Edinburgh International Conference of Medicine

Past, Present & Future

#PPFEd16
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Non-alcoholic fatty liver disease; a new epidemic?

Professor Chris Day
Newcastle University
**Definition**

**NAFL**
- Fat infiltration >5% with or without mild inflammation

**NASH**
- Steatosis and hepatocyte ballooning and inflammation (with or without fibrosis)

**Cirrhosis**

Importance
Prevalence of NAFLD in the general population (imaging based)

<table>
<thead>
<tr>
<th>Region</th>
<th>N</th>
<th>Prevalence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>2</td>
<td>13</td>
<td>6-29</td>
</tr>
<tr>
<td>Asia</td>
<td>14</td>
<td>27</td>
<td>23-32</td>
</tr>
<tr>
<td>Europe</td>
<td>11</td>
<td>24</td>
<td>16-33</td>
</tr>
<tr>
<td>Middle East</td>
<td>3</td>
<td>32</td>
<td>13-58</td>
</tr>
<tr>
<td>North America</td>
<td>13</td>
<td>24</td>
<td>20-29</td>
</tr>
<tr>
<td>South America</td>
<td>2</td>
<td>30</td>
<td>23-39</td>
</tr>
<tr>
<td>Overall</td>
<td>45</td>
<td>25</td>
<td>22-29</td>
</tr>
</tbody>
</table>
Risk factors for NAFLD

- Hypertension
- Hyperlipidemia
- Metabolic Syndrome
- Diabetes
- Obesity

Bar chart showing the percentage of risk factors for NAFLD, with categories for Normal, Hypertension (Hyperten), Hyperlipidemia (H’lipidemia), Metabolic Syndrome (Met S’drome), Diabetes, and Obesity. The chart indicates a higher percentage of NASH (Non-Alcoholic Steatohepatitis) and Fibrosis in individuals with Obesity.
NASH Is the Second Leading Etiology of Liver Disease Among Adults Awaiting Liver Transplantation in the United States
Presentation

• Symptoms
  – Unusual: ~ 60% asymptomatic
  – Majority discovered by chance
  – Fatigue most common

• Most common “presentation”
  – Incidental abnormal liver blood tests
  – Incidental hepatomegaly
  – Incidental “bright liver” on imaging

• Common scenarios
  – “Statin” monitoring
  – “Annual reviews” in Diabetic/Lipid clinics
  – Medical insurance/occupational health checks
Liver blood tests & NAFLD

• NAFLD is the commonest diagnosis in patients with “incidental” abnormal LFTs (ALT/ALP/GGT)
  – In secondary care (60-70%)  
    Skelly 2001, Pendino 2005  
  – In primary care (26%)  
    Armstrong 2012

• BUT:

• Most patients with NAFLD by MRS (~80-90%) have normal LFTs
  Browning 2004, Wong 2013

• ⇒ Screening/case finding in high risk groups (T2DM, Met S)?
  – Not advised in AASLD Practice Guidelines  
    Chalasani 2012  
  – Not advised in NICE Guidelines 2016  
  – Advised in EASL Practice Guidelines  
    Marchesini et al 2016  
  – With what?
### Tests for predicting steatosis (>5%)

<table>
<thead>
<tr>
<th>Test</th>
<th>Authors</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty Liver Index (FLI)</td>
<td>Borman 2013, Fedchuck 2014</td>
<td>0.81 0.76</td>
<td>0.49 0.87</td>
</tr>
<tr>
<td>Steatotest</td>
<td>Lassailly 2011</td>
<td>0.87</td>
<td>0.50</td>
</tr>
<tr>
<td>NAFLD-LFS</td>
<td>Fedchuck 2014</td>
<td>0.65</td>
<td>0.87</td>
</tr>
<tr>
<td>MRS</td>
<td>Wu 2014</td>
<td>0.85</td>
<td>0.94</td>
</tr>
<tr>
<td>MRI-PDFF</td>
<td>Kuhn 2012, Imajo, <em>Gastro in press</em></td>
<td>0.86 0.90</td>
<td>1.00 0.93</td>
</tr>
<tr>
<td>CAP</td>
<td>Shen 2014</td>
<td>0.82</td>
<td>0.80</td>
</tr>
<tr>
<td>USS</td>
<td>Jun 2014</td>
<td>0.73</td>
<td>0.85</td>
</tr>
</tbody>
</table>

- For primary care (and case-finding) Fatty Liver Index (fTG, BMI, GGT, Waist Circ) looks most promising - imaging either impractical and/or too expensive.
- For secondary (hospital/clinic) care USS remains the most commonly used test although MRI-PDFF is the most accurate.
Natural history
Fibrosis Stage Is the Strongest Predictor for Disease-Specific Mortality in NAFLD After Up to 33 Years of Follow-Up

Mattias Ekstedt, Hannes Hagström, Patrik Nasr, Mats Fredrikson, Per Stål, Stergios Kechagias, and Rolf Hultcrantz

Total number of deaths

Number at risk
NAS<5 & Fibrosis<3 76
NAS>4 & Fibrosis<3 57
Controls 2286

Log-rank test: p=0.17

Hepatology 2015
Fibrosis Stage Is the Strongest Predictor for Disease-Specific Mortality in NAFLD After Up to 33 Years of Follow-Up

Mattias Ekstedt,1 Hannes Hagström,2 Patrik Nasr,3 Mats Fredrikson,3 Per Stål,2 Stergios Kechagias,3 and Rolf Hulicrantz2

Total number of deaths

Log-rank test: p<0.001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Controls 2286</th>
<th>Fibrosis&lt;3 198</th>
<th>Fibrosis&gt;2 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>0 2085</td>
<td>184</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>10 1818</td>
<td>156</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>20 387</td>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>

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Hepatology 2015
www.pastpresentfuture2016.org
NAFLD is now the commonest cause of HCC in the North East UK and is increasing worldwide

Similar data reported from the US: 9% annual increase in NAFLD-HCC cases (2004-9)

Younossi et al 2015

Dyson et al  J Hep 2014
Diagnosis/staging: 2016

- Case finding in those with T2DM and/or MetS *probably* sensible (but ? cost effective)
- FLI (TG, BMI, GGT, WC) probably more cost-effective/practical than USS
- For staging fibrosis:
  - AST/ALT ratio <0.8, Fibroscan <10, NAFLD score < -1.455, ELF test < 10.51 excludes advanced fibrosis: NPV >90%
  - Of these only ELF > 10.51 has PPV >
- ELF recommended in NICE Guidelines 2016
Treatment
Therapies directed at Obesity/Metabolic Syndrome with potential “liver effects”

- Lifestyle changes directed at obesity and physical fitness
- Bariatric Surgery
- Insulin sensitizers/GLP-1 agonists
- Lipid lowering agents
Lifestyle changes: current status

• Weight reduction by lifestyle modification with diet *and* exercise should be recommended because it:
  – Improves cardiovascular risk profile
  – Improves steatosis *Sullivan 2012, Wong 2013*
  – *Probably* ↓ inflammation and fibrosis *Vilar-Gomez 2015*
• Improves QoL *Tapper 2016*
• Mediterranean diet may be best *Ryan 2013*
• Resistance = aerobic exercise *Hallsworth 2011, Bacchi 2013*
Bariatric Surgery

- Histological effects:
  - Improves steatosis: 92% [82-98%]
  - Improves steatohepatitis: 81% [62-95%]
  - Probably improves fibrosis (~ 35% at 1 year)


- NOT yet recommended as 1° treatment for NASH but NASH not a contraindication to Sx in an otherwise eligible patient

  AASLD Guidelines 2012
Drugs for Diabetes

• Metformin
  – Pilot data contradictory and recent RCT -ve
  – But: recent evidence of anti-HCC effect in diabetics + survival benefit in NASH cirrhosis Zhang 2012 & 2014

• Glitazones
  – Large RCT – “PIVENS” (in non diabetics) negative for fibrosis but ↓NASH Sanyal 2010
  – Pioglitazone and bladder cancer risk Tuccori 2016

• GLP-1 agonists – Liraglutide
  – ↓NASH and fibrosis Armstrong 2016
Pooled estimate of the odds ratio and 95% confidence interval of hepatocellular carcinoma associated with metformin therapy among 105,495 patients with type 2 diabetes.

Zhang et al JCEM 2012
Liraglutide

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Placebo</th>
<th>Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide vs placebo)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with paired liver biopsies</td>
<td>23</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patients with resolution of non-alcoholic steatohepatitis</td>
<td>9 (39%)</td>
<td>2 (9%)</td>
<td>4.3 (1.0 to 17.7)</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Changes from baseline in histopathological parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total NAFLD activity score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in score</td>
<td>-1.3 (1.6)</td>
<td>-0.8 (1.2)</td>
<td>-0.5 (-1.3 to 0.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>17 (74%)</td>
<td>14 (64%)</td>
<td>1.2 (0.8 to 1.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hepatocyte ballooning score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>-0.5 (0.7)</td>
<td>-0.2 (0.6)</td>
<td>-0.3 (-0.7 to 0.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>14 (61%)</td>
<td>7 (32%)</td>
<td>1.9 (1.0 to 3.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in score</td>
<td>-0.7 (0.8)</td>
<td>-0.4 (0.8)</td>
<td>-0.2 (-0.6 to 0.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>19 (83%)</td>
<td>10 (45%)</td>
<td>1.8 (1.1 to 3.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in score</td>
<td>-0.2 (0.6)</td>
<td>-0.2 (0.5)</td>
<td>-0.01 (-0.3 to 0.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>11 (48%)</td>
<td>12 (55%)</td>
<td>0.9 (0.5 to 1.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Kleiner fibrosis stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in score</td>
<td>-0.2 (0.8)</td>
<td>0.2 (1.0)</td>
<td>-0.4 (-0.8 to 0.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>6 (26%)</td>
<td>3 (14%)</td>
<td>1.9 (0.5 to 6.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Patients with worsening</td>
<td>2 (9%)</td>
<td>8 (35%)</td>
<td>0.2 (0.1 to 1.0)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Armstrong et al 2016

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Lipid lowering agents

• **Fibrates:**
  – good theory - PPARα agonists
  – No benefit in two RCTs

• **Statins**
  – Definitely **safe** in NAFLD patients
  – May protect vs *all stages* of NAFLD  *Dongiovanni 2015*
  – May also ↓ HCC risk (OR: 0.63 [0.5-0.8])  *El-Serag 2009, Singh 2013*

• **Omega-3 PUFAs**
  – Large negative RCT with 2 doses of EPA  *Sanyal 2014*
Statins and HCC

Singh et al. Gastroenterology 2013
Tested “Liver-directed” therapies

- Antioxidants:
  - Vitamin E: histological benefit in 2 RCTs “PIVENS” and “TONIC”  
    - Sanyal 2010, Lavine 2011
- FXR agonists
  - Neuschwander-Tetri 2014
- Dual PPARα/δ agonist (Elafibrinor)
  - Ratziu 2016
- Urso:
  - Neither 13-15 mg/kg nor 23-28 mg/kg/day any benefit in two large RCTs  
    - Lindor 2004, Leuschner 2010
- Probiotics
  - Reduced TAG (by MRS) and fibrosis (by TE)  
    - Wong 2013, Elamparast 2014
Vitamin E: panacea for NASH?

- PIVENS & TONIC indicate that Vitamin E may be effective in some patients

- BUT need for caution:
  - Increased all cause mortality risk at >400 IU/day
    
    **Miller 2005, Bjelakovic 2007**
  - Increased haemorrhagic stroke risk (although reduced embolic stroke risk)
    
    **Schwarts, 2010**
  - Increased prostate carcinoma risk
    
    **Lippman 2009, Klein 2011**
Obeticholic Acid for NASH RCT
The FLINT study *Lancet* 2014

- Multicentre, double blind RCT
- Non-cirrhotic NASH
- 25 mg obeticholic acid/placebo 72 weeks
- Stratified by Centre /presence of diabetes
- Primary endpoint = 2 point improvement in NAS with no worsening of fibrosis
- Interim analysis after 219/283 patients had 72 week biopsy recommended stopping trial early
## Histological data

<table>
<thead>
<tr>
<th>Feature</th>
<th>OCA</th>
<th>Placebo</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>110</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with improvement</td>
<td>50(45%)</td>
<td>23(21%)</td>
<td>1.9 (1.3-2.8)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pts with improvement in Fibrosis</td>
<td>36(35%)</td>
<td>19(19%)</td>
<td>1.8(1.1-2.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pts with improvement in Ballooning</td>
<td>47(46%)</td>
<td>30(31%)</td>
<td>1.5(1.0-2.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pts with improvement in lob inflammation</td>
<td>54(53%)</td>
<td>34(35%)</td>
<td>1.6(1.1-2.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Pts with improvement in Steatosis</td>
<td>62(61%)</td>
<td>37(38%)</td>
<td>1.7(1.2-2.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in NAS</td>
<td>-1.7(1.8)</td>
<td>-0.7(1.8)</td>
<td>-0.9(-1.3 to -0.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Adverse effects

<table>
<thead>
<tr>
<th>Feature</th>
<th>OCA</th>
<th>Placebo</th>
<th>Mean Change OCA vs placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>126</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>0.16(1.07)</td>
<td>-0.19(0.96)</td>
<td>0.38(0.16-0.60)</td>
<td>0.0009</td>
</tr>
<tr>
<td>LDL-Chol</td>
<td>0.22(0.90)</td>
<td>-0.22(0.80)</td>
<td>0.45(0.26-0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-Chol</td>
<td>-0.02(0.20)</td>
<td>0.03(0.19)</td>
<td>-0.06(-0.10 to 0.01)</td>
<td>0.01</td>
</tr>
<tr>
<td>Number with intense pruritus</td>
<td>33/141</td>
<td>9/142</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>
Summary

• OLTx and HCC 2° NAFLD are increasing
• Advanced fibrosis and not NASH is the important prognostic factor
• Lifestyle advice for all patients with NAFLD
• Low threshold for statin therapy
• For patients with NASH + DM
  – Metformin/Liraglutide?
• For patients with NASH only
  – Best evidence for Vitamin E
• ? OCA/Bariatric Surgery
• “Big” Pharma now very interested
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Prof Alastair Burt,
Prof Mike Trenell
Ms Kate Hallsworth
Mr Christian Thoma

....and all the FLIP /EPoS investigators

EPoS: Elucidating Pathways of Steatohepatitis
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