JOURNAL CLUB

Changing Paradigms in MASLD: The Promise of RESMETIROM

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Flow of my presentation

Definition of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
Prevalence of MASLD
Diabetes and MASLD
Comprehensive lifestyle approach to MASLD
Traditional Drug treatment of MASLD
Revolutionary treatment for MASLD
Take home message

CLD: Etiological changing Scenario over Decades

Changing Epidemiology of Chronic Liver Disease (CLD)

20 Years Back (~2000-2005)

- HBV: 35-45%
- HCV: 25-35%
- Alcohol-related CLD: 15-20%
- Cryptogenic (NAFLD/NASH): <5-10%

Predominant Pattern:
Infectious liver disease

Present(~2020- at present)

- MASLD/MASH: 55-60%
- HBV: 25-30%
- HCV: 5-10%
- Alcohol- related CLD: 10-20%

Predominant Pattern:
Metabolic liver disease

Major Shift: Infectious Etiology → Metabolic Etiology

Definition of MASLD

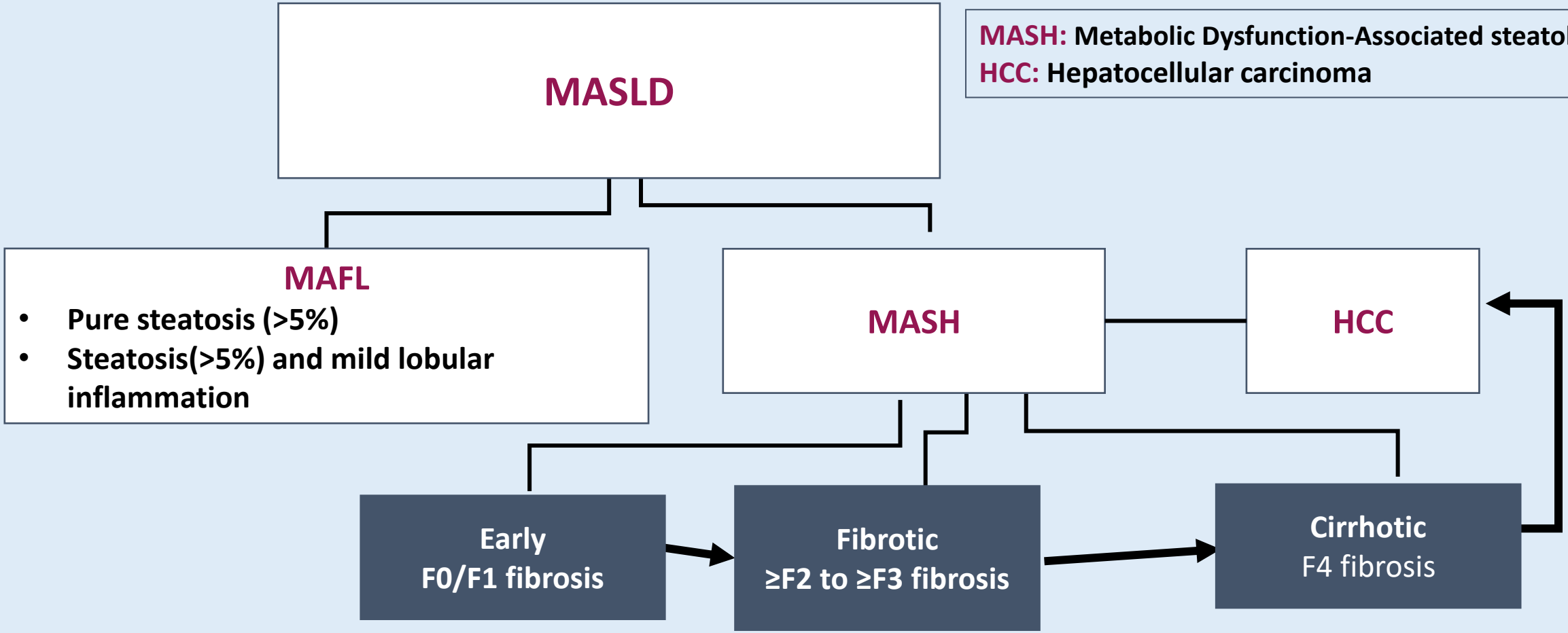
Excessive hepatic fat accumulation associated with insulin resistance (overweight/obesity, T2DM) and defined by presence of following criteria

- Presence of hepatic steatosis/HS (>5% of hepatocytes determined by histology or >5.6% hepatocytes determined by nuclear magnetic resonance techniques).
- No significant alcohol consumption (Ongoing or recent daily alcohol consumption ≥30 g (men) and ≥ 20 g (women)/ >21 standard drinks/week (men) and >14 standard drinks/week (women)- Met-ALD).
  (1 drink = 14 g of pure alcohol).
- No competing secondary etiologies for hepatic steatosis.

MASLD and Related Definitions

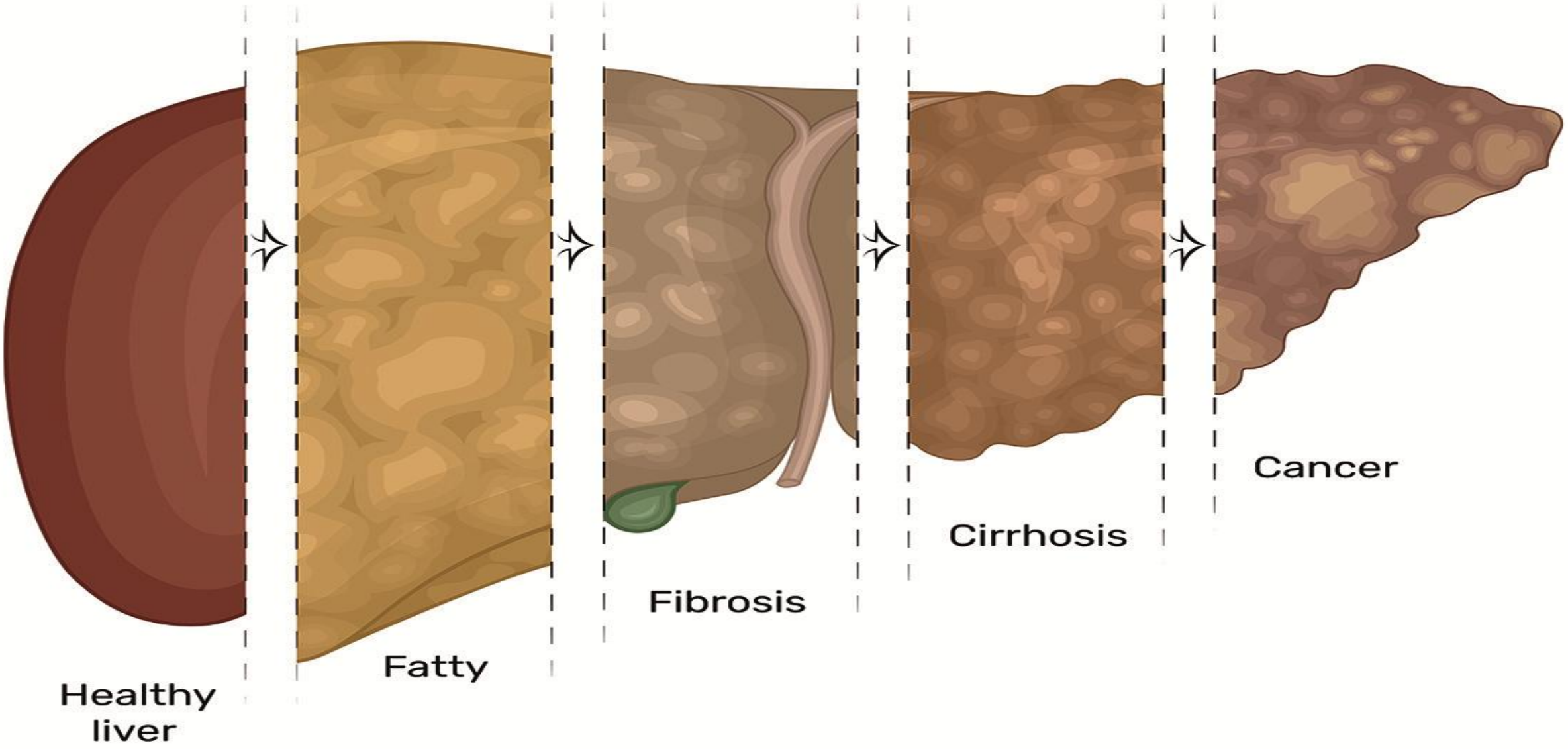
Term	Definition
MASLD	**Entire spectrum of FLD** in individuals without significant alcohol consumption, ranging from fatty liver to Steatohepatitis (SH) to cirrhosis.
MAFL	**>5% HS without evidence of hepatocellular injury** in the form of ballooning of hepatocytes or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is considered minimal.
MASH	**>5% HS with inflammation and hepatocyte injury (ballooning) with or without fibrosis** & covers a wide spectrum of disease severity including fibrosis, cirrhosis and HCC.

Spectrum of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)



Definitive diagnosis of MASH requires a liver biopsy

Spectrum of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)



Prevalence of MASLD Worldwide

- Commonest cause of chronic liver disease (60% of adults) and end stage liver disease requiring liver transplantation
- Commonest cause of asymptomatic abnormal LFTs.
- Also present in 7% of normal-weight persons, more frequently in females, at a younger age and with normal liver enzymes **(lean MASLD).**

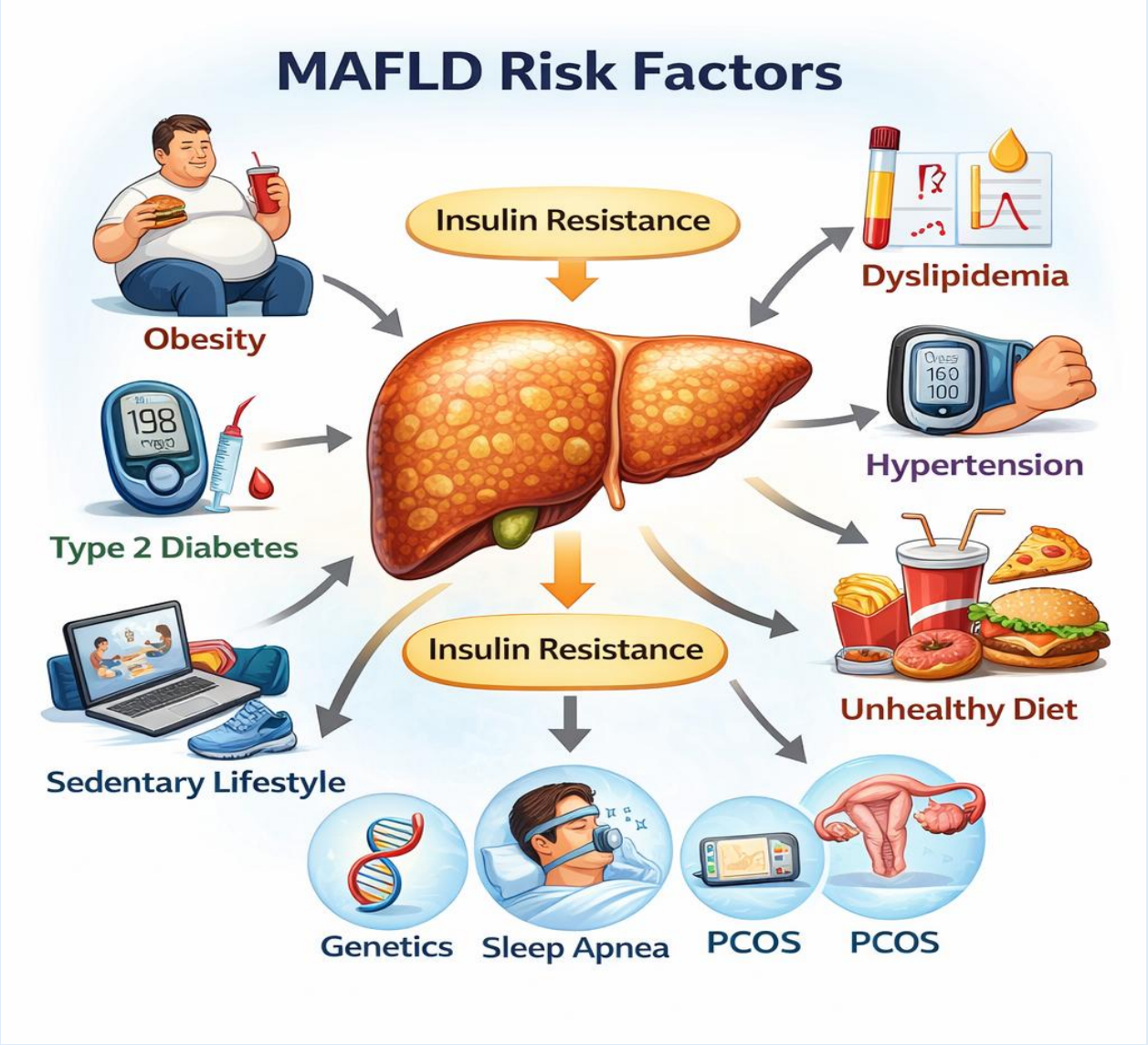
Prevalence of MASLD in Bangladesh

- A total of 2782 (1694 men and 1088 women) participants were included in the study conducted in 2024, with a mean age of 34.21 (±12.66) years.
- **The overall prevalence of MASLD was 33.86% (95% CI: 32.12 – 35.64).**
- Females living in the rural areas and midlife adults (45-54 years) had the highest prevalence of MASLD (P <0.05).

S Alam et al. Journal of gastroenterology and hepatology 2 (2018) 39–46

Risk factors for MASLD

- Type 2 Diabetes Mellitus
- Obesity and visceral adiposity
- Dyslipidemia
- Hypertension
- Sedentary lifestyle



Diabetes and MASLD

- MASLD estimated to be prevalent in 30-74% of patients with Diabetes.
- The reported prevalence of diabetes in patients with cirrhosis ranges from 44-71%.
- Despite unclear pathogenesis, Insulin resistance in diabetes is critical contributing factor of MASLD.
- Diabetes can hasten the progression of MASLD to MASH fibrosis, cirrhosis and hepatocellular carcinoma.

MASLD Treatment 2026:
From Evidence to Prescription

Comprehensive lifestyle approach to MASLD

Weight loss:

- **Target : Initially ≥10% weight loss over 6 months (rapid weight loss worsen liver injury or cause gall stones).**
- **≥5% weight loss: Improves hepatic steatosis**
- **≥7-10% weight loss: Improves MASH and normalizes liver enzymes**
- **≥10% weight loss: Best chance of improving or reversing liver fibrosis**

Diet

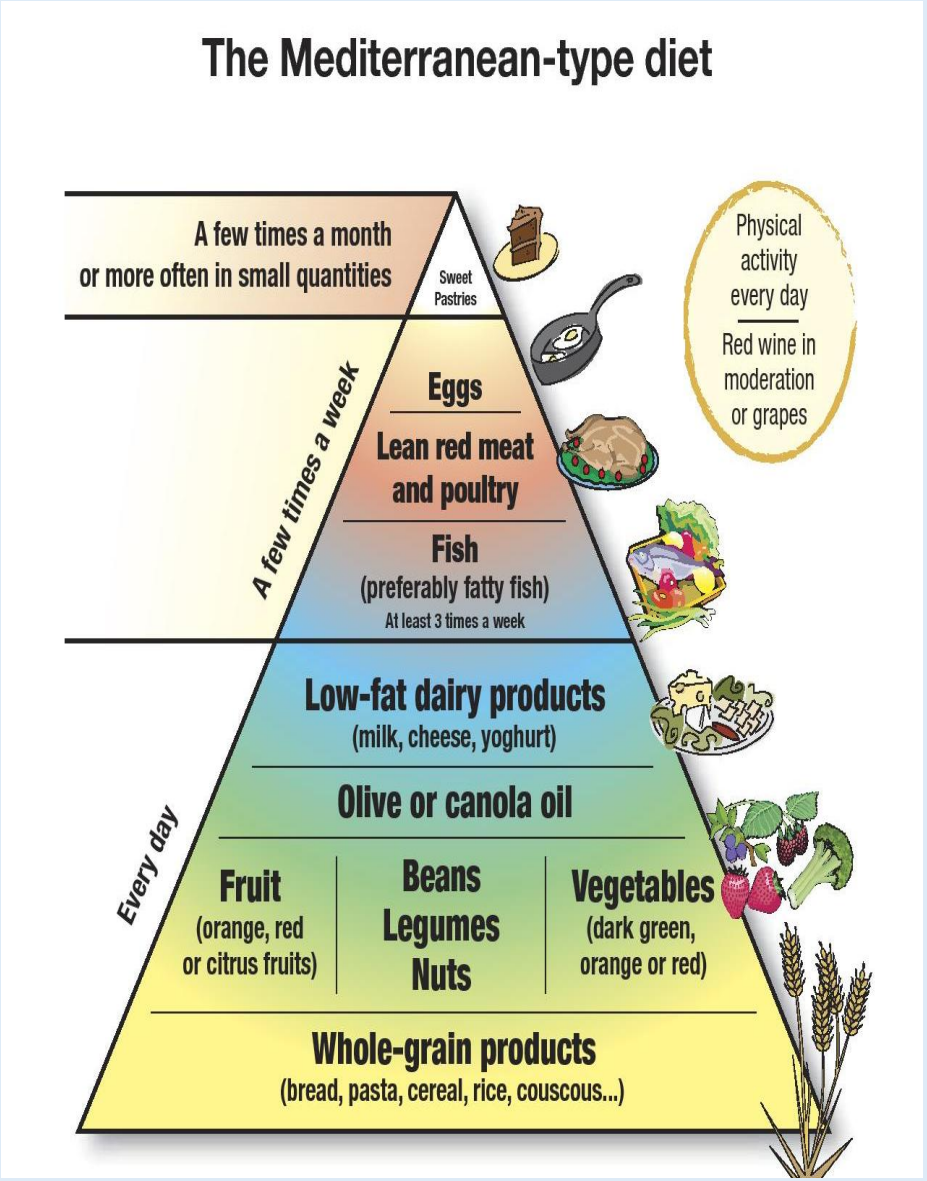
Elements	Suggested intervention
Energy restriction	Calorie restriction (800-1000 Kcal/day) to induce a weight loss of 0.5-1 Kg/week.
Macronutrient composition	Balanced diet to be followed. Adherence to the Mediterranean diet has been reported to reduce liver fat, when compared with other diet in a cross-over comparison.
Fructose intake	Avoid fructose-containing food and drink.

Mediterranean diet

Mediterranean diet is a way of eating based on traditional cuisine of countries bordering the Mediterranean Sea.

This diet is high in-

- **Vegetables**
- **Fruits**
- **Whole grains**
- **Beans**
- **Nuts and seeds**
- **Olive oil**
- **Seasoning with herbs and spices**



Ideal Balanced diet model

Ideal Balanced diet model

Reality of Bangladesh

Comparison with balanced diet and Keto diet

	Balanced diet	Keto diet
Carbohydrate	50%	5%
Protein	10-15%	20%
Fat	<35%	75%

Keto diet and steatotic liver disease

nutrients

MDPI

Review

Ketogenic Diet in Steatotic Liver Disease: A Metabolic Approach to Hepatic Health

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‡ These authors also contributed equally to this work.

Keto diet and steatotic liver disease

Results:

- Ketogenic diets significantly reduce hepatic fat content and improve metabolic parameters, including insulin sensitivity and liver enzyme levels **in short term.**

- Although short-term outcomes are encouraging, **potential adverse effects such as dyslipidemia, gastrointestinal disturbances, and transient 'keto flu' symptoms and increased risk of heart disease** require careful clinical monitoring.

Intermittent fasting

A pattern of eating that alternates between designated windows of feeding and fasting, with fasts lasting less than 2 days.

Intermittent fasting patterns

Patterns	How to do
16:8 method	Patients limit their feeding window to specific hours of day e.g. 16 hours of fasting & 8 hours of feeding
Alternate day fasting	Patient freely eat for a day, fast the next day and repeat
5:2 method	Patients choose 2 non-consecutive days to fast each week and consume ad libitum diet the other 5 days
24 hours fasting	One or two 24 hours fast per week

Benefits of Intermittent fasting

Patterns	Weight loss	Reduced fat mass	Reduced total Cholesterol, LDL, TG	Improved BP	Reduced insulin resistance	Improved leptin
16:8 method	**Yes**	**Yes**		**Yes**		**Yes**
Alternate day fasting	**Yes**	**Yes**	**Yes**			
5:2 method	**Yes**				**Yes**	

nature aging

REVIEW ARTICLE

https://doi.org/10.1038/s43587-020-00013-3

Check for updates

Intermittent and periodic fasting, longevity and disease

Valter D. Longo[1,2], Maira Di Tano[2], Mark P. Mattson[3] and Novella Guidi[1]

Danger of Intermittent fasting

American Heart Association. 100 YEARS Bold Hearts

Heart Attack And Stroke Symptoms | Volunteer | Donate

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Newsroom / Search News Releases / **8-hour time-restricted eating linked to a 91% higher risk of cardiovascular death**

Categories: Heart News, Scientific Conferences & Meetings | **Published: March 18, 2024**

8-hour time-restricted eating linked to a 91% higher risk of cardiovascular death

Related Images

Comprehensive lifestyle approach to MASLD

Elements	Suggested intervention
Daily Alcohol Intake	• Strictly keep alcohol below risk threshold (30 gm men and 20 gm women/day). • Total abstinence is mandatory in MASH-cirrhosis to reduce HCC risk.
Coffee Consumption	• No liver-related limitations. • Protective in MASLD as in liver disease of other etiologies, reducing histological severity and liver-related outcomes
Exercise/ Physical Activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions (brisk walking, stationery cycling)

Coffee consumption and MASLD

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Original article

The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis of 11 epidemiological studies

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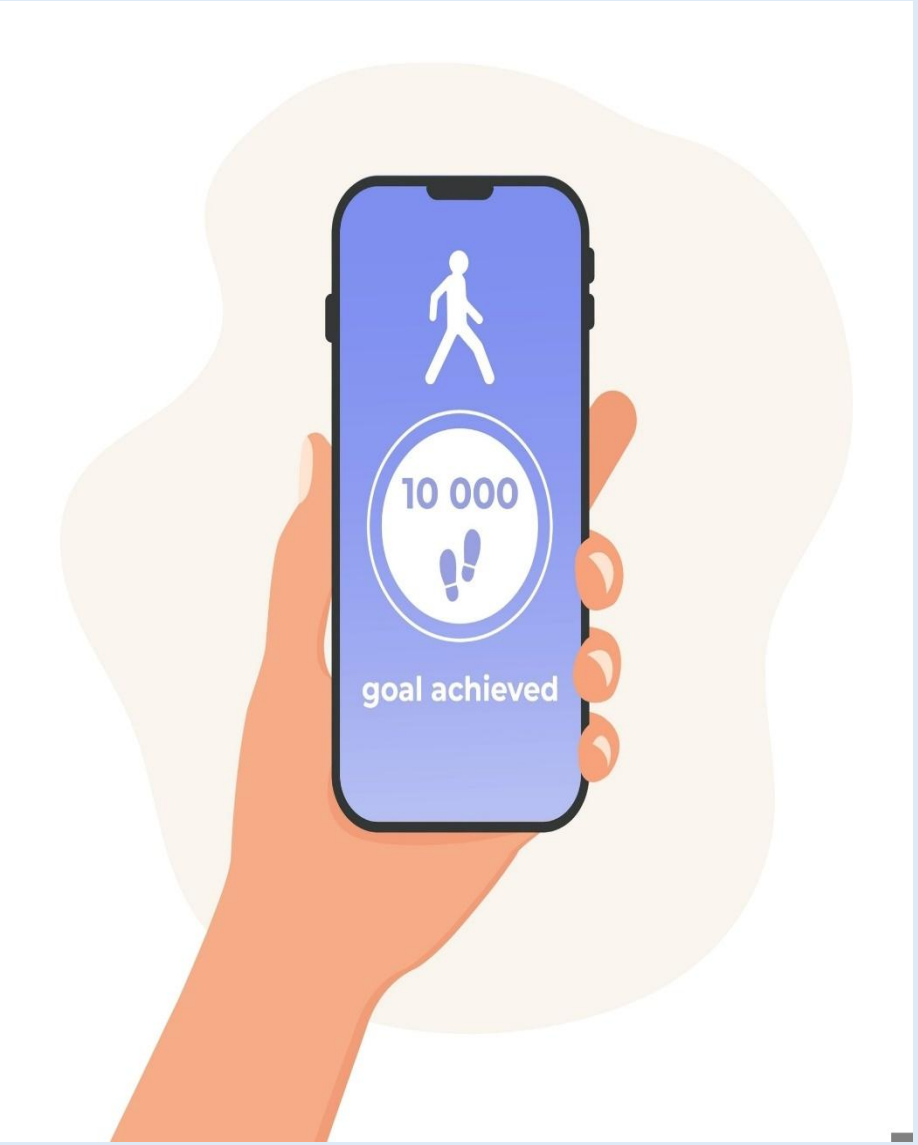
Regular coffee consumption is significantly associated with a reduced risk of MASLD. It is also significantly associated with a decreased risk of liver fibrosis development in already diagnosed MASLD patients.

10,000 steps per day



Drug Treatment of MASLD

Lots of US-FDA unapproved medications are in use ! ! !

Vitamin E

- Vitamin E (800 IU/day) is considered for the treatment of MASH in nondiabeic, noncirrhotic patients.
- Improves steatosis and fibrosis but improvement was not clearly significant.(PIVENS trial)
- Concerns about long-term safety of vitamin E exist, mainly an increase in overall mortality, in hemorrhagic stroke and prostate cancer in >50 years.

Obeticholic Acid

- Obeticholic acid is a farnesoid X receptor agonist at dose 5-10 mg once daily with or without food.
- Modest efficacy with uncertain long term clinical benefit.(FLINT and REGENERATE trial)
- Main issues with increased LDL cholesterol, gall stone and pruritus.

Saroglitazar

- Dual agonist of Peroxisome Proliferator-Activated Receptor (PPAR)-α/γ
- Clinical study in India only, useful in MASLD with hypertriglyceridemia(EVIDENCES IV trial)
- Some fibrosis benefit without long term clinical evidence
- Adverse effects are Gastritis, asthenia, peripheral edema.

Role of other medications in MASLD

Medication	Role in MASLD
Ursodeoxycholic acid	• Investigated in several RCTs, at different doses and for up to 2 years, but **only showed some biochemical but no histological improvements**.
Omega-3 fatty acids/ Fibrates	• Should not be used as a specific treatment of MASLD or MASH, but they may be considered to treat **hypertriglyceridemia** in patients with MASLD.
Statins	• Improve liver enzyme and steatosis with limited fibrosis progression, but they may be considered to treat **hypercholesterolemia** in patients with MASLD to reduce CV risk.

Obesity pharmacotherapy/ Bariatric surgery with MASLD

Gastric and Pancreatic Lipase inhibitor: Orlistat 120 mg TDS

GLP-1 receptor agonist:

- SC Liraglutide 3 mg daily
- Oral Semaglutide
- SC Semaglutide 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg once weekly

Dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA

- SC Tirzepatide 2.5mg, 5mg,7.5mg, 10mg, 12.5mg or 15 mg once weekly

Some anti-diabetic medication are also associated with weight benefit e.g. SGLT-2 inhibitors e.g Empagliflozin.

Metabolic/Bariatric surgery: BMI ≥35 kg/m^2 (>27.5 kg/m^2 in Asian individuals)

Efficacy of Anti-Diabetic medication on MASLD

Medication	Liver fat	Disease Activity (Steatohepatitis/MASH)	Limitation
Pioglitazone	Decreased	Improved	• Weight gain • Bone fracture • CCF
GLP-1 RAs	Decreased	Improved	• GI upset • Acute Pancreatitis (rare)
SGLT2 inhibitors	Decreased	Effect unknown	• UTI • Genital mycotic infections
Insulin	Decreased	Effect unknown	• Weight gain • Hypoglycemia
Metformin	Unchanged	Neutral	• GI upset

Only US-FDA approved medication for MASLD

Only US-FDA approved medication for MASLD

Resmetirom

Resmetirom (US-FDA approval)

FDA NEWS RELEASE

FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease

For Immediate Release: March 14, 2024

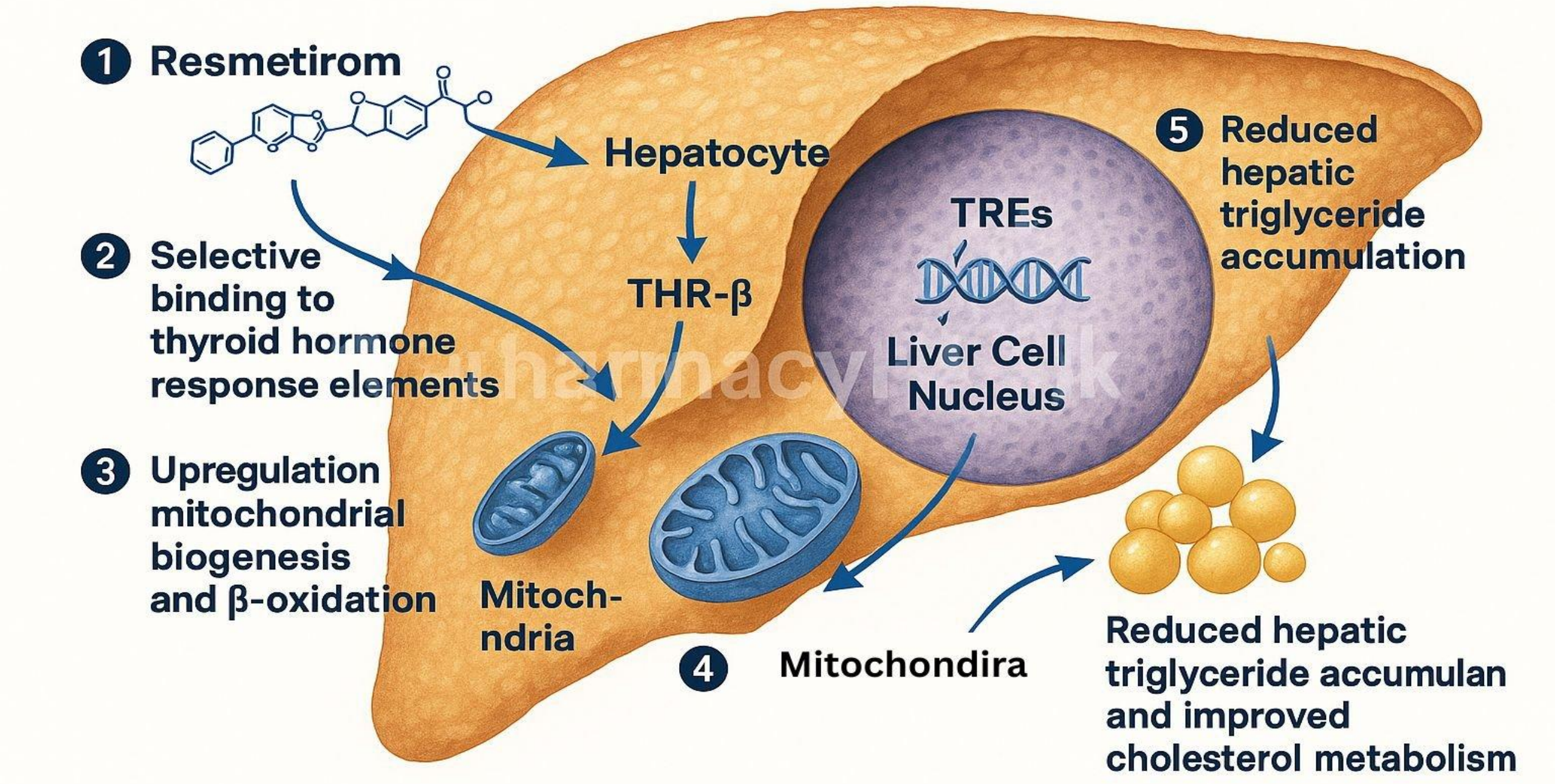
Español

Today, the U.S. Food and Drug Administration approved Rezdiffra (resmetirom) for the treatment of adults with noncirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced liver scarring (fibrosis), to be used along with diet and exercise.

Resmetirom (Indications and usage)

Resmetirom is a thyroid hormone receptor-beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (MASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

MECHANISM OF ACTION OF RESMETIROM



Fibroscan of Liver

Co-relation between Liver Stiffness (kPa) and Fibrosis stage

DISEASE	Liver Stiffness (kPa)			
	F0 - F1	F2	F3	F4
Chronic Hepatitis B*	1 - 7.4	7.4 - 9.5	9.5 - 12.5	12.5 - 75
HCV-HIV Co-infection*	1 - 7	7 - 11.4	11.4 - 14	14 - 75
Primary Biliary Cholangitis	1 - 8.8	8.8 - 10.7	10.7 - 16.8	16.8 - 75
Chronic Hepatitis-C*	1 - 7	7 - 9.5	9.5 - 12.6	12.6 - 75
Autoimmune Hepatitis	1 - 5.8	5.8 - 10.5	10.5 - 16	16 - 75
NAFLD**	1 - 7.8	7.8 - 8.8	8.8 - 11.6	11.6 - 75
Alcohol***	1 - 7.5	7.5 - 9.6	9.6 - 12.6	12.6 - 75

Interpretation of Liver Stiffness Measurement & CAP

F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis

Liver Steatosis Assesment by FibroScan

Diseases	CAP in dB/M CAP (dB/M)/Liver Histology-determined steatosis							
Chronic Hepatitis C	~224	S0 = 0 - 4 %	224 - 237	S1 = 5 - 33%	237 - 294	S2 = 34-66%	294 - 400	S = 67-100%
NAFLD/NASH	~235	S0 = 0 - 4%	235 - 268	S1 = 5 - 33%	268 - 302	S2 = 34-66%	302 - 400	S3 = 67-100%
Chronic Hepatitis B	~223	S0 = 0 - 10%	223 - 247	S1 = 11 - 33%	247 - 286	S2 = 34-66%	286 - 400	S3 = 67-100%
Meta-analysis	~248	S0 = 0-4/10%	248 - 268	S1 = 5/11-33%	268 - 280	S2 = 34-66%	280 - 400	S3= 67-100%

FibroScan of Liver with CAP (For MASLD)

Liver stiffness (kPa)	Fibrosis stage
1-7.8	F0 (No fibrosis)-F1 (Portal fibrosis without septa)
7.8-8.8	F2 (Portal fibrosis with few septa)
8.8-11.6	F3 (Numerous septa without cirrhosis)
11.6-75	F4 (Cirrhosis)

Liver steatosis (CAP)	Steatosis grade
<235	S0 (0-4%)
235-268	S1 (5-33%)
268-302	S2 (34-66%)
302-400	S3 (67-100%)

Resmetirom (Dosage forms and strengths)

- 60 mg
- 80 mg
- 100 mg

Thyroid Function Test and Resmetirom

- **TSH monitoring is recommended before and during treatment with resmetirom**, as the drug acts on thyroid hormone receptor pathways.
- The most recognized effect is a **reduction in free T4 with often normal TSH.**
- A **decrease in free T4 after starting resmetirom does not necessarily indicate true hypothyroidism**.
- Interpret results together with **TSH and clinical status**.

Resmetirom (Dosage and administration)

- The recommended dosage of Resmetirom is based on actual body weight.
- For patients weighing:
  - **<100 kg: 80 mg orally once daily**
  - **≥100 kg: 100 mg orally once daily**

  [NB: If the patient is getting statin, fibrates, clopidogrel or salmeterol, start with 60mg OD if body weight <100 kg and 80 mg OD if body weight is ≥100 kg]

- Administer Resmetirom with or without food.

Resmetirom (Contraindications)

Avoid use of Resmetirom in patients with decompensated cirrhosis.

Resmetirom (Adverse reactions)

The most common adverse reactions with Resmetirom (reported in at least 5% of patients and higher compared to placebo) are:

- Diarrhea
- Nausea
- Pruritus
- Vomiting
- Abdominal pain
- Dizziness

Resmetirom (Warnings and precautions)

Hepatotoxicity:

- Monitor patients for symptoms and signs of hepatotoxicity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia [>5%]) and elevations in liver function tests (SGPT, SGOT, total bilirubin).
- Need to discontinue Resmetirom and continue to monitor.
- Elevations in liver enzymes if accompanied by elevations in IgG levels, suggesting drug-induced autoimmune-like hepatitis (DI-ALH).

Resmetirom (Warnings and precautions)

Gallbladder-Related Adverse Reactions:

- **Cholelithiasis and cholecystitis** were observed more often in Resmetirom treated patients.
- If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.
- If an acute gallbladder event such as acute cholecystitis is suspected, interrupt Resmetirom treatment until the event is resolved.

Resmetirom (Drug interactions)

Strong or moderate CYP2C8 Inhibitors	
Clinical Impact	• Resmetirom is a Cytochrome P450 2C8 (CYP2C8) substrate. • Concomitant use with a strong or moderate CYP2C8 inhibitor can increase Resmetirom Maximum (peak) plasma concentration/Cmax which may increase the risk of Resmetirom adverse reactions.
Intervention	• **Concomitant use of Resmetirom with strong CYP2C8 inhibitors (e.g., Gemfibrozil) is not recommended.** • **Reduce Resmetirom dosage** if used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel, statin).

Resmetirom (Drug interactions)

Organic Anion-Transporting Polypeptides (OATP) 1B1 and OATP1B3 Inhibitors	
Clinical Impact	• Resmetirom is an OATP1B1 and OATP1B3 substrate. • Concomitant use with OATP1B1 and OATP1B3 inhibitors may increase Resmetirom Cmax, which may increase the risk of Resmetirom adverse reactions.
Intervention	• **Concomitant use of Resmetirom with OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine) is not recommended.**

Resmetirom (Drug interactions)

Clinically Significant Interactions Affecting Other Drugs	
Clinical Impact	• Resmetirom increased plasma concentrations of some statins **(Atorvastatin, Pravastatin, Rosuvastatin and Simvastatin)** which may increase the risk of adverse reactions related to these drugs.
Intervention	• **Atorvastatin and Pravastatin: Limit daily statin dosage to 40 mg.** • **Rosuvastatin and simvastatin: Limit daily statin dosage to 20 mg.**

Resmetirom (Use in specific populations)

- **Avoid use of Resmetirom** in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C)- **Decompensated cirrhosis**

- No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A)- **Compensated cirrhosis**

- The safety and effectiveness of Resmetirom have not been established in patients with MASH cirrhosis.

Child-Pugh score for classification of Cirrhosis

Parameters	1 point	2 points	3 points
Serum bilirubin (mg/dL)	<2	2-3	>3
Serum albumin (mg/dL)	>35	28-35	<28
Prothrombin time (Prolonged in seconds)	1-3	4-6	>6
Ascites	None	Mid/diuretic responsive	Moderate to severe/Refractory
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4

Nomenclature related to severity of Cirrhosis

Liver function	Child-Pugh score	Severity of cirrhosis
Preserved	A (5)	Compensated
Impaired (Slightly impaired)	A (6)	Compensated
Impaired (Moderately impaired)	B (7-9)	Decompensated
Impaired (Severely impaired)	C (10-15)	Decompensated

Resmetirom (Use in specific populations)

Pregnant women, lactating mother or pediatric patients	No available data.
Geriatric patients	No overall differences in effectiveness but numerically higher incidence of adverse reactions have been observed in patients 65 years of age and older compared to younger adult patients.
Renal impairment	The recommended dosage in patients with mild or moderate renal impairment is the same as in patients with normal kidney function. Resmetirom has not been studied in patients with severe renal impairment.

Evidence of Resmetirom use in Real World

A Phase 3, Randomized, Controlled Trial of Resmetirom in MASH with Liver Fibrosis (MAESTRO-MASH trial)

Published February 7, 2024, N Engl J Med 2024;390:497-509, DOI: 10.1056/NEJMoa2309000

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The NEW ENGLAND JOURNAL of MEDICINE

Study Question

Does the oral thyroid hormone receptor beta-selective agonist, Resmetirom, decrease fibrosis and produce resolution of metabolic dysfunction associated steatohepatitis (MASH) with fibrosis?

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Study Design

Design: 52-week phase 3, double-blind, randomized, placebo-controlled trial.

Setting: Conducted between March 2019 and July 2021 in 245 centers in 15 countries.

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Study Design

966 patients with biopsy-confirmed MASH with

- Fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]) and
- MASLD activity score of 4 or more (on a scale of 0 to 8, with higher scores indicating more severe disease), with a score of 1 or more for each component (steatosis [on a scale from 0 to 3], lobular inflammation [on a scale from 0 to 3], and hepatocellular ballooning [on a scale from 0 to 2]).

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Intervention

- **Participants randomized 1:1:1 to receive Resmetirom 80 mg daily, Resmetirom 100 mg daily, or placebo.**
- Patients were stratified according to status with respect to type 2 diabetes (presence or absence) and fibrosis stage (F1, F2, or F3).
- Throughout the trial, patients received nutrition and exercise counseling according to current recommendations.
- **A second liver biopsy was performed at week 52.**

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Outcomes & Definitions

Dual primary endpoints assessed at week 52:

- **MASLD activity score:** Ballooning score of 0, lobular inflammation score of 0-1, and reduction in MASLD activity score by ≥ 2 points with no worsening of fibrosis
- **Improvement (reduction) in fibrosis** by at least one stage with no worsening of the MASLD activity score.

Secondary endpoint was percent change in baseline low-density lipoprotein (LDL) at week 24.

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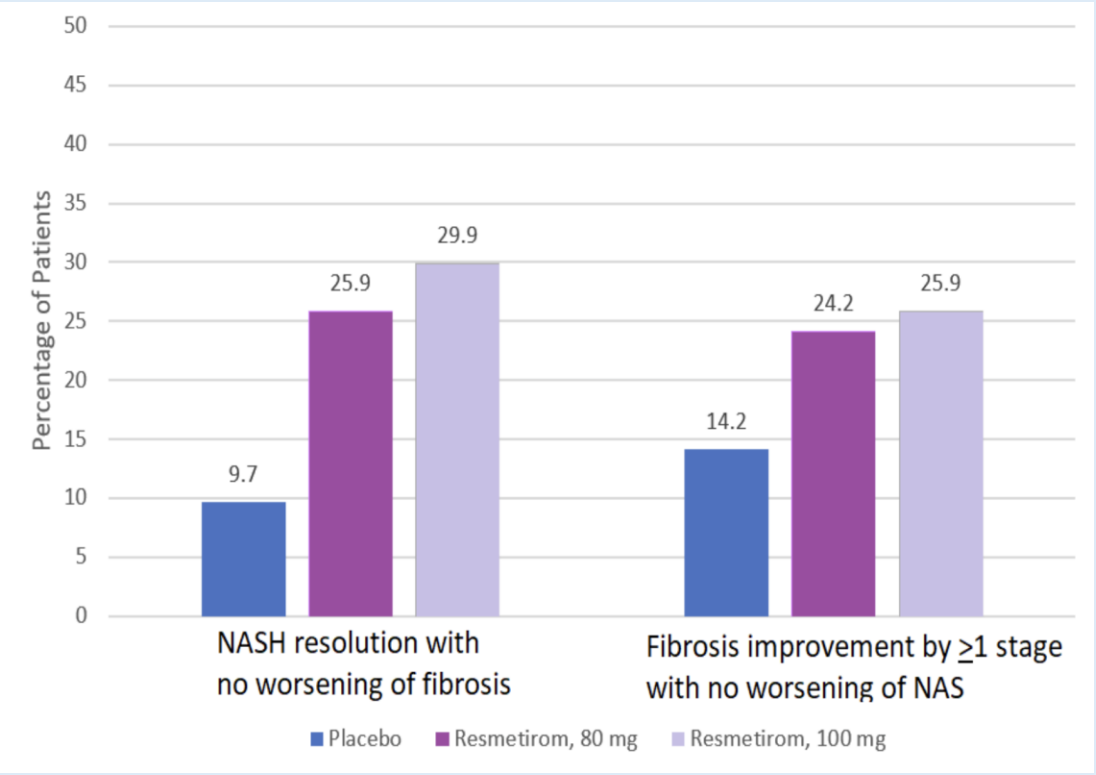
Results



- ❑ **MASH resolution with no worsening of fibrosis *[Primary endpoint]* →*Resmetirom 80 mg, 100 mg > placebo (25.9% & 29.9% vs 9.7% resp., P<0.001)***
- ❑ **Fibrosis score improvement ≥ 1 stage with no worsening of MASLD *[Primary endpoint]* →*Resmetirom 80 & 100 mg > placebo (24.2% & 25.9% vs 14.2%, resp., P<0.001)***
- ❑ **Percent change in LDL at week 24 →*Resmetirom 80 & 100mg > placebo (-13.6% & -16.3% vs 0.1%)***

Adverse events were mild/moderate and more frequent in resmetirom groups 80mg & 100mg vs placebo:

- **Diarrhea (27% & 33.4% vs 15.6%), self-limited with time**
- **Nausea (22% & 18.9% vs 12.5%)**

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Key Study Findings

- **Resmetirom** (both 80 mg and 100 mg doses) was superior to placebo regarding both histologic primary endpoints: **improvement in MASLD activity score and fibrosis stage.**

- Changes in lipid profiles, liver biochemistries and non-invasive steatosis and fibrosis assessments all favored Resmetirom.

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Changing Paradigm

Old Paradigm

- Fatty liver
- ALT- focused
- Biopsy-driven
- No single approved drug

New Paradigm

- Fibrosis-focused
- NIT (FIB 4 && Fibroscan)- driven care
- Cardiometabolic disease model
- Approved targeted pharmacotherapy

One-Liner Pearls

- MASLD is rising concern now a days.
- Normal ALT does not exclude advanced MASLD.
- Weight reduction and good glycemic control along with management of other CV risk factors is key steps for better outcome of MASLD.
- Fibrosis stage drives prognosis.
- Cardiovascular disease kills more MASLD patients than liver failure.
- Resmetirom is liver-targeted thyroid hormone receptor beta agonism.
- Biochemical response ≠ histologic cure.


Thank
YOU