Metabolic Dysfunction associated Steatotic Liver Disease(MASLD)

A New Name for Non Alcoholic Fatty Liver Disease(NAFLD) ?A Paradigm Shift

By Sirish Sanaka MD, MHA

Disclosure

- I have no actual or potential conflict of interest in relation to this presentation.

Objectives

- Describe Pathophysiology of MASLD
- Discuss Diagnostic approach to MASLD
- Outline current and upcoming treatment options for MASLD

MASLD

Definition

- It refers to liver steatosis in patients with at least one metabolic risk factor.
- Risk factors: Diabetes, Hypertension, Hyperlipidemia, Obesity.
- It can progress to MASH(Metabolic Dysfunction associated steatohepatitis and eventually lead to MASH cirrhosis(previously called NASH Cirrhosis).
- It is the leading cause of cryptogenic cirrhosis.

MASLD, MASH Projected to Grow by 23% in the US Through 2050

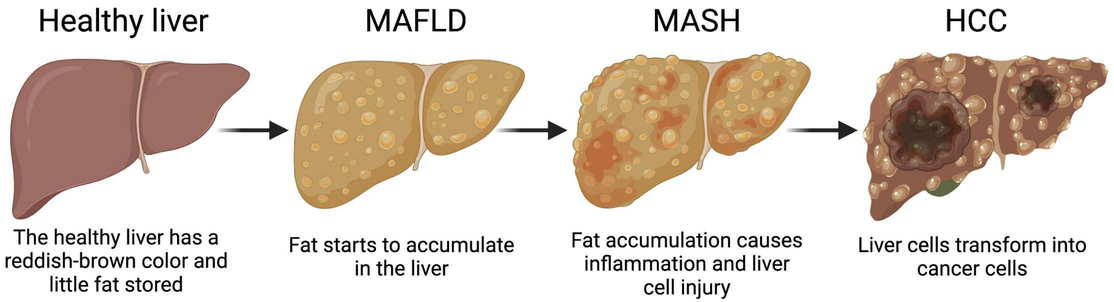
Neil Osterweil
November 08, 2023

BOSTON — The nomenclature may have changed, but the steady rise in the most common form of liver disease — metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as NAFLD) — is predicted to continue into the middle of this century.

That's according to Phuc Le, PhD, MPH, and colleagues at the Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio. They created a mathematical model incorporating data on the growth of the US population and the natural history of MASLD/NAFLD. The model projected a relative 23% increase in MASLD among US adults from 2020 to 2050.

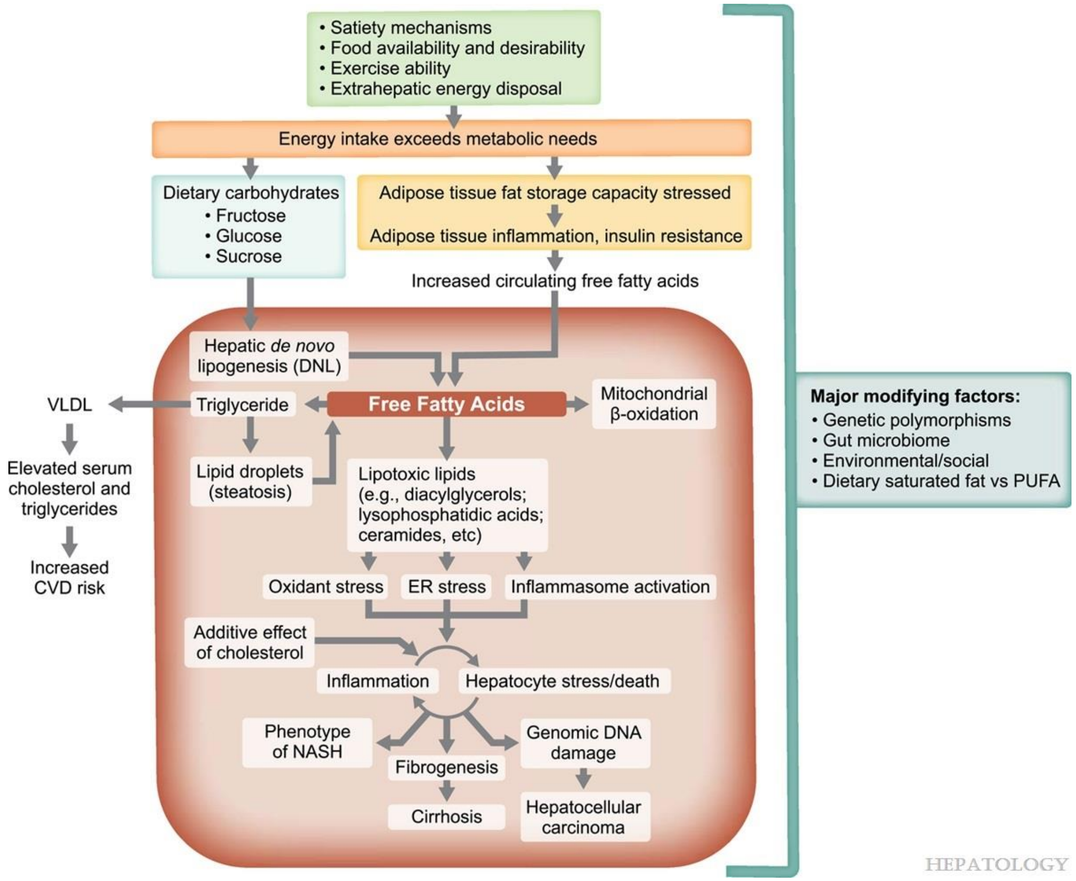
"Our model forecasts a substantial clinical burden of NAFLD over the next three decades. In the absence of effective treatments, health systems should plan for large increases in the number of liver cancer cases and the need for liver transplant," Le said in a media briefing held on November 7 prior to her presentation of the data at The Liver Meeting 2023: American Association for the Study of Liver Diseases (AASLD).

The estimated worldwide prevalence of MASLD is 38%. In the US, an estimated 27.8% of adults had MASLD as of 2020.



Pathogenesis

FIGURE 1



AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease

Rinella, Mary E.; Neuschwander-Tetri, Brent A.; Siddiqui, Mohammad Shadab; Abdelmalek, Manal F.; Caldwell, Stephen; Barb, Diana; Kleiner, David E.; Loomba, Rohit

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Pathogenic drivers of NAFLD as therapeutic targets. Overview of the major mechanisms that lead to the phenotype of NASH and its consequences, many of which can be leveraged therapeutically. Not shown are the many areas where genetic polymorphisms may play a role and where important modifying factors such as cholesterol, types of dietary fats consumed [saturated vs. polyunsaturated fatty acid (PUFA)], the gut microbiome, uric acid, and periodic hypoxia (sleep apnea) may also influence these pathways. A primary disease driver may be an oversupply of fat to adipocytes such that their ability to store triglyceride without inducing cell stress is exceeded, which activates inflammatory pathways and causes insulin resistance. Understanding the major drivers of NASH facilitates the rational development of therapies for patients with NASH. Specific sites of intervention that might prevent or resolve NASH include interventions that modulate food intake (eg, portion sizes, bariatric surgery, satiety regulators), increase energy disposal (eg, exercise, thermogenesis), improve adipocyte insulin sensitivity [eg, peroxisome proliferator-activated receptor (PPAR)γ ligands], impair de novo lipogenesis (eg, acetyl-coenzyme A carboxylase and fatty acid synthase inhibitors), increase hepatic oxidative metabolism (PPARα ligands and thyroid hormone receptor beta agonists), and attenuate inflammation, cell death, and fibrogenesis. Therapeutic agents affecting multiple metabolic pathways throughout the body with potential beneficial effects on the liver include peptide hormone analogs (eg, analogs of fibroblast growth factor-19, fibroblast growth factor-21, glucagon-like peptide-1, gastric inhibitory peptide, glucagon) and nuclear receptor ligands such as drugs that target PPARα, PPARδ, PPARγ, thyroid hormone receptor β, and farnesoid X receptor. Abbreviations: ER, endoplasmic reticulum; CVD, cardiovascular disease.

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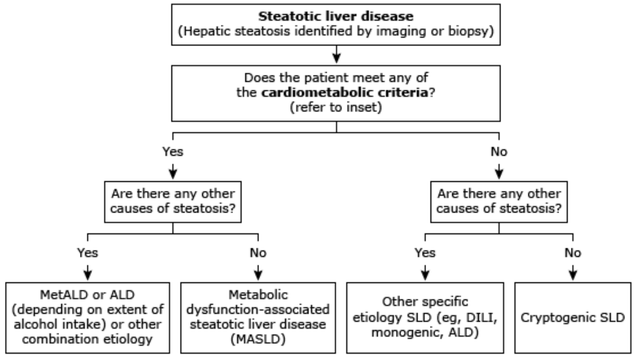
Diagnosis

Metabolic dysfunction-associated steatotic liver disease (MASLD) diagnostic criteria



Cardiometabolic criteria	
Adult criteria	**Pediatric criteria**
At least 1 out of 5: ☐ BMI ≥25 kg/m^2 (or BMI ≥23 kg/m^2 for Asian individuals) **or** WC >94 cm (males), >80 cm (females) or ethnicity-adjusted equivalent ☐ Fasting serum glucose ≥100 mg/dL [5.6 mmol/L] **or** 2-hour post-load glucose levels ≥140 mg/dL [7.8 mmol/L] **or** A1C ≥5.7% [39 mmol/L] **or** type 2 diabetes or treatment for type 2 diabetes ☐ Blood pressure ≥130/85 mmHg **or** specific antihypertensive drug treatment ☐ Plasma triglycerides ≥150 mg/dL [1.70 mmol/L] **or** lipid lowering agent ☐ Plasma HDL-cholesterol ≤40 mg/dL [1.0 mmol/L] (males) and ≤50 mg/dL [1.3 mmol/L] (females) **or** lipid lowering treatment	**At least 1 out of 5:** ☐ BMI ≥85th percentile for age/sex (BMI Z-score ≥+1) **or** WC >95th percentile **or** ethnicity-adjusted equivalent ☐ Fasting serum glucose ≥100 mg/dL [5.6 mmol/L] **or** random serum glucose ≥200 mg/dL [11.1 mmol/L] **or** 2-hour post-load glucose levels ≥140 mg/dL [7.8 mmol/L] **or** A1C ≥5.7% [39 mmol/L] or established diagnosis of type 2 diabetes **or** treatment for type 2 diabetes ☐ Blood pressure age <13 years, BP ≥95th percentile **or** ≥130/80 (whichever is lower); age ≥13 years, BP ≥130/85 mmHg **or** specific antihypertensive drug treatment ☐ Plasma triglycerides age <10 years, ≥100 mg/dL [1.15 mmol/L]; age ≥10 years, ≥150 mg/dL [1.70 mmol/L] **or** lipid lowering agent ☐ Plasma HDL-cholesterol ≤40 mg/dL [1.0 mmol/L] **or** lipid-lowering treatment

In the presence of hepatic steatosis, the finding of any cardiometabolic risk factor would confer a diagnosis of MASLD if there are no other causes of hepatic steatosis. If additional drivers of steatosis are identified, then this is consistent with a combination etiology. In the case of alcohol, this is termed MetALD or ALD, depending on extent of alcohol intake. In the absence of overt cardiometabolic criteria, other etiologies must be excluded. If none is identified, this is termed cryptogenic SLD, although depending on clinical judgment, it could also be deemed to be possible MASLD and thus would benefit from periodic reassessment on a case-by-case basis. In the setting of advanced fibrosis/cirrhosis, steatosis may be absent, requiring clinical judgment based on cardiometabolic risk factors and absence of other etiologies.

A1C: glycated hemoglobin; ALD: alcohol-associated liver disease; BMI: body mass index; BP: blood pressure; DILI: drug-induced liver disease; HDL: high-density lipoprotein; MetALD: metabolic dysfunction- and alcohol-associated steatotic liver disease; SLD: steatotic liver disease; WC: waist circumference.

Definitions of the metabolic syndrome

Parameters	NCEP ATP3 2005*	IDF 2009	EGIR 1999	WHO 1999	AACE 2003
Required			Insulin resistance or fasting hyperinsulinemia (ie, in top 25% of the laboratory-specific reference range)	Insulin resistance in top 25%Δ; fasting glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance◇ or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	**≥3 of:**	**≥3 of:**	**And ≥2 of:**	**And ≥2 of:**	**And ≥2 of:**
Glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	Fasting glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL)		Fasting glucose ≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol§	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides§	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)¥	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL: high-density lipoprotein; CVD: cardiovascular disease; BMI: body mass index.

* Most commonly agreed upon criteria for metabolic syndrome. Note that abdominal obesity is **not** a prerequisite for diagnosis; the presence of any 3 of the 5 risk criteria constitutes a diagnosis of metabolic syndrome.

¶ For South Asian and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

Δ Insulin resistance measured using insulin clamp.

◇ High risk of being insulin resistant is indicated by the presence of at least 1 of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthosis nigricans; family history of type 2 diabetes, hypertension or CVD; history of gestational diabetes or glucose intolerance; non-White race; sedentary lifestyle; BMI 25 kg/m^2 or waist circumference 94 cm (men) or 80 cm (women); and age 40 years.

§ Treatment with 1 or more of fibrates or niacin.

¥ In Asian patients, waist ≥90 cm (men) or ≥80 cm (women).

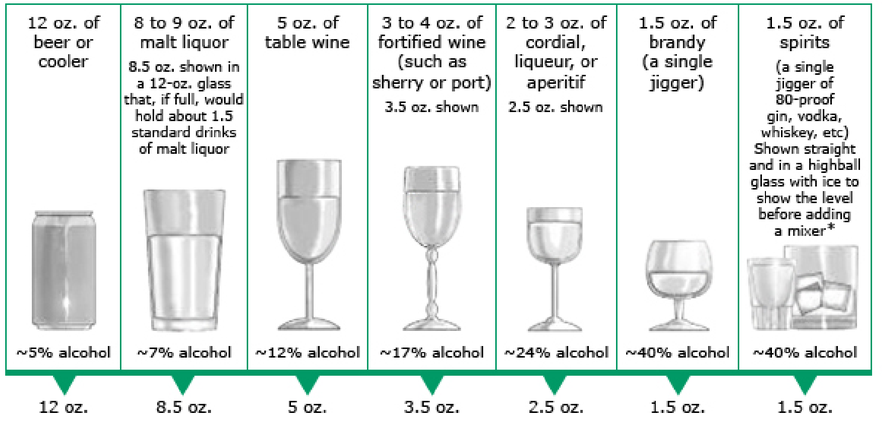
References:

1. *Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120:1640.*
2. *Meigs J. Metabolic syndrome and risk for type 2 diabetes. Expert Rev Endocrin Metab 2006; 1:57. Table 1. Updated data from the International Diabetes Federation, 2006.*
3. *Bloomgarden ZT. American Association of Clinical Endocrinologists (AACE) consensus conference on the insulin resistance syndrome: 25-26 August 2002, Washington, DC. Diabetes Care 2003; 26:933.*

- It is important to differentiate MASLD from MetALD.
- MetALD is Metabolic Dysfunction and Alcohol associated Liver Disease.
- MetALD patients are the ones with liver steatosis, at least one metabolic risk factor and moderate alcohol intake.
- Moderate alcohol intake defined as 20-50gm alcohol intake daily for females and 30-60gm alcohol intake daily for males.
- One standard alcohol drink is any drink with 10gm of alcohol.

What is a standard drink?

A standard drink in the United States is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are US standard drink equivalents. These are approximate, since different brands and types of beverages vary in their actual alcohol content.



Many people don't know what counts as a standard drink and so they don't realize how many standard drinks are in the containers in which these drinks are often sold. Some examples:

- For **beer**, the approximate number of standard drinks in:
  - 12 oz. = 1
  - 16 oz. = 1.3
  - 22 oz. = 2
  - 40 oz. = 3.3
- For **malt liquor**, the approximate number of standard drinks in:
  - 12 oz. = 1.5
  - 16 oz. = 2
  - 22 oz. = 2.5
  - 40 oz. = 4.5
- For **table wine**, the approximate number of standard drinks in:
  - a standard 750-mL (25-oz.) bottle = 5
- For **80-proof spirits**, or "hard liquor," the approximate number of standard drinks in:
  - a mixed drink = 1 or more*
  - a pint (16 oz.) = 11
  - a fifth (25 oz.) = 17
  - 1.75 L (59 oz.) = 39

US: United States; oz.: ounces.

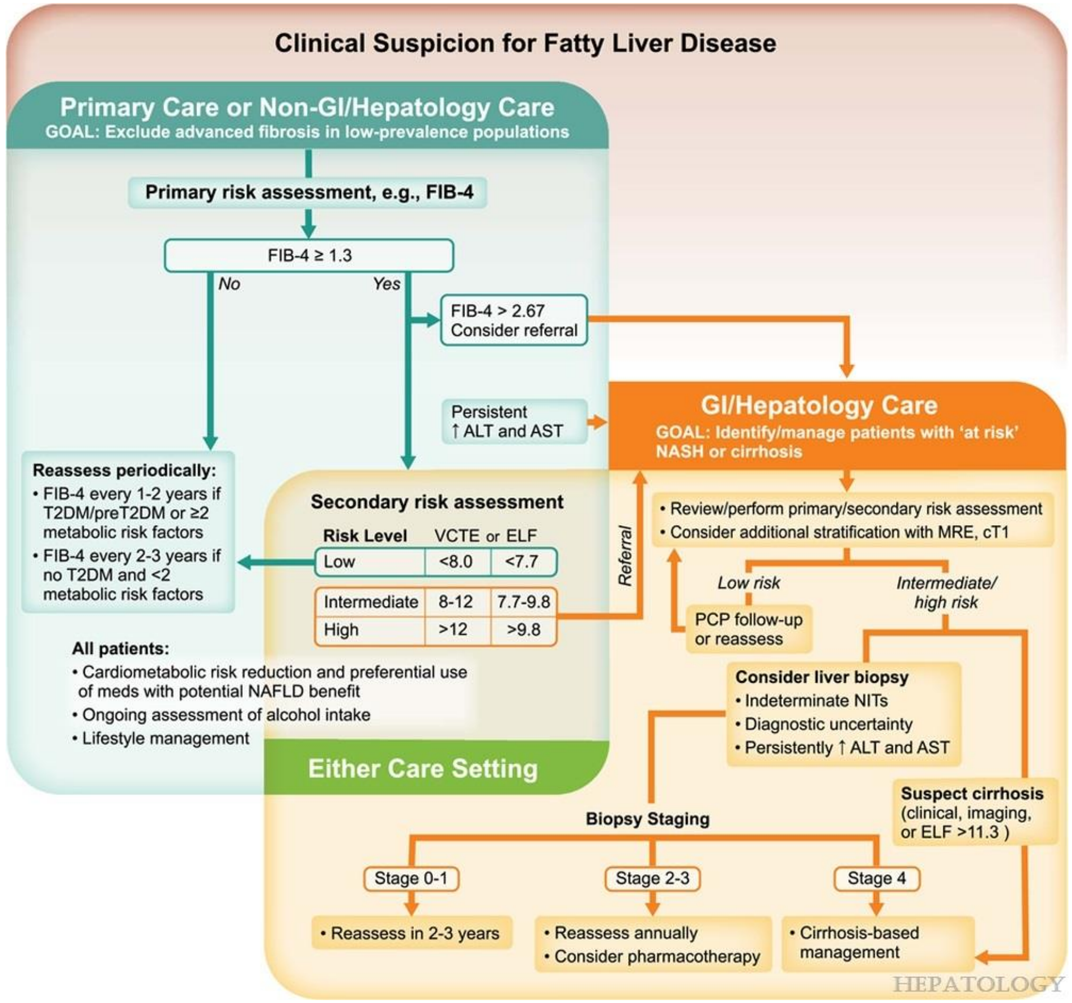
* It can be difficult to estimate the number of standard drinks in a single mixed drink made with hard liquor. Depending on factors such as the type of spirits and the recipe, a mixed drink can contain from 1 to 3 or more standard drinks.

TABLE 1 - Initial evaluation of a patient with NAFLD

History	Weight history; medical comorbidities; recent and current medications; family history of T2DM, NAFLD, or cirrhosis; screening for OSA; alcohol use, including amount, pattern of use, and duration
Physical examination	Body fat distribution (eg, android vs. gynoid, lipodystrophic), features of insulin resistance (eg, dorsal-cervical fat pad, acanthosis nigricans), features of advanced liver disease (eg, firm liver, splenomegaly, prominent abdominal veins, ascites, gynecomastia, spider angiomata, palmar erythema)
Laboratory tests	Hepatic panel, CBC with platelets, fasting plasma glucose and glycated hemoglobin (A1c), fasting lipid profile, creatinine and urine microalbumin or protein to creatinine ratio, hepatitis C if not previously screened. Consider as appropriate other causes of steatosis/steatohepatitis (). Additional evaluation if elevated liver chemistries present: autoimmune serologies, transferrin saturation, ceruloplasmin, alpha-1 antitrypsin genotype, or phenotype

Abbreviations: CBC, complete blood count; OSA, obstructive sleep apnea; T2DM, type 2 diabetes mellitus.

FIGURE 2



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Algorithm for the evaluation of patients at risk for or with established NAFLD across practice settings. Patients with steatosis noted on imaging or for whom there is a clinical suspicion of NAFLD, such as those with metabolic risk factors or unexplained elevation in liver chemistries, should undergo further evaluation. In settings with a low prevalence of advanced fibrosis, such as in the primary care setting, the emphasis is on excluding advanced fibrosis using a test with a high negative predictive value. When the fibrosis-4 index (FIB-4) is <1.3, patients can be followed in the primary care setting and reassessed periodically. Patients without prediabetes/type 2 diabetes mellitus (T2DM) and 1–2 metabolic risk factors can be reassessed every 2–3 years. Patients with prediabetes/T2DM or 2 or more metabolic risk factors are at higher risk for disease progression, and more frequent FIB-4 monitoring (eg, every 1–2 y) should be considered. In patients older than age 65, a FIB-4 cutoff of >2.0 should be used. FIB-4 has low accuracy in those under age 35; thus, secondary assessment should be considered in those <35 with increased metabolic risk or elevated liver chemistries. FIB-4 should not be used in acutely ill patients. In patients with FIB4 ≥1.3, a secondary assessment should be done [preferentially vibration-controlled elastography (VCTE) or Enhanced Liver Fibrosis (ELF) initially] or the patient referred for further risk stratification (if being seen in a nongastroenterology/hepatology setting). Direct referral to gastroenterology/hepatology should be considered in those with aminotransferases persistently (>6 mo) above normal to exclude other causes of liver disease or when FIB4 > 2.67 due to the increased risk of clinically significant fibrosis. In higher prevalence settings, such as gastroenterology/hepatology clinics, additional risk assessment with magnetic resonance elastography (MRE) may be appropriate when noninvasive tests (NITs) are indeterminate or there is clinical suspicion of more advanced disease. Identification of cirrhosis should prompt screening for HCC and esophageal varices. In addition, MRE or corrected T1 (cT1) may help identify patients with "at-risk" NASH (NASH with NAFLD activity score ≥4 and fibrosis stage ≥2) who may benefit from a therapeutic intervention as they become available. If cirrhosis is suspected based on NITs, clinical data, or imaging findings, then cirrhosis-based management may be initiated without a liver biopsy. Liver biopsy should be considered when NITs suggest significant fibrosis (≥F2), especially if additional evaluation suggests the presence of "at-risk" NASH (eg, using FAST, MEFIB, MAST, or cT1). NIT assessment is indeterminate, aminotransferases are persistently elevated (>6 mo), or additional/alternate diagnoses are suspected. Note that in patients with confirmed or suspected advanced fibrosis, an ELF ≥11.3 is a predictor of future liver-related events and is approved for this purpose; use of other ELF cutoffs in secondary risk assessment is based on expert option. Patients at all stages of disease should be counseled on lifestyle modifications, and those with ≥F2 fibrosis targeted for pharmacological interventions as they become available. Specific threshold values of NITs are approximations supported by current evidence and are meant to guide clinical management through primary care to gastroenterology/hepatology practices rather than be interpreted in isolation. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PCP, primary care provider.

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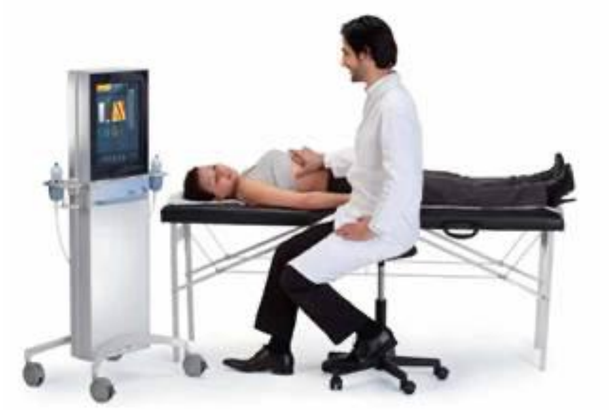
Non Invasive Testing

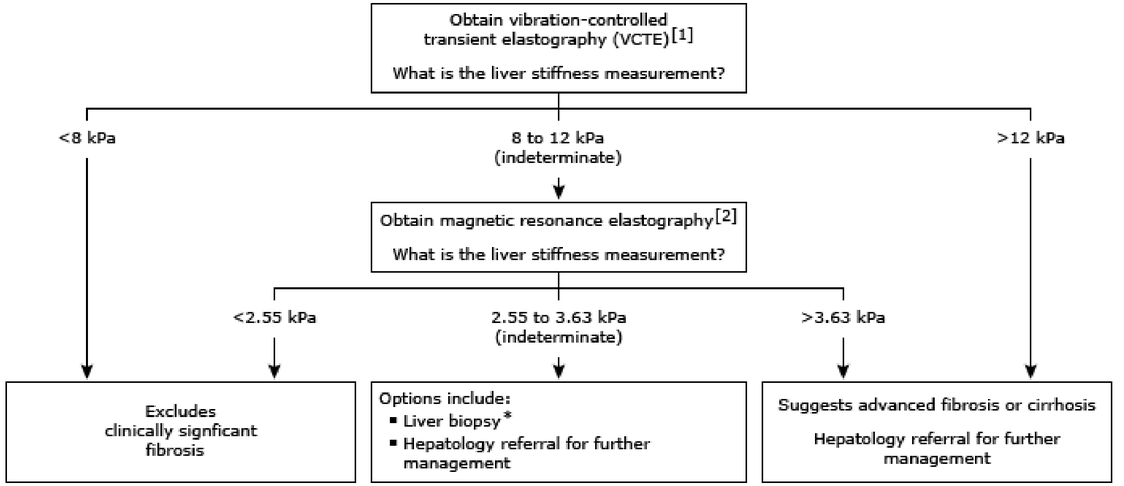


Transient elastography of the liver

Transient elastography showing the measurement of liver stiffness in kilopascals (kPa) along the left side of the screen. An A-mode image is displayed to assist the operator in selecting the measurement zone. On the right side, the values of 10 measurements are shown with the mean value depicted at the bottom of the screen.

UpToDate®

An approach to evaluating for fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD)



This figure summarizes an approach to evaluating for fibrosis in patients with MASLD. This algorithm is intended for use in conjunction with UpToDate content on the clinical features and diagnosis of MASLD. We use ultrasound-based elastography to evaluate for advanced fibrosis or cirrhosis. If imaging methods are not available, alternatives include serologic tests. Refer to UpToDate content on noninvasive assessment of hepatic fibrosis for details.

Further management of patients with cirrhosis includes screening for and preventing cirrhosis-related complications (eg, variceal bleeding, hepatocellular carcinoma).

MASLD: metabolic dysfunction-associated steatotic liver disease.

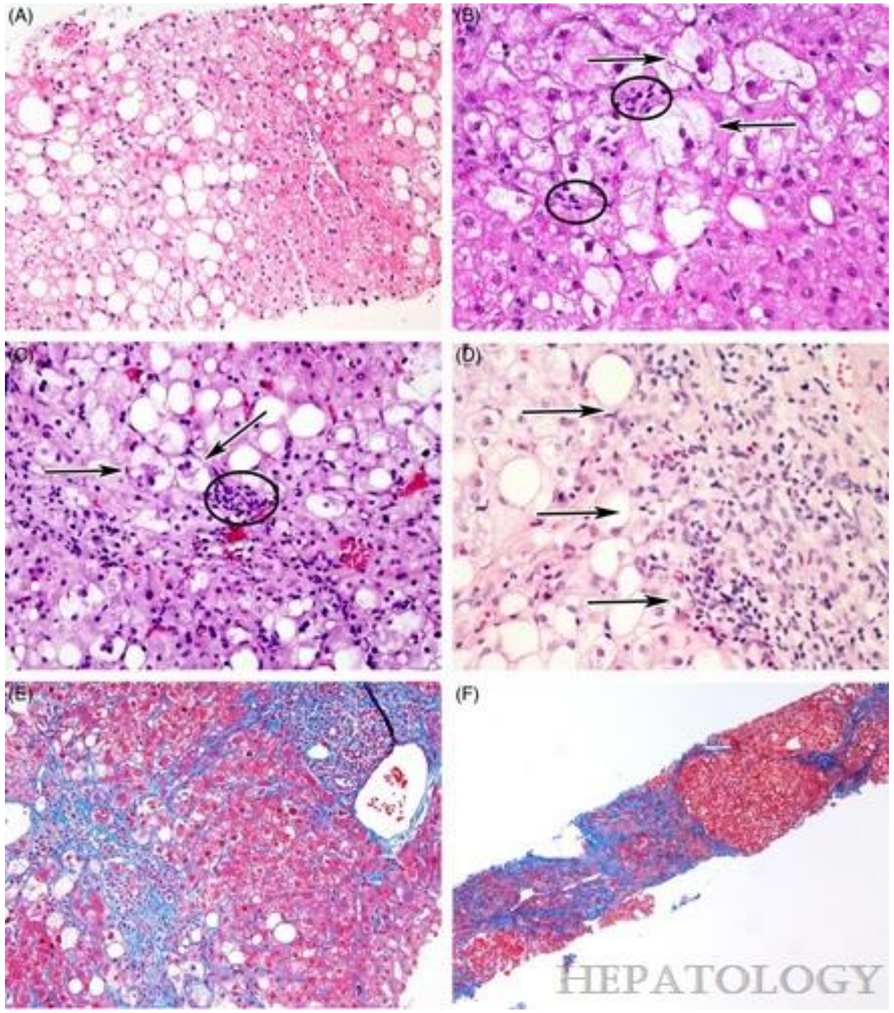
* Liver biopsy provides information on grading of necroinflammatory activity in addition to staging severity of fibrosis.

Data from:

1. *Mózes FE, Lee JA, Selvaraj EA, et al. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: An individual patient data meta-analysis. Gut 2022; 71:1006.*
2. *Loomba R, Wolfson T, Ang B, et al. Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: A prospective study. Hepatology 2014; 60:1920.*

Invasive Testing- Liver Biopsy

FIGURE 3



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Histology of NAFLD. Liver biopsy shows characteristic features of the spectrum of NAFLD. (A) Hepatic steatosis (typically zone 3) without ballooned hepatocytes or fibrosis [hematoxylin and eosin (H&E), ×200]. (B) Multiple ballooned hepatocytes with Mallory-Denk bodies (arrows) and mild lobular inflammation (circles) (H&E, ×400). (C) Ballooned hepatocytes (arrows) with moderate lobular inflammation (circle) (H&E, ×200). (D) Some cases of steatohepatitis may show significant portal inflammation and interface hepatitis (arrows) (H&E, ×200). (E) Dense perisinusoidal and periportal fibrosis (blue stain), with a thin connecting fibrotic bridge (Masson trichrome, ×200). (F) Cirrhosis (nodule formation) due to steatohepatitis (Masson trichrome, ×100).

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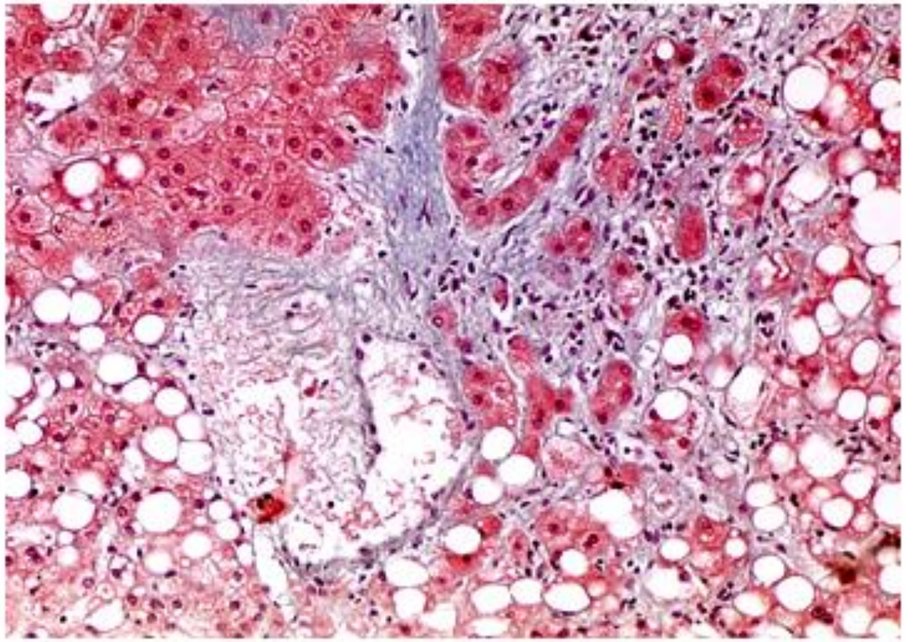
Liver biopsy showing metabolic dysfunction-associated steatohepatitis



Liver biopsy showing steatosis, hepatocyte balloon degeneration, mixed acute and chronic inflammation, and pericellular fibrosis. These are characteristic features of metabolic dysfunction-associated steatohepatitis (MASH), formerly termed nonalcoholic steatohepatitis (NASH).

Courtesy of Marshall M. Kaplan, MD.

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Treatment options

Guidance statements:

20. Patients with NAFLD who are overweight or obese should be prescribed a diet that leads to a caloric deficit. When possible, diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (e.g., Mediterranean diet) should be encouraged due to their additional cardiovascular benefits.

21. Patients with NAFLD should be strongly encouraged to increase their activity level to the extent possible. Individualized prescriptive exercise recommendations may increase sustainability and have benefits independent of weight loss.

Key points:

- *Weight loss improves hepatic steatosis, NASH, and hepatic fibrosis in a dose-dependent manner.*
- *The necessary support to manage comorbid disease and foster the adoption of liver protective health behaviors is best achieved using a multidisciplinary approach.*
- *Coffee consumption (caffeinated or not) of at least 3 cups daily is associated with less advanced liver disease.*

TABLE 6 - Potential impact of available medications on patients with NAFLD

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
Vitamin E (rrr-alpha) 800 IU daily[427,428]	NA	NASH without T2DM or cirrhosis	Liver related: improves steatosis, NASH resolution? No proven benefit on fibrosis	Hemorrhagic stroke, risk of prostate cancer?	No
Pioglitazone 30–45 mg po daily[429–431]	T2DM	NASH with and without T2DM	Liver related: improves steatosis, activity and NASH resolution, fibrosis improvement? Nonliver related: improves insulin sensitivity, prevention of diabetes, CV risk reduction and stroke prevention	Weight gain, risk of heart failure exacerbation, bone loss	Yes
Liraglutide[a] 1.8 mg s.c. daily (T2DM) 0.6–3 mg s.c. daily (obesity)[432]	T2DM, obesity	NASH without cirrhosis	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	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Semaglutide[b] 0.4 mg s.c. daily, 0.25–2.4 mg SQ weekly[433]	T2DM, obesity	NASH without cirrhosis	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	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Tirzepatide[434,435]	T2DM	T2DM or obesity with NAFLD	Liver related: reduces steatosis on imaging. Nonliver related: improvement in insulin sensitivity, significant weight loss	Gastrointestinal, gallstones related to weight loss, pancreatitis	Unknown
SGLT-2i[436–438]	T2DM	T2DM and NAFLD	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	Risk of genitourinary yeast infection, volume depletion, bone loss	Yes

Note: Available medications with demonstrable histological benefit in patients with biopsy-confirmed NASH. None of the medications are approved for treatment of NASH but can be used in carefully selected individuals with NASH and comorbid conditions such as diabetes and obesity or for off-label use.

Abbreviations: CV, cardiovascular; NA, not applicable; po, by mouth; s.c., subcutaneous; SGLT-2i, sodium glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus.

[a]Study with small sample size and underpowered to determine key histological outcomes (ie, fibrosis).

[b]Phase 3 trial to determine efficacy currently enrolling.

Guidance statements:

22. Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery, as it effectively resolves NAFLD or NASH in the majority of patients without cirrhosis and reduces mortality from CVD and malignancy.

Key points:

- *The type, safety, and efficacy of bariatric surgery in patients with well-compensated NASH cirrhosis is not established and requires a careful benefit–risk assessment by a multidisciplinary team of experts that includes a hepatologist.*
- *Decompensated cirrhosis should be considered an absolute contraindication for bariatric surgery due to increased risk and unproven liver-related benefit, unless performed in conjunction with liver transplantation at experienced centers.*

New Kid on the block

ORIGINAL ARTICLE

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Authors: Stephen A. Harrison, M.D., Pierre Bedossa, M.D., Ph.D., Cynthia D. Guy, M.D., Jörn M. Schattenberg, M.D., Rohit Loomba, M.D., M.H.Sc., Rebecca Taub, M.D., Dominic Labriola, Ph.D., +22, for the MAESTRO-NASH Investigators* Author Info & Affiliations

Published February 7, 2024 | N Engl J Med 2024;390:497-509 | DOI: 10.1056/NEJMoa2309000 | VOL. 390 NO. 6

CME

Abstract

BACKGROUND

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease with no approved treatment. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH with liver fibrosis.

METHODS

We are conducting an ongoing phase 3 trial involving adults with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]). Patients were randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.

RESULTS

Overall, 966 patients formed the primary analysis population (322 in the 80-mg resmetirom group,

Other options

Aspirin for Metabolic Dysfunction-Associated Steatotic Liver Disease Without Cirrhosis

A Randomized Clinical Trial

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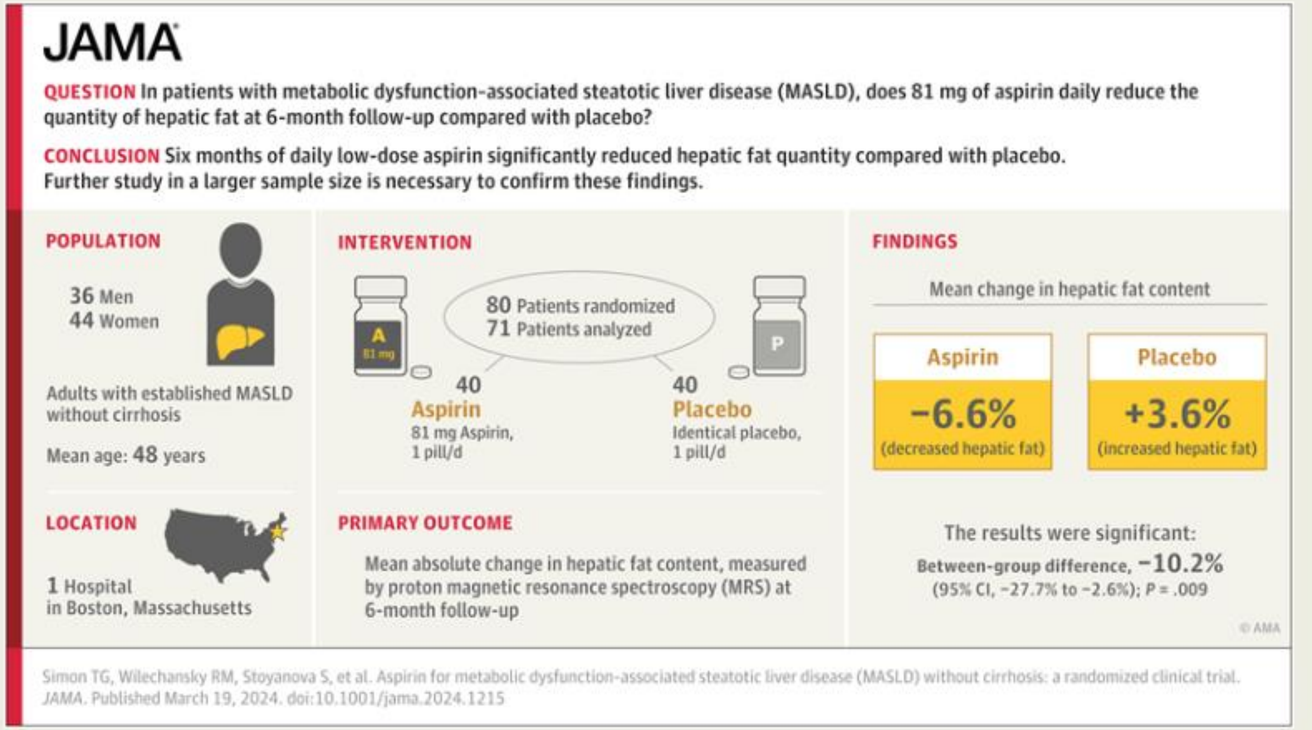
Visual Abstract



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SAVE

Topline data position GLP-1 newcomer survodutide as 'potential leading treatment' for MASH

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Key takeaways:

- Survodutide improved metabolic dysfunction-associated steatohepatitis in 83% of patients.
- Phase 2 data show improvement after 48 weeks without worsening of fibrosis stages F1, F2 and F3.

Perspective from Sobia Nasir Laique, MD

Topline findings from a phase 2 trial showed that survodutide achieved "statistically significant improvement" for metabolic dysfunction-associated steatohepatitis and liver fibrosis in 83% of patients, Boehringer Ingelheim announced.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH

Loomba R et al. DOI: 10.1056/NEJMoa2304286

CLINICAL PROBLEM

For patients with nonalcoholic steatohepatitis (NASH), the development of clinically significant fibrosis is associated with worse liver-related outcomes (e.g., progression to cirrhosis and hepatocellular carcinoma), cardiovascular events, and death. No pharmacologic treatment has been approved for NASH.

CLINICAL TRIAL

Design: A phase 2b, multicenter, double-blind, 24-week, randomized, placebo-controlled trial assessed the efficacy and safety of pegozafermin — a long-acting glycopegylated fibroblast growth factor 21 (FGF21) analogue — in adults with biopsy-confirmed NASH and moderate or severe fibrosis.

Intervention: 222 patients were assigned to receive subcutaneous pegozafermin (15 or 30 mg weekly or 44 mg once every 2 weeks) or placebo (weekly or once every 2 weeks). The primary end points, evaluated at week 24, were an improvement in fibrosis (defined as a reduction by ≥1 stage on a scale of 0 to 4) without worsening of NASH and NASH resolution without worsening of fibrosis.

RESULTS

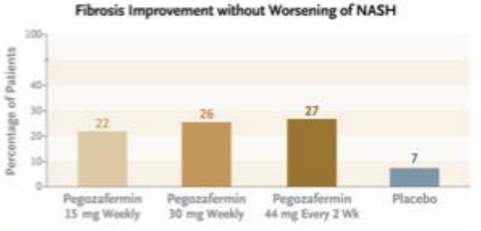
Efficacy: Treatment with the weekly 15-mg or 30-mg dose or every-2-week 44-mg dose of pegozafermin led to greater improvements in fibrosis than placebo.

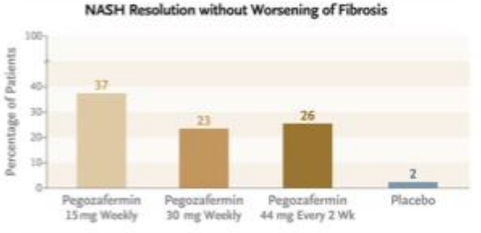
Safety: The most common adverse events were nausea, diarrhea, and injection-site erythema. No adverse events with a severity above grade 3 or deaths were reported.

LIMITATIONS AND REMAINING QUESTIONS

- Patients with newly diagnosed type 2 diabetes, or any illness that might affect the results of the trial or pose an additional risk to the participant, were excluded.
- Most of the patients were White, limiting the generalizability of the data.
- Longer-term data on safety and noninvasive biomarker assessments are needed.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

In patients with biopsy-confirmed NASH, pegozafermin treatment either weekly or every 2 weeks led to improvements in fibrosis over 24 weeks.

ENLIVEN extension topline data: Pegozafermin sustains 'robust benefits' in NASH at week 48

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Key takeaways:

- Pegozafermin sustained statistically significant improvements for nonalcoholic steatohepatitis at week 48.
- Patients with compensated cirrhosis and those on background GLP-1-based therapy showed robust benefits.

Perspective from Jamile' Wakim-Fleming, MD, FACG, FAASLD

Topline findings from an extension of the phase 2b ENLIVEN trial showed that pegozafermin sustained improvements in fibrosis and disease resolution for

Take Home Message

- MASLD leading to MASH and MASH cirrhosis is on the rise.
- Will be leading cause of liver cirrhosis.
- Weight reduction with Diet modification and exercise has been main stay till now.
- Newer treatment options on the Horizon.