Non-alcoholic fatty liver disease

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Objectives

- Define NAFLD and NASH
- List secondary conditions associated with NAFLD
- Understand the natural history of NAFLD
- Be aware of the association between NAFLD and cardiovascular disease
- Be aware of current and emerging treatments for NAFLD
Case

- 51 y.o. female referred in for a 2 year history of hepatomegaly

Past history:
- Obesity (weight gain 80 pounds x 10 years)
- DM x 10 years (neuropathy, nephropathy)
- Hyperlipidemia
- HTN
- MI at the age of 37 (angioplasty)
- Osteoarthritis, knee surgery, back surgery
- Depression
**Case**

**Medications:**
- Insulin 240 units in the am and 260 units in the evening; Glyburide; Metformin; Lopressor; Ramipril; Lipitor; Niacin; ASA; Oxycontin

**Family history:**
- Brother and father MI in their early 50's
- Strong history of DM and hyperlipidemia
Case

On examination:
- Height 170 cm, weight 120 kg
- **BMI**: 42
- **BP**: 140/70
- **Liver span**: 20 cm in the midclavicular line
- **Spleen**: palpable
- No chronic liver disease stigmata, no ascites
Case

Labs

- Hb 157, WBC 6.7, plts 207
- AST 66, ALT 47, ALP 98, bilirubin 6, INR 1.0, albumin 40
- HbA1C 9.9
- Cholesterol
  - Total: 4.26 mmol/L
  - HDL: 1.14 mmol/L
  - TG: 3.19 mmol/L
  - LDL: 1.65 mmol/L
Case

**Ultrasound:**
- Hepatomegaly and marked diffuse fatty infiltration
- Splenomegaly – 15.9 x 6.4 cm
What is the differential diagnosis of her liver enzyme abnormalities?
Differential diagnosis

- α-1 antitrypsin def
- Infiltrative
- Viral
- ETOH
- Autoimmune
- NAFLD
- Wilson’s
- Hemochromatosis
What are the fatty liver diseases?
Fatty Liver Diseases

- **Alcoholic fatty liver disease (AFLD)**
- **Nonalcoholic fatty liver disease (NAFLD)**
  - a spectrum of disorders characterized by macrovesicular hepatic steatosis...in the absence of consumption of alcohol in amounts considered harmful to the liver

- **Nonalcoholic steatohepatitis (NASH)**
  - the most severe form of NAFLD which may progress to cirrhosis

AGA Position Statement
Gastro 2002;123:1702-4
NAFLD

- Steatosis
- NASH
- Compensated Cirrhosis
  - Decompensated Cirrhosis
  - HCC
Pathogenesis of NASH
“The 2-Hit Theory”

Normal

1st Hit

Steatosis (Vulnerable)

Insulin Resistance

2nd Hit

Steatohepatitis

Oxidative Stress and Dysregulated cytokine production
Clinical presentation
History

- Largely asymptomatic
- Right upper quadrant pain, fatigue, lethargy
- Cirrhosis and its complications
- Risk factors for “primary” NAFLD
  - Metabolic syndrome, cardiovascular disease
- Risk factors for “secondary” NAFLD
What secondary conditions are associated with NAFLD?
## Associated conditions

### Nutritional/Metabolic
- accelerated weight loss
- acute starvation
- TPN

### Gastrointestinal
- JI bypass
- biliopancreatic diversion
- extensive SB resection

### Drugs
- amiodarone
- synthetic estrogens
- Tamoxifen
- tetracycline
- steroids
- HAART

### Miscellaneous
- Wilson’s disease
- Weber-Christian disease
- Abetalipoproteinemia
- Small bowel diverticulosis
Physical exam

- Central obesity
  >102 cm (M), >88 cm (F)
- Elevated BMI (kg/m²)
- Buffalo hump
- Hepatomegaly (75%)
- Signs of cirrhosis/portal hypertension
Labs

- Normal → elevated liver enzymes (<5x)
- Exclude alternate causes of liver disease
  - Iron studies, autoimmune markers, viral
- Features of more advanced disease
  - Thrombocytopenia, AST/ALT ratio >1
- Lipid profile, fasting glucose, fasting insulin level

Chitturi S, Hepatology 2002
Imaging

- Ultrasound, CT scan, MRI
  - Detect steatosis if >1/3 of the liver affected
  - Can look for signs of portal hypertension
  - Cannot distinguish between steatosis versus NASH
How common is NAFLD?
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Prevalence NAFLD (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>General population studies</strong></td>
<td></td>
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<tr>
<td><em>Ultrasound</em> (references 23-25,27)</td>
<td>~22</td>
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<tr>
<td>Bellentani et al. 24</td>
<td></td>
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<tr>
<td>Lean</td>
<td>16</td>
</tr>
<tr>
<td>Obese</td>
<td>76</td>
</tr>
<tr>
<td>PMRS (Browning et al. 26)</td>
<td>24-45*</td>
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<tr>
<td><strong>Liver enzymes (ALT level)</strong></td>
<td></td>
</tr>
<tr>
<td>Patt et al. 32</td>
<td>14-21</td>
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<tr>
<td>NHANES III 4,15</td>
<td>3-23</td>
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<tr>
<td><strong>Liver histology on selected groups</strong></td>
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<td><em>Liver biopsy</em></td>
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<tr>
<td>7 studies—see McCullough 15</td>
<td>15-84</td>
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<tr>
<td><em>Autopsy-random deaths</em></td>
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<tr>
<td>Hilden et al. 28</td>
<td>24</td>
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<tr>
<td>Ground 29</td>
<td>16 (NASH = 2.1)</td>
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<tr>
<td><em>Hospitalized deaths</em></td>
<td></td>
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<tr>
<td>Wanless and Lentz 33</td>
<td></td>
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<tr>
<td>Lean</td>
<td>3</td>
</tr>
<tr>
<td>Obese</td>
<td>19</td>
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<tr>
<td><em>Surgical patients</em></td>
<td></td>
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<tr>
<td>Adult living liver donors 30,31</td>
<td>20</td>
</tr>
<tr>
<td><strong>Type 2 DM</strong></td>
<td>40-70%</td>
</tr>
</tbody>
</table>

Farrell & Larter, Hepatology 2006
Prevalence of NASH (%)

- Non-obese
- Obese
- Morbidly obese

Wanless, Hepatology 1990
Prevalence of NAFLD vs. Prevalence of Obesity

General population

NAFLD was defined by ultrasound except in the U.S.A. Obesity, BMI ≥30 except in Asian countries, BMI ≥25

Lazo, Seminars in Liver Disease 2008
Obesity Trends* Among U.S. Adults
BRFSS, 1990, 1995, 2005
(*BMI ≥30, or about 30 lbs overweight for 5’4” person)
Obesity (%) by Province (2004)

Source: Canadian Community Health Survey 2004, Stats Canada
Does NAFLD matter?
Natural history of NAFLD

Ekstedt, Hepatology 2006

P=0.01
Causes of death in NASH

- Malignancy: 5.6%
- CAD: 15.5%, P=0.04
- Liver disease: 0.2%, P=0.04

Ekstedt, Hepatology 2006
NASH cirrhosis versus HCV cirrhosis

A

\[ \% \text{ ascites-free} \]

\[ P = .03 \]

D

\[ \% \text{ without hepatocellular cancer} \]

\[ P < .03 \]

Sanyal Hepatology 2006
Causes of death in NASH cirrhosis

- Infection: 41 cases, $P>0.05$
- CAD: 28 cases, $P=0.03$
- Liver disease: 24 cases, $P>0.05$

Sanyal Hepatology 2006
Natural History of NAFLD

Steatosis ➔ Cirrhosis ➔ No sig impact on mortality

1-2% over 20 y

Co-existing cause of liver disease (HCV, HH) ➔ May increase rate of fibrosis

Bellantani S, J Hepatol 2005
Day, C. Gastroenterol 2005
Natural History of NASH

- NASH 9-20%/15y → Cirrhosis
- Cirrhosis → Death
- Cirrhosis → Decompensation 45% at 10 y
- NASH → Cirrhosis 15% at 10 y
- Cirrhosis → HCC
- Cirrhosis → Liver transplant
- Cirrhosis → Post-transplant Recurrence
The link between NAFLD & atherosclerosis

There is some evidence that NAFLD may not only be the hepatic manifestation of the metabolic syndrome but that it also may contribute to atherosclerosis.

- May stimulate insulin resistance
- Chronic subclinical inflammation and oxidative stress
- Abnormal Lipid Profile/Metabolism

AASLD postgrad course 2008
NAFLD and CV disease

The histologic severity of NAFLD is an independent predictor of:

– Carotid artery intima-media thickness

– Endothelial dysfunction as measured by brachial artery flow-mediated vasodilation

– Left-ventricular dysfunction

Targher, Diabetes Care 2006
Villanova Hepatology 2005
Perseghin, Hepatology 2008
What tools can we utilize to distinguish simple steatosis from NASH ± advanced fibrosis?
Risk Factor for Fibrosis Progression in NAFLD

- Age >50
- BMI > 28
- AST/ALT >1
- TG’s > 1.7 mmol/L
- Insulin resistance
- Diabetes
- Systemic Hypertension
Unable to do because of subcutaneous fat layer
Histology

Fat = Steatosis

Inflammation = Hepatitis

Mallory Hyaline

Neutrophils

Fibrosis

Cirrhosis
Downsides of liver biopsy

- Invasive procedure
- Risk of complications in 0.5 – 1%
- Sampling variability
- Prevalence too high to biopsy all patients
I perform liver biopsy in selected cases...

- Suspicion of advanced fibrosis/cirrhosis
  - Peripheral stigmata of chronic liver dz, splenomegaly, thrombocytopenia, risk factors for advanced fibrosis

- To evaluate for concurrent causes of liver disease
  - High iron studies, positive autoimmune markers, drug-induced liver injury

- Persistent increase in enzymes despite correction of metabolic risk factors
Liver biopsy done because of suspicion of advanced fibrosis and to rule out alternate etiology given marked hepatomegaly.

- Steatohepatitis with irregular fibrosis
  - Grade 1/3 inflammation
  - Stage 3/4 fibrosis
Are there any therapies for NAFLD?

1) Treatment of co-morbidities
2) Pathophysiology based treatments
Treatments of co-morbidities

- **Diet & exercise for gradual weight loss**
- **Pharmacological anti-obesity agents**
  - Orlistat
  - Cannabinoid receptor 1 antagonist (rimonabant)
- **Bariatric surgery**
Bariatric surgery – improvement or resolution of steatohepatitis

Mummadi, Clin Gastro Hep 2008
Bariatric surgery – improvement or resolution of hepatic fibrosis

Mummadi, Clin Gastro Hep 2008
Treatment of co-morbidities

- Type 2 DM and insulin resistance
  - Metformin
  - Thiazolidinediones (TZDs)
- Dyslipidemia
- Hypertension
Metformin

Open-label RCT – 110 non-diabetic patients

- Metformin 2 g/day x 12 months
- Only 30% of metformin patients biopsied post
  - Reductions in steatosis and necroinflammation

No significant improvement in histology in other studies

Bugianesi, Am J Gastro 2005
Uygun A, APT 2004
Pioglitazone

- Insulin sensitizing, anti-inflammatory, anti-fibrotic properties
- RCT of 74 non-diabetic pts with NASH
  - 12 months of lifestyle modifications + 30 mg pioglitazone vs placebo
  - Increase in weight, reduction in ALT and improvement in histologic features (fibrosis and hepatocellular injury)

Aithal, Gastroenterology 2008
Hyperlipidemia

- No good evidence for histologic benefit
- Statins can be used safely in patients with elevated liver enzymes

Hypertension

- Animal models
  - Therapy directed at the RAAS system may be beneficial for reducing hepatic fibrosis

Browning, J. Hepatology 2006
Chalasani N, Gastro 2004
Pathophysiology based treatments...
Pathophysiology based treatments

- **Insulin sensitizers**
  - Thiazolidinediones, Metformin, GLP-1 agonist

- **Anti-oxidants**
  - Vitamin E, betaine, phlebotomy, probiotics/prebiotics

- **Anti-cytokine agents**
  - Pentoxifylline, Anti-TNF
Case

- Patient referred to a dietician and to the weight-wise program
- Optimizing control of lipids and diabetes
- Gastroscopy – varices
- U/S and AFP q 6 months – surveillance for HCC
Management Algorithm

Diagnosis of NAFLD

Exclude secondary NAFLD

Consider liver biopsy if at risk of advanced fibrosis
- diabetes
- obesity
- age > 50
- AST/ALT > 1

Evaluate and treat metabolic risk factors
- obesity
- hypertension
- dyslipidaemia
- glucose intolerance

Screen for HCC and varices if cirrhosis present

Improve insulin sensitivity
- weight loss
- exercise
- consider bariatric surgery if morbidly obese

Avoid excessive alcohol ingestion

Enrol in clinical trial if available

Questions??