Nonalcoholic Fatty Liver Disease

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I have no disclosures.

NAFL, NAFLD or NASH
What’s the difference?

NAFLD = the spectrum of fatty liver disease

- FAT (steatosis) ⇒ NAFL
- FAT + INFLAMMATION ⇒ NAFL
- FAT + HEPATOCYTE DAMAGE ⇒ NASH
- FAT + FIBROSIS ⇒ NASH

Why does it matter?

- PROGNOSIS!
  - NAFLD pts have overall increase in mortality
  - Most common cause of death is CVD!
  - Also increased risk of cancer-related mortality
  - NASH pts have increased liver-related mortality

Note that these are histologic diagnoses—there are no noninvasive clinical tests that reliably distinguish NAFL from NASH
Progressive Liver Disease

- Simple steatosis (NAFL) rarely progresses
- NASH does progress
  - ~25% will become cirrhotic
  - Increased risk for hepatocellular CA
    - Mostly but not exclusively once cirrhosis is present
- Changes of NASH may not be evident once cirrhosis develops
  - "Burned-out NASH" → cryptogenic cirrhosis

Obesity rates in the US increased 2.5-fold in 36 yrs

Obesity rates for adults ages 20-74

Source: CDC, USDA
Magnitude of the Problem

≥30% of US population has NAFLD

- Prevalence of NASH in general pop’n estimated 1.5 – 6.5%
- ~25% of pts with NASH at risk to develop cirrhosis
- NASH predicted to become most common indication for liver transplant within next decade
- Currently the third-most common cause of HCC
- Already the most common cause of chronic liver disease

Pathophysiology

- Fat in hepatocytes = triglycerides (TG)
- TGs accumulate when there is:
  - Excess substrate or overproduction
  - Impaired utilization (oxidation or secretion)
- Why steatosis causes inflammation and hepatocyte injury in some individuals and not others is not well-understood
  - Genetic variations identified to affect susceptibility to liver damage
**PNPLA3**

- Patatin-like phospholipase domain protein 3
- Polymorphism (replacement of isoleucine with methionine, rs738409 C>G) associated with steatosis on genome-wide screening
- G allele associated with impaired triglyceride metabolism in hepatocytes
- May be a risk factor for more aggressive disease
- Also associated with more severe forms of alcoholic liver disease

**NASH or ASH?**

- NASH by definition implies absence of significant alcohol use
- Original description of NASH was in pts who drank no alcohol at all
- How much alcohol is “significant” in the context of NAFLD is not known
- Not uncommon to encounter pts with NASH risk factors and heavy alcohol use, though “ASH/NASH” is technically a contradiction in terms

**Conditions associated with NAFLD**

- Elevated BMI
- Central adiposity*
- Type 2 DM*
- Dyslipidemia (high TG, low HDL)*
- Metabolic syndrome*
- Polycystic ovarian syndrome
- Hypothyroidism
- Obstructive sleep apnea

* Predictor for presence of steatohepatitis
Clinical Features

- Usually asymptomatic
- Dull RUQ pain not uncommon
- Elevated liver enzymes
  - ALT>AST, usually mildly increased
- Hepatomegaly
  - Not always evident on exam, esp in obese
- Ultrasound
  - Echogenic (“bright”)-appearing liver

Diagnosis

- Exclusion of other causes of liver test abnormalities
  - Appropriate serologic tests (HCV, HBV, etc.)
  - Ultrasound
- Risk factor assessment for NAFLD
- Liver biopsy?
  - consider in pts at increased risk of NASH and/or advanced fibrosis
  - consider in pts in whom competing etiologies and the presence of coexisting chronic liver diseases cannot be excluded

Hepatology pearl

- Elevations in the serum ferritin are very common in NAFLD (occurring in up to 60%) of pts
  - Elevated serum ferritin is NOT indicative of significant iron burden in most cases and the pt does NOT need phlebotomy!!!
- Hyperferritinemia is highly suggestive of a dx of NAFLD in appropriate clinical context
Noninvasive assessment of NAFLD

- Routine blood work and imaging (US, CT, MR) cannot reliably distinguish NAFL from NASH
- NAFLD fibrosis score (NFS) and FIB-4 are examples of noninvasive techniques that use available clinical data and that are reasonably accurate in identifying pts with advanced fibrosis

Should NAFLD pts undergo FibroScan (transient elastography)?

- Fibrosis makes the liver stiff
- Stiffness can be estimated by the velocity with which a shear wave passes through the liver
- FibroScan is an ultrasound probe with a transducer that generates a shear wave and then measures its velocity as it passes through the liver

Example in NAFLD patients

142 Japanese pts with NAFLD, 18 controls
All underwent liver bx
76% of NAFLD pts had NASH; mean BMI 28 (1)

Imajo et al. Gastroenterology 2016
FibroScan also estimates steatosis

![Box plot](image)

Steatosis score = % liver with fatty change

- **S1**: 11-33%
- **S2**: 34-66%
- **S3**: > 67%

**My take home on TE**

- Relatively good at discriminating F4 from F0-F1 (i.e., cirrhosis from no or minimal fibrosis)
- Not very good at discriminating lower stages of fibrosis from one another
- Not very good at discriminating grades of steatosis and insensitive to low (but still elevated) levels of fatty change
- **NOT A DIAGNOSTIC TEST**

**Treatment**

- **Weight reduction**
  - Liver enzymes often improve with modest weight loss, histologic improvement requires loss of 5-10% body weight
  - Gradual loss preferable
  - Unclear whether type of diet is important
- **Control of diabetes?**
  - Weight loss probably more important
- **Bariatric surgery**
  - No trials of bariatric surgery as specific Rx for NASH but retrospective studies show benefit
  - Known cirrhosis is at least a relative contraindication
Pharmacologic treatment of NAFLD

- Liver prognosis for pts with NAFL is good
- Rx of liver disease should generally be limited to those with biopsy-proven NASH and fibrosis
- Currently no Rx proven to confer long-term benefit/alter the natural history
- Drug development an area of intense interest

**Intervention Results Recommendation**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Results</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>Improvements in histology in both diabetics and non-diabetics</td>
<td>Consider in NASH pts with or without DM</td>
</tr>
<tr>
<td>Vitamin E (800 mg QD)</td>
<td>Improvements in liver enzymes and histology (but not fibrosis) in non-diabetics; also effective in children with NASH</td>
<td>Consider in NASH pts without DM</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>No improvement in liver histology</td>
<td>Not recommended for specific Rx of NASH</td>
</tr>
<tr>
<td>Metformin</td>
<td>May improve liver enzymes; no improvement in liver histology</td>
<td>Not recommended for specific Rx of NASH</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Improved histology but small studies</td>
<td>Inadequate data to recommend for Rx of liver disease</td>
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A few words about statins

- Statins are underused in pts with NAFLD
- Pts with NAFLD are *not* at increased risk of statin-related hepatoxicity
- If a statin is indicated, it can/should be used irrespective of underlying fatty liver
- Liver enzymes may improve in NAFLD pts treated with a statin
- Data regarding effects of statins on liver histology are scarce; not recommended for Rx of NASH per se

Screening for NAFLD?

- Most pts with NAFLD are not at risk of liver-related adverse outcomes
- Treatment implications? Lack of demonstrated long-term benefits, cost-effectiveness
- Screening currently not recommended

Summary

- NAFLD is the most common cause of elevated liver enzymes
- Diagnosis usually made on clinical grounds
- NAFLD pts have increased risk of cardiovascular disease; a proportion will develop cirrhosis, HCC
- Limited treatment options at present but this may change in the future
- Aggressive management of metabolic abnormalities is key