Fatty Liver Disease
Diagnosis & Implications

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“Intellectuals solve problems. Geniuses prevent them.”
The potential for, and cost of, intervention in relation to the course of liver disease
Number of hospital admissions for non-alcoholic fatty liver disease, 1998–2010. Admissions to hospital defined as first finished consultant episodes.

Data are from Hospital Episode Statistics
- Prevalence of obesity in UK ~23%
- Prevalence of NAFLD in obese individuals – 50%
- Prevalence in T2DM – 60%
- Prevalence in morbid obesity – 95%
- Prevalence of NAFLD in non-obese individuals – 16-20%
- Prevalence of NAFLD in UK – 20-30%
Prevalence of obesity in men and women aged 16 years or older, 1993–2010

Data are from Health Survey for England
Case 1

54 yr old male

Told that he has insulin resistance

‘not properly diabetic’

ALT 43

USS – 18cm bright liver, normal size spleen, suggest referral to liver clinic
Definition of NAFLD

Evidence of hepatic steatosis

• Imaging
• Biopsy

No causes for secondary fat accumulation

• Alcohol
• Drugs
• Hereditary disorders
Ultrasound diagnosis

- Parenchymal brightness
- Liver-to-kidney contrast
- Deep beam attenuation
- Bright vessel walls
- Gallbladder wall definition

Hernaez R et al Hepatology 2011
Chelsea and Westminster Hospital
NHS Foundation Trust
Which test is best

• 46 patients undergoing hepatic resection
• All had USS / CT / MR and MRS
• Compared with biopsy separate from resection specimen
Which test is best?
Population

• 100%

NAFL

• 30%

NASH

• 7%

NASH cirrhosis

• 2%

HCC & cirrhosis complications

30%
Nonalcoholic fatty liver disease (NAFLD)

Nonalcoholic fatty liver (NAFL)
(-70%-75% of individuals with NAFLD)

A. Steatosis alone (isolated hepatic steatosis)

Nonalcoholic steatohepatitis (NASH)
(-25%-30% of individuals with NAFLD)

B. Steatosis with mild lobular inflammation

C. Steatosis with lobular inflammation and cellular ballooning (inset)

D. Fibrosis

Risk factors for disease progression:
- Diabetes
- Insulin resistance
- Hypertension
- Weight gain >5 kg
- Increasing ALT, AST; AST:ALT >1

Disease progression:
- <4% of individuals with NAFL progress to cirrhosis
- ~20% of individuals with NASH progress to cirrhosis

E. Cirrhosis

400 enrolled
5 disqualified (2 known NAFDL, 3 over ETOH limit)
67 failed to get ultrasound

328 completed ultrasound

156 positive US
22 refused biopsy
134 liver biopsies performed

5 normal
89 not NASH
40 NASH

9 advanced fibrosis
<table>
<thead>
<tr>
<th></th>
<th>Negative USS (n=177)</th>
<th>Positive USS (n=151)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male %</td>
<td>40.7</td>
<td>58.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Age yrs</td>
<td>53.5</td>
<td>55.9</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>27.6</td>
<td>32.4</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>BMI≥30 (%)</td>
<td>26.6</td>
<td>67.5</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>33.9</td>
<td>68.2</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>7.9</td>
<td>26.3</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Nondiet soda ≥ 1/wk</td>
<td>39.5</td>
<td>48.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Fast food ≥ 1/wk</td>
<td>60.5</td>
<td>70.9</td>
<td>0.049</td>
</tr>
<tr>
<td>Exercise ≥ 30 min/wk</td>
<td>68.9</td>
<td>56.3</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Case 2

55 year old man

- Found to have abnormal LFTs on routine health check
- Repeated 6/12 later – still abnormal
- CLD screen negative
Indications for Testing in Incidental Abnormal LFTs (n=1118)

- Other
- Diabetes R/V
- Non-specific
- Hypertension R/V
- GI Symptoms
- Fatigue
- CVD R/V
- Medication R/V
- Lipid R/V
- Neurological symptoms
- MSS symptoms

Causes of incidental abnormal LFTS

Transaminases

- AST
  - Liver / cardiac and skeletal muscle
  - Normal AST : ALT ≈ 0.8
  - Higher in ALD (>2:1) and cirrhosis (>1)

- ALT
  - Liver specific
Pathophysiology of NAFLD

• Genetics
• Diet
• Metabolic syndrome
• Gut Microbiome
Genetics

• PNPLA3 (adiponutrin)

• Identified at GWAS – SNP I148M
• Predisposes to steatosis and disease progression
Diet

Fructose

- Increases insulin resistance
- Increases triglycerides
- Increases gut endotoxins
- Increases iron
- Decreases copper
Metabolic syndrome

- Central Obesity or BMI >30kg/m²
- Plus ≥ 2 or more
  - Triglycerides ≥ 1.7mmol/l
  - Reduced HDL cholesterol
  - Hypertension (sysBP≥130; diasBP≥85)
  - Fasting glucose>5.6mmol/l
The interplay between dietary factors, gut microbiota, and gut barrier integrity in the development of NAFLD. Both high fat or high fructose diets may cause dysbiosis and bacterial overgrowth. Intestinal bacteria alterations...
# NAFLD RISK

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Low risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;45</td>
<td>≥45</td>
</tr>
<tr>
<td>Diabetes / IFG</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>AST:ALT</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>&gt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;34</td>
<td>&lt;34</td>
</tr>
</tbody>
</table>

Refer if ≥3 criteria
Biomarkers for NASH

Procollagen 3P (PIIINP)

Biomarkers for NASH

Ferritin

Scoring systems for Fibrosis

• APRI = AST / (upper limit of normal) / platelet count X 100.

• FIB-4 score = age X (AST / platelet count) x √ALT

• The BARD score = (BMI>28=1 point, AST/ALT ratio>0.8=2 points, diabetes=1 point).

• The NAFLD fibrosis score =
  -1.675 + 0.037 X age (years) +
  0.094 X BMI (kg/m2) +
  1.13 X IFG or diabetes (yes=1, no=0) +
  0.99 x AST/ALT ratio -
  0.013 x platelet -
  0.66 x albumin

http://nafldscore.com/
Liver related events

A. NAFLD-FS: < -1.455
   NAFLD-FS: -1.455 to 0.676
   NAFLD-FS: > 0.676

B. APRI: < 0.5
   APRI: 0.5 to 1.5
   APRI: > 1.5

C. FIB-4: 1.30 to 2.67
   FIB-4: < 1.30
   FIB-4: > 2.67

D. BARD 0/1
   BARD 4
   BARD 2/3
Death or LTx
NAFLD Fibrosis Score

- Low cut off score - NPV 88-93%
- High cut off score - PPV 79-90%
- BALLETS study
  - 57% had low NFS
  - 7.6% had high NFS
  - 35.2% had indeterminate NFS
Elastography

• Real-Time Elastography (Hitachi)
• Fibroscan (Echosens)
  • Well validated
  • Only able to measure liver stiffness

• Acoustic Radiation Force Impulse (Siemens)
  • Growing evidence
  • Better than Fibroscan on ITT
  • Can perform USS simultaneously
The controlled attenuation parameter (CAP): A novel tool for the non-invasive evaluation of steatosis using Fibroscan®

A Steatosis quantification using CAP

B Steatosis quantification using $^1\text{H}$-MR spectroscopy

* p=0.002, ** p<0.001

* p=0.007, ** p=0.004
Use of elastography

- 12,368 patients in 2 GP practices
- Assessed for risk
  - Hazardous alcohol use
  - T2DM
  - Persistently raised ALT
- AST:ALT ratio $\geq 0.8$ or BARD score $\geq 2$
- Elastography performed
12,368 pts

at risk

920 pts

agreed to participate

504 had biomarkers

normal biomarkers

62 pts

underwent elastography

378 pts

significant fibrosis

72 pts

normal LFTs!

98 pts
NAFLD

Calculate NAFLD Fibrosis Score

Low Risk

Indeterminate / High Risk

Elastography

Normal

Abnormal

Discharge to GP

Liver Biopsy

Repeat @ 3-5 years
Case 3

35 yr old woman

BMI 48

Father died of cryptogenic cirrhosis

Bariatric surgery abandoned due to portal hypertension

Mother diagnosed with HCC due to NASH

What next?
NAFLD & PHT

1. Varices
2. Encephalopathy
3. Ascites
4. Splenomegaly

![Graph showing No. findings of portal hypertension vs Fibrosis Stage (0-4)]
NAFLD & Cirrhosis complications

- Ascites
- Variceal bleed
- Encephalopathy
- HCC
The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis
NAFLD & HCC

Clinical Gastroenterology and Hepatology, 2015, Available online 18 July 2015
Number of registrations for liver transplantation in the UK in which primary or secondary diagnosis was non-alcoholic fatty liver disease or cryptogenic cirrhosis.
NAFLD & CT coronary angio

- Napkin-ring Sign: 7.1% NAFLD, 3.4% No NAFLD, p = 0.080
- Positive Remodeling: 17.6%, p < .001
- Low HU Plaque: 12.1%, 5.7%, p = 0.022
- Spotty Calcium: 56.0%, 16.4%, p < .001
NAFLD and AF

OR 4.49
NAFLD and CRC

### A. NAFLD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Adenoma group</th>
<th>Nonadenoma group</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Huang 2013</td>
<td>120</td>
<td>216</td>
<td>500</td>
<td>1306</td>
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<tr>
<td>Hwang 2010</td>
<td>231</td>
<td>556</td>
<td>713</td>
<td>2361</td>
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<tr>
<td>Lin 2014</td>
<td>216</td>
<td>1946</td>
<td>47</td>
<td>369</td>
</tr>
<tr>
<td>Stadlmayr 2011</td>
<td>215</td>
<td>341</td>
<td>417</td>
<td>870</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>3322</td>
<td>5959</td>
<td>100.0%</td>
<td>1.56 [1.22, 1.99]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>923</td>
<td>2114</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 17.01$, df = 4 ($P = 0.002$); $I^2 = 76$

Test for overall effect: $Z = 3.59$ ($P = 0.0003$)

### B. Liver enzymes

#### ALT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Adenoma group</th>
<th>Nonadenoma group</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
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<tr>
<td>Huang 2013</td>
<td>29.7</td>
<td>17.6</td>
<td>255</td>
<td>26.2</td>
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<tr>
<td>Hwang 2010</td>
<td>33.1</td>
<td>19.6</td>
<td>216</td>
<td>29.7</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>772</td>
<td>3667</td>
<td>100.0%</td>
<td>3.48 [2.07, 4.88]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = 0.95$); $I^2 = 0$

Test for overall effect: $Z = 4.83$ ($P < 0.00001$)

#### AST

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Adenoma group</th>
<th>Nonadenoma group</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Huang 2013</td>
<td>24.3</td>
<td>8.4</td>
<td>216</td>
<td>23.5</td>
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<tr>
<td>Hwang 2010</td>
<td>27.4</td>
<td>10</td>
<td>556</td>
<td>25.8</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>772</td>
<td>3667</td>
<td>100.0%</td>
<td>1.30 [0.55, 2.05]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.02$, df = 1 ($P = 0.31$); $I^2 = 2$

Test for overall effect: $Z = 3.39$ ($P = 0.0007$)
Low Risk NAFLD

- Weight loss
- Treat other risk factors
  - Lipids
  - Thyroid
  - Diabetes
  - Hypertension
  - Drink sensibly (within current limits)
- Monitor in primary care
Diet and NAFLD

- >7% (4-14%) weight loss
- Diet and exercise
  - Low fat, low CHO
  - Low trans fat
  - Less meat, more oily fish
  - Reduce soft drink consumption
- Drink more coffee

Pharmacological treatment of NAFLD

- Orlistat
- Sibutramine / Rimonabant
- Exenatide / Liraglutide
- Metformin
- Thiazolidinediones
- Vitamin E
- ARBs
- Bariatric Surgery / Intragastric Balloons
- Pentoxifylline
- Statins
- Omega-3 PUFA
Weight Loss:
Diet & Exercise

Optimise Management of Metabolic Syndrome
1) Diabetes / IGT: Metformin
2) Hypertension: consider ARB
3) Lipids: Statin / Fibrate

Response to treatment based on:
- Changes in weight, ALT, steatosis, inflammation, fibrosis

BMI<27
Pioglitazone
Vitamin E

BMI>27
Orlistat

BMI>30
HbA1c>7.5
GLP-1 Analogues

BMI>35
Bariatric Surgery

Consider Metformin
Take Home Messages

- NAFLD is common and increasing

- Assess and treat for risk factors

- Measure AST and ALT

- Stratify risk – NAFLD FS / elastography
Any Questions?