Steatotic Liver Disease: New Nomenclature and Treatment

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Objectives

- New nomenclature
- Prevalence
- Associations
- Implications
- Treatment
Nothing to disclose
Nonalcoholic Fatty Liver Disease (NAFLD)

- Global term which includes all disease grades and stages
- Refers to a population in which > 5% of hepatocytes display macrovesicular steatosis in the absence of readily identified causes
  - Medications
  - Starvations
  - Monogenic diseases
  - Alcohol (<20g/d Women, <30g/d Men)
Nonalcoholic Fatty Liver Disease (NAFLD)

- Nonalcoholic Fatty Liver (NAFL)
- Hepatic steatosis mild to minimal inflammation

- Nonalcoholic Steatohepatitis (NASH)
- Presence of inflammation and cellular injury (ballooning), with or without fibrosis
Why the name change in June 2023?

The term non “Nonalcoholic”

- Does not capture the disease etiology

The term “Fatty” considered stigmatizing by some

Individuals with risk factors for NAFLD

- Consume more alcohol than the relatively strict thresholds
- Are not recognized with the existing nomenclature
- Excluded from trials and consideration for treatment

This factors led to growing dissatisfaction

Rinella, Mary E.1; Lazarus, Jeffrey V.2,3; Ratziu, Vlad4; Francque, Sven M.5,6; Sanyal, Arun J.7; Kanwal, Fasiha8,9; Romero-Gómez, Manuel51; Silva, Marcelo52; Singh, Shivram Prasad63; Sookeian, Silvia C.15,54,55; Spearman, C.15,54,55; Tiniakos, Dina11,57; Valenti, Luca58,59; Vos, Miriam B.60; Wong, Vincent Wai-Sun61; Xanthakos, Stavara62; Younossi, Zobair64; Hobbs, Ansley2; Villota-Rivas, Marcela65; Newsome, Philip N66,67; on behalf of the NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology () 10.1097/HEP.0000000000000520, June 24, 2023. DOI: 10.1097/HEP.0000000000000520
Eslam et al. 2020: Metabolic dysfunction-associated fatty liver disease (MAFLD)
This led to the name change

AASLD, EASL, ALEH, Asia-Pacific, MENA, Endocrine

Patient advocacy groups

• Fatty liver foundations
• ALD
• ELPA
• GLI
• ALF

Unified global approach to nomenclature and disease definition

• Disease awareness
• Driving policy change
• Identifying those at risk
• Facilitating diagnosis
• Access to care

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Overarching term: Steatotic Liver Disease (SLD)

Both “non-alcoholic” and “fatty” are perceived to be stigmatizing to some extent

For children/adolescents or parents, the term “fatty” is perceived to be stigmatizing

Therefore: more neutral, “scientific” term
What to know about SLD?

Overarching term to encompass the various etiologies of steatosis

The term steatohepatitis was felt to be an important pathophysiological concept that should be retained
Nonalcoholic fatty liver disease (NAFLD) will now be metabolic dysfunction-associated steatotic liver disease (MASLD)

MASLD encompasses patients who have hepatic steatosis and at least one of five cardiometabolic risk factors
What to know about SLD?

Metabolic dysfunction-associated Steatohepatitis (MASH) is the replacement term for NASH.
Steatotic Liver Disease

Help categorize other causes of steatosis

Does not alter natural history, clinical trials or biomarkers nor will it impede development

Staging and severity that we use today will stay the same

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Metabolic Dysfunction Associated Steatohepatitis (MASH)
MetALD

• Continue to limit alcohol intake (as previously limited for NAFLD) in the context of steatosis

• Separate category outside of pure MASLD, namely MetALD, with alcohol intake greater than that allowed for NAFLD/MASLD
Review

• SLD and the more specific term MASLD provide an affirmative non-stigmatizing description of the condition
• Proposed nomenclature is not intended to be static, but rather allows the flexibility for refinement as new evidence emerges about underlying pathophysiology and risk factors
Why is learning from MASLD important?

- Most common chronic liver disease around the world
- Affects more than 30% of the global population
Prevalance

Pooled Prevalence of NAFLD: 30.05% (95% confidence interval: 27.88 to 32.32%)

North America: 31.20% (25.86 to 37.08%)
Western Europe: 25.1% (20.55 to 30.28%)
East Asia: 29.7% (25.96 to 33.76%)
Asia Pacific: 28.02% (24.69 to 31.60%)
South East Asia: 33.07% (18.99 to 51.03%)
Australasia: 31.20% (25.86 to 37.08%)

Geographic regions are based on epidemiological similarities and geographical proximity from the Global Burden of Diseases study.

Younossi et al., Hepatology. 2023 Apr; 77(4): 1335–1347
Epidemiology

Incidence of hepatic decompensation, HCC and death

• Related to MASH cirrhosis -> 2-3x fold by 2030

MASH-related cirrhosis leading indication for liver transplant

• Women
• > 65 years of age
• Expected to increase further!!

Is on par with alcohol as the leading indication overall
Natural Disease History

Fibrosis and presence of steatohepatitis

- Primary predictors of disease progression

Fibrosis progression is influenced by many factors

- Co-morbid disease
- Genomic profile
- Environmental factors

The diagnosis of cirrhosis is important because it changes clinical management
Co-morbid Conditions Associated with MASLD

- Obesity
- Type 2 Diabetes Mellitus
- Hypertension
- Dyslipidemia
- Obstructive Spleen Apnea
- CVD
- Chronic Kidney Disease
- Hypothyroidism (Controversial)
- GH deficiency
- Hypogonadism
- PCOS

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# Co-morbid Conditions Associated with MASLD

<table>
<thead>
<tr>
<th>Most common causes of death in patients with MASLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cardiovascular Disease and Non-Hepatic Malignancy</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Death from liver disease complications predominates</th>
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<tbody>
<tr>
<td>• Patients with advanced fibrosis</td>
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</table>

<table>
<thead>
<tr>
<th>Linked to and often precedes development of metabolic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insulin resistance, dyslipidemia, central obesity and hypertension</td>
</tr>
<tr>
<td>• Having several metabolic abnormalities confers greater risk of histological progression and all cause mortality</td>
</tr>
</tbody>
</table>

| T2DM is the most impactful risk factor for development of MASLD, fibrosis progression and HCC |

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Drugs with potential mechanistic links to macrovesicular steatosis or steatohepatitis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Histological pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Hepatic steatosis and steatohepatitis, phospholipidosis, cirrhosis</td>
</tr>
<tr>
<td>5-FU</td>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Steatohepatitis</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Steatosis and steatohepatitis</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Steatosis, steatohepatitis, cirrhosis</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Steatosis</td>
</tr>
</tbody>
</table>
## Less common causes of hepatic steatosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical scenario</th>
<th>Diagnostic test</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypobetalipoproteinemia</td>
<td>Low LDL, low triglycerides, fat malabsorption</td>
<td>ApoB level, genetic testing (MTTP, PCSK-9)</td>
<td>Low-fat diet, fat-soluble vitamin supplementation</td>
</tr>
<tr>
<td>LAL deficiency</td>
<td>Markedly elevated LDL-C and low HDL-C, elevated triglycerides, xanthelasma, hypersplenism, advanced fibrosis in young age, predominately microvesicular steatosis on liver biopsy</td>
<td>Enzyme assay, genetic testing</td>
<td>LAL replacement</td>
</tr>
<tr>
<td>Nutrient deficiency (eg, carnitine, choline)</td>
<td>Anorexia, short bowel, bypass surgeries</td>
<td>Nutrient levels</td>
<td>Supplementation</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Younger age, neuropsychiatric symptoms, low alkaline phosphatase, low ceruloplasmin</td>
<td>24-h urine copper; quantitative copper on liver biopsy</td>
<td>Chelation</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Iron deficiency, abdominal pain, bloating, vitamin D deficiency, bone loss, diarrhea, dermatitis herpetiformis</td>
<td>Tissue transglutaminase IgA, duodenal biopsy</td>
<td>Gluten-free diet</td>
</tr>
</tbody>
</table>

Abbreviations: ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; IgA, immunoglobulin A; LAL, lysosomal acid lipase; LDL-C, LDL cholesterol.
Who should we screen and what screening method can be used?
Screening for advanced fibrosis in high risks populations

Noninvasive diagnosis of “at risk” NASH/MASH, advanced fibrosis and cirrhosis

Off-label use of available medications

Optimal care model
### Screening for advanced fibrosis in high-risk populations

<table>
<thead>
<tr>
<th>Screening recommended</th>
<th>Prevalence of advanced fibrosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>6–19</td>
</tr>
<tr>
<td>Medically complicated obesity</td>
<td>4–33</td>
</tr>
<tr>
<td>NAFLD/MASLD in context of moderate alcohol use</td>
<td>17</td>
</tr>
<tr>
<td>First-degree relative of a patient with cirrhosis due to NAFLD/NASH: MASLD/MASH</td>
<td>18</td>
</tr>
</tbody>
</table>

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Screening for Advanced Fibrosis and Risk Stratification

General population-based screening for NAFLD is not advised

All patients with hepatic steatosis should be screened for T2DM and OSA
Evaluate for Fibrosis via Non-Invasive Tests

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

<table>
<thead>
<tr>
<th>When to Use</th>
<th>Pearls/Pitfalls</th>
<th>Why Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Use with caution in patients &lt;35 or &gt;65 years old, as the score has been shown to be less reliable in these patients</td>
<td></td>
</tr>
</tbody>
</table>

AST
Aspartate aminotransferase
Norm: 15 - 41 U/L

Platelet count
Norm: 150 - 350 x 10^9/L

ALT
Alanine aminotransferase
Norm: 1 - 35 U/L

FIB-4 Risk Stratification and Referral to GI

- **< 1.3**
  - Management by PCP
  - Repeat risk assessment in 2-3 years

- **1.3-2.67**
  - Consider GI/Liver Referral
  - If NAFLD established, return to PCP

- **>2.67**
  - Refer to GI/Liver
  - Longitudinal specialty care as appropriate

Best Practice for ALL NAFLD Patients Regardless of Fibrosis Stage

- Referral to MOVE!
- CV Disease Risk Factor Management
- Alcohol Abstinence
- Viral Hepatitis Immunization

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Vibration Controlled Transient Elastrography (VCTE)
• Point of care tool for noninvasive assessment of liver fibrosis
• Performed at bedside in outpatient clinics with immediate results and good reproducibility
• Measurements in kPA
• CAP: Controlled attenuation parameter: % of fatty change in the liver
Vibration Controlled Transient Elastrography (VCTE)

- Avoid in CHF patients
- Fasting of at least 4 hours
- Obesity
- Ascites
- Acute liver injury (>5x ULN)
Enhance liver fibrosis (ELF)
- Serum blood test
- Identify patient at increase risk of progression to cirrhosis or related clinical events
- Prognostic biomarker
At “Risk F2” Cirrhosis
Pearls for the Assessment MASLD

- Aminotransferase levels are frequently normal in patients with advanced liver disease due to NASH/MASH.
  - **Should not** be used in isolation to exclude the presence of NASH/MASH.

  - Ultrasound can detect hepatic steatosis.
    - It is **not recommended** as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum.

  - Patient with suspected advanced NASH/MASH or discordant NITs should be referred to a specialist.

  - Patient with clinically significant hepatic fibrosis (F2+) **should abstain from alcohol use completely**.

  - Improvement in ALT or reduction in liver fat content by imaging in response to an intervention may indicate histological improvement in disease activity.

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Role of Alcohol Consumption

• Co-factor for liver disease progression and intake should be assessed on a regular basis

• Classified
  • Mild: 20g women and 30 g daily for men
  • Moderate: 21-39 g women and 31-59 g men per day
  • Heavy: > 40 g women and 60 g men per day

• Substantial variability in individual susceptibility to alcohol-induced injury

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There are currently **NO** FDA-approved drugs for the treatment of NASH at any disease stage.
Weight Loss (WL)
- 3-5% improves steatosis
- > 10% improves NASH/MASH and Fibrosis
- (<10%) achieve effective WL despite structured intervention in one 1 year
  - Fewer than half of these maintain the weight loss 5 years after intervention
- Multidisciplinary approach-> lifestyle changes
  - Patients support systems and family engagement
  - Behavioral medicine specialist
  - Dietitians
  - Nutritionist
Treatment: Role of Macronutrients

- Avoid diet containing excess calories
  - Excess saturated fats
  - Refined carbohydrates
  - Sugar-sweetened beverages
  - Fructose
- Mediterranean diet improvement in CV Health + reduction in liver fat
- Coffee consumption: may reduce NAFLD/MASLD and liver fibrosis
  - Independent of caffeine content
  - 3 or more cups, in the absence of contraindications
Treatment: Impact of Exercise

- Has hepatic and cardio metabolic benefit
  - Routinely recommended and tailored to the patient’s preference and physical abilities
- Prevent and/or improve NAFLD
  - Regular moderate exercise at least 5 times per week
    - 150 minutes per week
  - Increase in activity by more than 60 minutes per week
  - Some studies suggest more vigorous exercise is needed to improve NASH histology with higher intensity to reduce fibrosis.
Treatment: Bariatric Surgery (BS)

- Current criteria for BS
  - BMI > 40 kg/m² irrespective of metabolic co-morbid disease
  - BMI > 35 with co-morbidities (DMT2, Pre-DM, U-HTN, OA of hip or knee)

- MASLD/MASH
  - Increasingly accepted as a co-morbid condition that could benefit

- Can resolve MASH, improve hepatic fibrosis, induced sustained weight loss of up to 30%, cure diabetes and decrease all-cause morbidity and mortality

- (BRAVES): a multi-center, open-label, randomized trial
  - Publish in The Lancet 04/21/2023

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### Treatment: Available medications

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<thead>
<tr>
<th>Medication</th>
<th>FDA indication</th>
<th>Patient population</th>
<th>Clinical benefits</th>
<th>Potential side effects</th>
<th>Cardiac benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E (rrr-alpha) 800 IU daily</td>
<td>NA</td>
<td>NASH without T2DM or cirrhosis</td>
<td>Liver related: improves steatosis, NASH resolution? No proven benefit on fibrosis</td>
<td>Hemorrhagic stroke, risk of prostate cancer?</td>
<td>No</td>
</tr>
</tbody>
</table>

- Multi-center, (RCT), Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH (PIVENS), Treatment with rrr α-tocopherol (the natural form of vitamin E) 800 IU daily for 96 weeks improved histology (≥2-point reduction in NAS) compared with placebo
- Findings were supported by a meta-analysis showing that vitamin E improved serum aminotransferases in addition to steatosis, inflammation, and cellular ballooning on biopsy
- Reduction in serum ALT to ≤40 U/L and by ≥30% of baseline value after initiation of vitamin E is associated with improvement in histological parameters
- **No study has demonstrated that vitamin E meaning fully reduces fibrosis**
- A retrospective study of 236 patients with NASH and advanced fibrosis showed that vitamin E use was associated with lower rates of hepatic decompensation and higher transplant free survival
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<tr>
<td>Liraglutide(^a) 1.8 mg s.c. daily (T2DM) 0.6–3 mg s.c. daily (obesity)</td>
<td>T2DM, obesity</td>
<td>NASH without cirrhosis</td>
<td>Liver: improves steatosis, no proven impact on fibrosis. Nonliver related: improvement in insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease</td>
<td>Gastrointestinal, gallstones (related to weight loss), pancreatitis</td>
<td>Yes</td>
</tr>
<tr>
<td>Semaglutide(^b) 0.4 mg s.c. daily, 0.25–2.4 mg SQ weekly(^433)</td>
<td>T2DM, obesity</td>
<td>NASH without cirrhosis</td>
<td>Liver related: improves steatosis, activity, and NASH resolution, no proven benefit on fibrosis, but may slow fibrosis progression. Nonliver related: improvement in insulin sensitivity, weight loss, improves CV and renal outcomes, stroke prevention</td>
<td>Gastrointestinal, gallstones (related to weight loss), pancreatitis</td>
<td>Yes</td>
</tr>
<tr>
<td>Tirzepatide</td>
<td>T2DM, obesity with NAFLD</td>
<td>T2DM or obesity with NAFLD</td>
<td>Liver related: reduces steatosis on imaging. Nonliver related: improvement in insulin sensitivity, significant weight loss</td>
<td>Gastrointestinal, gallstones related to weight loss, pancreatitis</td>
<td>Unknown</td>
</tr>
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\(^a\)Study with small sample size and underpowered to determine key histological outcomes (ie, fibrosis). \(^b\)Phase 3 trial to determine efficacy currently enrolling.
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<tr>
<td>SGLT-2i</td>
<td>T2DM</td>
<td>T2DM and NAFLD</td>
<td>Liver related: reduction in steatosis by imaging. Nonliver related: may improve insulin sensitivity, improves CV and renal outcomes; benefit in heart failure, modest weight loss</td>
<td>Risk of genitourinary yeast infection, volume depletion, bone loss</td>
<td>Yes</td>
</tr>
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</table>

- Induce 2%–3% weight loss and have cardio renal protective benefits
- Role of SGLT-2i in the treatment of NAFLD/NASH are limited by relatively small sample sizes and lack of histological outcome
- Within these limitations, available data suggest SGLT-2i improve hepatic steatosis; however, the therapeutic impact of SGLT-2i on liver histology needs to be better defined
Medications Key Points

No FDA approve medication

Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with NASH, as it confers a cardiovascular benefit and improves NASH.

In compensated cirrhosis, semaglutide improved cardiometabolic risks parameters, but not fibrosis

Pioglitazone improves NASH and can be considered for patients with NASH in the context of patients with T2DM

Vitamin E can be considered in select individuals as it improves NASH in some patients without diabetes.

Available data on semaglutide, pioglitazone, and vitamin E do not demonstrate an antifibrotic benefit
SLD is the new overarching term

MASLD is the new NAFLD

MASH is the new NASH

Met-ALD (mixed), more studies

Risk stratify for advanced fibrosis with FIB-4

Standard liver US not recommended

Screen for T2DM in all patients with hepatic steatosis

Risk stratify for advanced fibrosis in all patients with T2DM

No alcohol in F2 or higher

General population screening not indicated

Excessive fructose consumption increases risk of MASLD/MASH and advanced fibrosis

Treatment
- Consider semaglutide/tirzepatide or bariatric surgery in those with indications
- Treat metabolic co-morbidities
Questions?