Update on Nonalcoholic Fatty Liver Disease

Kathleen E Corey, MD, MPH, MMSc
Director, Mass General Fatty Liver Clinic
Outline

Defining the phenotypes of nonalcoholic fatty liver disease

NAFLD Diagnostics

Treatment of NASH
What is NAFLD?

- Chronic liver disease characterized by excess storage of fat within the liver in the absence of significant alcohol use

<table>
<thead>
<tr>
<th>Major Comorbidities</th>
<th>Emerging Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Obesity</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Nonalcoholic Fatty liver Disease

Steatosis

Steatohepatitis

Cirrhosis
Fatty hepatocytes

Steatosis

Intracellular fat deposition

Fatty hepatocytes
Nonalcoholic Steatohepatitis (NASH)

- Fat deposits
- Inflammation, ballooning
- Fibrosis
Cirrhosis

Nodules surrounded by fibrosis
NAFLD is the Most Common Cause of Liver Disease in the US

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of NAFLD (Steatosis + NASH)</th>
<th>Prevalence of NASH</th>
<th>Prevalence of Advanced Fibrosis/Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adults</td>
<td>30-45%</td>
<td>3-12%</td>
<td>2-3%</td>
</tr>
<tr>
<td>Adults with obesity</td>
<td>70-90%</td>
<td>18-50%</td>
<td>1-7%</td>
</tr>
<tr>
<td>undergoing WLS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults with diabetes</td>
<td>50-74%</td>
<td>22-40%</td>
<td>20%</td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>

- ~80 million American Adults have NAFLD

Charlton et al. Gastro 2011
Gupter et al. J Gastro Hepatol 2004
Williams et al., Gastro 2011
Dixon et al., Gastro 2001
NASH Cirrhosis

• NASH cirrhosis is 3rd most common indication for LT

• NASH cirrhosis will be leading indication for LT by 2020

Charlton et al. Gastro 2011
Case: Fatty Infiltration and Elevated LFTs

- SC is a 35 year old man with diabetes, obesity and hypertension found to have fatty infiltration of the liver on ultrasound

- Labs are notable for ALT 65, AST 33, AP 90, TB 1.0

- What are the next steps in his evaluation?
Diagnostic Goals

Goal 1: **Confirm NAFLD** is the etiology of liver disease

Goal 2: Determine the **type** of NAFLD

Goal 3: Determine if **fibrosis** is present
Goal 1: Confirming NAFLD

Diagnosing NAFLD requires

A. Hepatic steatosis is present (imaging or histology)

B. Other causes of hepatic steatosis excluded

Chalasani et al. Hepatology 2012
Goal 1: Confirm Hepatic Steatosis

- Hepatic steatosis: lipid droplets in ≥ 5% hepatocytes

- Ultrasound, CT scan and MRI can all identify hepatic steatosis

- Ultrasound can detect ≥ 30% steatosis, when high clinical suspicion obtain CT scan

Chalasani et al. Hepatology 2012
Goal 1: Exclude Other Causes of Steatosis

- Alcoholic liver disease
- Hepatitis C
- Wilsons Disease
- Disorders of lipid metabolism
  - Abetalipoproteinemia (MTTP)
  - Hypobetalipoproteinemia (APOB)
- Medications
  - Highly active antiretroviral therapy
  - Tamoxifen
  - Methotrexate
  - Corticosteroids
- Celiac disease
- Hypothyroidism
Goal 1: Exclude Other Causes of Steatosis

• NAFLD is so common that it can travel with other forms of liver disease
• Evaluate for other causes of abnormal LFTs
  – Viral hepatitis
  – Autoimmune hepatitis
  – Hemochromatosis
## Case: Lab Results

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>Hepatitis C Antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis B Surface Antigen</td>
<td>Negative</td>
</tr>
<tr>
<td>TTG IgG</td>
<td>Negative</td>
</tr>
<tr>
<td>TSH</td>
<td>3.5 uIU/mL</td>
</tr>
<tr>
<td>Iron saturation</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Ferritin</strong></td>
<td><strong>650</strong> ug/L</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>45 mg/dL (normal 27-55)</td>
</tr>
<tr>
<td>24 hour urine copper</td>
<td>30 micrograms (normal 20-40)</td>
</tr>
<tr>
<td>ANA</td>
<td>Negative at 1:40</td>
</tr>
<tr>
<td><strong>ASMA</strong></td>
<td><strong>Positive at 1:40</strong></td>
</tr>
<tr>
<td>Globulin</td>
<td>2.5 g/dL (normal 1.9-4.1)</td>
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<tr>
<td>IgG</td>
<td>646 mg/dL (normal 614-1295)</td>
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<tr>
<td>LDL</td>
<td>133 mg/dL</td>
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Goal 1: Determine the Etiology: Confusing Aspects of NAFLD Diagnosis

- Autoimmune markers are frequently positive in patients with NAFLD (steatosis & NASH)
  - 21% ANA + (≥1:160) or ASMA + (≥1:40)
  - 5% ANA + and ASMA +
  - 4% AMA +

- Not associated with disease severity or progression

- Uncertainty about diagnosis is indication for biopsy

Neuschwander-Tetri et al. Hepatology 2010
Vuppalanchi et al. Hepatology International 2011
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Goal 1: Determine the Etiology: Confusing Aspects of NAFLD Diagnosis

- Serum ferritin levels are frequently elevated in NAFLD
- Transferrin saturation is generally normal
- If elevated ferritin and TS, perform genetic testing

Kowdley et al. Hepatology 2012
Goal 1B: Determine the Etiology: Confusing Aspects of NAFLD Diagnosis

- Ferritin > 1.5 ULN is associated with advanced fibrosis & disease activity
  - Men >450 ng/mL
  - Women >300 ng/mL

- Elevated ferritin provides evidence for the presence of NASH but not definitive

Kowdley et al. Hepatology 2012
Diagnostic Goals

Goal 1: Confirm NAFLD is the etiology of liver disease

Goal 2: Determine the type of NAFLD

Goal 3: Determine if fibrosis is present
Goal 2: Determine the type of NAFLD: Steatosis vs NASH

- No non-invasive way to distinguish steatosis and NASH

- No serum biomarkers for NASH, LFTs do not distinguish between steatosis and NASH

- Elastography and Fibroscan can detect fibrosis but not inflammation and cellular injury that characterizes NASH
Diagnostic Goals

Goal 1: Confirm NAFLD is the etiology of liver disease

Goal 2: Determine the type of NAFLD

Goal 3: Determine if fibrosis is present
Goal 3: Determine the Severity of Disease

- Goal is to identify patients with advanced fibrosis or cirrhosis

- Risk Factors for Cirrhosis
  - Age > 45-50 years and
    - Obesity or
    - Diabetes
Emerging NASH Diagnostics

• Further risk stratification for biopsy
  – NAFLD Fibrosis Score
  – Transient elastography, USE and MRE for risk stratification
NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. The NAFLD fibrosis score
A noninvasive system that identifies liver fibrosis in patients with NAFLD

Age (years) [ ]
BMI (kg/m²) [ ]
IGF/diabetes [ ]
AST [ ]
ALT [ ]
Platelets (x10⁹/l) [ ]
**Albumin (g/l) [ ]**

[calculate score]
NAFLD fibrosis score
Online calculator


Age (years) 35
BMI (kg/m²) 35
IGF/diabetes ✅
AST 65
ALT 33
Platelets (x10⁹/l) 250
Albumin (g/l) 40

Score 0.100

≤ -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)
Transient Elastography
“Fibroscan”

Liver stiffness determines the level of Fibrosis.

Soft liver = normal

Stiff liver = abnormal

Performed in MGH Liver Center
Does not provide imaging, only elastographic measurements
Limited by liver depth/body habitus
Requires 2 hour fast
Ultrasound Elastography

- Provides both ultrasound of the liver and elastography
- Best for patients in need of imaging
MR Elastography

• Available as add on to *clinically indicated MRIs* in consultation with radiology (ex. Patient with liver lesion requiring MRI)

• Reimbursement remains an issue
Summary of Results:

Score: 11.5 kPA

Correlation of LS with Metavir Fibrosis stage:
- < 7 kPa: stage 0 – 1
- 7 – 8.5 kPa: stage 1 – 2
- 8.8 – 11.5 kPa: stage 2 – 3
- 11.5 – 13 kPa: stage 3 – 4
- >13 kPa: Stage 4

Results Interpretation:

Fibroscan is used to measure liver stiffness, and has been well-studied in most types of chronic liver disease. A fibroscan score of < 7 kPa suggests fibrosis is not present; a score of 11.5 or higher suggests advanced fibrosis or cirrhosis; intermediate scores suggest the presence of mild to moderate fibrosis. However, there are certain situations where a fibroscan score may be inaccurate, including food intake within 2 hours of the test; the presence of significant ascites; acute hepatitis; or in cases of pregnancy.
Case Presentation

- Liver biopsy
  - 33-66% steatosis
  - Diffuse lobular inflammation with glycogenated nuclei
  - Hepatocyte ballooning
  - Fibrosis stage 4 of 4 c/w cirrhosis
Weight Loss & Exercise are Cornerstones of Therapy

- **Weight loss**
  - 7-10% weight loss needed to improve NASH

- **Weight loss surgery**
  - 69% complete resolution of NASH
  - 53-65% partial or complete improvement in fibrosis
    - 60% of stage 2-3 fibrosis
  - Associated with increased QALY and was CE for BMI>35 and all fibrosis stages, BMI25-35 F>2

- **Exercise in absence of weight loss decreases steatosis**

Ekstedt et al., J of Hepatology 2007
Mummadi et al., CGH 2008
Pomrat et al., Hepatology. 2010
Taitano et al., J Gastro Surg 2015
Corey et al., The Liver Meeting San Francisco, CA 11/2015
Preferred Diet in NASH

• Limited data regarding preferred diet

• Small study found reduction in steatosis by MRI after Mediterranean diet, not seen after low calorie diet

• With data on CVD prevention with Mediterranean diet, reasonable to recommend for NASH patients

Ryan et al. J Hep 2013
Estruch et al. NEJM 2013
Preferred Diet in NASH

- Fructose is associated with NAFLD development

- Recommend patients limit fructose and all added sugars to <3 servings per day

Oyang J Hep 2008
# Pharmacotherapy for NASH

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>800 units daily</td>
<td>NASH without DM</td>
<td>Improvement in steatosis and inflammation</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>30-45 mg daily</td>
<td>NASH with DM</td>
<td>Improvement in steatosis and inflammation</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>2-6 grams daily</td>
<td>NASH with and without DM</td>
<td>Improvement in radiographic steatosis, 3 RCTs ongoing</td>
</tr>
<tr>
<td>Metformin</td>
<td>500-2000 mg daily</td>
<td>NASH without DM or DM w/o insulin</td>
<td>No benefit</td>
</tr>
<tr>
<td>Ursodiol</td>
<td>10-35 mg/kg</td>
<td>All NASH</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

Musso et al. Hepatology 2010
Obetocholic acid (OCA)

- Bile acid analog, modulate pathways that regulate lipid, glucose and energy homeostasis
- First-in-class farnesoid X receptor (FXR) agonist

M Rinella Nature Reviews Gastro 2015
OCA: FLINT trial

- 283 patients with biopsy-proven NASH were randomized to OCA or placebo for 72 weeks

- Primary endpoint: decrease in the NAFLD Activity Score (NAS) of at least two points with no worsening of fibrosis

BA Neuschwander-Tetri et al., Lancet 2014
OCA Meets Primary Endpoint

% Meeting Primary Endpoint
\[ p < 0.001 \text{ vs. placebo}\]

- Placebo: 21% (n=109)
- OCA 25 mg: 46% (n=110)

Primary Efficacy Endpoint

- Primary Endpoint: improvement in NAFLD Activity Score (NAS) by ≥2 points with no worsening of fibrosis (centrally scored)
- Numerically higher response rates in patients with higher NAS, higher fibrosis score or diabetes at baseline
- Baseline NAS of 5.3 in OCA treatment group

% With Fibrosis Improvement
\[ p = 0.01 \text{ vs. placebo}\]

- Placebo: 19% (n=98)
- OCA 25 mg: 35% (n=102)

Secondary Histological Endpoints*

- More OCA patients also improved on following histological endpoints:
  - All NAS components improved \( p = 0.03 \text{ to } <0.001 \)
  - NASH resolution: 22% vs. 13% \( p = 0.09 \)
  - Fibrosis: 35% vs. 19% \( p = 0.01 \) with ≥ 1-point improvement; mean score benefit of 0.3 \( p = 0.01 \)
- No improvement in portal inflammation (12% vs. 13%, \( p = 0.76 \))

*Statistical significance indicated by \( p < 0.05 \). Results contained herein based on draft manuscript received by NIDDK and subject to further modification prior to publication.

Intercept Presentation, September 2014
Therapies in Development

- Gilead’s simtuzumab (LOXL-2 inhibitor)
- NGM-282 (FGF-19 analog)
- Conatus’ emricasan
- Novo’s Victoza
- Galectin’s GR-MD-02
- Tobira’s cenicriviroc
- Galmed’s Aramchol
- Lumena/Shire’s LUM001/LUM002
Clinicians at the Fatty Liver Clinic at Massachusetts General Hospital diagnose, treat and monitor patients with fatty liver disease.

Welcome to the Fatty Liver Clinic
The MGH Fatty Liver Clinic provides comprehensive care for patients with suspected or established fatty liver disease.

http://www.massgeneral.org/gastroenterology/services/fatty_liver_clinic/

Resources on NAFLD

HEPATOLOGY
AASLD PRACTICE GUIDELINE
The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Evaluation of Fatty Liver with Normal Liver Function Tests

Secondary causes of fatty liver
- Hepatitis C
- Alcohol use
- Diabetes
- Medications
- Tumors
- Ammonia
- Cystic fibrosis
- Anti-retroviral drugs
- Lipid disorders

Normal LFT and hepatic steatosis imaging

Assess for secondary causes of fatty liver disease

Stage secondary causes

Advise weight loss, exercise

Determine NAFLD纤维化 score

NAFLD Fibrosis score < 0.575
- NAFLD score > 0.575

Present with liver biopsy
Take Home Messages

Steatosis and NASH are the primary forms of NAFLD

Biopsy is needed for NASH diagnosis, NFS and elastography can risk stratify

Weight loss, WLS, Vitamin E and Pio
Thank you