Non-Alcoholic Fatty Liver Disease
Pathophysiology, Diagnosis, and Treatment

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Learning objectives:

1. Epidemiology of Non-Alcoholic Fatty Liver Disease (NAFLD)
2. Pathophysiology of NAFLD
3. Diagnosis of NALFD
4. Treatment and Management of NAFLD
Non-Alcoholic Fatty Liver Disease: Definition

- Hepatic steatosis in the absence of secondary causes of hepatic fat accumulation:
  - significant alcohol consumption:
    - >21 drinks per week in men
    - >14 drinks per week in women
  - long-term use of medications known to cause steatosis
  - other chronic liver diseases
NAFLD:
Epidemiology

• Most prevalent cause of liver disease in the developed world:
  – Affects 25% of the world’s population:
    • South America and Middle East: 31-32%
    • Northern Africa: 14%
  – Affects 30% of the U.S. population

• Second most common cause of end stage liver disease and need for liver transplantation in the U.S.
  – Predicted to become the most common indication for liver transplantation in the next decade

• Third most common cause of hepatocellular carcinoma in the U.S.

Non-Alcoholic Fatty Liver Disease

- 80%
  - Non-Alcoholic Fatty Liver (NAFL) (Simple Steatosis)

- 20%
  - Non-Alcoholic Steatohepatitis (NASH)

Risks for progression:
- Age
- Increased BMI
- DMII

NASH with fibrosis

20%

NASH cirrhosis

Fibrosis Stage: 0

Fibrosis Stage: 2-3

Fibrosis Stage: 4

Images: Rinella ME. JAMA. 2015
NAFLD:
Risk Factors

• Obesity: BMI >30
• DMII/Metabolic Syndrome

• Age >45
• Hispanic Ethnicity

Prevalence of Obesity

SOURCE: NCHS, *Health, United States, 2016*, Data from the NHANES.

NAFLD: Prevalence in High Risk Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>NAFLD Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbid Obesity</td>
<td>~90% in bariatric surgery patients</td>
</tr>
<tr>
<td>DMII</td>
<td>60-70%</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>53%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>50%</td>
</tr>
<tr>
<td>Male Gender</td>
<td>2x female</td>
</tr>
<tr>
<td>Hispanic Ethnicity</td>
<td>45-50%</td>
</tr>
</tbody>
</table>

Lonardo A. Digestive and Liver Dis. 2015
Non-obese NAFLD:

- Prevalence of NAFLD:
  - Lean NAFLD: 20% people with BMI <25
  - Non-obese NAFLD: 27% people with BMI <30

- Risk factors:
  - Visceral Obesity $\rightarrow$ Insulin resistance

Kim D. Hepatology 2012
Unhealthy Diet and Inactivity in NAFLD/NASH:

• Risks of increased consumption of fructose:
  – Increase in *de novo* lipogenesis, promotes dyslipidemia, increases visceral adiposity, increases insulin resistance
  – Gut dysbiosis, increased intestinal permeability, increased hepatic inflammation
  – Increased risk of fibrosis in patients with NASH

• Effects of inactivity:
  – Increases body weight, central adiposity, insulin resistance
  – Increases systemic and adipose inflammation
  – Promotes cancer and coronary heart disease

Kistler KD. Am J Hepatol. 2011
Kransoff JB. Hepatology. 2008
Romero-Gomez M. J Hepatol. 2017
Pathogenesis of Hepatic Steatosis:

- Dietary Sugars: Fructose, Glucose
- Dietary Fats
- Fatty Acids made in liver (de novo Lipogenesis)
- Insulin Resistance
- Visceral Adipose Tissue
- Insulin Resistance
- Decreased VLDL Assembly
- Decreased Oxidative Disposal
Pathogenesis of Steatohepatitis:

- **Gut Dysbiosis**
- **Compromise of the Intestinal Barrier**
- **Increased TNF**

FFAs → Lipotoxic Species → Mitochondrial deterioration

Fibrosis Progression → Cirrhosis → Hepatocellular Carcinoma

Hepatocellular Injury

Oxidative Stress and ROS

Division of Gastroenterology & Hepatology

Michigan Medicine
University of Michigan
NAFLD: Natural History

• Patients with NAFLD likely have increased overall mortality compared to those without:
  – 1.04 HR (Large, international cohort)

• Causes of death:
  1. Cardiovascular: HR 1.46
  2. Cancer
  3. Liver-related

Adams LA. Gastroenterology 2005
Younossi Z. Hepatology 2016
Ekstedt M. Hepatology 2015
NASH:
Natural History

- Increased overall mortality: 2.56 RR
- Increased liver-related mortality: 64.6 RR

Fibrosis stage predicts mortality in NASH:
- F0: reference
- F1-3: 1.82-1.91 HR
- F4: 6.35 HR

Younossi Z. *Hepatology* 2016
Angulo P. *Gastroenterology* 2015
NAFLD:

Diagnosis

- Steatosis seen on imaging performed for other reasons:
  - Ultrasound:
    - “Increased echogenicity” or “Increased echo texture”
    - Excellent sensitivity when steatosis is >30%
  
  ![Normal Liver](image1) ![Fatty Liver](image2)

- MRI or Non-contrast CT
  - Elevated ALT:
    - 30-60% of patients with NASH have normal ALT

- Symptoms:
  - Usually asymptomatic
  - RUQ fullness or discomfort
Noninvasive Assessment of Fibrosis
Serum-based tests

- NAFLD fibrosis score (NFS):
  - Age, BMI, Hyperglycemia, Platelet count, Albumin, AST/ALT

**NFS: <-1.455**
- No Adv. Fibrosis
  - NPV: 93%
  - Lifestyle Counseling
  - Repeat NFS in 2-3 years

**NFS: -1.455-0.676**
- Indeterminate
- ???
- Additional Testing

**NFS: >0.676**
- Adv. Fibrosis
  - PPV: 90%
  - No Adv. Fibrosis

Angulo P. Hepatology 2007
Noninvasive Assessment of Fibrosis
Transient Elastography (Fibroscan®)

Valid Test:
• 10 valid measurements
• IQR/median <30%

Test Considerations:
• Must fast for 3 hours
• No Pregnancy
• Falsely elevated with:
  • Active inflammation (ALT >100)
  • Significant Steatosis
  • Hepatic congestion
  • Significant EtOH use

Optimal liver stiffness cutoff for advanced fibrosis (F3/4): 9.9 kPa
95% sensitivity and 77% specificity
Liver Biopsy:

- When to consider liver biopsy:
  - Patients with risks for NASH and/or advanced fibrosis
    - NFS, Fib4 score, transient elastography, MR elastography
  - Patients at risk for alternative causes of liver disease

- Histopathology:
  - NAFLD activity score (NAS):
    - Grade: necroinflammatory activity
      - Steatosis
      - Ballooning
      - Lobular inflammation
    - Stage: degree of fibrosis
      - F0 (no fibrosis) – F4 (cirrhosis)

Chalasani N. Hepatology 2017
Management of NAFLD:

• NAFLD and NASH are REVERSABLE

[Image showing a transition from NAFLD to a healthy liver]
Management of NAFLD (simple steatosis):

- Screen for the development or worsening of metabolic diseases and treat if indicated:
  - Dyslipidemia, HTN and DMII
- Monitor liver chemistries
- Liver-directed therapy:
  - No proven benefit
- Other therapies:
  - Manage comorbidities
    - Statins are safe in patients with NAFLD
  - Lifestyle intervention to achieve weight loss
  - Consider bariatric surgery, if otherwise appropriate
Management of NASH:

- Screen for the development or worsening of metabolic diseases and treat if indicated:
  - Dyslipidemia, HTN and DMII
- Monitor disease progression:
  - Check labs to detect advanced liver disease
- Liver-directed therapy:
  - Consider treatment with pioglitazone or vitamin E
- Other therapies:
  - Manage comorbidities
    - Statins are safe in patients with NASH
  - Lifestyle intervention to achieve weight loss
  - Consider bariatric surgery, if otherwise appropriate
Management of NAFLD/NASH: Lifestyle Intervention

- Modification of diet and physical activity targeted at WEIGHT LOSS

- Goal Weight Loss:
  - 3-5% total body weight (TBW) loss can reverse hepatic steatosis
  - >5-7% TBW loss: can reverse hepatic steatosis and inflammation
  - ≥10% TBW loss: may improve hepatic fibrosis

Musso G. Diabetologia. 2012
Promrat K et al. Hepatology. 2010
Management of NAFLD/NASH: Weight Loss

- 52 week intervention of physical activity and calorie restricted diet
  - 30% of patients lost ≥5% TBW
    - 58% had resolution of NASH
    - 82% had a 2-point reduction in NAFLD activity score (NAS)
  - 10% of patients lost ≥10% TBW:
    - 100% had reduction in NAS
    - 90% had resolution of NASH
    - 45% had regression of fibrosis

Vilar-Gomez et al. Gastroenterology. 2015
Management of NAFLD/NASH: Diet Modification

Calorie Restriction:
- 500-750 kcal/day calorie deficit

Low Carbohydrate versus Low Fat:
- Similar reductions in hepatic fat with MR spectroscopy
- Similar reduction in ALT and insulin resistance

Mediterranean Diet:
- Beneficial for all-cause mortality, cardiovascular disease, cancer, obesity and DMII
- Reduces central obesity
- NAFLD patients: similar weight loss compared to low fat diet, but significant improvement in reduction of hepatic steatosis (MRS) and improvement in insulin sensitivity

Haufe S et al. Hepatology 2011
de Luis et al. Nutr Hosp 2010
Ryan MC. J Hepatol. 2015
Management of NAFLD/NASH: Physical Activity

• Liver-related benefits of exercise:
  – Improved peripheral insulin sensitivity \( \rightarrow \) Decreased hepatic *de novo* lipogenesis
  – Reduction in visceral fat \( \rightarrow \) Reduction of lipid delivery to the liver
  – Increased hepatic VLDL clearance

• Vigorous Activity in NAFLD:
  – >75 mins/week have a reduced risk of NASH (OR 0.65, CI 0.43-0.98)
  – >150 mins/week have a reduced risk of advanced fibrosis (OR 0.53, CI 0.29-0.97)

• Aerobic exercise vs. Anaerobic resistance training:
  – Both reduce hepatic fat content (20-30% relative reduction) independent of weight loss

Romero-Gomez M. J Hepatol. 2017
Kistler KD. Am J Gastroenterol. 2011
Hallsworth K. Gut. 2011
Management of NAFLD/NASH:

Weight Loss

• Effectiveness of weight loss as a therapeutic intervention:
  – Weight loss success:
    • <50% of patients in these trials were able to lose 5-7% of their body weight
  – Weight loss sustainability:
    • Half of the initial weight loss is typically regained within the first 3 years
    • Similar amount of weight regain within 3 years whether weight loss is rapid or gradual

Musso et al. Diabetologia. 2012
Benefits of Bariatric Surgery:

- **Weight reduction:**
  - 10 years: sustained 14-25% total body weight loss

- **Improvement/remission:**
  - DMII: 75% at 2 years
  - HTN: 70-79% at 1 year
  - HL: 60-100% of patients no longer require lipid lowering medication
  - Cardiovascular death
  - Overall mortality

Management of NAFLD/NASH: Bariatric Surgery

• Lassailly *et al.* 2015:
  – Prospective study; N=109 patients with NASH
  – Paired Bx: before and 1 year post- surgery:
    • BMI: 49 → 37
    • NASH resolution: 85%
    • Fibrosis regression: 34%

• AASLD Guidelines, 2017:
  – Bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH.
  – It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH.
Pharmacologic Treatment of NASH: Vitamin E

- Anti-oxidant to alleviate the oxidative stress associated with NASH pathophysiology

- The PIVENS trial (NEJM 2010); non-diabetics:
  - 42% had significant improvement in NAS vs. 19% in placebo at 24 months (p=0.001)
  - No improvement in fibrosis score (p=0.24)

- Adverse side effects:
  - Long-term use is associated with increased risk of prostate cancer and hemorrhagic stroke

Sanyal AJ. NEJM. 2010
Klein EA. JAMA. 2011
Pharmacologic Treatment of NASH: Pioglitazone

- PPAR agonist: reverses adipose tissue dysfunction and insulin resistance in obesity and DMII
- Cusi K et al 2016; prospective, RCT, preDM/DMII:
  - 58% had significant improvement in NAS vs. 17% placebo
  - 51% had significant resolution of NASH vs. 19% placebo
  - 39% had improvement in fibrosis vs. 25% placebo
- Musso G et al; Meta-analysis of NASH patients with advanced fibrosis (F3-4) treated with pioglitazone:
  - Primary outcome: improvement in fibrosis stage from F3-4 to F0-2
  - Results:
    - OR 3.15 (1.25-7.93) for improved fibrosis
    - OR 3.22 (2.17-4.79) for NASH resolution

Musso G et al. JAMA Intern Med 2017
Pharmacologic Treatment of NASH: Pioglitazone

• Adverse side effects:
  – Weight gain (2.5-4.7kg) in clinical trials
  – May promote bone loss in women

Musso G et al. JAMA Intern Med 2017
Non-Alcoholic Fatty Liver Disease: Key Points

• Most common cause of chronic liver disease in the developed world

• Slated to be the primary indication for liver transplantation in the next decade

• NAFLD is associated with increased overall mortality
  – Primarily from cardiovascular death

• Advanced fibrosis predicts overall and liver-related mortality in patients with NASH
Non-Alcoholic Fatty Liver Disease: Key Points

- Weight loss through lifestyle modification is the most effective therapy for NAFLD
- Goal Weight Loss: 
  - ≥10% associated with improved fibrosis
- Diet Modification:
  - Calorie restriction (500-750 kcal/day deficit)
  - Limit industrial fructose intake
- Increase Physical Activity:
  - Benefits independent of weight loss
  - Helps maintain weight loss
Non-Alcoholic Fatty Liver Disease: Key Points

• Bariatric Surgery:
  – Well-designed, large, prospective RCTs are lacking
  – Improves/reverses steatosis, inflammation and fibrosis in NASH
  – **Insufficient data to recommend as primary therapy for NAFLD/NASH**

• Pharmacologic Treatment of biopsy proven NASH:
  – Consider vitamin E (800 IU/day alpha tocopherol) in nondiabetics
  – Consider pioglitazone in patients with or without DMII after discussion of potential side effects