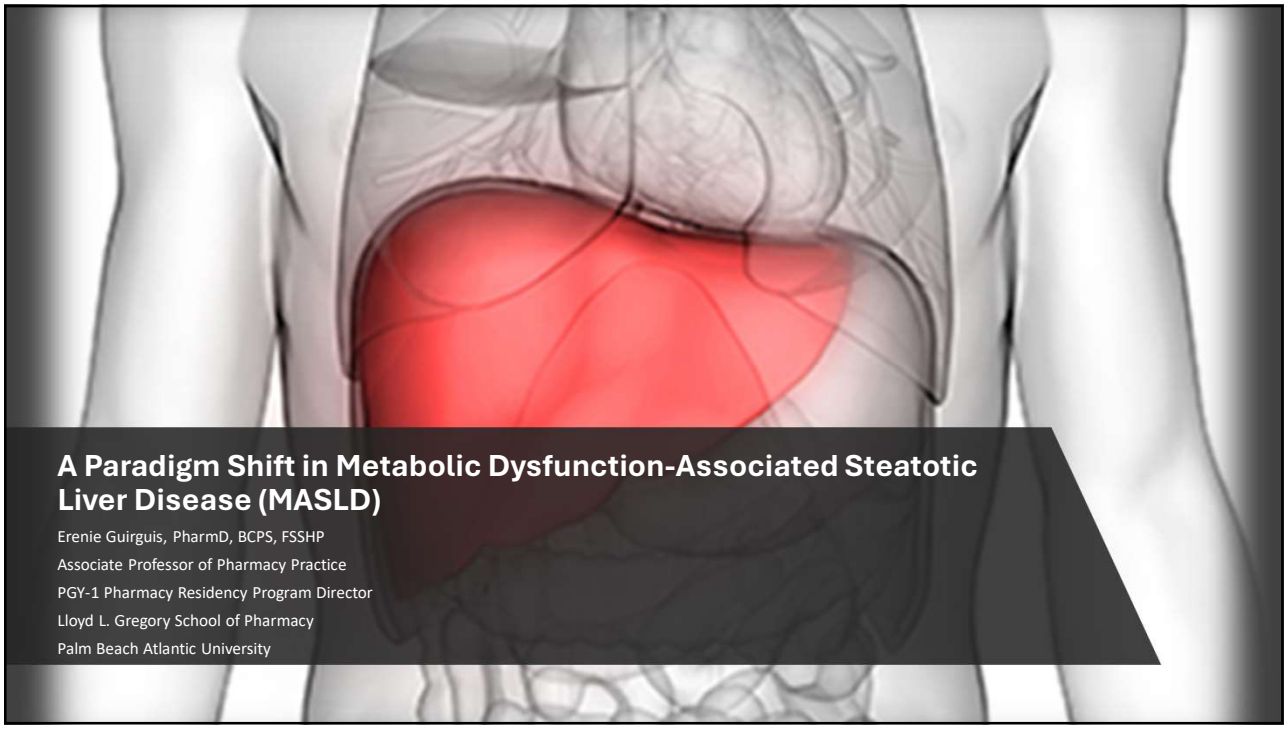

A Paradigm Shift in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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PGY-1 Pharmacy Residency Program Director
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Palm Beach Atlantic University

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Abbreviations

- **MASLD:** Metabolic dysfunction-associated steatotic liver disease
- **NAFLD:** Nonalcoholic fatty liver disease
- **MASL:** Metabolic dysfunction-associated steatotic liver
- **NAFL:** Nonalcoholic fatty liver
- **MASH:** Metabolic dysfunction-associated steatohepatitis
- **NASH:** Nonalcoholic steatohepatitis
- **HS:** hepatic steotosis
- **T2DM:** Type 2 diabetes mellitus
- **AST:** Aspartate aminotransferase
- **ALT:** Alanine transaminase
- **CKD:** Chronic kidney disease
- **OSA:** Obstructive sleep apnea
- **MAS**: MASLD Activity Score
- **FIB-4:** Fibrosis-4 Index
- **AASLD:** American Association for the Study of Liver Diseases
- **ADA:** American Diabetes Association
- **MRI-PDFF:** MRI-proton density fat fraction
- **NIT**: Noninvasive test
- **ELF:** Enhanced liver fibrosis
- **VCTE:** Vibration-controlled transient elastography
- **MRE:** Magnetic resonance elastography

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Objectives

- Discuss the nomenclature change from NAFLD to MASLD to increase disease awareness
- Recognize the associated burden of disease due to MASLD in adult patients
- Discuss the pathophysiology and clinical presentation of MASLD
- Review current national guideline recommendations for the treatment of patients with MASLD
- Evaluate recent literature on emerging treatment options and the real-world application for the management of MASLD patients

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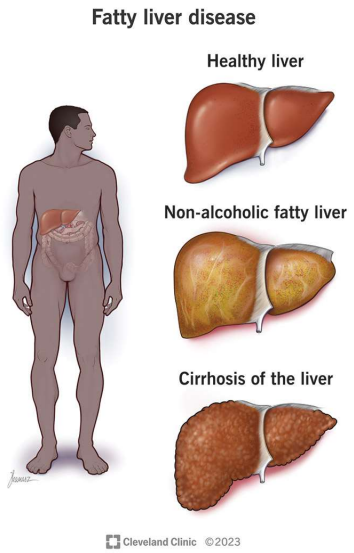
Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

- **≥5% of hepatocytes with macrovascular steatosis**
  - Absence of an alternative cause or significant alcohol intake
  - ≥1 cardiometabolic risk factor
    - Diabetes
    - Overweight/obesity
    - Hypotension
    - dyslipidemia
- Alternative causes
  - Drug induced
  - Nutrient deficiencies
  - Wilson's Disease
  - Celiac Disease
  - Significant alcohol
    - >21 drinks/week in men
    - >14 drinks/week in women



Rinella ME, *Hepatology*. 2023
Cusi K, *Endocr Pract*. 2022

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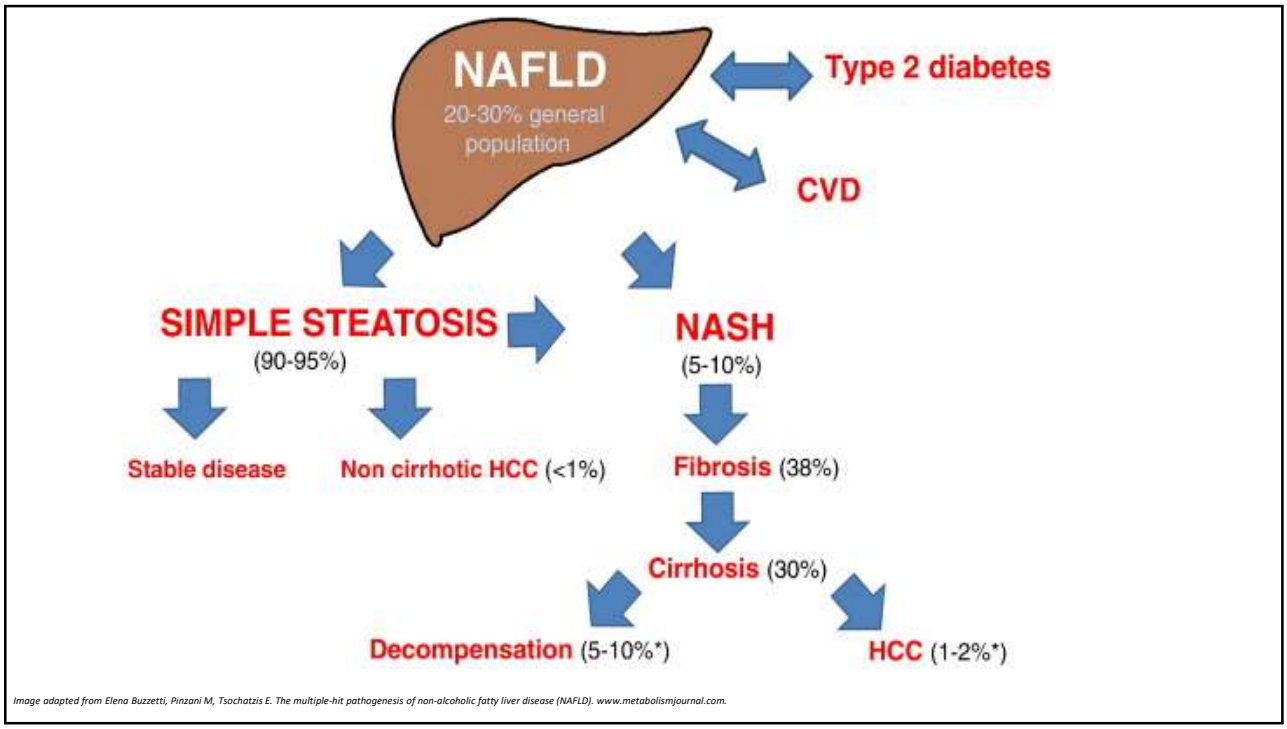

Image adapted from Elena Buzzetti, Pinzani M, Tsochatzis E. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). www.metabolismjournal.com.

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MASLD Spectrum

Risk Factors:
Obesity
Diabetes
Dyslipidemia
Metabolic Syndrome

MASL

Hepatosteatosis: fatty liver with no hepatocellular injury

Treatment options: currently limited to non-pharmacotherapy interventions

MASH

Steatohepatitis: fat accumulation + scarring

Treatment options:

Resmetirom

Insulin sensitizers

Vitamin E

Several agents in the pipeline

Advanced Liver Disease

Cirrhosis

Hepatocellular Carcinoma

MASLD is now a top indication for liver transplant

MASLD patients are TWICE a likely to die of cardiovascular disease than liver disease

Chalasani N et al. *Hepatology* 2018. ; 67: 328-357 doi:10.1002/hep.29367
Parikh NDet al. *Hepatology* 2019;70:487-495. doi:10.1002/hep.29473.

6

Nomenclature Change: Is it NAFLD or MASLD?

- NAFLD was potentially stigmatizing
- Online survey represented responses from 56 countries
- Steatotic liver disease (SLD) = overarching term that includes all etiologies of steatosis
- MetALD = those with MASLD who consume greater amounts of alcohol

Kanwal, et al. [6] Metabolic dysfunction–associated steatotic liver disease: Update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease. Hepatology. 2023

7

Prevalence

- Affects approximately 25% of adults worldwide
- MASLD (NAFLD) is the **most common form of liver disease in children** and has more than **doubled** over the past 20 years.
- Higher prevalence in South America, Middle East, and Asian countries
- Expected to be the top indication for liver transplant by 2030

Polyzos SA, et al. *Metab Clin Exp.* 2019;92;82-97. doi: 10.1016/j.metabol.2018.11.014.
Marchisello S, et al. *Int J Mol.* 2019;20:1-33. doi: 10.3390/ijms20081948.
Parikh ND, et al. *Hepatology* 2019;70:487-495. doi:10.1002/hep.29473.

8

Disease Costs

The annual burden is estimated as **$103 billion** in the United States ($1613 per patient).

The estimated lifetime direct medical costs were $222 billion for U.S. patients with NASH in 2017.

Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology*. 2016;64(5):1577-1586. doi:10.1002/hep.28785

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Pathophysiology

- MASLD results from the accumulation of fat in the liver in the form of triglycerides
- Triglycerides from free fatty acids (FFAs) are converted to very low-density lipoprotein (VLDL)
- When the triglycerides that need to be converted to VLDL exceed the livers capacity, the triglycerides accumulate within the hepatocytes termed hepatic steatosis (HS)
- Accumulation of fat then leads to inflammation and hepatocyte death, steatohepatitis (SH) which can eventually lead to end stage liver disease including cirrhosis, hepatocellular carcinoma, and ultimately liver failure

Petta S, et al. *Int J Mol Sci*. 2016;17(12):2082. doi:10.3390/ijms17122082

Rinella et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023. | DOI: 10.1097/HEP.0000000000000323

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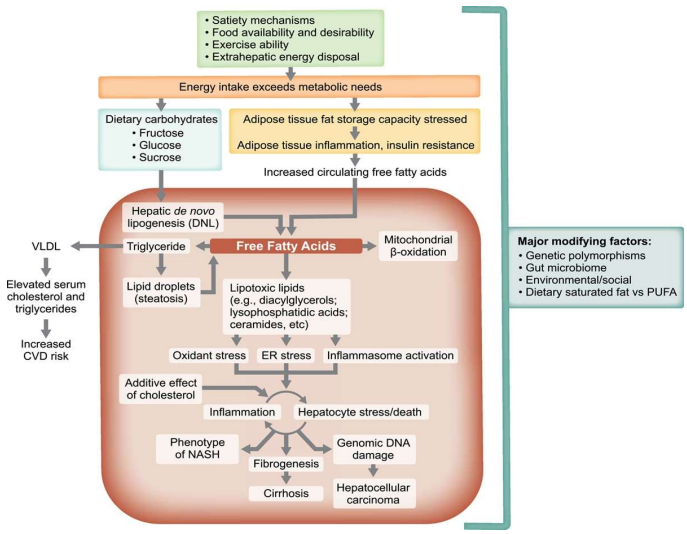
Pathogenic Drivers of MASLD



Rinella et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023. | DOI: 10.1097/HEP.0000000000000323

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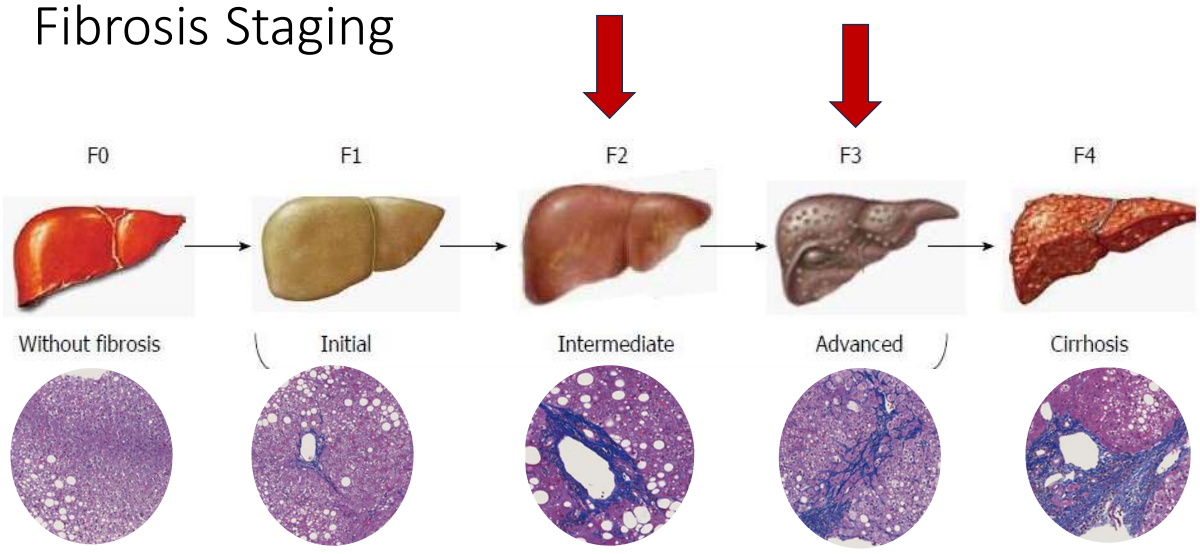
Fibrosis Staging



Rinella ME, *Hepatology*. 2023
Cusi K, *Endocr Pract*. 2022

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Knowledge Check

Which of the following statements accurately distinguishes MASH and MASLD?

A) MASH is a more advanced form of MASLD that involves inflammation and liver damage, whereas MASLD (MASL) is a less severe condition characterized by simple fat accumulation in the liver.

B) MASH and MASLD are two terms for the same condition with no significant differences between them.

C) MASLD is associated with significant liver inflammation and fibrosis, while MASH does not involve inflammation.

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Screening and Diagnosis

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Barriers and Solutions

Barriers

Lack of Awareness and Education:

Many healthcare providers and patients are not fully aware of MASLD and its implications, leading to underdiagnosis or misdiagnosis.

Limited Access to Diagnostic Resources:

Access to advanced imaging techniques (e.g., FibroScan, MRI-PDFF) and liver biopsy can be limited in some areas, especially in low-resource settings.

Solutions

Lack of Awareness and Education:

Increase education and training for healthcare professionals on MASLD. Public health campaigns can raise awareness among patients about the importance of liver health and screening, especially for those with risk factors like obesity, diabetes, and metabolic syndrome.

Limited Access to Diagnostic Resources:

Promote the use of non-invasive diagnostic tools like serum biomarkers and ultrasound, which are more widely available. Encourage the development and distribution of cost-effective diagnostic technologies.

Rinella ME, *Hepatology*. 2023
Cusi K, *Endocr Pract*. 2022

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Who should we screen for clinically significant fibrosis?

- Type 2 DM
- Family history of cirrhosis
- Imagining evidence of hepatic steatosis
- Moderate alcohol use
- ≥ 2 cardiometabolic risk factors:
  - Obesity (BMI ≥ 30 kg/m^2)
  - Prediabetes (A1c 5.7-6.4%)
  - Hypertension
  - Dyslipidemia

Rinella ME, *Hepatology*. 2023
Cusi K, *Endocr Pract*. 2022

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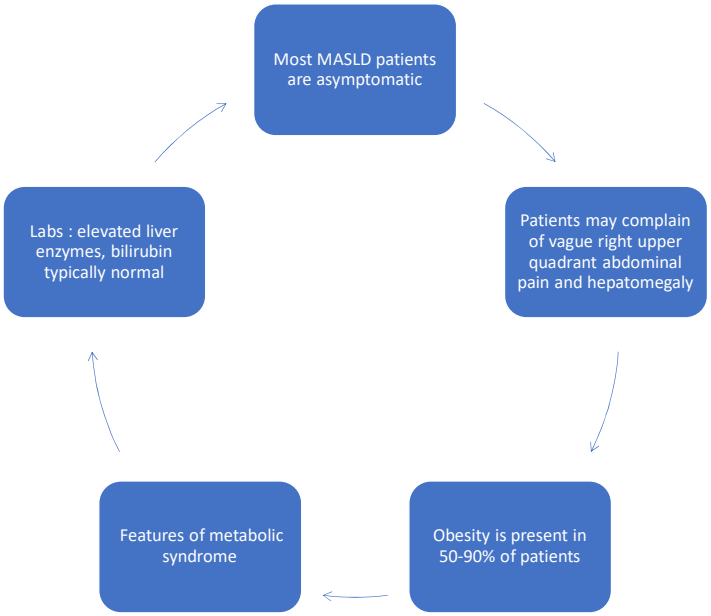
Clinical Manifestations



Rinella ME, *Hepatology*. 2023
Cusi K, *Endocr Pract*. 2022

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MASLD Complications

- Diabetes
- Cirrhosis
- Hepatocellular carcinoma
- Extrahepatic malignancy
- Microvascular complications
- Cardiovascular disease

Rinella ME, *Hepatology*. 2023

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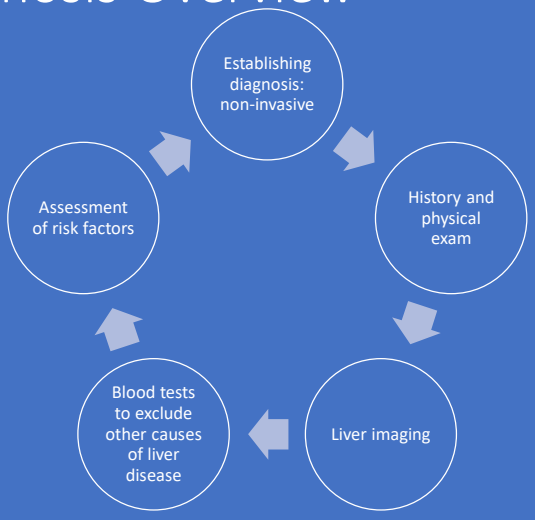
MASLD Screening/Diagnosis Overview

- Requires the following:
  - Increased liver fat content (MASL)
  - Presence of a cardiac metabolic risk factor (CMRF)
  - No other discernible cause of steatosis



Kanwal, F; Neuschwander-Tetri, Brent A. et al. [4] Metabolic dysfunction–associated steatotic liver disease: Update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease. Hepatology. 2023

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Diagnostic Tools

MASL: Liver Imaging

- Ultrasound (US)
- Magnetic resonance imaging (MRI)
- Computed tomography (CT)

Coupled with imaging tests, non-invasive scoring tools can predict the risk of fibrosis and inflammation (MASH)

- **Fibrosis-4 index (FIB-4)**
  - **Most cost effective for initial screening of advanced fibrosis**
  - **AASLD, AACE, and ADA all recommend initial screening with FIB-4 in primary care setting**
- ELF or VCTE for secondary risk assessment

MASH: Liver Biopsy (historically Gold Standard)

- Liver biopsy is the gold standard for diagnosis and staging (0-4)
- NAFLD activity score (NAS) or Steatosis Activity Fibrosis (SAF) score quantify the histological changes

Chalasani N et al. *Hepatology* 2018.; 67: 328-357 doi:10.1002/hep.29367

20

Non-invasive Test: FIB-4

FIB-4 $\frac{Age\ (years)\ x\ AST}{Platelet\ Count\ x\ \sqrt{ALT}}$

Different cutoffs to determine risk

- ≥1.3 requires action (secondary risk assessments)
- Cutoffs change for older adults

Determines need for biopsy

High negative predictive value

Rinella ME, *Hepatology*. 2023
Cusi K, *Endocr Pract*. 2022

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The NAFLD Activity Score (NAS)

Item	Definition	Score
Steatosis	<5%	0
	5-33%	1
	>33%-66%	2
	>66%	3
Lobular inflammation	No foci	0
	<2 foci/x200 field	1
	2-4 foci/x200 field	2
	>4 foci/x200 field	3
Hepatocyte ballooning	None	0
	Few balloon cells	1
	Many cells/prominent ballooning	2

"Definite" MASH:
NAS≥5

Common clinical outcome:
≥2 reduction in NAS

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Cusi K, *Endocr Pract*. 2022

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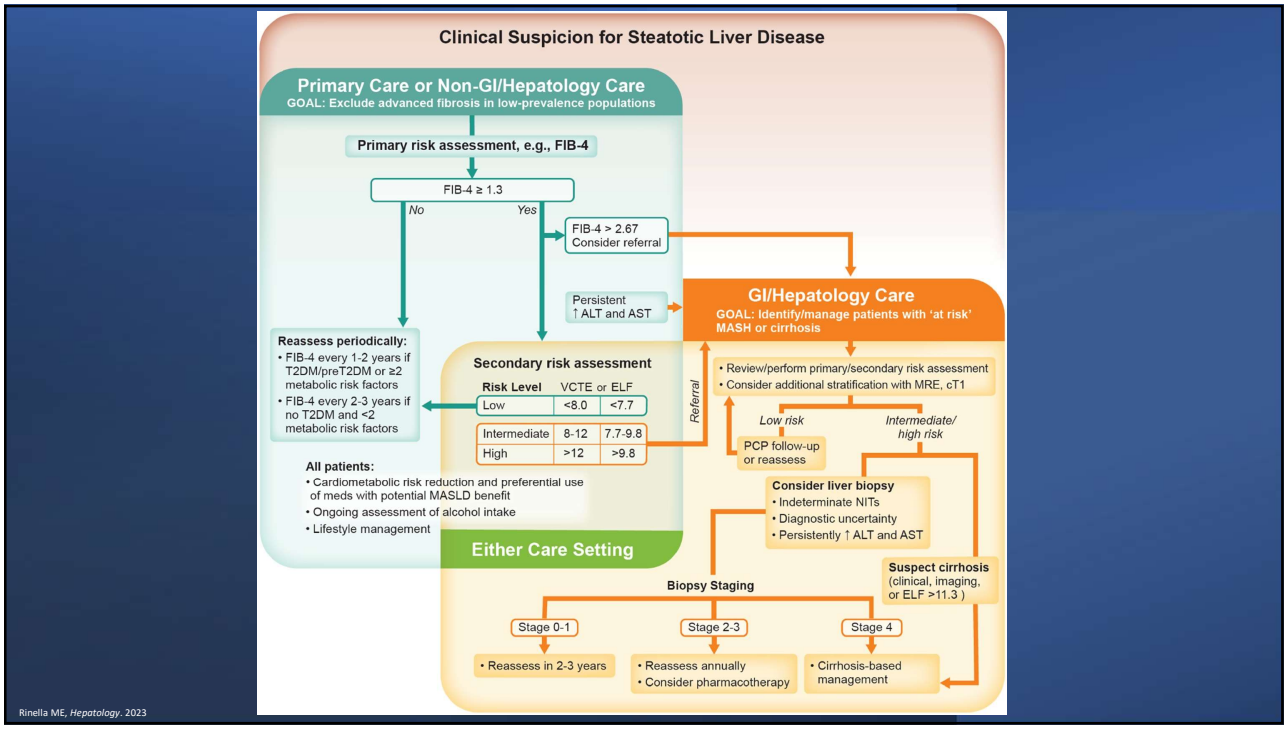

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Knowledge Check

Which of the following patients should be screened for clinically significant fibrosis?

A. 72 y/o male with obesity and osteoarthritis
B. 37 y/o female with endometriosis and type 2 diabetes
C. 64 y/o female with hyperlipidemia and osteoporosis
D. 55 y/o male with type 1 diabetes and hypertension

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Knowledge Check

For a 40-year-old individual with obesity, type 2 diabetes, and elevated liver enzymes, which of the following screening tools would be most appropriate to initiate for clinically significant fibrosis screening?

A) Liver Biopsy

B) Transient Elastography (FibroScan)

C) Magnetic Resonance Imaging (MRI)

D) FIB-4

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Treatment

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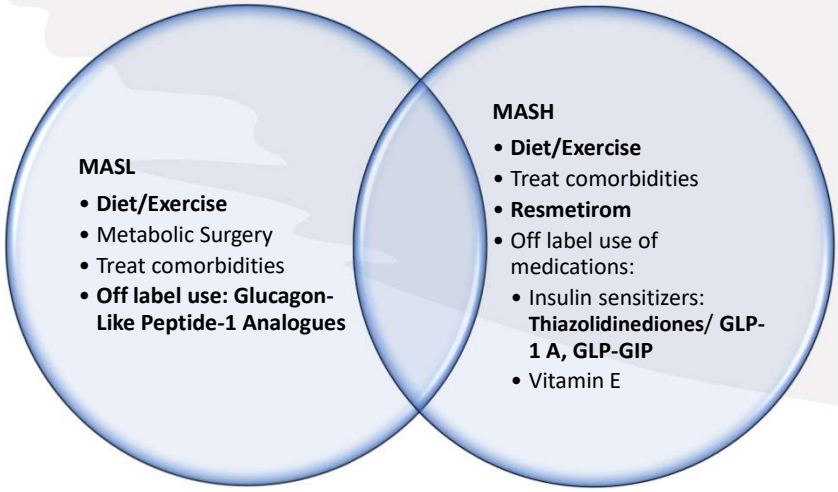
Treatment Overview



Rinella ME, *Hepatology*. 2023

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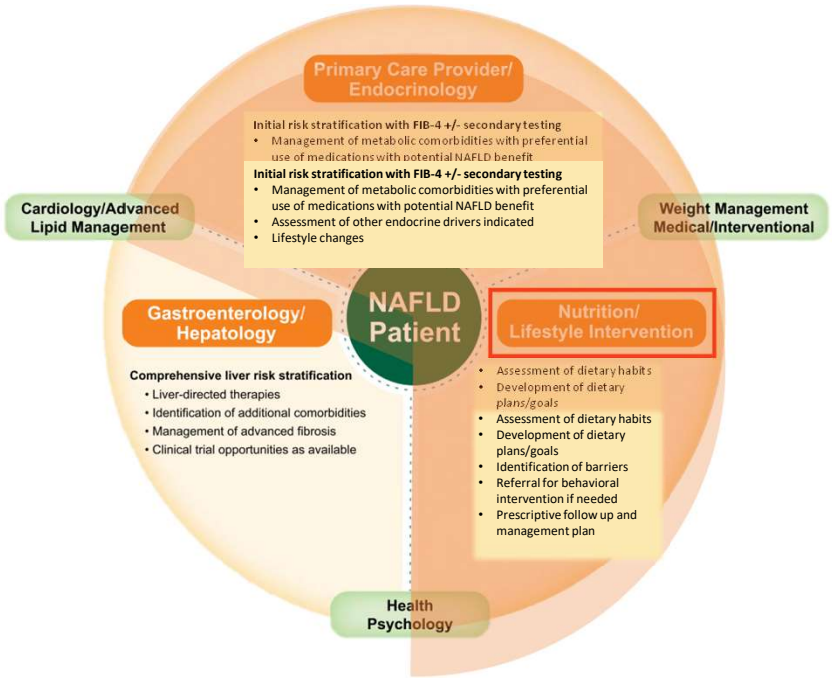

Rinella ME, *Hepatology*. 2023

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MASL: Treatment Options

Diet plus exercise

- 3-5% for improvement in HS
- Goal of 7-10% total body weight loss to improve liver histology
- Mediterranean diet has the highest evidence
- Avoid high fructose corn syrup
- Physical activity: > 150min/week

AASLD Guidelines: no current pharmacotherapy recommendations

Antidiabetic agents being studied:

- **Glucagon-like peptide-1 receptor agonist (GLP-1 RAs)**
- Sodium glucose cotransporter 2 inhibitor (SGLT2i)
- Dipeptidyl peptidase 4 inhibitors (DPP-4i)

Rinella ME, *Hepatology*. 2023
Doughtery et al. Annals of Pharmacotherapy. 2020. https://doi.org/10. 1177/1060028020935105
Ranjbar G et al. *Metabolism* 2019;101:1-23.doi.org/10.1016/j.metabol.2019.154001

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Proposed Mechanism: GLP-1RAs

Increase insulin sensitivity

Increase lipid metabolism and hepatic insulin signaling in hepatocytes

Appetite suppression/weight loss

Cardiovascular benefits

Doughtery et al. Annals of Pharmacotherapy. 2020. https://doi.org/10. 1177/1060028020935105

30

Trial Results: GLP-1 RAs

Study	Participants	Intervention Arms/Outcomes	Results
Khoo et al. *Liver Int.* 2019; 39:941-949. doi:10.1111/liv.14065.	Singaporean, NAFLD w/o T2DM Mean age~41 yo Mean BMI ~33 kg/m^2	LG vs diet and exercise Changes in LFF at 26 weeks via MRI	Significant reduction in LFC in both the LG and diet and exercise arm
Yan et al. *Hepatology* 2019;69:2414-2426. doi: 10.1002/hep.30320	Chinese, NAFLD w/T2DM Mean age~45 yo Mean BMI ~30 kg/m^2	Metformin + LG, vs metformin + sitagliptin, vs metformin + insulin glargine Changes in IHL 26 weeks using MRI-PDFF	LG and sitagliptin improved IHL; LG displayed better results
Petit et al. *J Clin Endocrinol Metab.* 2017;102:407-415. doi:10.1210/jc.2016-2775	French, NAFLD w/T2DM Mean age~57 yo Mean BMI~36 kg/m^2	Oral antidiabetic agents + LG vs intensification of insulin regimen Change in LFC at 6 months via MRI	LG arm caused a significant reduction in LFC

LG= liraglutide, LFC= liver fact content, IHL= intrahepatic lipid, IHF= intrahepatic fat

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Study	Participants	Intervention/Outcomes	Results
Feng et al. J Diabetes. 2017;9:800-809. doi:10.1111/1753-0407.12555.	Chinese, NAFLD w/T2DM Mean age~47 yo Mean BMI~28 kg/m^2	LG vs metformin or gliclazide Change in IHF 24 weeks by ultrasonography	LG arm reduced IHF significantly more than metformin or gliclazide
Tang et al. Diabetes Care 2015;38:1339-1346. doi:10.2337/dc14-2548.	Canadian, NAFLD w/T2DM Mean age~60 yo Mean BMI ~31 kg/m2	Oral antidiabetic agents + LG vs insulin glargine Change in LFC at 12 weeks via MRI	LFC decreased in both arms; LG displayed better results than insulin glargine
Shao et al. Diabetes Metab Res Rev. 2014 Sep;30(6):521-9. doi:10.1002/dmrr.2561.	Chinese, NAFLD w/T2DM Mean age~43 yo Mean BMI ~30 kg/m2	Insulin glargine + exenatide vs insulin glargine + insulin aspart Change in LFC at 12 weeks via US	LFC decreased statistically in the exenatide arm vs insulin aspart

LG= liraglutide, LFC= liver fact content, IHL= intrahepatic lipid, IHF= intrahepatic fat

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MASL: Trial Takeaways

- GLP-1RA studies demonstrated improvement in HS
- When GLP-1RAs were compared to diet and exercise, diet and exercise demonstrated more long-standing improvements in HS
- Off label use which limits patient access without other comorbidities

Doughtery et al. Annals of Pharmacotherapy. 2020.doi.org/10.1177/1060028020935105
Chalasani N et al. *Hepatology* 2018. ; 67: 328-357 doi:10.1002/hep.29367
Acharya T et al. *Prog Cardiovasc Dis* 2019;62:342–348. doi.org/10.1016/j.pcad.2019.08.003.

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MASL: Additional Considerations

- MASLD patients often have comorbid obesity, metabolic syndrome, and T2DM which increase the risk of cardiovascular disease
- Cardiovascular disease is the leading cause of mortality in MASLD patients
- GLP1-RAs assist with weight loss and have cardiovascular benefits
- These agents are preferred in the management of T2DM in the ADA 2024 guidelines

Doughtery et al. Annals of Pharmacotherapy. 2020.doi.org/10.1177/1060028020935105
Kinella ME, *Hepatology*. 2023
American Diabetes Association. *Standards of Medical Care in Diabetes – 2024*. Diabetes Care. 2024;47

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MASH Treatment

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Treatment Options

- **Resmetirom (only FDA approved agent)**
- GLP-1 Agonists
- Dual GLP-1/GIP Agonists
- Pioglitazone
- Vitamin E

Lifestyle Management!

Rinella ME, *Hepatology*. 2023

Younossi Z, et al. Tirzepatide for the treatment of non-alcoholic steatohepatitis: results from the SYNERGY-NASH study. *Lancet*. 2024. doi:10.1016/S0140-6736(24)00692-0

Smith J, et al. Effects of Tirzepatide on Liver Fat Content in Patients with Type 2 Diabetes: A Sub analysis of the SURPASS-3 MRI Study. *Diabetes Care*. 2024;doi:10.2337/dc24-1234.

Madrigal Pharmaceuticals Inc. *Resmetirom* [package insert]. Dallas, TX: Madrigal Pharmaceuticals Inc; 2024.

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Treatment Overview

- Lifestyle modifications
- Management of comorbid conditions
- Pharmacological interventions
  - **Remetirom (Razdiffra®): only FDA approved agent for F2/F3 fibrosis**
  - **Insulin sensitizers:**
    - Thiazolidinediones (pioglitazone)
    - GLP-1 receptor agonists
    - GIP/GLP-1 receptor agonists
  - Antioxidants: Vitamin E
    - Fallen out of favor due to bleed risk and relationship with prostate cancer
    - Limited recommendation in US guidelines and NOT recommended in European guidelines

Rinella ME, *Hepatology*. 2023
EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). Hepatology. 2024
Madrigal Pharmaceuticals Inc. *Resmetirom* [package insert]. Dallas, TX: Madrigal Pharmaceuticals Inc; 2024.

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Resmetirom (Rezdiffra®)

- MOA: thyroid hormone receptor (THR) agonist
- Administration: Resmetirom can be taken with or without food.
- Dosing :
  - Based on patients actual body weight:
    - For patients weighing less than 100 kg, the dosage is 80 mg taken orally once daily and patients weighing 100 kg or more, the dosage is 100 mg taken orally once daily.
- Drug-drug interactions
  - Substrate for CYP2C8, dosage adjustments are necessary when resmetirom is used alongside strong and moderate CYP2C8 inhibitors.
  - It is not recommended to administer resmetirom with potent CYP2C8 inhibitors such as gemfibrozil.
- Side effects
  - diarrhea and nausea (10%), self limiting

Madrigal Pharmaceuticals Inc. *Resmetirom* [package insert]. Dallas, TX: Madrigal Pharmaceuticals Inc; 2024.
Ratziu V et al. Efficacy and safety of MAESTRO-NASH in patients with nonalcoholic steatohepatitis: results from the Phase 3 MAESTRO-NASH study. *J Hepatol*. 2024. doi:10.1016/j.jhep.2024.04.003

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Resmetirom Evidence

Study	Intervention/Control	Pt Demographics	Outcomes	Results
Phase 2	Resmetirom 80mg Placebo	HFF of >10% , biopsy, liver biopsies w/ stages F1-3 w/ NAS of > 4	LFF Duration: 6 months	Significant reduction in LFF compared with placebo
MAESTRO-NASH Phase 3	Resmetirom 80mg/ 100mg Placebo	Biopsy proven NASH (F2-3), with MRI confirmed HS	NASH resolution; composite long-term outcomes (all-cause mortality, cirrhosis, and other liver-related events) 12 months	Resmetirom resulted in a significantly higher percent of NASH resolution and fibrosis improvement in both treatment arms

Harrison et al. The Lancet. 2019; 394(10213):2012-2024. doi:10.1016/S0140-6736(19)32517-6

Ratziu V et al. Efficacy and safety of MAESTRO-NASH in patients with nonalcoholic steatohepatitis: results from the Phase 3 MAESTRO-NASH study. *J Hepatol*. 2024. doi:10.1016/j.jhep.2024.04.003

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Insulin Sensitizers

- GLP-1 Agonists
  - Liraglutide
  - Semiglutide
- Pioglitazone
- Tirazepatide

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GLP-1RAs Evidence

LEAN trial	Interventions	Outcomes (after 48 weeks)	Results (Liraglutide vs. placebo)
Phase 2 multicenter RCT Overweight patients with NASH (n=52)	▪ Liraglutide 1.8 mg SC daily ▪ Placebo SC daily	Resolution of NASH	Significantly more resolution of NASH
		Fibrosis progression	Significantly less fibrosis progression

Newsome, et al. 2021	Interventions	Outcomes (after 72 weeks)	Results (SMG 0.4mg vs placebo)
Phase 2b RCT Patients with biopsy-confirmed NASH and fibrosis (F1-F3) (n=320)	▪ Daily semaglutide 0.1, 0.2, or 0.4 SC mg ▪ Placebo SC daily	Resolution of NASH	Significantly more resolution of NASH
		Improvement in fibrosis stage	• No difference in improvement in fibrosis

Armstrong MJ, *Lancet*. 2016
Newsome PN, *N Engl J Med*. 2021

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Tirzepatide Evidence: Dual GIP/GLP-1 As

SURPRASS-3 MRI Study	Interventions	Outcomes	Results
A sub study of the randomized, open-label, parallel-group, phase 3 SUPRPRASS-3 trial	Tirzepatide weekly	The impact of tirzepatide on liver fat content in patients with type 2 diabetes using MRI	Tirzepatide 10mg and 15mg had a significantly higher reduction in LFC than insulin degludec group

SYNERGY-NASH Study	Interventions	Outcomes	Results
Phase 2, dose-finding, multicenter, double-blind, randomized, placebo-controlled trial involving participants with biopsy-confirmed MASH and stage F2 or F3 fibrosis	Tirzepatide weekly (5 mg, 10 mg, or 15 mg	-Resolution of MASH without worsening of fibrosis at 52 weeks. -Improvement (decrease) of at least one fibrosis stage without worsening of MASH.	Tirzepatide had a significantly higher percent resolution of NASH and decrease in at least one fibrosis stage in all dose groups than placebo

Smith J, et al. Effects of Tirzepatide on Liver Fat Content in Patients with Type 2 Diabetes: A Sub analysis of the SURPASS-3 MRI Study. *Diabetes Care*. 2024;doi:10.2337/dc24-1234.
Younossi Z, et al. Tirzepatide for the treatment of non-alcoholic steatohepatitis: results from the SYNERGY-NASH study. *Lancet*. 2024. doi:10.1016/S0140-6736(24)00692-0.

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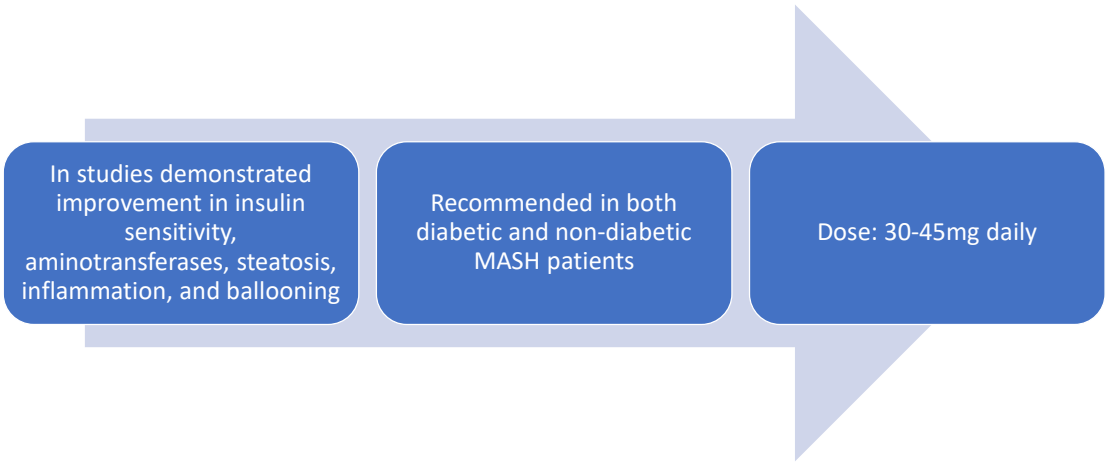
Pioglitazone



Sanyal AJ, *N Engl J Med*. 2010
Cusi K, *Ann Intern Med*. 2016

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Evidence for Pioglitazone

PIVENS trial	Interventions	Outcomes	Results* (PG vs. placebo)
Multicenter RCT Patients with NASH <u>without</u> diabetes (n=247)	96 weeks of treatment ▪ Pioglitazone 45 mg daily ▪ Vitamin E (rrr α-tocopherol) 800 IU daily ▪ Placebo daily	Histological improvement (≥2-point reduction in NAS)	Significant histological improvement
		NASH resolution	• Significantly more NASH resolution
Cusi, et al. 2016	**Interventions**	**Outcomes**	**Results (PG vs. placebo)**
RCT (single-center) Patients <u>with</u> T2DM or pre-DM and NASH (n=101)	18 months of treatment ▪ Pioglitazone 45 mg daily ▪ Placebo daily	Histological improvement (≥2-point reduction in NAS)	Significant histological improvement
		NASH resolution	Significantly more NASH resolution

Sanyal AJ, *N Engl J Med*. 2010
Cusi K, *Ann Intern Med*. 2016

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Antioxidants: Vitamin E

- MOA: antioxidant; inhibits oxidative stress
- In studies demonstrated improvement in steatosis, aminotransferases, inflammation, and ballooning with resolution in steatohepatitis
- Safety has been quested due to varying results in all-cause mortality in patients taking > 800 IU daily
- Currently only recommended in non-diabetic NASH patients in AASLD guidelines

Chalasani N et al. *Hepatology* 2018. ; 67: 328-357 doi:10.1002/hep.29367

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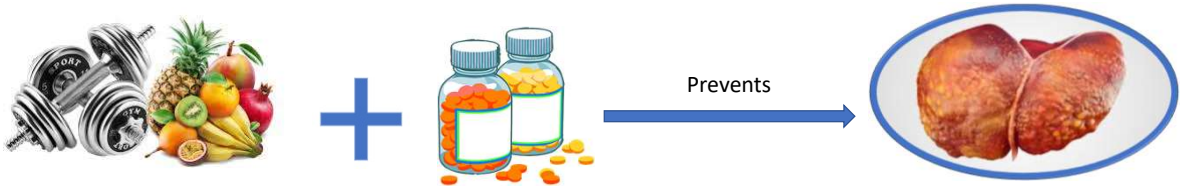
Take Home points

- If MASH is diagnosed and advanced fibrosis is present the only FDA approved treatment is resmetirom
- GLP-1s and GIP/GLP-1 agonists have positive data
- In MASH pioglitazone can be considered in diabetic and non-diabetic patients; while vitamin E can be considered in non-diabetic patients however falling out of favor
- Several novel agents are in phase 3 trials for the treatment of NASH



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Knowledge Check

Which of the following statements accurately describes the role of resmetirom in the treatment of MASH (Metabolic Associated Steatotic Hepatitis)?

A) **Resmetirom is an insulin sensitizer that improves blood sugar control in MASH patients.**

B) **Resmetirom is an oral medication that targets thyroid hormone receptors to reduce liver fat and inflammation in MASH.**

C) **Resmetirom is a type of statin used to lower cholesterol levels and directly address liver fibrosis in MASH.**

D) **Resmetirom is an antioxidant supplement that helps in reducing oxidative stress and improving liver function in MASH.**

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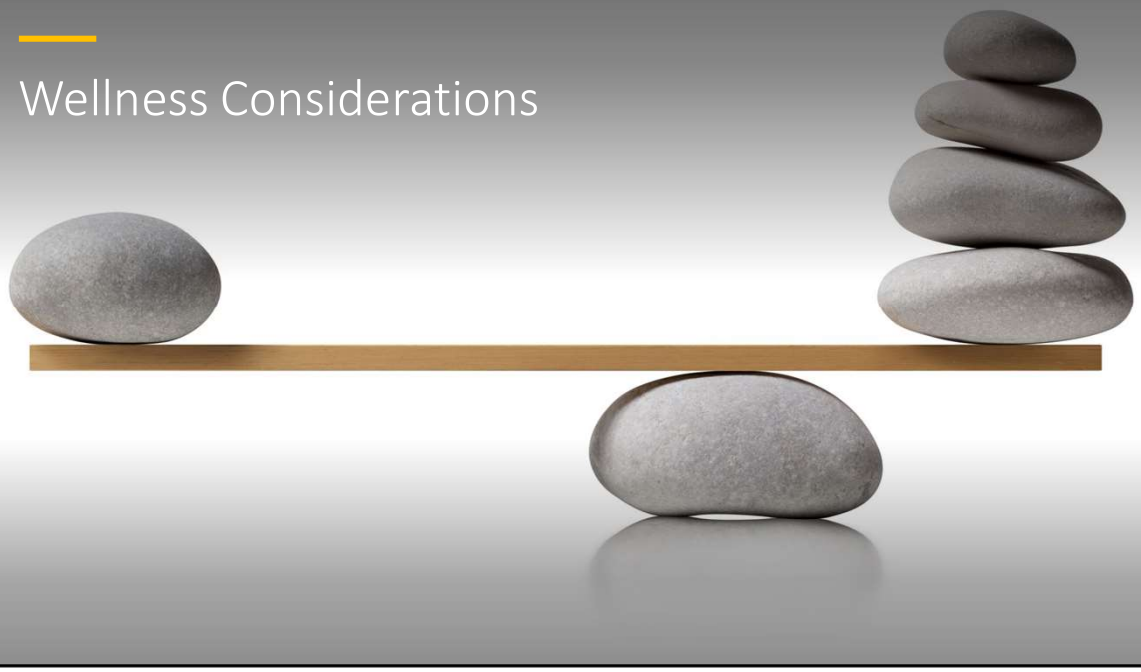
Wellness Considerations



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Preventing Complications

Ensure vaccines are up to date

Hepatitis A and B series complete

Pneumococcal vaccine

- 1 dose of PCV 30

Counseling points

Avoid alcohol use

Avoid foods with high saturated fats

Treatment will likely be multimodal

Ensure appropriate treatment of comorbid conditions

Avoid hepatotoxic medications and supplements

Rinella ME, Hepatology. 2023
Cusi K, *Endocr Pract*. 2022

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Pipeline Therapies

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Pipeline Medications: Phase 3

PPAR alpha/delta agonist

Elafibranor | Lanafibranor

↓

Fibroblast growth factor (FGF) analog

Pegozafermin

↓

CCR2/5 Dual Antagonists:

Cenicriviroc (CVC):

Doughtery et al. Annals of Pharmacotherapy. 2020.doi.org/10.1177/1060028020935105
Clinicaltrials.gov

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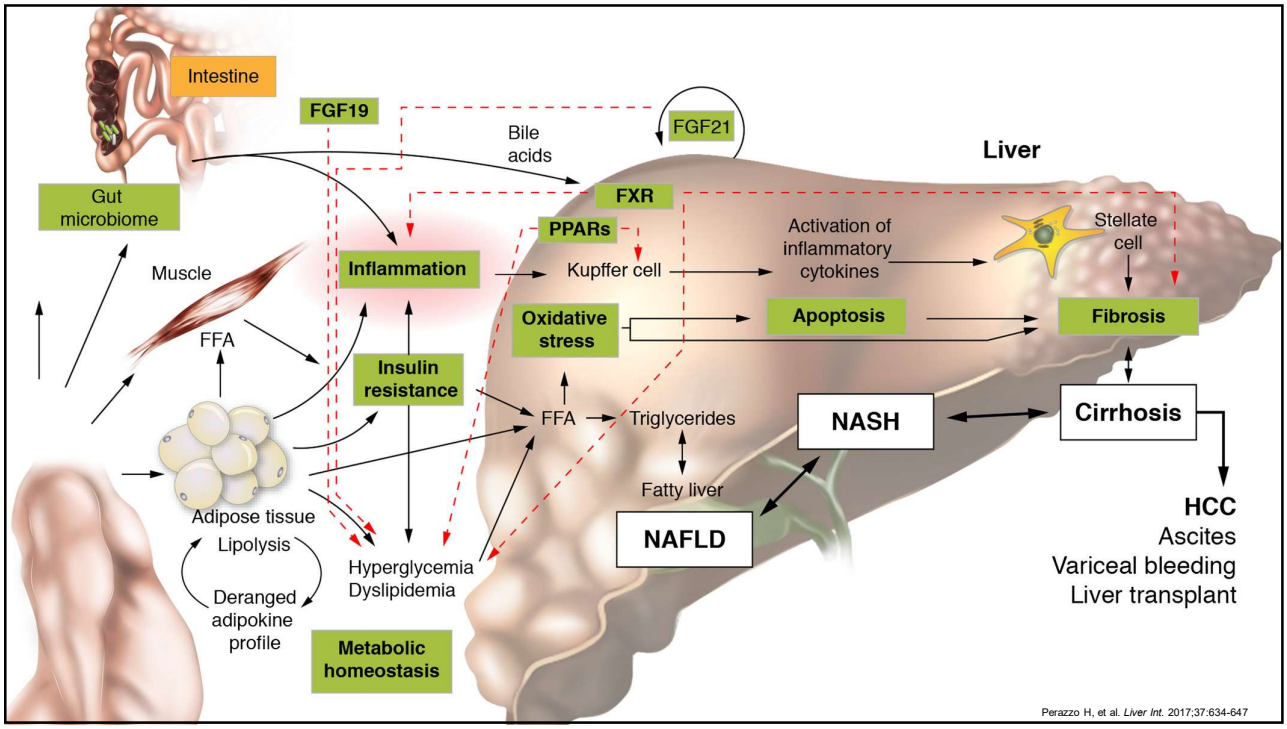

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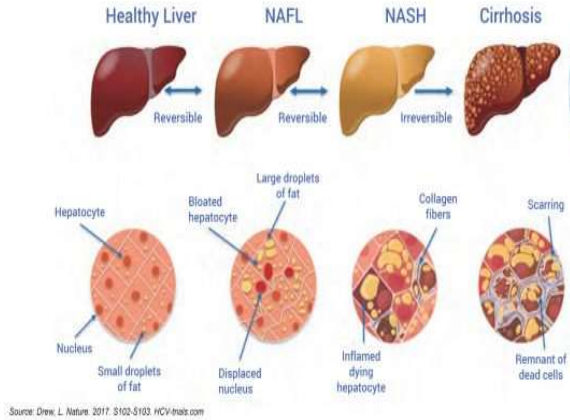
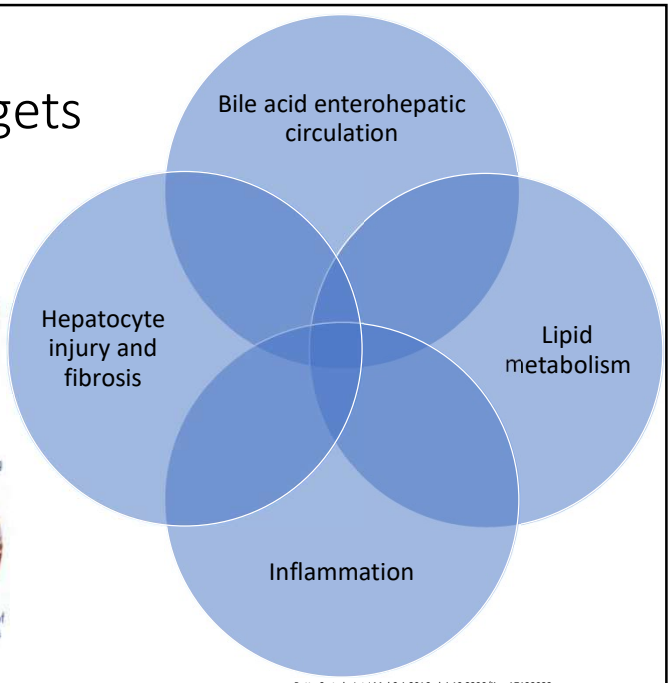
Novel Medication Targets





Petta S et al. *Int J Mol Sci*. 2016. doi:10.3390/ijms17122082

Carr RM et al. *Gastroenterol Clin North Am*. 2016. doi:10.1016/j.gtc.2016.07.003

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Elafibranor/Lanifibranor Pharmacology

- Medication class: peroxisome proliferator-activated receptor (PPAR) alpha/delta agonist
- Structurally similar to rosiglitazone and pioglitazone (TZDs)
- PPAR-alpha receptor activation increasing lipid metabolism
- PPAR-delta receptor activation reduces the production of atherosclerotic plaques as a result of decreasing tumor necrosis factor alpha (TNFa), adhesion proteins, and inflammatory chemoattractant proteins

Perazzo H, et al. *Liver Int*. 2017;37:634-647

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Elafibranor: Clinical Trials

Author/ Study Design	Intervention/ Control	Pt Demographics	Primary endpoint/Study duration	Results
RESOLVE-IT-Phase 3	Elafibrinor 120 mg (n=717) Placebo (n=353)	BMI<45 kg/m2, NAS≥4, NASH CRN F1≤F4	NASH resolution w/o worsening of fibrosis Duration: 18 mo	19.2% vs 14.7% p=0.0659

ClinicalTrials.gov. RESOLVE-IT

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Lanifibranor Clinical Trials

Trial name	Intervention	Patient Demographics	Primary Endpoint	Results
NATIV3	Lanifibranor	Biopsy prove "at risk NASH" patients	NASH resolution and no worsening of fibrosis and improvement of fibrosis with no worsening of NASH	Pending

ClinicalTrials.gov. NATIV3

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Trial Highlight: Pegozafermin

- Mechanism: fibroblast growth factor 21 (FFGF21) analog → endocrine messengers that regulate lipid and carbohydrate metabolism

ENLIVEN trial	Interventions	Patient Demographics	Primary Endpoints (at 24-weeks)	Results		
				15 mg vs placebo	30 mg vs placebo	44 mg vs placebo
Phase 2b RCT	▪ Pegozafermin	▪ Patients with biopsy-confirmed NASH (F2-F3) (n=222)	Improvement in fibrosis by ≥1 stage w/o worsening NASH	22% vs. 7% (CI -9-38)	26% vs. 7% (CI 5-32, p=0.009)	27% vs. 7% (CI 5-35, p=0.008)
			NASH resolution w/o worsening fibrosis	37% vs. 2% (CI 10-59)	23% vs. 2% (CI 9-33)	26% vs. 2% (CI 10-37)
FALCON Phase 3 study	▪ Pegozafermin	▪ Patients with biopsy confirmed NASH (F2-F3)	Improvement in liver fibrosis by at least one stage without worsening of NASH	Pending		

Loomba R, *N Engl J Med.* 2023
Clinicaltrials.gov

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Cenicriviroc Clinical Trials

- Mechanism of action: a dual CCR2/CCR5 antagonist which inhibits inflammatory cell trafficking, which can help reduce inflammation and fibrosis in the liver

Trial	Intervention	Patient Demographics	Primary Endpoints	Results
AURORA trial	Cenicriviroc	biopsy-confirmed NASH and fibrosis stage F2 or F3	proportion of patients achieving at least a 1-stage improvement in liver fibrosis without worsening of NASH	Pending

ClinicalTrials.gov. AURORA

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Assessment Questions

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Patient Case

- **CC:** DA is a 38 YO female pt sent by PCP to GI for abnormal liver labs**.** She is also very concerned about her weight and says diets just don't work well for her.
- **HPI:** Patient has a history of obesity and struggles with weight loss. In addition, her PCP told her that her liver enzymes were a little elevated so she may have fatty liver.
- **PMH:** DM2, HLD, HTN, PCOS, Ovarian mass
- **Allergies:** shellfish (lips swelling)
- **SH:** (-) tobacco and alcohol use
- **ROS:** (-), but complains of vague abdominal pain on occasion

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Patient Case

- Vital Signs: Height 5’5’’, weight 103kg, BMI 37 kg/m^2
- Home medications:
  - Cetirizine (ZyrTEC 10 mg oral tablet) 10 Milligram 1 Tabs By Mouth Daily x allergies
  - MetFORMIN (metFORMIN 1000 mg oral tablet) 1,000 Milligram 1 Tabs By Mouth Every AM
  - Multivitamin 1 tab By Mouth Daily x DM
  - Lisinopril 10mg daily
  - Amlodipine 5mg daily
- Pertinent labs: ALT is 68, AST 42, rest of the liver panel WNL. A1C 8%, lipid panel: LDL 192 mg/dL, HDL 36 mg/DL, TG 160mg/dL, TC 260mg/dL
- Liver Ultrasound demonstrates hepatic steatosis >10%
- FIB-4: indicates low suspicion for fibrosis, patient would like to hold off on liver biopsy for now
- GI physician diagnoses pt. with MASLD with low probability of MASH (other causes of hepatic steatosis ruled out)

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Which of the following medication changes can be recommended to decrease risk of progression to NASH?

A. Increase metformin to 1000mg BID
B. Initiate Vitamin E 800 IU/daily
C. Initiate pioglitazone 30mg daily
D. Initiate liraglutide 0.6 mg daily

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What other modifications would be recommended for DA at this time?

A. Initiate diet and exercise with a goal of 7-10% weight loss

B. Initiate Lipitor 40-80mg daily

C. Discontinue lisinopril 10mg daily

D. Consider bariatric surgery

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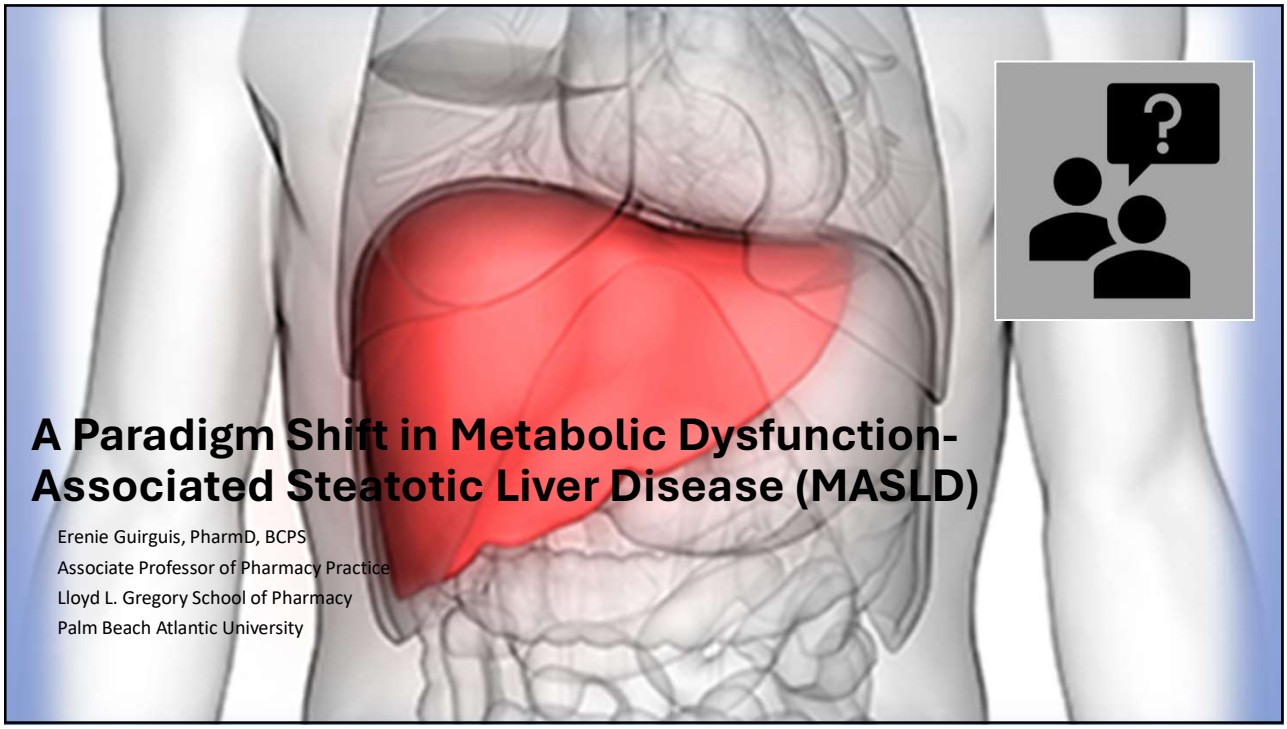

A Paradigm Shift in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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