NON-ALCOHOLIC STEATOHEPATITIS
UNDERSTANDING NASH, A MAJOR PUBLIC HEALTH ISSUE
Non-alcoholic steatohepatitis, or NASH, is a chronic liver disease characterized histologically by the presence of hepatic inflammation and cell injury (hepatocellular ballooning) due to hepatic fat accumulation (steatosis) of 5% or more. NASH develops in the absence of excessive alcohol consumption but is linked to unhealthy eating habits and lack of physical activity. It is often referred to as metabolic disease of the liver.

Patients with NAFLD having concomitant obesity and metabolic syndrome features such as insulin resistance, type 2 diabetes mellitus, hypertension and dyslipidemia, are at higher risk of progression to NASH.

NASH is associated with increased cardiometabolic risk, and is related to higher risk of death caused by cardiovascular events.

The most serious form of NAFLD

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term that encompasses the spectrum of fatty liver disease, from isolated steatosis to NASH. NASH is associated with higher cardiovascular risk and increased fibrosis which may lead to cirrhosis and liver cancer. 

A complex metabolic disease
NASH is usually discovered incidentally through imaging, surgery or liver enzyme tests performed for unrelated reasons. While patients can show non-specific symptoms such as fatigue, daytime tiredness or abdominal pain early in the disease, NASH-specific symptoms are usually not visible until the decompensated cirrhosis stage. It is predicted that NASH will become the leading cause of liver transplantation by 2020 in the United States.

NASH is a silent epidemic

- NASH is usually discovered incidentally through imaging, surgery or liver enzyme tests performed for unrelated reasons.
- While patients can show non-specific symptoms such as fatigue, daytime tiredness or abdominal pain early in the disease, NASH-specific symptoms are usually not visible until the decompensated cirrhosis stage.
- It is predicted that NASH will become the leading cause of liver transplantation by 2020 in the United States.

NASH is a driver of fibrogenesis

- As NASH evolves, it can result in excessive scarring in the liver (fibrosis), a natural response to injury which can lead to end-stage liver diseases such as cirrhosis or hepatocellular carcinoma.
- Hepatocellular ballooning and inflammation are commonly considered as the drivers of fibrogenesis, and as the underlying causes of the disease progression.
- In patients with NASH, the worsening of liver fibrosis which is scored from F0 to F4 is highly correlated with an increase of liver-related mortality.
- Improvement in NASH activity (inflammation and hepatocellular ballooning) is highly correlated with fibrosis regression.

KEY FACTS ABOUT NASH
**NATURAL HISTORY OF NASH**

**Isolated Fatty Liver:**
1- None to very minimal progression to fibrosis and to cirrhosis
2- No increased risk of death compared with the general population

1- Increased risk of death compared with general population.
   In order: 1- Cardiovascular  / 2- Malignancy / 3- Liver related
2- NASH with fibrosis leads to worse prognosis
   Fibrosis progression a/w DM, severe IR weight gain > 5kg,
   rising ALT, AST

1- Increased risk of death compared with general population.
   Cardiovascular / Malignancy / Liver related
2- NASH with fibrosis leads to worse prognosis
   Fibrosis progression a/w DM, severe IR weight gain > 5kg,
   rising ALT, AST

**HCC:**
~7.2% over 6.5 years

**Decompensation:**
~19-45% over 7-10 years

**Adverse lifestyle habits can lead to non-alcoholic fatty liver (NAFL) with isolated steatosis,** defined as an abnormal accumulation of fat in the hepatocytes.

**In people with NASH, liver homeostasis is impaired due to an accumulation of toxic lipids.** Certain gut bacteria-derived products can also penetrate the liver, where they activate immune responses. This contributes to local inflammation of hepatic tissue. This pathological environment provokes hepatocellular damage and leads to a state called ballooning. Steatosis, inflammation and ballooning are the three lesions that define NASH histologically.

**Hepatocellular damage, apoptosis and inflammation leads to the release of signaling molecules that contribute to the activation of hepatic stellate cells.** As a result, hepatic stellate cells secrete collagen fibers that form scar tissue, leading to hepatic fibrosis. NASH can evolve to cirrhosis (fibrosis stage F4) or hepatocellular carcinoma.
NAFLD prevalence in the general population has been estimated in several studies using different methodologies. In a meta-analysis conducted over 22 countries, worldwide prevalence of NAFLD was estimated at 25.2%.

- **31.8%** Middle Eastern countries
- **30.5%** South America
- **27.4%** Asia
- **24.1%** North America
- **23.7%** Europe
- **13.5%** Africa

**Worldwide**: 25.2%

Meta-analysis, 86 studies included with a sample size of 8,515,431 adults from 22 countries.

**United States**: 34%

Analysis of NHANES database, including 12,317 individuals.
PREVALENCE OF NAFLD BY ETHNICITY IN THE UNITED STATES

Prospective study enrolling 328 patients in Texas, age range: 28-70, mean age: 54.6 years. 

- 58.3% Hispanics
- 44.6% Caucasian
- 35.1% African American
NAFLD has become a leading cause of chronic liver disease in children and adolescents from developed countries\textsuperscript{10}.

There is a growing number of studies in pediatric populations, and they report a significant increase of NAFLD prevalence in children and adolescents over the last few decades\textsuperscript{11,12} with prevalence of NAFLD ranging from 3% to 10% in a general pediatric population and up to 70% in an obese population.
The exact prevalence of NASH in an adult population remains difficult to assess due to a lack of cost-effective and widely available minimally-invasive diagnostic test, and to the absence of specific symptoms before end-stages of the disease.

The prevalence of NASH is expected to increase by 63% between 2015 and 2030 in relation to the worldwide increase of diabetes and obesity.¹³

1,5-6,45%
Worldwide

Meta-analysis, 86 studies included with a sample size of 8,515,431 adults from 22 countries⁷

12,2%
United States

Prospective study enrolling 328 patients in Texas, age range: 28-70, mean age: 54.6 years⁸
PREVALENCE OF NAFLD/NASH AMONG PATIENTS WITH TYPE 2 DIABETES*

NAFLD: 65% to 70%\textsuperscript{14}

NASH: 25-30%\textsuperscript{15}

TRENDS IN TYPE 2 DIABETES: +55% increase of adults with diabetes worldwide by 2035 (592 million individuals affected in 2035 vs. 382 million in 2013)\textsuperscript{16}

* The above estimations of NAFLD/NASH prevalence are based on data found in the cited reviews. The existing data vary depending on the study design (diagnostic tools used, characteristics of the population - e.g. age, BMI, bariatric surgery, hospitalization, state…).
PREVALENCE OF NAFLD/NASH AMONG PATIENTS WITH OBESITY*

NAFLD: 70% or more\textsuperscript{17}

NASH: 25-30%\textsuperscript{15}

TRENDS IN OBESITY: 47\% of adults affected by obesity in US population by 2030\textsuperscript{18} vs. 39,8\% in 2015-2016\textsuperscript{19}

* The above estimations of NAFLD/NASH prevalence are based on data found in the cited reviews. The existing data vary depending on the study design (diagnostic tools used, characteristics of the population - e.g. age, BMI, bariatric surgery, hospitalization, state…).
RISK FACTORS WHEN DECIDING WHO TO SCREEN

Well-established risk factors\textsuperscript{20,21}

- Ethnicity
- Genetic variation related to PNPLA3
- Obesity
- Type 2 Diabetes
- Dyslipidemia
- Hypertension
- Insulin resistance
- ALT and AST level
- Metabolic syndrome*

Emerging conditions that are associated with NAFLD\textsuperscript{20}

- Obstructive sleep apnea
- Colorectal cancer
- Osteoporosis
- Psoriasis
- Endocrinopathies
- Hypothyroidism
- Polycystic ovary syndrome independant of obesity

*Any three of the five features: impaired fasting glucose; raised triglyceride level; low HDL; increased waist circumference; high blood pressure
OUTCOMES

NAFLD & mortality:
3 main causes of death\(^6\):

1. Cardiovascular disease (38%)
2. Non-hepatic malignancy (19%)
3. Liver-related death (9%)

NAFLD/NASH have been shown to increase the risk of:\(^{21, 1, 23}\)

- Cardiovascular disease
- Hepatocellular carcinoma
- Type 2 diabetes
Studies have shown that patients with NASH have an impaired health-related quality of life (HRQoL) compared to normative populations and NAFLD patients. NASH patients experience a range of symptoms responsible for this HRQoL:

- Fatigue and daytime tiredness
- Body pain/physical pain
- Pain in the upper-right quadrant of the abdomen

In general, patients with NASH have no specific symptoms before the stage of decompensated cirrhosis, when the liver cannot regenerate anymore. The physical signs and symptoms of cirrhosis include:

- Irregular sleep patterns
- Abdominal discomfort
- Gastrointestinal symptoms
- Hepatic encephalopathy
- Yellowing of the skin and eyes (jaundice)

- Signs of portal hypertension including:
  - Abdominal swelling (ascites)
  - Esophageal varices
  - Enlarged spleen
  - Enlarged blood vessels beneath the skin’s surface
- Red palms
- Prurit
Liver biopsy is considered the gold standard to diagnose NASH, but is an invasive and costly procedure which may cause pain and discomfort to patients, and remains impracticable as part of a standard clinical routine.

Clinical EASL and AASLD guidances recommend use of non-invasive techniques like imaging and blood tests to assess presence of NASH and advanced fibrosis in NAFLD patients.

Liver Function Tests (or LFTs), in conjunction with other risk factors like type 2 diabetes, hypertension and abdominal obesity, can help physicians identify patients at risk for having NASH but are not sufficient to diagnose NASH. Liver enzymes like ALT and AST can indeed be normal in a substantial proportion of patients having NASH or advanced fibrosis.

Non-invasive tests for diagnosing NASH and fibrosis, and particularly blood-based tests, are an area of intensive research although there are currently no minimally-invasive tests approved for NASH and/or fibrosis diagnosis on the market. However, some tests are in advanced stages of development.
## CURRENT RECOMMENDATIONS FOR THE SCREENING OF NAFLD

<table>
<thead>
<tr>
<th>Region</th>
<th>AASLD (AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES)</th>
<th>EASL (EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER)</th>
<th>NICE (NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE)</th>
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<tbody>
<tr>
<td></td>
<td>Region</td>
<td>United States</td>
<td>Europe</td>
</tr>
<tr>
<td>Systematic screening</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Screening in high-risk groups</td>
<td>No*</td>
<td>Yes Obesity</td>
<td>Yes Obesity</td>
</tr>
<tr>
<td></td>
<td>*«Active surveillance» is recommended for T2D patients, but not screening</td>
<td>Metabolic syndrome Abnormal liver enzymes</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Screening modality</td>
<td>Yes liver enzymes</td>
<td>No liver enzymes</td>
<td>Yes ultrasonography</td>
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</table>
There are currently **no approved medications for the treatment of NASH.**

Diet, lifestyle modification and exercise remain the top priorities and recommendations for patients.

**Ultimate goal is to achieve and sustain weight loss of 7% to 10% of bodyweight,** as this has been shown to improve the majority of histopathological features of NASH\(^{20}\).

Because NASH is a chronic and silent disease, therapies should be safe and well tolerated.

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We have developed a guide “NASH: An Explanatory Guide for Patients and their Families” downloadable in: [www.the-nash-education-program.com](http://www.the-nash-education-program.com). It contains a lot of information for your patients to better understand NASH, and tips for lifestyle change.
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