

LOVE, LIVER, LAUGH

MASLD for the Primary Care Clinician

Metabolic Dysfunction-Associated Steatotic Liver Disease
A Comprehensive Update for PCPs and APPs

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My One PCP, LLC but I wish I had more financial relationships to disclose

Learning Objectives

After this session, participants will be able to:

- 1) **Define, Diagnose, and risk-stratify** MASLD using updated nomenclature and a stepwise noninvasive testing approach with FIB-4 and VCTE to guide appropriate hepatology referral
- 2) **Select and initiate** evidence-based pharmacotherapy and lifestyle interventions tailored to fibrosis stage, comorbidities, and patient-specific factors
- 3) **Implement** HCC surveillance strategies and long-term monitoring plans for both cirrhotic and high-risk non-cirrhotic MASLD patients in the primary care setting



SECTION

The Normal Liver

Anatomy, Physiology & Metabolic Functions

Liver Anatomy & Structure

Weight	~1.5 kg — largest visceral organ
Blood Supply	75% portal vein (nutrient-rich GI blood) + 25% hepatic artery
Cardiac Output	Receives ~25% of resting cardiac output
Lobular Unit	Hexagonal lobules: hepatocytes radiate from central vein; portal triads at periphery
Zonation	Zone 1 (periportal): gluconeogenesis, bile acid synthesis Zone 3 (perivenous): glycolysis, lipogenesis
Cell Types	Hepatocytes (80%), Kupffer cells, stellate cells, sinusoidal endothelial cells

Liver Metabolic Functions

Why the liver is the metabolic hub of the body

GLUCOSE

Glycogen storage, gluconeogenesis during fasting, glucose homeostasis

LIPIDS

Fatty acid oxidation, VLDL synthesis, lipoprotein packaging & export

PROTEIN

Albumin, coagulation factors (I-VII, IX, X), acute-phase proteins

DETOX

CYP450 xenobiotic metabolism, ammonia → urea, bilirubin conjugation

BILE

Bile acid synthesis & secretion → fat emulsification & fat-soluble vitamin absorption

IMMUNE

Kupffer cells — phagocytosis; stellate cells — fibrosis when activated by injury

Metabolic zones of the liver

The hepatic lobule is divided into 3 functional zones based on oxygen tension and metabolic specialization

PORTAL TRIAD

CENTRAL VEIN

O₂ GRADIENT — HIGH → LOW

ZONE 1

Periportal

Acinar zone 1

High O₂ · Oxidative

- Gluconeogenesis (fasting glucose production)
- Fatty acid β-oxidation (fat burning)
- Urea synthesis (nitrogen disposal)
- Amino acid catabolism
- Drug & toxin detoxification (Phase I/II)
- Albumin synthesis

ZONE 2

Mid-lobular

Transitional zone

Intermediate O₂ · Adaptive

- Metabolic flexibility hub
- Bridges oxidative & glycolytic metabolism
- Responds dynamically to insulin signals
- Liver progenitor / regenerative activity
- Transitional lipid handling
- Least studied — emerging research focus

ZONE 3

Pericentral

Centrilobular zone

Low O₂ · Glycolytic

- De novo lipogenesis (fat synthesis from carbs)
- Glycolysis & glycogen synthesis (fed state)
- Ketone body formation
- Bile acid conjugation
- Xenobiotic metabolism (CYP450)
- First site of alcoholic & NAFLD injury

BLOOD SUPPLY

75% portal vein · 25% hepatic artery

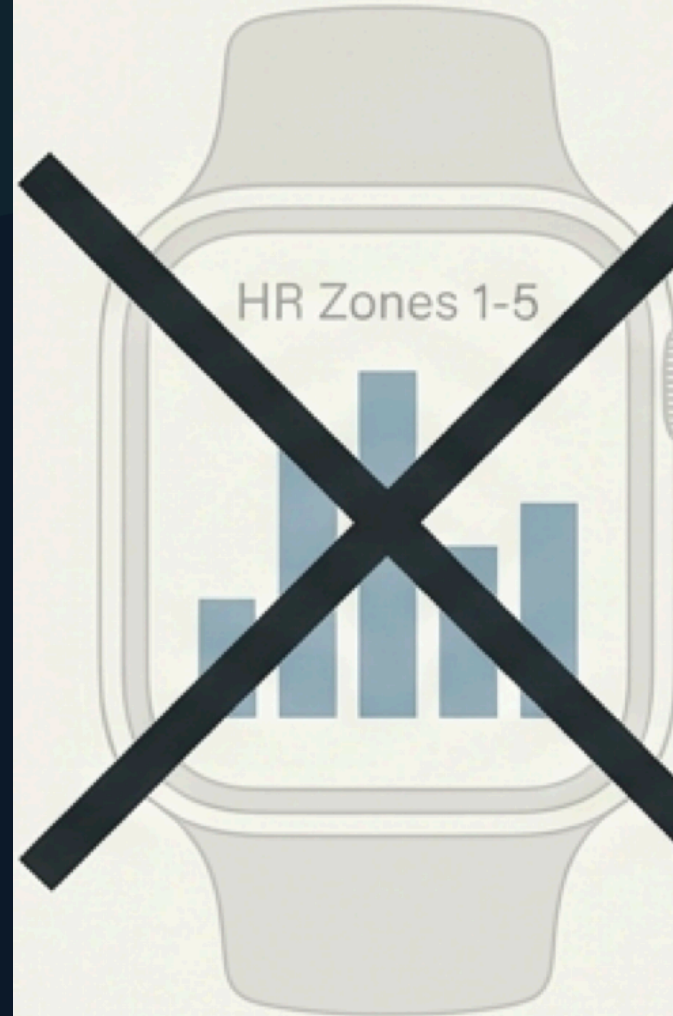
CLINICAL RELEVANCE

Zone 3 injury → MASLD · Zone 1 injury → ischemia, toxic hepatitis



CLASSIFICATION

Rappaport acinar model · Couinaud 8-segment system (surgical)



Cell types of the liver

The liver contains both parenchymal and non-parenchymal cells, each with distinct zonal distribution and metabolic roles

Hepatocytes

~60–80% of liver mass

All zones (zone-specific functions)

- Glucose metabolism — glycogen storage & gluconeogenesis
- Lipid metabolism — oxidation, synthesis, VLDL secretion
- Protein synthesis — albumin, clotting factors, acute-phase proteins
- Bile acid production & secretion
- Detoxification of drugs, toxins, ammonia → urea

Zone 3 hepatocytes: first injured in NAFLD & alcohol

Kupffer cells

~15% of liver cells

Zone 1 Zone 2

- Resident liver macrophages — primary immune sentinels
- Phagocytose bacteria, dead cells & debris from portal blood
- Secrete cytokines (TNF- α , IL-6, IL-1 β) driving inflammation
- Regulate hepatic immune tolerance
- Participate in TGF- β & TLR signaling cascades

Activated in NAFLD, alcoholic hepatitis & sepsis

Cholangiocytes

~3–5% of liver cells

Zone 1 (portal)

- Line the intrahepatic bile ducts
- Modify bile composition — water, electrolytes, IgA
- Secrete bicarbonate protecting bile duct epithelium
- Proliferate & act as progenitors after hepatocyte injury

Primary biliary cholangitis, PSC — cholangiocyte disease

Liver sinusoidal endothelial cells (LSECs)

~20% of liver cells

All zones — line sinusoids

- Form fenestrated lining allowing free nutrient exchange
- Act as gatekeepers between blood and hepatocytes
- Scavenge waste macromolecules from circulation
- Regulate vascular tone & portal pressure
- Participate in immune surveillance & xenobiotic clearance

Loss of fenestrae → capillarization → fibrosis progression

Hepatic stellate cells (HSCs)

~5–8% of liver cells

Zone 2 Zone 3

- Store vitamin A (retinoids) in quiescent state
- When activated → myofibroblasts producing collagen
- Primary drivers of hepatic fibrosis & cirrhosis
- Regulate sinusoidal blood flow via contraction
- Respond to TGF- β , PDGF, and oxidative stress signals

Central to all fibrosis pathways — key therapeutic target

Pit cells (liver NK cells)

Rare — ~1%

Zone 1 → Zone 3 (sinusoids)

- Liver-resident natural killer (NK) lymphocytes
- Patrol sinusoids for tumor cells & virus-infected hepatocytes
- Cytotoxic — kill targets without prior sensitization
- First-line defense against hepatic metastasis

Reduced in chronic liver disease — impaired tumor surveillance

Dr Jekyll

Mr Hyde

SECTION

MASLD: Definition & Pathophysiology

From steatosis to cirrhosis

Nomenclature: From NAFLD to MASLD

Why the name changed — 2023 Multi-Society Delphi Consensus

OLD TERM	NEW TERM	RATIONALE
NAFLD	MASLD	Removes stigmatizing 'fatty'; positive metabolic definition
NASH	MASH	Metabolic dysfunction-associated steatohepatitis
NAFLD Activity Score	MAS	Metabolic Activity Score
—	MetALD	NEW: moderate alcohol + metabolic dysfunction overlap
—	Cryptogenic SLD	No CMR factors, no alcohol, no other etiology

Path to Steatosis

CONTRIBUTION TO HEPATIC STEATOSIS

60%

30%

10%

60%

Peripheral adipose tissue

Unrestrained lipolysis → portal FFA overflow in insulin resistance

30%

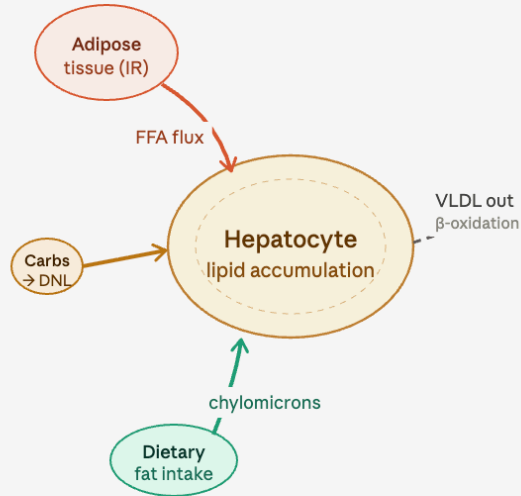
De novo lipogenesis

Dietary carbohydrates converted to fat via SREBP-1c / ChREBP upregulation

10%

Dietary fat

Chylomicron remnants and direct hepatic uptake of ingested lipids



DOWNSTREAM EFFECTS

- Hepatic IR amplifies FFA delivery
- Hyperinsulinemia drives DNL genes
- Excess fructose feeds DNL preferentially
- Impaired β -oxidation worsens retention
- Dietary fat minor unless massive load

Metabolic zones of the liver

The hepatic lobule is divided into 3 functional zones based on oxygen tension and metabolic specialization

PORTAL TRIAD



CENTRAL VEIN

O₂ GRADIENT — HIGH → LOW

ZONE 1

ZONE 2

ZONE 3

Docking Port

Overflow pool

Wast management
& toxic material
processing

Factory

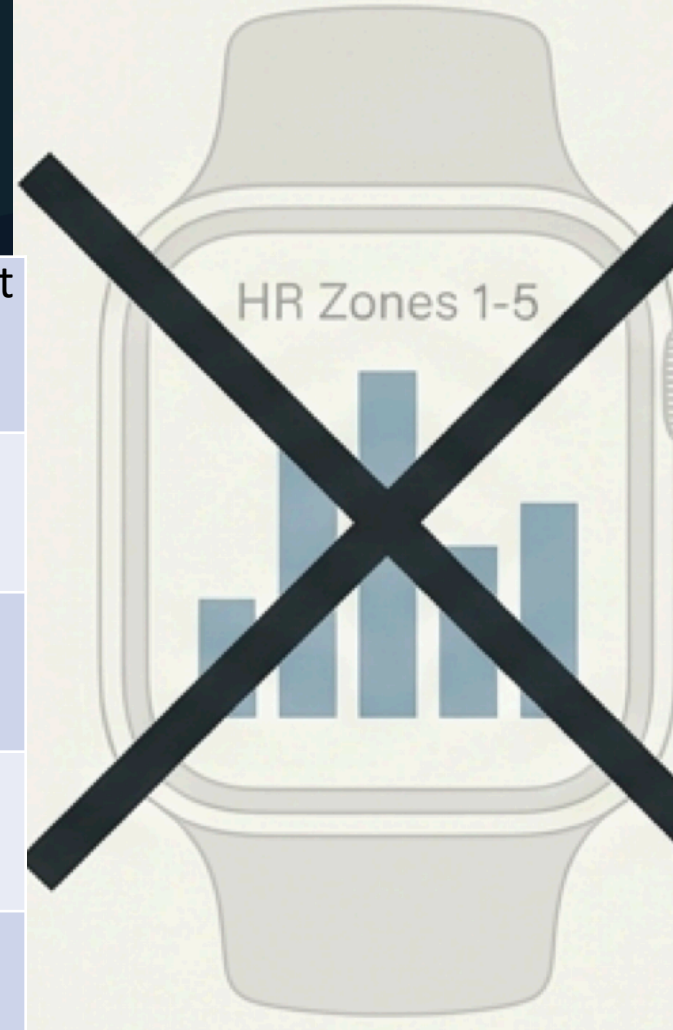
Back up workers &
Back up factory

Factory

Pediatric MASLD



Adult MASLD



MASLD Diagnostic Criteria

Hepatic steatosis + ≥ 1 cardiometabolic risk factor

STEP 1: Confirm hepatic steatosis (>5% on imaging , CAP >248 dB/m , or biopsy )

STEP 2: Confirm ≥ 1 cardiometabolic risk factor (CMR)

1. Overweight/Obesity

BMI ≥ 25 (≥ 23 Asian) or WC >94 cm M / >80 cm F (>37.0 in M or >31.5 in F)

2. Prediabetes/DM2

FG ≥ 100 , HbA1c $\geq 5.7\%$, 2h-glucose ≥ 140 , or DM2 meds

3. Hypertension

BP $\geq 130/85$ or antihypertensive treatment

4. Hypertriglyceridemia

TG ≥ 150 mg/dL or lipid-lowering meds

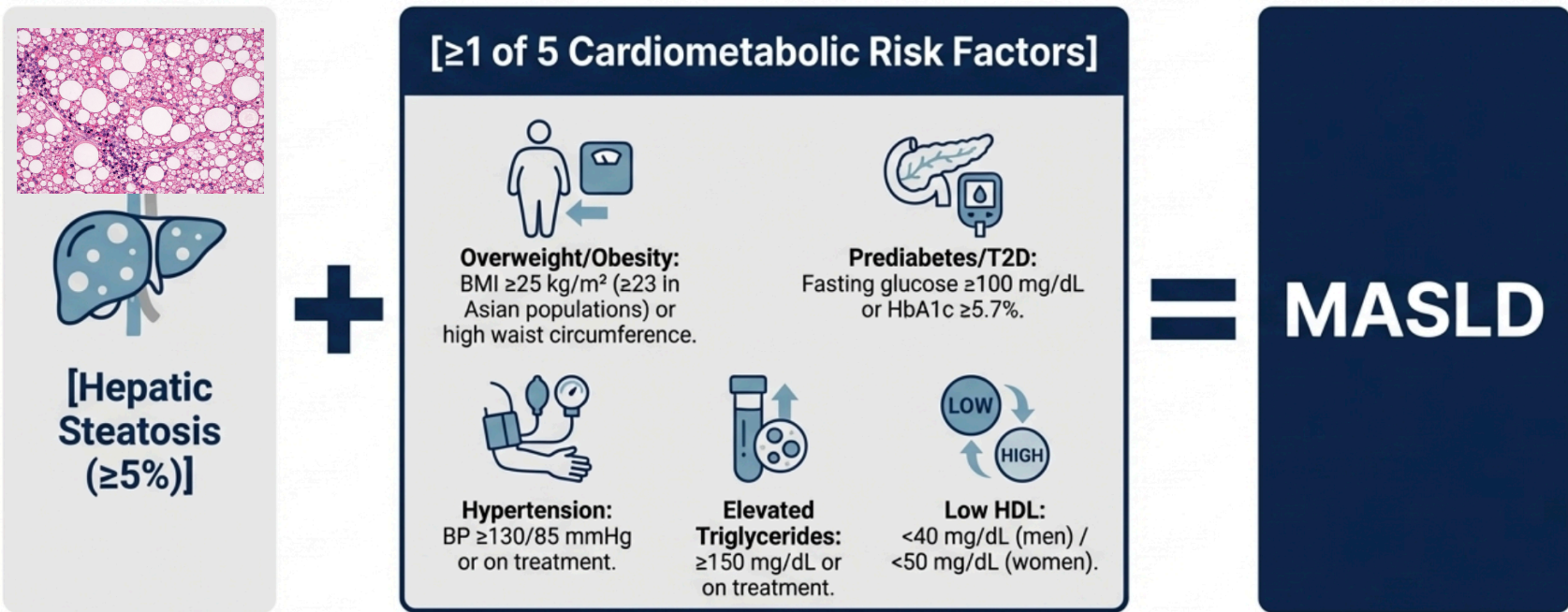
5. Low HDL

HDL <40 M / <50 F mg/dL or lipid-lowering meds

STEP 3: Exclude harmful alcohol (>140 g/wk women; >210 g/wk men), drugs causing steatosis, and other etiologies

MASLD Diagnostic Criteria

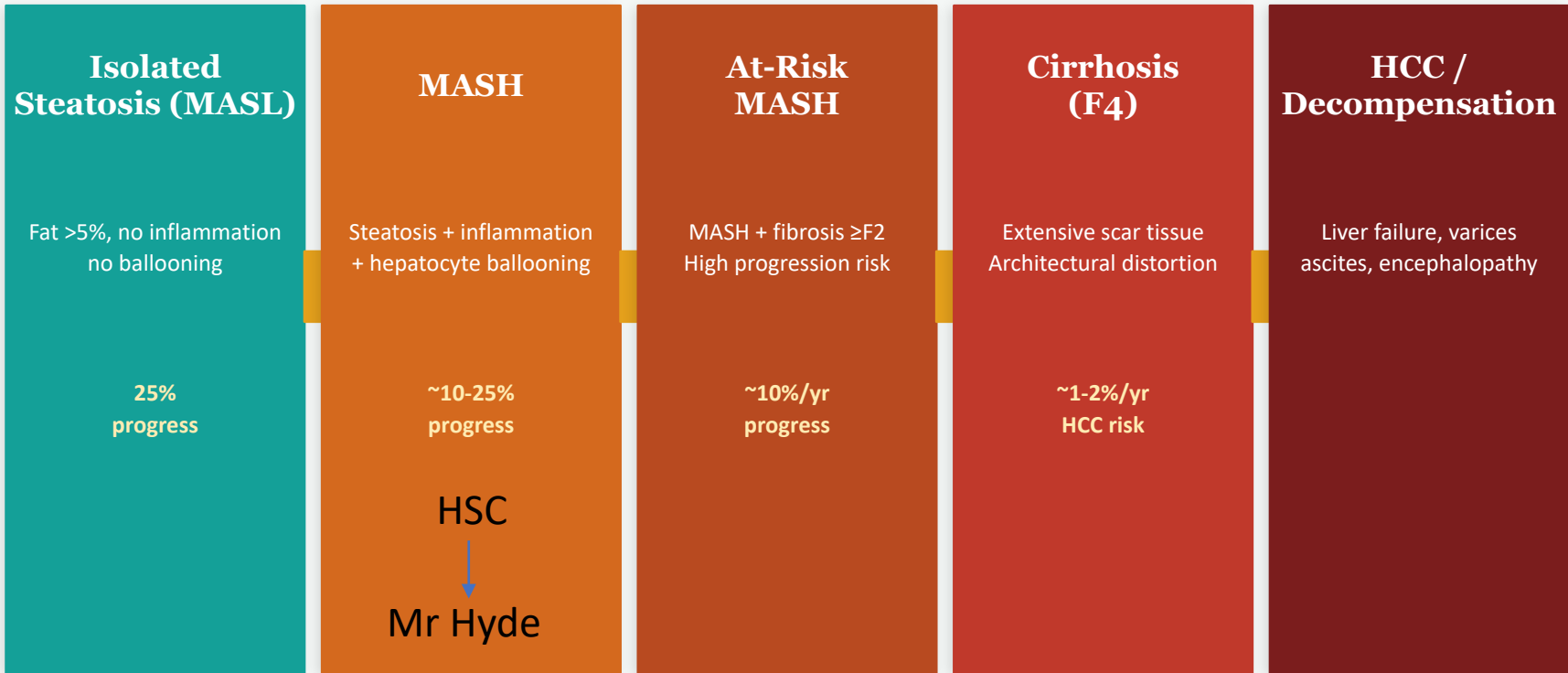
Hepatic steatosis + ≥ 1 cardiometabolic risk factor



Strict Alcohol Thresholds: Must be < 140 g/week for females, < 210 g/week for males.

The MASLD Disease Spectrum

Progressive liver injury over years to decades



Key insight: Disease is bidirectional — lifestyle intervention and pharmacotherapy can reverse steatosis, MASH, and even early fibrosis

Pathogenesis of MASLD

Multiple parallel hits drive steatosis → steatohepatitis → fibrosis

INSULIN RESISTANCE

Impairs suppression of lipolysis → free fatty acid flood into hepatocytes → triglyceride accumulation

LIPOTOXICITY

Excess hepatic FFAs generate reactive oxygen species, ceramides, and lysophosphatidylcholine → hepatocyte injury

GUT DYSBIOSIS

Altered microbiome → increased intestinal permeability → LPS → Kupffer cell activation → TNF- α , IL-6

ADIPOSE INFLAMMATION

Visceral adipose tissue → adipokines (\uparrow leptin, \downarrow adiponectin) → hepatic inflammatory signaling

GENETIC FACTORS

PNPLA3 I148M (3 \times risk), TM6SF2 E167K, HSD17B13 — modulate lipid handling and fibrosis risk

STELLATE CELL ACTIVATION

Chronic injury → hepatic stellate cells produce collagen → fibrosis. Cirrhosis = irreversible architectural disruption

SECTION

Epidemiology

Prevalence, Incidence & Burden of Disease



MASLD: A Global Epidemic

The most common chronic liver disease worldwide

~32%

Global adult prevalence

~1 in 3 adults worldwide

~10%

Global pediatric prevalence

~38%

US adult prevalence

~100 million Americans

~55–70%

T2DM prevalence

Majority have MASLD

~80%

Obesity prevalence

Of obese adults

MASLD is NOW the #1 cause of chronic liver disease and is projected to become the #1 indication for liver transplant in the US

- 35% of MASLD patients have MASH; ~7% have cirrhosis
- Incidence rising in parallel with obesity and T2DM epidemics
- Faster progression in Hispanic > White > African-American populations
- Can occur in lean individuals (BMI <25): 10–20% of cases in Asia and US
- Annual HCC incidence in cirrhotic MASLD: >1% per year (surveillance threshold)

Who Is at Risk? Screening Targets for PCPs

SCREEN THESE PATIENTS

- Type 2 diabetes or prediabetes (regardless of ALT)
- Obesity (BMI ≥ 30) or overweight + ≥ 1 metabolic factor
- Metabolic syndrome (≥ 3 components)
- Unexplained elevated ALT/AST for >3 –6 months
- Incidental hepatic steatosis on imaging

PROTECTIVE FACTORS

- Premenopausal status
- Regular aerobic exercise
- Mediterranean diet
- HSD17B13 gene variant

HIGH-RISK GENETICS

- PNPLA3 I148M — $\sim 3\times$ increased fibrosis risk
- TM6SF2 E167K — increased MASH progression
- Hispanic ethnicity — highest population prevalence

SECTION

Non-Invasive Fibrosis Assessment

FIB-4 Score & Transient Elastography

Fibrosis-4 Index (FIB-4)

First-line non-invasive fibrosis screening tool — endorsed by ADA, AASLD, EASL

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}}$$

< 1.3

LOW RISK

NPV 90–95%

Monitor FIB-4 yearly. Manage in primary care.

1.3 – 2.67

INDETERMINATE

Intermediate risk

Order transient elastography (VCTE/FibroScan)

> 2.67

HIGH RISK

PPV ~80%

Drug therapy and/or refer to hepatology

Note: For age ≥65, low-risk cutoff is raised to 1.9–2.0 | Not validated for age <35

FIB-4 Worked Example

Patient: 56-year-old man, HTN, HLD, DM2

LAB VALUES

Age **56 years**

AST **40 U/L**

ALT **55 U/L**

Platelets **$168 \times 10^9/L$**

CALCULATION

$$56 \times 40$$

$$168 \times \sqrt{55}$$

2,240

$$168 \times 7.42 = 1,247$$

$$\mathbf{FIB-4 = 1.80}$$

INDETERMINATE → Order FibroScan*

FIB-4 Practical Pearls & Pitfalls

Age \geq 65 years

Use higher low-risk cutoff of 1.9–2.0 (age-related AST rise inflates scores) — prevents over-referral ie Low risk < 2 & high risk > 2.67

Age $<$ 35 years

FIB-4 not validated in young adults — consider alternative approaches or direct specialist consultation ie ELF, MRE, Fibroscan

Normal ALT does NOT exclude MASLD

Up to 25% of patients with significant fibrosis have completely normal LFTs — screen by risk factors, not enzymes

Serial FIB-4 monitoring

Repeat every 1–3 years in low-risk; every 6–12 months in indeterminate; a rising FIB-4 demands re-evaluation

FIB-4 in MetALD

Validated with similar diagnostic performance in patients who fall in the MetALD category (moderate alcohol + metabolic risk)

Online calculators

Use MDCalc.com or your EMR's built-in FIB-4 calculator — most EHRs now auto-calculate from routine labs

A 52-year-old woman with type 2 diabetes (HbA1c 7.8%), BMI 32 kg/m², and hypertension presents for routine follow-up. Her ALT is 42 U/L (normal range 7–56 U/L). Her platelet count is 289 × 10³/μL (normal range 150–450 × 10³/μL). She drinks no alcohol. What is the most appropriate next step?

A Reassure her that normal ALT excludes liver disease

B Refer directly to hepatology

C Order abdominal ultrasound

D Calculate FIB-4 score to assess fibrosis risk

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A Reassure her that normal ALT excludes liver disease

B Refer directly to hepatology

C Order abdominal ultrasound

✓ **Calculate FIB-4 score to assess fibrosis risk**

KEY TEACHING POINT Adults with type 2 diabetes or prediabetes should be screened for MASLD-related fibrosis risk using FIB-4, even if liver enzymes are normal. Normal ALT does NOT exclude MASLD or significant fibrosis. FIB-4 is the recommended first-line noninvasive test for risk stratification in primary care.

A 48-year-old man with obesity (BMI 34 kg/m²) and prediabetes has hepatic steatosis on ultrasound. His FIB-4 score is 0.9. What is the most appropriate management?

- A** Refer to hepatology immediately
- B** Order liver biopsy
- C** Manage in primary care with lifestyle modification and repeat FIB-4 in 1–2 years
- D** Start resmetirom therapy

CASE 2**✓ ANSWER****FIB-4 INTERPRETATION**

A 48-year-old man with obesity (BMI 34 kg/m²) and prediabetes has hepatic steatosis on ultrasound. His FIB-4 score is 0.9. What is the most appropriate management?

- A** Refer to hepatology immediately
- B** Order liver biopsy
- ✓** **Manage in primary care with lifestyle modification and repeat FIB-4 in 1–2 years**
- D** Start resmetirom therapy

KEY TEACHING POINT FIB-4 <1.3 indicates low risk for advanced fibrosis with a negative predictive value of 85–90%. These patients can be managed in primary care with lifestyle interventions and repeat FIB-4 every 1–2 years. Hepatology referral is not needed for low-risk patients.

Transient Elastography (FibroScan®)

Non-invasive liver stiffness measurement — second-line testing for indeterminate FIB-4

HOW IT WORKS

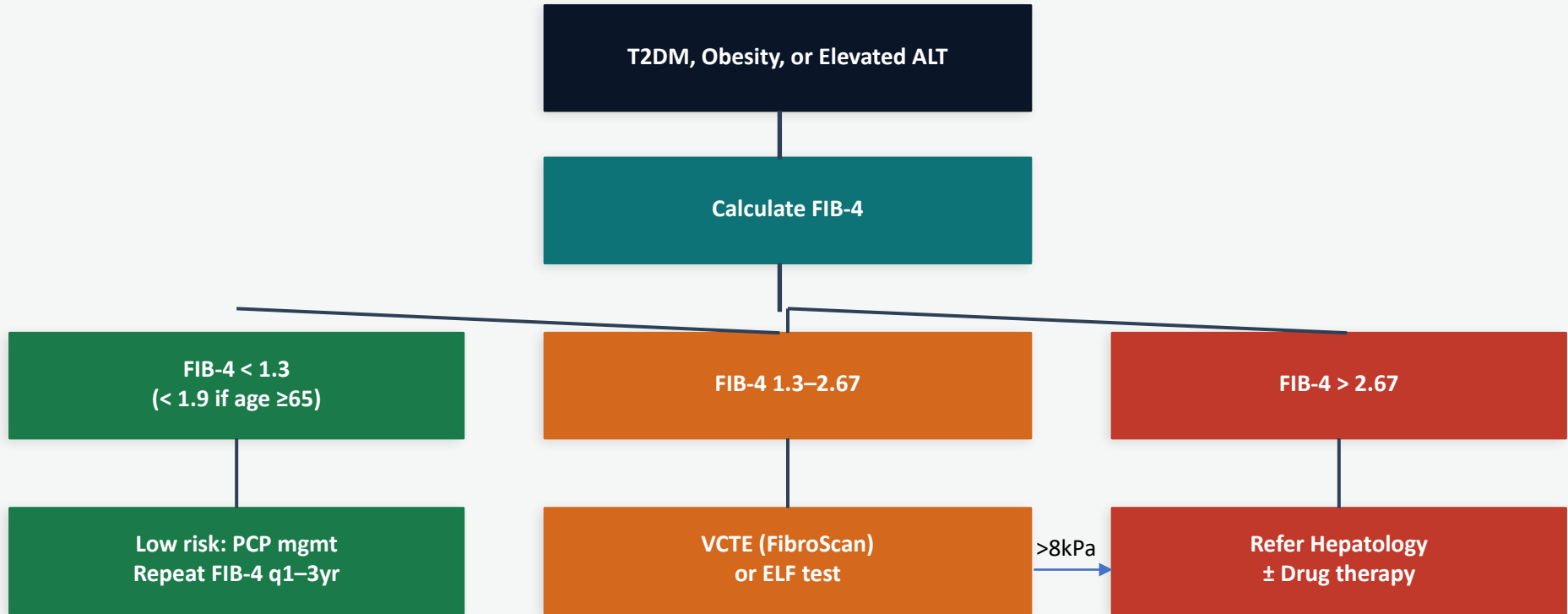
- Vibration probe placed between ribs over the right lobe of liver
- Low-frequency (50 Hz) vibration creates an elastic shear wave in liver tissue
- Ultrasound pulse-echo tracks wave speed through liver parenchyma
- Stiffer liver = faster wave = higher liver stiffness measurement (LSM) in kPa
- Also measures hepatic steatosis via Controlled Attenuation Parameter (CAP in dB/m)
- Quick (5–10 min), painless, no needles, no radiation, no sedation

LSM INTERPRETATION

< 8.0 kPa	F0–F1 Low risk — follow in primary care
8.0–12.0 kPa	F2–F3 Significant/advanced fibrosis → hepatology
≥ 12.0 kPa	F3–F4 Advanced fibrosis — likely cirrhosis
≥ 20 kPa	~F4 Cirrhosis — HCC surveillance indicated

MASLD Fibrosis Stratification Algorithm

Stepwise approach endorsed by ADA, AASLD, EASL-EASD-EASO



A 55-year-old woman with MASLD has a FIB-4 score of 1.8. What should you do next?

- A** Reassure and recheck in 5 years
- B** Proceed to vibration-controlled transient elastography (VCTE)
- C** Start pharmacotherapy immediately
- D** Order CT abdomen

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A Reassure and recheck in 5 years

✓ Proceed to vibration-controlled transient elastography (VCTE)

C Start pharmacotherapy immediately

D Order CT abdomen

KEY TEACHING POINT FIB-4 scores between 1.3–2.67 are indeterminate and require further evaluation with VCTE (or ELF testing). This two-step approach improves diagnostic accuracy for identifying patients with significant or advanced fibrosis who may need hepatology referral.

A 55-year-old woman with MASLD had baseline LSM of 10 kPa. After 2 years of lifestyle modification, her LSM is 12 kPa (20% increase). What is the clinical significance?

- A** Normal variation; continue current management
- B** A 20% increase in VCTE over 2 years is associated with 50% increased risk of hepatic decompensation
- C** Repeat testing is needed before making any conclusions
- D** This indicates laboratory error

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A Normal variation; continue current management

✓ **A 20% increase in VCTE over 2 years is associated with 50% increased risk of hepatic decompensation**

C Repeat testing is needed before making any conclusions

D This indicates laboratory error

KEY TEACHING POINT A 20% increase in VCTE over 2 years is associated with a 50% increased risk of hepatic decompensation, indicating disease progression despite lifestyle efforts. This patient warrants hepatology referral for consideration of pharmacotherapy and more intensive monitoring.

SECTION

Management of MASLD

Lifestyle, Medications & Hepatotoxic Drug Review

Alcohol Counseling in MASLD

Even modest alcohol intake accelerates liver injury

Alcohol + MASLD = Synergistic hepatotoxicity. No safe threshold identified in MASLD patients.

MetALD Classification

20–60 g/day women or 30–60 g/day men with metabolic risk factors → MetALD (not pure MASLD). Both conditions require treatment.

Threshold for ALD

Alcohol >350 g/week women or >420 g/week men with steatosis → classified as ALD, not MASLD.

Impact on Fibrosis

Even light drinking (14–21 drinks/week) doubles fibrosis progression risk in MASLD. Any alcohol use accelerates MASH → cirrhosis.

PCP Recommendation

Counsel complete abstinence in MASLD. Use AUDIT-C, motivational interviewing. Consider addiction medicine referral if AUD present.

HAV & HBV Vaccines

Vaccinate all MASLD patients against hepatitis A and B — additional viral hepatitis dramatically worsens prognosis.

Weight Loss: The Most Powerful Intervention

Ann Intern Med 2025;178:ITC1-16

3–5%

Resolution of hepatic steatosis (fatty liver)

Reduces fat, improves insulin sensitivity, lowers ALT

5–7%

Improvement in liver inflammation

Significant reduction in lobular inflammation scores

7–10%

Resolution of MASH (steatohepatitis)

64% achieve MASH resolution with 7-10% weight loss vs 10% controls

>10%

Reversal of fibrosis

Up to 45% fibrosis regression; 90% MASH resolution; preferred target for advanced disease

Take that Mr Hyde!

A 50-year-old woman with MASLD (FIB-4 0.8) asks about weight loss goals. What degree of weight loss is needed to potentially reduce hepatic fibrosis?

A 3–5%

B 5–7%

C >10%

D Any weight loss is equally beneficial

CASE 7✓ **ANSWER****LIFESTYLE MODIFICATION**

A 50-year-old woman with MASLD (FIB-4 0.8) asks about weight loss goals. What degree of weight loss is needed to potentially reduce hepatic fibrosis?

A 3–5%**B** 5–7%✓ **>10%****D** Any weight loss is equally beneficial

KEY TEACHING POINT Weight loss >10% can reduce fibrosis in MASLD. Weight loss of 5% reduces steatosis; 7–10% reduces inflammation. Greater weight loss provides incremental benefits. Counsel patients on realistic, progressive weight loss goals with lifestyle modification as the cornerstone of therapy.

Diet & Exercise for MASLD

Evidence-based lifestyle prescriptions

DIET RECOMMENDATIONS

- Mediterranean diet is the #1 recommended pattern (EASL, ADA)
- Emphasize: fruits, vegetables, whole grains, fish, olive oil
- Restrict: ultra-processed foods, refined carbs, fructose (HFCS), sugar-sweetened beverages
- Low-carb AND low-fat diets both reduce hepatic fat equally
- Hypocaloric deficit of 500–1000 kcal/day to achieve 0.5–1 kg/week loss
- Coffee consumption (≥ 2 cups/day) associated with reduced fibrosis risk

EXERCISE PRESCRIPTION

- Target: ≥ 150 min/week moderate aerobic OR ≥ 75 min/week vigorous
- Add: Resistance training 2–3x/week (reduces ALT independent of weight loss)
- Even 60–90 min/week reduces hepatic fat content significantly
- Exercise has direct anti-inflammatory and anti-fibrotic hepatic effects independent of weight loss
- High-intensity interval training (HIIT) especially effective for hepatic steatosis
- Sedentary behavior independently increases MASLD progression risk

NIH LiverTox: Identifying Hepatotoxic Medications

<https://www.ncbi.nlm.nih.gov/books/NBK547852/>

LiverTox = FREE NIH database of drug-induced liver injury (DILI) for every clinically used medication

COMMON HEPATOTOXIC DRUGS (Steatosis/DILI)

Amiodarone, Methotrexate, Tamoxifen, Corticosteroids, L-Asparaginase, Valproate, Didanosine, Stavudine, Cyclosporine, Highly active ART regimens

HOW TO USE LIVERTOX

1. Go to [ncbi.nlm.nih.gov/books/NBK547852](https://www.ncbi.nlm.nih.gov/books/NBK547852)
2. Search by drug name
3. Review 'Likelihood Score' (A–E)
4. Review mechanism of injury
5. Check for steatogenic potential
6. Consider drug holiday or alternative if appropriate

LIKELIHOOD SCORES

A = Well-documented hepatotoxicity
B = Strong evidence
C = Probable causation
D = Possible causation
E = Unlikely — other explanations more likely

Target: Review any drug with score A–C

PCP Action: Review ALL medications in MASLD patients. Discontinue or substitute steatogenic drugs when clinically safe.

Comorbidity Management in MASLD

CVD is the #1 cause of death in MASLD patients — not liver disease

DIABETES

GLP-1 RAs first-line (added liver benefit)
SGLT2i for CV/renal protection
Pioglitazone if biopsy-proven MASH
Metformin: discontinue in advanced liver disease (↑lactic acidosis risk)

HYPERTENSION

No specific antihypertensive preferred
ARBs may have mild anti-fibrotic benefit
Target BP <130/80 mmHg
Avoid NSAIDs (impair renal blood flow in cirrhosis)

DYSLIPIDEMIA

STATINS ARE SAFE in MASLD including compensated cirrhosis (Child-Pugh A)
Statins contraindicated only in decompensated cirrhosis
Ezetimibe: modest benefit on liver histology
Resmetirom also reduces LDL 24 mg/dL, TG 34 mg/dL

OBESITY

GLP-1 RAs / dual GIP+GLP-1 agonists preferred
Bariatric surgery if BMI ≥ 35 + comorbidities after failed lifestyle + pharmacotherapy
Target >7% weight loss minimum

SECTION

Pharmacotherapy for MASH

FDA-Approved Medications & Emerging Therapies

When Is Pharmacotherapy Indicated?

Target population: Adults with MASH and moderate-to-advanced fibrosis (F2–F3) — NOT all MASLD patients



Biopsy-proven MASH + F2–F3 fibrosis

Standard criterion for resmetirom eligibility



VCTE 8–15 kPa (+ MASLD criteria)

Non-invasive criterion for semaglutide eligibility (AASLD guidance)



MRE 3.1–4.4 kPa OR ELF 9.2–10.5

Alternative non-invasive tests for semaglutide selection (no biopsy required)



FIB-4 >2.67 + LSM ≥8 kPa

High risk — initiate pharmacotherapy discussion with hepatology



Isolated steatosis (MASL), no MASH, no fibrosis

Pharmacotherapy NOT currently indicated — lifestyle modification only



MASH-related cirrhosis (F4)

No MASH-targeted therapy currently approved or recommended for cirrhosis

Resmetirom (Rezdiffra®)

First FDA-approved drug for MASH with fibrosis — March 2024

MECHANISM OF ACTION

- Thyroid hormone receptor- β (THR- β) selective agonist — highly liver-selective
- Activates THR- β in hepatocytes \rightarrow restores normal T4 \rightarrow T3 conversion in liver
- Enhances hepatic mitochondrial fatty acid oxidation (burns fat in liver)
- Reduces hepatic de novo lipogenesis (reduces fat production)
- Improves VLDL export and reduces lipotoxic intermediates (ceramides, DAG)
- Also reduces LDL by \sim 24 mg/dL and TG by \sim 34 mg/dL (pleiotropic lipid benefit)
- Does NOT affect thyroid axis systemically — minimal extrathyroidal effects

CLINICAL USE & EVIDENCE

- FDA-APPROVED: Non-cirrhotic MASH + F2–F3 fibrosis
- Dose: 80 mg or 100 mg oral daily
- MAESTRO-NASH (N=966, 52 weeks):
MASH resolution: 26–30% vs 10% placebo (P<0.001)
Fibrosis improvement \geq 1 stage: 24–26% vs 14% placebo (P<0.001)
- Side effects: Diarrhea (27–33%), Nausea (19–22%), Pruritus
- Cost: \sim \$4,000/month retail — access/insurance major barrier
- Uncertainties: >70% non-responders; optimal treatment duration unknown

Semaglutide (Wegovy®) for MASH

FDA-approved August 15, 2025 for MASH with moderate-to-advanced fibrosis

FDA APPROVAL: August 15, 2025 — Semaglutide 2.4 mg/week SQ for MASH + F2–F3 fibrosis (Wegovy® formulation)

MECHANISM OF ACTION

- GLP-1 receptor agonist — incretin hormone analogy
- Reduces appetite via hypothalamic satiety signaling → weight loss
- Improves insulin sensitivity and pancreatic β -cell function
- Directly activates GLP-1 receptors on hepatocytes → ↓lipogenesis, ↑fatty acid oxidation
- Reduces hepatic inflammation via anti-inflammatory signaling
- Improves gut barrier function → ↓bacterial LPS translocation
- Preferred in MASLD + T2DM/obesity — dual metabolic + hepatic benefit

ESSENCE TRIAL RESULTS

- ESSENCE trial: N=1,197, MASH + fibrosis, 72-week interim (240-week study)
- MASH resolution: 63% semaglutide vs 34% placebo (P<0.001)
- Fibrosis improvement: 37% vs 22% placebo (P<0.001)
- Weight loss: ~13% body weight with semaglutide
- Adverse events: Nausea 36%, Diarrhea 27%, Constipation 22%
- AASLD selection criteria: VCTE 8–15 kPa or MRE 3.1–4.4 kPa or ELF 9.2–10.5
- Preferred for MASH + T2DM or obesity — addresses both conditions

Resmetirom vs Semaglutide: Side-by-Side

Choosing between the two FDA-approved MASH therapies

	RESMETIROM (Rezdiffra®)	SEMAGLUTIDE (Wegovy® for MASH)
FDA Approval	March 2024	August 2025
Indication	Non-cirrhotic MASH + F2–F3 (biopsy-based or high-risk NIT)	Non-cirrhotic MASH + F2–F3 (biopsy or VCTE 8–15 kPa)
Drug Class	THR-β agonist (liver-selective)	GLP-1 receptor agonist
Route/Dose	Oral daily (80 or 100 mg)	SQ weekly (2.4 mg Wegovy)
MASH Resolution	26–30% vs 10% placebo	63% vs 34% placebo
Weight Effect	Neutral (no weight loss)	~13% body weight loss
T2DM Benefit	No	Yes — improves glycemia
Side Effects	Diarrhea, nausea, pruritus	Nausea, diarrhea, constipation
Cost/Month	~\$4,000	~\$1,300 (Wegovy list price)
Best For	MASH without T2DM/obesity	MASH + T2DM or obesity

Combination therapy data limited — individualize; consult hepatology for complex cases

A 54-year-old woman with biopsy-proven MASH and F3 fibrosis (no cirrhosis) asks about medication options. Which statement is correct about resmetirom?

A It is approved for noncirrhotic MASH with F2–F3 fibrosis

B It is approved for all stages of MASLD

C It requires cirrhosis for approval

D It is only approved for pediatric MASLD

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B It is approved for all stages of MASLD

C It requires cirrhosis for approval

D It is only approved for pediatric MASLD

KEY TEACHING POINT Resmetirom is FDA-approved for adults with noncirrhotic MASH and moderate to advanced fibrosis (F2–F3). It is NOT approved for cirrhotic MASLD or patients without significant fibrosis. The MAESTRO-NASH trial demonstrated MASH resolution and fibrosis improvement in this population.

A 49-year-old man with MASLD, BMI 33 kg/m², and LSM of 10 kPa asks about semaglutide. According to AASLD guidance, what noninvasive test range supports semaglutide use for MASLD?

A VCTE 5–8 kPa

B VCTE 8–15 kPa

C VCTE >20 kPa

D Any VCTE value with steatosis

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✓ VCTE 8–15 kPa

C VCTE >20 kPa

D Any VCTE value with steatosis

KEY TEACHING POINT AASLD recommends patient selection for semaglutide using NITs including VCTE 8–15 kPa (or MRE 3.1–4.4 kPa, or ELF 9.2–10.5) rather than requiring liver biopsy. This patient's LSM of 10 kPa falls within this range, making him a candidate for semaglutide therapy.

A 56-year-old woman started resmetirom 3 weeks ago for MASH with F3 fibrosis. She reports frequent diarrhea (4–5 loose stools daily) but no other symptoms. What is the most appropriate management?

- A** Discontinue resmetirom immediately
- B** Reassure that diarrhea is common (27–33% vs. 15% placebo); consider symptomatic management and monitor
- C** Reduce dose by half
- D** Switch to semaglutide

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- ✓ **Reassure that diarrhea is common (27–33% vs. 15% placebo); consider symptomatic management and monitor**
- C Reduce dose by half
- D Switch to semaglutide

KEY TEACHING POINT Diarrhea is the most common adverse event with resmetirom, occurring in 27–33% vs. 15% with placebo in MAESTRO-NASH. Most cases are mild-moderate and manageable with supportive care. Unless severe or associated with other concerning symptoms, continuation with symptomatic management is appropriate.

Other Pharmacotherapy Options

Adjunct agents with evidence for MASH

PIOGLITAZONE (TZD)

- PPAR γ agonist — improves insulin sensitivity
- Recommended for T2DM + biopsy-proven MASH (ADA 2026)
- **Not FDA approved for MASLD or MASH** but cheap &
- Reduces steatosis, inflammation, ballooning; modest fibrosis benefit
- Dose: 30–45 mg daily
- Side effects: Weight gain (2–3 kg), fluid retention, fracture risk, possible bladder cancer (long-term)
- **Contraindicated in Class III/IV heart failure**
- Use with caution in patients prone to osteoporosis

VITAMIN E (α -tocopherol)

- Antioxidant — combats oxidative stress in MASLD
- NOT FDA-approved for MASLD indication
- Meta-analysis (7 studies, n=508): Significant \downarrow ALT, AST; improved steatosis and inflammation histology
- Dose: 400–800 IU daily
- Side effects: Possible \uparrow hemorrhagic stroke risk at high doses; may interact with anticoagulants
- Recommended: Non-diabetic MASH without cirrhosis (ADA)
- Not recommended for patients with T2DM or MASH cirrhosis

Emerging Pharmacotherapies for MASH

The pipeline is rich — expect rapid change in the next 3–5 years

Tirzepatide (Mounjaro/Zepbound)

Dual GIP+GLP-1 agonist

Combines GLP-1 and GIP receptor agonism → superior weight loss (20–22%)

SYNERGY-NASH Ph2b: MASH resolution 44–62% vs 10% placebo — Phase 3 ongoing

Phase 3

Lanifibranor

Pan-PPAR agonist ($\alpha/\delta/\gamma$)

Activates all 3 PPAR isoforms → anti-inflammatory, anti-fibrotic, metabolic benefit

NATIVE trial (Ph3): Significant MASH resolution + fibrosis improvement; NDA under review

NDA
Filed

FGF-21 Analogues (Pegbelfermin, Efruxifermin, Pegozafermin, Efimosfermin)

FGF-21 analogue

Fibroblast growth factor 21 → reduces hepatic lipogenesis, improves insulin sensitivity, anti-fibrotic

Dr Jekyll

Phase 3 trials ongoing (HARMONY, ENLIVEN) Phase 2 promising (SYMMETRY)

Phase
2/3

Obeticholic Acid (Ocaliva)

Withdrawn Nov 2025: Liver injury

Phase 3

Emerging MASLD Therapies

Phase 3 Pipeline — Beyond FDA-Approved Agents · Source: NEJM 2025 Review + Network Meta-Analysis

Semaglutide

FDA APPROVED

Ozempic / Wegovy · GLP-1 Agonist

★ #3 MASH Resolution (84.70)

- 2.4 mg/wk SC — FDA approved for MASH Aug 2025
- MASH resolution + fibrosis improvement (F2–F3)
- VCTE 8–15 kPa = NIT selection criteria
- Extrahepatic: weight loss, CV risk, CKD benefit

Lanifibranor

NDA FILED

IVA337 · Pan-PPAR Agonist ($\alpha/\delta/\gamma$)

- NATIVE Ph2b: 49% MASH resolution vs 22% placebo
- Fibrosis ≥ 1 stage reduction: 48% vs 29%
- Reduces insulin resistance + HbA1c
- Ph3 (NCT04849728): 72-wk F2–F3 trial ongoing

Efruxifermin

PHASE 3

EFX · FGF-21 Analogue

- HARMONY 96-wk: sustained efficacy demonstrated
- SYMMETRY (cirrhosis): 29% cirrhosis reversal vs 11%
- Benefits preserved in patients on GLP-1 RAs
- Ph3 NCT06215716 ongoing — safety + long-term data

Pegozafermin

PHASE 3

BIO89-100 · FGF-21 Analogue

★ #1 BOTH endpoints (Fibrosis 79.92 · MASH 91.75)

- Top-ranked agent in 2025 SUCRA network meta-analysis
- Ph2: up to 48% ↓ liver fat; ↓ Pro-C3, ELF, LSM
- Neutral effect on body weight (unlike incretins)
- Ph3 NCT06318169 ongoing — F2–F3 population

Survodutide

PHASE 3

BI 456906 · Dual GLP-1 / Glucagon Agonist

★ #2 MASH Resolution (SUCRA 90.87)

- Ph2: MASH resolution 47–62% vs 14% placebo
- Direct hepatic glucagon effect + GLP-1 weight loss
- Fibrosis improvement 32–36% vs 18% placebo
- GI discontinuation rate 20% — monitor closely

Weight Loss: The Most Powerful Intervention

Ann Intern Med 2025;178:ITC1-16

3–5%

Resolution of hepatic steatosis (fatty liver)

Reduces fat, improves insulin sensitivity, lowers ALT

5–7%

Improvement in liver inflammation

Significant reduction in lobular inflammation scores

7–10%

Resolution of MASH (steatohepatitis)

64% achieve MASH resolution with 7-10% weight loss vs 10% controls

>10%

Reversal of fibrosis

Up to 45% fibrosis regression; 90% MASH resolution; preferred target for advanced disease

FDA-Approved Anti-Obesity Medications (Long-Term Use)

Efficacy ranked by expected total body weight loss — JAMA 2024

MEDICATION	MECHANISM	WEIGHT LOSS	MAIN SIDE EFFECTS	MONTHLY COST	BEST FOR
Tirzepatide (Zepbound®)	Dual GIP+GLP-1 agonist	15–21%	Nausea 28–31% Diarrhea 11–13%	~\$1,081/mo	Obesity + T2DM or MASH
Semaglutide (Wegovy®)	GLP-1 receptor agonist	15–17%	Nausea 44% Diarrhea 30%	~\$902/mo	Obesity + CVD or MASH + T2DM
Phentermine- Topiramate ER (Qsymia®)	Sympathomimetic + GABA modulator	8–11%	Paresthesia 20% Dry mouth 19%	~\$116/mo	No CVD; need affordable option
Liraglutide (Saxenda®)	GLP-1 receptor agonist (daily SQ)	5–8%	Nausea 39% Diarrhea 21%	~\$905/mo	GLP-1 preferred; semaglutide unavail.
Naltrexone- Bupropion ER (Contrave®)	Opioid antagonist + DA/NE reuptake inhibitor	5–6%	Nausea 33% Constipation 19%	~\$638/mo	Depression / food cravings
Orlistat (Alli®/Xenical®)	Lipase inhibitor → fat malabsorption	3–5%	Oily stool 27% Fecal urgency 22%	\$78 OTC / \$679 Rx	OTC access; tolerates GI SEs

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Off label. No MASH / MASLD Indication					
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Drug Name	Mechanism of Action	% Body Weight Loss	Estimated Monthly Cost	Best For
Oral Semaglutide 25 mg (Wegovy)	GLP-1 receptor agonist (peptide)	~ 13.6% at 64 weeks (vs 2.2% placebo)	~\$1,000–1,350/month (list price)	Obesity/overweight with cm; MASH with F2-F3 fibrosis (FDA approved); T2DM; Cardiovascular risk reduction
Orforglipron (Foundayo)	Small-molecule (non-peptide) GLP-1 receptor agonist; biased agonism with low β -arrestin activation; high oral bioavailability (~79%)	~ 11.2% at 72 weeks (36 mg dose, vs 2.1% placebo)	Not yet established (expected lower)	Obesity/overweight with cm; T2DM; Patients preferring oral therapy without food/water restrictions

Choosing the Right Anti-Obesity Medication

A practical framework for primary care — comorbidity-driven selection

Efficacy hierarchy: Tirzepatide > Semaglutide > Phentermine-Topiramate > Liraglutide > Naltrexone-Bupropion > Orlistat

PATIENT HAS T2DM + OBESITY + MASLD

- 1st choice: Semaglutide 2.4 mg/wk (Wegovy®)
FDA-approved for MASH + T2DM/obesity
Dual liver + glycemic + CV benefit
- 2nd choice: Tirzepatide (Zepbound®)
Superior weight loss; SURMOUNT-NASH ongoing
- Avoid: Orlistat (GI SEs worsen in MASLD)
- Continue statins — safe in compensated cirrhosis

PATIENT HAS OBESITY + CVD (No T2DM)

- 1st choice: Semaglutide (SELECT trial)
20% ↓ MACE in obesity + established CVD
- 2nd choice: Tirzepatide
SURPASS-CVOT data pending; promising
- AVOID: Phentermine-topiramate (↑HR, ↑BP risk)
- AVOID: Naltrexone-bupropion (↑BP; CV warning)
- Cost barrier: Phentermine mono (~\$17/mo) short-term

COST IS THE BARRIER (No GLP-1 Coverage)

- Phentermine-Topiramate ER ~\$116/mo (Qsymia)
8–11% weight loss; generic available
- Phentermine alone ~\$17/mo
Short-term only (≤12 wks); monitor BP/HR
- Orlistat 60 mg OTC ~\$78/mo
If GI tolerated; modest 3–5% weight loss
- Pioglitazone ~\$10–30/mo if MASLD + T2DM
Histologic MASH benefit; not obesity-approved

A 61-year-old woman with MASLD (LSM 12 kPa), type 2 diabetes, and stage 3a CKD (eGFR 52 mL/min/1.73m²) is being considered for pharmacotherapy. Which medication offers potential benefits for both liver disease and kidney disease?

A Pioglitazone

B Vitamin E

C Semaglutide

D Ursodeoxycholic acid

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A Pioglitazone

B Vitamin E

✓ **Semaglutide**

D Ursodeoxycholic acid

KEY TEACHING POINT Semaglutide is FDA-approved for slowing CKD progression in type 2 diabetes and is also approved for MASH with F2–F3 fibrosis. It addresses multiple aspects of cardiometabolic disease without nephrotoxicity. Pioglitazone can cause fluid retention, which may be problematic in CKD.

A 58-year-old man with MASLD, type 2 diabetes, and heart failure with reduced ejection fraction (HFrEF) has biopsy-proven MASH with F2 fibrosis. Which medication should be avoided?

A Resmetirom

B Semaglutide

C Pioglitazone

D Metformin

A 58-year-old man with MASLD, type 2 diabetes, and heart failure with reduced ejection fraction (HFrEF) has biopsy-proven MASH with F2 fibrosis. Which medication should be avoided?

A Resmetirom

B Semaglutide

✓ **Pioglitazone**

D Metformin

KEY TEACHING POINT Pioglitazone should be avoided in patients with heart failure due to increased risk of fluid retention and worsening heart failure. Although pioglitazone has demonstrated efficacy in NASH trials, the cardiovascular risks outweigh benefits in HFrEF. Semaglutide and resmetirom do not cause fluid retention. Metformin is safe in HFrEF.

SECTION

Advanced Fibrosis & Cirrhosis

Management, HCC Surveillance & Hepatology Referral

Transient Elastography (FibroScan®)

Non-invasive liver stiffness measurement — second-line testing for indeterminate FIB-4

LSM INTERPRETATION

< 8.0 kPa

F0–F1

Low risk — follow in primary care

8.0–12.0 kPa

F2–F3

Significant/advanced fibrosis → hepatology

≥ 12.0 kPa

F3–F4

Advanced fibrosis — likely cirrhosis

≥ 20 kPa

~F4

Cirrhosis — HCC surveillance indicated

Management of Advanced Fibrosis (F3 — Bridging)

High-risk patients who need intensified care

1

Refer to Hepatology

FIB-4 >2.67 with LSM \geq 8 kPa \rightarrow hepatology referral. Specialist manages biopsy, advanced imaging, treatment selection.

2

Initiate MASH-Targeted Pharmacotherapy

Semaglutide (if T2DM/obesity) or resmetirom (if no DM). Discuss with hepatologist. Target FIB-4 regression over 12–18 months.

3

Intensify Metabolic Management

Aggressive T2DM control, statin therapy, BP optimization. GLP-1 RAs preferred for diabetes. Pioglitazone if biopsy-proven MASH + T2DM.

4

Screen for Complications

Upper endoscopy if cirrhosis suspected (varices screening). Abdominal ultrasound + AFP if cirrhosis present (HCC surveillance every 6 months).

5

Eliminate Cofactors

Absolute alcohol cessation. Review all medications using LiverTox — discontinue/replace steatogenic drugs. Treat OSA if present (\uparrow MASLD severity).

MASH-Related Cirrhosis: What PCPs Need to Know

NO MASH-targeted pharmacotherapy is currently approved or recommended for cirrhosis (F4)

COMPENSATED CIRRHOSIS (Child-Pugh A/B)

- Continue lifestyle: weight loss, diet, exercise
- Statins: SAFE and recommended for CVD reduction
- GLP-1 RAs: May continue for obesity/DM (with monitoring)
- Pioglitazone: Use with caution in compensated cirrhosis
- Metformin: DISCONTINUE (↑lactic acidosis risk)
- Aspirin: Generally safe in Child-Pugh A
- AVOID NSAIDs, nephrotoxic agents
- HCC surveillance every 6 months
- Upper endoscopy for varices if newly diagnosed cirrhosis

DECOMPENSATED CIRRHOSIS (Ascites, SBP, HE, Variceal Bleed)

- Refer to hepatology/transplant center immediately
- Insulin preferred for glycemia management
- Statins: CONTRAINDICATED in decompensated cirrhosis
- Avoid all nephrotoxins, sedating medications
- Lactulose/rifaximin for hepatic encephalopathy
- MELD score tracking — MELD ≥ 15 : transplant referral
- Sodium-restricted diet + diuretics for ascites
- Propranolol/nadolol for variceal prophylaxis

Hepatocellular Carcinoma (HCC) Surveillance

Who, when, and how to screen

Surveillance threshold: Annual HCC incidence $\geq 1\%$ justifies 6-month ultrasound \pm AFP screening

Cirrhosis (F4) — ANY CAUSE

Annual HCC incidence $>1.5\text{--}2\%$ — SCREEN

Ultrasound + AFP every 6 months

FIB-4 ≥ 3.25 OR LSM ≥ 20 kPa (non-cirrhotic)

Annual incidence exceeds 1% threshold even without biopsy-proven cirrhosis

Ultrasound + AFP every 6 months — do NOT wait for biopsy

FIB-4 1.3–3.25 + additional high-risk factors

LSM ≥ 15 kPa in two-step approach predicts high HCC risk

Consider surveillance — consult hepatology

Isolated steatosis / Low FIB-4 (<1.3)

Annual HCC incidence $<0.1\%$ — below surveillance threshold

No routine HCC surveillance indicated

A 62-year-old man with MASLD-related cirrhosis (confirmed by biopsy 2 years ago) is clinically compensated. What HCC surveillance strategy should be implemented?

A No surveillance needed unless symptoms develop

B Annual CT abdomen

C Liver ultrasound \pm AFP every 12 months

D Liver ultrasound \pm AFP every 6 months

A 62-year-old man with MASLD-related cirrhosis (confirmed by biopsy 2 years ago) is clinically compensated. What HCC surveillance strategy should be implemented?

A No surveillance needed unless symptoms develop

B Annual CT abdomen

C Liver ultrasound ± AFP every 12 months

✓ **Liver ultrasound ± AFP every 6 months**

KEY TEACHING POINT Patients with cirrhosis have annual HCC incidence exceeding 1% and require surveillance with liver ultrasound ± serum AFP every 6 months. This applies to all causes of cirrhosis, including MASLD. Annual surveillance is insufficient given the rapid growth potential of HCC.

A 57-year-old woman with type 2 diabetes, MASLD, FIB-4 of 3.5, and LSM of 22 kPa (no biopsy performed) asks about cancer screening. What should you recommend?

- A** Begin HCC surveillance with ultrasound \pm AFP every 6 months
- B** No HCC surveillance needed without cirrhosis
- C** Annual AFP only
- D** Wait until cirrhosis is biopsy-proven

A 57-year-old woman with type 2 diabetes, MASLD, FIB-4 of 3.5, and LSM of 22 kPa (no biopsy performed) asks about cancer screening. What should you recommend?



Begin HCC surveillance with ultrasound ± AFP every 6 months

B

No HCC surveillance needed without cirrhosis

C

Annual AFP only

D

Wait until cirrhosis is biopsy-proven

KEY TEACHING POINT Recent data show that patients with FIB-4 ≥ 3.25 OR LSM ≥ 20 kPa have annual HCC incidence exceeding 1%, justifying surveillance even without biopsy-proven cirrhosis. This patient meets BOTH criteria and should begin 6-month surveillance with ultrasound \pm AFP.

When to Refer to Hepatology

Clear indications for specialist involvement



FIB-4 >2.67 and/or LSM \geq 8 kPa

High-risk fibrosis — specialist evaluation for biopsy, advanced staging, and treatment selection



Suspected or confirmed cirrhosis

Child-Pugh assessment, portal hypertension workup, varices screening, transplant candidacy evaluation



Indeterminate FIB-4 (1.3–2.67) with LSM \geq 8 kPa after VCTE

Upper end of intermediate risk — specialist guidance on biopsy, treatment initiation, monitoring



Rapid FIB-4 progression (low \rightarrow high risk within 3 years)

Liver-related event rate escalates dramatically — requires urgent specialist evaluation



Considering pharmacotherapy (resmetirom or semaglutide for MASH)

Hepatology can confirm MASH diagnosis, review biopsy, guide drug selection and monitoring



Unexplained elevated liver enzymes unresponsive to lifestyle \times 3 months

Rule out other etiologies, confirm MASLD diagnosis, assess for MASH

Bariatric/Metabolic Surgery in MASLD

Most powerful weight loss intervention — MASH resolution in 56–84%

WHEN TO CONSIDER SURGERY

- BMI ≥ 40 kg/m² (any comorbidity)
- BMI ≥ 35 kg/m² + ≥ 1 comorbidity (T2DM, HTN, MASLD)
- Failed lifestyle modification + pharmacotherapy \times 6–12 months
- MASLD/MASH is now a recognized indication supporting surgery
- Consider earlier if MASH + progressive fibrosis

BRAVES Trial (2023):

MASH resolution at 1 year: RYGB 57%, Sleeve 56% vs Lifestyle 16% (P<0.0001)

OUTCOMES & CONTRAINDICATIONS

- 5-year MASH resolution: 84% post bariatric surgery
- Fibrosis improvement at 5 years: 70%
- 10-year: \downarrow major liver events 9.6% \rightarrow 2.3%; \downarrow CV events 15.7% \rightarrow 8.5%
- Roux-en-Y gastric bypass and sleeve gastrectomy: Comparable efficacy
- Preferred in older adults: Sleeve gastrectomy (safer profile)
- CONTRAINDICATED: Decompensated cirrhosis
- CAUTION: Compensated cirrhosis — refer to experienced center

Liver Transplantation for MASLD Cirrhosis

MASLD is a leading indication for liver transplant in the US

INDICATIONS FOR REFERRAL

- Decompensated MASH cirrhosis (ascites, HE, variceal bleed, SBP)
- MELD score ≥ 15 → transplant evaluation recommended
- Hepatocellular carcinoma meeting Milan or expanded criteria
- Median survival from first decompensation to death/transplant: ~2 years
- Ascites is most common first decompensation event (69.5% of cases)

TRANSPLANT EVALUATION

- MELD score determines waitlist priority (Model for End-Stage Liver Disease)
- Cardiac evaluation critical — CVD is major post-transplant cause of morbidity
- Metabolic syndrome management pre-transplant improves outcomes
- No upper age limit; carefully selected older adults have comparable outcomes
- Sobriety requirements if concurrent ALD component

POST-TRANSPLANT MASLD

- Metabolic syndrome and MASLD can RECUR post-transplant in 20–30%
- De novo MASLD occurs in ~30% of transplant recipients from other causes
- Maintain lifestyle modifications and metabolic risk management post-transplant
- Immunosuppressants (tacrolimus, corticosteroids) worsen metabolic profile

MASLD Monitoring: A Longitudinal View

How often to retest and what to watch for

RISK CATEGORY	FIB-4 INTERVAL	VCTE/ELF	LABS	HCC SCREEN	ACTION
Low Risk FIB-4 <1.3	Every 1–3 years	Not needed if FIB-4 stable	LFTs, FLP, HbA1c annually	Not indicated	PCP follow-up; lifestyle reinforcement
Indeterminate FIB-4 1.3–2.67	Every 6–12 months	At baseline; repeat if FIB-4 rises	As above + platelet count	Only if LSM \geq 20 kPa	Close PCP follow-up; hepatology if LSM \geq 8 kPa
High Risk FIB-4 >2.67	With hepatology	As directed by hepatologist	Full LFTs, CBC, INR, albumin	Yes if cirrhosis/FIB-4 \geq 3.25	Hepatology co-management; pharmacotherapy
On Drug Therapy	At 72 weeks (baseline)	Baseline + 72 weeks	Every 3–6 months	Per risk level	Assess response: \geq 30% LSM drop = response

Special Population: Lean MASLD

BMI <25 kg/m² — 10–20% of all MASLD cases

- Definition: MASLD occurring in individuals with BMI <25 kg/m² (Western) or <23 kg/m² (Asian)
- Often missed: Normal BMI creates false reassurance — metabolic dysfunction (visceral adiposity, insulin resistance) is the key driver
- Central obesity: Normal BMI but waist circumference >94 cm men / >80 cm women — still meets MASLD criteria
- Genetics: PNPLA3 and TM6SF2 variants disproportionately contribute in lean MASLD
- Prognosis: Similar fibrosis progression rates compared to obese MASLD — requires equivalent monitoring
- Management: Same FIB-4 stratification, lifestyle counseling, and pharmacotherapy eligibility
- Pitfall: Don't dismiss elevated ALT/AST in normal-weight patients — screen for MASLD if any CMR factor present

Special Population: Pediatric MASLD

Fastest-growing age group — paralleling childhood obesity epidemic

- Prevalence: ~10% of children (ages 2–19) in US; ~38% in obese children
- Diagnosis: Same hepatic steatosis + CMR criteria — but BMI z-score used, not absolute BMI
- Histology: Unique pattern — periportal (zone 1) fibrosis predominates vs perivenous in adults
- Pharmacotherapy: NO approved drugs specifically for pediatric MASLD — lifestyle is the ONLY evidence-based intervention
- GLP-1 agonists: FDA-approved for pediatric obesity and T2DM (age ≥ 12) but NO MASLD-specific efficacy data in children
- Vitamin E: Some evidence for non-diabetic pediatric MASH but not approved or routinely recommended
- Goals: Weight loss 7–10% of body weight, Mediterranean-style diet, 60 min/day physical activity
- When to refer: Hepatology referral for FIB-4 elevation or progressive liver disease; consider family-based behavioral intervention

Statins in MASLD: Dispelling the Myth

CVD is the #1 killer in MASLD — statins are safe AND beneficial

MYTH BUSTED: Statins are NOT contraindicated in MASLD, MASH, or compensated cirrhosis

Safe in compensated cirrhosis (Child-Pugh A/B)

Multiple studies confirm statin safety and reduction in cardiovascular events, HCC risk, and portal hypertension complications

Contraindicated ONLY in decompensated cirrhosis (C-P C)

Increased risk of hepatic decompensation; impaired drug metabolism; discontinue in decompensated patients

Statin-induced transaminase elevation

Transient, dose-dependent elevations are common but do NOT indicate liver toxicity. Discontinue only if ALT >3× ULN with symptoms, or >10× ULN

Statin myopathy in liver disease

Monitor for myalgia/myopathy; higher risk if cirrhosis due to impaired statin metabolism. Start at lower doses.

Possible hepatic benefit

Statins may reduce MASLD progression, portal hypertension severity, and HCC risk — emerging evidence

MASLD & Cardiovascular Disease

CVD is the leading cause of death in MASLD — not liver disease

Implication: Every MASLD patient needs comprehensive CVD risk management —

- **Statins,**
- **BP control,**
- **Diabetes management.**
- **Treating the liver in isolation is NOT sufficient.**

A 59-year-old man with MASLD, compensated cirrhosis (Child-Pugh A), and LDL cholesterol of 145 mg/dL asks if statins are safe given his liver disease. What should you advise?

- A** Statins are contraindicated in all liver disease
- B** Statins are safe in compensated cirrhosis and recommended for cardiovascular risk reduction
- C** Wait until after liver transplant to start statins
- D** Use fibrates instead of statins

A 59-year-old man with MASLD, compensated cirrhosis (Child-Pugh A), and LDL cholesterol of 145 mg/dL asks if statins are safe given his liver disease. What should you advise?

A Statins are contraindicated in all liver disease

✓ **Statins are safe in compensated cirrhosis and recommended for cardiovascular risk reduction**

C Wait until after liver transplant to start statins

D Use fibrates instead of statins

KEY TEACHING POINT Statins are SAFE in compensated cirrhosis and should be used for cardiovascular risk reduction, as cardiovascular disease is the leading cause of mortality in MASLD. Statins are contraindicated only in decompensated cirrhosis. This Child-Pugh A patient should receive statin therapy for his elevated LDL.

Obstructive Sleep Apnea & MASLD

An underrecognized cofactor in MASLD progression

- OSA prevalence in MASLD: ~50–80% of patients with MASH — much higher than general population
- Mechanism: Chronic intermittent hypoxia → oxidative stress → hepatic lipid peroxidation → hepatocyte apoptosis → fibrosis activation
- OSA independently associated with more severe MASLD, higher fibrosis stage, and greater MASH activity
- Screening: Screen all MASLD patients for OSA using STOP-BANG or Epworth questionnaire
- Treatment with CPAP: Associated with improvement in ALT, hepatic steatosis, and inflammatory markers
- CPAP does NOT fully replace lifestyle modification — weight loss remains essential
- Management: Treat OSA actively in MASLD patients — add to hepatotoxic cofactor review alongside alcohol and medications

LOVE, LIVER, LAUGH

SECTION

5 questions. The liver is watching. No pressure.

Q1

Q2

Q3

Q4

Q5

Every nutrient absorbed from your gut heads straight to the liver first. What do we call this express delivery route — and what's the liver's role when that cargo arrives?

- A** The hepatic autobahn — the liver speeds everything along without stopping
- B** The portal vein — the liver acts as the docking port, inspecting and processing every incoming shipment before anything reaches circulation
- C** The mesenteric express — the liver just signs for the package and passes it on unchanged
- D** The gastric pipeline — nutrients go to the stomach first, then the liver picks up whatever's left



Answer — Question 1 · The Docking Port

B is correct

A

The hepatic autobahn — the liver speeds everything along without stopping



The portal vein — the liver acts as the docking port, inspecting and processing every incoming shipment before anything reaches circulation

C

The mesenteric express — the liver just signs for the package and passes it on unchanged

D

The gastric pipeline — nutrients go to the stomach first, then the liver picks up whatever's left

KEY LIVER POINT

First-pass hepatic metabolism means EVERYTHING absorbed in the gut clears through the liver before reaching systemic circulation. The liver is the docking port — an extremely thorough customs officer who also happens to synthesize albumin.

A patient asks why the liver is basically running a one-organ pharmaceutical company. Which of the following is NOT something the liver actually manufactures?

- A** Albumin and clotting factors (fibrinogen, prothrombin)
- B** Bile acids for fat emulsification
- C** VLDL particles packed with triglycerides
- D** Insulin — to regulate the glucose it just processed



Answer — Question 2 · The Factory

D is correct

A Albumin and clotting factors (fibrinogen, prothrombin)

B Bile acids for fat emulsification

C VLDL particles packed with triglycerides

✓ **Insulin — to regulate the glucose it just processed**

KEY LIVER POINT

Insulin is made exclusively by the pancreatic beta cells. The liver makes albumin, clotting factors, bile, VLDL, IGF-1, CRP, complement proteins — about 500 things. But it politely outsources insulin production. The liver is insulin's biggest customer, not its supplier.

Your patient took a handful of supplements, two glasses of wine, and a Tylenol before bed. Which hepatic system is working overtime tonight?

- A** The urea cycle — turning all that protein into something the kidneys can handle
- B** The CYP450 enzyme system — the liver's industrial detox crew running the night shift
- C** Glycogenolysis — releasing glucose because the liver smelled alcohol and panicked
- D** Beta-oxidation — burning the supplement capsules for energy



Answer — Question 3 · Waste Management

B is correct

A

The urea cycle — turning all that protein into something the kidneys can handle



The CYP450 enzyme system — the liver's industrial detox crew running the night shift

C

Glycogenolysis — releasing glucose because the liver smelled alcohol and panicked

D

Beta-oxidation — burning the supplement capsules for energy

KEY LIVER POINT

CYP450 enzymes handle drugs, alcohol, toxins, and all 47 'wellness' supplements. Acetaminophen + alcohol is particularly unkind — both deplete glutathione, the liver's main antioxidant buffer. The overnight CYP450 crew really earns its keep here.

In insulin resistance, adipocytes basically develop a leak — releasing excess free fatty acids that flood the portal circulation. The liver absorbs them out of metabolic neighborliness. What's the eventual consequence?

- A** Nothing serious — the liver loves extra fat and stores it as a strategic reserve
- B** Hepatic steatosis progressing to MASH and potentially cirrhosis — the liver pays a steep price for being a good neighbor
- C** The liver converts all the excess fat to ketones and ships them to the brain, problem solved
- D** The fat is immediately re-exported as HDL, so the liver comes out ahead



Answer — Question 4 · The Good Neighbor

B is correct

A Nothing serious — the liver loves extra fat and stores it as a strategic reserve

✓ **Hepatic steatosis progressing to MASH and potentially cirrhosis — the liver pays a steep price for being a good neighbor**

C The liver converts all the excess fat to ketones and ships them to the brain, problem solved

D The fat is immediately re-exported as HDL, so the liver comes out ahead

KEY LIVER POINT

The cruel irony of MASLD: the liver steps in to absorb FFA overflow from insulin-resistant adipocytes. Chronic lipid accumulation → oxidative stress → stellate cell activation → MASLD → MASH → fibrosis → cirrhosis. No good deed goes unpunished.

A patient presents with advanced liver disease. You explain the liver is remarkably resilient. What makes it uniquely capable of bouncing back — up to a point?

- A** It has two lobes, so one can rest while the other works
- B** Hepatocytes contain a special protein called 'resiliase' discovered in 2019
- C** The liver is one of the only solid organs that can regenerate — even a remnant can restore near-full mass through hepatocyte proliferation
- D** It recruits stem cells from the bone marrow within 48 hours of any injury



Answer — Question 5 · The Resilient One

C is correct

A

It has two lobes, so one can rest while the other works

B

Hepatocytes contain a special protein called 'resiliase' discovered in 2019

✓

The liver is one of the only solid organs that can regenerate — even a remnant can restore near-full mass through hepatocyte proliferation

D

It recruits stem cells from the bone marrow within 48 hours of any injury

KEY LIVER POINT

Hepatic regeneration is one of medicine's most remarkable phenomena — the basis for living-donor transplant. A donor gives ~60%, both remnant and graft regenerate to full mass in weeks. Trigger: HGF, IL-6, TNF- α . The catch: cirrhosis replaces parenchyma with scar — at that point, resilience runs out.

Quiz Complete!

How liver-literate are you?

5 / 5

PCP Hepatologist-in-chief — The liver gives you a standing ovation. If it had arms.

4 / 5

Liver-literate — You know your portal veins from your CYP450. The liver approves.

3 / 5

Steatosis-level retention — The big ideas landed. A few details slipped — much like FFAs into the portal vein.

0-2 / 5

Hepatic encephalopathy vibes — The liver believes in second chances. Up to a point. Go re-read the slides.

You Are the Liver

Primary care is the liver of medicine. Here's the proof:

The liver does...	Primary care does...	
Docking port for all gut nutrients	First-contact for every patient problem	TRIAGE
Synthesizes 500+ proteins & factors	Generates the entire care plan	SYNTHESIZE
CYP450 detox — processes all drugs	Manages polypharmacy & drug interactions	METABOLIZE
Absorbs neighbors' fat overflow (MASLD)	Absorbs patient complexity no one else takes	PROTECT
Regenerates from 30% remnant	Bounces back through burnout, pandemics, chaos	RESILIENCE

Love the Liver.

Love Primary Care.

Screen every at-risk patient for MASLD — it is a primary care diagnosis

The FIB-4 score costs nothing and rules out advanced fibrosis in the office

You are already doing what the liver does — 500 functions before lunch

Celebrate that. Primary care is irreplaceable.

MASLD PCP Cheat Sheet

Recap for your clinic

SCREEN & DIAGNOSE

- Screen: T2DM, obesity, metabolic syndrome, elevated ALT
- MASLD = steatosis + ≥ 1 CMR factor
- Exclude harmful alcohol, steatogenic drugs
- Calculate FIB-4 from routine labs
- FIB-4 < 1.3 : Low risk \rightarrow watch & wait
- FIB-4 1.3–2.67: Order FibroScan
- FIB-4 > 2.67 : Refer + treat

TREAT & MONITOR

- Weight loss $\geq 7\%$: diet + exercise + GLP-1
- Mediterranean diet + alcohol cessation
- Check LiverTox — remove steatogenic drugs
- Vaccinate HAV/HBV
- Semaglutide: MASH + T2DM/obesity (F2-F3)
- Resmetirom: MASH without T2DM (F2-F3)
- Statins: SAFE — continue for CVD
- HCC: US \pm AFP q6m if cirrhosis/FIB-4 ≥ 3.25
- REFER: FIB-4 > 2.67 , cirrhosis, pharmacotherapy

Resources for Primary Care Providers

NIH LiverTox Database

ncbi.nlm.nih.gov/books/NBK547852/

Comprehensive drug-induced liver injury database — check any medication for hepatotoxicity

MASLD FIB-4 Calculator

mdcalc.com — search 'FIB-4'

Free online calculator; also available in most EMR systems including Epic and Cerner

AASLD Practice Guidance

aasld.org — MASLD/MASH 2024–2025

Resmetirom (Oct 2024) and Semaglutide (Nov 2025) guidance updates

EASL-EASD-EASO Guidelines

journal-of-hepatology.eu 2024

European comprehensive guidelines on MASLD management including fibrosis algorithms

ADA Standards of Care 2026

care.diabetesjournals.org

Section 4: Comprehensive medical evaluation — MASLD screening in T2DM

Open Evidence

Free Resource with an NPI

Daily clinic use — FIB-4 interpretation, treatment, referral criteria, **Prior Auth**

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Love, Liver, Laugh

Thank you for your attention, your passion for primary care, and your commitment to catching liver disease before it catches your patients.

I want to also thank Dr Lenny Mankin for helping me prepare this lecture and being an inspiration. Dr Mankin, you're the portal vein of this lecture

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My One PCP, LLC but I wish I had more financial relationships to disclose