Initial Work-Up and Evaluation of Patients with NAFLD

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Goals

- Exclude other etiologies
- Fatty Liver and SO WHAT?
- Identify risk factors for NASH
- Assess and quantify fibrosis
  - Serum and imaging biomarkers
  - Role of liver biopsy
Rule Out Other Causes of Hepatic Steatosis

Examples of other causes of fatty liver
- Excessive alcohol consumption
- Malnutrition

Examples of other liver diseases that can present with steatosis
- Hepatitis C, acute hepatitis D
- Wilson disease
- Hemachromatosis
- Medications
- Parenteral nutrition
- Lipodystrophy
- Lysosomal acid lipase deficiency
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NAFLD the dimension of the problem

- Hepatologist only see the most severe cases (the tip of the iceberg), and have a scarce idea of the global extent of the disease.

- Diabetes: over 380 million cases with expected increase to 500 millions in 2030.

- Obesity: 1 billion subjects overweight or obese around the world.
Under-recognition of NAFLD

39% Recognition of ALT increase
22% Diagnosis of NAFLD/NASH
15% Lifestyle modification
10% Referal specialist evaluation

No NAFLD care

The only predictive of NAFLD care was the magnitude of ALT elevation

Predictive Value of Aminotransferases in NAFLD

- Persistently elevated ALT can be associated with disease progression
- Serum ALT can be normal in up to nearly 60% of NAFLD patients with NASH [1,2]
- Serum ALT can be increased in up to 53% of NAFLD patients without NASH [1,2]
- Serum ALT alone is not predictive of NASH or fibrosis level [1-3]
  - Normal ALT cannot rule out progression or NASH
  - Increased ALT cannot predict NASH

Prevalence of NAFLD and NASH in Patients With T2DM and Normal Plasma AST or ALT

- Patients with T2DM and normal AST or ALT evaluated for liver triglyceride content by H-MRS, insulin sensitivity, and adipose tissue insulin resistance (N = 103)

- Prevalence of NAFLD in overall cohort: 50%
  - Among these patients, prevalence of NASH: 56%

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<table>
<thead>
<tr>
<th>Obese by BMI (kg/m²)</th>
<th>Nonobese (n = 31)</th>
<th>30.0-34.9 (n = 34)</th>
<th>35.0-39.9 (n = 29)</th>
<th>≥ 40.0 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD Prevalence (%)</td>
<td>36%</td>
<td>36%</td>
<td>68%</td>
<td>90%</td>
</tr>
</tbody>
</table>

P = .001
Mortality Risk Associated With Isolated Steatosis and NASH

- Liver Fibrosis Severity Independently predict:
  - Liver-specific morbidity
    - Ascites, varices, encephalopathy
    - F0-1 < F2 (7.5X) < F3 (13.8X) < F4 (47.5X)
  - Liver-specific mortality / OLT
    - 6.7X increased in F4 vs F0
  - All-cause mortality
    - 3.3X increased in F3-F4 versus F0

LDL Particle Size Is Reduced in NAFLD Regardless of Obesity

- Patients at high risk of NAFLD/NASH recruited from 3 US locations (N = 188)

NAFLD Associated With Dyslipidemia in Obese and Nonobese Patients

Increasing CV risk
Advanced Fibrosis in Patients With vs Without T2DM By Diagnostic Approach

- Meta-analysis (N = 3229)

![Pooled results of patients with and without T2DM](chart)

- General Population
- T2DM

<table>
<thead>
<tr>
<th>Test</th>
<th>Prevalence (%)</th>
<th>General Population</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibro Test</td>
<td>80</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>NAFLD Fibrosis Score</td>
<td></td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Vibration-controlled Transient Elastography</td>
<td></td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>
Staging and monitoring progression of fibrosis in NASH

- NASH + stage 0-1 fibrosis
- F2 fibrosis
- Advanced Fibrosis (F3)
- Cirrhosis
- HCC

Singh, Clin Gastroenterol Hepatol 2015
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Association Between NAFLD/NASH and Diabetes Mellitus Is Bidirectional

Patients with NAFLD/NASH have:

- Increased risk of developing diabetes\(^1,2\)

- Synergistic increase in risk of diabetes when combined with obesity or insulin resistance\(^3\)
  - Patients with obesity, NAFLD, or insulin resistance each have 2-4 x the risk of diabetes, but patients with all 3 have 14 x risk of diabetes

- High prevalence of diabetes\(^4\)

Patients with diabetes have:

- Increased risk of NASH with family history of diabetes\(^5\)

- Increased risk of dying from cirrhosis\(^6,7\)

- Up to 3-fold increased risk of dying from chronic liver disease, mostly attributable to NAFLD\(^8\)

- Increased risk of chronic liver disease\(^9\)

2. Shibata Diabetes Care. 2007;30:2940-2944
Risk Factors for NAFLD

Major Co-morbidities
- Type 2 Diabetes
- Dyslipidemia
- Obesity
- Metabolic syndrome

Other associations
- Hypothyroidism
- Sleep Apnea
- Hypopituitarism
- Hypogonadism
- Polycystic ovary syndrome
- Pancreatic resection
- Psoriasis

Lonordo A, J Hepatol 2006; 44: 1196-1207
# Clinical Predictors of NASH in Patients With NAFLD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age[1]</td>
<td>Greater duration of disease</td>
</tr>
<tr>
<td>Sex[2]</td>
<td>Postmenopausal women experience accelerated disease</td>
</tr>
<tr>
<td>Race[3]</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[4]</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,[7] low platelets[8]</td>
<td>Indicators of NASH cirrhosis</td>
</tr>
<tr>
<td>Persistently elevated ALT[9]</td>
<td>Can be associated with greater risk of disease progression</td>
</tr>
</tbody>
</table>

*Based on ATP III criteria.

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- **Assess and quantify fibrosis**
  - Serum and imaging biomarkers
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The easiest non-invasive tests for the diagnosis of steatosis is imaging

- US should be the first method to be used in a clinical setting.
- It is inexpensive, widely available
- Se: 60–94%
- Sp: 66–97% Sp for hepatic steatosis
- Elastography coupled to US may be available for fibrosis assessment
Biomarkers predicting fibrosis, with reasonable accuracies for advanced fibrosis, but not for mild/intermediate stages

<table>
<thead>
<tr>
<th>Score</th>
<th>Components</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original European Liver Fibrosis score</td>
<td>Age, Hyaluronic acid, type 3 collagen, TIMP-1</td>
<td>0.87</td>
</tr>
<tr>
<td>Fibro-test</td>
<td>Age, alpha-2 macroglobulin, bilirubin, GGT, Apolipoprotein A1</td>
<td>0.75-0.86</td>
</tr>
<tr>
<td>Gholam's model</td>
<td>ALT, HBA1C</td>
<td>0.822</td>
</tr>
<tr>
<td>NAFLD fibrosis score</td>
<td>Age, BMI, Diabetes, AST/ALT, platelet, Albumin</td>
<td>0.84</td>
</tr>
<tr>
<td>Simplified ELF</td>
<td>Hyaluronic acid, type 3 collagen, TIMP-1</td>
<td>0.87</td>
</tr>
<tr>
<td>BARD</td>
<td>BMI, AST/ALT, Diabetes</td>
<td>0.81</td>
</tr>
<tr>
<td>BAAT</td>
<td>Age, BMI, Triglyceride, ALT</td>
<td>0.86</td>
</tr>
<tr>
<td>Fibrometer</td>
<td>Glucose, AST, Ferritin, Platelet, ALT, Weight, Age</td>
<td>0.943</td>
</tr>
<tr>
<td>Fib-4</td>
<td>Age, AST, ALT, Platelets</td>
<td>0.86</td>
</tr>
<tr>
<td>NAFLD Diagnostic Panel</td>
<td>Diabetes, Triglycerides, TIMP-1, AST</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Machado. J. Hepatol. 2013, Pages 1007–1019
Noninvasive Assessment of Liver Fibrosis to Guide Treatment, Monitor Progression

- British study comparing identification of advanced fibrosis in patients with NAFLD (N = 145)

<table>
<thead>
<tr>
<th>AUROC</th>
<th>NPV, %</th>
<th>PPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIB-4: 0.86</td>
<td>FIB-4: 95</td>
<td>NAFLD fibrosis score: 79</td>
</tr>
<tr>
<td>AST/ALT ratio: 0.83</td>
<td>BARD: 95</td>
<td>FIB-4: 75</td>
</tr>
<tr>
<td>NAFLD fibrosis score: 0.85</td>
<td>AST/ALT ratio: 93</td>
<td>AST/ALT ratio: 55</td>
</tr>
<tr>
<td>BARD: 0.77</td>
<td>NAFLD fibrosis score: 92</td>
<td>APRI: 37</td>
</tr>
<tr>
<td>APRI: 0.67</td>
<td>APRI: 84</td>
<td>BARD: 27</td>
</tr>
</tbody>
</table>

- No data using elastography to assess response to intervention

NAFLD fibrosis score

- The NAFLD fibrosis score is calculated using ALT, albumin, AST, and glucose levels; platelet count; and age and BMI.

\[
\text{NFS} = -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (}\times10^9/\text{l}) - 0.66 \times \text{albumin (g/dl)}
\]

- NFS < -1.455 is consistent with the absence of significant fibrosis.
- NFS > 0.676 indicates the presence of significant fibrosis with 90% certainty.

- NAFLD fibrosis score has an AUROC = 0.85 for predicting advanced fibrosis (bridging fibrosis and cirrhosis).

Comparison of blood tests for liver fibrosis specific or not to NAFLD

<table>
<thead>
<tr>
<th>Test</th>
<th>$\kappa$</th>
<th>Se</th>
<th>Spe</th>
<th>+PV</th>
<th>-PV</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FibroMeter</td>
<td>0.769</td>
<td>78.5</td>
<td>95.9</td>
<td>87.9</td>
<td>92.1</td>
<td>0.943</td>
</tr>
<tr>
<td>NFSA</td>
<td>0.628</td>
<td>60.9</td>
<td>96.3</td>
<td>86.7</td>
<td>86.0</td>
<td>0.884</td>
</tr>
<tr>
<td>APRI</td>
<td>0.584</td>
<td>66.1</td>
<td>90.6</td>
<td>72.9</td>
<td>87.5</td>
<td>0.866</td>
</tr>
</tbody>
</table>
Prognostic significance of blood fibrosis tests and liver stiffness measurement in NAFLD

Non-invasive tests developed for the diagnosis of liver fibrosis are also prognostic markers in NAFLD

Boursier, J. Hepat. 2016
Sequential Algorithms to Detect Advanced Fibrosis due to NASH

- Study of baseline data from STELLAR trials (N = 3202) to determine performance of sequential combinations of noninvasive tests in diagnosing F3/F4 liver fibrosis

- Liver biopsy assessment
  - 41% fibrosis stage F4 (n = 1283)
  - 30% fibrosis stage F3 (n = 979)

- Algorithm based on noninvasive tests used low cutoff for sensitivity (to rule in F0-F2) and high cutoff for specificity (to rule in F3/F4)
  - Novel cutoffs from STELLAR study: FIB-4 (1.23, 2.10), ELF (9.35, 10.24), FibroScan (9.6, 14.53 kPa)
  - Published cutoffs: FIB-4 (1.30, 2.67), ELF (9.8, 11.3), FibroScan (9.9, 11.4 kPa)

Composite score developed to noninvasively identify patients with nonalcoholic steatohepatitis (NASH)

- Vibration-controlled transient elastography (VCTE), controlled attenuation parameter (CAP), and AST determined to be appropriate components

- Relevance of adding diabetes to score still being investigated

<table>
<thead>
<tr>
<th>Model</th>
<th>VCTE + CAP + AST Score</th>
<th>VCTE + CAP + ALT Score</th>
<th>VCTE + CAP + AAR Score</th>
</tr>
</thead>
</table>
| Variable importance by Wald test | VCTE: $P < 10^{-9}$  
AST: $P < 10^{-7}$  
CAP: $P < 10^{-3}$ | VCTE: $P < 10^{-11}$  
ALT: $P < 10^{-3}$  
CAP: $P = .004$ | VCTE: $P < 10^{-9}$  
CAP: $P < 10^{-3}$  
ALT: $P = .11$ |
| AUROC (95% CI)                | 0.83 (0.78-0.87)        | 0.80 (0.76-0.85)       | 0.78 (0.73-0.83)       |
| Delong test                   | --                      | $P = .03$              | $P = .01$              |

Guidance Statements:

2. Patients with unsuspected HS detected on imaging who have symptoms or signs attributable to liver disease or have abnormal liver chemistries should be evaluated as though they have suspected NAFLD and worked up accordingly.

3. Patients with incidental HS detected on imaging who lack any liver-related symptoms or signs and have normal liver biochemistries should be assessed for metabolic risk factors (e.g., obesity, diabetes mellitus, or dyslipidemia) and alternate causes for HS such as significant alcohol consumption or medications.

11. In patients with NAFLD, MetS predicts the presence of SH, and its presence can be used to target patients for a liver biopsy.

12. NFS or FIB-4 index are clinically useful tools for identifying NAFLD patients with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4).

13. VCTE or MRE are clinically useful tools for identifying advanced fibrosis in patients with NAFLD.
Risk Stratification in Patients With Suspected NAFLD

**Low-risk profile**
- BMI < 29.9
- Age < 40 yrs
- No T2DM or metabolic syndrome features
- Noninvasive fibrosis estimation:
  - FIB-4 < 1.30
  - APRI < 0.5
  - NFS < -1.455
- FibroScan < 5 kPa

Follow and reassess as risk factors evolve

**Intermediate-risk profile**
- BMI > 29.9*
- Age > 40 yrs
- Multiple features of the metabolic syndrome*
- Noninvasive fibrosis estimation:
  - FIB-4 1.30-2.67
  - APRI 0.5-1.5
  - NFS -1.455-0.675
- FibroScan 6-11 kPa

Consider liver biopsy

**High-risk profile**
- AST level > AST level
- Platelets < 150,000
- Noninvasive fibrosis estimation:
  - FIB-4 > 2.67
  - APRI > 1.5
  - NFS > 0.675
- FibroScan > 11 kPa

Consider liver biopsy or confirmatory testing for cirrhosis (eg, MRE)

*Risk factors in our patient.

Clinical Take-Home Points

- Any patient with NAFLD may have NASH irrespective of liver enzymes tests.
- Non invasive fibrosis markers composite scores may help identifying patients at risk of having liver injury.
- The most promising seems the Liver stiffness combined to fibrometer measurement or AST.
- Liver biopsy if in doubt of diagnosis.