NON-ALCOHOLIC FATTY LIVER DISEASE

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LECOM GASTROENTEROLOGY

NO DISCLOSURES
OBJECTIVES

- Define NAFLD and its subtypes
  - Differentiate between simple steatosis and steatohepatitis
  - Discuss the pathogenesis of NAFLD
- Discuss the scope and epidemiology of Non Alcoholic Fatty Liver Disease (NAFLD)
- Explain how to diagnosis NAFLD
- Discuss how to treat NAFLD

- What is NAFLD?
- How does NAFLD occur?
- How big of a problem is this?
- What populations are at higher risk?
- How can I diagnose NAFLD?
- How do I manage my patients with NAFLD?

WHAT IS NAFLD?

- Definition: presence of hepatic steatosis either by imaging or histology AND exclusion of alternate causes of fatty liver disease

- Non-alcoholic Fatty Liver (NAFL): presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes

- Non-alcoholic Steatohepatitis (NASH): presence of hepatic steatosis AND inflammation with hepatocyte injury (ballooning) with or without fibrosis
NAFLD (SIMPLE STEATOSIS)

- Hepatic steatosis - increased echogenicity and beam attenuation
- No inflammation
- Can be diagnosed with imaging alone
- Low risk for disease progression

NORMAL LIVER US
NASH

- Hepatic steatosis
- Active hepatocyte inflammation in the form of ballooning degeneration
- Risk of fibrosis and progression to cirrhosis → HCC

HOW DOES NAFLD OCCUR?

- We aren’t exactly sure….
- Unclear how some patients with steatosis develop inflammation and some do not
“TWO HIT” HYPOTHESIS

- Sedentary lifestyle
- High fat diet
- Insulin resistance
- Obesity
- Oxidative Stress
- Mitochondrial Dysfunction
- Inflammatory Cytokines
- Gut Dysbiosis, Endotoxins

“MULTI-HIT” HYPOTHESIS

- Multiple insults acting together on genetically predisposed patient (insulin resistance, altered gut bacteria, inflammatory cytokines..etc)
- Not necessarily a linear progression from simple steatosis to NASH
- Currently most accepted understanding of NAFLD
HSL
Chylomicrons
FFAs

B-oxidation
Reroxosome
Cholesterol
Phospholipids
VLDL

Esterification

FFAs
Cholesterol
Phospholipids
VLDL

1) Insulin Resistance

FFAs cause defective insulin signaling

Lipid droplets in hepatocytes

SREBP-1
IRS-2

DN
Glucose + Fructose

Peroxisome
FFAs cause defective insulin signaling.

1) Insulin Resistance
2) Mitochondrial Dysfunction
3) ER Stress

- Insulin Resistance
- Mitochondrial Dysfunction
- ER Stress

- Dec protein synthesis
- Incr Protein transit and degradation

- Impaired insulin signaling

- Chylomicrons
- FFA release
- Esterification
- Lipid droplets in hepatocytes
- Stellate cells
- VLDL

- Insulin
- HSL
- IRS-2
- SREBP-1
1) Insulin Resistance
2) Mitochondrial Dysfunction
3) ER Stress
4) Adipose tissue Dysfunction
5) Dysbiosis

FFAs cause defective insulin signaling

Inflammation
Fibrosis
Apoptosis

Dec protein synthesis
Incr Protein transit and degradation

Insulin
SREBP-1
IRS-2

ROS
B-oxidation

HSL

Chylomicrons

Lipid droplets in hepatocytes

ER

UPR

JNK

Insulin Resistance
Mitochondrial Dysfunction
ER Stress
Adipose tissue Dysfunction
1) Insulin Resistance
2) Mitochondrial Dysfunction
3) ER Stress
4) Adipose tissue Dysfunction
5) Dysbiosis
6) Inflammatory State

Insulin

HSL → FFA

Leptin

IL-6

TNF-α

Chylomicrons

LPS

HSL → FFA

ROS → B-oxidation

FFAs cause defective insulin signaling

Lipid droplets in hepatocytes

Esterification

Cholesterol

Phospholipids

VLDL

1) Insulin Resistance
2) Mitochondrial Dysfunction
3) ER Stress
4) Adipose tissue Dysfunction
5) Dysbiosis
6) Inflammatory State

UPR

• Dec protein synthesis
• Incr Protein transit and degradation

JNK

INFLAMMATION

APOPTOSIS

Impaired insulin signaling

NF-κB
How fast does NASH Progress?
Study using paired biopsies estimated an increase in 1 Fibrosis stage every 7-14 years

How big of a problem is NAFLD?
PREVALENCE\(^1\) OF SELF-REPORTED OBESITY AMONG U.S.
ADULTS BY STATE AND TERRITORY, BRFSS, 2012

\(^1\) Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.

PREVALENCE\(^1\) OF SELF-REPORTED OBESITY AMONG U.S.
ADULTS BY STATE AND TERRITORY, BRFSS, 2013

\(^1\) Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.
Prevalence of self-reported obesity among U.S. adults by state and territory, BRFSS, 2014

Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.

Prevalence of self-reported obesity among U.S. adults by state and territory, BRFSS, 2015

Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.
PREVALENCE\(^9\) OF SELF-REPORTED OBESITY AMONG U.S. ADULTS BY STATE AND TERRITORY, BRFSS, 2016

\(^9\) Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.

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HOW BIG OF A PROBLEM IS NAFLD?

- Fatty liver disease is a growing epidemic in the United States and worldwide
  - Est. prevalence overall of ~27-46% \(\text{??}\) (depends on the tool and the population)
  - NASH 3-7% \(\text{??}\)
- NASH annual liver transplant waitlist additions increased from 391 to 1605 from 2000-2014
- NASH related waitlist additions are anticipated to increased by 55.4% (1,354 to 2,104) between 2016 and 2030
- NASH surpassed ALD and became the second leading indication for LT beginning in 2008, accounting for 17.38% of LT in 2014 (2\(^{\text{nd}}\) to HCV)

\(\text{90\% of those undergoing bariatric surgery have NAFLD}\)

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Dig Dis Sci. 2017 Jul 25
Hepatology. 2017 Aug 17
GASTROENTEROLOGY 2011;140:1241
METABOLISM AND EXPERIMENTAL 65(2016)1017–1025
OUTCOMES IN PATIENT’S WITH NAFLD

- Increased overall mortality compared to control population
- Most common cause of death is cardiovascular disease
- 3rd most common cause of hepatocellular carcinoma
  - 13% of patients with HCC secondary to NASH did not have cirrhosis

WHAT POPULATIONS ARE AT HIGHER RISK FOR NAFLD?

- Risk Factors
  - Obesity, (↑ risk with advancing BMI and waist circumference)
  - Impaired fasting glucose
  - Hispanic heritage
  - Male gender
  - Advancing age
- Coined the “Hepatic Manifestation” of Metabolic syndrome
- AACE recommends screening all obese patients with liver enzymes and imaging
**Table 1. Demographic Data**

<table>
<thead>
<tr>
<th></th>
<th>Negative ultrasound (non-NAFLD) (n = 177)</th>
<th>Positive ultrasound (NAFLD to include NASH) (n = 151)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort, %</td>
<td>54</td>
<td>46</td>
<td>NA</td>
</tr>
<tr>
<td>Hispanic (n = 72), %</td>
<td>41.7</td>
<td>58.3</td>
<td>NA</td>
</tr>
<tr>
<td>Caucasian (n = 205), %</td>
<td>55.6</td>
<td>44.4</td>
<td>NA</td>
</tr>
<tr>
<td>African American (n = 37), %</td>
<td>64.9</td>
<td>35.1</td>
<td>NA</td>
</tr>
<tr>
<td>Other (n = 14), %</td>
<td>64.3</td>
<td>35.7</td>
<td>NA</td>
</tr>
<tr>
<td>Male, %</td>
<td>40.7</td>
<td>58.9</td>
<td>.001</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>53.5 (7.87)</td>
<td>55.9 (6.48)</td>
<td>.004</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.6 (4.94)</td>
<td>32.4 (5.30)</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>BMI ≥30 (obese), %</td>
<td>26.6</td>
<td>67.5</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>33.9</td>
<td>68.2</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>7.9</td>
<td>26.3</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>Nondiet soda (≥1 per wk), %</td>
<td>30.5</td>
<td>48.3</td>
<td>.11</td>
</tr>
<tr>
<td>Fast food (≥1 per wk), %</td>
<td>60.5</td>
<td>70.9</td>
<td>.049</td>
</tr>
<tr>
<td>Exercise (≥30 min/wk), %</td>
<td>68.9</td>
<td>56.3</td>
<td>.02</td>
</tr>
</tbody>
</table>

Why?  
- Waist to hip ratio?  
- Alcohol use?  
- Diet?

**Table 2**

Gender difference in the prevalence of nonalcoholic fatty liver disease from population-based studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study population</th>
<th>n</th>
<th>Definition of NAFLD</th>
<th>Prevalence of NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>Ruhl et al[1]</td>
<td></td>
<td></td>
<td>ALT</td>
<td>4.3%</td>
</tr>
<tr>
<td>Clark et al[2]</td>
<td></td>
<td></td>
<td>ALT or AST</td>
<td>5.7%</td>
</tr>
<tr>
<td>Browning et al[3]</td>
<td></td>
<td></td>
<td>MRS</td>
<td>42%</td>
</tr>
<tr>
<td>Ioannou et al[4]</td>
<td></td>
<td></td>
<td>ALT or AST</td>
<td>13.4%</td>
</tr>
</tbody>
</table>

Why?  
- Waist to hip ratio?  
- Alcohol use?  
- Diet?
Why?
- Diet?
- Central obesity?
- Insulin resistance?
- Genetics?

Table 1
Prevalence rates of nonalcoholic fatty liver disease from population-based studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Definition of NAFLD</th>
<th>Overall</th>
<th>NHW</th>
<th>Hispanic</th>
<th>NHB</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruhl et al[11]</td>
<td>ALT$^1$</td>
<td>2.8%</td>
<td>2.6%</td>
<td>8.4%</td>
<td>1.9%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Clark et al[12]</td>
<td>ALT or AST$^2$</td>
<td>5.4%</td>
<td>4.8%</td>
<td>9.9%</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>Browning et al[13]</td>
<td>MRS$^3$</td>
<td>31%</td>
<td>33%</td>
<td>45%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Ioannou et al[15]</td>
<td>ALT or AST$^4$</td>
<td>8.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younessi et al[17]</td>
<td>Ultrasound</td>
<td>18.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lazo et al[18]</td>
<td>Ultrasound</td>
<td>19%</td>
<td>17.8%</td>
<td>24.1%</td>
<td>13.3%</td>
<td></td>
</tr>
<tr>
<td>Schneider et al[19]</td>
<td>Ultrasound</td>
<td>12.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smits et al[20]</td>
<td>Ultrasound</td>
<td>30.2%</td>
<td>29.8%</td>
<td>30.4%</td>
<td>23.1%</td>
<td></td>
</tr>
<tr>
<td>Liangpunskol et al[21]</td>
<td>ALT$^2$</td>
<td>4.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HOW DO YOU DIAGNOSIS NAFLD?

- Increased echogenicity
- Hepatomegaly
- Low attenuation compared with the spleen

WHAT IS NAFLD?

- Definition: presence of hepatic steatosis either by imaging or histology AND exclusion of alternate causes of fatty liver disease
- Alternate causes of fatty liver:
  - Alcohol
  - Wilson’s Disease
  - Hepatitis C (genotype 3)
  - Starvation
  - TPN
  - Medications (EX: methotrexate, tamoxifen, corticosteroids)
Suggested “safe” amount of alcohol is suggested to be 7-14 units/wk for women and 21 units/wk for men with no other chronic liver disease

1 Unit = 8gm of alcohol

(Cut-off for NAFLD vs AFLD is typically accepted as 20gm/day for women and 30gm/day for men)
HOW DO YOU DIAGNOSE NASH?

- Liver biopsy is the GOLD standard

Do we have to do a biopsy on EVERYONE with fatty liver disease??
CLINICAL PREDICTORS OF FIBROSIS

- NAFLD Fibrosis Score (Age, AST, ALT, PLT, BMI, Albumin)
- BARD Score (AST:ALT ratio, DM, BMI)
- Fib-4 (age, ALT, AST, platelet count)
- Presence of underlying risk factors (diabetes, hyperlipidemia, etc)

NAFLD fibrosis score
Online calculator


Age (years)
BMI (kg/m²)
IGF/diabetes
AST
ALT
Platelets (>105/μL)
Albumin (g/L)

BMI: body mass index
IGF: impaired fasting glucose
HOW DO YOU DIAGNOSE NASH? NON-INVASIVELY?

- Vibration Controlled Transient Elastography (Fibroscan)
- MRI Elastography (MRE)
- Multiparametric MRI (LiverMultiscan)
The Lowly fellow’s algorithm for elevated LFTS and/or concern for NAFLD:

1) Review of clinical history
2) RUQ US
3) Full liver enzymes evaluation (rule out viral hepatitis, autoimmune disease, hemochromatosis, etc)

US(-)

Continue LFT evaluation as necessary

Encourage lifestyle modifications
  ?Vitamin E
  Weight loss accountability
  Continue to reassess need for staging (if not already done)

US(+), no clear alternate etiologies

1) Imaging assessment of Fibrosis (Fibroscan or MRE)
2) Review clinical risk

Normal liver stiffness

Continue liver enzyme evaluation as necessary

Elevated Liver stiffness Clinically increased risk

No liver Biopsy

Liver biopsy for staging

Non NASH NAFLD

NASH

HOW DO I TREAT NAFLD?

• Lifestyle Modifications

• Antioxidants?

• Insulin sensitizers?

• There are no FDA approved drugs for the treatment of NAFLD…… (But LOTS of clinical trials)
**LIFESTYLE MODIFICATIONS**

- Gradual weight reduction achieved by caloric restriction, with or without increased physical activity, leads to an improvement in serum liver enzymes, liver fat, degree of hepatic inflammation and fibrosis.

- Decrease in body weight by >5% has been shown to reduce liver fat.

- Decrease in body weight by ≥ 10% has been shown to improve liver inflammation and reduce fibrosis by at least one stage.

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![Chart showing 52 weeks of lifestyle intervention and the associated weight loss and improvements in NASH-resolution, FIBROSIS-regression, STEATOSIS improvement, and patients achieving weight loss (WL)].

<table>
<thead>
<tr>
<th>% Weight loss (WL)</th>
<th>5%</th>
<th>7%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH-resolution</td>
<td>10%</td>
<td>26%</td>
<td>64%</td>
</tr>
<tr>
<td>FIBROSIS-regression</td>
<td>45%</td>
<td>38%</td>
<td>50%</td>
</tr>
<tr>
<td>STEATOSIS improvement</td>
<td>35%</td>
<td>65%</td>
<td>76%</td>
</tr>
<tr>
<td>% Patients achieving WL</td>
<td>70%</td>
<td>12%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*J Hepatol. 2017 May 23; pii:S0168-8278(17)32052-4*
LIFESTYLE MODIFICATIONS FOR TREATMENT OF NAFLD

- Diets rich in polyunsaturated fats (i.e. Mediterranean diet) has been shown to reduce liver fat even without weight loss
  - 7-week RCT overeating Saturated fatty acids (SFAs) or omega 6-polyunsaturated fatty acids (PUFAs) led to a similar weight gain, but the SFAs markedly increased liver fat compared with PUFAs and caused a twofold increase in visceral fat compared to PUFAs.
  - 6-week low fat high carbohydrate diet vs Mediterranean diet revealed 35% greater decrease in liver fat content in Mediterranean diet despite stable weight

LIFESTYLE MODIFICATIONS

- Foods with “Added Sugars” defined as refined sugars such as sucrose, fructose, and high fructose corn syrup (HFCS) added to beverages and other foods have been strongly associated with NAFLD.
  - A sucrose of fructose-rich diet increased hepatic synthesis of triglycerides
  - In animal studies fructose intake is associated with altered intestinal flora, increased gut permeability, and increased hepatic inflammatory markers, and steatosis
LIFESTYLE MODIFICATIONS

• Coffee consumption has been associated with a lower risk of metabolic syndrome and a reduced diabetes risk in a dose dependent manner.

• A study in NAFLD patients indicated an inverse association between coffee consumption and liver fibrosis.

• Large prospective cohort study demonstrated that those who drank 2-3 cups of coffee per day had a 38% risk reduction for HCC compared with non-coffee drinker.

J Hepatol. 2017 May 23. pii: S0168-8278(17)32052-4

LIFESTYLE MODIFICATIONS

• Sedentary behavior is reported to be higher in people predisposed to the metabolic syndrome, excessive adiposity and type 2 diabetes.

• Prospective study monitoring TV viewing over 5 years demonstrated an increase in weight circumference, diastolic blood pressures, and clustered cardio-metabolic risk score, independent of physical activity.

• Exercise without weight loss (2-3 sessions/week of 30-60 minutes for 6 to 12 weeks) demonstrated reduce liver fat content.

Medicine & Science in Sports & Exercise Issue: Volume 42(8), August 2010, pp 1511-1518
ANTI-OXIDANTS/VITAMINS

- The use of vitamin E (800IU/day) is associated with a decrease in aminotransferases, improvement in steatosis, inflammation, and ballooning, but has not shown to reverse fibrosis in NASH patients.

- Vitamin C and D have been studied but there is no conclusive evidence that is helpful in the treatment of NAFLD.

INSULIN SENSITIZERS?

- Thiazolidinediones (Rosiglitazone, Pioglitazone) activate peroxisome proliferator-activated receptors (PPARs) with the net effect on increasing storage of fatty acids in adipocytes, thus decreased fatty acids in the circulation.

- Several studies using Thiazolidinediones demonstrated improvement in aminotransferases and hepatic steatosis, ballooning and inflammation scores, but not fibrosis.

- Rosiglitazone is no longer recommended due to increased risk of coronary events.

- Pioglitazone MAY be used for treatment of biopsy-proven NASH but with caution since long term safety and efficacy have not yet been demonstrated in diabetic patients.
GLUCAGON-LIKE PEPTIDE ANALOGUES

- They are associated with weight loss but impact on inflammation is unclear
- At this time they are not utilized as a treatment
- Metformin had similar results and is not currently recommended

BARIATRIC SURGERY

- Roux-en-y gastric bypass is currently covered in patient with metabolic syndrome and NASH and should be considered in patients without cirrhosis and difficulty with losing weight
- Patient's benefit from nutrition counselling in a multi-disciplinary approach
STATIN THERAPY

- Though Statin therapy has not been shown to reverse the course of NASH, patient's with NASH are at high risk for cardiovascular mortality
- Aggressive modification of CVD risk factors is paramount
- Patient's with NASH are not at increased risk of liver injury due to statin therapy and these can be used safely

PHARMACOTHERAPY FOR OBESITY (AACE GUIDELINES)

- The addition of pharmacotherapy produces greater weight loss and maintenance that lifestyle modifications alone
- Avoid all weight loss medications in patient with severe hepatic impairment (Child-Pugh>9)
- Dose reductions of naltrexone/bupropion and phentermine/topiramate
- Liraglutide- 39% of patients with NAFLD had resolution of steatosis and normalization of liver enzymes
PHENTERMINE

- Norepinephrine releasing agent - suppresses appetite
- Approved for short term weight loss - < 3 months
- When used with topiramate ER approved for long term use (Qysmia)
  - Patient’s with BMI > 30 or > 27 with weight related co-morbidity
  - 3.75mg/23mg daily x 14 days then increase to 7.5mg/46mg for 12 weeks then reassess
  - If patient has not lost 3% of weight, DC or increase dose
  - If stopping, take every other day for a week

LORCASERIN (BELVIQ)

- 5-HT$_{2C}$ receptor agonist - reduces appetite
- 10mg BID
- Patient’s with BMI > 30 or > 27 with weight related co-morbidity
- No hepatic impairment dose adjustment
NALTREXONE ER/BUPROPION (CONTRAVERE)

- Bupropion- dopamine and norepinephrine reuptake inhibitor
- Naltrexone- mu-opiod receptor antagonist
- Combination suppresses appetite via a central mechanism
- Patient’s with BMI > 30 or > 27 with weight related co-morbidity
- Increased risk of suicidal behavior
- Dose escalation to 2 pills BID

LIRAGLUTIDE

- GLP-1 receptor agonist- approved for T2D and weight loss
- Injection subcutaneously at 3 mg/day- reduces appetite, increases satiety and lowers energy intake via central mechanism
- Patient’s with BMI > 30 or > 27 with weight related co-morbidity
- Saxenda is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached
NASH INDUCED CIRRHOSIS

• Screen for HCC q 6 months
• Screen for gastroesophageal varices with EGD
• Monitor for ascites and encephalopathy

SUMMARY

• What is NAFLD?
  • Fat in the liver +/- inflammation and/or fibrosis
• How does NAFLD occur?
  • Excess fat, insulin resistance, oxidative damage
• How big of a problem is this?
  • HUGE!! 2nd leading cause of liver transplant in the U.S. and climbing.
• What populations are at higher risk?
  • Those with obesity, diabetes, HLD, HTN, and of Hispanic heritage
• How can I diagnose NAFLD?
  • Imaging. Diagnosing with NASH takes specialized tests.
• How do I manage my patients with NAFLD?
  • Lifestyle modifications!! Weight loss is key.