Non-alcoholic fatty liver disease

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CAHN Presentation
CDDW 2015

Objectives

- To appreciate the extent of NAFLD in the general population
- Gain an understanding of the risk factors that lead to the development of NAFLD
- Realize the prognosis and effects of NAFLD
- To understand the treatment options for NAFLD and NASH
NAFLD vs NASH

NAFLD

Simple Steatosis → NASH → Cirrhosis

12% over 8 years

1-2% over 15-20 years


The spectrum of NAFLD

Healthy liver

Fatty liver (Simple fat accumulation)

NASH (Non-Alcoholic steatohepatitis)

Cirrhosis (Scar tissue)

NAFLD develops from simple steatosis to steatohepatitis (NASH), and then cirrhosis. Cirrhosis is no more reversible.
The Impact of NAFLD

- In Western countries, the prevalence of NAFLD in the general adult population is 20-30\%\textsupERS 1, whereas it approaches 90\% in the morbidly obese\textsupERS 2.

- NASH (non-alcoholic steatohepatitis) – presence of both fat (steatosis) and inflammation (hepatitis) within the cells of the liver
  - Seen in 2-3\% of the general population\textsupERS 3, and in 37\% of morbidly obese patients.

- These numbers are likely an underestimate of the true prevalence of the disease, as autopsy studies have demonstrated that fat (steatosis) is seen in about 36\% of lean patients, and 72\% of obese patients. NASH is seen in 3\% of lean patients and about 20\% of obese patients.

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 2000, 2010

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)
Fatty Liver Under the Microscope

NAFLD – Etiology

- **Primary**
  - Obesity
  - DM/glucose intolerance
  - Hypertriglyceridemia
  - Low HDL
  - Hypertension

- **Secondary**
  - Drugs
  - Metabolic
  - Toxins
  - Infections
Secondary Causes of NAFLD

<table>
<thead>
<tr>
<th>Nutritional</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein calorie malnutrition</td>
<td>Dysbetalipoproteinemia</td>
</tr>
<tr>
<td>Rapid weight loss</td>
<td>Hypopituitarism/hypothyroid</td>
</tr>
<tr>
<td>TPN</td>
<td>Glycogen storage disorder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones</td>
<td>Amanita phalloides</td>
</tr>
<tr>
<td>Steroids</td>
<td>Phosphorus poisoning</td>
</tr>
<tr>
<td>Estrogen</td>
<td>B. cereus toxin</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anio/MTX/Diltiazem/Valproate/Tetracycline/cocaine/HAART</td>
<td>HIV</td>
</tr>
<tr>
<td>ASA (Reye’s)</td>
<td>HCV</td>
</tr>
<tr>
<td></td>
<td>SBBO</td>
</tr>
</tbody>
</table>

Pathophysiology of NAFLD

“Two/multi-hit hypothesis”

- Initial accumulation of steatosis in hepatocyte
- Excessive accumulation of intrahepatic TG
- Main proposed mechanism is insulin resistance
- Second hit is necessary for the development of necroinflammation in the hepatocyte, which results in NASH and fibrosis.
- Multiple possible etiologies for second insult to hepatocyte
Metabolic Syndrome

- Any 3 of the following:
  - Abdominal obesity
  - Hypertriglyceridemia
  - Low HDL-C
  - Hypertension
  - Elevated fasting glucose OR patient is on medication for elevated blood glucose

NCEP ATPIII; JAMA 2001; 285: 2486-97

NAFLD and Insulin Resistance

Postic, C. J Clin Invest 2008; 188:829-38
Development of Inflammation (NASH)

Diagnosis of NAFLD

- No specific symptoms or complaints that are suspicious for NAFLD
- Often discovered incidentally (annual bloodwork or insurance bloodwork reveals elevated liver tests)
- The diagnosis of fat in the liver can be made with a simple abdominal ultrasound, as a fatty liver is often “bright” on ultrasound
- Often, the combination of an ultrasound showing fat in the liver, in combination with risk factors for NAFLD are enough to make the diagnosis
- However, as other diseases can cause fat in the liver, your liver doctor may do other bloodwork to rule out other causes of liver disease
**Findings on Exam and Labs in NAFLD**

- **Hx:**
  - Usually no Sx until cirrhotic
  - Features of metabolic syndrome
  - FHx of NAFLD

- **O/E:**
  - Obesity
  - Acanthosis nigricans
  - Hepatomegaly

- **Labs:**
  - \( \uparrow \)AST and ALT (AST:ALT < 1); occasionally \( \uparrow \)ALP and GGT (< 3x ULN)
  - Elevated TG (occur Tchol), hyperinsulinemia;
  - Increased ferritin

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**Natural History of NASH**

- RF for Progression
  - Men > Women
  - Hispanics > Caucasian > Blacks > Aboriginals
  - OSA, hypopituitarism, hypogonadism, PCOS

- Increased mortality with NASH (as compared to simple steatosis, or matched control population)

- Although increased liver enzymes are associated with NASH, normal liver enzymes do not rule out NASH
Effect of NASH on the Rest of the Body

- The risk factors for the development of NAFLD and NASH are the same as those for the development of various cancers, heart disease and strokes.

- In studies examining the causes of death in patients with NAFLD and NASH, it has been found that patients with NASH have higher rates of death due to cardiac disease and cancers than the general population.

- The leading causes of death were:
  - Heart disease
  - Cancer
  - Liver-related death

### Table 2. Cause of Death

<table>
<thead>
<tr>
<th>Etiology</th>
<th>N (%) (N = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>15 (28%)</td>
</tr>
<tr>
<td>Breast</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Venous thromboembolus</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Seizis</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Aortic aneurysm dissection</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Retroperitoneal hemorrhage</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

### Table 3. Baseline Predictors of Mortality by Multivariate Proportional Hazard Modeling

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>Standard error</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per decade)</td>
<td>0.08</td>
<td>0.01</td>
<td>2.2 (1.7-2.7)</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>IFG/diabetes</td>
<td>0.97</td>
<td>0.34</td>
<td>2.6 (1.3-5.2)</td>
<td>.005</td>
</tr>
<tr>
<td>Cirrhosis at baseline</td>
<td>1.13</td>
<td>0.48</td>
<td>3.1 (1.2-7.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.35</td>
<td>0.29</td>
<td>1.4 (0.8-2.9)</td>
<td>.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.12</td>
<td>0.29</td>
<td>2.3 (0.8-7.3)</td>
<td>.3</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0.08</td>
<td>0.37</td>
<td>1.1 (0.5-2.3)</td>
<td>.5</td>
</tr>
</tbody>
</table>
### Eksted Study - Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NAFLD Group n (%)</th>
<th>Comparator Group n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disease</td>
<td>11 (15.5)</td>
<td>5 (8.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cancer outside of the liver</td>
<td>4 (5.6)</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Liver-related complications</td>
<td>2 (2.8)</td>
<td>1 (1.7)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Progression of Liver Disease

<table>
<thead>
<tr>
<th>Complications of end stage liver disease</th>
<th>Simple Steatosis</th>
<th>Baseline Inflammation/Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>3 (22%) of S2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (25%) of S3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (not Bx’ed due to Dx of HCC)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (46%)</td>
<td>30 (71%)</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>4 (9%)</td>
<td>12 (29%)</td>
</tr>
</tbody>
</table>
Treatment of NAFLD and NASH

Treatment of NAFLD/NASH

- **Lifestyle Modifications**
  - Weight Loss
  - Diet
  - Exercise

- **Drugs**
  - Insulin sensitizing agents
  - Statins
  - UDCA
  - Anti-oxidants

- **Supplements**
  - Vit E
  - Omega-3 supplements
  - Probiotics
The Effect of Exercise Alone

Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Baseline</th>
<th>Placebo Posttreatment</th>
<th>Exercise Baseline</th>
<th>Exercise Posttreatment</th>
<th>Treatment x Time Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>47.3 (5.6)</td>
<td>-</td>
<td>48.1 (2.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>98.8 (6.0)</td>
<td>98.8 (6.3)</td>
<td>94.4 (3.8)</td>
<td>94.1 (4.0)</td>
<td>0.838</td>
</tr>
<tr>
<td>BMI, kg m⁻²</td>
<td>31.1 (1.1)</td>
<td>31.0 (1.2)</td>
<td>32.2 (0.8)</td>
<td>32.1 (0.8)</td>
<td>0.962</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂max, ml kg⁻¹ min⁻¹</td>
<td>25.6 (1.6)</td>
<td>25.1 (1.7)</td>
<td>26.9 (1.4)</td>
<td>29.0 (1.9)</td>
<td>0.017</td>
</tr>
<tr>
<td>Plasma glucose, mmol L⁻¹</td>
<td>6.1 (0.00)</td>
<td>6.0 (0.00)</td>
<td>5.6 (0.2)</td>
<td>5.6 (0.3)</td>
<td>0.553</td>
</tr>
<tr>
<td>Plasma insulin, pmol L⁻¹</td>
<td>16.69 (2.63)</td>
<td>17.48 (2.61)</td>
<td>18.39 (2.40)</td>
<td>17.38 (2.83)</td>
<td>0.438</td>
</tr>
<tr>
<td>Plasma FFAs, μmol L⁻¹</td>
<td>558 (60)</td>
<td>533 (53)</td>
<td>500 (42)</td>
<td>498 (39)*</td>
<td>0.047</td>
</tr>
<tr>
<td>Plasma TC, mmol L⁻¹</td>
<td>1.84 (0.15)</td>
<td>1.59 (0.20)</td>
<td>1.26 (0.14)</td>
<td>1.26 (0.14)</td>
<td>0.498</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>4.75 (1.09)</td>
<td>4.81 (0.93)</td>
<td>4.39 (0.49)</td>
<td>4.60 (0.76)</td>
<td>0.733</td>
</tr>
<tr>
<td>ALT (U L⁻¹)</td>
<td>37.7 (4.6)</td>
<td>38.4 (5.0)</td>
<td>35.7 (6.5)</td>
<td>32.9 (5.8)</td>
<td>0.158</td>
</tr>
<tr>
<td>Cholesterol (mmol L⁻¹)</td>
<td>5.7 (0.3)</td>
<td>5.5 (0.2)</td>
<td>5.5 (0.4)</td>
<td>5.1 (0.4)</td>
<td>0.455</td>
</tr>
<tr>
<td>Diet recall analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy intake (kcal kg⁻¹)</td>
<td>9821 (1083)</td>
<td>9703 (1089)</td>
<td>10083 (867)</td>
<td>10196 (751)</td>
<td>0.503</td>
</tr>
<tr>
<td>% carbohydrate</td>
<td>52 (2)</td>
<td>54 (3)</td>
<td>54 (2)</td>
<td>55 (2)</td>
<td>0.878</td>
</tr>
<tr>
<td>% fat</td>
<td>31 (2)</td>
<td>30 (3)</td>
<td>32 (2)</td>
<td>31 (2)</td>
<td>0.921</td>
</tr>
<tr>
<td>% protein</td>
<td>17 (3)</td>
<td>16 (1)</td>
<td>15 (1)</td>
<td>14 (1)</td>
<td>0.906</td>
</tr>
</tbody>
</table>

ALT, aspartate aminotransferase; FFAs, free fatty acids; HOMA-B, homeostasis model assessment of insulin resistance; TC, triglycerides; VO₂peak, aerobic capacity.
Values are means (SD); n = 19; *Significant treatment x time interaction (exercise versus Placebo) (P < 0.05).

Table 2. Hepatic Lipid Content and Composition and Abdominal and Muscle Triglyceride Content

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Posttreatment</th>
<th>Baseline</th>
<th>Posttreatment</th>
<th>P Value</th>
<th>Treatment × time interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2HDC, %</td>
<td>9.18 (3.80)</td>
<td>9.64 (2.89)</td>
<td>8.55 (2.49)</td>
<td>8.78 (1.90)*</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>Hepatic SI</td>
<td>0.122 (0.037)</td>
<td>0.152 (0.043)</td>
<td>0.188 (0.034)</td>
<td>0.186 (0.034)</td>
<td>0.891</td>
<td></td>
</tr>
<tr>
<td>SAT area, cm²</td>
<td>169.5 (48.3)</td>
<td>168.9 (48.3)</td>
<td>167.4 (49.5)</td>
<td>167.4 (49.5)</td>
<td>0.789</td>
<td></td>
</tr>
<tr>
<td>Average SAT, cm²</td>
<td>395.7 (44.1)</td>
<td>395.7 (44.1)</td>
<td>395.7 (44.1)</td>
<td>395.7 (44.1)</td>
<td>0.884</td>
<td></td>
</tr>
<tr>
<td>VAT area, cm²</td>
<td>154.3 (21.2)</td>
<td>154.3 (21.2)</td>
<td>144.1 (18.3)</td>
<td>143.6 (18.3)**</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Average VAT, cm²</td>
<td>1339 (262)</td>
<td>1340 (263)</td>
<td>151.2 (18.2)</td>
<td>151.3 (18.3)**</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>VATG, %</td>
<td>1.20 (0.19)</td>
<td>1.38 (0.27)</td>
<td>1.39 (0.19)</td>
<td>1.64 (0.16)</td>
<td>0.685</td>
<td></td>
</tr>
</tbody>
</table>

2HDC, hepatic triglyceride concentration; VATG, visceral adipose tissue triglyceride concentration; SAT, subcutaneous adipose tissue area (cm²); VAT, visceral adipose tissue area (cm²).

Values are means (SE); n = 19 for 2HDC, VATG; n = 15 for SATG. *Significant treatment × time interaction Exercise versus Placebo (P < 0.05). **Significant treatment × time interaction Exercise versus Placebo (P < 0.01).

Resistance Exercise

Figure 1. Effect of 8 weeks resistance exercise training (Exercise) on hepatic triglyceride content (2HDC) and visceral adipose tissue triglyceride content (VATG). Values are means (SE); n = 19 for 2HDC, VATG; n = 15 for SATG. *Significantly different from control (P < 0.05).
Exercise - Summary

Exercise appears to improve both hepatic TG content and VAT stores, independent of the changes wrought by weight loss, or effect on insulin levels/sensitivity.

Thought that this effect is due to increased FA oxidation from adipose, intramyocellular and hepatic sources, as well al improving mitochondrial FA transport and oxidation.

Increased VLDL secretion and VLDL clearance by skeletal muscle, which may then result in the removal of FA from hepatic TG storage.

Therefore, encourage patients to continue exercising regularly (150 minutes of aerobic exercise/wk, approximately 400 calories/session), even if they are not losing weight\textsuperscript{1,2}.

\textsuperscript{1}Johnson, NA. Hepatology 2009; 50:1105-12

A weight loss of ≥7% resulted in significant improvements in histology (both overall NAS and individual components of NAS).
NAFLD and Diet

1 Ouyang, X et-al. J Hepatol 2008; 48:993-9
2 Zelber-Sagi, S et-al. J Hepatol 2007; 47:711-7
### NAFLD and Diet

#### Table 1 Summary of studies of effect of diets and exercise

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>n</th>
<th>Duration of study (months)</th>
<th>Main outcome and biochemical findings</th>
<th>Liver histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocaloric diet</td>
<td>52</td>
<td>4</td>
<td>Reduction in weight, insulin resistance and ALT</td>
<td>Not studied</td>
</tr>
<tr>
<td>Hypocaloric diet</td>
<td>5</td>
<td>6</td>
<td>Not studied</td>
<td>Improved</td>
</tr>
<tr>
<td>Hypocaloric and very low-fat diet in type 2 diabetes individual</td>
<td>8</td>
<td></td>
<td>Decreased weight, fasting glucose and intrahepatic lipid</td>
<td>Not studied</td>
</tr>
<tr>
<td>Low-fat diet</td>
<td>10</td>
<td></td>
<td>Decreased liver fat</td>
<td>Not studied</td>
</tr>
<tr>
<td>Dietary counselling for biopsy-proven NASH</td>
<td>23</td>
<td>12</td>
<td>Decreased weight, ALT, fasting insulin and triglyceride</td>
<td>Improved</td>
</tr>
<tr>
<td>Exercise</td>
<td>65</td>
<td>3</td>
<td>Decreased weight and ALT; ALT not normalized in patients failed to comply with exercise</td>
<td>Not studied</td>
</tr>
<tr>
<td>Exercise and diet</td>
<td>31</td>
<td>15</td>
<td>Decreased weight, ALT and fasting insulin</td>
<td>Not studied</td>
</tr>
<tr>
<td>Exercise and diet</td>
<td>25</td>
<td>3</td>
<td>Decreased ALT, fasting glucose and cholesterol</td>
<td>Improved</td>
</tr>
</tbody>
</table>

NASH, non-alcoholic steatohepatitis.

Ahmed MH and Byrne, C. Diabetes, Obesity and Metab 2009;11:188-95

### Medical Management of NASH
Preventative medicine in NASH

- Patients with NAFLD and NASH have higher risks for the development of DM, CVD, and CVA than patients without NAFLD.
- Physicians should have a lower threshold for investigating possible cardiac symptoms.
- Treatment of underlying risk factors for CVD/CVA should be undertaken in patients with NASH.
  - Antiplatelet agents may have a slightly increased risk of resulting in bleeding in patients with cirrhosis, but often the risk-benefit ratio favours their use, and they are relatively well-tolerated.
  - Statins should be used to treat underlying hyperlipidemia and decrease risk of CAD/CVA.
    - No effect of statins on NASH alone, especially in patients who do not have hyperlipidemia.

Antihyperlipidemics and NAFLD

- **Statins:**
  - Small handful of clinical trials in humans have shown an improvement in biochemical and histological parameters (steatosis and inflammation) with atorvastatin.
  - One study showed that patients with NASH and DM on statins have lower rates of HCC (OR: 0.74).

- **Ezetimibe:**
  - Animal studies demonstrate improved biochemistry, steatosis, inflammation and fibrosis.
  - Only 1 human study with histological outcomes ➔ Improvements seen in steatosis and overall NAS.
  - Improvements in ALT and lipid profile, no changes seen on U/S.

- **Fibrates:**
  - Majority of studies are in animal models, 2 pilot studies (fenofibrate and clofibrate).
  - Activates PPAR-α receptors, thereby increasing insulin sensitivity and lipid metabolism.
  - No change in liver histology in patients given fibrates, although parameters of metabolic syndrome improved.
Anti-Oxidants in NAFLD

- **ARB**
  - Mechanism of action: inhibition of oxidative stress, release of inflammatory cytokines
  - Losartan - small studies have demonstrated improvements in transaminases, hepatic inflammation and fibrosis, but larger trials are needed.

- **Pentoxifylline**
  - Inhibits TNF-α production
  - Largest study to date (n=55) showed improvements in NAS (≥2 points) in 38.5% (13.8% in placebo group; p = 0.01) → main effect is on steatosis and lobular inflammation, mild improvement in fibrosis, but no change in ballooning

- **UDCA**
  - No significant histological change seen when UDCA administered as monotherapy.

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Zein, CO et al Hep 2011; 54:1610-9

Weight loss agents and surgery in NASH

- **Orlistat**
  - Enteric lipase inhibitor
  - No better than placebo for improvement in histology or liver enzymes
  - 2 RCTS showed that it was unable to cause weight loss

- **Bariatric Surgery**
  - Currently no RCTs evaluating the effect of foregut bariatric surgery as a treatment of NASH
  - Prospective and retrospective cohort studies show improved hepatic steatosis and liver enzymes
  - Mathurin et al – correlated metabolic and clinical data with histology before and after (1 and 5 years) in ~400 obese patients undergoing bariatric surgery → significant improvement in steatosis, ballooning, NAS, and resolution of probable/definite NASH in F/U; no decrease in fibrosis
  - 2 meta-analyses showed improved steatosis, steatohepatitis and fibrosis after surgery
  - Cochrane review: lack of RCTs prevents definitive assessment of benefits/harms of bariatric surgery as treatment of NASH
NAFLD and Vit E Studies

- Initial studies in pediatric populations (not placebo controlled) showed improvement in both liver enzymes and histological parameters.
- Randomized, controlled studies (Vit E in addition to diet) done in early 2000s did not show any benefit to adding Vit E to diet and exercise.
- 2 recent multicentre, placebo controlled RCTs with histological improvement as primary outcome:
  - Lavine et al: 57 pediatric patients, 800 IU Vit E x 96 weeks → improvement in ballooning in NAS, no effect on fibrosis or inflammation.
  - PIVENS study → 84 Tx, 83 placebo, 80 pioglitazone; higher rates of improvement in Vit E arm than in placebo, however, equal improvement in steatosis and inflammation in both Tx arms; no change in fibrosis level.

Vit E Summary

- Vit E may be of use in the improvement of liver enzymes and certain histological features of NASH, but only in the early stages of the disease.
- No effect on portal inflammation or fibrosis.
- Although may be useful as adjunct, especially in the early stages of disease, unlikely to play a role as a sole treatment of NASH.
- Need to consider cardiac status in patients being considered for this therapy – need to use with caution in patients with moderate-severe cardiac disease.
- Recent meta-analyses have shown increased risk of hemorrhagic stroke, prostate cancer, and increased overall mortality.
Other Therapies

Probiotics:
- Trials in adults show no benefit, but recent study in children with NAFLD showed decreased steatosis as measured by US, as well as decreased BMI.

Pentoxifylline:
- Conflicting studies, with some studies showing only transaminase improvement, while others show improved histology (steatosis, inflammation and fibrosis).
- Recent meta-analysis showed improved transaminases and histological markers of NASH.

Zeng Eur J Gastro Hep 2014; 26: 646-653

Newer Agents for the Treatment of NASH

- Omega-3:
  - Recent meta-analysis showed that omega-3 FA can reduce hepatic steatosis, although minimal change is seen in transaminases.

- Endocannabinoid Receptor Antagonists:
  - Patients from ADAGIO-Lipids trial examined to see whether rimonabant had effect in NAFLD reversed CT-assessed steatosis in 48% (placebo – 19%; p = 0.03).

- Semi-Synthetic BA:
  - FXR is a bile sensor that regulates cholesterol and bile metabolism.
  - 2 studies of synthetic receptor agonists demonstrated improved fibrosis markers, weight loss. One study in rats demonstrated improved fibrosis and inflammation.
  - Farnesoid X Receptor Ligand (Obetocholic Acid) – FLINT trial awaiting results.
**FLINT Trial**

- Multicentre, placebo controlled DB trial comparing Obeticholic acid 25mg (FXR agonist) to placebo for 72 weeks in NASH
- Primary endpoint – reduction in NAS by ≥2 points
- 50 patients in treatment arm had improved histology (45%) compared to 23 (21%) patients in the placebo arm
- Significant pruritus in the treatment arm
- Not available in Canada at this time

**Alcohol intake in NASH**

- Avoid heavy alcohol consumption in any liver disease
  - >3 drinks/d (F) or >4 drinks/d (M)
  - >7 drinks/wk (F) or >14 drinks/wk (M)
- Cross-sectional studies have shown that light alcohol consumption (~3 drinks/wk in women and <5 drinks/wk in men) may have beneficial effect on NAFLD
Metformin and NASH

- Mechanism of action:
  - Improved insulin sensitivity
    - Decrease hepatic gluconeogenesis
    - Stimulate glucose uptake in muscle
    - Increases adipose tissue FA oxidation
  - Phosphorylation of AMPK, which then inactivated HMG-CoA reductase, thereby decreasing FAS expression → ↓ FA and cholesterol synthesis

- Many recent systematic reviews examining the role of metformin for the treatment of NASH (Cochrane 2009, Shyangdan 2011, and van Wagner 2011).
  - Improvements in biochemistry are more marked with metformin and diet than diet alone (2007 Cochrane review)
  - Conclusion: Although insulin resistance is improved with Metformin, the results of studies examining the histological parameters in NAFLD are too heterogeneous to make an accurate assessment

- Therefore, although there is an improvement in ALT, HbA1C, and weight with Metformin, there is no evidence that it improves NAFLD/NASH.

TZD and NASH

- Musso et-al examined the 5 high quality trials using TZDs for NASH.
  - Conclusion: TZDs improve steatosis and inflammation, but not fibrosis

- Drawbacks:
  - TZDs associated with weight gain (not fluid related)
  - Rosiglitazone associated with higher risk of CAD, although pioglitazone has been shown to decrease ischemic cardiac events.
  - PPARγ stimulated Na retention → Leads to the development (4-6%) or worsening of CHF (RR: 1.7-2.1).
  - Fluid retention (pedal and pulmonary edema) resistant to diuretics, but responds to drug cessation.
  - Both weight gain and edema occur more often when used concomitantly with insulin therapy.

Musso, G. Diabetologica 2012
Treatment of NAFLD/NASH - Summary

- **Non-Pharmacologic - Lifestyle modification**
  - Change in diet (both caloric restriction and restriction of both high fat foods and high fructose foods)
  - Exercise – 150 minutes/wk shown to decrease hepatic steatosis
  - Weight loss- 5-10% over 6-12 months reduces inflammation, steatosis and possibly fibrosis

- **Pharmacologic**
  - Modification of risk factors
    - DM
    - Dyslipidemia (statins)
  - Vitamin E
  - Omega 3/fish oil
  - Obetocholic acid

Summary of Various Drugs in NAFLD

- **Metformin** ➔ Although it does result in weight loss, it does not have any significant effect on liver histology, and so is not recommended as a treatment for NASH

- **TZDs:**
  - Pioglitazone ➔ causes weight gain, but improves enzymes, steatosis and inflammation

- **Vitamin E** ➔ When given to non-diabetic adults, shown to improve NASH ➔ recommended as first line treatment in this population by AASLD

- **UDCA** ➔ no benefit over placebo

- **Omega-3 oils** ➔ Possible use in patients with hypertriglyceridemia

- **Statins** ➔ Should be used to treat dyslipidemia in NAFLD patients
Questions?