EPIDEMIOLOGY OF NAFLD/NASH

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Conflict of interest (period 2015-2016) : Consultant for ROTTAPHARM-MEDA
OUTLINES OF MY SPEACH

- Definition
- Prevalence
- Incidence
- Risk factors
- Natural History
- The future of Hepatology
Forms and etiology of NAFLD/NASH

✓ “Primary” NAFLD/NASH: Associated with the metabolic syndrome

✓ “Secondary” NAFLD: Associated with different conditions

  Drugs: Steroids, Amiodarone, Tamoxifen, anti-HIV drugs, etc.

  Metabolic or genetic alterations: Lipodystrophy, Dysbetalipoproteinemia, Weber-Christian disease

  Nutritional: TPN, Rapid weight loss, Bariatric surgery, Starvation

  Small bowel diseases: IBD, Bacterial overgrowth

  Environmental hepatotoxins: e.g. Petrochemicals

✓ Steatosis accompanying other forms of liver disease
Fatty Liver at US or alteration of LE

Exclude HBV and HCV infection and other causes of liver diseases

Evaluate with accuracy alcohol intake

Alcohol intake < 20 g/day
- NAFLD

Alcohol intake > 20 g/day
- AFLD

Insulin resistance (Metabolic Syndrome)
Components of the Metabolic Syndrome

- NAFLD
- Obesity
- Hypertension
- Hyperlipidemia
- Diabetes and Insulin Resistance
Similar entities: different names and acronyms

NASH Non Alcoholic Steatohepatitis
ASH Alcoholic steatohepatitis
BASH Both alcoholic and non alcoholic steatohepatitis
DASH Drug induced steatohepatitis
CASH Chemotherapy associated steatohepatitis
PASH PNPLA3 associated steatohepatitis
NAFLD/NASH Prevalence

Diagnosis ? Different series...
- Liver Biopsy
- Post-mortem studies
- Cryptogenic cirrhosis
- Surrogate alteration LFT (GGT, ALT, etc.)
- Surrogate indexes (FLI, USFLI)
## Italy: The Dionysos Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Liver disease Prevalence</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Among exposed</td>
</tr>
<tr>
<td>HCV</td>
<td>3,2% (221/6917)</td>
</tr>
<tr>
<td>HBV</td>
<td>1,2% (83/6917)</td>
</tr>
<tr>
<td>Alcohol*</td>
<td>21% (1349/6917)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>25% (1729/6917)</td>
</tr>
</tbody>
</table>

*Risk threshold for developing liver disease (> 30 gr/day x both sexes)

Bellentani S et al, Dig Dis 2010
Bedogni G et al, Hepatology 2005
Bellentani S et al, Gut 1999
Bellentani S et al, Gut 1997
Bellentani S et al, Hepatology 1994
THE GLOBAL PREVALENCE OF NAFLD

- Pubmed and MEDLINE databases were searched from 1989-2015 for terms involving epidemiology and progression of NAFLD.
- Out of 729 studies, 86 were included with a sample size of 8,515,431 from 22 countries.
- Global prevalence of NAFLD is **25.24% (22.10-28.65)** with highest prevalence in Middle East and South America and lowest in Africa.

Prevalence of NAFLD as a function of obesity in different part of the world

From Lazo et al. Semin.Liver Dis., 2008 modified
PREVALENCE OF NAFLD/NASH IN DIFFERENT POPULATIONS

Lonardo A, Bellentani S, et al., DLD 2015
Prevalence NASH and advanced fibrosis in children/adolescents

<table>
<thead>
<tr>
<th>Time Intervals</th>
<th>NAFLD P (%)</th>
<th>NASH P (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998-1994</td>
<td>3.3</td>
<td>0.74</td>
</tr>
<tr>
<td>1999-2004</td>
<td>8.8</td>
<td>3.1</td>
</tr>
<tr>
<td>2005-2010</td>
<td>10.1</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Selvakumar et al.: AASLD 2016 Abstr. n. 202
ECONOMIC BURDEN OF NAFLD/NASH

• In the US, over 64 million people with NAFLD, with annual direct medical costs of about $103 bn [$1,613 PP].

• In EU-4 countries ~52 million people with NAFLD with an annual cost of about € 35 billion (€ 354 to € 1,163 PP)

• Costs are highest in patients aged 45-65.

• Burden is higher when societal costs are included.

PREVALENCE OF NAFLD/NASH
TAKE HOME MESSAGES 1

The global average prevalence in general population:
ADULTS NAFLD=25-30%, NASH (20% of NAFLD =5-6%),
CHILDREN NAFLD=8-10%, NASH=2-5%

• Increases with age;
• Higher in males vs female;
• Higher in Caucasian and Hispanic;
• Increase trends in time (Big epidemic public health burden in the next future !)
PREVALENCE OF NAFLD/NASH
TAKE HOME MESSAGES 2

• About one fourth of world’s population have NAFLD

• The subgroup of NASH (5-6%) is progressive in 20-30% of the cases to cirrhosis/HCC

• In the US, NASH is the second leading indication for liver transplantation

• NAFLD is higher in patients with hyperthension, diabetes or alteration of lipid metabolism

• The economic and public health burden of NAFLD is enormous and increasing
RISK FACTORS FOR NAFLD/NASH

Lonardo A, Bellentani S, et al., DLD 2015
EATING HABITS MODIFIES THE RISK OF NAFLD

Consuming a greater percentage of the daily calories in the morning decreased the odds of steatosis by 14% and 21%. Conversely, the odds of steatosis were 20% greater when morning and midday meals were skipped or when meals were consumed late in the night (73%). Late eating also increased the probability of developing significant fibrosis (61%).

CONCLUSIONS: Eating breakfast and lunch, and avoiding Latenight meals, reduce the risk of NAFLD

Esteban J et al., AASLD 2016 Abstr. n. 34
Prevalence of NAFLD/NASH is higher in:

- Obese subjects (36-78%)
- Pts. with hyperglycemia or diabetes (43-62%)
- Pts. with hyperlipemia (45-65%)
- Pts. with hypertension (35-45%)
- Pts. with metabolic syndrome
- Pts. with HCV infection (55%)
- Pts. consuming artificial fructose in the diet (soft drinks and junk food) and NOT consuming coffee
- Pts. consuming late-night meals and skipping breakfast and lunch

RISK FACTORS OF NAFLD
TAKE HOME MESSAGES
NAFLD: main causes of mortality

Extrahepatic malignancies (28 % of all causes)
- Breast and ovarian cancer (lifestyle, obesity, hormonal status)
- Colorectal cancer (lifestyle, production of adipokines)

Ischemic heart diseases (25 % of all causes)

Liver-related diseases (13% of all causes)

Musso G et al; Ann Med 2011
Progression of fibrosis in NASH

Time estimation for development of cirrhosis:
From NASH: 28 ys, from FL: 57 ys

Singh, Clin Gastroenterol Hepatol 2015
Progression of fatty liver and increased incidence of cardiovascular disease and HCC

- ↑ Insulin
- ↑ Hepatocyte proliferation
- ↑ ROS damage
- ↑ Hepatocyte turnover

Genotype
Maldpt. Resp.
Soft drinks
Fructose
Smoke
Aging
Obesity/ T2DM
Met Syndrome
Sedentary lifestyle
Poor dietary habits

Targher G et al. NEJM 2010
Miele L et al. Gastroenterology 2008
Miele L et al. Hepatology 2009
Miele L et al. J Hepatol 2009
Miele L et al. Gut 2001
Beale G, Miele L et al. BMC Cancer 2009
THE BURDEN OF NAFLD/NASH AND NASH-RELATED CIRRHOSIS AND PREVALENCE OF HCC IN THE GENERAL POPULATION
CLINICAL PATTERNS OF HEPATOCELLULAR CARCINOMA (HCC) IN NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD): A MULTICENTER PROSPECTIVE STUDY

756 patients with either HCC-NAFLD (145) or HCC-HCV (611) were enrolled in Secondary Care Italian Centers.

RESULTS  

HCC-NAFLD vs HCC-HCV:

• Significantly increased volume, more often an infiltrative pattern
• Cirrhosis was present in only about 55% vs 95% in HCC-HCV
• Propensity score analysis showed no significant difference in survival.
• Additionally, no difference in survival between the 2 groups in patients within Milan criteria (38.6 vs 41.0 months, p=n.s.)

NAFLD/NASH warrants screening for cardiovascular diseases (proved increased mortality !!), colorectal and breast cancer, and progressive liver disease.

Progression to cirrhosis/HCC is slow.

HCC-NASH is associated with lifestyle risk factors and with metabolic diseases (obesity, diabetes, etc.).

HCC-NASH could develop in the absence of cirrhosis (45%).

Survival of treated HCC-NAFLD is similar to treated HCC-HCV.

Prevention and surveillance strategies for HCC-NAFLD are lacking.
THE FUTURE:
Modeling NAFLD in Italy and US
April, 2016
Relative Incidence of NAFLD (Italy)

- An estimated 13.6 million NAFLD cases in 2015 will increase to 16.2 million by 2030.
- An estimated 2.5 million NASH cases in 2015 will increase to 3.8 million by 2030.
The Hepatologist Menu - 2017

- HCV
- NAFLD
- HEREDITARY
- AUTOIMMUNE
- HBV
- ALCOHOL
The Hepatologist Menu - 2030

- NAFLD/NASH
- AUTOIMMUNE
- HCV
- HBV
- HEREDITARY
- ALCOHOL

NEW THERAPY !!!
ARE WE READY TO CHANGE FROM A NEGATIVE DEFINITION (=NASH) TO A POSITIVE ONE ?

An International Consensus event is needed with these priorities:

1- Change the name from NASH to MESH (MEtabolic Steato Hepatitis) ? or simply Dis-metabolic Chronic Hepatitis (DCH).

2- Develop new protocols for the diagnosis, treatment of patients with NASH and new policies for the surveillance of patients with NASH at risk to progress to cirrhosis and HCC.
THANK YOU VERY MUCH FOR YOUR ATTENTION!

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