NASH:
WHAT YOU NEED TO KNOW

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Disclosures, Conflicts of Interest and Off-Label Use of Medications

• Disclosures
  – None

• Conflicts of Interest
  – None

• Off-Label use of Medications
  – Metformin
  – Pioglitazone
  – Statins
  – Vitamin E
  – Lorcaserin
  – Ursodeoxycholic acid
CASE #1

- 48 year old male
- HTN and type II DM
- Tired, but working 60 hours/week
- Alcohol 2 glasses/week
- Non smoker
- Abnormal liver tests at recent check up
- BMI 32,
- 3 cm palpable hepatomegaly
- ALT 87 IU/ml, AST 73 IU/ml,
- Alkaline phosphatase 155, total bilirubin 1.0
- Albumin 3.9, INR 0.9
- Iron stores normal, ANA negative
- Anti HCV Ab neg, HBsAg neg, HBsAb neg, HAV total positive
- US: increased echodensity
Should he have a liver biopsy?

• When?

• Non-invasive alternatives
  – Prediction models
    • Probability of NASH= 0.042 x ALT + 0.095 x fasting insulin − 4.246. Sensitivity and specificity ~ 75%\(^1\)
    • NAFLD score, BARD score, Fib-4 score
  – Serum markers
    • CK-18: Sensitivity and specificity 78 and 87%, respectively\(^2\)

• Pitfalls
  – Stigma and cost
  – Sampling error and inaccurate reads

• Prognostic value?

2. Williams CD et al, Gastro 2011; 140: 124-31
NECESSARY COMPONENTS FOR DIAGNOSIS (and NAS score)
- >5% steatosis, macrovesicular > microvesicular
- Mixed lobular inflammation, including scattered PMN
- Hepatocellular ballooning, typically in zone 3 (perivenular)
- + Variable degrees of fibrosis
DEFINITIONS

• Fatty liver: fat in the liver, usually benign prognosis
• NAFLD: Non-alcoholic fatty liver disease
  – Less than 20 gm/day of alcohol for women
  – Less than 30 gm/day for men
  – Usually benign prognosis
• NASH: Non-alcoholic steatohepatitis
• ASH: Alcoholic steatohepatitis
• Insulin resistance: HOMA-IR >2
  – Fasting serum glucose x fasting serum insulin / 405
Metabolic Syndrome
(3 or more of the following)

- Increased body mass index (>30 kg/m²)
- Central adiposity (waist >102 cm in men, >88 cm in women)
- Hypertension (SBP >130, or DBP >85 mm/Hg)
- Dyslipidemia (TG >150 mg/dL, HDL <40 mg/dL (M) or <50 mg/dL (F))
- Fasting glucose level >110 mg/dL
EPIDEMIOLOGY

- Obesity prevalence in the US --------- 33.8%
- Diabetes in adults in the US --------- 10.6%
- NAFLD in the US --------------- 2.8% to 46%
- NASH (autopsy data) ------------------ 2.7%
- NASH (cohort biopsy data) ------------ 12.2%
- NAFLD and NASH in obese patients undergoing bariatric surgery --- 91% and 37%
From Metabolic Syndrome to Fatty Liver and Steatohepatitis

• Fat accumulates in the liver as a consequence of insulin resistance

• What leads to and perpetuates the inflammation in the liver is less clear
  – Elevated levels of circulating inflammatory cytokines and adipokines
  – Increased levels of endotoxin secondary to small bowel bacterial overgrowth, release of lipopolysaccharide and impaired intestinal barrier integrity
Genetic Predisposition

- Obesity is a recognized risk factor for NAFLD that may be modified by genetic factors
- Romeo et al. identified a I148M substitution at the PNPLA3 locus of the adiponutrin gene.
  - This allele is more common in individuals of Hispanic descent.
- Hepatic fat content was >2 fold higher in PNPLA3 I148M homozygotes than in noncarriers
- Higher ALT and AST levels in I148M carriers
- Another allele of the PNPLA3 gene, S453I, is more common in African patients and is associated with less fat in the liver
- Recent meta-analysis found an association in between I148M and NASH and hepatic fibrosis
Apolipoprotein C3 Gene Variants in NAFLD

- Two single-nucleotide polymorphisms in the gene encoding apolipoprotein C3 may be associated with hypertriglyceridemia
  - C482T and T455C
- 95 Asian Indian men (BMI 24.7): 20% were WT and 80% had at least 1 mutation
- Plasma ApoC3 was 30% higher in heterozygotes, fasting plasma [TG] were 60% higher
  - No difference in plasma cholesterol, HDL or LDL
- 38% of heterozygotes had NAFLD vs. none of the WT p<0.001
- ApoC3 variants increase ApoC3 plasma concentration, which in turn inhibit LPL and TG clearance. This results in increased [chylomicron-remnant particles] that are uptaken by the liver leading to NAFLD

THE MANY FACETS OF THE METABOLIC SYNDROME

• Cardiology -- coronary artery disease (the most common cause of death in NASH patients)
• Neurology -- CVA
• Endocrine -- diabetes, dyslipidemia, hypopituitarism, hypothyroidism, polycystic ovarian syndrome
• Rheumatology -- arthritis
• ENT -- sleep apnea
• GI -- fatty liver, more severe hepatitis to other insults
• Oncology -- Increased cancer risk
NAFLD

- Cardiovascular disease
- OSA
- Vitamin D deficiency
- Diabetes
- PCOS
- Hypothyroidism
- Elevated ferritin
- Adenomatous polyps
- Hyperuricemia

Courtesy of Dr Stephen Harrison
NAFLD vs. NASH

• Diagnosis of fatty liver
  – Clinical +/- liver US

• Diagnosis of NASH
  – Liver biopsy

• Why does it matter
  – Both increase all cause mortality
  – NASH increases liver death from cirrhosis and HCC
DIAGNOSIS

• Fatty liver can be diagnosed by non-invasive imaging, but cannot be distinguished from NASH
  – Neither imaging or biochemical tests can differentiate stage of disease

• The diagnosis and grading/staging of NASH can only be done with liver biopsy
  – Known downsides: Invasive and costly procedure, sampling error, others
  – Non-invasive prediction models are being developed
CLINICAL PRESENTATION

• Asymptomatic elevation in ALT & AST
  – Usually below 100 IU/mL
  – NAFLD and NASH may present with normal LFTs
• Fatigue, RUQ fullness, ache
• Cirrhosis
• Hepatoma
PHYSICAL EXAM

- BMI
- Central obesity
- HTN
- Hepatomegaly
- Signs of cirrhosis
LABORATORY WORK-UP

- Fasting serum glucose and insulin (+/- HbA1c), LFTs, lipid panel
- CBC, INR and chem-7 if cirrhosis is suspected
- Anti HCV-Ab, HBsAg, anti HAV total
- ANA, SMA, AMA, iron studies, TTG-Ab, QIGS
- A1AT phenotype and ceruloplasmin
IMAGING

• US: Bright hepatic echotexture
  – Cheap and reliable
  – US-based transient elastography (Fibroscan)
• CT: Decrease in attenuation compared to spleen and kidneys
• MRI: Lower signal intensity compared to surrounding tissues
  – MR Elastography
• Liver biopsy is still the gold standard to differentiate NAFLD and NASH
NATURAL HISTORY- NAFLD

• Isolated fatty liver has very little risk of progression
  – Other risks, associated with obesity, dyslipidemia, glucose intolerance and HTN still apply
  – GGT but not ALT was associated with all cause mortality including cancer and diabetes, whereas ALT was only associated with liver-related mortality in the NHANES population¹

CAUSES OF DEATH:
- 1. Cardiac; 2. Malignancy; 3. Liver

PROGRESSION TO CIRRHOSIS
- YES: 3-15%
- Risk factors: Diabetes, severe insulin resistance, BMI, weight gain >5 kg, smoking, rising LFTs. Alcohol?

PROGRESSION TO LIVER DECOMPENSATION
- YES, ~31% over 8 years

PROGRESSION TO HEPATOCELLULAR CARCINOMA
- YES: 2.6%/year in decompensated pts

RECURRENCE AFTER LIVER TRANSPLANTATION
- YES
NAFLD and DIABETES

- **NAFLD prevalence in diabetics**
  - 60-76%
- **NASH prevalence in diabetics**
  - 22%
- **Patients with NAFLD and diabetes**
  - Higher mortality
  - Higher prevalence of cardiovascular disease than non-diabetic NAFLD patients
- **In patients with advanced liver disease, diabetes is an independent predictor of**
  - Advanced fibrosis
  - Decompensation of liver function
  - Progression to HCC
NATURAL HISTORY -
Advanced fibrosis

- 247 patients with NASH and advanced fibrosis
- Mean F/U 7.1 years
- Liver-related complications: 19.4%
- HCC: 2.4%
- 10 year survival: 81.5%

HCC in NASH

- 510 pts with NASH-F4 (195) vs HCV-F4 (315) referred to CCF for LTx eval ‘03-’07
- CT + AFP Q6 months
- HCC developed in 89 pts over 3.2 years after cirrhosis diagnosis (biopsied 59%)
  - 25/195 (12.8%) NASH-F4 developed HCC. 2.6% per year
    - Older age at time of F4 diagnosis was only risk factor for HCC
  - 64/315 (20.3%) HCV-F4 developed HCC. 4% per year
- Patients who reported never drinking alcohol were significantly less likely to develop HCC compared to those who reported any lifetime drinking

NATRUAL HISTORY: HCC

• Yearly incidence 2.4%-2.7%
• Risk factors¹:
  – Age
  – Obesity
  – Diabetes mellitus
  – Iron deposition
  – ?Alcohol, tobacco, coffee?

PRINCIPLES OF THERAPY

• Lifestyle modification
  – Diet
  – Exercise
  – Weight loss

• Multiple targets for therapeutic intervention
  – Insulin sensitizers: Metformin and Pioglitazone
  – Dyslipidemia
  – HTN
  – Iron overload
  – Medications: Steroids, tamoxifen, amiodarone, methotrexate
  – Bariatric surgery
Meta-Analysis of RCT for the Treatment of NAFLD-NASH

• Weight reduction
  – NASH: Weight loss is safe and can improve histology and metabolic parameters
  – NAFLD: Exercise per se improves hepatic steatosis independent from weight loss

• Pioglitazone
  – Improved insulin sensitivity, hepatic steatosis and inflammation. No improvement in hepatic fibrosis
  – Weight gain and peripheral edema

• Metformin
  – Enhanced weight loss and improved insulin sensitivity

Meta-Analysis of RCT for the Treatment of NAFLD-NASH

- **Statins**
  - Beneficial long term effects derived from lipid lowering (and maybe less carcinogenicity)

- **UDCA**
  - Improves liver enzymes but not histology or metabolic parameters

- **Antioxidants**
  - NASH: No improvement in liver enzymes or histology except in 2 RCTs, including the NIH trial
  - NAFLD: Improved ALT

- **Bariatric surgery**
  - Overall safe and effective if it achieves significant weight loss

Diet and Exercise

• Patients who increase physical activity to $\geq 150$ minutes per week had greater improvement in LFTs and metabolic indices.

• When looking at HbA1c in 251 diabetics, a combination of aerobic and resistance training was better than either by itself.

• 811 patients assigned to one of four diets and F/U over 2 years:
  – Average weight loss over 2 years was 4 kg
  – The composition of the diet did not make a difference
    • High fructose corn syrup and short chain fatty acids are BAD!

DIET and EXERCISE for NASH

- Control group (N=10) received basic education on NASH and about principles of healthy eating, physical activity and weight control
- Lifestyle intervention group (N=20) received intensive weight loss intervention with a goal of achieving 7-10% weight loss in 6 months and maintaining thereafter (diet, exercise, behavioral monitoring)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change</td>
<td>-0.5 kg</td>
<td>-8.7 kg</td>
</tr>
<tr>
<td>&gt;10% weight loss</td>
<td>None</td>
<td>40%</td>
</tr>
<tr>
<td>NAS</td>
<td>4.9 to 3.5</td>
<td>4.4 to 2.0</td>
</tr>
<tr>
<td>Fat</td>
<td>1.9 to 1.6</td>
<td>1.9 to 0.8</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1.7 to 1.3</td>
<td>1.4 to 0.9</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>1.7 to 1.4</td>
<td>1.4 to 1.4</td>
</tr>
<tr>
<td>ALT</td>
<td>86 to 69</td>
<td>84 to 42</td>
</tr>
</tbody>
</table>
How can we enhance patient compliance with lifestyle modification?

- Communicate with empathy
- Be sensitive to general stigma against obesity
- Discuss pros and cons of proposed changes to lifestyle
- Explore reasons for perpetual poor dietary and exercise choices
- Offer specific choices for diet and exercise
- Explain treatment adherence benefits

WEIGHT LOSS MEDICATIONS

• Orlistat
  – Improvement related to weight loss
  – No improvement in fibrosis

• Lorcaserin
  – Not validated

• Rimonabant
  – Pulled from the EU market for neuro-psychiatric side effects
METFORMIN

• Mechanism: decreased gluconeogenesis, decreased glucose absorption and facilitates glucose uptake and utilization
• Improved ALT normalization when compared to diet alone (OR 2.83, CI 1.27-6.31)
• Improved steatosis by imaging (OR 5.25, CI 1.09-25.21)
• +/- effect on histology
• Ongoing trial comparing to vitamin E (TONIC)
PIOGLITAZONE

- Selective peroxisome proliferator-activated receptor gamma agonist
- Improves insulin resistance
- Redistributes fat from muscle and liver to adipose tissue
- Increases circulating levels of adiponectin (produced by fat, insulin-sensitizer)
- Shown to improve biochemistries and histology while the patient is taking the medication
PIOGLITAZONE, VITAMIN E or PLACEBO FOR NASH

- 247 patients randomized
  - Placebo = 83;
  - Vit E (800 IU/day) = 84
  - Pioglitazone (30 mg/day) = 80

- Primary end point: paired histology after 96 weeks of therapy
  - 25 patients without 2nd biopsy were counted as treatment failures

Sanyal et al. NEJM 2010; 362: 1275-85
RESULTS

- The study was designed to find a 26% improvement in NASH in between groups with 80 patients each (p<0.025)
- 17%, 18% and 28% of the baseline liver biopsies showed no ballooning
- 43% of patients treated with vit E vs. 19% with placebo showed histologic improvement (p=0.001)
- 34% treated with Pioglitazone vs. 19% treated with placebo showed histologic improvement (p=0.04 NS)

Sanyal et al. NEJM 2010; 362: 1275-85
<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
<th>P=Vit E vs Plac</th>
<th>P=Pio vs Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>83</td>
<td>84</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy x2</td>
<td>72</td>
<td>80</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% improved</td>
<td>19</td>
<td>43</td>
<td>34</td>
<td>0.001</td>
<td>0.04</td>
</tr>
<tr>
<td>Steatosis (%)</td>
<td>31</td>
<td>54</td>
<td>69</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobular inflam. (%)</td>
<td>35</td>
<td>54</td>
<td>60</td>
<td>0.02</td>
<td>0.004</td>
</tr>
<tr>
<td>Ballooning (%)</td>
<td>29</td>
<td>50</td>
<td>44</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Change in NAFLD activity score</td>
<td>-0.05</td>
<td>-1.9</td>
<td>-1.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>-0.1</td>
<td>-0.3</td>
<td>-0.4</td>
<td>0.19</td>
<td>0.10</td>
</tr>
<tr>
<td>NASH resolution (%)</td>
<td>21</td>
<td>36</td>
<td>47</td>
<td>0.05</td>
<td>0.001</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>-4.0</td>
<td>-14.0</td>
<td>-21.1</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.4</td>
<td>0.4</td>
<td>-0.7</td>
<td>0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>-6.7</td>
<td>-0.6</td>
<td>-19.8</td>
<td>0.45</td>
<td>0.16</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>-5.8</td>
<td>-12.0</td>
<td>-8.1</td>
<td>0.07</td>
<td>0.26</td>
</tr>
</tbody>
</table>
VITAMIN E

- Not as benign as once thought?
- Doses greater than 400 IU/day have been linked to an increase in all cause mortality
- A recent study found greater incidence of prostate cancer with vitamin E supplementation
OTHERS

- Statins
- Ezetimibe
- Angiotensin-receptor blockers
- Betaine
- Incretin mimetics (liraglutide and exenatide)
- Vitamin D
- Antibiotics
- Obeticholic acid
Bariatric Surgery

- Recommended for
  - Well informed and motivated patient
  - Obese patients with BMI >40
  - BMI >34 and serious coexistent medical conditions
  - Having failed conservative approach
  - Adequate surgical risk
- Careful patient selection
- 0.1-0.5% 30 day mortality
- 20% morbidity, less with laparoscopic approach by experienced surgeon
Bariatric Surgery

- Excess weight lost ~ 60%
- Diabetes improves or resolves in >80% patients
- Dyslipidemia improves in > 70%
- HTN improved or resolved in 79%
- OSA improved or resolved in >85%
- Improved QOL
- Decreased $ spent on medications
- Not a practical approach for the patient population as a whole
MY APPROACH

- Diagnose and stage – Liver biopsy
- Identify other comorbidities
  - Team approach
- Lifestyle modification
  - Emphasize lifestyle and dietary modification
  - De-emphasize weight
- Office visits every 3 months the 1st year
- LFTs +/- HOMA/HbA1c +/- lipid panel +/- iron tests every 3 months
CONCLUSIONS

• Look for it
• Consider biopsy in those with:
  – Chronic transaminitis for 10 or more years
  – Diabetes
  – Coexistent liver disease
• Treat the metabolic syndrome
• Mainstay of therapy:
  – Lifestyle change with dietary modification, aerobic exercise and weight loss (>6% body weight)
“Do not follow where the path may lead
Go instead where there is no path and leave a trail”

Ralph Waldo Emerson