Non-Alcoholic Fatty Liver Disease: Evaluation and Management

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Relevant Disclosure and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

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I have no relevant financial relationships or affiliations with commercial interests to disclose.
The Case

A 49 yo man with PMH of HTN, OSA, and GERD presents for routine annual f/u. He has no new complaints. His medications include lisinopril, HCTZ, and esomeprazole. His OSA is well-treated with auto-CPAP. He does not smoke, drinks 2 drinks per night an average of 4 nights per week.


Fasting laboratory testing reveals: T. bili 1.7 mg/dl, AST 44 U/L, ALT 77 U/L. Cholesterol 191 mg/dl, HDL 48 mg/dl, LDL 122 mg/dl, TG 104 mg/dl. Alb 4.7 g/dL. Platelet count 248 K/mm3.

RUQ U/S reveals borderline hepatomegaly with prominent hepatic steatosis.
The Case

The best next step in this patient’s management would be:

A. Refer for liver biopsy.
B. Start metformin 500mg po daily.
C. Initiate workup for common causes of chronic liver disease
D. Order an abdominal MRI with liver protocol
E. Refer for stress echocardiogram to screen for cardiac disease
Objectives

• Understand the definition and basic pathophysiology of the disease
• Understand the clinical assessment and management NAFLD and NASH
• Know how to select patients for liver biopsy
• Know how to counsel patients on alcohol intake
Scope of the Problem

• Prevalence
  • Most common cause of liver disease worldwide
  • NAFLD 6-45% prevalence worldwide
  • 75 to 100 million Americans may have NAFLD
  • Approx. 6 million Americans with NASH
  • 600,000 Americans with NASH-related cirrhosis
  • Age > 50yrs + DM or obesity: 66% have NASH based on 2 large cohort studies

Rinella JAMA 2015
Ratziu Gastroenterology 2000
Angulo Hepatology 1999
Scope of the Problem

• Ties to Obesity
  • 1988-2008 obesity prevalence increase: 22 to 33%
  • Same time period NAFLD: 5.5 to 11% of chronic liver disease (NHANES)
  • Weight loss can reverse NAFLD
  • Improvement in liver histology is directly proportional to amount of weight lost

Rinella JAMA 2015
Scope of the Problem

• Risk
  • Approx. 10-30% of NAFLD may have NASH
  • Cirrhosis lifetime risk:
    • NAFLD <4%
    • NASH 20%
  • Mortality: Retrospective, Iceland, N=151 NAFLD
    • CV disease 42%
    • Malignancy 18%
    • Liver-related disease 18%

Rinella JAMA 2015
Haflitadottir BMC Gastroenterol 2014
Definition of the Disease

• Pathophysiology
  • Excessive TG accumulation in the liver
  • Spectrum:
    • Fatty accumulation without or with minimal non-specific inflammation
    • Steatohepatitis with necroinflammation
    • Fibrosis
    • Cirrhosis
  • Liver component of the metabolic syndrome
  • Insulin resistance + oxidative stress/inflammation

Petta Int J Mol Sci 2016
Definition of Disease

• Insulin resistance
  • Increased lipolysis and FFA production
  • Lipid intermediates promote lipotoxicity, free oxygen radicals, and mitochondrial dysfxn
  • ↑ ER and oxidative stress to the hepatocytes
  • ↓ Adiponectin levels → ↑ Cytokine mediated inflammation

Petta Int J Mol Sci 2016
Definition of Disease

• Pathophysiology
  • Leptin
    • ↑ Levels in obesity and NAFLD
    • ↑ Pro-inflammatory cytokine
    • Correlates with NAFLD severity
  • GLP-1
    • Potentiates insulin secretion, inhibits appetite and glucagon
    • Produced in gut
    • Anti-inflammatory mediated through GLP-1R receptors
    • Receptors reduced in NASH

Petta Int J Mol Sci 2016
Definition of Disease

• Pathophysiology
  • Glucagon
    • Up’d in NAFLD
      • Stimulates peripheral lipolysis and fatty acid oxidation
  • Insulin: Promotes fibrinogenesis
  • Iron: may contribute to oxidative stress in the liver

Petta Int J Mol Sci 2016
Definition of Disease
Definition of Disease

Figure 1. Liver histology
Histologic features of NAFLD as seen by hematoxylin and eosin staining of liver biopsy core tissue. A) normal liver, B) Non-alcoholic fatty liver—only macrosteatosis seen, and C) NASH—macrosteatosis is seen with ballooned hepatocytes, lobular inflammation, and pericellular fibrosis.

http://praxis.iuhealth.org/article/non-alcoholic-fatty-liver-disease
Definition of the Disease

• Risk Factors
  • Metabolic Syndrome
    • HTN, DM, hyperlipidemia, central obesity
  • Hispanic > White > Black
  • Prior cholecystectomy
  • Medications: amiodarone, methotrexate, tamoxifen, corticosteroids, valproate, antiretroviral medicines
  • PCO/hypothyroid/OSA/inborn errors of metabolism

Mishra J Clin Exp Hepatol 2012
Natural History

- **NAFLD**
  - **NASH**
    - Stable
    - Fibrosis
      - 25-35%
    - Cirrhosis
      - 9-20%
      - 10% over 7 years
    - Hepatoma
      - 22-33%
    - Liver Failure
      - 40-60% over 5-7 years
  - Stable
    - Death/Liver Transplant
      - 65-75%
    - 10% over 7 years

- **Non-NASH**
  - Stable
    - 70-90%
    - Majority
  - Key diagnostic points

Ong, et al. NHANES III, 2007 (mod)
Clinical Approach: Diagnosis

• Presentation
  • Majority are asymptomatic
  • RUQ pain, rest non-specific
  • Obese (57-95%)
  • Hepatomegaly (10%)
  • Incidental transaminitis
  • Ancillary finding on US
Clinical Assessment: Diagnosis

• Differential Dx:
  • Alcoholic (>210gms or 140gms/week over 2 years)
  • Viral hepatitis
  • Wilson
  • Autoimmune
  • Hemachromatosis
  • PBC
  • A1AT
Clinical Assessment: Diagnosis

1 Drink = 14gms EtOH

https://www.rethinkingdrinking.niaaa.nih.gov/
Clinical Approach: Diagnosis

• Diagnosis of NAFLD
  • Ultrasound
    • Detects > 30% fat
    • Sens: 82-100%, spec: up to 100%
  • MRI (preferred over MRS)
    • Detects down to 5% steatosis
    • MRI sens 77-90%, spec 87-91%
  • CT
    • Non-contrast
    • Best for moderate to severe steatosis
    • Sens 73-82%, spec 91-100%
Clinical Approach: Management

• *Lifestyle Modification*
  
  • Weight loss
    • Degree of histologic improvement directly proportional to amount to weight lost
    • 10% weight loss associated with histologic improvement
    • ITT trial of 154 subjects NAFLD by MRS, looking at dietician-supported lifestyle modification: 12 months
    • 64% resolved in treatment group, 20% control
    • 97% who lost more than 10% achieved resolution of NAFLD (MRS)

• *Exercise*
  
  • Unclear if independent effect on NAFLD
  • Does reduce peripheral, adipose, and hepatic insulin resistance

Rinella JAMA 2015    Wong J Hepatol 2013
Clinical approach: Management

• Pharmacologic
  • Pioglitazone
    • TZD that increases insulin sensitivity, lowers free fatty acids, enhances insulin signaling, reduces TNF alpha, and remolds adipose tissue
    • Multiple trials showing improvement in NAFLD, transaminases, and NASH
    • 12-month RCT of 74 patients on pioglitazone showed significant reduction in hepatocellular injury, Mallory bodies and fibrosis
    • AGA guideline recommends for bx-proven NASH with long-term safety caveat (1B)
    • Others limit use to those with DM.

Takahashi World J Gastro 2015
Guruprasad Gastroenterology 2008
Clinical approach: Management

• Vitamin E (alpha-tocopherol)
  • Fat-soluble vitamin with antioxidant properties
  • Heterogeneous studies
  • Decreases transaminase levels
  • Can improve steatosis, ballooning, inflammation, and can resolve steatohepatitis
  • No clear effect on fibrosis
  • Safety concerns: prostate cancer and hemorrhagic stroke
  • Recommended for non-DM patients with bx-proven NASH

Takahashi World J Gastro 2015
Clinical approach: Management

• Obeticholic acid (synthetic bile acid variant)
  • Farnesoid X nuclear receptor activator
  • Raises insulin sensitivity, decreases gluconeogenesis and circulating TGs
  • RCT/ITT trial of 283 patients with NASH/borderline NASH treated x 72 weeks. Improved histology in 45% vs 21%
  • No difference in NASH resolution
  • Pruritus and lipid elevation noted. Long-term safety not determined.

Neuschwander-Tetri Lancet 2015
Clinical approach: Management

• Liraglutide (Victoza)
  • GLP-1 receptor activator
  • ↑’s insulin secretion, ↓’s glucagon.
  • 48-week RCT of 52 patients with bx-proven NASH
  Resolution of NASH: 39% vs 9%
  • Progression of fibrosis: 9% vs 36%
  • Limited additional data, cannot be recommended

Armstrong Lancet 2016
Clinical approach: Management

• Metformin
  • Does not improve liver histology
  • Not recommended for treatment of NAFLD

• Statins
  • Limited studies with mixed results
  • Not recommended for treatment of NAFLD
  • Certainly beneficial for various comorbidities

Takahashi WJG 2015
Clinical approach: Management

- Coffee consumption
  - Meta-analysis of 5 studies
  - RR of developing NAFLD 0.71 (0.6-0.85)
  - RR of progressing to fibrosis 0.70 (0.6-0.82)
  - Amount of coffee consumption varied
  - Basic research supports antifibrotic effect
  - Unclear if caffeine is responsible agent

Wijarnpreecha Eur J Gastro Hepat 2017
Clinical Approach: Management

• Bariatric Surgery
  • Reduction in incidence of NAFLD
  • 22/23 studies that measured steatosis showed improvement
  • Restrictive and bypass both effective
  • Out of 23 studies: fibrosis improved in 14, unchanged in 6, worsened in 3
  • Rapid weight loss possibly fibrosis culprit
  • Mechanisms independent of weight loss include increased GLP-1 secretion and subsequent decrease in inflammation.
  • Increased adipocytokine levels likely tied to weight loss.

Bower Eur J Gastro Hepat 2015
Mattar Ann Surg 2005
Difficult Issues

- Differentiating NASH and fibrosis from NAFLD
- Should I biopsy?
- What about alcohol?
NAFLD vs NASH vs Fibrosis: Who to Bx?

• Biopsy
  • Gold Standard for NASH/fibrosis/cirrhosis
  • Metavir scoring system for fibrosis
    • F0: no fibrosis
    • F1: portal fibrosis without septa
    • F2: portal fibrosis with few septa
    • F3: numerous septa without cirrhosis.
    • F4: cirrhosis
  • Invasive, expensive, not popular with patients
  • Preferred diagnostic test in the U.S. for NASH and fibrosis

Rinella JAMA 2015
NAFLD vs NASH vs Fibrosis: Who to Bx?

• AASLD/ACG/AGA Recommendations:
  • Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis. (1B)
  • The presence of metabolic syndrome and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis. (1B)
  • Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and coexisting chronic liver diseases cannot be excluded without a liver biopsy. (1B)

Chalasani Am J Gastroenterol 2012
NAFLD vs NASH vs Fibrosis: Who to Bx?

• NAFLD Fibrosis Score
  • [http://nafldscore.com/](http://nafldscore.com/)
  • Age, BMI, glucose handling, transaminases, platelets, albumin
  • Developed in confirmed NAFLD patients
  • PPV and NPV for detecting significant fibrosis (F2): 82% and 88% (90% Caucasian, 98% > 21 yo)
  • Liver Bx avoided in 76%, correct prediction of Dx in 90%

Angulo Hepatol 2007
NAFLD vs NASH vs Fibrosis: Who to Bx?

• NAFLD Fibrosis Score cont.
  • Sens/spec = 77%/70% (Sun, 2016)
  • LR+ 2.6, LR- 0.33
  • Pre-test prob of 50%, positive result, post-test prob 72%
  • Pre-test prob of 50%, negative result, post-test prob 25%

Sun Hepatol Res 2016
NAFLD vs NASH vs Fibrosis: Who to Bx?

**NAFLD fibrosis score**

Online calculator


- **Age (years)**: 41
- **BMI (kg/m²)**: 27
- **IGF/diabetes**: □
- **AST**: 45
- **ALT**: 55
- **Platelets (x10⁹/μl)**: 289
- **Albumin (g/l)**: 4.7

**Score**: -0.877

- $< -1.455$: 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)

BMI: body mass index
IGF: impaired fasting glucose
NAFLD vs NASH vs Fibrosis: Who to Bx?

**NAFLD fibrosis score**

Online calculator


| Age (years) | 49 |
| BMI (kg/m²) | 26 |
| IGF/diabetes | off |
| AST | 44 |
| ALT | 77 |
| Platelets (×10⁹/µl) | 248 |
| Albumin (g/l) | 4.7 |

**Score** -0.386

≤ -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)

BMI: body mass index
IGF: impaired fasting glucose
NAFLD vs NASH vs Fibrosis: Who to Bx?

• Transient elastography
  • Prospective study, n=72 with NAFLD, bx gold standard
  • Sens 76% and spec 80% Metavir F2 LR+ 3.8, LR- 0.3.
  • Positive result: Pre-test prob 50%, post-test prob 79%
  • Negative result: Pre-test prob 50%, post-test prob 23%

Gaia J Hepatol 2011
NAFLD vs NASH vs Fibrosis: Who to Bx?

• Serologic testing
  • Fibrosure (patented serum panel)(LabCorp)
    • Most widely validated panel
    • ALT, α2-macroglobulin, apolipoprotein A1, total bilirubin, GGT, haptoglobin, age, and sex
    • For F2 fibrosis: Sens 61%, spec 83%
    • LR+ 3.59, LR- 0.47
    • Pretest prob of 50%: + result post-test prob 78%, - result post-test prob 32%
  • AST to Platelet Ratio Index (indirect serum markers)
    • (AST/ULN AST)/platelet count X 100
    • For F2 fibrosis: Sens 77%, spec 72% (cutoff of 0.7)(Lin 2011)
    • LR+ 2.75  LR- 0.32
    • Pretest prob of 50%: + result post-test prob 73%, - result post-test prob 24%

Sebastiani Aliment Pharmacol Ther 2011
Papastergiou Annals of Gastroenterology 2012
NAFLD vs NASH vs Fibrosis: Who to Bx?

• So, why biopsy?
  • Confirm the diagnosis when in question
  • Establish prognosis
  • Determine whether a candidate for pioglitazone or vitamin E
  • Follow disease progression
NAFLD vs NASH vs Fibrosis: Who to Bx?

- 619 patients with NAFLD, over half with non-NASH, almost 1/3 with NASH
- Retrospective analysis covering 12.6 years
- Causes of death: CV > non-liver malignancy > cirrhosis complications
- Long-term survival shorter with fibrosis, independent of NASH or non-NASH

Angulo Gastroenterology 2015
NAFLD vs NASH vs Fibrosis: Who to Bx?

• Outcome: HR for death or transplant based on fibrosis stage
  • Stage 1 HR 1.88 (1.28-2.77)
  • Stage 2 HR 2.89 (1.93-4.33)
  • Stage 3 HR 3.76 (2.4-5.89)
  • Stage 4 HR 10.9 (6.06-19.62)
  • Age HR 1.07 (1.05-1.08)
  • Current smoking HR 2.62 (1.67-4.10)
  • Statin use HR 0.32 (0.14-0.70)

• Outcome: HR for Liver-related events (ascites, HE, GE varices...)
  • Stage 3 HR 14.2 (3.38-59.68)
  • Stage 4 HR 51.5 (9.87-269.2)

Angulo Gastroenterology 2015
What about alcohol?

2012 Joint Guidelines AASLD/ACG/AGA:

“Patients with NAFLD should not consume heavy amounts of alcohol. (1B) No recommendation can be made with regards to non-heavy consumption of alcohol by individuals with NAFLD. (1B)”

Chalasani Am J Gastro 2012
What about alcohol?

“What several recent cross-sectional studies (147–153) suggest a beneficial effect of light alcohol consumption (on average less than one drink per day) on the presence (defined either biochemically or by imaging) and severity of NAFLD. There are no studies reporting the effect of ongoing alcohol consumption on disease severity or natural history of NAFLD or NASH. The effects of light drinking on the cardiovascular system and cancer risks, if any, have not been investigated in individuals with NAFLD.”

Chalasani Am J Gastro 2012
What about alcohol?

“In this article, authors reviewed the published literature relating to alcohol consumption and NAFLD and conclude that (a) heavy alcohol consumption has many harmful effects including those on the liver and should be discouraged regardless of whether an individual has NAFLD or not, (b) it is not known if cardiovascular and metabolic benefits of light to moderate alcohol consumption observed in the general population are extended to those with NAFLD, (c) epidemiological and cohort studies, that suggest light to moderate drinking may have hepatic benefits, are largely cross-sectional in nature and utilized surrogate endpoints, and (d) until further data from rigorously conducted prospective studies become available, we believe that individuals with NAFLD should avoid consuming alcohol of any type or amount.”

Liangpunsakul Am J Gastro 2012
What About Alcohol?

• Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with nonalcoholic fatty liver disease (NAFLD) (Dunn J Hepatol 2012)
  • 583 patients, questionnaire-based, avoided heavy drinkers and binge drinkers
  • Bx-based
  • Modest drinkers vs non-drinkers: OR for NASH 0.56 (0.39-0.84), fibrosis 0.56 (0.41-0.77), ballooning hepatocellular injury 0.66 (0.48-0.92)
  • More drinking the better for histology as long as not heavy...

• Roles of alcohol consumption in fatty liver: A longitudinal study (Moriya J Hepatol 2015)
  • Japanese trial, cross-sectional, U/S-based, 1-3 years only.
  • 5297 patients
  • Drinking as much as ≥ 280 grams/week in men protective against fatty liver OR 0.68.
The Case

The best next step in this patient’s management would be:

A. Refer for liver biopsy.
B. Start metformin 500mg po daily.
C. Initiate workup for common causes of chronic liver disease
D. Order an abdominal MRI with liver protocol
E. Refer for stress echocardiogram to screen for cardiac disease
The Case

• Viral hepatitis panel, AMA, ANA, anti-SM, A1AT level, ceruloplasmin, and ferritin/iron panel all normal.
• NFS was “intermediate”
• He was counseled to lose weight and avoid alcohol
• 2 years later, the patient has lost 6 pounds. He continues to consume alcohol at less than 210 gms/week.
• Repeat U/S 18 months after dx was unchanged.
• He has not been referred for bx.
Summary and Recommendations

• NAFLD is a spectrum ranging from NAFLD with no or minimal inflammation to NASH to fibrosis to cirrhosis
• Leading cause of death is CV
• Pathophysiology involves insulin resistance and oxidative stress resulting, to a large extent, from obesity
• Diagnosis is mainly by U/S or MRI in US.
• Treatment is largely weight loss, with as little as 5% improving histology and losses over 10% associated with resolution
• Biopsy should be considered for those in which the diagnosis is unclear or to estimate prognosis (?)
• Continued alcohol intake cannot be recommended based on current evidence
References


• Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA 2015;313:2263-73.


• Lee SS, Park SH. Radiologic evaluation of nonalcoholic fatty liver disease. World J Gastroenterol 2014;20:7392-402.


References

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• Liangpunsakul S, Chalasani N. What should we recommend to our patients with NAFLD regarding alcohol use? Am J Gastroenterol 2012;107:976-8.


Questions?