FATTY LIVER DISEASE

ITS NOT JUST FOR BIG BOYS ANYMORE

Ken Flora, MD, FAASLD, FACG, AGAF

Common situation...

- Normal ALT for men 30 IU/L  
  36% US males abnormal
- Normal ALT for women 20 IU/L  
  28% US females abnormal

Abnl ALT
  Assess alcohol use/meds
  Recheck in 6-8 weeks
  still pos
    HCV Ab  HBsAg  Esr/TIBC  Ultrasound
Definitions:

“Fatty Liver”
- Found on imaging, histology or intraop inspection

NAFLD

NAFL vs NASH
- >5% cells with fat
- NO injury
- Injury
- Inflammation
- Fibrosis
- Cirrhosis

Alcohol
Hepatitis C
Starvation/TPN
Pregnancy
Meds
Amiodarone
Methotrexate
Tamoxifen
Corticosteroids
Diltiazem
Valproic acid
HAART

Normal
Inflammation
Stage 1

HISTOPATHOLOGY

Stage III
Incidence:

• Not well known – no prospective biopsy studies

• Recent meta analysis suggested
  • Asia 52/1000 person-years
  • West 28/1000 person years

Younossi ZM Hepatology 2016. 64:73

Prevalence:

Global 25% NAFLD
1.5 – 6.5% NASH

Mid East/South America 30%   Africa 13%

Younossi ZM Hepatology 2016. 64:73
Prevalence in ‘high risk’ pops:

<table>
<thead>
<tr>
<th>Common Conditions With Established Association</th>
<th>Other Conditions Associated With NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>T2DM</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Polycystic Ovary Syndrome</td>
<td>Pancreatoduodenal resection</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
</tr>
</tbody>
</table>

*The Adult Treatment Panel III clinical definition of MetS requires the presence of three or more of the following features: (1) waist circumference greater than 102 cm in men or greater than 88 cm in women; (2) TG level 150 mg/dL or greater; (3) HDL cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women; (4) systolic blood pressure 130 mm Hg or greater or diastolic pressure 85 mm Hg or greater; and (5) fasting plasma glucose level 110 mg/dL or greater.*

AASLD Practice Guidance. Hepatology 2017
Obesity

- Prevalence of NAFLD increases with BMI
- 95% of bariatric surgery candidates

Sasaki. Front Endocrinol 2014;5:164
Obesity Trends* Among U.S. Adults
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)

Obesity Trends* Among U.S. Adults
BRFSS, 1995

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2015

Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion April 2017
T2DM

• 30-60% have NAFLD

• Can appear simultaneously

Leite. Liver Int 2009;29:113

Dyslipidemia

50% NAFLD among lipid clinic patients

Assy, Dig Dis Sci 2000;45:1929

Mortality risk related to NASH

Isolated hepatic steatosis

- 8.6% CVD
- 1.7% Liver related

P = NS

NASH

- 15.5% CVD
- 5.6% Extrahep malignancy
- 2.8% Liver related

P < 0.01

Annual Cumulative Incidence of HCC

- HCV
- NASH
  - P = 0.099

- 4%/Year
- 2.6%/Year

Predictors of “Bad” NASH:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age*</td>
<td>Greater duration of disease</td>
</tr>
<tr>
<td>Sex*</td>
<td>Postmenopausal women ↑ disease</td>
</tr>
<tr>
<td>Race*</td>
<td>↑ Prevalence, severity in Hispanic, Asian patients; ↓ Prevalence, severity in black patients</td>
</tr>
<tr>
<td>HTN,* central obesity, dyslipidemia (↑ TG, ↓ HDL), insulin resistance/diabetes*</td>
<td>Risk increases with metabolic syndrome, ↑ 66% prevalence of bridging fibrosis if older than 50 yrs of age and obese or diabetic[5,6]</td>
</tr>
<tr>
<td>AST/ALT ratio &gt; 1,* low platelets*</td>
<td>Indicators of NASH cirrhosis</td>
</tr>
<tr>
<td>Persistently elevated ALT*</td>
<td>Can be associated with ↑ disease progression</td>
</tr>
</tbody>
</table>

*Strongest predictors of advanced disease, regardless of liver enzyme elevation.
What Are the Clinical Predictors of Liver-Related Mortality in NAFLD?

Multivariate Survival Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistically significant predictors</td>
<td></td>
</tr>
<tr>
<td>NASH</td>
<td>9.16 (2.10–9.88)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>2.19 (1.00–4.81)</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.02–1.10)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>1.44 (0.62–3.34)</td>
</tr>
<tr>
<td>White race</td>
<td>1.85 (0.62–5.47)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.88 (0.38–2.04)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.48 (0.19–1.23)</td>
</tr>
</tbody>
</table>

Key Diagnostic Challenges

- Lack of disease awareness and potential severity among clinicians
- Lack of highly sensitive and specific noninvasive diagnostic tools that are readily available
- Lack of treatment approved by FDA
Predictive Value of Liver Aminotransferases in NAFLD

- Serum ALT can be normal in up to nearly 60% of NAFLD patients with NASH\textsuperscript{1,2}
- Serum ALT can be increased in up to 53% of NAFLD patients with no NASH\textsuperscript{1,2}
- Therefore, serum ALT level alone is not predictive of NASH or fibrosis level\textsuperscript{1-3}
  - Normal ALT cannot rule out progression or NASH
  - Increased ALT cannot predict NASH

Noninvasive Tests for Liver Fibrosis

- Clinical or laboratory tests
  - NAFLD Fibrosis Score
  - FIB-4 index
  - BARD
  - AST/ALT ratio
- Imaging modalities
  - Shear-wave elastography
    - Supersonic imaging, Fibroscan, ARFI
    - MRE
  - MRI-based
    - Liver MultiScan
Calculating the NAFLD Fibrosis Score

Formula¹

\[-1.675 + (0.037 \times \text{age [years]}) + (0.094 \times \text{BMI [kg/m²]}) + (1.13 \times \text{IFG/diabetes [yes =1, no = 0]}) + (0.99 \times \text{AST/ALT ratio}) - (0.013 \times \text{platelet [10⁹/L]}) - (0.66 \times \text{albumin [g/dL]})\]

Online calculator²

Measures:
- Age
- BMI (kg/mL)
- IGF/diabetes
- AST
- ALT
- Platelets
- Albumin

Available at: http://nafldscore.com


< -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)
**NAFLD Fibrosis Score**

- Derivation and validation of the scoring system
- 733 NAFLD patients: 480 derivation; 253 validation
- Multivariate analysis
  - Age, hyperglycemia, BMI, platelet count, albumin, AST/ALT ratio are independent predictors of advanced fibrosis

<table>
<thead>
<tr>
<th>Cutoff point</th>
<th>Group</th>
<th>Predictive value for advanced fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low cutoff point</td>
<td>Derivation</td>
<td>NPV 93%</td>
</tr>
<tr>
<td>&lt;1.455</td>
<td>Validation</td>
<td>NPV 88%</td>
</tr>
<tr>
<td>High cutoff point</td>
<td>Derivation</td>
<td>PPV 90%</td>
</tr>
<tr>
<td>&gt;0.676</td>
<td>Validation</td>
<td>PPV 82%</td>
</tr>
</tbody>
</table>

**Calculating the FIB-4**

**Formula**

\[
\text{FIB-4} = \frac{(\text{Age [years]} \times \text{AST [U/L]})}{(\text{Platelet [x10^9]} \times \sqrt{\text{ALT [U/L]}})}
\]

**Online calculator**

\[
\text{FIB-4} = \frac{\text{Age (years)}}{\sqrt{\text{Platelet Count (10^9/L) \times AST Level (U/L)}}}
\]
FIB-4 Index
- Originally developed to predict advanced fibrosis in HIV/HCV coinfection
- Subsequently studied in 541 patients with NAFLD
  – AUROC 0.80

<table>
<thead>
<tr>
<th>Cutoff Point</th>
<th>Predictive Value for Advanced Fibrosis</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>Low cutoff point:</td>
<td>PPV 43%</td>
<td>Absence of advanced fibrosis: F0–1</td>
</tr>
<tr>
<td>&lt;1.30</td>
<td>NPV 90%</td>
<td></td>
</tr>
<tr>
<td>High cutoff point:</td>
<td>PPV 80%</td>
<td>Presence of advanced fibrosis: F3–4</td>
</tr>
<tr>
<td>&gt;2.67</td>
<td>NPV 93%</td>
<td></td>
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Elastography:

High-powered u/s pulse generates “shear waves” the velocity of which are measured
Transient Elastography

- Measures velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver\(^1\)
- Allows painless and simultaneous measurement of 2 quantitative parameters
  - Liver stiffness expressed in kPa: correlates with fibrosis stage\(^2\)
    - Correlated to liver fibrosis stage\(^2\)
  - Controlled attenuation parameter expressed in dB/meter: correlates with steatosis\(^3\)
- Volume of liver tissue is 100 times bigger than biopsy\(^4\)
- False positives: recent meal ingestion, acute hepatitis, extrahepatic cholestasis, and congestion\(^1\)
- Low applicability: obesity, ascites, operator inexperience\(^1\)

Magnetic Resonance Elastography
Liver biopsy:

- AASLD Practice Guidance for NAFLD 2017

“Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis.”

“Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and the presence and/or severity of (the) co-existing chronic liver diseases cannot be excluded without a liver biopsy.”


Management:

Life style- dietary change and exercise

Treatment: % \textbf{Weight Loss} Associated with Histological Improvement

- Fibrosis (45%) $\text{Weight Loss} \geq 10\%$
- NASH Resolution (64% – 90%) $\text{Weight Loss} \geq 7\%$
- Ballooning/inflammation (41% – 100%) $\text{Weight Loss} \geq 5\%$
- Steatosis (35 – 100%) $\text{Weight Loss} \geq 3\%$

Diet:

- Long-term compliance is important
- The specific composition of the diet less important—decrease caloric intake by >30% (~750-1,000 kcal/day)
- Not enough data to recommend a specific diet though the Mediterranean-style diet seems best currently and that advised by societies.
Exercise:

- Exercise, without weight loss, improves LFTs and prevents/improves NAFL somewhat—effect on NASH unknown. Only vigorous activity seems to do that.
- Real effect is on the heart

Medications:

- Metformin – not recommended- ineffective for NASH
- Rosiglitazone – not recommended- helped NAFL, not NASH
- Pioglitazone – improvement (signif in some studies) in NASH with or without T2DM- wt gain most sig SE
- Vitamin E (pure rrr α-tocopherol) 800IU/day better for NASH than placebo or metformin. Concern over all-cause mortality and higher risk of prostate CA at higher doses.
- Urso – not recommended- ineffective
- Omega-3 Fas – not recommended- ineffective- may help hyperTGemia
- Statins are OK
Nonalcoholic Fatty Liver Disease: Epidemiology, Natural History, and Diagnostic Challenges