NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) & NON-ALCOHOLIC STEATOHEPATITIS (NASH)

ADDRESSING A GROWING SILENT EPIDEMIC
PREVALENCE OF NAFLD/NASH

USA Prevalence in Middle Age Patients

- San Antonio, Texas (Williams et al., Gastroenterology 2011; 140:124-31)
- Dallas Heart Study Prevalence Numbers (Browning et al., Hepatology 2004;40:1387-95)

Worldwide prevalence of NAFLD: 20–30%
- 13-44% in Middle Eastern countries
- Approx. 20% in Asian countries
- Approx. 30% in European countries
- NASH worldwide prevalence unknown (estimate from U.S. study: 6-8%)

NAFLD/NASH PREVALENCE AMONG PATIENTS WITH DIABETES

- NAFLD: 80-90%
- NASH: 56-69%
- Advanced Fibrosis: 37-50%

NAFLD/NASH PREVALENCE AMONG OBESE PATIENTS

- Prevalence among bariatric surgery patients
  - NAFLD: 70-90%
  - NASH: 25-30%
NAFLD is an umbrella term that encompasses the spectrum of fatty liver disease, from isolated steatosis to cirrhosis and liver cancer with underlying CVD risk.
Progression of isolated steatosis to cirrhosis is very rare

Fatty liver with inflammation but not NASH may progress but at a slower rate than NASH

NASH with fibrosis is at greater risk for disease progression

Patients with NASH and metabolic syndrome are also an enriched population for disease progression

NAFLD/NASH is now the second leading cause for liver transplantation in the U.S.

HIERARCHY OF HISTOLOGIC FEATURES

Associated with disease progression and mortality

A

INCREASED MORTALITY OR LT

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hazard Ratio</th>
<th>95% CI of HR</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Fibrosis, stage 1</td>
<td>1.16, 2.81</td>
<td>.007</td>
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<tr>
<td>Fibrosis, stage 2</td>
<td>1.20, 3.03</td>
<td>.007</td>
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<td>Fibrosis, stage 3</td>
<td>1.16, 3.12</td>
<td>.01</td>
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<td>Fibrosis, stage 4</td>
<td>3.35, 12.94</td>
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<tr>
<td>Age (years)</td>
<td>1.05, 1.08</td>
<td>&lt;.001</td>
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<tr>
<td>Diabetes (yes)</td>
<td>1.11, 2.30</td>
<td>.01</td>
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<tr>
<td>Smoking</td>
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<td>.005</td>
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<td>Statins use (yes)</td>
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<td>.198</td>
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<tr>
<td>Never</td>
<td>1.67, 4.10</td>
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<tr>
<td>Former</td>
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<tr>
<td>Current</td>
<td>1.11, 2.30</td>
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B

INCREASED RISK OF LIVER-RELATED EVENTS

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<td>1.18, 2.81</td>
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<tr>
<td>Fibrosis, stage 2</td>
<td>2.20, 4.94</td>
<td>&lt;.001</td>
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<tr>
<td>Fibrosis, stage 3</td>
<td>4.25, 9.65</td>
<td>&lt;.001</td>
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</tr>
<tr>
<td>Fibrosis, stage 4</td>
<td>11.94, 188.61</td>
<td>&lt;.001</td>
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</tbody>
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MAJOR PROGNOSIS FACTORS

- Ballooning
- NASH
- Portal inflammation
- Fibrosis

NAFLD & MORTALITY: TOP 3 CAUSES

1. CARDIOVASCULAR DISEASE (CVD)
2. ALL CAUSE MALIGNANCY
3. LIVER-RELATED DEATH

CONDITIONS ASSOCIATED WITH NAFLD

NAFLD

CVD
OSA
Hyper-lipidemia
Vitamin D deficiency
Hypothyroidism
Diabetes
Hypertension
PCOS
Adenomatous polyps
Metabolic Syndrome

DIAGNOSIS

- AASLD practice guidelines require liver biopsy to diagnose NASH
- Liver enzymes can be normal in up to 60% of patients with NASH
- No non-invasive test with sufficient sensitivity or specificity to rule in or rule out NASH

RED FLAGS INCREASING PROBABILITY FOR NASH

When deciding who to biopsy

- Age
- Gender
- Hispanic
- Hypertension
- Obesity
- ALT and AST level
- AST/ALT ratio
- Insulin level
- PNPLA3

No lab test or imaging study will be able to predict with 100% accuracy

All variables have been shown to predict NASH
Diet and exercise are not always satisfactory options, and there is a lack of treatment. To address this unmet need, enrollment in one of the clinical trials underway can be considered.

TREATMENT

- Diet, lifestyle modification and exercise remain the top priority. Ultimate goal is to achieve 10% weight loss as this has been shown to improve all histopathologic parameters of NASH.

- No approved therapies for the treatment of NASH.

NASH: KEY CONSIDERATIONS

- NASH is the liver manifestation of metabolic diseases. NASH patients are often obese, have type 2 diabetes, and cardiovascular disease.

- NASH is the underlying cause of cirrhosis and its complications: treating NASH is the appropriate approach to prevent progression to cirrhosis.

- Liver biopsy is required to diagnose NASH.

- How to reverse NASH: stop the disease activity i.e. necroinflammation (ballooning + inflammation) that is the driver leading to liver fibrosis and progressive liver fibrosis.

- NASH therapies should be efficacious against both the underlying liver disease and comorbid conditions associated with NAFLD such as insulin resistance, diabetes, and hyperlipidemia.

- Because NASH is a chronic and silent disease, therapies should be safe and well tolerated.