Non-Alcoholic Fatty Disease (NAFLD) : Overview and Emergent Trends

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I have no financial interest to disclose
Definition

Non-Alcoholic Fatty Liver Disease (NAFLD)

- Alcohol-like liver disease in individuals who do not consume excessive alcohol
- Histologic spectrum of liver damage
  - NAFL - fatty liver (steatosis)
  - NASH - fatty liver + increased hepatocyte death (steatohepatitis)
  - Cirrhosis - regenerative nodules + fibrosis
- Diagnosis of exclusion
  - Blood tests and imaging - insensitive, non-specific
Causes of NAFLD

• Metabolic syndrome related
• Starvation
• TPN
• Drugs: amiodarone, diltiazem, tamoxifen, PI
• HIV infection
• Celiac disease
• Jejuno-ileal bypass
• Genetic disorders of lipid metabolism: abetalipoproteinemia
Non-Alcoholic Fatty Liver Disease Clinical Implications

- Few symptoms / signs of liver disease
- Benign course?
  - <10% go to cirrhosis
  - Risk factor for cirrhosis in HCV & AFLD
  - Decreases efficacy of HCV anti-viral therapy

Steatosis
NASH (non alcoholic steatohepatitis)

- Hepatocyte injury
  - Ballooning
  - Mallory bodies
  - Dead cells

- Inflammatory cell infiltration

- Overwhelmed anti-oxidant & survival responses

NAFLD activity score 0-8 (grade activity of disease)
NASH Clinical Implications

Steatohepatitis

- Subtle symptoms common
- More severe metabolic syndrome
- Inflammatory cytokine excess
- ~30% advanced fibrosis
- May promote HCC

McCullough AJ. Et al Clin Liver Dis 2004;8:521-533,
Clinical predictors of NASH in patients with NAFLD

1. Advanced age
2. Sex: post menopausal women
3. Race: Increased prevalence and severity in Hispanic, Asian patients
4. Metabolic Syndrome (based on ATP III criteria): 66% prevalence of bridging fibrosis if older than 50 years of age obese or diabetic
5. AST/ALT ratio > 1 or thrombocytopenia: suggest NASH cirrhosis
6. Persistently elevated ALT

Rinella M. AASLD 2017, Emergent trends in NAFLD
Non-Alcoholic Fatty Liver Disease Clinical Implications

Cirrhosis (F4)

- Morbidity / mortality significant
- Liver-related co-morbidities
- May be reversible
- HCC risk high
# Metabolic Abnormalities Associated with NAFLD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Incidence (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>62.2% (45.3%–76.5%)</td>
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<tr>
<td>Obesity*</td>
<td>47.4% (34.2%–60.9%)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>43.3% (29.4%–58.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38.6% (32.1%–45.7%)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>37.3% (25.4%–51.0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18% (13.6%–23.5%)</td>
</tr>
</tbody>
</table>

Prevalence of Hepatic Steatosis Varies with Ethnicity

- Hispanics: 45%
- Whites: 33%
- Blacks: 24%
Non alcoholic fatty liver disease

Most common causes of morbidity and mortality

- **Cardiovascular** (atherogenic dylipedimia, endothelial dysfunction)
- **Malignancy** (metabolic syndrome, visceral fat gut dysbiosis)
- **Liver related** (fibrosis extent degree, portal hypertension).

*Rinella M. AASLD 2017 Emergent trends in NAFLD*
NAFLD Natural History

NAFLD → 74% stable

NASH ↓ 26%

NASH → 65-35% stable

Fibrosis progression: 25-35%
Cirrhosis: 9-20%
Liver failure or HCC: 40-60% of cirrhotic patients over 5-7 years
OLT or death: 22-33% of cirrhotics

1.- Koenig Hepatology 2015: 62 (Suppl 1)
2.- Ong JO Clinic Liv Dis 2007: 11,1-16
Fat-Derived Factors Regulate Hepatic Inflammatory Response

- Fat free fatty acids
- Hepatocyte TNF alpha production
- Adiponectin Activity
- ROS
- Hepatocyte oxidant stress
- Antioxidant depletion
- Hepatocyte death

Fat-Derived Factors

Liver

Fat

Fatty Acids

Hepatocyte steatosis

insulin resistance
Metabolic Syndrome
Cytokine Imbalance

TNF
- Pro-apoptotic
- Recruits WBC’s
- Promotes insulin resistance

Adiponectin
- Inhibits FA uptake
- Stimulates FA oxidation & lipid export
- Enhances insulin sensitivity

Steatosis (NAFL) + cell death + inflammation (NASH) & insulin resistance
Intestinal Bacteria: Role in NAFL / NASH

**Gut flora promote**
- absorption of dietary lipids
- hepatic fatty acid synthesis

**Gut-derived bacterial products**
- escape steatotic livers
- stimulate cytokine production by peripheral fat

![Diagram showing the role of intestinal bacteria in NAFL/NASH](Image)
Fat-Derived Fibrogenic Factors Activate Hepatic Stellate Cells

Leptin
Neuroendocrine

Angiotensin

Hepatic stellate cell

Collagen

Ob-R
Ad-R
A-R
AT-R

Anania, Hepatology 2002
Bataller Gastroenterology 2003
Oben, BBRC 2003
Obesity

Metabolic Syndrome
Chronic Inflammatory State
(High TNF + Low Adiponectin)

Tissue Injury
NAFL, NASH
Obesity

Metabolic Syndrome
Chronic Inflammatory State
(High TNF + Low Adiponectin)

Tissue Injury
NAFL, NASH

Repair

Adiponectin
Healthy
(Nonprogressive Disease)
Obesity

Metabolic Syndrome
Chronic Inflammatory State
(High TNF + Low Adiponectin)

Tissue Injury
NAFL, NASH

Repair

Leptin, norepinephrine, Ang, PAI-1

Unhealthy (Cirrhosis)
Diagnosis Goals

- Confirm etiology of liver disease
- Confirm specific type of fatty liver
- Establish clinical severity
Determine Etiology

Who might have NAFLD?

Anyone with:

- The Metabolic Syndrome
  - obese
  - type 2 diabetics
  - hypertensives
  - dyslipidemics
- Fatty liver on an imaging study
- Elevated serum AST or ALT
- Cryptogenic cirrhosis
Establish Severity

Blood Tests

- Aminotransferase level not useful
  Can be normal in advanced disease

- AST/ALT ratio may help
  High in cirrhotic NAFLD

- Thrombocytopenia suggests cirrhosis

- ↑ bili, ↓ albumin appear late
Establish Severity

Liver Biopsy = Gold standard

Limitations

- Sampling error
- Risk
- Expense
Establish Severity

Non invasive tests for liver fibrosis

Clinical laboratory tests
- NAFLD fibrosis score
- FIB-4 Index
- AST/ALT ratio

Transient Elastrography

MRE (Magnetic Resonance Elastrography)

Liver Multiscan/Multiparametric MRI
Current management of NASH

- Lifestyle intervention:
  Weight loss 5-10% of body weight

- Vitamin E 800 U/day

- Pioglitazone 30-45 mg/day

No long-term data on clinical outcomes
No FDA approved therapy

Vitamin E > Pioglitazone > Placebo

Vitamin E: Not validated in those with NASH + DM
   Not validated in those with cirrhosis
   Need to monitor cardiac profile
   Does not work for everyone (60% NR)

Pioglitazone: Increase weight
   Increase Fracture risk
   CHF
Targets used for treatment of NAFLD/NASH

Dyslipidemia

NAFLD

Obesity

Insulin resistance

Oxidative stress

Pro-inflammatory pathways

NASH

Fibrosis

LIVER RELATED OUTCOMES

## Therapies in phase II/III testing for NASH

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Status</th>
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<tbody>
<tr>
<td>Farnesoid X receptor agonist</td>
<td>Obethicolic acid</td>
<td>III</td>
</tr>
<tr>
<td>Fatty acid/bile acid modifier</td>
<td>Aramchol</td>
<td>IIb</td>
</tr>
<tr>
<td>Dual inhibitor for CCR2/CCR3</td>
<td>Cenicriviroc</td>
<td>lib</td>
</tr>
<tr>
<td>Anti-lysil oxidase like-2 monoclonal</td>
<td>Simtuzumab</td>
<td>lib</td>
</tr>
<tr>
<td>Galectin 3 inhibitor</td>
<td>GR-MD-02</td>
<td>II</td>
</tr>
<tr>
<td>Niemman Pick like 1 protein</td>
<td>Ezetimibe</td>
<td>II</td>
</tr>
<tr>
<td>Selective blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual peroxisome proliferator</td>
<td>Elafibrinor</td>
<td>lib</td>
</tr>
<tr>
<td>Activated receptor alpha/delta agonits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apoptosis signal-regulating kinase-1</td>
<td>Selonsertib</td>
<td>II</td>
</tr>
<tr>
<td>Inhibitor</td>
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</table>
Targets used for treatment of NAFLD/NASH

- **Dyslipidemia**
  - OCA
  - ezetimibe

- **Insulin resistance**
  - Aramchol
  - Elafibrinor

- **Oxidative stress**

- **NAFLD**

- **Fibrosis**
  - Simtuzumab

- **NASH**

- **Pro-inflammatory pathways**

- **Obesity**
  - Bariatric surgery/endoscopy

- **LIVER RELATED OUTCOMES**

Other treatments mentioned:
- GR-MD-02
- selonsertib
- cenicriviroc

References:
Loomba R Diagnostic and treatment breakthroughs 2016
Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the World.

Patient with metabolic syndrome have a high prevalence of NAFLD and have a higher risk of developing NASH.

Nonalcoholic steatohepatitis (NASH) is the progressive form of NAFLD.
The Gold standard to diagnose NASH remains to be liver biopsy, but in clinical practice, there are good alternative non-invasive tools to assess presence and degree of liver fibrosis and monitor disease progression.

Currently there are no FDA therapies approved for NASH, but there are many exciting new molecules in development.