Strategies to increase awareness of NAFLD

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Brussels, January 8th, 2019
Conflict of interest

• Scientific advisor to Janssen-Cilag, Intercept, Genfit, NovoNordisk, Medimmune, Gilead.

• Speaker-Bureau: Janssen-Cilag, MSD, Roche, Abbvie, BMS, Gilead.

• Grants: Abbvie, Gilead e Intercept.

• Manuel Romero-Gómez es co-owner of DeMILI (a non-invasive MR-based method for NASH diagnostic).
Clinical case

Male 66 years old.
Obesity grade 1
Unrecognized Type 2 diabetes
No allergic reactions.
Hyperlipidemia treated with statins
Barrett’s esophagus without dysplasia
Symptomatic cholelithiasis
Laparoscopic cholecystectomy

Glycemia: 181 mg/dl
AST: 44 U/L
ALT: 55 U/L
Triglycerides: 193 mg/dl
Total Cholesterol: 216 mg/dl
HDL-Cholesterol: 30 mg/dl
Platelets: 169.000 plat
Albumin: 5140 mg/dl
AFP: 4.4 mg/dl
BMI: 33 kg/m2
Weight: 96 kg
Height: 170 cms.
Prevalence

- EU General population
  - NAFLD: 23%-25%
  - NASH: 2%-3%
  - Cirrhosis: 0.5%-1%

- Kwok et al. GUT 2015
- Anstee et al. Nat Rev 2013

Healthy liver → NAFLD → Simple steatosis → Steato-hepatitis → Fibrosis → HCC → Cirrhosis

1/3 General population
1/4 People at risk
1/5 Transient Elastography

n=20868 General population
N=2368 People at risk
N=919 Transient Elastography

(n=899 Successful TE)
N=230 kPa >8 (25.6%)
N=27 Cirrhotic (2.9%)

Harman DJ et al. AP&T 2018
Ampuero J, Romero-Gómez M. AP&T 2018
Extrahepatic manifestations of NAFLD/NASH: a systemic disease

NAFLD/NASH as a multi-systemic disease

Liver-Related
- Psoriasis
- Extrahepatic Malignancies

Psoriasis
- Polycystic ovary syndrome

Polycystic ovary syndrome
- LALD
- Hypobetalipoprotein

LALD
- Hypobetalipoprotein

Hypobetalipoprotein
- CV disease
- Sleep apnea

CV disease
- Osteoporosis

Osteoporosis
- Type 2 Diabetes
- Obesity

Type 2 Diabetes
- Metabolic syndrome

Metabolic syndrome
- NAFLD

NAFLD
- PNPLA3
- PCOS, HypoTyr, GH def

PCOS, HypoTyr, GH def
- Lipodystrophy

Lipodystrophy
- HAART in HIV

HAART in HIV
- Methotrexate
- Amiodarone
- Tamoxifen

Methotrexate
- Amiodarone
- Tamoxifen

Angulo et al. Gastro 2015
Adams et al. GUT 2017
N=728 biopsy-proven NAFLD patients (with no T2DM at baseline) followed-up prospectively, belonging to the Spanish Hepamet Registry.

Steatosis degree did not influence on T2DM occurrence.

Age, BMI, GGT, glucose and triglycerides were associated with T2DM incidence.

Cirrhosis [HR 4.05 (95%CI 1.19-13.8); p=0.025], F2-F3 stage [HR 2.43 (95%CI 1.07-5.48); p=0.033] and NASH at baseline [HR 2.34 (95%CI 1.02-5.37); p=0.044] were independently linked to the incidence of new onset of T2DM.

Ampuero et al. AASLD 2018
Non-alcoholic fatty liver disease

- Breast cancer:
  - HR 1.92; p = 0.01

- Hepatocellular carcinoma:
  - HR 16.73, p = 0.008

- Colorectal cancer:
  - HR 2.01, p = 0.02

- 25,947 subjects with median 7.5 years of follow-up
- Overall cancer incidence rate per 100,000 person-years:
  - 782.9 (NAFLD) vs. 592.8 (no NAFLD)
NAFLD and Atherosclerosis-CV events

N=111,492

>40y
10y follow-up

No NAFLD

NAFLD

2.14 (1.59-2.89)

NFS< - 1.455

NFS> - 1.455

1.70 (1.22-2.36)

1.86 (1.22-2.84)

NAFLD (US) & subclinical atherosclerosis

NAFLD (Biopsy) & subclinical atherosclerosis

*Myocardial Infarction

Ampuero et al. REED 2015;107:10-16
Liver-related outcomes in NAFLD

Ekstedt M et al. Hepatology 2015;61:1547-1554
The Long-Term Clinical Course of Histologically Advanced NAFLD. Impact of Fibrosis Severity on Major Clinical Outcomes.

N=458

Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>F3 (n=159)</th>
<th>F4 CTP A5 (n=222)</th>
<th>F4 CTP A6 (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or transplant</td>
<td>4 (3)</td>
<td>32 (14)</td>
<td>48 (62)</td>
</tr>
<tr>
<td>Deaths</td>
<td>4 (100)</td>
<td>19 (59)</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Liver-related</td>
<td>2 (50)</td>
<td>15 (79)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Unliver-related</td>
<td>2 (50)</td>
<td>4 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>0 (0)</td>
<td>13 (41)</td>
<td>30 (63)</td>
</tr>
</tbody>
</table>

* Adj. Log-rank P < 0.01 for difference among groups

(Adjusted analysis by center, race/ethnicity, age and gender*)

Transplant-Free Survival
Stratified analysis by fibrosis and CTP classes

Cirrhosis CTP A5
Bridging fibrosis
Cirrhosis and CTP A5
Cirrhosis and CTP A6

Vilar et al. Gastroenterology 2018
Hepatic outcomes
(Adjusted analysis by center, race/ethnicity, age and gender*)

Development of hepatic decompensation
Stratified analysis by fibrosis and CTP classes

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>F3 (n=159)</th>
<th>F4-CTP A5 (n=222)</th>
<th>F4-CTP A6 (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st event of decompensation</td>
<td>5 (3)</td>
<td>40 (18)</td>
<td>45 (58)</td>
</tr>
<tr>
<td>Ascites</td>
<td>2 (40)</td>
<td>28 (70)</td>
<td>33 (77)</td>
</tr>
<tr>
<td>Variceal hemorrhage</td>
<td>3 (60)</td>
<td>9 (22)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>0 (0)</td>
<td>3 (8)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Development of HCC
Stratified analysis by fibrosis and CTP classes

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>F3 (n=159)</th>
<th>F4-CTP A5 (n=222)</th>
<th>F4-CTP A6 (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC development</td>
<td>2 (1)</td>
<td>21 (9)</td>
<td>19 (25)</td>
</tr>
</tbody>
</table>
**Non-hepatic outcomes**  
(Adjusted analysis by center, race/ethnicity, age and gender*)

### Development of major vascular events

*Stratified analysis by fibrosis and CTP classes*

- **F3 (n=159):**
  - Major vascular events: 8 (5)
  - Heart ischemic disease: 7 (88)
  - Stroke: 1 (12)

- **F4-CTP A5 (n=222):**
  - Major vascular events: 5 (2)
  - Heart ischemic disease: 3 (60)
  - Stroke: 2 (40)

- **F4-CTP A6 (n=77):**
  - Major vascular events: 1 (1)
  - Heart ischemic disease: 0 (0)
  - Stroke: 1 (100)

* Adj. Fine and Gray P=0.01 for F3 vs. F4 groups

### Development of non-hepatic malignancies

*Stratified analysis by fibrosis and CTP classes*

- **F3 (n=159):**
  - Non-hepatic malignancies: 13 (8)

- **F4-CTP A5 (n=222):**
  - Non-hepatic malignancies: 10 (5)

- **F4-CTP A6 (n=77):**
  - Non-hepatic malignancies: 7 (9)

* Adj. Fine and Gray P=0.13 for F3 vs. F4 groups

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Vilar et al. Gastroenterology 2018
The good, the ugly and the bad in NAFLD’s movie

Romero-Gómez et al.
NAFLD: a disease throughout life

Increasing awareness to fight against:
- Obesity >> Metabolic syndrome >> Alcohol consumption
EUROPE

500M people obese
1.400M people overweight

PREVALENCE OF OBESITY (%) (BMI \geq 30.0 KG/M²) AMONG ADULTS IN THE WHO EUROPEAN REGION BASED ON WHO 2008 ESTIMATES

Notes: The country codes refer to the ISO 3166-1 Alpha-3 country codes. Data ranking for obesity is intentionally the same as for the overweight data. BMI: body mass index.
Source: WHO Global Health Observatory Data Repository (1).

The Regional Office is grateful to the European Commission (EC) for its financial support for the preparation of this country profile and the development of the nutrition, obesity and physical activity database that provided data for it.
To promote a Healthy Life Education during childhood

Interventions are needed at multiple levels

Politicians >> General population >> Organizations >> Primary Care >> Non-Hepatologists & Hepatologists
10-18/PL-000001
A legislative proposal to promote healthy lifestyle including a balanced diet in Andalucía

**AIMS**

a) To **encourage people** to adopt **healthy eating and living habits**.

b) To **promote** daily healthy **physical activity** in the population.

c) To facilitate and promote **active transport**.

d) To **fight against weight stigma** and develop specific policies that help people with eating disorders.

e) To **regulate access to unhealthy food** in public places.

f) To **regulate** the **advertising** and the **information available** of these products.
PAFASA: A plan to promote physical exercise and healthy eating habits in Andalucía

**OBJECTIVE:** To establish a set of indicators related to nutrition and physical activity in Andalucía that help to reduce the prevalence of obesity and that are also:

a) **Measurable:** Using indicators and other tools that allow to measure the achievements of purposed objectives.

b) **Accurate:** Based on scientific evidence and supervised by a scientific committee.

c) **Personalized:** Taking in consideration populations at risk (childhood, adolescence, pregnancy, elderly), gender and socioeconomics.
1. EDUCATION

i. Facilitate campaigns and support groups, associations and events that promote healthy habits and physical activity and fight against weight stigma at school and work.

ii. Teacher training courses with activities to promote healthy habits and physical activity in students.

iii. Promote basic and applied research focused on preventing obesity and developing new strategies that promote healthy diet and physical habits.

iv. Encourage the consumption of fresh and seasonal food.

v. More physical exercise at school and stimulate and facilitate the use of public sport facilitates and other infrastructures to promote physical exercise in young people.
2. REGULATION

i. Creation of an **experts commission** and a **scientific committee** that supervises implemented measures.

ii. **Regulate and/or restrict access to food with poor nutritional value in public places**, including schools and other buildings frequented by young people.

iii. **Supervise** the accuracy and visibility of the **information provided by food suppliers**.

iv. **Regulate food advertising**, paying special attention to the adverts that reach kids and teenagers.

v. **Penalties of up to 250000 €**

vi. **Awards to innovation projects** that promote **healthy habits**.
3. TOWN PLANNING.

i. Favor breastfeeding providing specific rooms in public places and a regional network of breast milk for newborns.

ii. City planning that favors and promotes active transport.

iii. Ensure access to free drinking water in public places.

4. HEALTH

i. Network of breast milk for newborns.

ii. Dynamic maps of overweight and obese populations in Andalucía before and after measures are implemented to determine their efficiency.

iii. Creation of a synthetic nutritional global index that allows to compare the nutritional properties of different products (SIGNA).

iv. Specific training in prevention and treatment of obesity for health care practitioners.

v. Specific healthcare protocols for patients diagnosed with morbid obesity and eating disorders.

vi. At least one bariatric surgical unit per province.
HEPAMET FIBROSIS SCORE

Calculadora Online

HFS SCORE:
Introduzca todos los valores

<table>
<thead>
<tr>
<th>Variables</th>
<th>Estimación</th>
<th>Validación (N=1076)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=758</td>
<td>N=288</td>
</tr>
<tr>
<td>Male sex</td>
<td>44.9%</td>
<td>62.5%</td>
</tr>
<tr>
<td>Age</td>
<td>53.9 ± 12.4</td>
<td>46.2 ± 13.3</td>
</tr>
<tr>
<td>BMI</td>
<td>36.4 ± 10.1</td>
<td>29.9 ± 5</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30)</td>
<td>64.9%</td>
<td>44%</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>27.6%</td>
<td>21.5%</td>
</tr>
<tr>
<td>HOMA</td>
<td>4.73 ± 4.3</td>
<td>4.05 ± 3</td>
</tr>
<tr>
<td>AST (IU/mL)</td>
<td>35 ± 26</td>
<td>46 ± 31</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>155 ± 81</td>
<td>146 ± 78</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.38 ± 0.40</td>
<td>4.60 ± 0.39</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>251 ± 73</td>
<td>232 ± 69</td>
</tr>
<tr>
<td>Significant Fibrosis</td>
<td>22%</td>
<td>46.9%</td>
</tr>
<tr>
<td>Advanced Fibrosis</td>
<td>12.1%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2.9%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>
Hepamet Fibrosis Score

FIB-4

NAFLD Fibrosis Score

HFS: Diagnostic accuracy and calibration

Ampuero et al. EASL 2018

Net benefit

ESTIMATION (n=758)

<table>
<thead>
<tr>
<th></th>
<th>Hepamet</th>
<th>NFS</th>
<th>FIB-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUROC F2-F4</td>
<td>0.783</td>
<td>0.718</td>
<td>0.741</td>
</tr>
<tr>
<td>AUROC F3-F4</td>
<td>0.867</td>
<td>0.775</td>
<td>0.772</td>
</tr>
<tr>
<td>AUROC F4</td>
<td>0.933</td>
<td>0.834</td>
<td>0.88</td>
</tr>
</tbody>
</table>

VALIDATION (n=1076)

<table>
<thead>
<tr>
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<th>NFS</th>
<th>FIB-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUROC F2-F4</td>
<td>0.746</td>
<td>0.678</td>
<td>0.713</td>
</tr>
<tr>
<td>AUROC F3-F4</td>
<td>0.835</td>
<td>0.773</td>
<td>0.796</td>
</tr>
<tr>
<td>AUROC F4</td>
<td>0.888</td>
<td>0.875</td>
<td>0.863</td>
</tr>
</tbody>
</table>
Age: 55±15
Males: 58.9% (259/440)
Females: 41.1% (181/440)

HFS > 0.12 51/402 (12.7%)
HFS < 0.12 (87.3%)

HFS < 0.12 ---- RISK OF CIRRHOSIS 0.9%
---- RISK OF F3: 8.8% (<10%)
Increasing awareness

Increasing detection

Improving outcomes
@SeLiver_group