Preparing for the NASH Epidemic: A call for action to PAs

Rick Davis, PA-C
Division of Gastroenterology
University of Florida

Conflicts of Interest

- Rick Davis, PA-C has no disclosures to report

NASH Epidemic
Learning Objectives

- Define and differentiate Non-alcoholic steatohepatitis (NASH) from NAFLD
- Review the epidemiology of NASH, association as a multi-system disease, and mortality
- Be able to diagnose NASH by non-invasive testing and assess stage of disease
- Become familiar with treatment regimens for NASH to reduce steatosis, delay fibrosis, and monitor complications of cirrhosis

NASH Epidemic: Call to Action

Gastroenterol 2021;161: 1030-42

- American Gastroenterological Association (AGA) + 7 professional international societies held a conference to address the increasing global burden of NAFLD/NASH
- Included 50% PCP, GI, Hepatology, Endocrinology
- Urged a unified public health response
- NASH becoming most common cause of liver disease worldwide
- Increasing morbidity and mortality
- Leading indication for liver transplantation

NAFLD: Definitions

- NAFLD: Histology of > 5% macrovessicular steatosis in individual without significant EtOH use (< 30 g/d men;< 20g/d women)
- NASH (Non-Alcoholic Steatohepatitis): histologic evidence of steatosis, cellular ballooning degeneration, and lobular inflammation.
- Ref: Clin Gastro Hepatol 2015;13: 2062

NASH

- Metabolic Syndrome related features:
  - Abdominal obesity, increased waist circumference
  - Dyslipidemia, increased triglyc, decr HDL
  - Impaired glucose tolerance
- NAFLD is the hepatic manifestation of metabolic syndrome

NASH: Mortality

- Fibrosis stage strongest predictor of mortality
- C-V disease: 13-30%
- All cause malignancy: 6-28%
- Liver related death: 2.8-19%

- Clin gastro hepatol 2015;13: 2062

NASH: Diagnosis

- How Can We Identify Patients at Risk for NASH?

NAFLD Presentation

Symptoms

- Usually asymptomatic, majority discovered by chance
- Fatigue frequently present

- Often an "incidental finding"
  - Incidental abnormal LFTs
  - Incidental "bright liver" on imaging
  - Incidental hepatomegaly

Common Scenarios

- Statin monitoring
- "Annual reviews" in T2DM/lipid/ hypertension clinics
- Medical insurance/occupational health checks

NAFLD

- NAFLD is the most common diagnosis in patients with ‘incidental’ abnormal LFTs
- **Liver enzymes may be normal in up to 80% of NAFLD patients**
  - Transaminases are not a sensitive test for NAFLD/NASH
  - Poor correlation between ALT and histology
  - **ALT typically falls with advanced fibrosis**
  - **ALT > AST → ALT < AST**
- Severity of histology in NAFLD with normal LFTs no different from those with abnormal LFTs
- Mofred et al. Hepatology, 2003

Clinical Predictors of NASH in Pts With NAFLD

Characteristic	Outcome
Advanced age	Greater duration of disease
Sex	Postmenopausal women experience accelerated disease
Race	↑ Prevalence, severity in Hispanic, Asian pts; ↓ prevalence, severity in black pts
HTN, central obesity, dyslipidemia (↑ TG, ↓ HDL), insulin resistance/diabetes	Risk increases with metabolic syndrome,* 66% prevalence of bridging fibrosis if older than 50 yrs of age and obese or diabetic[6,7]
AST/ALT ratio > 1,low platelets	Indicators of advanced fibrosis/cirrhosis in NASH
Persistently elevated ALT	Can be associated with greater risk of disease progression

*Based on ATP III criteria.

Hepatol 2008;48: 792; Gut 2010;59: 1265

NAFLD: Assessment of Fibrosis

- Liver biopsy, best but invasive
- Fibrosis calculators from readily available routine labs
- Imaging: U/S, CT, MR
- Fibrosis scans: elastography, fibroscan, MR-elastography; measure ‘stiffness’ of liver, not anatomy

Calculators for Liver Fibrosis/Function

- FIB-4
  - (Age*AST/(Platelets*Sq root [ALT])
  - FIB-4 score < 1.45 neg pred value 90% for advanced fibrosis, with 81% sensitivity
  - > 3.25 PPV 65% for advanced fibrosis, with 97% specificity

Reference: Sterling et al, Hepatol 2006;43: 1317

APRI: AST to Platelet Ratio Index)

- APRI score = AST/ULN AST /plts x 100
- -APRI > 1.0 sensitivity 76%, specificity 72% for predicting cirrhosis
- -APRI < 0.5 neg pred value to r/o cirrhosis
- -Should be used with multiple indices to assess for advanced fibrosis

Reference: Lin ZH, et al. Hepatol 2011;53: 726

NAFLD Fibrosis Score

- Age, BMI, impaired fasting glucose (y/n), AST, ALT, Plts, Albumin
- Score < -1.455, no significant fibrosis F0-F2, neg pred valued 93%
- Score > 0.676, likely F3-F4 advanced fibrosis/cirrhosis, pos pred value 90%
- “nafldscore.com”

Ref: Angelo P, et al. Hepatol 2007;45(4): 846

FibroSure (proprietary)

- 6 serum markers: alpha-2 macroglobin, haptoglobin, GGT, ALT, Apolipoprotein A1, bilirubin
- Fibrosis score:
  - < 0.21 stage 0, no fibrosis
  - > 0.74 stage 4, cirrhosis

Ref: Ratziu et al. BMC Gastroenterology 2006;6:6.

Goals of NASH Treatment

- Improve metabolic abnormalities
- Decrease inflammation
- Prevent/arrest/reverse liver fibrosis
  - AASLD recommends pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis
- Prevent advanced liver disease, liver failure, liver cancer and related outcomes
- Systemic outcomes (eventually)

NAFLD: Treatment

- Exercise: 120 min aerobic exercise weekly (running/swimming)
- Diet: Men: 1200-1600 cal/d,Women 1000-1200 cal/d
- Weight loss of > 7%/year may improve histology of NASH
- NHANES study: 2 cups caffeinated coffee/d, decreased risk of NAFLD, risk reduction of NASH fibrosis

Ref: Clin Gastro Hepatol 2015;13: 2062

AASLD (2018) use of Pioglitizone in NASH

- Improves liver histology in patients with and without T2DM and biopsy-proven NASH
  - May be used in treatment
- Should not be used in NAFLD without biopsy-proven NASH
- 2.5 to 4.7-kg weight increase in body weight with 12- to 36-month treatment
- Recent meta-analysis refutes concern about bladder cancer
- Black box warning of possible CHF in susceptible individuals
- Bone loss may occur

AASLD Vitamin E in NAFLD Treatment

- Vitamin E, 800 IU/d
  - Beneficial in non-Diabetes Mellitus
  - Avoid in NASH cirrhosis
  - Avoid in patients with DM
  - Avoid in NAFLD patients without a biopsy

- Chalasani, N, et al. Hepatology 2018;67: 328-35.

(AASLD): Bariatric surgery in NASH

- Improved all cause mortality of 30-40% within 7-10 yrs of surgery
- Roux-Y gastric bypass
- Gastric sleeve
- Usually deferred in advanced fibrosis and risk of portal hypertension, high MELD score

AASLD NASH Treatment Guideline

- Management of NAFLD should consist of treating liver disease and associated metabolic comorbidities such as obesity, hyperlipidemia, insulin resistance, and type 2 diabetes
  - Pharmacologic treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis

AASLD NASH Treatment Guideline

- Dietary and lifestyle modification (basis of any management strategy, but challenging for many patients to achieve and maintain)
  - Weight loss (hypocaloric diet ± physical activity)
    - 3% to 5% loss: generally reduces hepatic steatosis
    - 7% to 10%: needed to improve most histopathologic features of NASH, including fibrosis
  - Exercise alone
    - May improve or reduce hepatic steatosis
    - Impact on liver histology is unknown

Future Therapies for NASH/NAFLD

- Various targets affecting steatosis, inflammation, and fibrosis
- Side effect profiles

NASH: Summary

- Most common cause of elevated ast/alt
- Advanced disease can occur with normal enzymes
- NASH with risk of progressive liver disease and complications of cirrhosis and primary liver cancer (HCC)
- Pathogenesis: caloric excess with development of obesity and insulin resistance, genetic predisposition, metabolic syndrome

NASH: A Call to Action

- “The upward trend in NAFLD/NASH incidence and prevalence underscores the importance and urgency of developing and implementing effective screening, diagnosis, and treatment strategies in the United States and globally, particularly among emerging at-risk cohorts, such as patients with diabetes and obesity.”

- Gastroenterol 2021;161: 1030-42.

NASH: A Call for Action by PAs

- Do not ignore mild elevations of ast/alt or ‘fatty liver’ on imaging
- Use Fibrosis calculators to identify pts at risk
- Non-invasive fibrosis measures, e.g. Elastography, Fibroscan more readily available
- Refer to GI/Hepatology for advanced fibrosis
- Initiate therapies as discussed
- Treatments are available for select patients with NAFLD/NASH and more in development