NAFLD: Diagnostics, management and screening

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Non-alcoholic fatty liver disease
Diagnosis

• Definition of NAFLD

• Liver biopsy

• Non-invasive techniques
Fatty liver
(≥5% steatotic hepatocytes)

Secondary FLD
- Alcohol
- Drugs
- Hereditary disorders

Non-alcoholic fatty liver disease (NAFLD)
- Non-alcoholic fatty liver (NAFL)
- Non-alcoholic steatohepatitis (NASH)

Definition of NAFLD

Liver biopsy: The Gold Standard

Steatosis?

Balloning?

Lobular inflammation?
Liver biopsy: The Gold Standard

Steatosis?

- No alcohol, drugs etc

FLD absent

NAFLD

Balloning?

No

- NAFL

Yes

NAFL

Lobullar inflammation?

Yes

NASH

No

Bedosa et al. Hepatology 2012; 56: 1751
Natural history of NAFLD

- NAFL to NASH: 44%-64% (3-4 years), 7% (3-7 years)
- NASH to Advanced fibrosis/cirrhosis: 0.16% (6 years)
- Advanced fibrosis/cirrhosis to Hepatocellular carcinoma: 10%-25% (8-14 years), 2%-13% (3-7 years)

Non-invasive diagnosis of NAFLD: First detect steatosis

Imaging techniques
- US
- CT
- MRI
- VCTE-CAP

Steatosis

Balloning?

Lobular inflammation?
Diagnosis of steatosis with VCTE-CAP

- CAP is an estimation of the attenuation of the ultrasound wave with the M probe of Fibroscan®.
- CAP uses the same data required for liver stiffness.

Performance of CAP according to liver biopsy*

- n=115 patients: (42 HCV; 17 HBV; 39 alcohol; 17 NAFLD).
- Steatosis: (S0: < 10%, S1: 11-33%, S2: 34-66%; S3: > 67%).

NAFLD & VCTE-CAP: Improved CAP cut-offs to predict steatosis

Meta-analysis of individual data from 19 studies (n=2735, 37% HBV, 36% HCV, 20% NAFLD/NASH, 7% other).

Steatosis in biopsy: <5% or <10% 10%-33% 33%-66% >66%

MRI can decompose the liver signal into its fat and water signal components. MRI techniques measure the proton density fat-fraction (the fraction of the liver proton density attributable to liver fat), which is a direct measure of liver fat content.

MRI-PDFF and steatosis

Adult patients with clinical indication for liver biopsies for suspected NAFLD (N=104, October 2011-May 2016)

Non-invasive diagnosis of NAFLD
First detect steatosis, then see fibrosis


*P<0.01 compared with F0, F1, and F4, P<0.05 compared with F2;
**P<0.001 compared with all other fibrosis stages
Fibrosis and NAFLD: Blood biomarkers

Ruling out F≥3

Panels with best diagnostic yield to predict histologic advanced fibrosis or cirrhosis in NAFLD (N = 145).

<table>
<thead>
<tr>
<th>Test</th>
<th>AUROC (95% CI)</th>
<th>Cut-off</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIB-4</td>
<td>0.86 (0.78-0.94)</td>
<td>1.30</td>
<td>36%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.25</td>
<td>75%</td>
<td>85%</td>
</tr>
<tr>
<td>NAFLD fibrosis score</td>
<td>0.81 (0.71-0.91)</td>
<td>-1.455</td>
<td>30%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.676</td>
<td>79%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Indeterminate fibrosis: FIB-4 or NAFLD fibrosis score values between cut-off points.

FIB-4: (Agex AST)/platelets (10^9/L) x V ALT
NALFD fibrosis score: -1.675 + 0.037 x age + 0.094 x BMI (Kg/m²) + 1.13 x abnormal FPG/DM (yes=1, no=0) + 0.99 x AST/ALT - 0.013 x platelets (10^9/L) - 0.66 x albumin (g/dL)

AUROC: Area under the ROC curve; 95% IC: 95% confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

Non-invasive diagnosis of NAFLD: Summary imaging techniques

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>US</th>
<th>VCTE-CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steatosis</strong></td>
<td>Measurement of liver fat content</td>
<td>Low sensitivity</td>
<td>Quantification of fat</td>
</tr>
<tr>
<td></td>
<td>High precision</td>
<td>Unable to quantify fat</td>
<td>Precise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td>MRI-E</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Bed side</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Expensive</td>
<td>Low cost</td>
<td>Intermediate cost</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Appropriate</td>
<td>Not appropriate</td>
<td>Very appropriate</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Obesity</td>
<td>Obesity</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Claustrophobia</td>
<td></td>
<td>Ascites</td>
</tr>
</tbody>
</table>

NAFLD: Management

• How severe is NAFLD?

• Identify the potential causes of NAFLD

• Treatment
Assessing the severity of NAFLD Fibrosis and risk of liver mortality

- Meta-analysis of 5 cohort studies with N = 1495 pts with NAFLD followed for 17,452 pt-yrs
- Liver-related mortality exponentially increased with fibrosis stage

Causes of NAFLD: General population

The 10 Most Obese Countries on Earth

According to the World Health Organization | % Obesity Rate

1. United States of America - 33.8%
2. New Zealand - 26.5%
3. Australia - 24.6%
4. Czech Republic - 24.2%
5. United Arab Emirates - 23%
6. Slovakia - 23%
7. Norway - 22.4%
8. Canada - 22%
9. Germany - 20.2%
10. Hungary - 18.8%
Causes of NAFLD:
Fat and getting fatter

Diet
- People who become overweight eat just a little more calories
- 100 Kcal per day (half a tin of soda) means 4 Kg of extra fat a year

Exercise
- They exercise a little less-they walk less often, take the lift more, walk more slowly, play fewer games
Treat the cause, if possible

**Soft drink serving sizes have grown**

Critics of the food and beverage industry say that we live in an environment where it is difficult to make healthy decisions.

![Graph showing the growth of soft drink serving sizes from 1950s to 2011](SOURCE: HARVARD SCHOOL OF PUBLIC HEALTH, DEPT. OF NUTRITION)

**The Cost of Healthy Eating**

The cost of many unhealthy foods, like soda, butter and beer, has fallen in the last three decades, while the cost of fruits and vegetables has risen substantially.

**Change in Monthly Food Prices**

<table>
<thead>
<tr>
<th>Year</th>
<th>Fresh Fruits</th>
<th>Fresh Vegetables</th>
<th>Beer</th>
<th>Butter</th>
<th>Sodas</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>1.46%</td>
<td>1.41%</td>
<td>0.85</td>
<td>0.71</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Lines show change in price of items since 1978, relative to overall inflation as measured by the Consumer Price Index. The price of vegetables, for example, has risen 40 percent faster than the overall index.

*Source: Bureau of Labor Statistics, via Haver*
Approaching weight loss

**Individual**
- Diet
- Exercise
- Medication
- Surgery

**Community**
- Rationing
- Taxation
- Advertising
- Health warnings
- Legislation

Modified from: Sims P. Obesity-a global epidemic. WHO Collaborating Center University of Pittsburgh
Available at: www.pitt.edu/~super4/37011-38001/37771.ppt
Treatment of NAFLD
Lose weight!!!

Weight loss

Changes in liver histology

> Steatosis and liver stiffness

7% - 10%\(^1,3\)

↓ NASH

≥ 5%\(^1,2\)

≥ 10%\(^3\)

↓ NASH and fibrosis

Treatment of NAFLD
Lose weight!!!

BMI=31 Kg/m²
CAP=330 dB/m
LS=3.4 KPa

≥10% loss

BMI=26 Kg/m²
CAP=210 dB/m
LS=3.6 KPa
Drugs for NAFLD: Phase 3 trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Steatosis, % decrease</th>
<th>NASH, % resolution</th>
<th>Fibrosis, % decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone¹</td>
<td>PPAR agonist</td>
<td>69%</td>
<td>47%</td>
<td>44%</td>
</tr>
<tr>
<td>Vitamin E¹</td>
<td>Oxidation inhibitor</td>
<td>54%</td>
<td>36%</td>
<td>41%</td>
</tr>
<tr>
<td>Elafibranor²</td>
<td>PPAR agonist</td>
<td>35%</td>
<td>29%</td>
<td>NR</td>
</tr>
<tr>
<td>Obeticholic acid³</td>
<td>FXR agonist</td>
<td>61%</td>
<td>22%</td>
<td>35%</td>
</tr>
<tr>
<td>Selonsertib⁴</td>
<td>ASK1 inhibitor</td>
<td>31%</td>
<td>&lt;1%</td>
<td>37%</td>
</tr>
<tr>
<td>Cenicriviroc⁵</td>
<td>CCR2/5 inhibitor</td>
<td>16%</td>
<td>8%</td>
<td>20%</td>
</tr>
</tbody>
</table>

PPAR: peroxisome proliferator-activated receptors; FXR: Farnesoid X receptor; ASK1: Apoptosis signal regulating kinase 1; NR: Not reported.

NAFLD Screening

Who?

• No cost-utility study on NAFLD screening
• Individuals at risk
  – Insulin resistance
  • Risk factors: Obesity, metabolic sd
  • High risk patients (look for NASH-fibrosis): T2DM

How?

• Availability of techniques
  – US, liver function tests
  – VCTE CAP
  – Unsuitable for unselected screening: MRI

EASL-EASD-EASO guidelines. Diabetologia 2016; 59:1121-1140
NAFLD: Screening
NAFLD: Diagnostics, management and screening

• Diagnosis:
  – Non-invasive detection of steatosis and fibrosis
  – Non-invasive diagnosis of NASH: Pending problem

• Management:
  – Weight loss
  – Diet and exercise, keep it simple
  – Drugs are coming

• Screening? Prevent instead