</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.21</td>
<td>0.02, 0.20</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>6.89</td>
<td>4.00, 12.31</td>
<td>&lt;0.0001</td>
<td>2.70</td>
<td>1.33, 5.62</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>0.15</td>
<td>0.09, 0.25</td>
<td>&lt;0.0001</td>
<td>0.51</td>
<td>0.25, 1.05</td>
<td>0.073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>1.68</td>
<td>1.21, 2.40</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (×10^9/l)</td>
<td>0.98</td>
<td>0.98, 0.99</td>
<td>&lt;0.0001</td>
<td>0.987</td>
<td>0.98, 0.99</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/platelet</td>
<td>2.23</td>
<td>1.72, 3.00</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5.86</td>
<td>3.79, 9.19</td>
<td>&lt;0.0001</td>
<td>3.12</td>
<td>1.77, 5.51</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.19</td>
<td>2.71, 6.50</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0.65</td>
<td>0.43, 0.99</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>2.10</td>
<td>1.35, 3.25</td>
<td>0.0003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.61</td>
<td>1.70, 4.04</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR (continuous)</td>
<td>1.11</td>
<td>1.05, 1.18</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy length (mm)</td>
<td>1.003</td>
<td>0.97, 1.04</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal areas (mm)</td>
<td>1.03</td>
<td>0.92, 1.14</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Think NASH in persons with MetS

- Consists of cluster of inter-related factors
  - Truncal obesity
  - Dysglycemia
  - Dyslipidemia
  - Hypertension

- NHANES: MetS prevalence of 34.7% in 2011
  - Women > Men
  - Hispanics have highest prevalence in N America

Again...think NAFLD in everybody

- Four phenotypes of patients with NAFLD have been defined:
  1. Obese
  2. Type 2 diabetes
  3. Metabolic syndrome
  4. Lean patients (smokers, older age, Hispanic & Asian, ? AI/AN)

- *Excess caloric consumption* leading to obesity and related comorbidities is a leading risk factor for NAFLD.
  - Even a modest 3–5 kg weight gain may predicts the development of NAFLD, regardless of baseline BMI.

Pearl:

• “Overweight or obese persons with the metabolic syndrome, elevated serum aminotransferase levels, and a negative noninvasive workup for other causes of liver disease are likely to have NASH.”

*Assumes LFTS and/or ultrasound/CT showing steatosis

Next steps:

• Patient felt to be at risk for NAFLD:

  ➢ Assess for confounding risk factors for disease progression

  ➢ Assess for NASH-related liver damage

  ➢ Grade the severity of this injury & stage fibrosis

  ➢ Formulate a disease management plan.
Evaluation of chronic liver injury according to health care level

Primary health care

- Physical examination
- Liver function tests
- APRI or other simple tests

Secondary health care

- Ultrasound
- Fibroscan®
- Serum markers & algorithms

Tertiary health care

- Liver biopsy
- Fibroscan®
- ARFI*
- MR elastography*
- HVPG

* Promising but currently under investigation

ARFI: Acoustic Radiation Force Impulse Imaging
HVPG: Hepatic Venous Pressure Gradient
Further assessment after NAFLD diagnosis

• Patient history and exam
  • Associated conditions (Hypopituitarism*, etc)
  • Confounding medications
    • Corticosteroids, tamoxifen, amiodarone, methotrexate
  • Alcohol use
    • AUDIT > CAGE
  • Exam:
    • Truncal obesity, acanthosis nigricans, etc.
    • Stigmata of portal hypertension
• DM-II, MetS

Order Serum ("wet") Biomarkers

- Albumin
- Prothrombin time
- Platelets
- Transaminases:
  - NAFLD is an ALT driven process
  - **AST:ALT ratio is typically <1 in absence of fibrosis**
  - Ratio tends to increase to >1 as the degree of fibrosis progresses
- Ferritin
  - Independent predictor of advanced fibrosis

Biomarkers for NAFLD

<table>
<thead>
<tr>
<th>Score</th>
<th>Factors Included in Scoring</th>
<th>Cutoff Values for Advanced Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>Age, Hyperglycemia, BMI</td>
<td>-1.455 = F0-F2</td>
</tr>
<tr>
<td>Fibrosis Score</td>
<td>Platelet count, Albumin, AST/ALT ratio</td>
<td>-1.455 to 0.675 = indeterminate</td>
</tr>
<tr>
<td>FIB-4</td>
<td>Age, AST</td>
<td>&lt; 1.30: F0-F1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 2.67: ≥ F3</td>
</tr>
<tr>
<td>BARD</td>
<td>BMI, AST/ALT ratio</td>
<td>&gt; 2: advanced fibrosis</td>
</tr>
<tr>
<td>BAAT</td>
<td>BMI, Age</td>
<td>&gt; 2.86: ≥ F3</td>
</tr>
</tbody>
</table>
AST: Platelet Ratio (APRI score)

<table>
<thead>
<tr>
<th>Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>ppv</th>
<th>npv</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>0.98</td>
<td>75%</td>
<td>86%</td>
<td>54%</td>
</tr>
<tr>
<td>NFS</td>
<td>-1.31</td>
<td>76%</td>
<td>69%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Table 1. Sensitivity, specificity, positive and negative predictive value of APRI v. NFS

Fig. 3b. APRI and association with grading of NAFLD.
Who should be referred to a biopsy or VCTE (Fibroscan®)?

<table>
<thead>
<tr>
<th>Defer</th>
<th>Consider Fibroscan if available</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≤ 2 features of the MetS</td>
<td></td>
</tr>
<tr>
<td>• Absence of DM-II and normal LFTs</td>
<td></td>
</tr>
<tr>
<td>• Motivated patient (lifestyle changes, etc)</td>
<td></td>
</tr>
<tr>
<td>• NFS ≤ -1.455</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Refer</th>
<th>Recommend Fibroscan if available</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Features of MetS and obesity</td>
<td></td>
</tr>
<tr>
<td>• DM-II and elevated LFTs</td>
<td></td>
</tr>
<tr>
<td>• Patient who is not motivated to make lifestyle changes</td>
<td></td>
</tr>
<tr>
<td>• NFS &gt; -1.455</td>
<td></td>
</tr>
</tbody>
</table>
No algorithm for guiding NASH referrals.

- Need to consider risk factors for worse outcomes
  - MetS
  - Obesity
  - DM-II (especially with other risks)
  - Smoking
  - Hypertension
  - Age
  - Increasing AST over time, AST:ALT >1
  - NFS, FIB-4 scores
But here is an algorithm for consideration...

![Algorithm Diagram]

...And another one...
...And one for the diabetes practitioner (combine with first)
For indeterminate or high-risk patients for advanced fibrosis

- Three options:
  1. Liver biopsy:
     - Remains the gold standard!
     - But some considerations
       - Severe complication rate of 1.1% and mortality rate of 0.3%.
       - Sampling error as high 25-30%.
  2. Transient Elastography (VCTE)
     - Noninvasive, quick, highly accurate, low cost
  3. Magnetic Elastography (ME)

Fibroscan® device

- Electronic platform
  - Ultrasonic signals acquisition
  - Numerical signal processing
- Integrated computer
  - Stiffness measurement
  - Examinations database
- Dedicated probes with unique technology

Fibroscan® (Echosens, Paris, France)
ROC curves for FibroScan, FibroTest, & APRI for cirrhosis (F0 – F3 vs F4)

VCTE:

CAP (262) and kPa (6.5-7 range)

Median CAP Score for Steatosis

<table>
<thead>
<tr>
<th>Grade 0  (n = 17)</th>
<th>Grade 1  (n = 139)</th>
<th>Grade 2  (n = 107)</th>
<th>Grade 3  (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>274</td>
<td>306</td>
<td>340</td>
<td>340</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>F0 to F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>2 to 7 kPa</td>
<td>8 to 9 kPa</td>
<td>8 to 11 kPa</td>
<td>18 kPa or higher</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>2 to 7 kPa</td>
<td>8 to 9 kPa</td>
<td>9 to 14 kPa</td>
<td>14 kPa or higher</td>
</tr>
<tr>
<td>HIV/HCV Coinfection</td>
<td>2 to 7 kPa</td>
<td>7 to 11 kPa</td>
<td>11 to 14 kPa</td>
<td>14 kPa or higher</td>
</tr>
<tr>
<td>Cholestatic Disease</td>
<td>2 to 7 kPa</td>
<td>7 to 9 kPa</td>
<td>9 to 17 kPa</td>
<td>17 kPa or higher</td>
</tr>
<tr>
<td>Non-alcoholic Fatty Liver Disease (NAFLD or NASH)</td>
<td>2 to 7 kPa</td>
<td>7.5 to 10 kPa</td>
<td>10 to 14 kPa</td>
<td>14 kPa or higher</td>
</tr>
<tr>
<td>Alcohol Related Disease</td>
<td>2 to 7 kPa</td>
<td>7 to 11 kPa</td>
<td>11 to 19 kPa</td>
<td>19 kPa or higher</td>
</tr>
</tbody>
</table>

SOURCE: https://www.mskcc.org/
VCTE and Obesity

- New XL probe has overcome many of the limitations for patients who are overweight/obese.

**Table 5. Optimal Liver Stiffness Cutoffs Using the M and XL Probes According to Liver Disease Etiology**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Cutoff (kPa)</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2-4 vs. F0-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>&gt;7.8</td>
<td>82 (72-90)</td>
<td>78 (67-87)</td>
<td>80 (70-88)</td>
<td>80 (70-89)</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>&gt;8.5</td>
<td>96 (85-99)</td>
<td>72 (51-88)</td>
<td>86 (74-94)</td>
<td>90 (88-99)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>&gt;7.8</td>
<td>84 (67-95)</td>
<td>79 (64-90)</td>
<td>75 (58-88)</td>
<td>87 (73-96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F4 vs. F0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>&gt;21.5</td>
<td>84 (60-97)</td>
<td>91 (85-95)</td>
<td>55 (36-74)</td>
<td>98 (94-100)</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>&gt;14.0</td>
<td>92 (62-100)</td>
<td>83 (71-92)</td>
<td>52 (30-74)</td>
<td>98 (89-100)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>&gt;22.3</td>
<td>80 (28-99)</td>
<td>91 (82-97)</td>
<td>40 (12-74)</td>
<td>98 (92-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;6.4</td>
<td>83 (64-89)</td>
<td>68 (59-77)</td>
<td>72 (63-79)</td>
<td>80 (71-88)</td>
</tr>
<tr>
<td></td>
<td>&gt;8.8</td>
<td>79 (66-88)</td>
<td>77 (60-90)</td>
<td>85 (72-93)</td>
<td>69 (52-83)</td>
</tr>
</tbody>
</table>

*Subgroup analyses restricted to patients with >10 valid measurements with the respective probes and interpretable liver biopsies. See Supplementary Table 1 for the numbers of patients within each analysis. Optimal liver stiffness cutoffs defined by the maximal sum of sensitivity and specificity.*

MR Elastography: Future in Dx & Prognostication

Use for patients at high risk in absence of cirrhosis by PE, Fibroscan, & biomarkers.

- NFS > 0.675
- VCTE > 7-8 kPa
- If MRE > 3kPa → biopsy

Who should be referred for liver biopsy?

It’s easier to say who may be reasonable deferred with close monitoring of LFTs over time.

<table>
<thead>
<tr>
<th>Defer Liver Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≤ 2 features of the MetS</td>
</tr>
<tr>
<td>• Absence of DM-II and normal LFTs</td>
</tr>
<tr>
<td>• Motivated patient (lifestyle changes, etc)</td>
</tr>
<tr>
<td>• NFS ≤ -1.455</td>
</tr>
<tr>
<td>• VCTE &lt; 6.5 kPa</td>
</tr>
</tbody>
</table>
Who should be referred for liver biopsy?

• NFS > -1.455 AND
• VCTE > 6.5-8.0 kPa  +/-  MRE > 3 kPa
• Risk factors for NASH with advanced fibrosis
  • DM-II
  • MetS
  • Age & smoking status
• Findings suggesting cirrhosis
  • Thrombocytopenia, AST > ALT, low albumin

When in doubt, refer to a GI or hepatologist
Treating NAFLD
Management of NAFLD

• Treatment should address
  • Liver disease*
  • Underlying metabolic comorbidities
    • Obesity
    • Hyperlipidemia
    • Insulin resistance
    • Type 2 diabetes mellitus
  • Immunization

<table>
<thead>
<tr>
<th>NAFLD Subtype</th>
<th>Treatment Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFL</td>
<td>Address metabolic comorbidities</td>
</tr>
<tr>
<td>NASH w/o advanced fibrosis</td>
<td>Address metabolic comorbidities</td>
</tr>
<tr>
<td>NASH with advanced fibrosis</td>
<td>Address metabolic comorbidities +/- Pharmacotherapy</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>List for Liver Transplant</td>
</tr>
</tbody>
</table>
Lifestyle Interventions

- **Weight loss** ➔ Cornerstone of treatment of NAFLD.
- Entails:
  - Exclusion of processed food and *fructose*
  - Calorie restrictions to achieve 5%-10% weight loss
    - Improves clinical biochemistry, histologic steatohepatitis, and fibrosis.
- Consider: Mediterranean diet
  - Easier to follow
  - Reduces steatosis & improve insulin sensitivity/glucose tolerance*

*B* independent of weight loss.

Weight loss

- Weekly-biweekly group meetings.
- Calorie goal based on their starting weight)
- Daily fat gram goal designed to produce a 25% fat diet (28 –33 g for 1000-1200 kcal diet).
- Meal plans provided x 8 weeks (including commercial plans)
- Focus on moderate intensity activities (walking).
- Given pedometers and encouraged to self-monitor their eating and exercise
- Self-monitoring records were reviewed weekly by the therapist

**Weight Loss > 7% may be the best therapy**

**Table 4. Baseline Characteristics and Change (mean [SD]) in Histological Parameters According to Study Goal Weight Reduction (≥7%)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weight Loss &lt; 7% (n = 17)</th>
<th>Weight Loss ≥ 7% (n = 11)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI category, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overweight (25-29.9 kg/m²)</td>
<td>5 (26.3)</td>
<td>3 (27.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>obesity class I (30-34.9 kg/m²)</td>
<td>5 (26.3)</td>
<td>6 (54.5)</td>
<td></td>
</tr>
<tr>
<td>obesity class II (35-40 kg/m²)</td>
<td>9 (47.4)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>10 (52.6)</td>
<td>4 (36.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>On metformin, N (%)</td>
<td>7 (36.8)</td>
<td>2 (18.2)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Histological parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat (0-3)</td>
<td>-0.41 (0.80)</td>
<td>-1.36 (0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobular inflammation (0-3)</td>
<td>-0.24 (0.75)</td>
<td>-0.82 (0.75)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ballooning injury (0-2)</td>
<td>-0.53 (0.80)</td>
<td>-1.27 (0.47)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fibrosis (0-4)</td>
<td>+ 0.06 (0.83)</td>
<td>-0.45 (0.93)</td>
<td>0.10</td>
</tr>
<tr>
<td>NAS (0-6)</td>
<td>-1.18 (1.59)</td>
<td>-3.45 (1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Participants with ≥3 points’ improvement in NAS from baseline, N (%)</td>
<td>4 (23.5)</td>
<td>9 (81.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Participants with NAS ≤2 at follow-up, N (%)</td>
<td>4 (23.5)</td>
<td>10 (90.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Again, weight Loss > 7% may be the best therapy
Mediterranean Diet

Fig. 2 (colour online) Mediterranean diet pyramid: a lifestyle for today

Mediterranean Diet

NAFLD and Bariatric Surgery

- Decrease in NASH noted in several observational studies.

Alcohol and NAFLD

• Heavy alcohol use should be avoided.
  • Men: more than 14 drinks per week or 4 drinks on any day
  • Women: more than 7-10 drinks per week or 3 drinks on any day

SOURCE: https://www.drugabuse.gov/sites/default/files/files/AUDIT.pdf
AUDIT to identify at-risk drinkers

### The Alcohol Use Disorders Identification Test: Self-Report Version

**PATIENT:** Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question.

<table>
<thead>
<tr>
<th>Questions</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have a drink containing alcohol?</td>
<td>Never</td>
<td>Monthly or less</td>
<td>2-4 times a month</td>
<td>2-3 times a week</td>
<td>4 or more times a week</td>
</tr>
<tr>
<td>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</td>
<td>1 or 2</td>
<td>3 or 4</td>
<td>5 or 6</td>
<td>7 to 9</td>
<td>10 or more</td>
</tr>
<tr>
<td>3. How often do you have six or more drinks on one occasion?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>4. How often during the last year have you found that you were not able to stop drinking once you had started?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>5. How often during the last year have you failed to do what was normally expected of you because of drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>8. How often during the last year have you been unable to remember what happened the night before because of your drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>9. Have you or someone else been injured because of your drinking?</td>
<td>No</td>
<td>Yes, but not in the last year</td>
<td>Yes, during the last year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?</td>
<td>No</td>
<td>Yes, but not in the last year</td>
<td>Yes, during the last year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total**
Other lifestyle recommendations:

• Moderate physical activity
• Smoking cessation
• Coffee?
Pharmacotherapy and NAFLD

• Not used for most cases of NAFLD
• Reserved for those with NASH w/ advanced fibrosis on biopsy (F2+)
• Could be considered in those not meeting lifestyle modification goals
  • Need to discuss risks, benefits, alternatives.

TREAT THE CVD RISK FACTORS!
# Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect on liver histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>No improvement</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Improvement in HS but not necro-inflammation and fibrosis</td>
</tr>
<tr>
<td>Pioglitazone*</td>
<td>Improved NAS &amp; steatosis in diabetics with NASH. Less clear benefit for NAS in non-diabetics with NAFLD but resolution of NASH has been demonstrated (PIVENS 47% versus 23% NASH resolution).</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 agonists</td>
<td>Possible improvement in SH</td>
</tr>
<tr>
<td>Vitamin E*</td>
<td>Improvement in steatosis, inflammation, ballooning, NAS scores in non-diabetics. (PIVENS 43% vs 19%, TONIC 58% vs 28%) Resolution of NASH compared to placebo (PIVENS 52% v 23%) Unclear effect on fibrosis.</td>
</tr>
<tr>
<td>UDCA (“Ursodiol”)</td>
<td>No histologic benefit</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>No clear benefit in limited POC studies. Can be considered in NAFLD patients with hypertriglyceridemia.</td>
</tr>
</tbody>
</table>

Vitamin E & Pioglitazone (PIVENS)

Vitamin E & mortality risk

Figure 3. Dose-response relationship between vitamin E supplementation and all-cause mortality in randomized, controlled trials.
Pearl:

• Address CVD risk factors!!
NAFLD: Address CVD Risk & Dyslipidemia

- NAFLD $\rightarrow$ “risk marker” for CVD
  - Possible mechanistic links
- CVD risk factor modification should be approached aggressively
  - Treating dyslipidemia in patients with DM & MetS reduces CVD and improves mortality
- GREACE Study:
  - Statins improve transaminases presumed attributed to NAFLD
- Studies have demonstrated statin safety in patients with liver disease regardless of transaminases

- AASLD (2018):
  
  "Several studies have established the safety of statins in patients with liver disease regardless of baseline elevation in liver chemistries."

AASLD (2018):
“Several studies have established the safety of statins in patients with liver disease regardless of baseline elevation in liver chemistries.”
Pearls

- Weight loss and diet modification remain the mainstays of NAFLD therapy.
- Addressing dyslipidemia and CVD risk should be priorities in all patients with elevated risk profiles (ASCVD).
- Vitamin E (rrr α-tocopherol) can be considered in NASH patients with advanced fibrosis or in NAFLD patients at higher risk unable to meet lifestyle goals.
- Pioglitazone can be considered in patients +/- DM-II with NASH and biopsy-proven advanced fibrosis.
- Cirrhotic patients need HCC & varices screening, OLT referrals.
NASH and Liver Transplantation

• NASH will become the most common indication for OLT in forthcoming years.

• Good Practice: Refer cirrhotic patients early!
  • MELD ≥ 10 or HCC.

• Higher BMI $\rightarrow$ increased risk of mortality and allograft failure
  • Sleeve gastrectomy as adjunct at time of OLT.
Other Considerations:

• HCC Screening in patients with NASH cirrhosis
  • RUQ US +/- AFP every 6 months
• Varices Screening in NASH cirrhosis
• Other considerations:
  • Encephalopathy
  • Renal Function
  • Ascites
• Immunizations
• Concomitant liver disease
Monitoring NAFLD/NASH

• NAFL or NASH without advanced fibrosis:
  • Obtain serum aminotransferases q 3-6 months as patients try to meet their weight goals
    • If the aminotransferases do not return to normal levels with weight loss or if they increase → liver biopsy (if not done) and consider other causes.
  • Unable to meet goals or felt at risk, refer to GI-hepatology

• NASH with fibrosis on biopsy (but not cirrhosis)
  • Non-invasive assessment q 3 years (biomarkers, VCTE)
  • More aggressive if unable to meet their goals or LFTs are not improving.
  • If fibrosis is worsening on monitoring, consider repeat liver biopsy

Note: guidance is less clear on this. If in doubt refer to hepatologist.
Pearls:

• Referral to a hepatologist
  • Aminotransferases that remain elevated despite loss of ≥5-7% of body weight (to evaluate for other etiologies of liver disease)
  • Clinical features of advanced liver disease (eg, ascites, splenomegaly, jaundice)
  • Steatohepatitis on liver biopsy
  • Advanced fibrosis (fibrosis stage ≥F3) on a noninvasive liver assessment
• Refer cirrhotic patient with MELD >10 to a transplant center.
Thank You

• Questions?