MASLD in Type 2 Diabetes
Management –Medications & Monitoring

August 27, 2025

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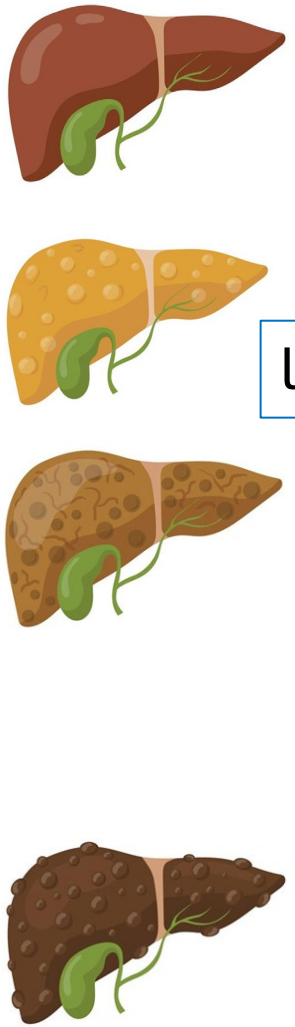
Pre-Question – which one answer is most correct

If a PWT2D has or is at risk for MASLD, potential liver benefit is most likely from:

A. Increasing the dose of metformin
B. Addition of vitamin E 800 mg
C. Adding a GLP1 RA or Dual GLP1 + GIP RA medication
D. Adding a SGLT2i medication

Types of MASLD

- Normal liver - <5% fat content
- MASLD – "fatty liver" (>5-10% fat content)
  - Mild – up to 1/3 of cells laden with fat droplets
  - Moderate – 1/3 to 2/3 cells w/ fat droplets
  - Severe – over 2/3 cells w/ fat droplets
- MASH – steatohepatitis (liver cell injury)
  - Fibrosis
    - F0, no fibrosis
    - F1, mild
    - F2, moderate (significant)
    - F3, severe (advanced)
    - F4, cirrhosis



lipotoxicity

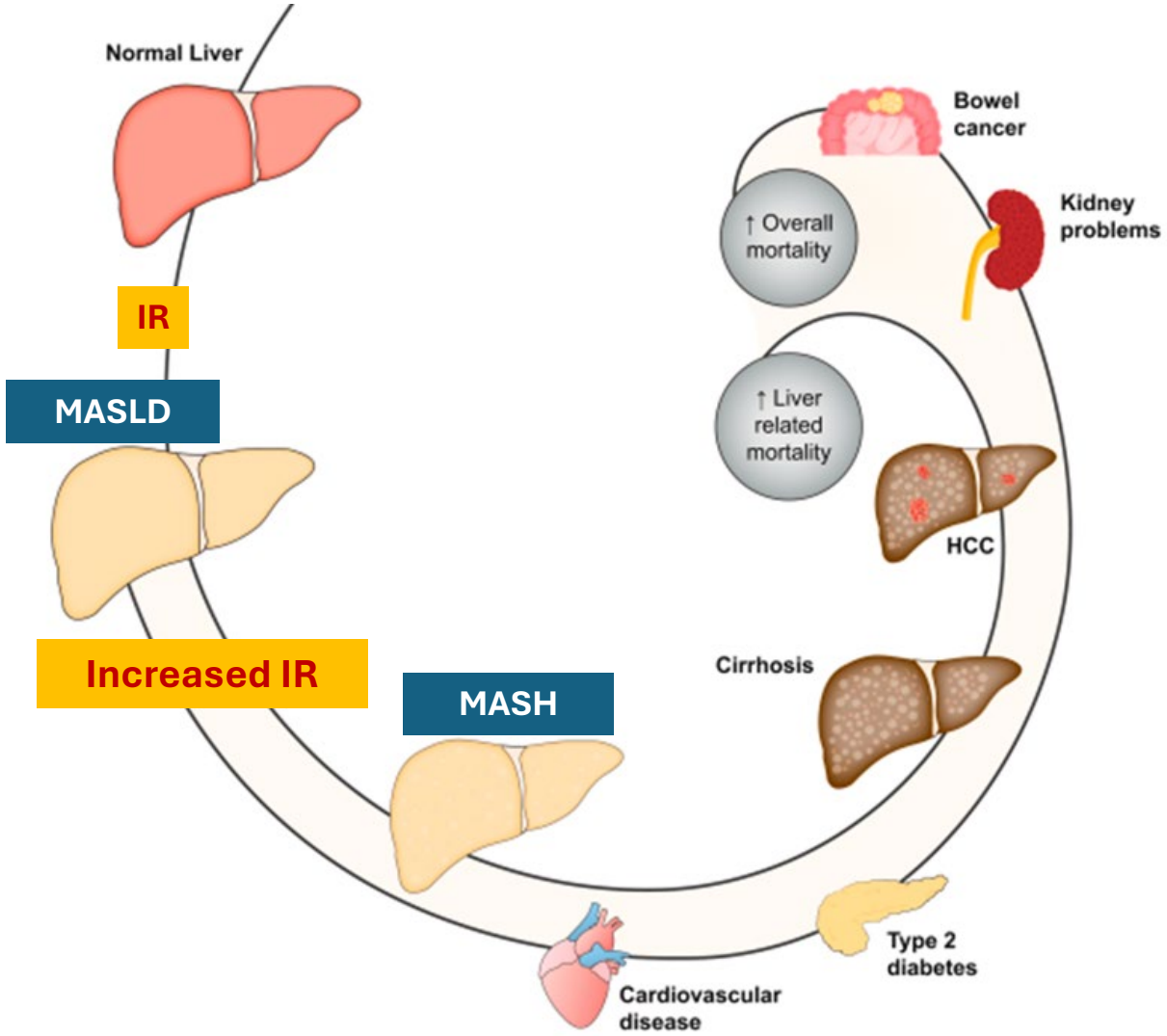
Excess calories, high sat fat, ~high HFCS intake → toxicity:

- saturated fatty acids (SFA)
- sphingolipids
- free cholesterol
- ceramides
- diacylglycerols (DAGs)
- long-chain acyl-CoAs
- acylcarnitines,
- lysophospholipids

The stage of fibrosis is the most important single predictor of significant morbidity and mortality in chronic liver disease

Key Points to Consider as Goals of Management

- Main cause of death in people with MASLD is
  - CVD
  - Non-hepatic cancer
  - Liver related (ESLD/ HCC)
- T2D, Prediabetes & Obesity are major risk factors for MASH & cirrhosis
  - Further weight gain increases risk of advanced fibrosis
  - Diabetes increases the risk of HCC (hepatocellular carcinoma) 3X above those without diabetes
- We want to prevent CVD, cancers, CKD as well as prevent progression to MASH, worsening fibrosis/cirrhosis & HCC



Lifestyle Management Recap – Key Points

- Lifestyle interventions are the foundation to preventing & reversing MASLD/MASH & its complications. These include
  - Reducing calorie intake – weight loss (sustained 5-10%)
  - Healthy diet composition & patterns
    - Avoid SSB, added sugars/HFCS, saturated fats , red & processed meats, ultraprocessed foods
    - Include fruits & vegetables, fiber, healthy fats/oils, fish & lean protein, nuts & seeds
    - More home cooked meals, less “fast food”
  - Avoid alcohol consumption & tobacco use
  - Reduce sedentary time & increase physical activity/exercise as much as possible

“Successful lifestyle modification is highly effective across all stages of liver disease, including compensated cirrhosis.”

- Control of *all cardiometabolic risk factors* important to reduce risk

Suggested Multidisciplinary Team Composition

- MASLD & MASH with F0-F1 (low risk MASH)
  - Primary Care team (physicians, APPs, PharmDs, etc.)
    - Possible Endocrinology/Diabetes Care specialists
  - RDNs
  - CDCES
  - Behavioral Health
  - Exercise specialists/ Exercise program team
  - Obesity Management team
  - Bariatric/ Metabolic Surgery per ADA SoC
- MASLD/MASH with F2-F3 ("at-risk fibrosis")
  - As above
  - Add on Hepatology or GI care team
  - Possible Endocrinology/Diabetes Care specialists
- Cirrhosis (F4)
  - Same as for F2-3 fibrosis
  - Consider referrals to
    - Transplant team for decompensated cirrhosis
    - Social support team

"RDNs and DCES should consider a FIB-4 score calculation, if all components are available, for risk stratification and a better understanding of, along with educating people on, the importance of medical nutrition therapy for a person's liver health" ADA 2025 Consensus Report on MASLD

Primary Care, RDNs, CDCES, BH at all levels

*"Even after an individual progresses to advanced fibrosis or cirrhosis and is under a liver specialist's care, the **primary care and interprofessional teams must remain involved** for management of **behavioral and nutritional care and care for cardiometabolic risk** factors and other MASLD-related comorbidities"*
ADA 2025 Consensus Report on MASLD

Management of MASLD - Agenda Recommendations & Reasons

- Lifestyle
  - Weight loss - Reduced calories
  - Diet composition (liver fat, lipotoxicity, inflammation, etc.)
  - Increased physical activity / exercise / reduced sedentary time
  - Alcohol avoidance
  - Smoking cessation
- **Medications**
  - **For Cardiometabolic Risk Reduction**
    - **Diabetes – weight loss, CVD/renal risk reduction, Steatosis or MASH benefits**
    - **For Obesity – CVD risk reduction, improvement in MASH parameters/fibrosis**
    - **Statins – CVD risk reduction, do NOT need to stop**
  - **“Liver- directed Therapy” - for advanced fibrosis F2-F3**
    - first agent FDA approved 3/24 – Resmetirom
    - second agent approved 8/25 – Semaglutide 2.4 mg injection
- Messaging & **Monitoring**

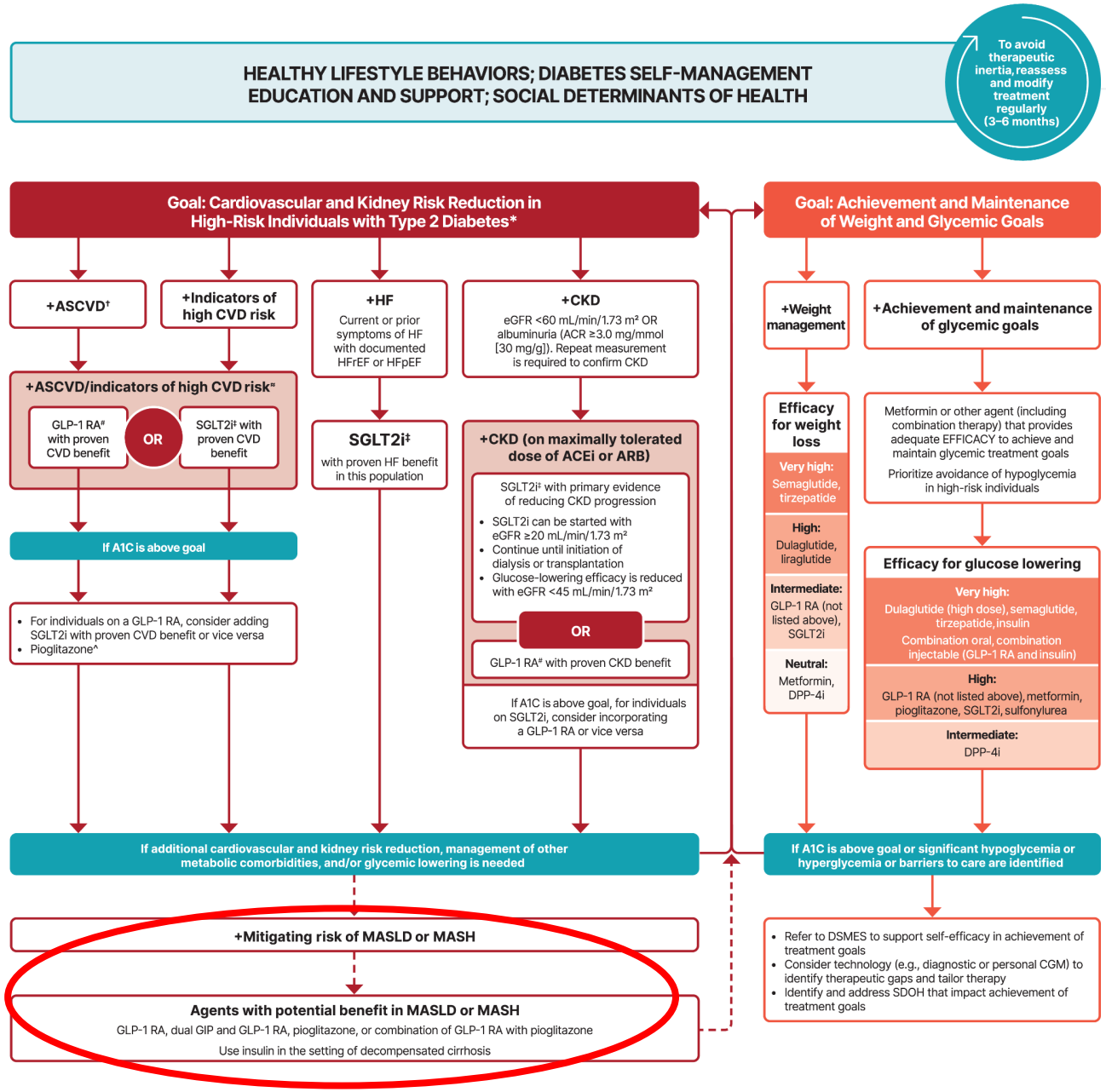
The Impact of Diabetes Management on MASLD

- Diabetes-related Hyperglycemia
  - can alter the way the liver processes and stores lipids, contributing to **fat accumulation and inflammation - lipotoxicity**
    - can lead to the formation of **AGEs (advanced glycosylation end-products**), which can **damage liver cells and contribute to fibrosis**
    - can increase **oxidative stress and inflammation** in the liver, further ***damaging liver cells*** and ***accelerating fibrosis***.
  - can increase the **risk of HCC**

"The longer someone has T2D, the greater the chance they will develop or experience progression of MASLD, highlighting the importance of diabetes management in preventing liver complications"

"Glycemic control and cirrhosis management tend to be synergistic, so improving one often helps with the other"

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



American Diabetes Association®

Glycemic Treatment

Standards of Care in Diabetes 2025

- 9.15 In adults with type 2 diabetes, metabolic dysfunction–associated steatotic liver disease (**MASLD), and overweight or obesity**, consider using a **GLP-1 RA or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA** with potential benefits in metabolic dysfunction–associated steatohepatitis (MASH) for **glycemic management** and *as an adjunctive to healthy interventions* for **weight loss**. B

- 9.16a In adults with type 2 diabetes and ***biopsy-proven MASH or those at high risk for liver fibrosis*** (based on noninvasive tests), **pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA is preferred for glycemic management** due to potential beneficial effects on MASH. B

- 9.16b **Combination therapy** with ***pioglitazone plus a GLP-1 RA*** can be considered for the **treatment of hyperglycemia** in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) due to ***potential beneficial effects on MASH***. B

Management of MASLD/MASH
ADA 2025 Standards of Care

- 4.26 In adults with **type 2 diabetes, MASLD, and overweight or obesity**, consider using a **glucagon-like peptide 1 (GLP-1) receptor agonist (RA)** or a **dual** glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA for the ***treatment of obesity*** *with potential benefits in MASH as an* ***adjunctive therapy to lifestyle interventions for weight loss.*** B

- 4.27a In adults with type 2 diabetes and ***biopsy-proven MASH or those at high risk for liver fibrosis*** (based on noninvasive tests), **pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA** is *preferred* for **glycemic management** because of **potential beneficial effects on MASH**. B

- 4.27b Combination therapy with **pioglitazone plus GLP-1 RA** can be considered for the **treatment of hyperglycemia** in adults with type 2 diabetes with ***biopsy-proven MASH or those at high risk of liver fibrosis*** (identified with noninvasive tests) because of potential beneficial effects on MASH.B

Reasoning for Recommendations
ADA 2025 Standards of Care

- **Optimizing** the pharmacological **management of hyperglycemia and obesity** in people with type 2 diabetes **with medications that also help improve MASH** could ***serve the dual purpose of addressing these comorbidities while treating the liver disease***
  - The recommendation to treat hyperglycemia with GLP-1 RAs and/or pioglitazone in people with type 2 diabetes and MASLD is based on consistent **histological benefit for steatohepatitis and to slow fibrosis progression** in several ***phase 2 RCTs*** with GLP-1 RAs and with pioglitazone compared with no benefit with metformin or other glucose-lowering medications in MASH
    - **Combined pioglitazone and GLP-1RA** treatment is associated with **a greater decrease in hepatic steatosis** as compared with pioglitazone alone in people with T2D
- They may also **decrease CVD**, which is the number one cause of death in people with type 2 diabetes and MASLD
- [Increasing evidence for GLP1 RA agents reducing ORC *(obesity related cancers*)]

Clinical Trials – Current Focus is "at-risk-MASH" (F2 & F3) considered *"clinically significant fibrosis"*

- The two primary **liver-associated end points** currently accepted by regulatory agencies for conditional approval of a new drug for the treatment of MASH
  - **MASH resolution** without worsening of liver fibrosis
  - **Reduction (improvement) in fibrosis** by at least one stage without worsening of MASH

A beneficial long-term effect on the risk of **major adverse liver outcomes** is required for a drug to receive final approval.

GLP1 RA Effects on MASLD

- GLP-1 RAs are effective at inducing weight loss and ameliorating elevated plasma aminotransferases and steatosis
  - "Real world" observations – GLP1 RA meds appear "hepatoprotective"

- Phase 2 RCTs of GLP-1 RAs in individuals with MASH proven by biopsy:
  - A small RCT reported that **liraglutide** improved some features of MASH and may delay fibrosis progression .
  - Subcutaneous **semaglutide** treatment in 320 people with MASH (62% having type 2 diabetes) led to
    - ***resolution of steatohepatitis without worsening of fibrosis*** in **59%** of individuals at the higher dose (equivalent to 2.4 mg/week semaglutide) compared with 17% in the placebo group ($P < 0.001$).
    - no significant effect on the stage of liver fibrosis but, over 72 weeks***, slowed the progression of liver fibrosis*** (4.9% with the GLP-1 RA at the highest dose compared with 18.8% on placebo).

Patients in all groups (including PBO) received counseling on nutrition and exercise

Tirzepatide Effects on MASLD

Phase 2 paired-biopsy study of 190 adults with overweight or obesity with MASH (50–60% of whom had type 2 diabetes)

Resolution of steatohepatitis without worsening of fibrosis

- Tirzepatide doses of
  - 5 mg/day – 44% of participants
  - 10 mg/day- 56%
  - 15 mg/day - 62%
  - placebo – 10% of participants

Improvement of at least one fibrosis stage without worsening of MASH

- Tirzepatide doses of
  - 5 mg/day – 55% of participants
  - 10 mg/day- 51%
  - 15 mg/day - 61%
  - placebo – 30% of participants

Phase *3* Trial of Semaglutide in Metabolic Dysfunction – Associated Steatohepatitis NEJM April 30, 2025

- Semaglutide, a glucagon-like peptide-1 receptor agonist, is a candidate for the treatment of metabolic dysfunction–associated steatohepatitis (MASH).
- In this *ongoing* phase 3, multicenter, randomized, double-blind, placebo-controlled trial, we assigned 1197 patients with ***biopsy-defined MASH and fibrosis stage 2 or 3*** in a 2:1 ratio to receive once-weekly subcutaneous *semaglutide at a dose of 2.4 mg* or placebo for *240 weeks*.
  - Age – average 55
  - BMI – average 35
  - Type 2 diabetes - ~ 56%
  - Fibrosis stage — stage 2 ~ 31% and stage 3 ~ 69%
  - Median score on Fibrosis-4 Index: 1.58 (1.12–2.24)
  - Enhanced liver fibrosis score - 9.95±0.94
  - Liver stiffness — 12.8±6.6 kPa
- The results of a planned *interim analysis* conducted at *week 72* involving the first 800 patients are reported here (part 1)

Phase 3 Trial of Semaglutide in Metabolic Dysfunction – Associated Steatohepatitis NEJM

Resolution of steatohepatitis without worsening of fibrosis

- Sema – 62.9%
- PBO – 34.3%

Reduction in liver fibrosis without worsening of steatohepatitis

- Sema – 36.8%
- PBO – 22.4%

Combined resolution of steatohepatitis and reduction in liver fibrosis

- Sema – 32.7%
- PBO – 16.1%

CONCLUSIONS: In patients with MASH and moderate or advanced liver fibrosis, once-weekly semaglutide at a dose of 2.4 mg improved liver histologic results – The ESSENCE trial

Adding Pioglitazone for Glycemic & MASLD benefits

ADA 2025 Standards of Care

- Pioglitazone improves IR→ improves glucose and lipid metabolism and **reverses steatohepatitis** in people with prediabetes or type 2 diabetes and even in individuals without diabetes.
- **Fibrosis** also improved in some trials.
  - A meta-analysis concluded that pioglitazone treatment results in resolution of MASH and may improve fibrosis.
    - These studies are based on *phase 2 clinical trials* and await further phase 3 evidence.
  - Pioglitazone is attractive because it offer potential benefit compared with lack of histological benefit (or clinical trial data) from other oral glucose-lowering therapies in MASLD.
- In the context of treating hyperglycemia in people with type 2 diabetes with MASLD, where the *low cost of pioglitazone* and any *liver improvement would be an added benefit* to glycemic management, these plans would be potentially *cost-effective* for the treatment of MASLD

Pioglitazone even at low dosage improves NAFLD in type 2 diabetes: clinical and pathophysiological insights from a subgroup of the TOSCA.IT randomised trial. Diabetes Res Clin Pract. 2021 Aug:178

Abstract

- Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) and type 2 diabetes (T2D) share pathophysiological mechanisms and possible therapeutic strategies. We evaluated the effects of 1-year treatment with pioglitazone or sulphonylureas on indirect indices of NAFLD in people with T2D and the role of insulin-resistance and glucotoxicity in determining these effects.
- Methods: Patients with T2D (n = 195) aged 50-75 years, poorly controlled with metformin 2 g/day, were randomly allocated to add-on pioglitazone (n = 98) or sulphonylureas (n = 97) within the TOSCA.IT trial. Plasma insulin, glucose, and liver enzymes were measured at baseline and after 1-year. Indirect indices of NAFLD (Liver Fat Equation [LFE], Hepatic Steatosis Index [HSI], and Index of NASH [ION]), and insulin resistance (HOMA-IR, Visceral Adiposity Index [VAI] and adipose tissue Insulin Resistance [ADIPO-IR]) were calculated.
- Results:
  - Indices of NAFLD improved after pioglitazone, but not after sulphonylureas;
  - Indices of insulin resistance decreased after pioglitazone, but not after sulphonylureas
  - **Changes in NAFLD indices were similar with different doses of pioglitazone (15, 30, or 45 mg/day),** and were independent of blood glucose control.
- Conclusions: One-year treatment with pioglitazone ***even at low dosage*** significantly improved
  - ***liver steatosis and inflammation***
  - systemic and adipose tissue ***insulin resistance*** in patients with T2D

Cautions with Pioglitazone

- Pioglitazone can cause dose-dependent weight gain
  - 15 mg/day, mean weight gain of 1–2%
  - 45 mg/day, mean weight gain of 3–5%
  - can be blunted or reversed if combined with SGLT2 inhibitors or GLP-1 RAs
  - [start with 15 mg daily, increase to 30 mg if needed for glycemic control]
- Pioglitazone
  - may increase fracture risk (especially postmenopausal women)
  - may promote heart failure in individuals with *preexisting* heart failure (HF)
    - Avoid if history of HF
  - may increase the risk of bladder cancer, although this remains controversial
    - Avoid if history of bladder cancer

Combination of glucagon-like peptide 1 receptor agonist and thiazolidinedione for mortality and cardiovascular outcomes in patients with type 2 diabetes JAMA Network Open. Published online March 31, 2025

- The study authors concluded, “This study found that GLP-1RA plus thiazolidinedione combination therapy was associated with **a significant reduction in all-cause mortality and CV mortality.**”
- Patients receiving GLP-1RA and thiazolidinedione dual therapy, compared to those who did not receive either, had significantly lower risk of
  - **all-cause mortality** (adjusted hazard ratio [AHR], **0.20**; 95% CI, 0.19-0.21; P < .001),
  - **cardiovascular mortality** (AHR, **0.20**; 95% CI, 0.18-0.23; P < .001)
- Suggests a potential *synergistic effect* on mortality
- This study showed that *GLP-1RAs could mitigate the risk of HF* associated with thiazolidinedione use.

ADA 2025 Standards of Care

- 4.30a In adults with type 2 diabetes and MASLD, use of glucose-lowering therapies other than pioglitazone or GLP-1 RAs may be *continued as clinically indicated*, but these therapies lack evidence of benefit in MASH. B
- 4.30b Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with *decompensated cirrhosis*. C

- SGLT2 inhibitors and insulin *reduce hepatic steatosis*, but their effects on steatohepatitis remain unknown (study recently released showing improvement in MASH & fibrosis with dapagliflozin)
- Other agents have either failed to improve steatohepatitis in paired-biopsy studies (metformin) or have no RCTs with liver histological end points (i.e., sulfonylureas, glitinides, dipeptidyl peptidase 4 inhibitors, or acarbose)
- GLP-1 RAs are safe in individuals with compensated cirrhosis –
- *Insulin* is the preferred glucose-lowering agent for the treatment of hyperglycemia in adults with *type 2 diabetes with decompensated cirrhosis* given the lack of robust evidence about the safety and efficacy of oral agents and GLP-1 RAs and dual GIP and GLP-1 Ras (sarcopenia is an issue)

Vitamin E not recommended for T2D

- Vitamin E may be beneficial for the treatment of MASH in people *without* diabetes.
- However, in **people with type 2 diabetes**, vitamin E monotherapy was found to be ***ineffective*** in a small RCT, and it did not seem to enhance pioglitazone's efficacy when used in combination, as reported in an earlier trial in this population.

- Risks of high dose vitamin E
  - increased risk of bleeding and stroke
  - potential link to prostate cancer and increased mortality

Liver Directed Therapy
Recommendations regarding Resmetirom
ADA 2025 SoC

- 4.28 For consideration of treatment with a *thyroid hormone receptor-β agonist* [resmetirom (brand name – Rezdiffra)] **in adults with type 2 diabetes or prediabetes with MASLD** with ***moderate (F2) or advanced (F3) liver fibrosis*** on liver histology, or by a validated imaging-based or blood-based test, ***refer to a gastroenterologist or hepatologist*** with expertise in MASLD management. A
- 4.29 Treatment initiation and monitoring should be individualized and within the context of an interprofessional team that includes a ***gastroenterologist or hepatologist***, consideration of individual preferences, and a careful shared-decision cost-benefit discussion. B

- ~$47,000 / year

Resmetirom – Phase 3 RCT

MASH resolved without worsening of fibrosis

- 80 mg daily - 25.9%
- 100 mg daily – 29.9%
- Placebo – 9.7%

Fibrosis improved by at least 1 stage with no worsening of MASH

- 80 mg daily - 24.2%
- 100 mg daily - 25.9%
- Placebo - 14.2%

- ***Diarrhea and nausea*** were more frequent with resmetirom than with placebo, but resmetirom was well tolerated overall.
- The optimal *duration of treatment is uncertain*
- Effect of combination with other meds such as GLP1 RA meds uncertain
- As of October 2024, resmetirom was *available only through specialty pharmacie*s. This and its ***high cost*** will likely limit access. (Cost for resmetirom (Rezdiffra) set at $47,400 annually)
- Given its mechanism of action, careful surveillance for early endocrine disease related to thyroid, gonadal, or bone disease may be needed.

Accelerated FDA Approval of Semaglutide 2.4 mg injection to treat MASH in adults with moderate-to-advanced fibrosis August 15, 2028

https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-serious-liver-disease-known-mash

- This approval is for adults with moderate to advanced liver fibrosis (F2-F3) due to MASH, but without cirrhosis.
- The trial will continue for a total of 240 weeks to determine whether inflammation and scarring improvements seen after 72 weeks translate into decreases in death, liver transplant, and other liver-related events.

- Many unknowns –
  - In clinical practice can NITs be used to determine F2-F3 and r/o F4 (cirrhosis) vs liver biopsy?
  - Will hepatology assistance be considered helpful vs required to use Semaglutide 2.4 mg injections as “Liver-directed therapy”? (currently many people with risk already treated for weight loss +/- CVD risk reduction) – may be determined by payers
  - Effect of other forms/doses of semaglutide?
    - We already use semaglutide in patients with MASLD, MASH and even c-cirrhosis for diabetes management & CVD risk reduction – do these “Cardiometabolic risk reduction doses” reduce MASH?

Don’t Stop the Statin !!

ADA 2025 Standards of Care

- 4.31a Adults with type 2 diabetes and MASLD are *at increased cardiovascular risk*; therefore*, comprehensive management of cardiovascular risk factors* is recommended. B
- 4.31b **Statin therapy is safe** in adults with type 2 diabetes and compensated cirrhosis from MASLD and ***should be initiated or continued for cardiovascular risk reduction*** as clinically indicated. B
  - In people with decompensated cirrhosis, statin therapy should be used with caution, and close monitoring is needed, given limited safety and efficacy data. B

- Some studies even suggest that *statin use* in people with chronic liver disease may *reduce episodes of hepatic decompensation and/or overall mortality*

Metabolic Surgery

ADA 2025 Standards of Care

- 4.32a Consider metabolic surgery in appropriate candidates as an option
  - to treat MASH in adults with type 2 diabetes B and
  - to improve cardiovascular outcomes. B
- 4.32b Metabolic surgery should be used with caution in adults with type 2 diabetes with compensated cirrhosis from MASLD B
  - and is not recommended in decompensated cirrhosis. B

- Metabolic surgery leading to sustained weight loss and improvement of type 2 diabetes can improve MASH and cardiometabolic health, altering the natural history of the disease. Meta-analyses report that
  - 70–80% of people have improvement in hepatic steatosis
  - 50–75% of people have improvement in inflammation & hepatocyte ballooning (necrosis)
  - 30–40% of people have improvement in fibrosis
  - It may also reduce the risk of HCC

Survival and Cost-Effectiveness of Bariatric Surgery Among Patients With Obesity and Cirrhosis.

JAMA Surg. Published online April 02, 2025. Bansal S, Bader A, Mahmud N, Kaplan DE.

- This VA study found that bariatric surgery improves survival and is cost-effective for patients with obesity and *compensated cirrhosis*.
  - The study compared bariatric surgery to a lifestyle modification program and found that bariatric surgery was associated with
    - a 72% lower risk of developing serious liver complications and
    - an 80% lower risk of progressing to decompensated cirrhosis

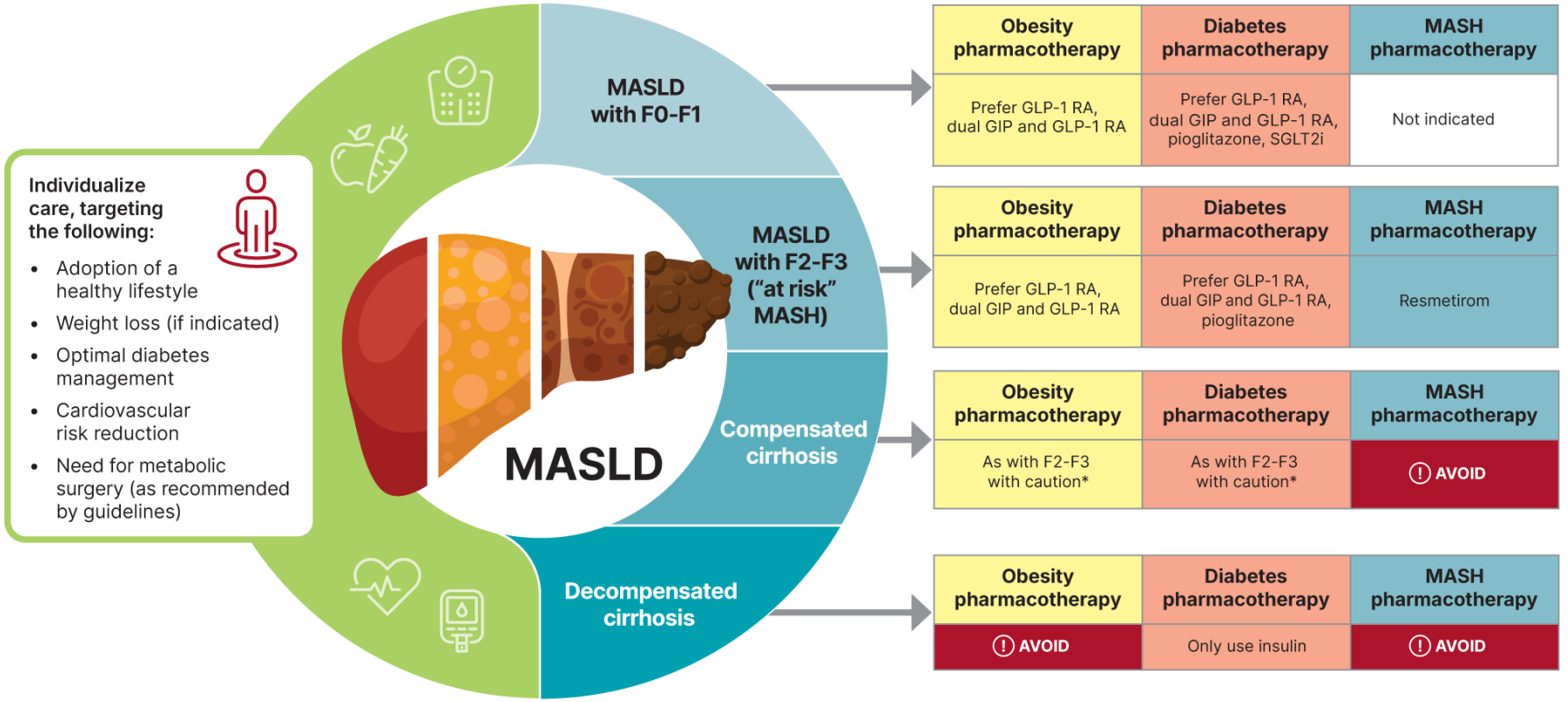
- https://jamanetwork.com/journals/jamasurgery/article-abstract/2832074

American Diabetes Association.

From: **4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2025**

Diabetes Care. 2024;48(Supplement_1):S59-S85. doi:10.2337/dc25-S004

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) Treatment Algorithm



Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, SGLT2i	Not indicated

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone	Resmetirom

Semaglutide 2.4 mg

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
As with F2-F3 with caution*	As with F2-F3 with caution*	ⓘ AVOID

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
ⓘ AVOID	Only use insulin	ⓘ AVOID

*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm. F0-F1, no to minimal fibrosis; F2-F3, moderate fibrosis; F4, cirrhosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Summary – Key Points for Medication Management

- In patients at risk for or determined to have MASLD, GLP1 or Dual RA medications are preferred for glycemic management & as an adjunctive to lifestyle for weight loss since they also benefit (reduce) liver risk as well as CVD risk
  - Safe to use in patients w/ compensated cirrhosis & appear to improve outcomes
  - No data for use w/ decompensated cirrhosis (want to avoid weight loss/sarcopenia)
- For patients at risk for or with MASH, use of [low dose]pioglitazone for glycemic management can reduce liver risk & CVD risk
  - Combination with GLP1 RA agents is safe & appears to improve mortality benefits & mitigates HF risk
- Do not stop statins – statins benefit CVD risk & appear to reduce liver risk
- Use of Resmetirom requires referral to hepatology [GLP1 based agents appear superior – recent accelerated approval of semaglutide 2.4 mg injection (lower cost & reduces multiple risks)]
- Metabolic surgery w/sustained weight loss can improve MASH & c- cirrhosis

Post-Question – which one answer is most correct

If a PWT2D has or is at risk for MASLD, potential liver benefit is most likely from:

A. Increasing the dose of metformin
B. Addition of vitamin E
C. Adding a GLP1 RA or Dual GLP1 + GIP RA medication
D. Adding a SGLT2i medication

Post-Question – which one answer is most correct

If a PWT2D has or is at risk for MASLD, potential liver benefit is most likely from:

A. Increasing the dose of metformin
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D. Adding a SGLT2i medication

Monitoring

- Individual patient self-monitoring
  - Setting SMART (specific, measurable, achievable, relevant, timely) goals for weight loss, dietary composition and/or physical activity [& medication taking]
    - An example of a SMART exercise goal could be to swim 10 lengths, twice a week at the local pool for the next month or increase walking time by 10 minutes over next 4 weeks
    - Another example of a SMART dietary goal could be to stop buying sugar-sweetened beverages for the next four weeks
  - Tools
    - Scale – weight
    - Waist circumference
    - CGM – glycemia targets & effects of lifestyle
    - Apps – calorie and/or activity trackers
      - Clinicians can review data from devices – e.g., step counts, etc.

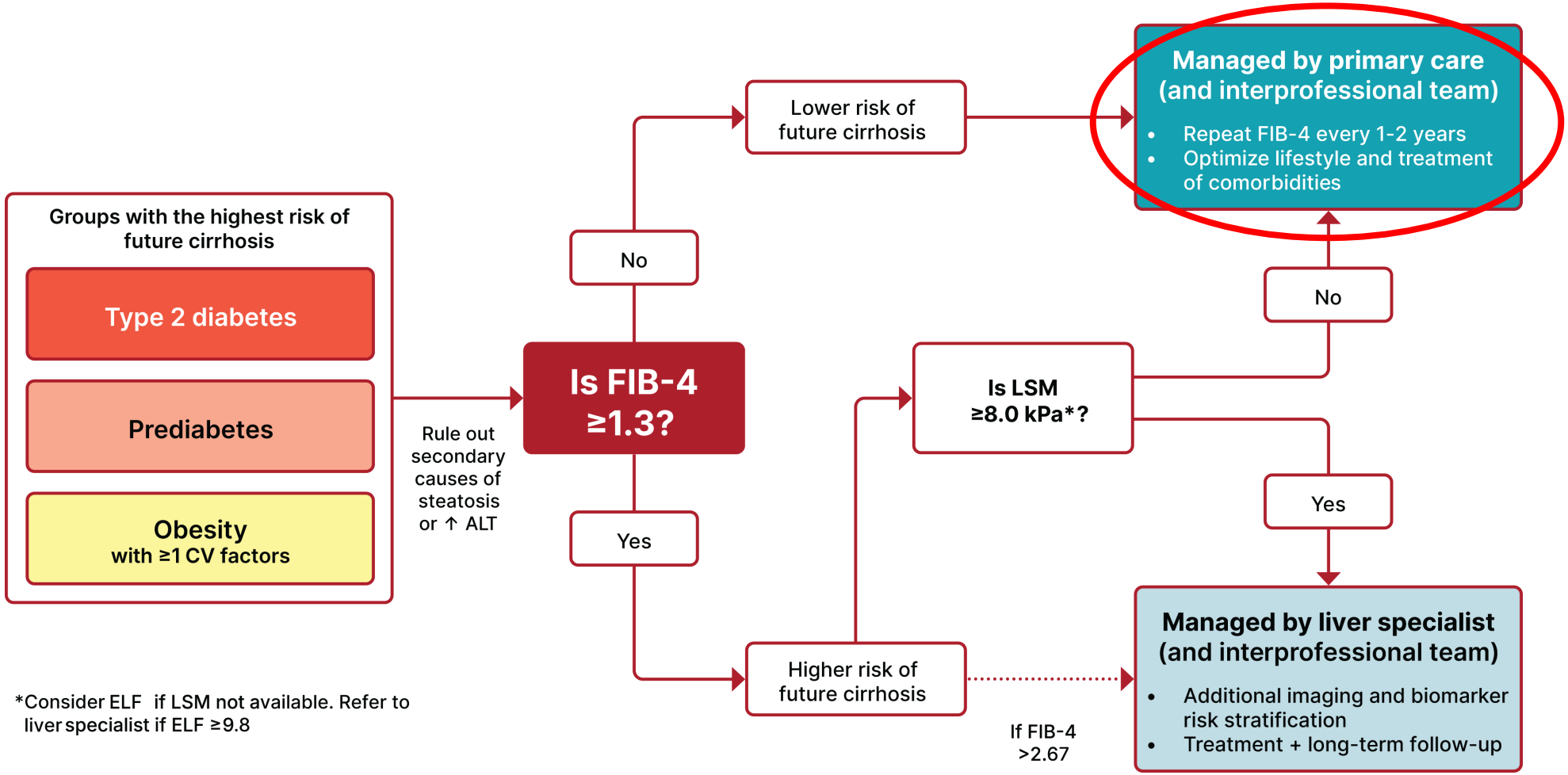
Monitoring

- **Cardiometabolic risk factors** – at target or in process of improving
  - Glycemia
  - Lipids
  - BP
  - Activity level
  - Sedentary time
  - Weight/BMI, Waist Circumference
  - Alcohol use
  - Tobacco use

From: **4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2025**

Diabetes Care. 2024;48(Supplement_1):S59-S85. doi:10.2337/dc25-S004

Diagnostic Algorithm for the Prevention of Cirrhosis in People With Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)



*Consider ELF if LSM not available. Refer to liver specialist if ELF ≥9.8

Limitations to Reliability of FIB4 Index

- **Age ≤35** – FIB4 underestimates risk of fibrosis – ***AASLD recommends LSM or ELF score***
- Age ≥ 65 – FIB4 overestimates risk

- Type 2 diabetes – FIB4 can underestimate risk of fibrosis
  - *"With respect to misclassification, compared with those without diabetes, a higher proportion of* ***individuals with diabetes and advanced fibrosis had low FIB-4 <1.3*** *(4% vs. 13%, respectively)."*

- High alcohol intake (AST>ALT, lower platelets) – overestimate risk of fibrosis

- Another condition such as ITP that reduces platelet count
- Another condition such as myositis that elevates ALT & AST
- Co-existing liver condition
  - NIT cut-off values specific to liver condition – MASLD vs HCV vs PBC, etc.
  - Co-existing condition might predominate, exacerbate MASLD or progress while MASLD improves (e.g., autoimmune hepatitis with MASLD) – liver biopsy may be needed

Conditions that can affect Fibroscan/LSM results
(tendency to overestimate risk)

- Obesity - body mass index (BMI) > 30 (Asian >25)
  - class 3 obesity was strongly linked to the overestimation of fibrosis by at least 2 stages by Fibroscan *Journal of Clinical Gastroenterology* – MRE more accurate, especially if BMI $\geq$ 40
- Ascites
  - Fluid build up in the belly.
- Biliary obstruction
- Scar tissue around/outside of the liver
  - Scar tissue from previous surgeries or radiation therapy near the liver can interfere with the ultrasound waves.
- Liver inflammation or congestion:
  - Liver inflammation, either caused by recent liver illness or drinking alcohol, or liver congestion (when the liver is too full of blood or other fluids) can lead to inaccurate readings.
- Liver tumors:
  - Both benign and cancerous tumors in the liver can also affect the accuracy of the test.

How should patients with T2D & MASLD be monitored?

- ***The ADA Soc & Consensus paper on MASLD*** recommends that individuals (with T2D or prediabetes) with an initial FIB-4 score <1.3 be reassessed with repeat FIB-4 measurements in **1–2** years.
  - Hopefully, most will have stable or lower (improved) FIB4 index
  - Those whose FIB-4 index **increases from <1.3 to >1.3** should be referred for transient elastography (VCTE/Fibroscan for LSM) and/or ELF score
  - Given the *potential for underestimation of fibrosis severity in individuals with T2D*,
    - For PWT2D & multiple risk factors suggest perfprming secondary tests if initial FIB4 ≥1.0
    - Those who progress **from <1.0 to values between 1.0 and 1.3** may also be considered for secondary assessment with VCTE or an ELF test - especially if coexisting multiple risk factors

  - Individuals with **LSM >8.0 kPa or ELF > 9.8** should be referred to gastroenterology or hepatology specialists for additional diagnostic testing.
    - VCTE can overestimate risk with class 3 obesity and certain other conditions – ELF score & MRE can be helpful

How should patients with *MASH* be monitored?

- Patients with *indeterminate to high risk for fibrosis* on FIB-4 & VCTE or ELF testing "*should be referred to a specialist*"
  - *Due to limited access to liver specialists – PC may need to help manage & monitor*
  - FIB-4 index - not very sensitive to fibrosis change
    - short-term improvement (6–12 months) in FIB-4 likely reflects changes in inflammation rather than fibrosis – but change correlates with change in liver & CVD risk
  - LSM (VCTE) – has been shown to reflect responses to therapeutic intervention
    - Improvement (reduction in kPa) by >20 - 30% represents therapeutic response
    - Worsening (increase in kPa) by >20 - 30% reflects disease progression.
  - ELF score – change of 0.5 significant
  - For all NITs still determining what reflects change in inflammation vs fibrosis

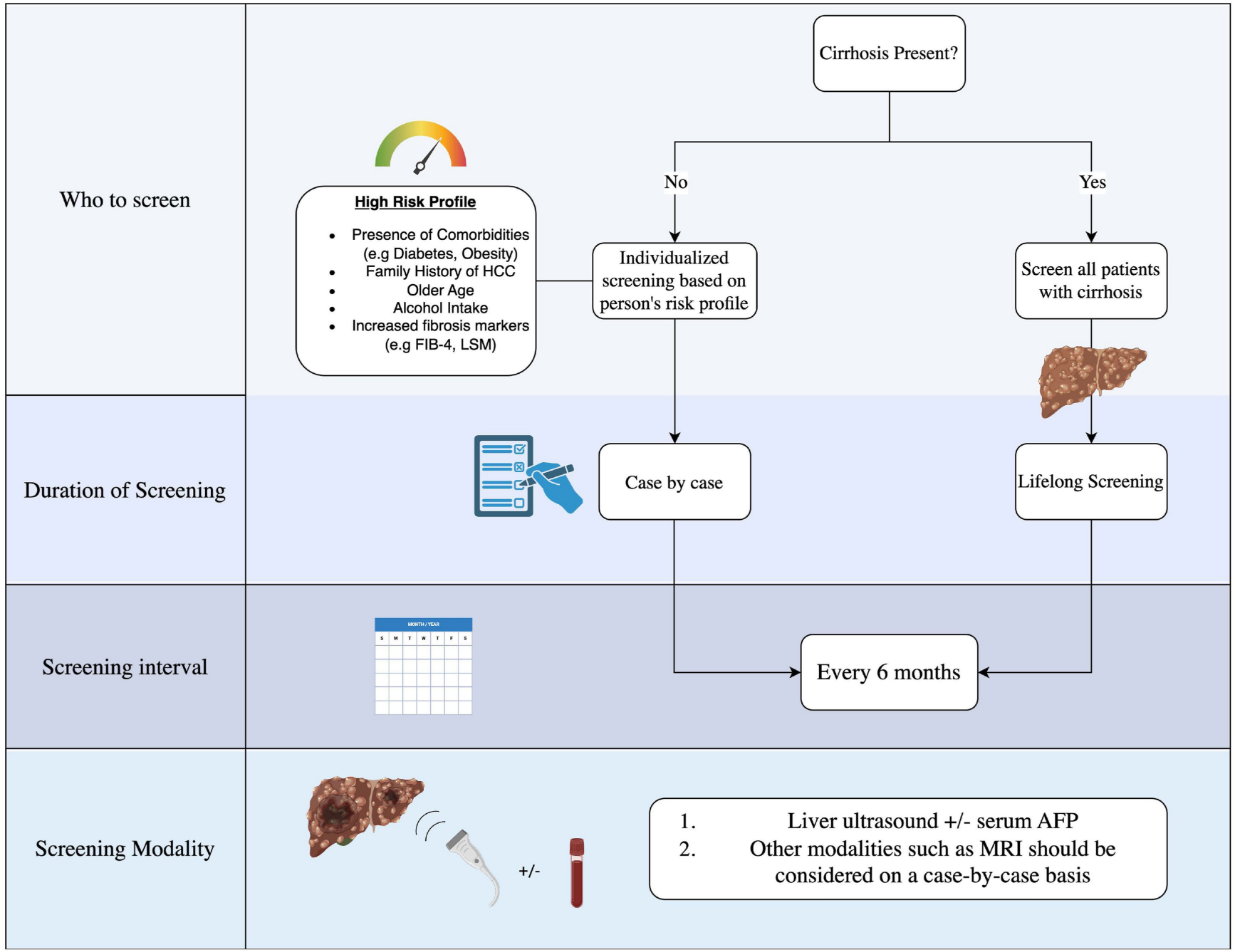
- Those with advanced fibrosis should be seen at least every 6 months
  - to monitor for signs of liver decompensation (jaundice, ascites, hepatic encephalopathy)
    - laboratory evaluation (CBC, INR, hepatic & renal panel)
  - HCC screening (AFP & US)

Monitoring - Screening for HCC

- Recommendations for HCC screening in patients with **MASH-associated cirrhosis (F4)** are the same as those for cirrhosis of other etiologies
  - semi-annual(every 6 months) ultrasound scans and alpha-fetoprotein (AFP) testing

- Although patients with **non-cirrhotic MASH** can be at risk for HCC, their risk is below the screening threshold, so widespread screening cannot be recommended for this population.
  - Certain patients with non-cirrhotic fibrosis should be assessed on a case-by-case basis due to an **increased risk of HCC**, including patients with:
    - MASH and bridging fibrosis (on biopsy results)
    - family history of HCC
    - multiple cardiometabolic risk factors (especially T2D)
    - continuous alcohol use

Screening for MASLD-Associated HCC



Anticipate Updates/Revisions (Evolution) of Guidelines

- Screening & Monitoring – better Non-Invasive Tests & better-defined cutoff values

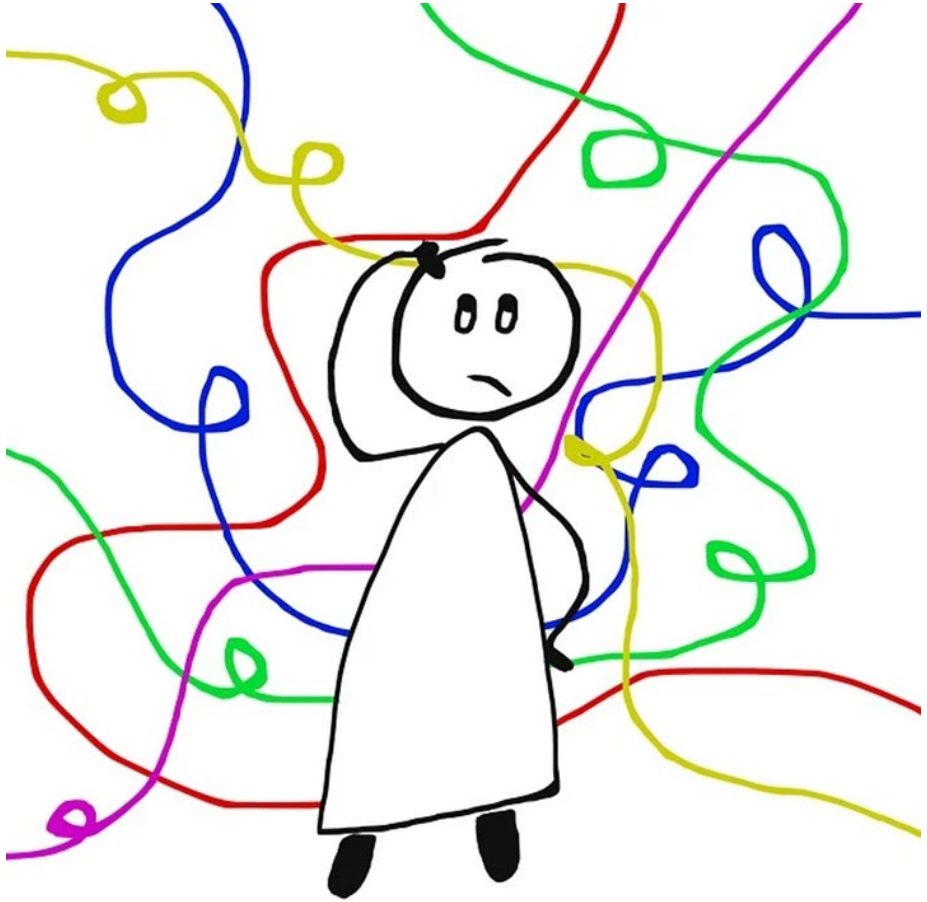
- Management
  - Although now 2 pharmacologic agent has been approved by the U.S. Food and Drug Administration (FDA) for treatment of MASLD/ “at-risk-MASH”, several other pharmacologic therapies are in the pipeline – including trials in patients with F4 (compensated cirrhosis) for regression
    - Additional thyroid hormone receptor b-selective agonist medications
    - FGF21 analogs
    - Pan-PPAR agents
    - Incretin therapies
      - New dual & triple agents – some of these show potential to be very effective
    - SGLT2 inhibitors

Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo-controlled trial. BMJ 2025; 389 (Published **04 June 2025**)

Study from China

- The dapagliflozin trial included younger patients who were predominantly male and of Asian descent, with a lower body mass index (BMI), a lower prevalence of type 2 diabetes, and *less fibrosis* than participants in the resmetirom and semaglutide trials.
- **MASH resolution** without worsening of fibrosis occurred in **23% of those on dapagliflozin versus 8% of those on placebo** (RR 2.91, 95% CI 1.22-6.97, P=0.01)
- **Fibrosis improvement** by at least one stage without worsening of MASH was reported in **45% versus 20%,** respectively (RR 2.25, 95% CI 1.35-3.75, P=0.001).

Questions, Comments, Clarification



What are your barriers &/or concerns regarding addressing MASLD in your patients with type 2 diabetes or prediabetes?

Extra Slides

Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes.

Hepatology. 2014 Dec;60(6):2008-16.

- Abstract: The risks and benefits of metformin use in patients with cirrhosis with diabetes are debated. Although data on a protective effect of metformin against liver cancer development have been reported, metformin is frequently discontinued once cirrhosis is diagnosed because of concerns about an increased risk of adverse effects of metformin in patients with liver impairment.
- This study investigated whether continuation of metformin after cirrhosis diagnosis improves survival of patients with diabetes. Diabetic patients diagnosed with cirrhosis between 2000 and 2010 who were on metformin at the time of cirrhosis diagnosis were identified (n = 250). Data were retrospectively abstracted from the medical record. Survival of patients who continued versus discontinued metformin after cirrhosis diagnosis was compared using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were calculated using Cox's proportional hazards analysis. Overall, 172 patients continued metformin whereas 78 discontinued metformin.
- Results: Patients who ***continued metformin had a significantly longer median survival*** than those who discontinued metformin (11.8 vs. 5.6 years overall, $P < 0.0001$; 11.8 vs. 6.0 years for Child A patients, $P = 0.006$; and 7.7 vs. 3.5 years for Child B/C patients, $P = 0.04$, respectively).
  - **After adjusting for other variables, continuation of metformin remained an independent predictor of better survival, with an HR of 0.43 (95% CI: 0.24-0.78; P = 0.005).**
- No patients developed metformin-associated lactic acidosis during follow-up.
- Conclusion: **Continuation of metformin after cirrhosis diagnosis reduced the risk of death by 57%.** Metformin should therefore be continued in diabetic patients with cirrhosis if there is no specific contraindication.

- Kaplan DE, Serper M, John BV, et al. Veterans Outcomes and Cost Associated with Liver disease Study Group. Effects of metformin exposure on survival in a large national cohort of patients with diabetes and cirrhosis. Clin Gastroenterol Hepatol. 2021;19:2148–2160.

Dual metformin and glucagon-like peptide-1 receptor agonist therapy reduces mortality and hepatic complications in cirrhotic patients with diabetes mellitus

Annals of Gastroenterology, 2023•pmc.ncbi.nlm.nih.gov

- Background: Type 2 diabetes (T2DM) can accelerate the progression of cirrhosis.
- Methods: We compared the effectiveness of dual metformin and glucagon-like peptide-1 receptor agonists (GLP1-RA) vs. metformin treatment alone in reducing mortality and hepatic complications in cirrhotic patients with T2DM.
  - We evaluated propensity score-matched cohorts of T2DM and cirrhosis patients treated with metformin or dual metformin and GLP1-RA therapy. Data were obtained from the TriNetX Research Network. Our outcomes were all-cause mortality, composite risk of hepatic decompensation, and hepatocellular carcinoma (HCC).
- Results Compared to patients on metformin alone, dual metformin and GLP1-RA therapy users had a lower risk for both
  - death (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.42-0.89; P=0.011) and
  - hepatic decompensation (HR 0.65, 95%CI 0.46-0.93; P=0.02) over 5 years.
  - Patients on dual therapy had a lower risk for HCC (HR 0.44, 95%CI 0.26-0.74; P=0.001) compared to mono-metformin therapy patients.
- Conclusion: In our multicenter retrospective study, dual therapy was associated with better mortality and morbidity in cirrhosis patients with T2DM compared to those on metformin alone.

Pioglitazone & MASH Studies Summary

- Thiazolidinediones (such as pioglitazone) are peroxisome proliferator-activated receptor agonists that are approved as third-line treatment for T2D and also show promise in the treatment of MASLD.
- A meta-analysis of 8 RCTs of thiazolidinedione treatment in patients with MASH included 5 studies with pioglitazone. This meta-analysis confirmed that, compared with placebo, treatment with pioglitazone resulted in significantly higher likelihood of MASH resolution (odds ratio [OR], 3.65; P < 0.001) and liver fibrosis improvement (OR, 1.77; P ¼ 0.009) (50).
- A more recent meta-analysis of 4 double- blind RCTs on the effect of pioglitazone in patients with prediabetes or T2D and MASLD reported improvement in steatosis and resolution of steatohepatitis (OR, 1.78; P ¼ 0.03) but not fibrosis. Potential adverse effects of pioglitazone are increased risk for dose-dependent weight gain (1% to 2% at 15 mg/d and 3% to 5% at 45 mg/d).
- The improvements in steatosis and steatohepatitis were not seen with rosiglitazone.

Resmetirom

- Resmetirom is a thyroid hormone receptor-β agonist approved by the FDA for the treatment of adults with MASLD with moderate (F2) or advanced (F3) liver fibrosis on liver histology or a validated imaging- or blood-based test.
  - In a phase 3 RCT, resmetirom for 52 weeks in 966 adults at the highest dose of 100 mg (or placebo) met the primary end point of MASH resolution without worsening of fibrosis in 29.9% of participants compared with 9.7% on placebo ($P < 0.001$) (283). Fibrosis improved in up to 25.9% and 14.2%, respectively ($P < 0.001$).
  - Nausea, vomiting, and diarrhea occurred more often with resmetirom. The gastrointestinal side effects are dose dependent and improve with continued treatment.
  - Resmetirom decreased free thyroxine (T4) levels by ~20% and increased sex hormone-binding protein levels two- to threefold. Although a recent review of the data concluded that there is little concern about these changes, long-term postmarketing data must be collected .
  - Guidance by the American Association for the Study of Liver Diseases (AASLD) about optimal individual identification for treatment, safety, and long-term monitoring has recently been published . This is especially relevant because hypothyroidism and hypogonadism are more prevalent in people with MASLD than in the general population, and clinicians should monitor all individuals with MASLD for symptoms of endocrine deficiency and manage according to clinical practice guidelines.
- Per its label, candidates for resmetirom treatment are those with MASLD and moderate (F2) to advanced (F3) liver fibrosis but not with cirrhosis or other active liver disease (i.e., alcohol-related liver disease, autoimmune hepatitis, or primary biliary cholangitis) or unmanaged hypothyroidism or hyperthyroidism.
- Given complexities associated with selection of an individual for therapy, drug cost, and treatment monitoring, therapy should be individualized and initiated by a hepatologist or gastroenterologist with expertise in MASH within an interprofessional team.

[Statin Use and Risk of Hepatocellular Carcinoma and Liver Fibrosis in Chronic Liver Disease | Hepatobiliary Disease | JAMA Internal Medicine | JAMA Network]

- Conclusions: This cohort study found that statin use, particularly lipophilic statin use and longer duration of therapy, was associated with reduced HCC risk and slower fibrosis progression in patients with CLD and intermediate to high fibrosis risk.
  - These findings underscore the potential of statins as chemopreventive agents against HCC through their role in mitigating fibrosis progression.

  - Lipophilic statins include atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin
  - Hydrophilic statins include rosuvastatin and pravastatin.

Renin-angiotensin-aldosterone system inhibitor use improves clinical outcomes in patients with metabolic dysfunction–associated steatotic liver diseases: Target trial emulation using real-world data

- Conclusions: ACEi/ARB use in patients with metabolic dysfunction–associated steatotic liver diseases was associated with a reduced risk of mortality, major adverse liver outcomes, and major adverse cardiac events compared with CCB use.
  - Use of an ACE inhibitor or ARB was associated with a significantly decreased risk of
    - mortality (hazard ratio [HR], 0.59; 95% CI, 0.51 to 0.68),
    - major adverse liver outcomes (HR, 0.70; 95% CI, 0.61 to 0.80), including
    - ascites (HR, 0.78; 95% CI, 0.63 to 0.98) and
    - hepatic encephalopathy (HR, 0.67; 95% CI, 0.57 to 0.78), and
    - major adverse cardiovascular events (HR, 0.82; 95% CI, 0.76 to 0.90),
    - but not incident cancer (HR, 0.97; 95% CI, 0.86 to 1.10).
  - A large prospective study is needed for external validation.

GLP-1 agonists halve risk of obesity-related cancers

- A study published in The Lancet's *eClinicalMedicine* showed that GLP-1 receptor agonists liraglutide and exenatide nearly halved the risk of obesity-related cancers (ORC) and offered protection comparable to bariatric surgery, despite less weight loss. Experts call the findings transformational, pointing to the anti-inflammatory effects of these drugs and urging large-scale trials to explore their potential in cancer prevention.
- ORC, defined as any of the following diagnoses: multiple myeloma, meningioma, adenocarcinoma of esophagus; stomach, colorectal, liver or bile duct, gallbladder, pancreas, corpus uteri, ovary, renal-cell kidney, thyroid, and postmenopausal breast cancer.

Pharmacotherapy for Obesity and T2D[2-4,a]

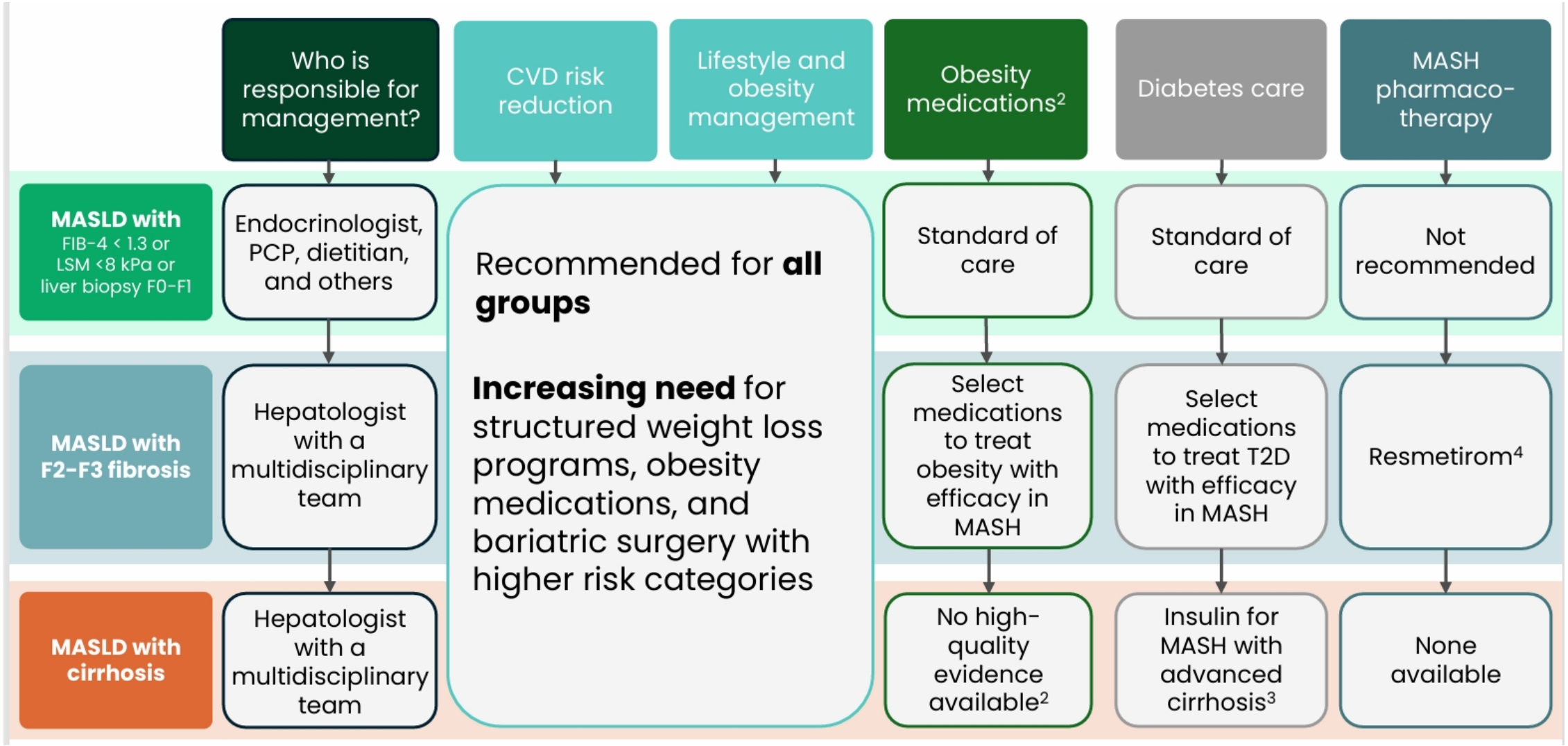
Fibrosis risk category	Recommended obesity medications	Recommended T2D medications
Low	Standard-of-care obesity medications	Consider agents that reduce liver fat (pioglitazone, GLP-1 RA–based therapy, or SGLT2i)
Intermediate	GLP-1 RA–based therapy preferred for MASH	Strongly consider agents with proven efficacy in MASH (pioglitazone, GLP-1 RA-based therapy). Insulin is the only therapy for T2D in people with decompensated cirrhosis
High	GLP-1 RA–based therapy preferred for MASH	

[a] Pioglitazone and GLP-1 RA–based therapy are not FDA approved for the treatment of MASH. Resmetirom, the first pharmacotherapy approved for MASH, was approved by the FDA 2024 and should be considered for people with MASH and F2 or F3 fibrosis, who are being cared for by a multidisciplinary team that includes a liver specialist. BMI, body mass index; FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic-associated steatotic liver disease; SGLT2i, sodium glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

1. Zelber-Sagi S, Moore JB. *Diabetes Spectr*. 2024;37(1):39-47
2. Cusi K, et al. *Endocr Pract*. 2022;28(5):528-562; 3. American Diabetes Association Professional Practice Committee. *Diabetes Care*. 2024;47(Suppl 1):S52-S76
4. Kanwal F, et al. *Gastroenterology*. 2021;161:1657-1669

Approaches to MASLD & MASH

Endocrine Society & Institute for Medical and Nursing Education



ADA 2025 Standards of Care – Management of MASLD

- 4.25 Adults with type 2 diabetes or prediabetes, particularly with overweight or obesity, who have metabolic dysfunction–associated steatotic liver disease (MASLD) should be recommended lifestyle changes using an interprofessional approach that promotes weight loss, ideally within a structured nutrition plan and physical activity program for cardiometabolic benefits B and histological improvement. C
- 4.26 In adults with type 2 diabetes, MASLD, and overweight or obesity, consider using a glucagon-like peptide 1 (GLP-1) receptor agonist (RA) or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA for the treatment of obesity with potential benefits in MASH as an adjunctive therapy to lifestyle interventions for weight loss. B
- 4.27a In adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis (based on noninvasive tests), pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA is preferred for glycemic management because of potential beneficial effects on MASH. B
- 4.27b Combination therapy with pioglitazone plus GLP-1 RA can be considered for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) because of potential beneficial effects on MASH.B
- 4.28 For consideration of treatment with a thyroid hormone receptor-β agonist in adults with type 2 diabetes or prediabetes with MASLD with moderate (F2) or advanced (F3) liver fibrosis on liver histology, or by a validated imaging-based or blood-based test, refer to a gastroenterologist or hepatologist with expertise in MASLD management. A
- 4.29 Treatment initiation and monitoring should be individualized and within the context of an interprofessional team that includes a gastroenterologist or hepatologist, consideration of individual preferences, and a careful shared-decision cost-benefit discussion. B
- 4.30a In adults with type 2 diabetes and MASLD, use of glucose-lowering therapies other than pioglitazone or GLP-1 RAs may be continued as clinically indicated, but these therapies lack evidence of benefit in MASH. B
- 4.30b Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis. C
- 4.31a Adults with type 2 diabetes and MASLD are at increased cardiovascular risk; therefore, comprehensive management of cardiovascular risk factors is recommended. B
- 4.31b Statin therapy is safe in adults with type 2 diabetes and compensated cirrhosis from MASLD and should be initiated or continued for cardiovascular risk reduction as clinically indicated. B In people with decompensated cirrhosis, statin therapy should be used with caution, and close monitoring is needed, given limited safety and efficacy data. B
- 4.32a Consider metabolic surgery in appropriate candidates as an option to treat MASH in adults with type 2 diabetes B and to improve cardiovascular outcomes. B
- 4.32b Metabolic surgery should be used with caution in adults with type 2 diabetes with compensated cirrhosis from MASLD B and is not recommended in decompensated cirrhosis. B

Issues with FIB4

- The FIB-4 test is used to detect fibrosis in fatty liver disease but has limited accuracy in predicting liver stiffness, resulting in high rates of false positives and negatives.
- The FIB-4 index may not be effective in accurately detecting advanced liver fibrosis in individuals with *diabetes* and fatty liver disease.
- The FIB-4 index may not reliably detect individuals with liver stiffness measurements of 8 kPa or higher, potentially leading to false negative results in about 20% of cases https://eurjmedres.biomedcentral.com/articles/10.1186/s40001-024-02032-x#:~:text=The%20FIB%2D4%20test%20is,of%20false%20positives%20and%20negatives.

Diabetes Medications & MASLD

- Glucagon-like peptide-1 receptor agonists
- Semaglutide, dulaglutide, liraglutide (1.8 mg/day), exenatide and lixisenatide have been shown to be effective in reducing steatohepatitis, compared with controls and glucagon-like peptide-1 (GLP-1) receptor agonists has the additional benefit of aiding weight loss
- Thiazolidinediones
- Pioglitazone, a thiazolidinedione, has also been demonstrated in placebo-controlled biopsy studies in patients with diabetes to be an effective long-term treatment to reduce steatosis and inflammation in MASLD.61Expand Reference Care should be taken in patients at risk of heart failure and pioglitazone is also associated with weight gain.62Expand Reference
- Sodium-glucose cotransporter-2 inhibitors
- Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have not been studied in paired biopsy studies in MASLD, however multiple placebo or active-controlled studies, utilizing reduction in serum liver enzyme levels or liver fat content on imaging as end points, have been undertaken. A meta-analysis of these studies (in which 90% of the patients had T2D) demonstrated SGLT-2i were effective at reducing liver enzymes (ALT and gamma-glutamyltransferase [GGT]) and liver fat content measured with magnetic resonance imaging (MRI), suggesting they may have utility in treating steatohepatitis associated with MASLD.63Expand Reference

- Conversely metformin, sulphonylureas, dipeptidyl peptidase-4 (DPP4) inhibitors and insulin have not been demonstrated to have additional benefit in the treatment of MASLD beyond improvement in diabetes control and should not be preferred treatments for patients with T2D and MASLD if the above treatments could be used in the first instance