Therapy in NAFLD/NASH and Related Metabolic Disorders

Giulio Marchesini
Malattie del Metabolismo e Dietetica Clinica
“Alma Mater Studiorum” University of Bologna
Key concepts in NAFLD/NASH & MS

- NAFLD is the hepatic manifestation of the metabolic syndrome, associated with insulin resistance
- The liver is not an innocent bystander, but participates (and possibly triggers) metabolic dysfunction
- Consequently, subjects with NAFLD have a high prevalence of cardiovascular involvement
- The presence of NAFLD is an additional risk factor for CV disease, after adjustment for traditional risk factors (diabetes, blood pressure, lipid profile)
- In the long-term, cardiovascular disease is a common cause of death in NAFLD patients, affecting prognosis more than liver disease itself
Prevalence of features of Met Syn in NAFLD

Visceral obesity: ~20-30%
High BG: ~20-30%
High TG / Low HDL: 50%
High BP: 60%
Met Syn: 40%

Trans fats and HFCS diet

- Hyperinsulinemia
- Impaired insulin responsiveness
- Increased leptin and resistin levels

ALIOS = American lifestyle-induced obesity syndrome

Glucose tolerance test

Tetri et al, AJP Gastrointest Liver Physiol 2008
Trans fats and HFCS diet

Increased hepatic TNF-α and procollagen α1 mRNA expression

Tetri et al, AJP Gastrointest Liver Physiol 2008
Differential effects of dietary sugars on obesity, steatosis and oxidative stress

Different sugars in water in exp mice
AS: artificial sweetener

Bergheim, J Hepatol 2008
Supersize Me
Effect of Fast Food on liver fat

18 subjects doubled caloric intake by a fast food-based diet for 4 weeks
Limited physical activity <5000 steps/day

+6.4 kg, 10% weight gain in 4 weeks
Serum ALT, on average from 22 U/L to 68 (+220%)
Liver fat (MRS), 1.1% to 2.8 (+155%)

Kechagias, Gut 2008
International Guidelines on Treatment of Different Features of Metabolic Syndrome (WHO, NIH, ADA, ISH, NAASO)

Non Pharmacologic Treatment: Correct CV Risk Profile by a Behavioral Approach

Pharmacologic Treatment

An ounce of prevention is worth a pound of treatment (B. Franklin, 1735)
Diabetes Prevention Study
Long-term follow-up

• In the long-term, the difference between the control and the intervention group continues to increase

• Diabetes is delayed by 4 years

Lindstrom, Lancet 2006
China Da Qing Diabetes Prevention Study
Long-term follow-up

Figure 2: Cumulative incidence of diabetes mellitus during follow-up in China Da Qing Diabetes Prevention Outcome Study

Li, Lancet 2008
Suggested algorithm for NAFLD treatment

NAFLD

Assess CVD risk

Consider treatment with statin, consider ACEI or AR receptor blocker and low dose aspirin

NAFLD + obesity or type 2 diabetes

Weight loss and lifestyle modifications (reduce alcohol intake + increase physical activity + weight loss (± orlistat/sibutramine/rimonabant))

Morbid obesity

Consider bariatric surgery

Diabetes:
Consider metformin + TZDs

Ahmed, Diab Obes Metab 2008
Potential targets of therapy

- Dietary weight loss
- Medications associated with weight loss
  - Exenatide
  - Orlistat
  - Rimonabant
  - Exercise

- Pentoxifylline
- TZDs
- FFA
- TNF-α

- Adipocytes
- Adiponectin

- Stellate cells
- Oxidative stress
- Triglyceride synthesis
- Intestinal lumen

- Triglycerides
- ARBs?
- Dietary modifications
  - Fructose
  - Altered lipid profiles
  - Ezetimibe
  - Orlistat

- TZDs
- Metformin
- Exercise

- Glucose
- FFA

- Myocytes

Torres & Harrison, Gastroenterology 2008
Pioglitazone in NAFLD/NASH

- 55 Pts (age, 51 y, BMI 33)
- Hepatic fat by NMR spectroscopy
- at 6 mo:
  - 21 Pl, 26 PIO
  - PIO: 45 mg/day

Figure 1. Plasma Aspartate Aminotransferase (Panel A) and Alanine Aminotransferase (Panel B) Concentrations during the Run-in Period (Weeks -4 to 0), the Treatment Period (Weeks 0 to 24, Shaded Area), and the Post Treatment Follow-up Period (Weeks 24 to 36); Hepatic Fat Content Assessed by Means of Magnetic Resonance Spectroscopy before and after the Study Treatment (Panel C); and Plasma Adiponectin Concentrations before and after the Study Treatment (Panel D).
Pioglitazone in NAFLD/NASH

No data on long-term maintenance of positive effects
Pioglitazone and NAFLD

![Graph showing ALT and AST levels over time with data points and error bars.]

Table 2. Comparison of Different Histological Parameters Before and After 48 Weeks of Treatment with Pioglitazone and Again 48 Weeks After Stopping Pioglitazone

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline*</th>
<th>48 Weeks on Pioglitazone*</th>
<th>48 Weeks off Pioglitazone*</th>
<th>P* 1 vs. 2</th>
<th>P* 2 vs. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal Inflammation</td>
<td>3.0 ± 1.1</td>
<td>1.2 ± 0.7</td>
<td>2.9 ± 1.4</td>
<td>&lt;0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Steatosis</td>
<td>2.6 ± 1.0</td>
<td>0.9 ± 0.6</td>
<td>2.1 ± 1.3</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>Cell injury</td>
<td>1.8 ± 0.7</td>
<td>0.4 ± 0.7</td>
<td>1.2 ± 1.0</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>NASH Activity Index</td>
<td>7.1 ± 2.4</td>
<td>2.6 ± 0.9</td>
<td>6.2 ± 3.0</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>NASH fibrosis</td>
<td>2.1 ± 1.2</td>
<td>1.1 ± 1.2</td>
<td>1.2 ± 1.3</td>
<td>0.03</td>
<td>1.00</td>
</tr>
<tr>
<td>Diagnostic criteria for NASH</td>
<td>9 (100%)</td>
<td>1 (11%)</td>
<td>7 (76%)</td>
<td>&lt;0.001c</td>
<td>0.02</td>
</tr>
<tr>
<td>Interval between biopses (wks)</td>
<td>50.6 ± 4.4</td>
<td>50.2 ± 6.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± S.D., *Wilcoxon Ranked Sum Test and *Fisher's Exact Test, NASH Activity Index Score of ≥ 4.

Lutchman, Hepatology 2007
Intensive lifestyle approach to obese subjects with liver disease

**Figure 2** Correlation between the decrease in waist circumference and the percentage of initial alanine aminotransferase (ALT) after 6 months follow-up. Univariate Spearman’s correlation, $P < 0.01$, $r_s = -0.45$.

**Figure 3** Change in alanine aminotransferase (ALT) and waist circumference in patients with and without a minimum of 2 cm decrease in waist circumference. Mean $\pm$ SEM waist measurements (white bars) shown on left Y axis and mean $\pm$ SEM ALT levels (black bars) shown on right Y axis. **Independent t-tests, $P < 0.001$.**

Osland, J Gastroenterol Hepatol 2007
Intensive lifestyle approach to obese subjects with liver disease

Table 2  Results of dietetic service provision for intensive intervention group at 6 months

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean weight loss (total group)</td>
<td>4.3 kg</td>
</tr>
<tr>
<td>No. patients achieving weight loss</td>
<td>26 (83%)</td>
</tr>
<tr>
<td>Cost per patient ($AU)</td>
<td>$87.50</td>
</tr>
<tr>
<td>Cost per kilogram lost ($AU)</td>
<td>$31.00</td>
</tr>
</tbody>
</table>

Intensive intervention costs include 12 weeks of intensive intervention (6 weeks of group sessions and 6 weeks of individual review) and monthly follow-up for 3 months. Costs extrapolated from total costs incurred divided by total weight balance (losses + gains) of all patients continuing in follow-up at 6 months.
Effect of Counseling

Results remarkably better in 9 patients compliant to treatment

Huang et al, Am J Gastroenterol 2005
### Macronutrients in NAFLD

<table>
<thead>
<tr>
<th>Macronutrient</th>
<th>Found In</th>
<th>Action</th>
<th>Findings in NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fatty acids</td>
<td>Lard, butter, coconut oil, palm oil</td>
<td>Increases LDL</td>
<td>Higher intake in NASH patients</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>Olive oil, nuts, avocados, peanut butter, peanut oil</td>
<td>Higher intake decreases LDL, increases HDL</td>
<td>Uncertain</td>
</tr>
<tr>
<td>PUFAs (n-6)</td>
<td>Sunflower, corn oil</td>
<td>Decreases HDL, ? Increase oxidative stress</td>
<td>High n-6/n-3 ratio in NASH patients</td>
</tr>
<tr>
<td>PUFAs (n-3)</td>
<td>Fish oil, walnuts, salmon, shellfish</td>
<td>Decreases ITA, glucose, insulin, TNF-s</td>
<td>Higher intake decreases hepatic steatosis (small studies)</td>
</tr>
<tr>
<td>Trans fatty acids</td>
<td>Fast foods, baked goods, deep fried foods</td>
<td>Increases inflammatory markers and LDL</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Dairy products (~8%)</td>
<td>Dairy products (~8%)</td>
<td>(Naturally derived trans FAs do not have above actions)</td>
<td></td>
</tr>
<tr>
<td>Ruminants (cows/sheep)</td>
<td>Ruminants (cows/sheep)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose/fructose</td>
<td>Sweetened drinks/sodas, candy</td>
<td>worsens insulin resistance</td>
<td>Higher intake in NASH patients</td>
</tr>
<tr>
<td>Protein</td>
<td>Meat, fish, eggs, dairy</td>
<td></td>
<td>Uncertain</td>
</tr>
<tr>
<td>Fiber</td>
<td>Whole grains, fruits, and vegetables</td>
<td>improve insulin resistance</td>
<td>Lower intake in NASH</td>
</tr>
</tbody>
</table>

TNF, tumor necrosis factor; ?, conflicting data.

Potential deleterious effect of a fat-rich or a refined carbohydrate-rich diet

Torres & Harrison, Gastroenterology 2008
Intensive lifestyle intervention & cardiorespiratory fitness in NAFLD

- 50 adults with NAFLD and 120 controls.
- At baseline, CR fitness was inversely associated with the amount of liver fat (MRS spectroscopy). Subjects in the higher vs. lower CRF quartile were very likely to resolve NAFLD (OR, 8.0; 1.5-54.4)

Figure 1  Cardiorespiratory fitness and change in fat compartments.

Kantartzis, Gut 2009
Intensive lifestyle intervention & physical activity in NAFLD

- 141 NAFLD cases enrolled into a low- or moderate-intensity activity program vs. control group
- Patients who increased their physical activity and those who increased their level of CR fitness had the greatest weight loss and improved liver enzymes

St. George, Hepatology 2009
RCT of weight loss in NAFLD

Change in histological parameters

- Controls
- Lifestyle

Promrat, Hepatology 2010
RCT of weight loss in NAFLD

Outcome is dictated by percent weight loss, independent of treatment assignment

Promrat, Hepatology 2010

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weight Loss &lt; 7%</th>
<th>Weight Loss ≥ 7%</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI category, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overweight (25-29.9 kg/m²)</td>
<td>5 (26.3)</td>
<td>3 (27.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>obesity class I (30-34.9 kg/m²)</td>
<td>5 (26.3)</td>
<td>6 (54.5)</td>
<td></td>
</tr>
<tr>
<td>obesity class II (35-40 kg/m²)</td>
<td>9 (47.4)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>10 (52.6)</td>
<td>4 (36.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>On metformin, N (%)</td>
<td>7 (36.8)</td>
<td>2 (18.2)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Histological parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat (0-3)</td>
<td>-0.41 (0.80)</td>
<td>-1.36 (0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobular inflammation (0-3)</td>
<td>-0.24 (0.75)</td>
<td>-0.82 (0.75)</td>
<td>0.03</td>
</tr>
<tr>
<td>Biliary injury (0-2)</td>
<td>-0.53 (0.80)</td>
<td>-1.27 (0.47)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fibrosis (0-4)</td>
<td>+ 0.06 (0.83)</td>
<td>-0.45 (0.93)</td>
<td>0.10</td>
</tr>
<tr>
<td>NAS (0-8)</td>
<td>-1.18 (1.59)</td>
<td>-3.45 (1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Participants with ≥3 points’ improvement in NAS from baseline, N (%)</td>
<td>4 (23.5)</td>
<td>9 (81.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Participants with NAS ≥2 at follow-up, N (%)</td>
<td>4 (23.5)</td>
<td>10 (90.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
CBT & Δ BMI >7% initial b.w.

CBT vs. Diet (comparator)

6-month

Unadjusted
4.15 (1.76-9.75)

Adjusted for PS
2.09 (0.80-5.46)

2-year

Unadjusted
3.05 (1.24-7.49)

Adjusted for PS
3.87 (1.32-11.31)
CBT & ALT within normal limits

CBT vs. Diet (comparator)

6-month

- Unadjusted
- Adjusted for PS
- Adjusted for PS + D BMI

2-year

- Unadjusted
- Adjusted for PS
- Adjusted for PS + D BMI

3.46 (1.76-6.81)
3.45 (1.57-7.42)
3.22 (1.47-7.07)
3.80 (1.74-8.32)
4.74 (1.84-12.27)
4.31 (1.63-11.43)
CBT & improved MS score

CBT vs. Diet (comparator)

6-month
- Unadjusted
- Adjusted for PS
- Adjusted for PS + D BMI

2-year
- Unadjusted
- Adjusted for PS
- Adjusted for PS + D BMI

0.95 (0.49-1.84)
1.10 (0.52-2.36)
1.47 (0.61-3.52)
2.30 (1.05-5.03)
2.75 (1.08-7.01)
1.98 (0.75-5.21)
L’epidemia di obesità e diabete finirà per mettere a rischio di NAFLD/NASH un numero sempre maggiore di persone nel mondo.

La terapia farmacologica, per quanto efficace nel breve termine, non appare un mezzo definitivo di trattamento.

Occorre realizzare interventi strutturati in grado di arrestare questa l’epidemia, ben oltre gli ambiti della Sanità.

E’ questa probabilmente l’unica strada percorribile a livello di popolazione.