Fatty liver: The Silent Epidemic

What is it and what can we do to fight it?

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Outline

▪ NAFLD basics
▪ NAFLD: diagnosis and staging
▪ Complications of NAFLD
▪ Management of NAFLD
What is nonalcoholic fatty liver disease (NAFLD)?

- Nonalcoholic fatty liver disease (NAFLD) occurs when fat is deposited in the liver, without other causes of fatty liver identified.
NAFLD: Non-Alcoholic Fatty Liver Disease

Spectrum of disease

- NAFLD
  - NAFL: Fat without inflammation
  - NASH: Fat + inflammation
    - NASH + fibrosis
    - Cirrhosis: 20-30% of NASH
    - HCC
NAFLD: Non-Alcoholic Fatty Liver Disease

Spectrum of disease

NAFLD

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Fat without inflammation

NASH
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HCC
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HCC
Who is at risk for NAFLD?

• Metabolic syndrome:
  – Obesity (“apples” > “pears”)
  – High blood sugar
  – High blood pressure
  – High cholesterol (and/or low “good” cholesterol)
Who is at risk for NAFLD?

- Other risk factors
  - Hispanic ethnicity
  - Hereditary/genetic
  - Polycystic ovarian syndrome (PCOS)
  - HIV
  - Sleep apnea
  - Hypothyroidism
Prevalence of Self-Reported Obesity Among Adults, 2016
Epidemiology

- Prevalence of NAFLD: ___ US population
- Prevalence of NASH: ___% population
Epidemiology

- Prevalence of NAFLD: 16-29% US population

- Prevalence of NASH: 2-7% population

Epidemiology

- Prevalence of NAFLD: **16-29%** US population
  - 2/3 of obese adults
  - **84-96%** bariatric surgery population
  - Up to **76%** of diabetics

- Prevalence of NASH: **2-7%** population
  - **10-30%** of NAFLD
  - **20%** of obese adults

How would I know if I have NAFLD?

- Symptoms
  - Many (up to 77%) of patients may have none
  - Fatigue (50-75%; may in part be related to sleep apnea)
  - Right-sided abdominal pain
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- **Presence of risk factors** (e.g., obesity, diabetes)

- **Lab tests:** elevation of $\text{ALT} > \text{AST}$ (usual pattern)

- **Radiology:** fat can be seen on ultrasound, MRI, or CT scan
How would I know if I have NAFLD?

- Screening of the general population is not currently recommended
  - US guidelines (AASLD) suggest high level of suspicion in high risk patients
  - European guidelines (EASL) recommend screening all patients with obesity or metabolic syndrome with liver enzymes and ultrasound
Should I see a liver specialist if I have NAFLD?
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- **Accurate diagnosis**
  - Make sure no other forms of liver disease
  - Determine which sub-type of NAFLD you may have (NAFL vs NASH)
  - Evaluate for liver scar (fibrosis)
  - Liver biopsy may be needed

- **Monitoring**
  - Look for signs of worsening of liver scar
  - Special monitoring if cirrhosis present
How is NAFLD diagnosed?
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- Establish presence of fat in the liver: ultrasound, MRI, or biopsy
- Eliminate other causes of liver disease (blood tests)
- Alcohol intake < 2 drinks per day
- No medications known to cause fatty liver (e.g., prednisone, tamoxifen)
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NAFLD is a diagnosis of exclusion
Role of liver biopsy in NAFLD

- Classify NAFLD accurately: NASH vs NAFL
- Determine fibrosis stage
- Eliminate other causes of liver disease
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Pros

• Most reliable means for excluding alternative etiology/co-existing liver disease

• "Gold standard" for diagnosis and staging
Liver Biopsy in NAFLD

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**Pros**
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**Cons**
- Sampling error
- Risk of complications
- Expense
- Impossible to apply to large NAFLD population
Transient Elastography: Fibroscan
Fibroscan

- Factors that may produce inaccurate results:
  - Obesity
  - NASH
  - Alcohol use
  - Nonfasting state
  - Abnormal liver tests (ALT>100, elevated alkaline phosphatase)
  - Hispanic ethnicity

- Requires adequate experience to produce reliable results
Why is accurate diagnosis and staging important?
NAFLD: Non-Alcoholic Fatty Liver Disease

Spectrum of disease

NASH
- 7 years per 1 stage
- ~28 years 0 → cirrhosis

NAFL
- 14 years per 1 stage
- ~56 years 0 → cirrhosis
Prognosis of NAFLD by fibrosis stage

- **Steatosis**: 12-40%
- **NASH ± F1-F2 fibrosis**: 14%
- **Advanced F3 fibrosis**: 5-10%
- **Cirrhosis**: 8%
- **Death/LTx**: 25-50%
- **HCC**: 7%

What are the consequences of NAFLD?
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- Leading causes of death
  1. Heart disease
  2. Cancer
  3. End stage liver disease
NAFLD and Liver-related events

- Severity of liver fibrosis is the most important predictor of death
- Patients with NAFLD are at risk for liver cancer (HCC)
  - 7-8-fold greater than the general population
  - Risk in NASH cirrhosis: 6.7-15% at 5-10 years
- Unlike other diseases, cirrhosis may not need to be present
NASH is increasing as an indication for liver transplantation

Wong, Gastroenterology, 2015.
NASH is the leading indication for LT in women

Noureddin, AJG, 2018.
What treatments are available that improve NASH?
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Weight Loss

- **Goal:** loss of 7-10% baseline weight to improve NASH and fibrosis

- **Diet**
  - Portion control and simple carbohydrate avoidance
  - Avoid fructose-sweetened beverages

Promrat, *Hepatology*, 2010
Weight Loss

- Exercise
  - Exercise alone reduces liver fat
    - Aerobic >150-250 minutes per week
    - Resistance training 45 minutes/day x 3 days/week

## Exercise

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<th>Level</th>
<th>Examples</th>
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<td>Light</td>
<td>Walking slowly, computing, cooking, washing dishes</td>
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<tr>
<td>Moderate</td>
<td>Walking briskly, light biking, vacuuming, mowing lawn</td>
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<tr>
<td>Vigorous</td>
<td>Jogging, fast biking, Zumba, shoveling, carrying heavy loads</td>
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Barriers to exercise
Associated comorbidities

- Obstructive sleep apnea: fatigue, headache
- Osteoarthritis: pain, decreased mobility
- Depression: decreased activity and motivation
- Balance problems
- Generalized weakness
- Cognitive deficits

Prescription for exercise: behavioral strategies

- Motivation
- Attainable
- Measurable
- Memory
- Positive thoughts
- Reinforcement
- Environmental support
- Stress management
- Social support
- Problem solve

Weight Loss

- Bariatric Surgery
  - Foregut procedures (Sleeve gastrectomy, Roux-en-Y gastric bypass, Lap band)
  - Improvement in NAFL/NASH +/- fibrosis
  - Relatively contraindicated in patients with cirrhosis
    - If needed, laparoscopic sleeve gastrectomy by an experienced surgeon is the operation of choice

Promrat, *Hepatology*, 2010
Treatment of Metabolic Syndrome in NAFLD

- **Statins**
  - Safe for use in NAFLD
  - Potential benefits of NAFLD/liver enzyme improvement and reduced risk of liver death or HCC
    - Not proven in randomized controlled trials

- **Metformin**
  - Safe for use in NAFLD
  - Some studies show improvement in liver biopsy and liver enzymes
    - Not proven in randomized controlled trials
  - Possible anti-neoplastic effects
Medications to treat NAFLD

- Only patients with biopsy-proven NASH need liver-specific treatment
- Medications currently available recommended for treatment of NASH
  - Vitamin E
  - Pioglitazone (Actos)
Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D.,

Improvement in NASH on Liver Biopsy

- **Vit E:** 43% (P = 0.001)
- **Placebo:** 19% (P = 0.04)
- **Pioglitazone:** 34%

Study included only non-diabetics.
NAFLD pathways/targets for treatment
Future potential NASH treatment

- Phase 3 clinical trials:
  - Cenicriviroc
  - Elafibranor
  - Obeticholic acid

- At least 40 other medications in phase 1 and phase 2 trials
NAFLD: shared management between primary care and hepatology
Is it safe to drink alcohol if I have NAFLD? If so, how much?
Harvard Medical School, and
National Institute on Aging

Study in Progress
RX = 100 Bottles of Red Wine/Day

To Science!
Alcohol and NAFLD

- NASH prevention?
  - Possible benefits of modest alcohol intake on presence of NASH
- Any alcohol use may prevent improvement in NAFLD over time and may increase fibrosis progression

Alcohol and NAFLD

- Once NASH/NAFL diagnosed:
  - Modest or moderate alcohol intake may prevent improvement in NAFL/NASH
  - Binge drinking is associated with fibrosis progression in patients with pre-existing NAFLD

Dunn, J Hepatol, 2012.
Alcohol and NAFLD

No recommendations/data regarding “safe” alcohol intake in patients with established NASH
Summary

- NAFLD is common, and most patients with metabolic syndrome comorbidities will have NAFLD, with at least 16 million in the US having NASH.
- NAFLD is an umbrella term that includes NAFL and NASH.
  - NASH>>>NAFL has risk of progression to cirrhosis.
  - Biopsy is needed to characterize NAFLD.
- Leading cause of death in NAFLD: Heart disease.
- NAFLD is an important contributor to liver cancer and need for liver transplant.
Summary

- Management hinges on weight loss, exercise, avoiding carbohydrates, metabolic syndrome control
  - Vitamin E (?pioglitazone) only for biopsy-proven NASH
  - Many drugs in the pipeline for NASH and fibrosis
Future/ongoing areas for research

- Best method for screening and diagnosis
- Which patients are at greatest risk for disease progression
  - NAFL $\rightarrow$ NASH
  - NASH or NAFL $\rightarrow$ cirrhosis
- Impact of future treatments on outcomes
  - Need for liver transplant
  - Development of HCC
  - Liver-related death
  - Cardiovascular disease
Thank you!

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