Non-Alcoholic Fatty Liver Disease: An American Epidemic

Jeff Hunt DO, FACOI
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BMI 32: OBESE

Disclosures

- Speaker for Abbvie
- Consultant for Janssen Pharmaceuticals
- Research projects with Abbvie

Objectives

- Prevalence
- Pathogenesis
- Diagnosis
- Testing
- Treatment
Nonalcoholic Steatohepatitis: Mayo Clinic Experiences With a Hitherto Unnamed Disease

- Jurgen Ludwig, M.D., Dept. Pathology and Anatomy
- Thomas Viggiano, M.D., Resident in Gastroenterology
- Douglas McGill, M.D., Division of GI and IM
- Beverly Ott, M.D., Division of GI and IM

Mayo Clinic Proceedings, 55; 434-438, 1980
**NAFLD is the Hepatic Component of Dysmetabolic Syndrome**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Categorical Cut-Offs</th>
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</thead>
<tbody>
<tr>
<td>Elevated Waist Circumference</td>
<td>&gt;94 cm in men; &gt;80 cm in women</td>
</tr>
<tr>
<td>Elevated TG (or on lipid medication)</td>
<td>&gt;150 mg/dl</td>
</tr>
<tr>
<td>Reduced HDL-C (or on lipid medication)</td>
<td>&lt;40 mg/dl in men; &lt;50 mg/dl in women</td>
</tr>
<tr>
<td>Elevated BP (or on antihypertensive medication)</td>
<td>Systolic &gt;130 and/or diastolic &gt;85 mm/Hg</td>
</tr>
<tr>
<td>Elevated Fasting Glucose (or on DM medication)</td>
<td>&gt;100 mg/dl</td>
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** Definitions **

- **Non-Alcoholic Fatty Liver Disease: NAFLD**
  - Includes the entire spectrum of fatty liver disease in patients who have no history of significant alcohol consumption.
  - (Encompasses steatosis to steatohepatitis and steatohepatitis with cirrhosis)
  - By Definition: The liver contains more than 5% fat by weight

- **Non-Alcoholic Fatty Liver (NAFL)**
  - **NAFL:** Presence of hepatic steatosis (fat) with no evidence of hepatocellular injury (no balloon degeneration of hepatocytes, and no fibrosis)
Fatty Liver

- Histologically no distortion of the nucleus
- Acute Fatty Liver of Pregnancy/HELLP
- Reye's Syndrome
- Nucleoside analogues, Tetracyclines, valproic acid
- Congenital Defects/Inborn Errors of Metabolism
  - LCAT deficiency
  - Wolman disease
  - Cholesterol ester storage disease

Microvesicular Steatosis

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Macrovesicular Steatosis

- Histologically see distortion of the nucleus
- MC form of steatosis
  - Hepatitis C (Genotype 3)
  - Obesity/Insulin Resistance
  - Obstructive Sleep Apnea
  - Alcohol
  - Malnutrition/Starvation
  - TPN
  - ASA, Vit A, MTX, Steroids, Amiodarone, CCBs
  - Wilson's disease
  - Abetalipoproteinemia
Steatohepatitis:
Fat deposition in the liver with subsequent liver inflammation

NASH:
Clinical disorder in which pt has no significant EtOH hx but liver biopsy resembles alcoholic steatohepatitis.
Fatty liver + inflammation with hepatocyte injury (ballooning degeneration)

NASH Cirrhosis is fatty liver + inflammation + fibrosis

Steatohepatitis with Fibrosis

The Spectrum of NAFLD

- Fatty Liver: Fat accumulates in the liver
- NASH: Fat plus inflammation and scarring
- Cirrhosis: Scar tissue replaces liver cells
**Prevalence of NAFLD**

- Nonalcoholic Fatty Liver Disease (NAFLD)
  
  - MCC of chronic liver disease in the US
  
  - Adolescent obesity has quadrupled in the past 10 years
  
  - 1 in 10 pediatric patients in the US. NAFLD seen as early as age 2 with NASH cirrhosis seen at age 8!

  **In US**
  
  - NAFLD: 10-46%
  
  - NASH: 3-5%

  **Worldwide**
  
  - NAFLD: 6-35%

  - NASH: 3-5%

- Adolescents and obesity
  
- Williams CD. Gastroenterology 2011;140:124-131

- Vernon G. Aliment Pharmacol Ther 2011;34:274-285

**Prevalence of NAFLD in the US**

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>NAFLD (%22</th>
<th>Obesity (5.5%)</th>
<th>DM2 (5.5%)</th>
<th>% Chronic Liver Dz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988 to 1994</td>
<td>5.5%</td>
<td>22%</td>
<td>5.5%</td>
<td>47%</td>
</tr>
<tr>
<td>1999 to 2004</td>
<td>9.8%</td>
<td>31%</td>
<td>7.9%</td>
<td>63%</td>
</tr>
<tr>
<td>2005 to 2008</td>
<td>11%</td>
<td>33%</td>
<td>9.1%</td>
<td>75%</td>
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</table>

- In some studies...
  
  - Bariatric surgery patients: 90% had NAFLD and 5% had cirrhosis
  
  - T2DM: 75% had NAFLD
  
  - Lipid Clinics: 51% had NAFLD


**Differential for Steatohepatitis**

- Also called centrilobular (zone III) macrovesicular hepatic steatosis
  
  - Alcohol
    
    (but already stated no hx of significant EtOH consumption, so only leaves...)

  - Diabetes

  - Obesity
### Risk Factors for NASH

- Central obesity (69-100% of pts)
- Dyslipidemia (20-80% of patients)
- DM2 (34-75% of patients)
- Slight male predominance
- Older age (most cases seen in ages between 40-60)

### Risk Factors for Steatosis

- Metabolic disorders
  - TPN, rapid weight loss, acute starvation, hypothyroidism, Wilson’s Disease
- Drugs/Toxins
  - Amiodarone, tamoxifen, glucocorticoids, estrogens, HAART, tetracycline/minocycline
- Obstructive Sleep Apnea/Hypoxemia
- Gut Microbiome

### Pathogenesis

- Insulin resistance (hormonal)
- “Second Hit”: oxidative stress is considered to be a key mechanism of hepatocellular injury and disease progression in NASH patients
  - Iron
  - Antioxidant deficiencies
  - Intestinal bacteria/overgrowth
Non-alcoholic fatty liver disease has a very high prevalence in the obese, type 2 diabetes mellitus and dyslipidemic patient populations.

- Malaise
- Fatigue
- Mild RUQ pain
- Hepatomegaly (on CT = liver span of >18 cm)
- ~75% ARE ASYMPTOMATIC!
Elevated Aminotransferases (MC presentation)
- High in about 90% with NASH, but could be normal (in ~10%): <400
- AST/ALT ratio <1 (with EtOH is >2, ~2.7)

Degree of aminotransferase elevation does not predict grade or stage of liver injury!

Lab Manifestations
- Alk Phos/GGT may be up 2- to 3-fold (but could be normal)
- Bilirubin/albumin usually normal
- If NO History of ETOH and AST/ALT ratio >or =2, this is suggestive advanced FIBROSIS/CIRRHOSIS!!!
Which of the following tests would be the best predictor of the presence of fibrosis/cirrhosis in a patient with NAFLD?

1. Low Soluble Cytokeratin 18
2. Elevated ESR
3. NASH Activity Score (NAS) <2
4. AST/ALT ratio >2
5. Elevated platelet count

Differential for LFT Abnormalities

- Alcohol
- Viral hepatitis (B, C and D)
- Hereditary hemochromatosis
- Wilson’s disease
- Alpha-1 antitrypsin deficiency
- Autoimmune hepatitis
- Drug/toxin history
- Nutrition history
- NASH

ALD/NAFLD Index (ANI)

- AST:ALT ratio
- BMI
- Male gender
- MCV

- ANI > zero favors ALD
- ANI < zero favors NAFLD
ALD/NAFLD Index Calculator

- [Online calculator](http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/alcoholic-liver-disease/nonalcoholic-fatty-liver-disease-index)

Imaging Studies

- **US**
  - Hyperechoic or bright liver (fat)
  - US is challenging in obese individuals

- **CT**
  - Non-contrasted images worse with higher BMIs
  - Contrasted images do not accurately reflect steatosis

Fatty Liver on CT

![Fatty Liver on CT Image](image-url)
Imaging Studies

- MRI
  - Normal MRI can exclude significant steatosis but may not reflect slight fatty changes

- MR Spectroscopy/Elastography
  - Can be more quantitative with fat appearance

- Transient Tissue Elastography (fibroscan)
  - Limited by BMI >30

Predictors of Disease
Severity/Progression in NASH

- Serum ferritin >1.5 times ULN
- >45 y/o, obesity, DM, female
- Obesity with BMI >28, >50 y/o, elevated TG, ALT >2 times ULN
- Age, BMI, platelets, albumin, AST/ALT ratio>1
Visceral Adiposity Index of VAI:
- Waist circumference, BMI, TG, HDL=predictor of fibrosis

No clinical or lab feature can predict progression!
- Even with serial biopsies

103 pts with NASH over 3-2 years: 37% progressed, 34% stable, 29% regressed

Liver Biopsy
- Only way to confirm or exclude NASH
- Shows severity of disease (NAFLD vs. NASH vs. NASH cirrhosis)
- Presence and severity of fibrosis (stage) and inflammation (grade)

If cirrhotic then need...
- Screening for esophageal/gastric varices
- US/AFP q 6 months
- Vaccinations for HBV/HAV (and other vaccines)

Perform in Patients with:
- Physical stigmata of chronic liver disease
- Splenomegaly
- Cytopenias
- Abnormal iron studies
- DM, Obesity, age >45
Risks of Liver Biopsy

- Painful and expensive
- Inadequate sampling size
- Sampling error
- Variability in pathologist interpretation
- Serious complications in 0.3%
  - Mortality ~1 in 10,000

NAFLD Activity Score (NAS)

- NAS: represents the sum of scores for steatosis, lobular inflammation, and ballooning, and ranges from 0-8
- NAS scores of 0-2: considered not diagnostic of NASH
- Scores of 3-4: evenly divided among those considered not diagnostic, borderline, or positive for NASH
- Scores of 5-8: largely considered diagnostic of NASH

Clinical Predictors of Steatosis

- SteatoTest (Biopredictive, Paris)
  - 6 variables: BMI, cholesterol, TG, glucose, age, sex
  - Cutoff of 0.3 has a sensitivity of 85%
  - Cutoff of 0.7 has a specificity of 80%
- Fatty Liver Index (FLI)
  - BMI, waist circumference, TG, GGT
  - Score of ≤ 30 has sensitivity of 87%
  - Score of > 60 has specificity of 86%
- Lipid Accumulation Product (LAP)
  - Waist circumference, TG, sex

Poynard T. Comp Hepatol 2005;4:10
Bedogni G. BMC Gastroenterol 2006;6:33
Bedogni G. BMC Gastroenterol 2010;10:98
Clinical Predictors of Advanced Fibrosis

- NAFLD Fibrosis Score: Age, BMI, AST:ALT ratio, DM, Plts, Albumin
- BARD Score: Age, AST:ALT ratio, DM
- Fib-4 Score: Age, ALT, Plts

Treatment

**Diet**
- Increase omega-3 FAs
- Decrease omega-6 FAs
- Avoid fructose containing foods/beverages
- Caffeinated Coffee?

**Exercise**
- Vigorous exercising
  - MET value >6, treadmill, step machine, etc
- Resistance training
  - 45-60 minutes with a 10 minute warm-up
- Cardiovascular/Aerobic training
Treatment

- Slow Weight Loss (over ~6 months)
  - Can help improve LFTs, histology, lower serum insulin levels and improve quality of life
  - 7% wt reduction showed histologic improvement in 72% (of 31 pts)
  - 3-5% wt decrease improves steatosis
  - 7-10% wt loss needed to improve necro-inflammation, NAS score

- Bariatric Surgery
  - Histologic improvement (inflammation and fibrosis) noted with wt loss 1-2 years post-op on repeat liver biopsy
  - Not contraindicated if NASH/NAFLD present but not recommended for treatment of NASH (Not Approved YET!)

  - Mathew P. Gastroenterology, 2009;137:2, 532-540
  - Ghany MG. Gastroenterology, 2012;142:1592-1609

- Gradual weight loss
  - Not exceed 3.5 lbs or 1.6 kg/week in adults
  - Too rapid can worsen liver disease

- Vitamins E and C
  - Reduced aminotransferases when vitamin E was used alone
    - In combination, vitamin E with pioglitazone (Actos, 30mg), showed improved histology
  - Vitamin E and C (1000 IU and 1000 mg/day) for 6 months
    - Improved liver fibrosis, no change in inflammation activity
  - Vitamin E dosed beyond 150 IU/day in increased all-cause mortality (39 excess deaths/10,000) with 400 IU/day
Vitamin E

- 247 pts with NASH without DM2, compared Vitamin E 800 IU daily vs. Actos 30 mg daily vs. placebo over 96 weeks:
  - Vitamin E improved global histology scores vs. placebo, 43% vs. 19%
  - Actos showed no statistically significant histological improvement vs. placebo
  - But steatosis and lobular inflammation was slightly better in actos treated arm

- Vitamin E: Improved steatosis, inflammation, ballooning. No effect on fibrosis

- Vitamin E (alpha-tocopherol), 800 IU/day, improves liver histology in non-diabetic adults with biopsy proven NASH and should be considered as a first-line pharmacotherapy for this population.
- Vitamin E is NOT recommended to treat NASH in diabetic pts, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis until further data is available.
- Controversial whether Vitamin E increases all-cause mortality (meta-analyses)
  - Recent RCT demonstrated 400IU daily increased risk of prostate CA in healthy men with absolute risk of 1.6/1000 person years of Vitamin E use

Metalformin

- 110 pts with NASH, Metformin 2gm/day vs. vitamin E 800IU/day vs. dietary wt loss over 12 months
  - LFTs improved with metformin more than with vitamin E or wt loss
  - Only mild change in steatosis/inflammation
  - Other studies failed to show major benefit from metformin on hepatic insulin sensitivity, LFTs or histology

- Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH
  - Rakoski M. Aliment Pharmacol Ther 2010;32:1211-1221
TZDs: Actos/Pioglitazone and Avandia/Rosiglitazone

- Rosiglitazone improved AST/ALT and steatosis but not inflammation and fibrosis
- Pioglitazone improved AST/ALTs and steatosis, ballooning and inflammation and NAFLD activity score (NAS) and trend toward improved fibrosis
  - Pts in the trials were non-diabetic!
  - Long-term safety and efficacy not established
  - Caution in cardiac/CHF pts
  - Some pts had wt gain of 2.5-4.5kg
- Actos can be used to treat steatohepatitis in pts with biopsy-proven NASH

- Mahady S. J. Hepatology 2011

Ursodiol

- Has anti-apoptotic and anti-inflammatory effects
- 2 years of treatment/NO histological improvement
  - Lindor KD. Hepatology 2004;39(3):770
- 18 months high dose treatment/NO improvement
  - Leushner UF. Hepatology 2010;52(2):472
  - Not recommended

Omega-3 Fatty Acids

- Can treat hypertriglyceridemia with NAFLD but not recommended for NASH or treatment of NAFLD

Obeticholic Acid (6-ethychenodeoxycholic acid)

- Farnesoid X nuclear receptor agonist
  - Promotes insulin sensitivity
  - Decreases lipid synthesis, increases peripheral clearance of VLDL/TG
  - Increases expression of hepatic scavenger receptors (SRB1)
- Compared to placebo (P value <0.05)
  - Improved Histology: 45% to 21%
  - Improved Fibrosis: 35% to 19%
  - Improved NAS: -1.7 to -0.7
  - Improved Steatosis: -0.8 to -0.4
  - Lobular Inflammation: -0.5 to -0.2

Neuschwander-Tetri BA. Lancet 2014
Treatment

- Obeticholic Acid

  - Drawback is that 1/3 of patients had pruritis!

Liver Transplant for NAFLD

Three-year patient and graft survival according to indication for liver transplantation among adults in the United States
Transplants for NAFLD

- The problem...
- NAFLD can recur following liver transplant!
- Up to 7-42% of patients will get NAFLD or NASH again

Watt KD. Clinical Liver Disease Vol. 1, No. 4, August 2012

Future Therapies?

- GFT505: Dual peroxisome proliferator-activated receptor alpha/delta
- Cenicriviroc: C-C motif chemokine receptor type2 (CCR2) and CCR5 antagonists
- Simtuzumab: Antifibrotic agent
- TGR5: Takeda G-protein coupled receptor 5 agonist with or without farnesoid X receptor agonist
- Aramchol: Bile acid conjugate

Future Therapies?

- (GR-MD-02 and GM-CT-01)
  - Treatment with galectin protein inhibitors significantly reduced fibrosis and reversed cirrhosis in a toxic model of liver fibrosis
  - IV formulation
  - Weekly infusion

- EASL 2013
  - “Regression of fibrosis and reversal of cirrhosis in thioacetamide-induced liver fibrosis following treatment with galectin inhibitors”
Galectin

- Animal model presented a very high hurdle for drug treatment: Cirrhosis induced with high dose tocile and continued throughout drug treatment
- Treatment with four weekly doses

Alcohol Use in Patients with NAFLD and NASH

Heavy consumption is a risk factor and should be avoided
- More than 4 drinks/day or >14 drinks/week in men
- More than 3 drinks/day or >7 drinks/week in women

Statin Use in Patients with NAFLD and NASH

- Statins: Can be use to treat dyslipidemia in patients with NAFLD and NASH
- No evidence that patients with chronic liver disease are at higher risk for serious liver injury from statin use!
**Fatty Liver Disease**
**Question #3**

* True or False

If a patient is diagnosed with NAFLD, they should stop their statin medication immediately as they are at an elevated risk for drug induced liver injury (DILI).

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* True or **False**

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**Screening Recommendations for NAFLD in High-Risk Patients**

* **THERE ARE NONE!**

* Not certain which test to order for screening

* Not many good treatment options at this time

* No good data yet related to the long-term benefits and cost-effectiveness of screening
There are current guidelines that recommend screening all high-risk groups (obese, T2DM, dyslipidemic patients) for NAFLD using either US, CT or MRI.

Current guidelines recommend screening all high-risk groups (obese, T2DM, dyslipidemic patients) for NAFLD using either US, CT or MRI.

- Screen for HCC every six months with US (and AFP)
- Screen for Varices with EGD
- Vaccinate patients for HBC, HAV, Pneumococcal, Yearly Influenza
Objectives

- Prevalence
- Pathogenesis
- Diagnosis
- Testing
- Treatments

THANK YOU!