Non-alcoholic Fatty Liver Disease (NAFLD)

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In the context of my participation in this CME activity:

There is no conflict of interest to disclose.
The Spectrum of NAFLD

Fatty Liver
- Steatosis

NASH
- Fatty liver
- Inflammation
- Liver injury

Cirrhosis
- Fibrosis and nodular regeneration
NAFLD: Hepatic Manifestation of the MS

Metabolic Syndrome: Definition

Having at least 3 of the following means that an individual has metabolic syndrome:

- Abdominal circumference (> 40 inches for men or 35 inches for women)
- Elevated triglycerides
- Low levels of HDL
- Hypertension
- Hyperglycemia
The Metabolic Syndrome

Obesity

Insulin Resistance

Hyperglycemia

Hypertension

Hyperlipidemia
Age-Specific Prevalence of the MS Among US Adults

Prevalence (%)

- Men
- Women

Ford et al. JAMA. 2002;287:356.
Obesity is perhaps the most important and most modifiable risk factor
Percent of Obese (BMI $\geq 30$) in U.S. Adults
Estimated Prevalence of NAFLD in US General Population

Fatty liver without inflammation or fibrosis

NASH

~3% (6%?)

~30%

Harrison et al. Drugs. 2003;63:2379-2394;
Prevalence of NAFLD in Severely Obese Patients

12 observational and transversal studies totaling 1620 patients

Highest prevalence of NASH: Mexican and Greek cohorts

Prevalence of steatosis: 91%
Prevalence of NASH: 37%

Conditions most frequently associated with NASH:
Diabetes and insulin resistance

Natural History of NASH

• Classical endpoints to understand the natural history:
  – Survival (Death)
  – Hepatocellular carcinoma
Natural History of NASH

Mortality higher than general population (SMR: 1.34)

1-2% risk of progression over 15-20 years

~30% of western populations

~3% general population; 20-40% of pts w/BMI >35 kg/m²

~12-20% risk of progression over 8 years

Long-term prognosis similar to HCV-related cirrhosis once Child-Turcotte-Pugh Class B or C

Natural History of NASH

- Cirrhosis: 39-62%
- End-Stage Liver Disease Complications: 22-33%
- Liver-Related Death: 5%-6.8% yearly

HCC as an Endpoint in the Natural History of NAFLD
Relative Risk of Malignancies in individuals with BMI $\geq 35$ (compared to BMI < 25)

RR = 4.52

Calle EE, et al. NEJM 2003 (data based on 900,000+ Men and Women)
Cumulative Risk of HCC in 173,643 patients with DM and 650,620 non-DM

Cumulative Incidence (%)

Diabetes
No Diabetes

Follow up (Years)

P<0.0001

NASH and HCC: Limitations

• Prospective studies are essentially nonexistent.

• Cross-sectional and retrospective studies are limited by difficulties identifying NASH once cirrhosis has been established

• A study has provided some more concrete human data
NASH and HCC

420 NAFLD Patients in Olmsted County, MN

7.6 Years

7/420 (1.7%) developed Cirrhosis
2 developed HCC

Cumulative incidence and risk factors of hepatocellular carcinoma (HCC) in patients with end-stage liver disease secondary to nonalcoholic steatohepatitis (NASH)
Incidence of HCC

Entire population (n=510)
- 17.6%

Median Follow-up Time = 3.2 Years
(P25, P75: 1.7, 5.7)

HCV Cirrhosis (n=315)
- 20.3%
P = 0.03

NASH Cirrhosis (n=195)
- 12.8%
Annual Cumulative Incidence of HCC

NASH: 2.6% per year
HCV: 4.0% per year

P = 0.09
Treatment Options for NAFLD

• Lifestyle modification (Diet and exercise)
• Weight loss
• Insulin sensetizing agents and Antioxidants (Vitamin E)
• Emerging concepts
Dietary Habits

• NASH patients: diets higher in saturated fat/cholesterol and lower in polyunsaturated fat, fiber, and antioxidant vitamins C and E\(^1\)

• Energy intake significantly higher in NASH patients\(^2\)

• High fructose diets may also contribute to NAFLD\(^3\)

• These dietary differences seemes to be associated with increased inflammation by liver biopsy in addition to its association with steatosis.

Exercise

• Effect of exercise 60 minutes/day; 3x/wk for 4 wks
  – Physical training: 20 minutes of biking/running; 20 minutes of swimming; 20 minutes of warm up/cool down:
    – Whole body glucose uptake improved;
    – Fasting insulin concentrations decreased

• Effect of exercise on hepatic steatosis
  – Improvement of steatosis (histologically confirmed)

Exercise and NAFLD

813 Patients

Sedentary Activity
438

Moderate Physical Activity
162

Vigorous Physical Activity
213

Additional Benefits
77

Additional Benefits
125
Adjusted Odds Ratio for NASH by Exercise Intensity

Vigorous

Moderate

NASH

Fibrosis
(Additional Activity)

Adjusted Odds Ratio (Log scale)
Weight Loss
Weight-Loss Surgery
<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Baseline Wt./BMI</th>
<th>Surgery</th>
<th>Follow-Up</th>
<th>Change in Wt/BMI</th>
<th>Effect on NASH (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon (30)</td>
<td>45.9 kg/m²</td>
<td>LAGB</td>
<td>29.5 months</td>
<td>31.5 kg</td>
<td>NASH 80% resolved (AASLD score)</td>
</tr>
<tr>
<td>de Almeida (16)</td>
<td>53.4 kg/m²</td>
<td>RYGBP</td>
<td>23.5 months</td>
<td>22.3 kg/m²</td>
<td>Complete regression lobular inflammation and Mallory bodies (Brunt criteria)</td>
</tr>
<tr>
<td>Barker (19)</td>
<td>47 kg/m²</td>
<td>RYGBP</td>
<td>21.4 months</td>
<td>52.4 kg</td>
<td>89% (17/19) resolved NASH (Dixon scoring)</td>
</tr>
<tr>
<td>Mattar (70)</td>
<td>56 kg/m²</td>
<td>RYGBP (41) LSG (23) LAGB (6)</td>
<td>15 months</td>
<td>103 lb</td>
<td>80% improved steatosis 37% resolved steatosis and inflammation 20% resolved fibrosis (Brunt)</td>
</tr>
<tr>
<td>Klein (7)</td>
<td>58 kg/m²</td>
<td>RYGBP</td>
<td>1 yr</td>
<td>45 kg</td>
<td>100% improved steatosis, no change in inflammation and fibrosis (Kleiner)</td>
</tr>
<tr>
<td>Mathurin (50)</td>
<td>47.1 kg/m²</td>
<td>Biliointestinal bypass, LAGB</td>
<td>1 yr</td>
<td>27 kg</td>
<td>75% resolved NASH (Brunt), fibrosis Increased</td>
</tr>
<tr>
<td>Mottin (90)</td>
<td>Not specified</td>
<td>RYGBP</td>
<td>1 yr</td>
<td>46.7 kg/m²</td>
<td>54.4% resolved, 27.8% improved steatosis</td>
</tr>
<tr>
<td>Clark (16)</td>
<td>51 kg/m²</td>
<td>RYGBP</td>
<td>305 days</td>
<td>118 lb</td>
<td>81% resolved (Brunt), 80% improved inflammation (12/15), 94% improved steatosis (15/16)</td>
</tr>
</tbody>
</table>

LAGB = laparoscopic adjustable gastric banding; RYGBP = Roux-en-Y gastric bypass; LSG = sleeve gastrectomy.
A Practical Goal

• An 8% weight loss is associated with a 39 ± 5% liver fat loss

Treatment of NAFLD

• Diet and exercise ± Weight loss
• Insulin sensetizing agents and Antioxidants (Vitamin E)
• Other emerging concepts
Background

- Both insulin resistance and oxidative stress have been implicated in the pathogenesis of NASH.
- Several small single center studies have provided evidence that pioglitazone, an insulin-sensitizing PPAR-γ agonist, as well as vitamin E, an anti-oxidant, improve histologic features of NASH.
## Thiazolidinediones-Early Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Dose of Medication</th>
<th>Duration</th>
<th>Insulin Sensitivity</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promrat et al</td>
<td>Pioglitazone</td>
<td>Open-Label</td>
<td>12 months</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>18</td>
<td>30 mg daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanyal et al</td>
<td>Pioglitazone</td>
<td>Randomized</td>
<td>6 months</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>10</td>
<td>30 mg + vit E 400 IU daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuschwander-Tetri et al</td>
<td>Rosiglitazone</td>
<td>Open-Label</td>
<td>12 months</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>22</td>
<td>4 mg bid</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Belfort et al</td>
<td>Pioglitazone</td>
<td>Randomized Placebo Controlled</td>
<td>6 months</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>48</td>
<td>30 mg × 2 months, then 45 mg daily</td>
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</table>
Pioglitazone or Vitamin E for Nonalcoholic Steatohepatitis (PIVENS)

The NIDDK Clinical Research Network (NASH CRN)
Study Design

Randomization
Eligibility assessed by local pathologist
(1:1:1)
Wk 0

Month -6
Liver biopsy

Vitamin E 800 IU/day

placebo

Pioglitazone (30 mg/day)

End of treatment
Liver Biopsy
Wk 96

Wk 96

Week 120
end of study
Both Vitamin E and Pioglitazone improve steatosis.

Improvement in severity of steatosis grade:
- Vit E vs placebo: $p < 0.0001$
- Pio vs placebo: $p < 0.0001$

- Improvement in severity of steatosis grade:
  - Vit E: $\Delta $ grade 0.7
  - Placebo: $\Delta $ grade 0.1
  - Pioglitazone: $\Delta $ grade 0.8
Both vitamin E and pioglitazone increased the proportion of subjects with resolution of NASH.

![Bar chart showing the proportion of subjects for different treatment groups.](chart)

- Vitamin E: 44/84
- Placebo: 23/83
- Pioglitazone: 40/80

\[ P < 0.0008 \] for Vitamin E vs. Placebo

\[ P < 0.01 \] for Pioglitazone vs. Placebo
Neither Vitamin E nor Pioglitazone improved fibrosis scores or proportion of subjects with improved fibrosis.

Improvement in severity of fibrosis scores:
Vit E vs placebo: $p = 0.19$ (n.s.)
Pioglitazone vs placebo: $p = 0.1$ (n.s.)
Concerns over use of pioglitazone

- CHF
- Bladder cancer
- Bone loss

Based on a recent meta-analysis of 19 RCT. Lincoff A, et al. JAMA 2007
Concerns over use of Vitamin E

• Increase all-cause mortality (reported in some meta-analysis but not confirmed)

• Increased risk for prostate cancer in healthy men reported in one RCT (at dose 400 IU/day)
• Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, long-term safety and efficacy has not been established.

• Vitamin E administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as first-line therapy in this patient population.
Conclusions

• Metabolic abnormalities including obesity and DM have emerged as important risk factors for NAFLD.

• NAFLD is common and is associated with cirrhosis and HCC.

• Correction of metabolic abnormalities may potentially prevent NASH complications.

• Drug therapy for NAFLD remains suboptimal.