Non alcoholic fatty liver disease in 2019

Sandeep Mukherjee, MD
CHI Health Creighton University
Division of Gastroenterology

Disclosures and Terminology

• Principal investigator: Regenerate study
• Section editor: Dynamed Plus
• NAFLD non alcoholic fatty liver disease
• NASH non alcoholic steatohepatitis
Nonalcoholic fatty liver disease

• Epidemiology
• Etiology and risk factors
• Natural history
• Pathophysiology
• Pathology
• Diagnosis-invasive vs non-invasive
• Treatment-current and future
• Summary

Epidemiology

• Prevalence of obesity increasing in developed (29 to 37%) and developing countries (8-13%) from 1980-2013
• Paralleled by increasing prevalence of NAFLD – influenced by screening test
e.g. 30% by MRI in Dallas Heart study 2004; 46% by ultrasound 2011
• Prevalence of NASH more challenging as biopsy required ...
• **USA: 12%** prevalence in middle aged patients, **56-69%** if diabetes present and advanced fibrosis in **37-50%**

Bazick J et al. Clinical model for NASH and advanced fibrosis in adult patients with diabetes and NAFLD/ Diabetes Care 2015;38:1347-55
Epidemiology

- Prevalence of both NAFLD and NASH underestimated in the United States
- Up to 100 million adults may have NAFLD and up to 25 million with NASH
- Approximately 750,000 have stage 2 or higher fibrosis (scale from 0-4; 4 is cirrhosis)

Etiology and risk factors

- Most common: obesity and insulin resistance
- Can NAFLD/NASH occur in patients with a normal BMI?
- Younger patients, not obese, elevated liver tests and fatty liver on imaging...... think outside the box
Natural history

- Good news and bad news...
- Good news-vast majority of NAFLD patients progress slowly or not at all
- 70-75% with NAFLD have isolated steatosis +/- inflammation
- Steatosis only: zero to minimal progression
- Steatosis +/- inflammation: some will progress but much longer than biopsy proven NASH (non-NASH NAFLD)
Natural history

• NASH patient with fibrosis at baseline: different prognosis
• Fibrosis progresses by 1 stage every 7 years
• 33 year follow-up study from Sweden; fibrosis was a strong predictor of
  • (1) overall mortality
  • (2) cardiovascular disease
  • (3) infectious disease
  • (4) cirrhosis and
  • (5) hepatoma
• Now surpassed alcoholic liver disease as the 2nd leading indication for liver transplantation after HCV in USA

Ekstedt M, et al. Fibrosis stage is the strongest predictor for disease specific mortality in NAFLD after up to 33 years if follow up. Hepatology 2015;61:1547-54
Wong RJ, et al. NASH is the second leading etiology of liver disease among adults awaiting liver transplantation in the US. Gastroenterology 2015;149:278-81

Pathophysiology of NASH
Pathophysiology of NASH

Pathogenesis of Nonalcoholic steatohepatitis. Machado MV, Diehl AM. Gastroenterology 2016;150: 1769‐77

Pathology of NASH and disease progression

Rinella ME. Nonalcoholic Fatty Liver Disease A Systematic Review. JAMA. 2015;313:2263-2273
Nonalcoholic fatty liver disease Activity Score (NAS)

<table>
<thead>
<tr>
<th>LIVER HISTOLOGY</th>
<th></th>
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<tbody>
<tr>
<td>Steatosis</td>
<td>0-3</td>
</tr>
<tr>
<td>Portal inflammation</td>
<td>0-3</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td></td>
</tr>
<tr>
<td>Ballooning</td>
<td>0-2</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0-4</td>
</tr>
<tr>
<td>NAS score</td>
<td>0-12 [NASH &gt;5..controversy]</td>
</tr>
</tbody>
</table>

Liver pathology in pediatric NAFLD

- Different from adults
- More steatosis, less ballooning and more PORTAL based inflammation and fibrosis
- Role of hedgehog and Wnt/β pathways
- Zone 1 steatosis-more likely to have advanced fibrosis vs Zone 3 (more likely to have steatohepatitis)


Diagnosis of NASH-why?

- Confirm diagnosis, determine prognosis (remember NASH patients with fibrosis are at highest risk for disease progression)
- Non-invasive tests better at detecting advanced disease
- Clinical trials - histological diagnosis required
- Only 31% of providers perform liver biopsies in patients with NAFLD to confirm NASH
## Diagnosis of NASH

**Non-invasive (cannot distinguish NAFLD from NASH)**
- Serum markers (indirect and direct)
- Imaging modalities utilizing shear wave technology
- US, CT, MRI

**Invasive (liver biopsy)**
- Low risk but not inconsequential
- Inconvenience for patient with morbidity


## Serum markers

**NAFLD Fibrosis score** (Age, BMI, impaired fasting glucose or diabetes, AST:ALT ratio, plt, albumin)

**FIB-4** (Age, AST, ALT, plt )

BARD score (BMI, impaired fasting glucose or diabetes, AST, ALT )

AST/ALT ratio

http://gihep.com
http://mdcalc.com
Imaging modalities

- Vibration controlled transient elastography / VCTE (Fibroscan) - FDA approved
- Supersonic shear imaging (SSI)
- Acoustic radiation force impulse (ARIF)
- Magnetic resonance elastography (MRE)
  Quality of shear wave transmission influenced by ascites, visceral fat, recent food ingestion
- MRI based Liver MultiScan

MRI based Liver MultiScan

- Measures iron and fat with a novel method for calculating inflammation and fibrosis using corrected T1 technique

Treatment of NASH

Tilg H. How to approach a patient with nonalcoholic fatty liver disease. Gastroenterology 2017;153;345-99

Treatment-current and future

- Risk factor reduction (obesity, insulin resistance)
- Weight loss effective in improving NASH
- 3% wt.loss: steatosis ↓ (35-100%)
- 5% wt.loss: inflammation, ballooning ↓ (41-1005)
- 7% wt.loss: resolution of NASH (64-90%)
- ≥10% or wt.loss: fibrosis ↓ (45%)

Vilar Gomez E, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149;367-78
Current Treatment

- However.....
- No specific diet produces benefit in absence of weight loss
- Recommend net negative of 500 kcal per day with limiting fructose and increase in physical activity
- Most patients unable to achieve or maintain weight loss

*Dudekula A, et al. Weight loss in NAFLD patients in an ambulatory care setting is largely unsuccessful but correlates to the frequency of clinic visit. PLoS One 2014;9:e111808*

Current Treatment

- Morbidly obese individuals with NASH-bariatric surgery may be appropriate in selected patients
- No FDA approved medications for NAFLD or NASH
- Pioglitazone and Vitamin E-best studied in PIVENS trial but limitations

The Future

• Exciting time for NAFLD
• Multiple compounds in various stages of development (>20)
• One example: OBETICHOLIC ACID (farnesoid X nuclear receptor agonist) vs placebo studied in 238 patients for 72 weeks-stopped early and phase 3 study in progress


Teaching points

• Fatty liver disease is a public health problem (adults and children)
• 2nd most common cause of liver transplantation in the United States
• Be aware of limitations of non-invasive tests
• NASH patients with fibrosis at highest risk for disease progression
• Refer patients with NASH to specialty clinics/clinical trials

Chalasani N et al. Hepatology 2018;67:328-57
The most common indication for liver transplantation in the United States is NASH

True
False

The most common risk factors for fatty liver disease are:

- Alcohol
- Hepatitis C
- Obesity and insulin resistance
- Wilson disease
- Lipodystrophy
What percentage of patients with NAFLD undergo liver biopsies to confirm NASH?

- 10% A
- 20% B
- 30% C
- 40% D
- 50% E

What is the main source of hepatic fatty acids in patients with NASH?

- De novo lipogenesis
- Lipolysis in adipocytes
- Diet
- Hepatitis C
- Alcohol
Which of the following medications is FDA approved for the treatment of histologically-confirmed NASH in patients with obesity and diabetes?

- Obeticholic acid
- Ursodeoxycholic acid
- Vitamin E and pioglitazone
- Simvastatin
- None of the above