Update on Diagnosis and Management of Non-Alcoholic Fatty Liver Disease

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Incidense of Liver Diseases is Rising!

Outpatient and hospital diagnosis “liver disease” 1979-2004

The obesity pandemic...
Non-alcoholic fatty liver disease - Definition

Ludwig et al. Mayo Clin Proc 1980:

“...poorly understood and hitherto unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis....nonalcoholic steatohepatitis of unknown cause.....presence of striking fatty changes with evidence of lobular hepatitis, focal necroses with mixed inflammatory infiltrates,......evidence of fibrosis was found in most specimens, and cirrhosis was diagnosed.....more common in women. Most patients were moderately obese, and many had obesity-associated diseases, such as diabetes mellitus and cholelithiasis. Currently, we know of no effective therapy.“
## Non-alcoholic fatty liver disease - Definitions

<table>
<thead>
<tr>
<th>NAFLD (non-alcoholic fatty liver disease)</th>
<th>Entire spectrum of fatty liver disease in the absence of significant alcohol consumption and other competing liver diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFL (non-alcoholic fatty liver)</td>
<td>Hepatic steatosis without any hepatocellular injury (risk of progression minimal)</td>
</tr>
<tr>
<td>NASH (non-alcoholic steatohepatitis)</td>
<td>Hepatic steatosis with varying degrees of necro-inflammation with/without fibrosis. Progression to cirrhosis, liver failure and HCC is possible</td>
</tr>
<tr>
<td>NASH cirrhosis</td>
<td>Presence of liver cirrhosis with current of previous evidence of NAFLD</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>Presence of cirrhosis with no obvious etiology. Majority of patients reveal obesity and/or features of the metabolic syndrome</td>
</tr>
</tbody>
</table>

Incidence & Prevalence

NAFLD Incidence: general population

- Hamaguchi, 2005
- Suzuki, 2005
- Bruno, 2005
- Whalley, 2007

Cases per 100

NAFLD prevalence: general population

- Chen, 2008 (US)
- Radu, 2008 (US)
- Kim, 2004 (US)
- Browning, 2004 (HTGC)
- Ioannou, 2006 (enzymes)
- Suzuki, 2005 (enzymes)
- Bedogni, 2005 (enzymes)
- Patt, 2003 (enzymes)
- Ruhl, 2003 (enzymes)
- Clark, 2003 (enzymes)
- Lee, 2007 (biopsy)
- Marcos, 2000 (biopsy)
- Amarapurkar, 2007...
- Ground, 1982 (autopsy)

Percent
# Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors Associated with NAFLD</th>
<th>Established Association</th>
<th>Emerging Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (visceral distribution)</td>
<td></td>
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<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
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<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
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<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
<td></td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyogonadism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreateo-duodenal resection</td>
</tr>
</tbody>
</table>
# Alcohol Consumption

## Thresholds of "significant" alcohol consumption (g/week)

<table>
<thead>
<tr>
<th>0</th>
<th>40</th>
<th>140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludwig et al.</td>
<td>Powell et al.</td>
<td>Bacon et al.</td>
</tr>
<tr>
<td>Diehl et al.</td>
<td>Angulo et al.</td>
<td>Teli et al.</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>George et al.</td>
<td>Bonkovksy et al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Matteoni et al.</td>
</tr>
</tbody>
</table>

## Current consensus

<table>
<thead>
<tr>
<th>Males</th>
<th>21 drinks/week (210g/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>14 drinks/week (140g/w)</td>
</tr>
</tbody>
</table>
10. ESBRA Congress, Canterbury 2005

While searching for a place for wine and dine...
NAFLD → NASH → NASH cirrhosis → HCC

General population:
- 20%
- 3-5%
- unknown
- Annual incidence 2-3%?

BMI > 40:
- 90%
- 40%
- 20%?
- 5%?
Natural Course

Metabolic Syndrome

- Fatty acids
- Insulin
- Adipokines
- Cytokines

Steatosis

- Fatty acid oxidation
- Reactive aldehydes
- ER stress
- ROS

Inflammation

- mTOR↑, NFκB↑, JNK↑, MAPK↑, STAT3↑, PTEN↓

Oncogenesis

- Apoptosis/Tumor suppression

Insulin Resistance

DNA damage

HCC Risk

- Inflammation
- Fibrosis

Non-Alcoholic Fatty Liver Disease

- Steatosis Hepatitis
- Steatohepatitis
- (Cryptogenic) Cirrhosis

References:

Stickel & Hellerbrand
GUT 2010;59:1303-7
Screening Recommendations

• Screening for possible NASH in patients with features of MS and steatosis on imaging and symptoms/signs of liver disease (1B)

• Patients with NASH should be screened for gastroesophageal varices according to accepted guidelines (APASL, AASLD, EASL)

• Patients with NASH should be screened for HCC according to accepted guidelines (APASL, AASLD, EASL)

• Patients with decompensated NASH cirrhosis should be considered eligible for liver transplantation
Diagnostic Evaluation

- Exclude significant alcohol consumption
- Exclude competing etiologies for steatosis and chronic liver disease (1A)
- In pts with steatosis on imaging, assess metabolic risk factors (glucose intolerance, insulin resistance, lipid tests etc.)
- Elevated ferritin and transferrin saturation should raise suspicion of iron storage disease (genetic testing); if negative – dysmetabolic iron overload
- Elevated autoantibodies (ANA, SMA) are common and considered epiphenomena (up to 1:160)
Non-Invasive Assessment

• AST/platelet ratio  \textit{(Wai et al. Hepatology 2003)}
• FIB-4 score  \textit{(Sterling et al. Hepatology 2006)}
• NAFLD fibrosis score  \textit{(Angulo et al. Hepatology 2007)}
• BARD score  \textit{(Harrison et al. GUT 2008)}
• CK18 fragments  \textit{(Wieckowska et al. Hepatology 2006)}
• ELF panel  \textit{(Guha et al. Hepatology 2008)}
Non-Invasive Assessment: FibroScan® (Transient elastography)
FibroScan® (Transient elastography) for NAFLD
Wong et al. Hepatology 2010;51:454-62

- 2 NASH cohorts (Hong Kong, n=118; French, n=128)
- Histology for all 246 patients
- Extensive clinical characterization
- All with liver stiffness data
- Assessed for AST/ALT ratio, APRI, FIB-4, NAFLD fibrosis score, BARD score

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**Table 3. Area Under the Receiver Operating Characteristics Curves for Transient Elastography and Noninvasive Markers for the Diagnosis of Advanced Fibrosis and Cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>AUROC (95% CI)</th>
<th>AUROC for Fibroscan (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ F3</td>
<td>F4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT</td>
<td>245</td>
<td>0.66 (0.58–0.74)</td>
<td>0.93 (0.89–0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APRI</td>
<td>245</td>
<td>0.74 (0.67–0.82)</td>
<td>0.93 (0.89–0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FIB-4</td>
<td>245</td>
<td>0.80 (0.74–0.87)</td>
<td>0.93 (0.89–0.96)</td>
<td>0.001</td>
</tr>
<tr>
<td>NAFLD fibrosis score</td>
<td>228</td>
<td>0.75 (0.67–0.83)</td>
<td>0.92 (0.89–0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BARD score</td>
<td>244</td>
<td>0.69 (0.61–0.77)</td>
<td>0.93 (0.89–0.96)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>F4</th>
<th>AUROC (95% CI)</th>
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<th>P</th>
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<tr>
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</tr>
<tr>
<td>NAFLD fibrosis score</td>
<td>228</td>
<td>0.80 (0.69–0.92)</td>
<td>0.95 (0.91–0.99)</td>
<td>0.022</td>
</tr>
<tr>
<td>BARD score</td>
<td>244</td>
<td>0.62 (0.50–0.75)</td>
<td>0.95 (0.91–0.99)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Liver Biopsy/Histology

Perform a liver biopsy

• in patients at risk for NASH (metabolic syndrome); 1B

• if suspicion of competing etiology; 1B

• with results of non-invasive tests suggestive of progressive NAFLD; "eminence-based"

• Use established histology score (Kleiner et al. Hepatology 2005), 1A
Liver Biopsy/Histology

- Systematic review of case series and retrospective studies (n=10) on liver histology progression in NAFLD
- Data from 1980-2005
- Reanalysis of individual case data

Therapeutic Management

• Lifestyle change (weight loss, physical activity)

• Insulin sensitization (thiazolidinediones)

• Vitamin E

• Statins

• Bariatric surgery
Therapeutic Management – Life Style Modification

Weight Loss

<table>
<thead>
<tr>
<th>Author</th>
<th>Mean Difference (95% CI)</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison et al. 2009</td>
<td>-2.50 (-3.52, -1.48)</td>
<td></td>
</tr>
<tr>
<td>Nobili et al. 2008</td>
<td>-1.10 (-2.11, -0.09)</td>
<td></td>
</tr>
<tr>
<td>Promrat et al. 2009</td>
<td>-2.30 (-3.38, -1.22)</td>
<td></td>
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<tr>
<td>Vilar Gomez et al. 2009</td>
<td>-2.40 (-3.51, -1.29)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-2.05 (-2.58, -1.58)</td>
<td></td>
</tr>
</tbody>
</table>

Musso et al. Diabetologia 2012;55:885-904
Therapeutic Management – Life Style Modification

Physical Activity

NMR liver fat

ALT

Body weight

Waist circumference

HOMA score

Fasting glucose

Musso et al. Diabetologia 2012;55:885-904
Therapeutic Management – Thiazolidinediones

Insulin sensitization

Caveat

- significant weight gain
- no long-term safety data
- risk of congestive heart failure?
- bladder cancer?
- osteoporosis?
- rosiglitazone withdrawn
Therapeutic Management – Vitamin E

- **Therapeutic rationale**: oxidative stress key mechanism of hepatocellular injury in NAFLD

- Earlier trials indicated improvement of liver biochemistry

- Heterogeneity due to variable entry criteria and end points, different vitamin E doses and formulations

- 2 metaanalyses indicated no benefit from vitamin E on histology (*Musso et al. 2010, Bjelakovic et al. 2010*)
PIVENS Trial
(Pioglitazone vs. Vitamin E for the treatment of NASH)

- Randomized controlled trial in patients with biopsy-proven NASH to test the efficacy of 96 weeks treatment with
  - Pioglitazone 30mg/d (n=80)
  - Vitamin E 2x400 IE/d (n=84)
  - Placebo (n=83)

- No diabetics included

- Primary endpoint: composite endpoint of standardized histologic scores (steatosis, balloning, inflammation, fibrosis)

- Level of significance set at 0.025 (two planned comparisons)

PIVENS Trial
(Pioglitazone vs. Vitamin E for the treatment of NASH)

A) Alanine Aminotransferase

B) Aspartate Aminotransferase

C) Insulin Resistance

D) Weight

Therapeutic Management – Statins

• Hyperlipoproteinemia (HLP) is typically associated with NASH

• NAFLD/NASH patients are at increased risk for cardiovascular disease

• No increased incidence of drug-induced liver injury (DILI) from statins in NASH patients

• Thus: statins can be used safely in NAFLD patients to treat HLP

• Several studies (including GREACE) indicate improvement of liver biochemistry and reduction of cardiovascular endpoints (stroke, myocardial infarction) in NAFLD patients treated with statins (atorvastatin)

• But: no RCT on statins in NAFLD available, thus: statins should not be used to specifically treat NAFLD
Therapeutic Management – "Famous Failures"

- **Ursodeoxycholic acid** *(Lindor et al. Hepatology 2005)*
- **Metformin** *(Musso et al. Diabetologia 2012, Rakoski et al. Alim Pharm Ther 2010)*
- **Orlistat** *(Harrison et al. Hepatology 2009)*
- **Vitamin C** *(Harrison et al. Am J Gastro 2003)*
Therapeutic Management – Bariatric Surgery

• >90% of morbidly obese have NAFL, ~40% reveal NASH, ~20% present with advanced fibrosis/cirrhosis

• No RCTs evaluating the effect of bariatric surgery on NASH

• Metaanalysis of retrospective and prospective cohort studies indicates significant improvement of steatosis, necro-inflammation and fibrosis

Therapeutic Management – Bariatric Surgery

- No contraindication for bariatric surgery in patients with NAFLD/NASH (exception: cirrhosis); 1A

- Optimal type of surgical procedure remains to be established; 1B

- Recommending bariatric surgery as a treatment for NASH premature; 1B
Conclusions

• NAFLD represents an increasing challenge worldwide

• Diagnostic and prognostic assessment is established, and screening should embrace subjects with evidence of liver injury with coexisting features of the metabolic syndrome

• Backbone of treatment is lifestyle intervention targeting a moderate weight loss and increase of physical activity

• Drug therapy with vitamin E and pioglitazone improve liver biochemistry and histology; prognostic benefit yet unclear

• Bariatric surgery may be an option in those in whom conservative interventions fail
Thank you!