Fatty Liver in 2016 – Update for Primary Physicians

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KTPH
Lack of awareness in patients

- Patients in an outpatient diabetes clinic had 70% rate of NAFLD
- Only 18% of patients were aware (1)

1. Wieland AC, Mettler P, McDermott MT, Crane LA, Cicutto LC, Bambha KM. Low awareness of nonalcoholic fatty liver disease among patients at high metabolic risk. Journal of clinical gastroenterology. 2015;49(1):e6-e10
Lack of awareness amongst doctors?

- Questionnaires to hospital medical staff – Princess Alexandra Hospital Brisbane Australia (2)
  - Majority 75% believed NAFLD prevalence to be < 10%
  - 2/3rd believe incidence will increase markedly
  - 93% believe that NASH has increased mortality
  - 60% feels that simple steatosis confers increased liver-related mortality
  - 71% make no referrals to hepatologists

1. Wieland AC, Mettler P, McDermott MT, Crane LA, Cicutto LC, Bambha KM. Low awareness of nonalcoholic fatty liver disease among patients at high metabolic risk. Journal of clinical gastroenterology. 2015;49(1):e6-e10
75% believed NAFLD prevalence to be < 10%?

Are they correct?
NAFLD Prevalence

- Prevalence worldwide in developed countries ~ 20-35%
- High prevalence populations
  - 57-98% obese
  - 60-73% DM
  - Up to 50% hyperlipidaemia
Majority clinicians (2/3rd) feel incidence of NAFLD will increase markedly

Are they correct?
Fatty liver rates in the US over the last 3 decades
Obesity closely related to NAFLD
Worldwide obesity epidemic

Past and projected future overweight rates in selected O.E.C.D. countries

Proportion overweight

USA, Spain, England, Canada, Austria, Australia, Italy, France, Korea

Years


Downey Obesity report 2012
93% think that NASH has increased mortality

60% clinicians thought simple steatosis confers increased liver-related mortality
Fatty Liver (Steatosis) – Ballooning
NASH

Mallory Bodies - Hyaline
NASH Fibrosis

Fibrosis with bridging septa (F2-3)
Cirrhosis (Nodularity & Scarring)

Bridging fibrosis and nodules
Survival: All NAFLD vs general population

Mortality ratio 1.34
Cause of death
Malignancy 28%
IHD 25%
Liver disease 13%

Figure 2. Overall survival of patients diagnosed with NAFLD in Olmsted County, Minnesota, between January 1, 1980 and January 1, 2000. Survival is compared with the general population of Minnesota of the same age and sex.

Adams 2005
Survival: NASH/Fibrosis, Steatosis vs General Population

SMR 1.55

SMR 1.86

Soderberg 2010
Survival: All NAFLD vs matched population
NASH prognosis worse than Steatosis compared to matched populations

NASH survival ~ 70%
vs ~ 80% matched population
p = 0.01

Steatosis
No significant difference to matched population

Ekstedt 2006
Survival NASH vs Steatosis

18 yr study
Difference due to liver related mortality
17.5% NASH vs 2.7 Non NASH, p < 0.05

Rafiq 2009
## Summary of prognosis

<table>
<thead>
<tr>
<th>NAFLD phenotype</th>
<th>General Population mortality relative risk</th>
<th>Matched Population (adjusted for metabolic syndrome) mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.34 RR in 10yrs</td>
<td>1.038 in 8yrs but Liver related mortality 9.32</td>
</tr>
<tr>
<td>Simple Steatosis</td>
<td>1.55 RR in 30yrs</td>
<td>• No difference to matched population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2.7% death in 18yrs</td>
</tr>
<tr>
<td>NASH/Fibrosis</td>
<td>1.86 RR in 30yrs</td>
<td>• Increased risk to Matched population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 17.2% death in 18yrs</td>
</tr>
</tbody>
</table>
Natural History of NAFLD

General Population

Steatosis 75%

- Stable ~ 91-94%

NASH 25%

- Fibrosis (25-35% of NASH)
  - Cirrhosis (10-20% of NASH)
    - Decompensated Liver Failure or HCC (40-60% of cirrhotics over 5-7 yrs)
    - Death or LT (22-33% of cirrhotics)
Referral to Hepatologist

• 71% do not refer to hepatologist
• Possible clinical reasons?
  • Unaware of the increased mortality of NASH - addressed
  • Unaware of the prevalence of NAFLD and NASH/cirrhosis – addressed
  • Fatty liver can be diagnosed by ultrasound and liver panel: Is a hepatologist needed?
  • Treatment is diet + exercise and treatment of metabolic risk factors: what would they do extra that I would not do?
How to diagnose Simple Steatosis vs NASH vs fibrosis?

• Can ultrasound help?
• Can LFTs diagnose NASH?
Ultrasound in NAFLD

• Steatosis
  – 84.8% sensitivity and 93.4% specificity for severe or moderate steatosis (cannot detect minor steatosis)
  – Uses 3 criteria (not often used in clinical practice)
    • Echogenicity, deep attenuation and vessel blurring

• NASH
  – Unable to detect

• Fibrosis
  – Unable to detect

Liver Biochemistry

• ALT AUROC for NASH is 0.62 and fibrosis 0.46
• Serum ALT is normal in 60% of NAFLD patients with NASH
• Serum ALT is elevated in 53% of NAFLD patients with NO NASH
• ALT level alone is NOT predictive of NASH/NAFLD or fibrosis level

Diagnosing NASH

• Current AASLD guidelines suggests Liver Biopsy only
• Non – invasive tests
  • Serum CK-18 – most widely studied
    – Liver cytokeratin, levels increased in NASH Meta-analysis of 11 studies with 822 patients
      • 66% sensitivity and 82% specificity
• Others
  – Many Models which incorporate clinical features and special laboratory tests
  – Many also use CK-18
  – Not enough evidence, not widely validated, not readily available

## Table 1 | Clinical models for predicting NASH

<table>
<thead>
<tr>
<th>Study</th>
<th>Name</th>
<th>Component/formula</th>
<th>Study population</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younossi et al.</td>
<td>NASH Diagnostics</td>
<td>1. Cleaved CK-18, 2. CK-18 minus cleaved CK-18, 3. Adiponectin, 4. Resistin, 5. undiluted formula</td>
<td>69 – training group, 32 – validation group</td>
<td>AUROC 0.85, Se 72%, Sp 91% (threshold 0.4320)</td>
<td>Re-evaluated in 79 patients by same group – AUROC 0.70, Se 67%, Sp 69%, PPV 68%, NPV 63% (threshold 0.389)</td>
</tr>
<tr>
<td>Younossi et al.</td>
<td>NASH Model of NAFLD Diagnostic Panel</td>
<td>1. Type 2 diabetes mellitus, 2. Geader, 3. BMI, 4. Triglyceride, 5. Cleaved CK-18, 6. CK-18 minus cleaved CK-18</td>
<td>79 NAFLD patients</td>
<td>AUROC 0.81, Se 91%, Sp 47%, PPV 61%, NPV 86% (threshold 0.220)</td>
<td></td>
</tr>
<tr>
<td>Anty et al.</td>
<td>Nice Model</td>
<td>1. ALT, 2. CK-18, 3. Metabolic syndrome</td>
<td>464 morbidly obese patients, 310 – training group, 154 – validation group</td>
<td>AUROC 0.83–0.89, Se 84%, Sp 86%, PPV 44%, NPV 98% (logarithmic transformation, threshold 0.1400)</td>
<td>Model = −5.654 + 3.780E−02 × ALT + 2.71E−03 × CK-18 = 1.825 × (presence of metabolic syndrome = 1)Logarithmic transformation = 1/(1 + Exp(Nice Model))</td>
</tr>
<tr>
<td>Feldstein et al.</td>
<td>oxNASH</td>
<td>1. 13-HODE/LA ratio, 2. Age, 3. BMI, 4. AST</td>
<td>73 – training group, 49 – validation group</td>
<td>AUROC 0.74–0.83, Se 81–84% (threshold 55), Sp 63–97% (threshold 73)</td>
<td>Model = 100x exp(f) / (1 + exp(f)) = −10.021 + 0.0463 × age (years) + 0.147 × BMI + 0.0293 × AST + 2.658 × 13-HODE/LA ratio</td>
</tr>
<tr>
<td>Dixon et al.</td>
<td>HAIR</td>
<td>1. Hypertension, 2. (increased) ALT, 3. IR</td>
<td>105 morbidly obese patients</td>
<td>AUROC 0.90, Se 82%, Sp 89% (threshold 0.90)</td>
<td>Hypertension = 1, ALT &gt; 60 IL/L = 1, IR index &gt; 5.0</td>
</tr>
</tbody>
</table>

NASH, non-alcoholic steatohepatitis; α2-MG, alpha2-macroglobulin; GGT, gamma-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver-operating curve; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; CK-18, cytokeratin-18; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; 13-HODE, 13-hydroxy-eicosadecanoic acid; LA, linoleic acid; IR, insulin resistance.

Diagnosing Fibrosis

- Most widely studied is Fibroscan: Meta-analysis of 9 studies 1047 pts

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>F≥2</td>
<td>79%</td>
<td>75%</td>
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<tr>
<td>F≥3</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>F=4</td>
<td>92%</td>
<td>92%</td>
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</table>
Other biomarkers and prediction scores

- Not as accurate, widely validated or readily available as Fibroscan

<table>
<thead>
<tr>
<th>Score</th>
<th>Components</th>
<th>Class I or II biomarkers</th>
<th>F2 Sensitivity</th>
<th>F2 Specificity</th>
<th>F3 Sensitivity</th>
<th>F3 Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific for NAFLD</td>
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<tr>
<td>NAFLD fibrosis score</td>
<td>Age, hyperglycaemia, BMI, platelet, albumin,</td>
<td>II</td>
<td>0.77</td>
<td>0.96</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>AST/ALT ratio (dual cut-offs)</td>
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<tr>
<td>BARD score</td>
<td>BMI, AST/ALT ratio, diabetes</td>
<td>II</td>
<td>0.62</td>
<td>0.66</td>
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<tr>
<td>FibroMeter</td>
<td>Glucose, AST, ferritin, platelet, ALT, body</td>
<td>II</td>
<td>0.79</td>
<td>0.96</td>
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<tr>
<td></td>
<td>weight, age</td>
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<tr>
<td>Not specific for NAFLD</td>
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<tr>
<td>AST/ALT ratio</td>
<td>AST, ALT</td>
<td>II</td>
<td>0.21</td>
<td>0.90</td>
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<tr>
<td>APRI</td>
<td>AST, platelets (dual cut-offs)</td>
<td>II</td>
<td>0.65</td>
<td>0.97</td>
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</tr>
<tr>
<td>ELF</td>
<td>Hyaluronic acid, TIMP1, PIIINP (dual cut-offs)</td>
<td>I</td>
<td>0.80</td>
<td>0.67</td>
<td>0.80</td>
<td>0.90</td>
</tr>
<tr>
<td>FIB-4</td>
<td>Age, AST, platelet, ALT (dual cut-offs)</td>
<td>II</td>
<td>0.74</td>
<td>0.98</td>
<td></td>
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</tr>
<tr>
<td>FibroTest</td>
<td>Total bilirubin, GGT, α₂-macroglobulin, ApoA1,</td>
<td>I and II</td>
<td>0.71</td>
<td>0.98</td>
<td>0.88</td>
<td>0.99</td>
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<tr>
<td></td>
<td>haptoglobin (dual cut-offs)</td>
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Management

• Losing weight with lifestyle interventions is still the standard of care
• Currently no guideline or FDA approved therapy
• Hotbed of research, many new promising drugs
  – Phase III/IIb trials
  – Obeticholic acid, aramchol, cenicriviroc
Treatment by Hepatologist at KTPH

• Weekly Fatty Liver Clinic
• Fibroscan available, perform any time during business hours. Medisave deductible
• Encourage multidisciplinary approach
  – Dieticians
  – Physiotherapists
  – Exercise gym
  – Weight management program
  – Chronic disease management physician: prescribe pharmacotherapy for weight loss in selected cases
  – Obesity surgeon
• Involved in trials
  – Current: NAFLD levothyroxine trial
  – 2 more pending ethics
• Introduce new drugs as they emerge