Non-alcoholic steatohepatitis (NASH): Definition, natural history and current therapeutic interventions

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University Hospital Aachen, Germany

EMA Workshop on Liver Diseases
London, Dec 3rd, 2018
Disclosures Frank Tacke

• *Research support (materials, funding):* Tobira/Allergan, Galapagos, Inventiva, BMS

• *Speaker/Consulting:* Tobira/Allergan, Gilead, AbbVie, BMS, Falk, Boehringer, Galapagos, Intercept, Inventiva
Non-alcoholic Fatty Liver Disease: The epidemiological challenge

Total population

20-30% NAFLD (EU: ~116 M)

3% NASH (EU: ~10 M)

0.2%-0.5% HCC (EU 200,000 – 500,000)

HEPAMAP. A roadmap for hepatology research in Europe: An overview for policy makers. EASL 2015

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Projection for Germany

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HEPAMAP. A roadmap for hepatology research in Europe: An overview for policy makers. EASL 2015

Projection for UK

Non-alcoholic Fatty Liver Disease: The clinical challenge

- Old(er) age, high(er) body-mass index
- Many comorbidities (diabetes, kidney, cardiovascular…)
- Substantial proportion unaware of their liver condition
- High(er) rate of malignancies
Non-alcoholic Fatty Liver Disease: The clinical challenge

https://broadly.vice.com
Extrahepatic complications of non-alcoholic fatty liver disease

- Type 2 Diabetes
- Cardiovascular Disease
- Colorectal cancer
- Hypothyroidism
- Osteoporosis
- PCOS (Polycystic Ovary Syndrome)
- OSAS (Sleep Apnea)
- Chronic Kidney Disease

Byrne CD & Targher G, J Hepatol 2015; 62: S47–S64
Management of fatty liver disease: EASL multidisciplinary Clinical Practice Guideline

• Chairs
  – EASL: Giulio Marchesini
  – EASD: Michael Roden
  – EASO: Roberto Vettor

• Panel members
  – EASL: Christopher P Day, Jean-François Dufour, Ali Canbay, Valerio Nobili, Vlad Ratziu, Herbert Tilg
  – EASD: Amalia Gastaldelli, Hannele Yki-Järvinen, Fritz Schick
  – EASO: Gema Frühbeck, Lisbeth Mathus-Vliegen

• Reviewers
  – Elisabetta Bugianesi, Helena Cortez-Pinto, Stephen Harrison
Natural history of fatty liver disease: Definitions of NAFLD, NAFL and NASH

NAFLD
- Excessive hepatic fat accumulation with IR
- Steatosis in >5% of hepatocytes*
- Exclusion of secondary causes and AFLD†

NAFL
- Pure steatosis
- Steatosis and mild lobular inflammation

NASH

Fibrotic
≥F2 to ≥F3 fibrosis

Cirrhotic
F4 fibrosis

HCC

Early
F0/F1 fibrosis

Definitive diagnosis of NASH requires a liver biopsy

*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women

Diagnosis and staging of fatty liver disease: Role of liver biopsy

- Liver biopsy is essential for the diagnosis of NASH
  - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis
- NAFL encompasses
  - Steatosis alone plus **ONE** of lobular or portal inflammation **OR** ballooning
- NASH requires
  - Steatosis **AND**
  - Lobular or portal inflammation **AND**
  - Ballooning
- NAS scoring indicates disease severity*
  *Should not be used for initial diagnosis

**Recommendations**

<table>
<thead>
<tr>
<th>Grade of evidence</th>
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<tr>
<td>NASH has to be diagnosed by a liver biopsy showing <strong>steatosis</strong>, <strong>hepatocyte ballooning</strong> and <strong>lobular inflammation</strong></td>
<td>A</td>
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Diagnosis and staging of fatty liver disease: Role of liver biopsy

normal

NAFLD

NASH

fibrosis

Courtesy of Dr. Thomas Ritz, Institute of Pathology, University Hospital Aachen
Natural history of fatty liver disease: Estimated progression rates

NAFLD / NASH
12–40% NASH
~10% NASH-fibrosis (F3)
30-50% NASH-cirrhosis

NAFLD
0.25-3% /year

NASH-fibrosis
0.3-2.6% /year

cirrhosis
0.04-0.3% /year

HCC
Fibrosis determines the prognosis of non-alcoholic fatty liver disease

- Meta-analysis of 5 studies on fibrosis-related mortality
- 1,495 NAFLD patients with 17,452 patient years of follow-up

**Mortality rate by fibrosis stage**

- All Cause
- Liver Related

**Mortality rate ratio by fibrosis stage**

- All Cause
- Liver Related

PYF, patients years of follow-up
Mortality rate ratio = actual mortality versus expected mortality

Fibrosis determines the prognosis of non-alcoholic fatty liver disease

- 458 NAFLD patients (bridging fibrosis, F3, n=159; Child A5 cirrhosis, n=222; Child A6 cirrhosis, n=77); 4 tertiary centers, mean follow-up 5.5 years
- Deaths: n=37, Liver Transplant: n=37, decompensation: n=88, Liver Cancer (HCC): n=41, Cardiovascular events: n=14, non-liver cancer: n=30

![Graph showing overall survival without transplant over years](image)

<table>
<thead>
<tr>
<th>Years</th>
<th>No. at risk</th>
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<tbody>
<tr>
<td></td>
<td>F3</td>
</tr>
<tr>
<td>0</td>
<td>159</td>
</tr>
<tr>
<td>1</td>
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<td>8</td>
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<td>9</td>
<td>31</td>
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<td>20</td>
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**Fibrosis Severity as a Determinant of Cause-specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease**

*International cohort study*
458 biopsy proven NAFLD

**Bridging fibrosis**
F3 (n=159)

**Liver cirrhosis**
F4 (n=299)

<table>
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<tr>
<th>Cause-Specific Mortality</th>
<th>Annual Incidence</th>
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<tbody>
<tr>
<td>Vascular events</td>
<td>0.9</td>
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<tr>
<td>Non-hepatic cancers</td>
<td>1.2</td>
</tr>
<tr>
<td>All deaths or liver transplantation</td>
<td>2.1</td>
</tr>
<tr>
<td>Decompensation</td>
<td>3.3</td>
</tr>
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<td>HCC</td>
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Risk factors:
- Liver fat <33%
- Moderate alcohol consumption

**CTP**
A5: 11.1
A6: 15.6

**Gastroenterology**

A potential algorithm for risk assessment in non-alcoholic fatty liver disease

- **Hepatic steatosis on imaging ± elevated serum ALT levels**
  - **Evaluate alcohol consumption**
    - **Low-risk profile**
      - BMI < 29.9
      - Age < 40 yrs
      - No T2DM or metabolic syndrome features
      - **Noninvasive fibrosis estimation:**
        - FIB-4 < 1.30
        - APRI < 0.5
        - NFS < -1.455
        - **FibroScan** < 5 kPa
      - Follow and reassess as risk factors evolve
    - **Intermediate-risk profile**
      - BMI > 29.9
      - Age > 40 yrs
      - Multiple features of the metabolic syndrome
      - **Noninvasive fibrosis estimation:**
        - FIB-4 1.30-2.67
        - APRI 0.5-1.5
        - NFS -1.455-0.675
        - **FibroScan** 6-11 kPa
      - Consider liver biopsy
    - **High-risk profile**
      - ALT level > AST level
      - Platelets < 150,000
      - **Noninvasive fibrosis estimation:**
        - FIB-4 > 2.67
        - APRI > 1.5
        - NFS > 0.675
      - **FibroScan** > 11 kPa
      - Consider liver biopsy or confirmatory testing for cirrhosis (eg, MRE)
  - **Confirm NAFLD**
    - Exclude alternate causes of ↑ALT levels

A potential algorithm for risk assessment in non-alcoholic fatty liver disease

EASL-Guideline 2016:
Recommendation for liver biopsy, if NASH or fibrosis is suspected

- NASH has to be diagnosed by a liver biopsy showing steatosis, hepatocyte ballooning and lobular inflammation (A1)

Low-risk profile
- BMI < 29.9
- Age < 40 yrs
- No T2DM or metabolic syndrome features
- Noninvasive fibrosis estimation:
  - FIB-4 < 1.30
  - APRI < 0.5
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Evaluate alcohol consumption

Confirm NAFLD

Exclude alternate causes of ↑ALT levels

Hepatic steatosis on imaging ± elevated serum ALT levels

Follow and reassess as risk factors evolve

Evaluate alcohol consumption

Confirm NAFLD

Exclude alternate causes of ↑ALT levels

Natural history of fatty liver disease: Estimated progression rates

- NAFLD / NASH
  - Progression to NASH-fibrosis: 0.25-3% /year

- NASH-fibrosis
  - Progression to cirrhosis: 0.3-2.6% /year

- Cirrhosis
  - Progression to HCC
  - Risk of developing HCC: 0.04-0.3% /year
Natural history of fatty liver disease: Progression and Regression

NAFLD / NASH

NASH-fibrosis

cirrhosis

HCC

0.25-3% /year

0.3-2.6% /year

0.04-0.3% /year
Progression of fatty liver disease: Relevance of cofactors and lifestyle

**NAFLD / NASH**

**NASH-fibrosis**

**cirrhosis**

**HCC**

**Diabetes**
**Obesity**
**Genetic factors** (PNPLA3, TM6SF2...)
**Age**
**Alcohol**
**Lifestyle**

0.25-3% /year
0.3-2.6% /year
0.04-0.3% /year

**Coffee**
**Exercise**
**Mediterranean diet**
**Vegetables**
Current therapeutic strategies in non-alcoholic fatty liver disease

- Weight reduction (nutrition, GLP1-agonists, bariatric surgery)
- Lifestyle changes
- Optimal diabetes therapy (metformin, GLP1-agonists etc.)
NAFLD Lifestyle Treatment Pyramid

- **Physical activity:***
  - Aerobic & Resistance activity independently:
    - Reduce liver fat
    - NASH and fibrosis – little evidence

- **Dietary composition:**
  - Modifications of diet without weight loss
    - Reduce liver fat
    - NASH and fibrosis – less evidence
    - Reduce risk for HCC?

- **Weight reduction:**
  - Consistently beneficial
    - Steatosis $\geq 5\%$
    - Few studies with histopathology
    - NASH $\geq 7\%$
    - Fibrosis $\geq 10\%$

Lifestyle Modification in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

Energy restriction
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake
- Avoid fructose-containing food and drink

Coffee consumption
- No liver-related limitations

Comprehensive lifestyle approach

Macronutrient composition
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Daily alcohol intake
- Strictly below 30 g men and 20 g women

Physical activity
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

Pharmacological Options in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

- Insulin sensitizers
  - Little evidence of histological efficacy with metformin
  - PPAR\(_\gamma\) agonist pioglitazone better than placebo
    - Improved all histological features except fibrosis
    - Achieved resolution of NASH more often

- Antioxidants
  - Vitamin E may improve steatosis, inflammation and ballooning and resolve NASH in some patients
    - Concerns about long-term safety exist

### Recommendations

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While no firm recommendations can be made, pioglitazone* or vitamin E† or their combination could be used for NASH

The optimal duration of therapy is unknown: in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy‡

*Most efficacy data, but off-label outside T2DM; †Better safety and tolerability than pioglitazone in the short-term; ‡No recommendations can be made in patients with normal baseline ALT

Pharmacological Options in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

- **Insulin sensitizers**
  - Little evidence of histological efficacy with metformin
  - PPARγ agonist pioglitazone better than placebo

- **Antioxidants**
  - Vitamin E may improve steatosis, inflammation and resolve NASH in some patients
  - Concerns about long-term safety exist

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**No drugs are approved for NASH**

No specific therapy can be recommended

Any drug treatment is off label

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Surgical Treatment Options in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

- Bariatric surgery is an option in patients unresponsive to lifestyle changes and pharmacotherapy
  - Reduces weight and metabolic complications
  - Stable results in the long term
- NAFLD-associated cirrhosis is one of the top three indications for LTx

Recommendations for bariatric surgery

Bariatric surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis

Grade of evidence: B
Grade of recommendation: 1

Recommendations for liver transplant

LTx is an accepted procedure in patients with NASH and end-stage liver disease. Overall survival is comparable to other indications, despite a higher cardiovascular mortality. Patients with NASH and liver failure and/or HCC are candidates for liver transplantation

Grade of evidence: A
Grade of recommendation: 1

Therapeutic Targets in Steatohepatitis und Fibrose

Metabolic
- BMS-986026
- FGF-21
- Adiponectin
  - ↓TNFα
  - ↑FFA
- PPAR agonists e.g., elafibranor
- MGL-3196
- Aramchol
- ↑SHP
- ↑SREPB-1
- ↑DNL
- INT-767
- ↑FXR/TGR5
- NGM 282
- FXR agonists e.g., obeticholic acid
- Bile acids
- Volixibat

Cell death
- ACC inhibitor GS-0976
- MGL-3196
- Mitochondrial dysfunction
- ↑ROS
- ↑JNK
- Apoptosis

Inflammation
- Emricasan ASK1 inhibitor selonsertib
- CCR2/5 inhibitor cenicriviroc
- Galectin 3 inhibitor GR-MD-02
- Kupffer cells
- Inflammatory monocytes
- Lymphocytes
- AOC3 inhibitor BI 1467335

Extracellular matrix

Fibrosis
- LOXL2?
  - e.g., simtuzumab

Gut-liver axis
NASH: Definition, natural history and current therapeutic interventions

- **Metabolic liver diseases** increase tremendously and will become the main cause for **cirrhosis**, liver **transplantation** and liver **cancer**

- **Fibrosis** is considered the key mechanism for prognosis – can be assessed by non-invasive tests, risk scores and (if needed) liver biopsy

- **Effective lifestyle changes or bariatric surgery** can improve liver histology - no general recommendation for vitamin E, pioglitazone, UDCA, silymarin

- Surveillance for **liver-related complications** (cirrhosis, portal hypertension, HCC) and **comorbidities** (cardiovascular, metabolic, renal, malignancies) is needed in high-risk patients
Thank you for your attention!