Fatty Liver- how important is it?

Jeremy F.L. Cobbold MA PhD MRCP
Clinical Lecturer in Hepatology
Imperial College London
Fatty liver - how important is it?

Importance in terms of:
• Prevalence
• Pathogenesis
• Other liver diseases
• Morbidity and mortality
• Treatable?
Definitions

• Hepatic steatosis (fatty liver) is defined *pathologically* as the presence of vesicles of fat, predominantly triglycerides, accumulating within hepatocytes.

• Non-alcoholic fatty liver disease (NAFLD) is the presence of hepatic steatosis as part of the metabolic syndrome of obesity, insulin resistance/ type 2 diabetes, dyslipidaemia and hypertension.
Causes of fatty liver

Primary, associated with the metabolic syndrome
- (Abdominal) Obesity
- T2DM
- Dyslipidaemia

Secondary:
- Alcohol
- Drugs
  - Steroids
  - Amiodarone
  - HAART
- Hepatitis C infection
- Parenteral nutrition
- …and others…
Fatty liver is important…
...because it is common
Prevalence

Depends on:

**Case definition** (biopsy, imaging, liver enzymes, scoring systems)

**Sample frame** (population vs clinic-based, all-comers vs high risk groups)
Case definition

Techniques for diagnosis

• Histology
• US
• MR
• Biometrics/ blood test indices
• Liver enzymes
Techniques for the diagnosis of NAFLD
Techniques for the diagnosis of NAFLD

Thomas et al. 2005, O'Regan et al. 2008
Sample frame

- Populations
  - Race
  - Geography
  - Socio-economic groups

- “at risk” groups
  - Diabetics
  - Obese
  - Alcohol excess
Prevalence- population studies

Dallas Heart Study (Dallas County, USA)
- 2349 subjects
- 345 of these had no r.f.s for NAFLD
- 95th centile of this subset was a MR-derived lipid content of 5.56%
- =33.6% of the wider population

Race
- Hispanic 45%
- White 33% (men 42%, women 24%)
- Black 24%

Dionysos (Italy)
- 20%-25% northern Italian adults (including those with suspected liver disease)
Prevalence- at risk groups

Obese:
• 60% (obese)-90% (morbidly obese)

Diabetic:
• 50% (T2DM)

Obese and diabetic:
• 100%

Angulo 2002
Fatty liver is important…

...because its pathogenesis is increasingly understood
Standard model of disease progression

Steatosis
Steatohepatitis (NASH)
Fibrosis
Cirrhosis

“2 hit” hypothesis

Day and James 1998
Hepatic lipid metabolism schematic

1. Dietary intake
   - LPL
   - HSL

2. Carbohydrate
   - Synthesis
     - ChREBP
     - SREBP-1c

3. Fatty acids
   - Oxidation
     - PPARα
     - CPT1
     - Peroxisomal β-Oxidation
     - Mitochondrial β-Oxidation
     - Microsomal ω-Oxidation
   - Acetyl CoA
   - Kreb's cycle

4. Esterification
   - Triglyceride
   - MTT
   - ApoB100
   - VLDL

Hepatocyte

Anstee and Goldin 2006
Fatty liver- how important is it?

Liver fat is important…
…but is it always bad?
Inhibiting Triglyceride Synthesis Improves Hepatic Steatosis but Exacerbates Liver Damage and Fibrosis in Obese Mice with Nonalcoholic Steatohepatitis

Kanji Yamaguchi,1 Liu Yang,1 Shannon McCall,2 Jiawen Huang,1 Xing Xian Yu,3 Sanjay K. Pandey,3 Sanjay Bhanot,3 Brett P. Monia,3 Yiu-Xiong Li,1 and Anna Mae Diehl1

(HEPATOLOGY 2007;45:1366-1374.)

Inhibition of diacylglycerol transferase 2 (DGAT2) in the db/db (leptin deficient) and db/db MCD mouse model…
Lipotoxicity

Yamaguchi et al. 2007
Lipotoxicity

Yamaguchi et al. 2007
Updated model- “one hit” or “many hits”
“Free” or non-esterified fatty acids (FFA) are hepatotoxic.

FFA are produced as part of normal hepatic glucose metabolism and to excess in obesity, systemic inflammation, insulin resistance, high fructose ingestion etc.

Production of relatively inert triacylglycerol (TAG) in lipid droplets represents an adaptive response to the presence of FFA.

When the TAG synthesis capacity is exceeded, inflammation and disease progression ensues…

…but when and why is this capacity exceeded?
Fatty liver- how important is it?

Fatty liver is important…

…but what type of fat is important
What *type* of fat?... Beyond FFA and TAG

PUFA reduced in NAFLD/NASH

- in mice

- in humans
$^1$H MAS MRS in mice with NAFLD/NASH

A

B

C

D

E

F

### Liver fatty acid composition in humans

The table below presents the liver fatty acid composition in different conditions, expressed as a percentage of total fatty acids.

<table>
<thead>
<tr>
<th>Fatty acids</th>
<th>MF (n = 12)</th>
<th>SS (n = 10)</th>
<th>NASH (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:0</td>
<td>27.7 ± 1.9</td>
<td>26.9 ± 1.7</td>
<td>30.3 ± 0.6</td>
</tr>
<tr>
<td>18:0</td>
<td>24.1 ± 2.0</td>
<td>21.3 ± 2.6</td>
<td>22.9 ± 1.3</td>
</tr>
<tr>
<td>20:0</td>
<td>3.7 ± 1.1</td>
<td>2.5 ± 0.9</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>16:1 n9</td>
<td>0.9 ± 0.1(^a)</td>
<td>1.2 ± 0.2</td>
<td>1.6 ± 0.1(^b)</td>
</tr>
<tr>
<td>18:1 n9</td>
<td>12.1 ± 1.8(^a)</td>
<td>16.2 ± 2.1</td>
<td>18.1 ± 1.4(^b)</td>
</tr>
<tr>
<td>18:2 n-6</td>
<td>3.3 ± 0.7</td>
<td>4.7 ± 1.1</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>18:3 n-3</td>
<td>0.3 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.2 ± 0.04</td>
</tr>
<tr>
<td>20:4 n-6 (AA)(^A)</td>
<td>3.8 ± 0.7(^a)</td>
<td>1.7 ± 0.5</td>
<td>1.2 ± 0.3(^b)</td>
</tr>
<tr>
<td>20:5 n-3 (EPA)(^B)</td>
<td>0.3 ± 0.2</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.02</td>
</tr>
<tr>
<td>22:6 n-3 (DHA)(^C)</td>
<td>0.5 ± 0.1(^a)</td>
<td>0.3 ± 0.1</td>
<td>0.1 ± 0.04(^b)</td>
</tr>
<tr>
<td>Total n-6 PUFA</td>
<td>7.4 ± 1.2</td>
<td>7.9 ± 1.5(^a)</td>
<td>4.6 ± 0.6(^b)</td>
</tr>
<tr>
<td>Total n-3 PUFA</td>
<td>2.4 ± 0.7(^a)</td>
<td>1.4 ± 0.3</td>
<td>0.9 ± 0.1(^b)</td>
</tr>
<tr>
<td>n-6/n-3</td>
<td>4.6 ± 0.8</td>
<td>9.1 ± 3.0</td>
<td>6.4 ± 1.1</td>
</tr>
<tr>
<td>EPA + DHA</td>
<td>0.8 ± 0.2(^a)</td>
<td>0.4 ± 0.1</td>
<td>0.2 ± 0.04(^b)</td>
</tr>
<tr>
<td>EPA + DHA/linolenic</td>
<td>4.1 ± 1.5(^a)</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.3(^b)</td>
</tr>
<tr>
<td>AA(^A)/linoleic acid</td>
<td>1.6 ± 0.7</td>
<td>0.5 ± 0.2</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>Total trans fatty acids</td>
<td>8.6 ± 1.6</td>
<td>9.8 ± 1.8</td>
<td>9.8 ± 0.9</td>
</tr>
</tbody>
</table>

*Allard et al 2008*
Fatty liver is important…
…because it is associated with increased morbidity and mortality
Morbidity and mortality

- Most studies cross-sectional rather than prospective longitudinal
- Proportion progressing unknown
- Biopsy-proven NAFLD have worse outcomes

- 345 patients with NAFLD diagnosed between 1980 and 2000
- Mean follow-up 7.6 years
- All cause mortality increased compared to general population
- Liver related mortality 3rd biggest cause of death (compared to 13th biggest cause of death in the general population)

Adams et al. 2005
150 patients with cirrhosis due to NAFLD were compared to a control group of patients with cirrhosis due to HCV
• Both groups most likely to die with complications of sepsis
• HCV had greater all cause and liver-related mortality
• NAFLD had greater cardiovascular mortality

Hepatocellular carcinoma in NAFLD
• Obesity is a risk factor for HCC
• DM is a risk factor for HCC
• Metabolic syndrome is an independent risk factor for HCC
  • 31 patients with HCC and only metabolic syndrome as a rf were compared to 81 HCC pts with overt causes of CLD
  • In MS, backgound liver was free of significant fibrosis in 65%

Paradis V et al. 2009
Sanyal et al. 2006
Fatty liver is important…
…because it is a morbid co-factor in other diseases
Fatty liver- a morbid co-factor

The presence of steatosis and insulin resistance is associated with increased liver injury and accelerated disease progression in

- Chronic viral hepatitis
- Alcoholic liver disease
- Haemochromatosis

“fuel for raging flames”?
Steatosis associated with HCV
  • “Viral” steatosis (genotype 3)
  • “Metabolic” steatosis (genotype 1)

Correlation with severity in genotype 1
No correlation in genotype 3

Patients who failed to respond to antiviral treatment had significantly higher levels of intrahepatic lipid

G1: 
  \( r=0.5, \ p=0.02 \)

G3: 
  \( r=-0.04, \ p=0.91 \)

\( p<0.0005 \)
Fatty liver- how important is it?

Fatty liver is important...

...because it is modifiable
Interventions

- Calorie limitation
- Exercise
- Reduced SFA
- Weight reduction
- Reduced Fructose
- Increased PUFA (n-3, n-6)
- Increased MUFA

Zivkovic et al 2007
Weight reduction associated with reduced liver fat

\[ r^2 = 0.80, \ p < 0.0005 \]

Cobbold et al.
Clin Sci 2009
Weight reduction associated with reduced liver fat

Thomas, Mehta, O’Regan et al. unpublished data
Conclusions

Fatty liver is important because…
• It is common and getting commoner
• It is detectable
• Its pathogenesis increasingly understood
• It is associated with increased liver-related and all-cause mortality
• It is a morbid co-factor for other liver diseases
• It is modifiable

…and there a still many unanswered questions…

So, fatty liver, how important is it? VERY!
Acknowledgements

Dr Quentin Anstee
Prof Jimmy Bell
Dr Jane Cox
Prof Gary Frost
Dr Rob Goldin
Dr Sanjeev Mehta
Dr Declan O'Regan
Prof Simon Taylor-Robinson
Dr Louise Thomas
Prof Howard Thomas
Prof Mark Thursz

Staff at the Liver Unit, St Mary's Hospital

Funding:
• Centenary Fellowship, Hammersmith Hospital Trustees Research Committee
• NIHR