Beyond Obesity: The Spectrum of Nonalcoholic Fatty Liver Disease

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Non Alcoholic Fatty Liver Disease (NAFLD) Definitions
Accumulation of fat within the liver (hepatic steatosis) with no other known cause of hepatic fat accumulation
No evidence of excessive alcohol use
Men: 3 drinks / day  Women: 2 drinks / day
Presence of fat defined by imaging or biopsy of liver

Classification of Fatty Liver
Nonalcoholic fatty liver disease (NAFLD): Simple steatosis or fat build up within the liver
Nonalcoholic steatohepatitis (NASH): Fatty liver with associated inflammation and possible fibrosis (mild to advanced cirrhosis)
Cryptogenic cirrhosis: often a result of end stage NASH. Fat may be absent at that point

NAFLD Spectrum
Normal Liver  Fatty liver (Steatosis)  Cirrhosis  Steatohepatitis with inflammation and fibrosis

NAFLD Risk Factors
• Obesity
• Metabolic syndrome
• Type 2 diabetes
• Hyperlipidemia

Other Causes of hepatic steatosis
• Hepatitis C, especially genotype 3
• Starvation and rapid weight loss
• Parenteral nutrition
• Reyes syndrome
• Acute fatty liver of pregnancy / HELLP syndrome
• Inborn errors of metabolism
• Medications: amiodarone, tamoxifen, methotrexate, steroids, HIV meds, valproate
• Occupational exposure to organic solvents
Portion size escalation and obesity
Average commercial cheeseburger

20 years ago
333 calories

Now
1300 Calories

Prevalence of obesity and metabolic syndrome is on the rise
NAFLD/NASH is often the earliest manifestation of the metabolic syndrome / type 2 DM and presents with increased ALT
Is a disease of all ages, ethnicities, and genders
Higher risk among hispanics, lower in African Americans

NAFL/NASH

* NAFLD—Histological Spectrum
  - Cirrhosis
  - Fibrosis
  - Lobular Inflammation
  - Macrovesicular Steatosis

328 pts in Texas
Av. BMI 30
Liver bx if usg abnormal
17% NASH pts had nl alt

Fatty Liver: Natural History

Clinical Evaluation of NAFLD / NASH

Typical patient: Middle age, overweight, asymptomatic and found to have abnormal liver tests or liver imaging

Potential symptoms: RUQ discomfort, fatigue, signs and symptoms of cirrhosis if advanced

Potential co-morbidities: diabetes, htn, ↑lipids

Potential physical findings: hepatomegaly, findings of cirrhosis if advanced

Lab findings: elevated liver tests, abnormal imaging of liver

NAFLD — Pathogenesis

First Hit → NAFLD → Second Hit → NASH

Insulin resistance
↑ Fatty acids
↑ Triglycerides in liver
Type 2 Diabetes
Hyperlipidemia

Hepatic iron
Leptin
Oxidative stress
Intestinal bacterial microbiome
Lipid peroxidation
Altered cytokines

Potential targets for treatment...

Genetic predisposition to NAFL

PNPLA 3
NCAN
LYPLAL1

Clinical Evaluation of NAFLD / NASH

Top causes for elevated liver enzymes in my own practice

• Fatty liver / NAFL / NASH
• Alcohol
• Medications and herbal supplements
• Hepatitis C / B / A
• Structural liver disease: stones, strictures, tumors
• Heart disease
• Rare conditions: iron overload, other viruses, autoimmune disease, wilsons, Alpha 1 antitrypsin deficiency

• Abnormal liver tests in majority of patients with ALT > AST. Alk Phos and bili typically normal
• Low albumin or platelet count suggests cirrhosis
• By definition, other liver serologies are all normal

Hepatitis B surface antigen
Hepatitis C Antibody
Iron, Ibc, ferritin
ANA, +/- anti smooth muscle and mitochondrial ab,
celiac serology (TTG IgA), Alpha 1 anti trypsin,
ceruloplasmin, HIV

• Work up for DM, ↑lipids, BP, etc
• Liver biopsy: NAFL vs NASH vs Cirrhosis

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Liver Imaging in NAFLD

Ultrasonography
- Echo texture of liver tissue
- Blurring of vasculature
- 85-95% sensitive if liver fat is > 30%
- Findings are nonspecific with PPV of 62%

CT Imaging in NAFLD
- Decreased liver attenuation when compared to spleen
- High sensitivity with better specificity than USG with PPV of 76%

MRI Imaging in NAFLD
- More sensitive than CT for detecting fat
- Much more specific and can quantify fat which is useful for research

Assessment of liver fibrosis in NAFLD
- Liver biopsy: Stage 0 – 4 / F0 – F4. Sampling error is an issue. Identifies NASH
- Fibrosis blood tests (fibrosure, etc)
- Ultrasound based transient elastography
  - Fibroscan
  - ARFI (acoustic radiation force interface)
- MRI elastography: Allows for quantification and evaluation of distribution of fibrosis. Helpful for research

MRI Elastography

MRI Imaging in NAFLD

Natural History of NASH
Natural history of survival in patients with liver cirrhosis: Systematic review of 118 trials


Complications of Cirrhosis
- Ascites
- Encephalopathy
- Liver cancer
- Esophageal varices
- Malnutrition
- Death

Cardiovascular Disease and NAFLD
- NAFLD is an independent risk factor for CV disease
- CV disease is the leading cause of death in NAFLD, more than liver disease

Treatment of NAFLD / NASH
- Weight loss, diet, and exercise are the most important factors in treatment
  - Decreased liver enzymes
  - Decreased steatosis
  - Improved histology
  - Improved lipids / BS with benefit on CV morbidity
  - Improved quality of life
- Weight loss meds may provide benefit
- Exercise has a benefit independent of weight loss

Cirrhotic Ascites – Survival

Bariatric surgery
Bariatric Surgery and NAFLD

- Frequently leads to significant and sustained weight loss
- Multiple uncontrolled studies have shown benefit with decreased steatosis, inflammation, and fibrosis
- Increased surgical morbidity if portal htn present but not if early cirrhosis is present without portal htn
- Viable option for some but not all patients

Barker JB, et al, Am J Gastro 2006;101(2);368-373

Coffee consumption and NAFLD

Coffee consumption of > 3 cups per day has been associated with lower hepatic fibrosis levels in patients with alcoholic liver disease, Hepatitis C, and NASH in observational studies


NAFLD: What about alcohol?

- Heavy alcohol clearly associated with liver disease, fatty liver, and obesity
- However, multiple longitudinal studies have now shown potential benefit of light alcohol use in NAFLD
- Is the type of ETOH important?

Vitamin E and NASH: PIVENS Trial

- 247 non-diabetic patients with NASH randomized to placebo, vitamin E 800 iu daily, or pioglitazone for 2 years
- Pre and post liver biopsies performed
- Significant histologic improvement seen with both vitamin E and Pioglitazone

Vitamin E and Thiazolidinediones (TZD’s) may be of benefit for treatment of NASH

Pioglitazone and NASH

- Recent RCT with 101 prediabetic and type 2 diabetics with biopsy proven NASH
- Weight loss diet + pioglitazone 45 mg / day or placebo; biopsies at 0,18, and 36 months
- 58% vs 17% had histologic improvement of NASH and 51% vs 19% had NASH resolution
- Pioglitazone patients gained 2.5 kg vs placebo
- No improvement in fibrosis levels (short f/u)

Ken Cusi et al, Annals of Internal Medicine Online, June 21, 2016; Long Term Pioglitazone Treatment for Patients With NASH and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Controlled Trial

Incretin Mimetics for NASH

Victoza (Liraglutide) GLP-1 Analogue
- 3 y study of 52 patients
  - 39% resolved NASH vs 9% on placebo
  - 9% had progression of fibrosis vs 36% on placebo
Byetta (Exenatide) decreased steatosis and fibrosis markers


Other agents with potential benefit in NASH

Obeticholic acid (Ocaliva): Novel bile acid / Farnesoid X ligand

Emricasan: antifibrosis, caspase inhibitor. In development
Pentoxifylline (Trental): preliminary data promising and can be considered in severe disease
Elafibranor: PPAR agonist. Preliminary studies show resolution of NASH without worsening of fibrosis

Conclusions

NAFLD and NASH are extremely common and are related to the obesity epidemic
Insulin resistance and genetics are the driving factors
NAFL alone is relatively benign but NASH has significant morbidity risk
Sustained gradual weight loss along with exercise are the hallmark therapies
Pharmacologic therapies for NASH remain in early stages of development