Non-Alcoholic Fatty Liver Disease: An American Epidemic

Jeff Hunt DO, FACOI
Richard C. Staab Memorial Symposium
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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
Foie Gras
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>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Waist Circumference</td>
<td>&gt;94 cm in men; &gt;80 cm in women</td>
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<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</td>
<td>Systolic &gt;130 and/or diastolic &gt;85 mm/Hg</td>
</tr>
<tr>
<td>medication)</td>
<td></td>
</tr>
<tr>
<td>Elevated Fasting Glucose (or on DM</td>
<td>&gt;100 mg/dl</td>
</tr>
<tr>
<td>medication)</td>
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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
Microvesicular Steatosis

- 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
Macrosvesicular 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
  
  Adams LA. NAFLD. Ann Epidemiol 2007;17:863-869

- 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
  - 6-35%

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</th>
<th>Obesity</th>
<th>DM2</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>
</tr>
</tbody>
</table>

Younossi Z. Clin Gastro Hepatol. 2011;9:524-530

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)
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
Clinical Manifestations

* Malaise
* Fatigue
* Mild RUQ pain
* Hepatomegaly (on CT = liver span of >18 cm)
* ~75% ARE ASYMPTOMATIC!
Lab Manifestations

* 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!!!
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

* Dunn W. Gastroenterology 2006; 131: 1057-1063
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
 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)
Indications of Liver Biopsy

- 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 \( \leq 30 \) has sensitivity of 87%
    * Score of \( \geq 60 \) 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
    * Bedgoni 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, AST, ALT, Plts
Diet

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

* Paredes AH. Clinical Liver Disease 2012: Vol. 1 (4); 117-118
* **Exercise**

  * Vigorous exercising
    * MET value >6, treadmill, step machine, etc

  * Resistance training
    * 45-60 minutes with a 10 minute warm-up

  * Cardiovascular/Aerobic training

* Paredes AH. Clinical Liver Disease 2012: Vol. 1 (4); 117-118
 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 31pts)
  * 3-5% wt decrease improves steatosis
  * 7-10% wt loss needed to improve necro-inflammation, NAS score

* Paredes AH. Clinical Liver Disease 2012: Vol. 1 (4); 117-118
* Harrison SA. Hepatology 2009; 49: 80-86
* Keating SE. J Hepatology 2012; 57: 157-166
Treatment

* **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!)

  * Mathurin P. Gastroenterology, 2009;137:2, 532-540
  * Chalasani N. Gastroenterology, 2012;142:1592-1609

* **Gradual weight loss**
  * Not exceed 3.5lbs or 1.6kg/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 400IU/day

- Klein EA. JAMA 2011;306 (14):1549-1556
247 pts with NASH **without** DM2, compared Vitamin E 800 IU daily vs. Actos 30 mg daily vs. placebo over 96 weeks:

- Vit 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

Metformin

- 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
Treatment

* 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-ethylenodeoxycholic acid)
- Farsenoid 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

[Graph showing trends in liver transplant percentage for Hepatitis C, Alcoholic Liver Disease, NASH + 50% CC, NASH]
Three-year patient and graft survival according to indication for liver transplantation among adults in the United States

* Charlton MR. Gastroenterology 2011;141(4):1249-1253
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
Galectin

- Animal model presented a very **high hurdle** for drug treatment: Cirrhosis induced with high dose toxin and continued throughout drug treatment
- Treatment with four weekly doses
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
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!
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
If NASH Cirrhosis

* Screen for HCC every six months with US

* Screen for Varices

* Vaccinate patients for HBC, HAV, Pneumococcal, Yearly Influenza
Objectives

* Prevalence
* Pathogenesis
* Diagnosis
* Testing
* Treatments
THANK YOU!