Epidemiology of NAFLD in Europe

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The Hepatologist Menu - 2023

- NAFLD
- HCV
- ALCOHOL
- HBV
- AUTOIMMUNE

NEW THERAPY !!!
<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Liver disease Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Among exposed</td>
</tr>
<tr>
<td><strong>HCV</strong></td>
<td>3,2%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>(221/6917)</td>
<td>(110/221)</td>
</tr>
<tr>
<td><strong>HBV</strong></td>
<td>1,2%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>(83/6917)</td>
<td>(21/83)</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>21%</td>
<td>5,5%</td>
</tr>
<tr>
<td>*</td>
<td>(1349/6917)</td>
<td>(74/1349)</td>
</tr>
<tr>
<td><strong>NAFLD</strong></td>
<td>25%</td>
<td>7,9-11,9%</td>
</tr>
<tr>
<td></td>
<td>(1729/6917)</td>
<td>(138-207/1729)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></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
CHRONIC LIVER DISEASES ETIOLOGIES: PAST, PRESENT AND FUTURE

![Bar chart showing the change in etiologies from 1990 to 2030]

- **1990**: 80% Viral, 25% Onco, 4% Metabolic
- **2010**: 70% Viral, 25% Onco, 13% Metabolic
- **2030**: 80% Viral, 20% Onco, 25% Metabolic
NAFLD wide spectrum ranging from fatty liver to nonalcoholic steatohepatitis (NASH) that may progress to cirrhosis and end-stage liver disease.
Forms and aetiology of NAFLD

✓ “Primary” NAFLD: 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

Exlude HBV and HCV infection and other causes of liver diseases

Evaluate with accuracy alcohol intake

Alcohol intake \( \leq 20 \text{ g/day} \)
- NAFLD

Alcohol intake \( > 20 \text{ g/day} \)
- Insulin resistance (Metabolic Syndrome)
- AFLD
Fatty Liver in the Dionysos Study

Prevalence
FL = 58.3%

PREVALENCE OF IN THE GENERAL POPULATION IN ITALY:
NAFLD = 25-30%
NASH = 2-3%

Systematic review: the epidemiology and natural history of NAFLD and NASH in adults

General population

- Incidence 0.2-10%
- Prevalence 3-50%
- Large heterogeneity !!

Vernon et al APT 2011
35,781 primary LT in the US from 2001–2009
1959 for NASH

- NASH increased from 1.2% in 2001 to 9.7% in 2009
- 3rd most common indication for LT in the US

Charlton, Gastroenterology 2011
Prevalence of NAFLD as a function of obesity in different part of the world

From Lazo et al. Semin.Liver Dis., 2008 modified
EPIDEMIOLOGY OF NAFLD IN USA

• The prevalence of NAFLD in USA is 22%

• Patients with NAFLD have higher overall mortality than control patients

• Most deaths were due to cardiovascular events

• The independent predictors of mortality in patients with NAFLD are male sex, older age, increased waist circumference, and low high-density lipoprotein levels

• Serum alanine aminotransferase (ALT) levels and the presence of metabolic syndrome are not predictive of mortality

## Prevalence of NAFLD in High-Risk Populations in Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Diabetes (%)</th>
<th>Obesity (%)</th>
<th>Dyslipidaemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>40-50</td>
<td>50-80</td>
<td>42-58</td>
</tr>
<tr>
<td>China</td>
<td>35</td>
<td>70-80</td>
<td>57</td>
</tr>
<tr>
<td>South Korea</td>
<td>35</td>
<td>10-50</td>
<td>26-35</td>
</tr>
<tr>
<td>India</td>
<td>39-90</td>
<td>15-20</td>
<td>Not reported</td>
</tr>
<tr>
<td>Indonesia</td>
<td>52</td>
<td>47</td>
<td>56</td>
</tr>
</tbody>
</table>

## Prevalence of NAFLD in Europe

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>Case Identific.</th>
<th>Prevalence NAFLD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 EU Countries</td>
<td>FLI*</td>
<td>33% <em>adults</em></td>
<td>Gastaldelli et al., Hepatol., 2009</td>
</tr>
<tr>
<td>Germany</td>
<td>US and LE</td>
<td>2% (36% in obese children)</td>
<td>Imhof et al., Eur.J.Epidemiol., 2007</td>
</tr>
<tr>
<td>Germany</td>
<td>US</td>
<td>30% <em>adults</em></td>
<td>Haring et al., Hepatol., 2009</td>
</tr>
<tr>
<td>Greece</td>
<td>Histology</td>
<td>31% <em>adults</em></td>
<td>Zois et al., WJG, 2010</td>
</tr>
<tr>
<td>Italy</td>
<td>US</td>
<td>26% <em>adults</em></td>
<td>Bedogni et al., Hepatol., 2007</td>
</tr>
<tr>
<td>Italy</td>
<td>US</td>
<td>12.5% (adolescents)</td>
<td>Caserta et al., Am.J.Epidemiol., 2010</td>
</tr>
<tr>
<td>Italy</td>
<td>US</td>
<td>69.5% (diabetic pts)</td>
<td>Targher et al., Diabetes Care, 2007</td>
</tr>
<tr>
<td>Romania</td>
<td>US</td>
<td>20% <em>adults</em></td>
<td>Radu et al., J.Gastroint.Liver Dis., 2008</td>
</tr>
<tr>
<td>Spain</td>
<td>US</td>
<td>25.8% <em>adults</em></td>
<td>Caballeira et al., Eur.J.Gastroint.Hepatol., 2010</td>
</tr>
<tr>
<td>UK</td>
<td>US</td>
<td>46.2% (diabetic pts)</td>
<td>Williamson et al., Diabetes Care, 2011</td>
</tr>
</tbody>
</table>

* GGT, TG, BMI and WC
## Prevalence of NAFLD in East and West Part of the World

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>East</th>
<th>West</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>10-20%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Rural vs Urban</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prevalence of obesity</td>
<td>Low but rising</td>
<td>High</td>
</tr>
<tr>
<td>Prevalence in type 2 diabetes</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>NAFLD in those with normal weight</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Natural history data</td>
<td>Limited data</td>
<td>Cohort studies</td>
</tr>
</tbody>
</table>

PREVALENCE OF NAFLD: TAKE HOME MESSAGES

• **General population:**
  • 12–20% in children

• 20–33% in adults - average 25%
  • Increases with age;
  • Higher in males vs female;
  • Higher in Caucasian and Hispanic;
  • Not significantly higher in subjects with alteration of ALT vs normal
PREVALENCE OF NAFLD
TAKE HOME MESSAGES

Selected population

- 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: the risk of progression vs more severe stages of chronic liver disease is significantly increased
  - Pts. with HCV infection (55%)
- NAFLD is associated to insulin-resistance and is now considered the hepatic manifestation of the metabolic syndrome
Incidence of NASH in living liver donors according to liver enzymes (n= 589)

Normal AST, ALT
NASH: 2.1%

Raised AST, ALT
NASH: 3.4%

Lee JY, J. Hepatol. 2007
INCIDENCE OF NASH
TAKE HOME MESSAGES

• By extrapolation of data available in autopsy and liver biopsy studies (few !!):

  • 10-15% of people with NAFLD, equivalent to 2-4% of the general population may have NASH, thus a progressive chronic liver disease to cirrhosis and HCC
Risk factors for NAFLD/NASH

Risk factors for NAFLD/NASH are similar in all countries:

- The most documented one is obesity (BUT 30% of obese have not NAFLD) especially visceral obesity (WC)
- Age > 45 (risk factors increase with age)
- Male sex
- Hypertension
- Hyperlipidaemia
- Diabetes type 2 or IR
- Metabolic syndrome
- Fructose in the diet
- Grade of inflammation at initial biopsy
Risk factors for NAFLD/NASH

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- Age > 45 (risk factors increase with age)
- Male sex
- Hypertension
- Hyperlipidaemia
- Diabetes type 2 or IR
- Metabolic syndrome
- Fructose in the diet
- Grade of inflammation at initial biopsy
Components of the Metabolic Syndrome

- NAFLD
- Obesity
- Hypertension
- Hyperlipidemia
- Diabetes and Insulin Resistance
Risk factors for NAFLD/NASH are similar in all countries:

- The most documented one is obesity (BUT 30% of obese have not NAFLD) especially visceral obesity (WC)
- Age > 45 (risk factors increase with age)
- Male sex
- Hypertension
- Hyperlipidaemia
- Diabetes type 2 or IR
- Metabolic syndrome
- Fructose in the diet
- Grade of inflammation at initial biopsy
HFCS consumption
Energy consumption of fructose from sweetened beverages in patients with NAFLD was estimated as 356 kcal /day compared with 170 kcal /day in control patients with non-steatotic livers (p<0.05).

Ouyang X et al. J.Hepatol., 2008
Industrial, not Fruit Fructose Intake is Associated with the Severity of Liver Fibrosis in Genotype 1 Chronic Hepatitis C Patients

Salvatore Petta, Giulio Marchesini, Linda Caracausi, Fabio Salvatore Macaluso, Calogero Cammà, Stefania Ciminnisi, Daniela Cabibi, Rossana Porcasi, Antonio Craxì, Vito Di Marco
Risk factors for NAFLD/NASH

The most documented one is obesity (BUT 30% of obese have not NAFLD) especially visceral obesity (WC)

Age > 45 (risk factors increase with age)

Male sex

Hypertension

Hyperlipidaemia

Diabetes type 2 or IR

Metabolic syndrome

Fructose in the diet

Grade of inflammation at initial biopsy
Lack of advanced fibrosis stratified by initial biopsy inflammation grade (metanalysis>: 221 pts; 10 studies)

INFLAMMATION RR= 2.4-5.7

The risk of NASH to evolve in fibrosis/cirrhosis depends critically on initial stage of inflammation
NAFLD
12 - 40%
NASH and/or F1-F2 fibrosis
8%
Advanced (F3) fibrosis
13%
Cirrhosis
0 - 50%
Liver Death
Liver transplantation
25-50%
HCC,
14%
? 7%
CVD
T2DM
“The current body of evidence argues for careful monitoring and evaluation of the risk of cardiovascular disease in all patients with NAFLD. Such patients, especially those with NASH, are candidates not only for early treatment of their liver disease but also for early and aggressive treatment aimed at their associated cardiovascular risk factors, because many patients with more severe forms of NAFLD will have major cardiovascular events and will ultimately die from cardiovascular disease before advanced liver disease develops”.

Targher et al., NEJM, 2010
NAFLD AND CVD: SUMMARY

Insulin resistance “per se” is enough to induce dislipidaemia and atherosclerosis in the experimental animal.

In man NAFLD is associated with:

1- Disfunction of endotelium
2- Alteration of surrogate markers of atherosclerosis
3- Alteration of the energetic metabolism of left ventricolum
4- Increased of expression of inflammation mediators

Ratziu V, Bellentani S et al. EASL NAFLD/NASH Position Paper  J.Hepatol., 2010
TAKE HOME MESSAGES

• Given the strong association of NAFLD with metabolic syndrome and the worldwide epidemic of obesity, the prevalence of NAFLD and NASH are increasing (Public health issue)

• NAFLD warrants screening for cardiovascular diseases (proved increased mortality !!) and progressive liver disease

• 10-15% of people with NAFLD (2-4% of the general population) may have NASH, thus a progressive chronic liver disease leading to cirrhosis and HCC
THE BURDEN OF NAFLD/NASH AND NASH-RELATED CIRRHOSIS AND PREVALENCE OF HCC IN THE GENERAL POPULATION

General population

NAFLD 25-30%

NASH 3-10%

Cirrhosis 2-3%

HCC incidence: 0.5-1%/year

0 - 2.8%

4 - 27%
**Italian HCC/NASH observatory:**
*Risk Factors for HCC in NASH are Metabolic*

<table>
<thead>
<tr>
<th>Age, sex, mortality</th>
<th>Mean ± SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN (n=127; 78%)</td>
<td>68.2 ± 8.2</td>
<td>68.8</td>
</tr>
<tr>
<td>WOMEN (n=35; 22%)</td>
<td>68.4 ± 10.5</td>
<td>70.2</td>
</tr>
<tr>
<td>Total (n=162)</td>
<td>68.2 ± 8.7</td>
<td>69.0</td>
</tr>
</tbody>
</table>

M/F ratio = 3.6; 9.6 % MORTALITY/YEAR; 13.2% per year Males vs 4.7% per year Females, p<0.05

At univariate and multivariate analysis major and significant risk factors were:
- Male sex
- Presence of diabetes, MS or dislipidemia
- Increase of GGT
### Italian HCC/NASH observatory:

**HCC in NASH is often not associated with cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>WC</th>
<th>Total Nodule size (mm)</th>
<th>Nodules number</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN (127)</td>
<td>29.2 ± 4.3</td>
<td>105.6 ± 12.1</td>
<td>52 ± 34</td>
<td>2.0 ± 1.7</td>
</tr>
<tr>
<td>WOMEN (35)</td>
<td>29.4 ± 6.3</td>
<td>97.8 ± 19.4</td>
<td>43 ± 36</td>
<td>1.3 ± 0.9*</td>
</tr>
<tr>
<td>TOTAL (162)</td>
<td>29.2 ± 4.8</td>
<td>103.8 ± 14.2</td>
<td>50 ± 34</td>
<td>1.8 ± 1.5</td>
</tr>
</tbody>
</table>

* p< 0.05

68 out of the 162 patients enrolled underwent liver biopsy or histology (42%) and of these only 25 (= 37%) had CIRRHOSIS
CONCLUSION

- **Cirrhosis was not always present**: 63% (94/162) of patients developed HCC without cirrhosis.
- **The number of HCC nodules** was significantly higher in males vs females.
- **Mortality rate per year** was significantly higher in males vs females.
- Patients with cirrhosis vs non-cirrhosis tended to be similar in age, BMI, WC, gender ratio, but different in:
  - Number of nodules (Higher)
  - Size of nodules (Higher)
HCC-NASH : Specific Distinct Features

1. The tumor develops in the context of well-known metabolic and lifestyle risk factors (and not environmental).

2. The tumor is strictly associated with metabolic diseases (obesity, diabetes, etc.), but not necessarily with the presence of cirrhosis.

3. The mortality rate is higher in males vs females.

4. The size and number of HCC nodules are higher when cirrhosis is not present.

5. Prevention and surveillance strategies are lacking.

6. The current guidelines for the management of HCC have no specific recommendations for HCC associated with NASH.
EPIDEMIOLOGY OF NAFLD IN EUROPE

• The prevalence of NAFLD is 20-33% in the adult general European population

• The prevalence of NAFLD in the children population is 2-12.5%

• The prevalence of NAFLD is higher in obese children and adults (36-70%)

• The prevalence of NAFLD is higher in people with type 2 diabetes (42.6-69.5%)

• There is the potential for this condition to become a serious problem in light of the obesity epidemic

• This liver disease is amenable to prevention and treatment

• Strategies are urgently required to reduce the burden of liver disease and of NAFLD in Europe
Fibrosis progression is absent or minimal in simple steatosis, but it is present in more than 1/3 of patients with NASH.

Final stage of NASH is the most frequent cause of cryptogenic cirrhosis.

NASH significantly increase general mortality, liver-related mortality and cardiovascular mortality.

HCC could develop both in NASH-cirrhosis, and in NASH without cirrhosis (50-60% of the cases), therefore the surveillance and prevention strategy (by ultrasound) should be revisited.

All the patients with NAFLD should be screened for the cardiovascular risk and this risk should be calculated every 1-2 years.

Ratziu V et al. EASL NAFLD/NASH Position Paper  J. Hepatol., 2010
NAFLD AND NASH IN THE REAL LIFE: Awareness, opinions, and management
Management of chronic liver disease by general practitioners in Southern Italy: Unmet educational needs

Carmela Loguercio<sup>a</sup>,<sup>*</sup>, Angelo Tiso<sup>a</sup>, Gaetano Cotticelli<sup>a</sup>, Camillo Del Vecchio Blanco<sup>a</sup>, Giovanni Arpino<sup>b</sup>, Matteo Laringe<sup>b</sup>, Luigi Napoli<sup>b</sup>, Gaetano Piccinocchi<sup>b</sup>, Leonilde Bonfrate<sup>d</sup>, Ignazio Grattagliano<sup>c</sup>, Enzo Ubaldi<sup>c</sup>, Piero Portincasa<sup>d</sup>

<sup>a</sup> Interuniversity Center for Research on Food, Nutrition and Digestive Tract, Gastroenterology School Second University, Naples, Italy
<sup>b</sup> COMEGEN, Naples, Italy
<sup>c</sup> Italian College of General Practitioners, Florence, Italy
<sup>d</sup> Clinica Medica "A. Murrì", Department of Internal and Public Medicine, University of Bari, Italy

Aim:

To assess the management of chronic liver diseases by general practitioners in a large area of Southern Italy.

Methods: This was a 5-year retrospective analysis from 104 physicians in charge of a population of 143,159 adult subjects.
Management of chronic liver disease by general practitioners in Southern Italy: Unmet educational needs

Carmela Loguerco, Angelo Tiso, Gaetano Cotticelli, Camillo Del Vecchio Blanco, Giovanni Arpino, Matteo Laringe, Luigi Napoli, Gaetano Piccinocchi, Leonilde Bonfante, Ignazio Grattagliano, Enzo Ubaldo, Piero Portincasa

Results:

Amongst 6550 patients with chronic liver disease (4.7%, 3400 M, median age 57 years), 1330 (20.3%) had HCV infection, 226 (3.4%) HBV infection, and 293 (4.5%) liver cirrhosis (25 alcohol-related).

Hypertransaminasemia and liver steatosis had a prevalence of 6.7% and 2.4%, respectively.

Although transaminases were checked 3 times over 5 years in 80% of cases, few patients were investigated for viral infection, and less than 50% underwent ultrasonography and consultation, leaving undefined a consistent number of cases.

Alcohol consumption, body mass index and ultrasonography were poorly checked even in hypertransaminasemic patients.
Methods

56 GPs filled a questionnaire before and after attending a tailored workshop on NAFLD, and performed a clinical survey in patients with persistent hypertransaminasemia including screening and liver biopsy when indicated.

Four months after a training workshop, GPs were questioned again about their practice changes with NAFLD.
Improving Nonalcoholic Fatty Liver Disease Management by General Practitioners: a Critical Evaluation and Impact of an Educational Training Program

Ignazio Grattagliano1,2, Gaetano D’Ambrosio1, Vincenzo O. Palmieri3, Antonio Moschetta2, Giuseppe Palasciano1, Piero Portincasa2 and the “Steatostop Project” Group*
Methods
current beliefs and practices regarding NAFLD was administered to specialists and specialists-in-training across six specialties (internal medicine, cardiology/cardiac surgery, endocrinology, thoracic medicine, rheumatology and nephrology).
Results: 100 clinicians were surveyed with 99% returning completed questionnaires (>89% questions answered).
- 75% of respondents believe the prevalence of NAFLD in the general population to be ≤ 10% although 2/3 feel that its incidence will rise markedly.
- >90% appreciate that traditional cardiovascular risk factors (obesity, hyperTG and T2D) are risk factors for NAFLD and acknowledge that these are common in non-hepatology patients. Despite this, most believe that NAFLD uncommon in their own patients (89% indicated a prevalence ≤ 30%)
- 93% agree that NASH is associated with increased overall mortality, but 60% also believe that simple steatosis confers increased liver-related mortality.
- 74% agree that a diagnosis of NASH cannot be made using liver enzymes, but 67% support 6-monthly liver function tests as the most effective way to monitor progression of NAFLD.
- 71% make no referrals to hepatology
Survey assessing the clinical burden, perceived severity, and management patterns of NAFLD among 352, board-certified, Hepatogastroenterologists in France.

Most NAFLD patients were referred by GPs and only 20% by specialists. Conversely, 87% of hepatologists referred NAFLD patients for specialistic evaluation of potential co-morbidities.

65% would diagnose NASH irrespective of the concurrent CLD due to other etiology if MRFs were present.

No agreement on the threshold of daily alcohol consumption that rules out NASH.

Most physicians would over-rate the importance of raised transaminases for the diagnosis of NASH.

22% did not measure waist circumference.

73% monitored NAFLD patients themselves; most with yearly US and only 16% with fasting insulin/HOMA.

72% of patients were treated with non-pharmacological measures, often following referral to the endocrinologist/ nutritionist. 42% recommended total abstinence from alcohol.

Drugs treatment (metformin, UDCA, venesection, glitazones and vitamin E) was prescribed in only 28% of NAFLD patients.

THANK YOU VERY MUCH FOR YOUR ATTENTION!

Stefano Bellentani, MD, PhD
bellentanistefano@gmail.com