NASH – metabolic syndrome of the liver

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NASH (NAFLD): the metabolic syndrome of the liver?

- The metabolic syndrome
- Clinical associations
- Disease mechanisms
- Cause or effect?
- NAFLD and CVD in the MetS
- Treatment implications
The Metabolic Syndrome


- Genetic + Environmental Factors
- Insulin Resistance
- Hyperglycemia/T2DM
- Dyslipidemia
- Hypertension
- Endothelial dysfunction/Microalbuminuria
- Hypofibrinolysis
- Inflammation (↑ CRP)

Atherosclerosis

Obesity (Central/Visceral)
### NCEP clinical classification of the metabolic syndrome

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>Men</td>
<td>&gt; 102 cm (&gt; 40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt; 88 cm (&gt; 35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 150 mg/dl or 1.7 mmol/L</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg/dl or 1.04 mmol/L</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 50 mg/dl or 1.30 mmol/L</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥ 130/≥ 85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 110 mg/dl or 6.1 mmol/L</td>
</tr>
</tbody>
</table>

Clinical associations
Features of metabolic syndrome are common in NAFLD (n=450)

<table>
<thead>
<tr>
<th>Feature</th>
<th>NAFL</th>
<th>NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>RUQ pain</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Hepar</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Obesity</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>65</td>
<td>69</td>
</tr>
</tbody>
</table>
NAFLD is common in patients with features of the MetS

USS study of 2,839 T2DM
Targher, Day et al
Diabetes Care 2007
Disease mechanisms
Steatosis in NAFLD is 2° obesity/insulin resistance
Necro-inflammation & fibrosis in NAFLD are 2° of obesity/insulin resistance.
NAFLD: cause or effect of metabolic syndrome?
NAFLD is a cause not simply an effect of insulin resistance/Met S

- Hepatic insulin resistance is universal in patients with NAFLD  
  Sanyal 2001

- Ins R/T2DM ↓ post-OLTx in T2DM transplanted for NASH cirrhosis  
  Cauble 2001

- Abnormal LFTs predict the future risk of T2DM and MetS  
  Sattar 2004, Hanley 2005

- Mechanisms now elucidated
  - FFA-induced cytokine release  
  - FFA/DAG-induced PKC activation  
    Shulman et al
Abnormal LFTs predict IR/Diabetes in obesity

Sattar et al Diabetes 2004
Abnormal LFTs predict development of Metabolic Syndrome

Hanley et al. Diabetes 2005
Hepatic (+muscle) fat as the cause of Ins Res

Savage, Shulman et al Physiol Rev 2007
NAFLD and CVD in the metabolic syndrome
NAFLD as a cause of/contributor to CVD in metabolic syndrome

NAFLD associated with

- Endothelial dysfunction & intimal media thickness
- ↑ CV risk profile \[\text{Villanova 2005}\]
- ↑ risk of future CV events/death \[\text{Adams 2005, Ekstedt 2006}\]
- Independent of T2DM/ metabolic syndrome \[\text{Targher 2005, 2007}\]

? Mechanisms

- Ins Res, FFA, VLDL, oxLDL, cytokines, ROS, PAI-1, fibrinogen …….
PROCAM CV Risk profile

Risk of cardiac event at 10yrs

Villanova et al 2005
NAFLD independently associated with CVD in T2DM

Targher, Day et al Diabetes Care 2007
Treatment implications
Treatment of NAFLD: treat the metabolic syndrome!

“Lifestyle intervention”
- Weight loss & ↑ physical activity
- 58% ↓ in Ins R → T2DM  
  \[\text{DPP NEJM 2002}\]

Treat CV risk factors if they persist
- Diabetes
- Dyslipidaemia (Statins for all T2DM)  
  \[\text{HPS 2003}\]
- Hypertension

All shown to ↓ mortality

Any good for the liver?
Weight loss & exercise
(Harrison & Day, Gut in press)

- Sound theoretical basis (↓IR, Insulin, Glu, FFA)
- Lots of uncontrolled evidence of benefit on steatosis NOT inflammation/fibrosis
- Encouraging pilots with Orlistat
  - Recent small RCT: ↓ steatosis, → N/I, fibrosis
    - Zelber-Sagi 2006
- Surgery
  - Gastric banding, Roux-en-Y diversion beneficial for steatosis and ± N/I, NOT for fibrosis (yet!)
Treatment of diabetes & NAFLD

- Insulin sensitisers rational choice
- Mechanism is via ↓ liver/muscle steatosis
- Metformin drug-of-choice for obese type 2 DM (↓mortality) \textit{PDS Lancet 1998}
- Insulin may improve steatosis \textit{Juurinen 2007}
- \underline{But} may increase fibrosis (via CTGF/ Foxo1) \textit{Paradis et al 2001, Adachi et al 2007}
Insulin sensitisers (1) metformin

- **Sound theoretical basis**
  - $\downarrow$ Lipogenesis, $\uparrow$ fat oxidation \textit{Zhou 2001}
  - $\downarrow$ steatosis/ALT in ob/ob mouse \textit{Lin 2000}

- **Contradictory pilot data**
  \textit{Marchesini 2001, Tiikkainen 2004, Nair 2004}

- **In RCT vs vit E or diet, metformin $\Rightarrow$**
  - Greater $\downarrow$ in ALT (p<0.0001)
  - $\downarrow$ steatosis/necrosis/fibrosis (p<0.012) \textit{Bugianesi 2005}
Insulin sensitisers (2) glitazones

- Sound theoretical basis - PPARγ agonists
  - Anti-steatotic \textit{Maeda 2001, Mayerson 2002}
  - Anti-inflammatory \textit{Jiang 1998, Xu 2003}
  - Anti-fibrotic \textit{Galli 2002}
  - PPARγ mutations $\rightarrow$ NASH \textit{Savage 2003}

- "Encouraging" pilot studies:

- NIH sponsoring pioglitazone vs vit E RCT
55 patients with IGT/T2DM + bx-proven NASH
6 months Pio (45mg) + diet vs Placebo + diet
## Rosiglitazone and CV risk: Nissen et al NEJM 2007

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,280 (0.43)</td>
<td>22/6105 (0.36)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td>9/2634 (0.34)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td>41/2895 (1.44)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Death from cardiovascular causes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,557 (0.38)</td>
<td>7/3700 (0.19)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,365 (0.51)</td>
<td>10/2634 (0.38)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td>5/2854 (0.18)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Lipid lowering agents

**Fibrates**: good theory - PPARα agonists
- ↓NASH in MCD mouse model
  - Ip 2003 & 2004
- 1 RCT of gemfibrozil (4/52) - ↓ LFTs
  - Basaranoglu 1998 Laurin 1996
- 1 open trial of clofibrate (52/52) – no benefit

**Statins**
- No rationale but appear to be safe
  - Chalasani 2004 & 2005
Anti-hypertensives

- RAS system
  - Anti-fibrotic
    - Animal models
    - Humans
      - Yokohama 2004
  - α-blockers
    - Anti-fibrotic
      - May also ↑ progenitor cell proliferation
        - Oben 2003
AIIR1B – Olmersartan in MCD
NASH *Hirose et al 2007*
Future therapies for T2DM/MetS with potential liver benefits

- **ER stress (chaperones)**
  - TUDCA, 4-phenylbutyrate, Ozkan Science 2006
  - Urso: No benefit in large RCT, Lindor 2004

- **IKK inhibitors (eg. Sulphasalazine)**
  - Insulin sensitising, Yuan Science 2004
  - Anti-inflammatory/anti-fibrotic, Oakley 2005
  - Improve NASH in experimental models, Beraza EASL 2007

- **? Rimonabant (CB₁ blocker)**
  - Antifibrotic, Teixeira-Clerc Nat Med 2006
  - Antisteatotic, Gary-Bobo Hepatology in press

- **Lindor 2004**
  - Urso: No benefit in large RCT

- **Oakley 2005**
  - Anti-inflammatory/anti-fibrotic

- **Beraza EASL 2007**
  - Improve NASH in experimental models
Rimonabant is anti-steatotic

Gary-bobo et al. Hepatology in press

### A

<table>
<thead>
<tr>
<th></th>
<th>Liverbody weight ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vehicle</strong></td>
<td>4.55</td>
</tr>
<tr>
<td>Lean rats</td>
<td>5.5</td>
</tr>
<tr>
<td>Obese fa/fa rats</td>
<td>5.5</td>
</tr>
<tr>
<td><strong>RIMO</strong></td>
<td><strong>4.55</strong></td>
</tr>
<tr>
<td><strong>Pair-fed</strong></td>
<td>4.55</td>
</tr>
</tbody>
</table>

### B

- **Lean / Vehicle**
- **Obese fa/fa / Vehicle**
- **Obese fa/fa / RIMO**
- **Obese fa/fa / Pair-fed**

### C

<table>
<thead>
<tr>
<th></th>
<th>ALT (U/L)</th>
<th>GGT (U/L)</th>
<th>ALP (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean / Vehicle</td>
<td>59.20 ± 8.97</td>
<td>0.09 ± 0.09</td>
<td>246 ± 10.28</td>
</tr>
<tr>
<td>Obese fa/fa / Vehicle</td>
<td>119.58 ± 6.23</td>
<td>10.67 ± 2.52</td>
<td>351 ± 14.43</td>
</tr>
<tr>
<td>Obese fa/fa / RIMO</td>
<td>86.78 ± 6.69**</td>
<td>2.50 ± 0.91**</td>
<td>290 ± 7.45**</td>
</tr>
<tr>
<td>Obese fa/fa / Pair-fed</td>
<td>121.01 ± 9.60</td>
<td>7.18 ± 1.03</td>
<td>358 ± 15.62</td>
</tr>
</tbody>
</table>
Conclusions

- NAFLD is the liver manifestation of the metabolic syndrome
- NAFLD is both a cause and a result of insulin resistance/metabolic syndrome
- NAFLD contributes independently to CVD in T2DM/MetS
- Treatment directed at features of the MetS is beneficial for NAFLD