Next Steps: Management of MASLD/MASH in Type 2 Diabetes

Part 2

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Case - Roger

- You calculate a FIB4 Index of 1.97 for a 56-year-old male with T2D, hypertension & dyslipidemia
  - Current meds are
    - metformin 500 mg twice daily & sitagliptin 100 mg daily
    - lisinopril 20 mg daily & amlodipine 10 mg daily
    - atorvastatin 40 mg daily
  - BMI is 39, BP 132/84, A1c 7.8%, LDLc 65, HDLc 43, TGs 180, Cr 1.1, ALT 36 and AST 32
  - Fibroscan shows LSM of 7.6 kPa

- What are the next steps for this case?
  - Will a higher dose of metformin help reduce the hepatic steatosis & inflammation?
  - Should you have him stop the statin since his FIB4 & LSM show intermediate risk for liver damage ?
  - Does he qualify for liver-directed therapy?

Learning Objectives

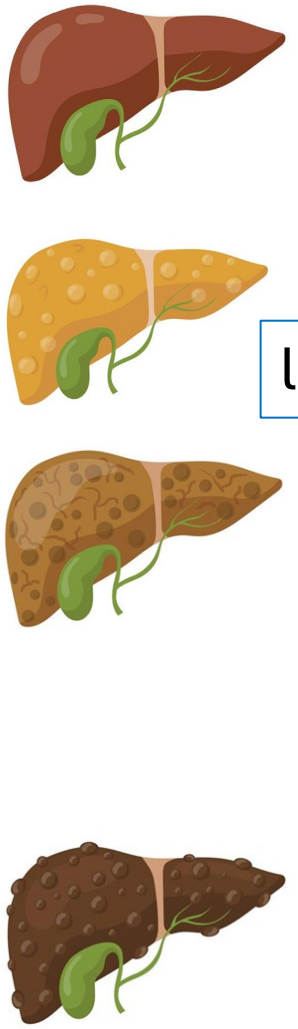
- Incorporate management strategies to help reverse or prevent worsening of MASLD and MASH & reduce associated risks
  - Employ lifestyle efforts that can prevent and/or reverse MASLD and its associated risks
  - Identify which medications for glycemic management of type 2 diabetes also benefit MASLD
  - Examine the benefits of initiating or continuing statin therapy in patients with MASLD and MASH.
  - Describe options for liver-directed therapy
- Utilize non-invasive tests for monitoring patients with MASLD.

MASLD Recap – Key Points

- MASLD & MASH (Metabolic-dysfunction Associated Steatotic Liver Disease & Steatohepatitis) replace the NAFLD & NASH terminology along with some differences to the definition
  - Steatosis with at least one Cardiometabolic risk factor associated with insulin resistance
  - Allows for co-existence of other liver conditions
- MASLD increases the risk of CVD, cancers & CKD as well as the risk of liver complications (cirrhosis, liver failure & hepatocellular carcinoma (HCC))
  - Risks increase with increasing fibrosis of the liver
  - CVD is main cause of death in people with MASLD)
- Type 2 diabetes (T2D) is a major risk factor for developing MASLD, MASH & HCC
- Most (>70%) people with T2D have MASLD and at least 35% have MASH with 10-20% having significant fibrosis – often with *normal liver tests*
  - therefore, the ADA recommends *presuming* the presence of MASLD & *screening for the risk of significant fibrosis* in all patients with T2D (even with *normal liver tests*) using Non-invasive Tests (NITs)
    - FIB4 index &
    - Secondary NITs: Liver Stiffness Measurement (LSM) (e.g., Fibroscan) and/or ELF score

Types of MASLD

- Normal liver - <5% fat content
- MASLD – “fatty liver” (>5-10% fat content)
- MASH – steatohepatitis (liver cell injury)
  - Fibrosis
    - F0, no fibrosis
    - F1, mild
    - F2, moderate (significant)
    - F3, severe (advanced)
    - F4, cirrhosis



lipotoxicity

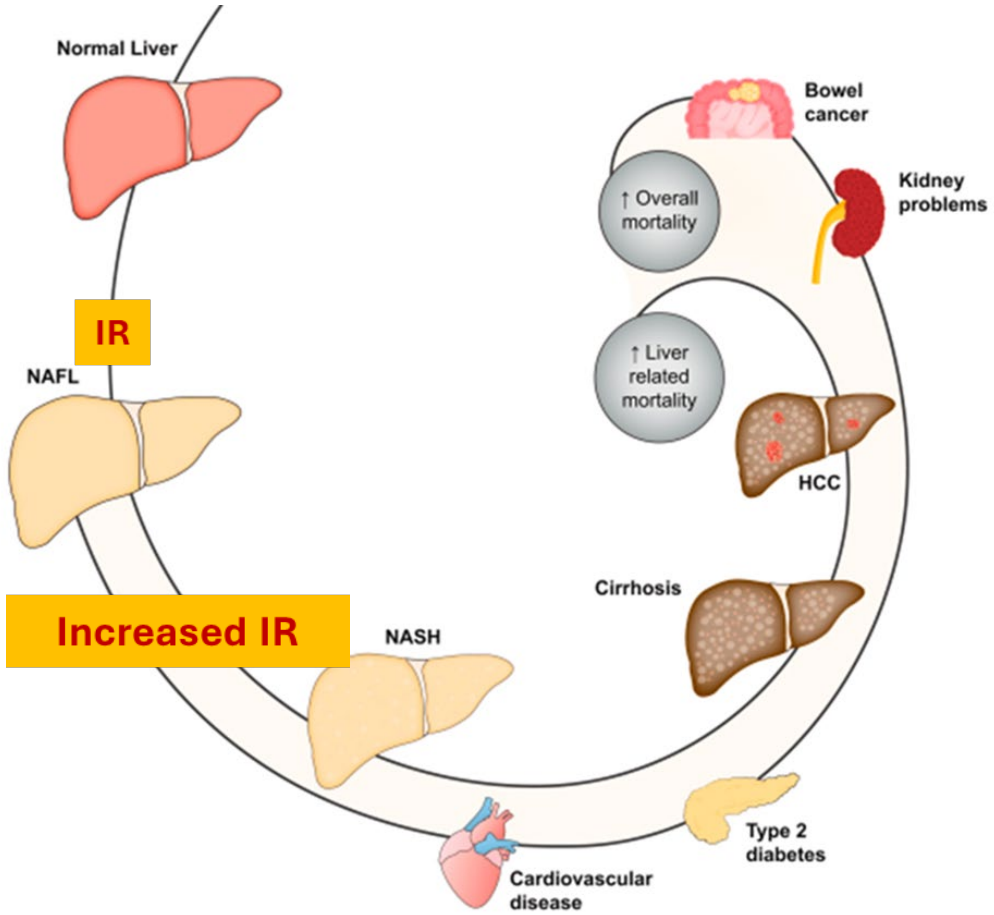
Excess calories, high sat fat, ~high HFCS intake → toxicity:

- 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

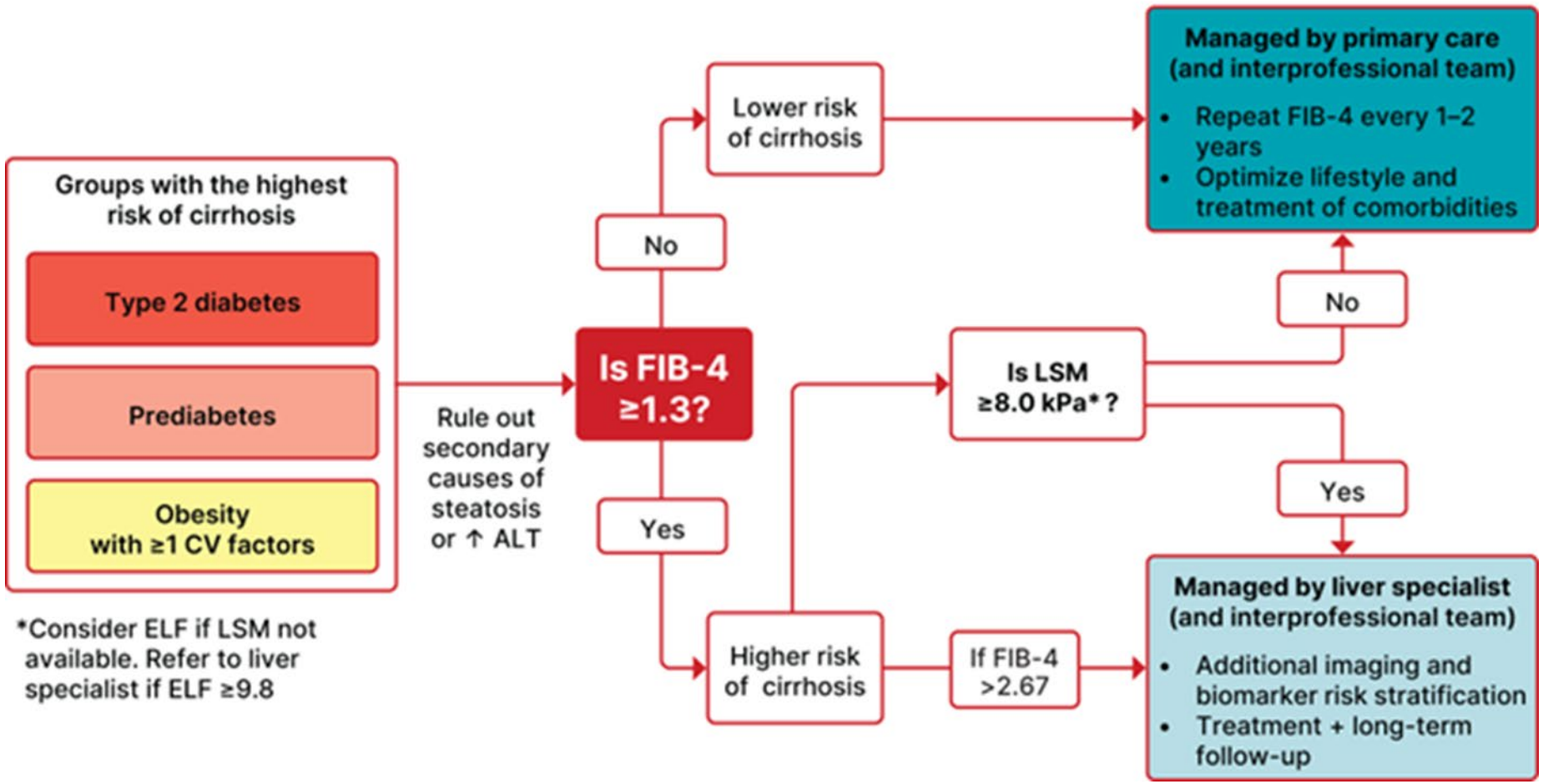
Key Points to Consider as Goals of Management

- Main causes of death in people with MASLD
  - CVD
  - Non-hepatic cancer
  - Liver related outcomes (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



MASLD adds Additional Risk on to Risk

Diagnostic algorithm for the prevention of cirrhosis in people with metabolic dysfunction–associated steatotic liver disease (MASLD)

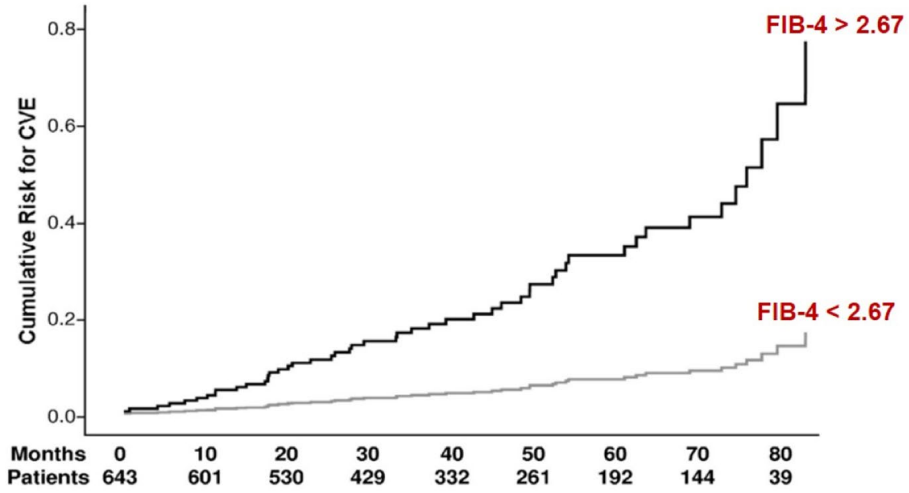


Goal of Screening with FIB-4

- FIB4 does *not* tell you who has MASLD – most people with type 2 diabetes have MASLD
  - Need for intensified lifestyle interventions & management of comorbidities
    - to prevent future liver-related adverse events in addition to all-cause mortality (CVD, CKD, malignancy)
- FIB4 is a screening tool to help identify people with **at-risk MASH (i.e., with significant fibrosis)**
  - Helps determine who needs "***liver-directed care***" in addition to attention to intensified lifestyle interventions and management of comorbidities
  - The goal is to prevent future cirrhosis, HCC (hepatocellular carcinoma), liver transplantation, or to help manage if already present
- The ***primary care team*** remains involved in **management** even with and after a referral to a liver specialist (GI or hepatology)
  - Intensification of lifestyle interventions
  - Management of co-morbidities (glycemia, blood pressure, lipids, etc.)
  - Ongoing care and monitoring of non-hepatic aspects of health

Elevated FIB4 /Advanced Fibrosis Increases the Risk of CVD, CKD & Non-hepatic Cancers as well as Liver Complications – Ongoing Role for *Primary Care* to Intensify Management for these Comorbidity Risks

FIB-4 Predicts CV Risk



CVE, cardiovascular event.
Baratta F, et al. Clin Gastroenterol Hepatol. 2020;18:2324-2331.e4.

≥8.0 kPa

Hepatology referral

- Diagnostic work-up and management plan for liver-related outcomes
- Intensified management of comorbidities (in a multidisciplinary team)

Messaging

- PWD at high risk of MASLD are largely ***unaware*** of the disease and/or that their conditions are risk factors for MASLD
  - corresponds with a ***limited level of knowledge of MASLD among the general population***
- HCPs need to be aware of **stigma around liver disease**
  - family and friends – and their physicians - assuming patients are likely "alcoholic" and questioning patients' honesty regarding their alcohol intake
- **Clear and simple messages** are critical to help improve the understanding of MASLD

- Recommend **avoid scare tactics**, instead **share strategies**
  - Avoid – *"If you don't eat better, exercise & get your blood sugars under better control, you will end up with cirrhosis of your liver"*
  - Consider – *"We have learned that type 2 diabetes can cause fat build up inside the liver. If not corrected, this can damage the liver and cause scar tissue, called fibrosis, in the liver which can lead to cirrhosis or liver failure. There are things we can do together to stop or even reverse the fat build up as well as the damage and scar tissue– I would like to work with you on this."*

Management of MASLD
Lifestyle changes are the keystone strategy for managing MASLD

- We want to **prevent or reduce liver fat & inflammation & any fibrosis in all our PWT2D**
  - **Steatosis** is a critical factor that influences the development, severity, and progression of MASH - **Managing and reducing steatosis is therefore a primary goal in treating and preventing MASH.**
- **For all PWT2D with MASLD – including those with low-risk FIB4/NITs & those waiting for referral (high risk):**
  - **Lifestyle**
    - **Weight loss - Reduced calories**
    - **Diet composition (can impact liver fat, lipotoxicity, inflammation, etc. independent of weight loss)**
    - **Synergistic dietary patterns (e.g., the Mediterranean diet)**
    - **Increased physical activity / exercise / reduced sedentary time**
    - **Alcohol avoidance**
    - **Smoking cessation**

Most of us are already encouraging lifestyle changes in our patients with diabetes and prediabetes …. prevention & treatment of MASLD / MASH needs to intensify this emphasis

Lifestyle Changes are the Keystone Strategy for Managing MASLD

- *Sustained* lifestyle changes can *prevent MASLD from progressing* and can *reverse* MASLD/MASH (best response in early stages but even w/ compensated cirrhosis).
  - Need comprehensive, *structured* lifestyle interventions with dietary, physical activity, and behavioral plans that offer continued support from a multidisciplinary team
    - More than "you need to lose weight"
    - **Treating all the metabolic factors associated with MASLD** is recommended in any patient regardless of disease severity [adiposity, glycemia, BP, lipids, tobacco, sedentary time, etc.]
  - If available – Lifestyle program, Obesity Management program, Exercise program, etc.
  - Suggestions: Set SMART goals & take advantage of tracking/monitoring devices & apps
    - An example of a SMART dietary goal could be to "stop buying sugar-sweetened beverages for the next four weeks" or "Reduce SSB intake by 2 cans/day over the next 4 weeks"

    or

    - A physical activity SMART goal could be "increase daily steps by 500 steps per day over the next 4 weeks" or "over the next 4 weeks work up to 5000 steps per day" and
      - Utilize step tracker on phone app or another device to track progress

Weight Loss

- In patients with MASLD and MASH, weight loss of
  - 5% of the total body weight can decrease hepatic steatosis
  - 7% can lead to MASH resolution
  - 10% can result in fibrosis regression or stability
  - However, there is significant *individual variability in histological outcomes* with weight loss.

- Weight loss can be achieved by any [healthy] dietary method that *reduces calorie intake*
  - Many different types of diet have been shown to be effective for inducing weight loss
    - For example, *"a low-carbohydrate diet appears to be similarly effective as a low-fat diet in reducing liver fat and the liver enzyme alanine aminotransferase longer term"*
  - Help the patient choose a ***diet with health benefits*** that they feel *able to follow in the long-term* with ongoing guidance by the care team (*diet composition matters!)*
    - ADA: "Obesity pharmacotherapy may assist with weight loss in the context of lifestyle modification if not achieved by lifestyle modification alone"

Diet Composition

Often improvement (or worsening) *independent* of weight change

Avoid or Reduce Intake

- Sugar sweetened beverages (SSB)
- Added sugars/ high-fructose corn syrup (HFCS)
- Saturated fat
- Red meat (such as beef, lamb & pork)
- Processed meats (e.g., hot dogs, salami, sausages)
- Refined carbohydrates & highly processed foods

- Increased intake associated with
  - Increase in hepatic steatosis & lipotoxicity
  - Increased insulin resistance & inflammation
  - Increased risk of HCC

Ensure Adequate Intake

- Fruits & Vegetables
- Nuts & seeds
- Whole grains
- Plant oils
- Coffee & tea

- Sources of fiber, vitamin & non-vitamin anti-oxidants such as phenols & isoflavones

What you eat matters regardless of weight loss

Good news – same interventions help improve glycemia & reduce risk for CVD & many cancers

Recommend Reducing Saturated Fat

- Saturated fat has been shown in several studies to *increase liver fat accumulation & lipotoxicity*
    - For example, in a study comparing the addition of muffins high in saturated fat vs. muffins high in unsaturated fat to the habitual diet Overeating Saturated Fat Promotes Fatty Liver and Ceramides Compared With Polyunsaturated Fat: A Randomized Trial - PMC
        - there was a similar increase in body weight across both groups
        - only the muffins with the **high saturated fat** (palm oil) markedly **increased liver fat**, **liver enzymes, ceramides** and serum lipids (LDLc)

- Foods rich in saturated fat include
    - coconut oil
    - palm oil, which is found mostly in processed food
    - butter and high-fat dairy products
    - high-fat meat (e.g. internal organs like liver, brain and processed meats like sausages)
    - cakes, cookies, ice cream and other sweets.

Reduce Commercial Fructose NOT Whole Fruits

- AGA: "*limit or eliminate consumption of **commercially produced fructose** - increased fructose* consumption is associated with fibrosis severity, **independent of total caloric intake**"* *(Commercial fructose (HFCS) / not fructose in fruit)
  - **Naturally occurring sugar** refers to the sugar that is an integral constituent of whole fruit, vegetable, and milk products.
  - **Added sugar** refers to **sucrose** (table sugar - 50% glucose + 50% fructose) or other refined sugars (**high-fructose corn syrup** – glucose + 55% fructose) incorporated into food, fruit drinks, and other beverages.
    - HFCS starts with corn starch, which is broken down into glucose. Then, an enzyme is used to convert some of the glucose into fructose, creating HFCS.
    - The most common types of HFCS are HFCS 42 (42% fructose) and HFCS 55 (55% fructose).
    - **Free fructose is metabolized in the liver → lipogenic & increases oxidative stress & inflammation.**

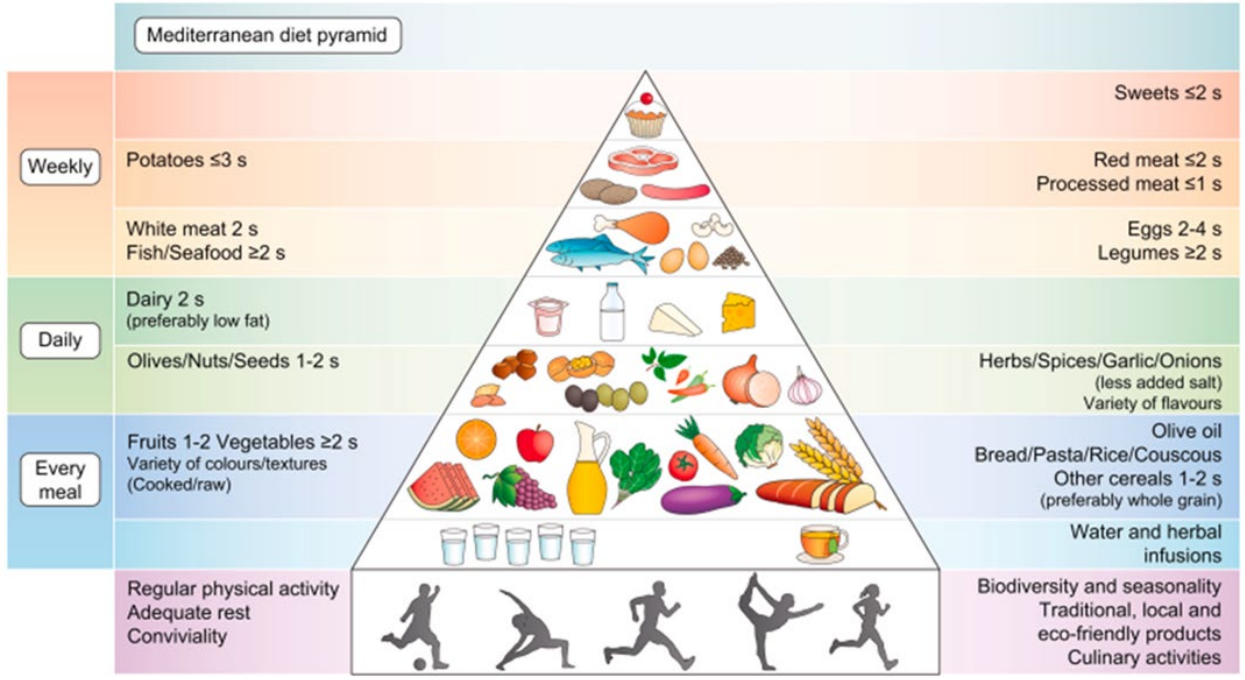
  - "*Importantly, naturally fructose-containing whole fruits such as mangos, grapes, and apples have not been associated with hepatic steatosis or MASLD development, likely because of their fiber and overall nutritional composition. Therefore, consumption of whole fruits remains recommended despite its naturally occurring fructose content.*" Grace Kim MD

Dietary Patterns
many guidelines recommend the Mediterranean diet for people with MASLD/MASH

- **Dietary patterns** represent the overall ***combination of foods*** that can produce ***synergistic* health effects**.
- One of the most studied dietary patterns is the traditional **Mediterranean diet -** frequently recommended due to its beneficial effect on cardiovascular health and on reducing liver fat.
  - In two studies, two months of a Mediterranean diet led to **a significant decrease in liver fat *independent of any weight loss*.**
- The Med diet is high in fiber and unsaturated fat and limited in refined carbohydrates and saturated fat and characterized by
  - a high intake of
    - Olive oil (which is rich in a healthy type of fat and polyphenols that act as antioxidants)
    - Vegetables and fruits
    - Nuts and legumes
    - Whole grains
    - Fish and seafood
  - a low intake of
    - red meat and processed foods
    - sugars and refined carbohydrates
  - one of the principles of the Mediterranean diet is to minimize processed or “fast foods” and to have more home-cooked meals

Adapt Mediterranean Diet to Culture

- The Mediterranean diet "*may not be universally applicable across diverse cultures.*" AASLD
- Challenges to adherence:
  - Foods in the Mediterranean diet tend to be expensive in countries outside of the Mediterranean region.
- Even partial adherence to this dietary pattern (*especially a* ***reduction of sugar, saturated fat and processed food****)* and a more ***culturally adjusted approach*** can be beneficial.
  - Allows connection to traditional diets/food sovereignty programs ("heritage diets")



Impact of Food /Housing Insecurity

https://pmc.ncbi.nlm.nih.gov/articles/PMC12073359/

AGA Patient Info on MASLD – Diet Suggestions

https://gi.org/topics/steatotic-liver-disease-masld/

- Various diets can lead to a reduction in liver fat, as long as there is a decrease in calories eaten in a day compared to a person's daily required calories to maintain their current weight, with a goal of 500 fewer calories daily.
- Water is best. Avoid juice or sugary drinks.
- Avoid foods with added sugar including candy, desserts, and soda pop, especially high fructose corn syrup.
- Avoid highly processed snacks, fried foods, and fatty foods.
- Watch your portion size (how much food you choose to eat at one time). Use measuring cups to help control your portion.
- In a meal, fill half of your plate with fruits and vegetables, one quarter with a grain (like brown rice or whole wheat pasta), and one quarter with protein. [My Native Plate]
- Limit 1-2 healthy snacks during the day. Keep fruits and vegetables around for snacks.
- Try to eat at least 2.5 cups of fruit and vegetables every day.
- Try keeping a food log or diary, which may help to see how many calories you are eating.
- Meeting with a nutritionist or dietitian may be helpful for more information and to get personalized recommendations for healthy eating.

Physical Activity & Exercise

- Exercise is not just for weight loss → metabolic & functional benefits of having an adequate & healthy muscle mass, muscle function, and muscle strength … & CV fitness

- Physical activity is likely to **reduce the loss of muscle mass** that is commonly observed in MASLD
  - There is increasing insight that **low muscle mass (& function)** or ***sarcopenia*** plays a role in the severity of MASLD and the complications that come with the more severe stages of the disease.
    - Multiple factors: BMR, IR, “fatty muscle”, Myokines, etc.

- Studies have shown that physical activity is effective in reducing liver fat *even without significant weight loss*
  - It is also effective in reducing the risk associated with other comorbid metabolic diseases such as T2D, CVD and obesity…. and some cancers

Physical Activity/ Exercise

Often improvement or worsening *independent* of weight change

Reduce Sedentary Time

- Sedentary behavior refers to "*any waking activity characterized by a low level of energy expenditure in a sitting or reclining posture*"
  - (e.g., watching television, using a computer, travelling by car or bus).
- Research has identified sedentary behavior as an independent risk factor for MASLD
  - A 1.15% increase in liver fat was associated with each additional hour of time spent sedentarily per day.
- ADA: *"Minimizing sedentary time and engaging in brief sessions (~10 min) of simple activities such as walking with the goal of meeting activity guidelines should be encouraged."*
  - Decreasing overall sedentary time and breaking up sedentary time throughout the day is a useful treatment strategy for all people with MASLD/MASH and may be more achievable initially than increasing physical activity levels

Increase Physical Activity

- Guidelines recommend that patients be advised to increase their activity level to the extent possible
  - Exercise offers both cardiovascular and hepatic [& glycemic] benefits and should be routinely recommended and tailored to the patient
- Often a **combination of aerobic and resistance exercise** provides the greatest health benefits.
  - ADA: Both aerobic and resistance training improve MASLD in proportion to treatment engagement and intensity of the program
    - Guidelines recommend over 150 min/week of moderate intensity physical activity over 3-5 sessions + two sessions a week of resistance training
  - Higher volumes of physical activity/exercise are also associated with greater weight loss and systematic improvement of comorbidities
    - A consensus guideline recommends performing **150–300 min of moderate activity** or 75–150 min of vigorous activity each week. Global Consensus Recommendations for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis

Studies suggest a synergistic effect of dietary & exercise interventions on MASLD

More might be Better, but Even a Few Minutes or a Few Days makes a Difference

- Even though there appears to be a dose-response relationship of more benefit with more activity/exercise, ***all* levels of physical activity were inversely associated with hepatic fibro-inflammation.**
  - A large retrospective study showed that engaging in **moderate-to-vigorous exercise** lasting **at least 10 min** on each occasion **5 or more times per week** was associated with
    - a ***reduced risk of developing*** incident hepatic steatosis and
    - a ***higher likelihood of resolving*** existing **hepatic steatosis *independent of change in body mass index (BMI)***
  - ***"Exercise snacks"*** – 1–3-minute bouts throughout the day offer some metabolic benefits
  - Another study: The **Weekend Warrior PA pattern** (150 min over ~2 days**)** is associated with *significant health benefits*, including reduced risks of mortality, cardiovascular diseases, and metabolic syndrome & also shows ***benefit for GI disorders (including MASLD***)

MASLD in people with a normal BMI
(<25 kg/m2 BMI in Caucasian, and <23 kg/m2 in Asian individuals)

- Sometimes called ‘lean disease’ (MASLD) - these normal-weight patients are not always metabolically healthy
  - Often have greater or disproportionate “visceral” obesity (abdominal fat – an apple body shape) and decreased muscle mass (sarcopenia), along with adipose dysfunction & early beta cell failure
- They can benefit from ***increasing their physical activity/exercise levels*** which **decreases abdominal fat** and **increases muscle mass** independent of weight loss.
- Normal-weight patients with MASLD will also benefit from ***reducing their intake of added sugars & commercial fructose, sugared-sweetened beverages, saturated fats and processed foods*** (dietary composition)
- Switching to a Mediterranean diet without weight loss can help reduce liver fat
- A modest 3–5% weight reduction can help to achieve MASLD remission

Dietary and lifestyle recommendations for adults with Advanced Liver Disease

- The PC team has a role as part of the multidisciplinary team caring for patients with advanced cirrhosis & while waiting for referral to hepatology:

- For patients with **MASH-related cirrhosis**, adapt dietary and lifestyle recommendations to the severity of liver disease, nutritional status, and the presence of *sarcopenia/sarcopenic obesity* (EASL/EASD/EASO Strong recommendation).
  - For patients with **compensated cirrhosis and obesity**, consider suggesting ***moderate weight reduction, emphasizing a high-protein diet and physical activity*** to maintain muscle mass and reduce the risk of sarcopenia (EASL/EASD/EASO Weak recommendation).
  - Recommend a ***high-protein diet*** with a ***late-evening snack*** for ***sarcopenia, sarcopenic obesity,*** or **decompensated cirrhosis** (EASL/EASD/EASO Strong recommendation). [*do not calorie restrict* those with decompensated cirrhosis]

Avoid Alcohol Consumption

- High alcohol consumption can worsen MASLD/MASH.
  - The combination of ***alcohol and obesity*** increases the probability of developing MASLD and increases the severity of liver disease, reflecting a ***synergistic effect***.
  - Even mild-to-moderate drinking has been found to ***increase the risk of MASH, fibrosis, decompensated liver disease, liver cancer, and mortality***
    - Patients with MASLD who drank more alcohol than the threshold of ≥3 drinks/day for men and ≥2 for women[meeting MetALD criteria], were ***3x more likely to have advanced fibrosis***
    - **Overall mortality** was higher in adults with MASLD who consumed excess alcohol.

- Anyone with ***cirrhosis*** should ***avoid alcohol*** since any regular alcohol consumption puts them at significantly greater risk of developing liver cancer.
  - Uncertainty remains regarding moderate alcohol consumption (up to 2 drinks per day) among patients without cirrhosis
  - The AASLD guidelines recommend
    - **complete abstinence** from alcohol for patients with ***clinically significant hepatic fibrosis***
    - **minimizing alcohol** use is a reasonable approach for patients *without clinically significant hepatic fibrosis*

- **Consider calories**: alcoholic drinks contain **many "empty" calories**, which have no nutritional value.
- Consider increased risk of colorectal, pancreas and breast cancer

There is discussion about whether a safe limit for alcohol consumption exists if you have a pre-existing liver disease. If you have any liver damage, it is advisable to avoid alcohol as it can worsen your liver disease. Two factors that damage the liver could reinforce each other's damaging effect, making the liver disease progress more rapidly towards more severe stages.
You should not forget that alcohol also represents calories, so it is useful to stop drinking alcohol if you are trying to lose weight!

1 unit of alcohol equals 8 g of alcohol. Here are some examples of common alcoholic drinks with their alcohol content and the number of calories they contain (data from drinkaware.co.uk):

- 1 pint (568 ml) of 4% beer/lager = 18.4 g or 2.3 units = 182 calories
- 330 ml bottle of 5% beer = 13.6 g or 1.7 units = 142 calories
- 1 pint (568 ml) of 4.5% cider = 20.8 g or 2.6 units = 216 calories
- Single/25 ml of 40% spirit = 8 g or 1.0 units = 61 calories
- 175 ml glass of 13% wine = 18.4 g or 2.3 units = 159 calories
- 125 ml glass of 12% champagne = 12 g or 1.5 units = 89 calories
- 330 ml bottle of 4% alcopop = 8.8 g or 1.1 units = 170 calories

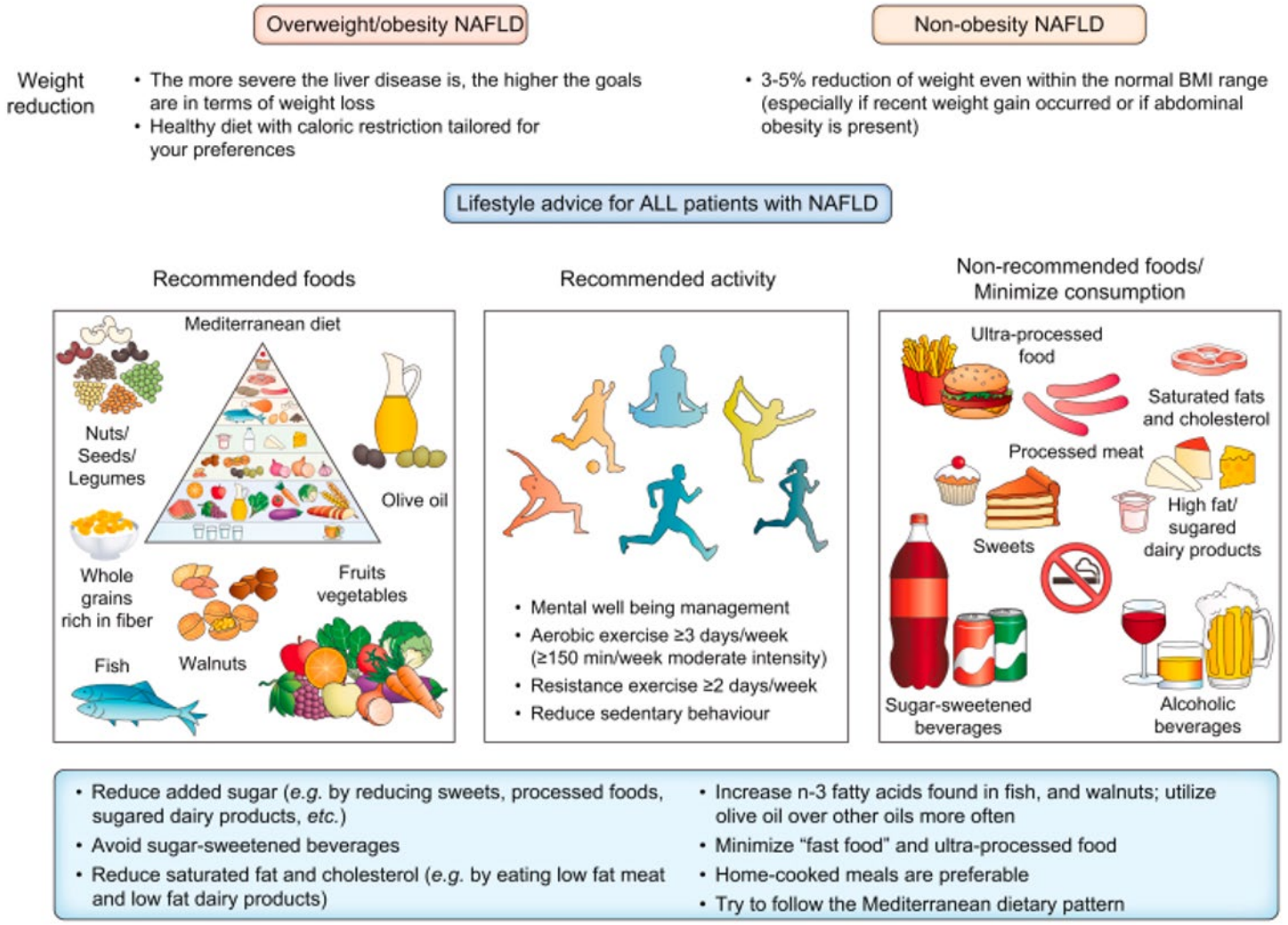
You can check how many units of alcohol you drink per week (and how many calories this adds up to) using the online calculator at (1 unit = 8 g of alcohol):
https://www.drinkaware.co.uk/understand-your-drinking/unit-calculator

Smoking can accelerate MASLD progression

- In current smokers, the risk of MASLD increases with an increase in the number of cigarettes smoked in a dose-response manner.
  - A large cohort study of >400,000 **people living with T2D** demonstrated that **smoking** was associated with a **60% increased risk of severe liver disease** during follow-up.
  - Smoking is associated with **progression of fibrosis**
  - Smoking is also an extremely important **risk factor for HCC (liver cancer)**
    - current smokers have about a 50% increased risk compared to never smokers
- Smoking is related to an increased risk of ***CVD*** in people with MASLD, with a 33% increased risk after accounting for other risk factors.
- Smoking also increases the risk of several of the ***non-hepatic cancers*** increased by MASLD/MASH
  - Pancreas, Colorectal, Bladder & Kidney

Lifestyle interventions can prevent and reverse disease progression.

In patients with MASLD and MASH, both diet and exercise *in the absence or presence of weight loss* can reduce levels of liver fat and inflammation

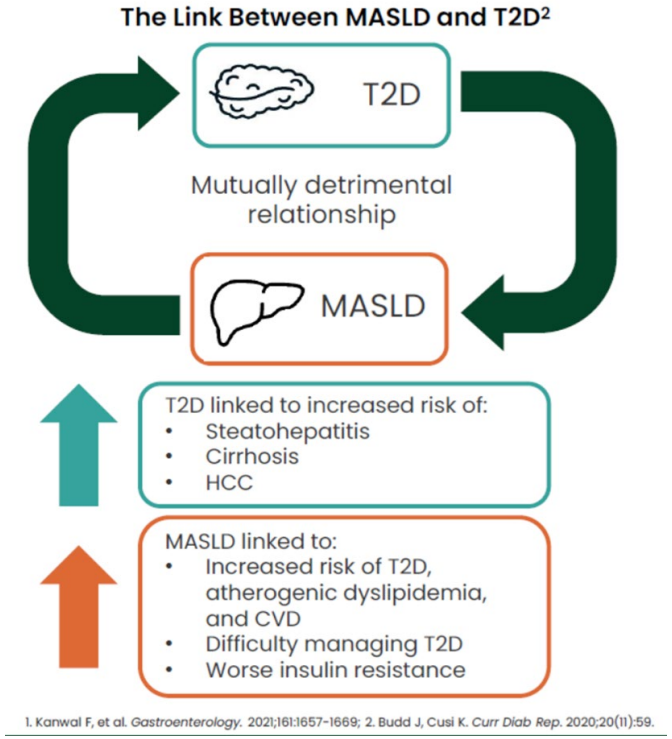


Foundation for all additional therapies

Lifestyle interventions implemented in all trials of liver-directed therapies

Optimize Management of Comorbidities

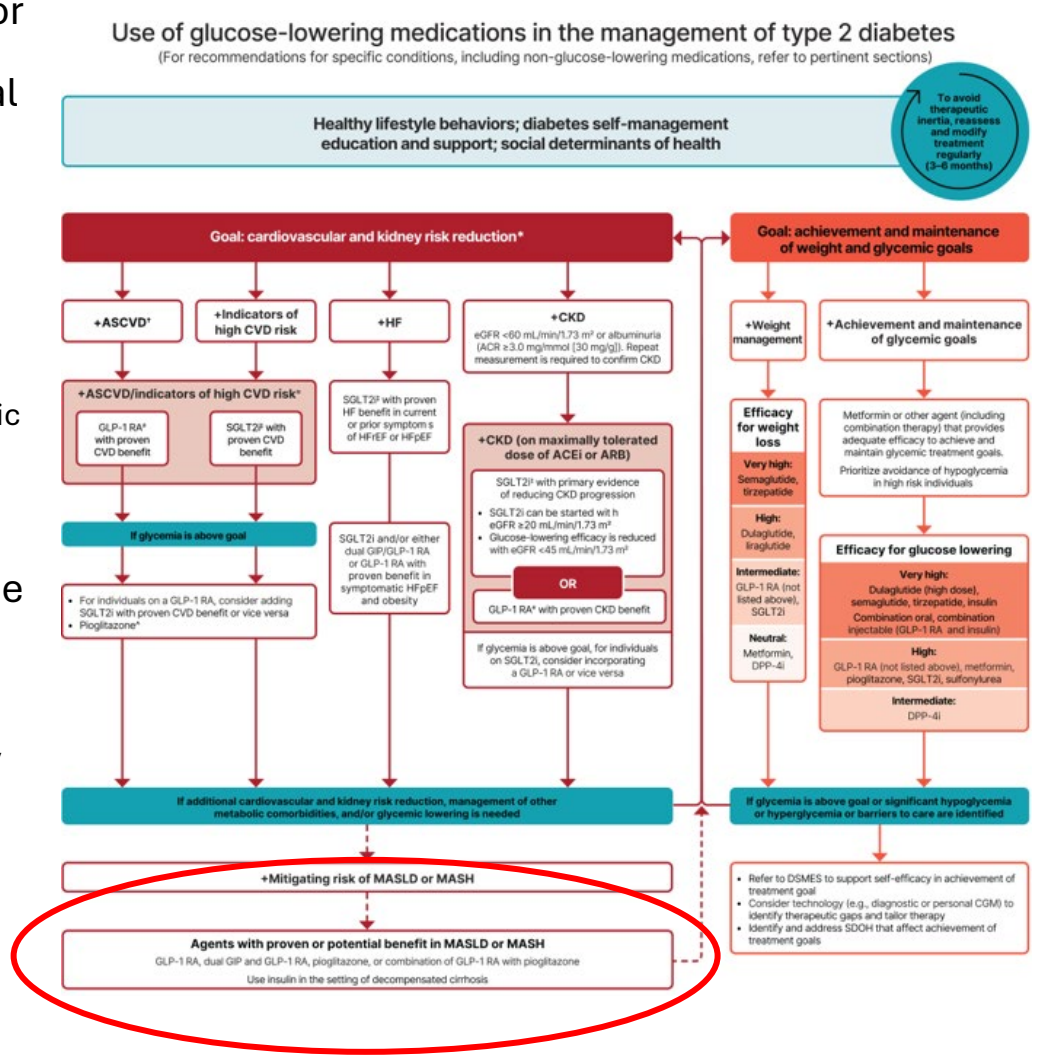
- For PWT2D, this includes **glycemic management**
- Diabetes-related Hyperglycemia
  - can alter the way the liver processes and stores lipids, contributing to **fat accumulation and inflammation - lipotoxicity**
    - can lead to the formation of **AGEs (advanced glycosylation end-products**), which 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**
- Prefer to use agents for glycemia that also offer hepatic, CV, renal & other benefits
  - 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)]



1. Kanwal F, et al. *Gastroenterology.* 2021;161:1657-1669; 2. Budd J, Cusi K. *Curr Diab Rep.* 2020;20(11):59.

ADA 2026 Standards of Care
Glycemic Management

- 9.12 In adults with type 2 diabetes, **MASLD**, and overweight or obesity, consider using a **GLP-1 RA** with demonstrated benefits in MASH A or a **dual GIP and GLP-1 RA** with potential benefits in MASH B for **glycemic management** and as an *adjunctive* therapy to interventions for **weight loss**.
- 9.13a In adults with **type 2 diabetes and biopsy-proven MASH** or those at high risk for liver fibrosis (based on noninvasive tests), a **GLP-1 RA** is preferred for glycemic management due to beneficial effects on MASH. A
  - **Pioglitazone or a dual GIP and GLP-1 RA** B can be considered for glycemic management due to potential beneficial effects on MASH. B
- 9.13b **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
  - 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.
  - ***Insulin therapy*** is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with ***decompensated cirrhosis***



Don’t Stop the Statin !!

ADA 2026 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 suggest that statin use in people with chronic liver disease may reduce episodes of hepatic decompensation and/or overall mortality

Metabolic Surgery

ADA 2026 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

Clinical Trials – Liver Directed Treatments
MASH Pharmacotherapy –
Focus on "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.

- Phase 2 trials: Proof of Concept
  - Primary Goal: Does the treatment work, and what is the optimal dose?
  - Fewer participants (usually 100-300) & shorter duration (months to 2 years)
- Phase 3: Pivotal Confirmation
  - Primary Goal: Is the treatment better than what is already available?
  - Larger (300 to 3,000+ across multiple centers & countries) & longer (1 to 4 years) to monitor long-term safety.
  - Study Design: Almost entirely randomized, double-blind, and controlled.
  - Provide the key clinical data needed to submit a New Drug Application (NDA) for **regulatory (FDA) approval**

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%

- Approved by FDA March 2024 for treatment of noncirrhotic MASH with moderate to advanced liver scarring/fibrosis (F2-3) – liver outcomes still to be determined for final approval
- Brand name Rezdiffra, once-daily oral medication, THR (thyroid hormone receptor)-Beta agonist
  - Given its mechanism of action, careful surveillance for early endocrine disease related to thyroid, gonadal, or bone disease may be needed.
  - Reduces hepatic fat, MASH & fibrosis and also lowers LDLc but no weight loss
- Cost ~ $47,400 per year/ $4,130 to $4,500 for a 30-day supply
- Requires order through specialty pharmacy

Accelerated FDA Approval of Semaglutide 2.4 mg injection to treat MASH in adults with moderate-to-advanced fibrosis
August 15, 2025

Resolution of steatohepatitis without worsening of fibrosis

- Sema – 62.9%
- PBO – 34.3%

Reduction in liver fibrosis without worsening of steatohepatitis

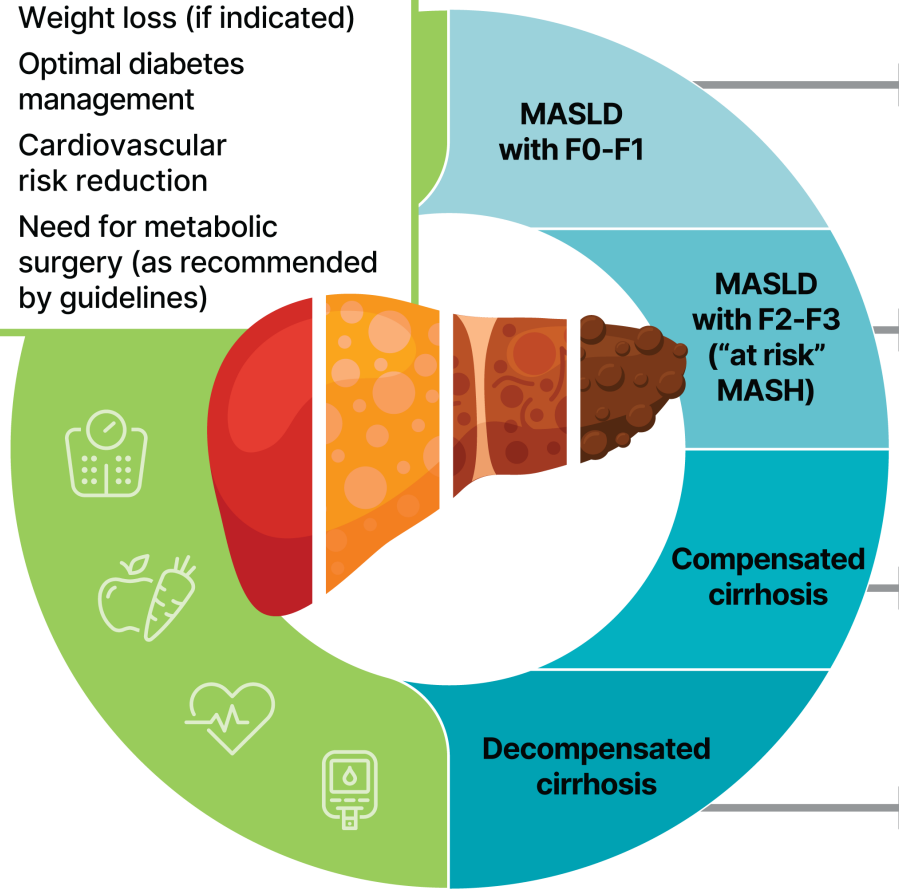
- Sema – 36.8%
- PBO – 22.4%

- Approved adults with moderate to advanced liver fibrosis (F2-F3) due to MASH, but without cirrhosis.
- Brand name Wegovy, weekly subQ injection
- Approved based on the interim results at 72 weeks in the ESSENCE trial
- 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.

Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm

Individualize care, targeting the following:

- Adoption of a healthy lifestyle
- Weight loss (if indicated)
- Optimal diabetes management
- Cardiovascular risk reduction
- Need for metabolic surgery (as recommended by guidelines)



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, GLP-1 RA†

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

† Only semaglutide among GLP-1 RAs has been approved by the FDA for treatment of MASH.

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

Monitoring

Optimizing Management of Comorbidities - Reducing Risk

Individual Factors & Self-monitoring – at target or in process of improving

- SMART goals (specific, measurable, achievable, relevant, timely)
  - goals for weight loss, dietary composition and/or physical activity [medication taking, tobacco use]
- 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.

Cardiometabolic risk factors - at target or in process of improving

- Glycemia
- Lipids
- BP
- Activity level
- Sedentary time (<10, closer to 6 hours/day)
- Weight/BMI, Waist Circumference
- Alcohol use
- Tobacco use

Monitoring Fibrosis Risk

- 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 (Alpha-Fetoprotein) & US

Many Phase 2 & 3 Trials Underway with Promising Results

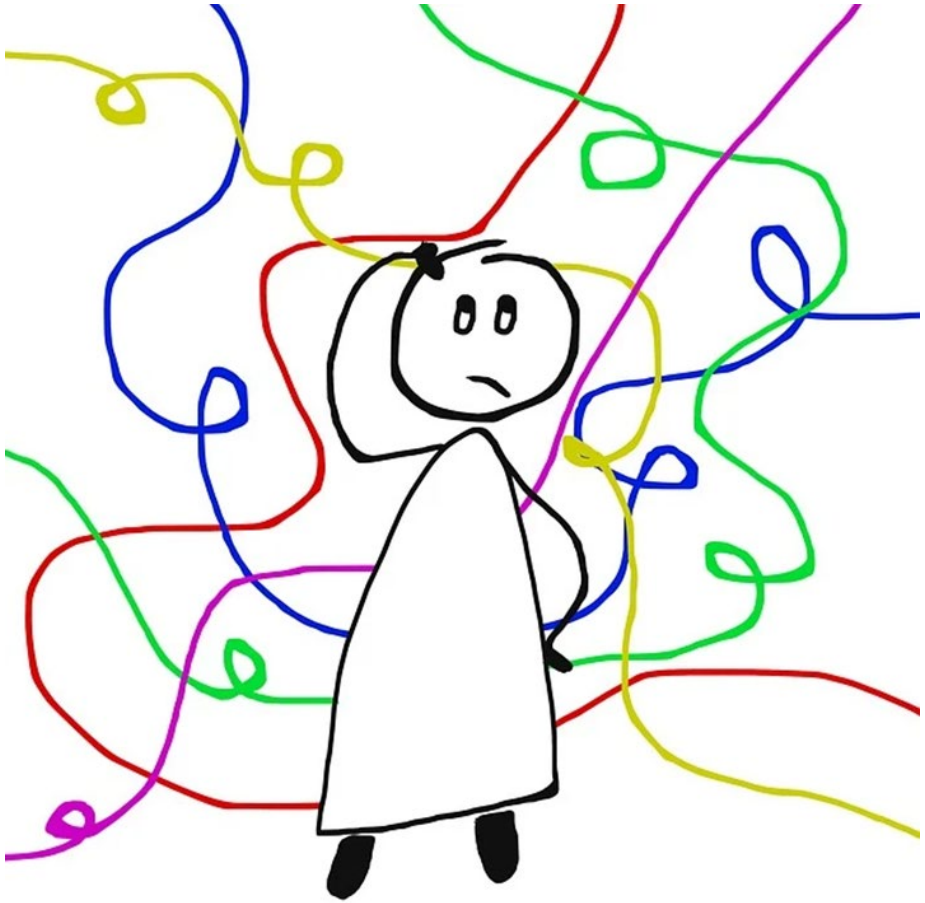
- Many incretin trials (“poly-agonists”), including:
  - Tirzepatide
  - Retatrutide (GLP1, GIP and Glucagon Receptor agonist)
  - Survodutide (GLP1 and Glucagon Receptor agonist)
- FGF21 agonists (critical in glucose, lipid & energy metabolism)
  - Reduces hepatic triglycerides and mitigates cellular stress to slow the progression of MASLD and MASH
- Additional THR-Beta agonists

- Anticipate
  - new/additional NITs (non-invasive tests)
  - refinements of risk prediction/ cut-off values and stratification and monitoring
  - meds to help reverse cirrhosis (F4)
  - SGLT2i & GLP1 RA med use in cirrhosis – preliminary observations of hepatic benefits

Summary -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, tea& coffee
  - More home cooked meals, less “fast food”
  - Avoid alcohol consumption & tobacco use
  - Reduce sedentary time & increase physical activity/exercise as much as possible
- Control of all cardiometabolic risk factors is important for improving outcomes in 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
  - For patients at risk for or with MASH, use of [low dose]pioglitazone for glycemic management can reduce liver risk & CVD risk
  - Do not stop statins – statins benefit CVD risk & appear to reduce liver risk
  - Metabolic surgery w/sustained weight loss can improve MASH & c- cirrhosis
- Semaglutide 2.4 mg & Resmetirom are approved for treating MASH with F2 & F3 fibrosis
  - Many new meds in the pipeline
- Primary care teams play a critical role in helping PWT2D prevent & reverse MASLD/MASH

Questions, Comments, Clarification



Extra Slides

Nutrition. 2019 May:61:119-124. doi: 10.1016/j.nut.2018.10.016. Epub 2018 Oct 23.

No association between fruits or vegetables and non-alcoholic fatty liver disease in middle-aged men and women

- Objective: It has been hypothesized that fruit and vegetable intake is inversely associated with non-alcoholic fatty liver (NAFLD). However, some studies have speculated that fruit intake might be positively associated with NAFLD owing to the fructose content of the fruit. This might cause consumers to hesitate consuming fruit. The aim of this study was to assess the association between fruit and vegetable consumption and NAFLD.
- Methods: This was a cross-sectional study of 977 men and 1467 women, 40 to 69 y of age without current liver disease other than NAFLD and who did not report excess alcohol intake (i.e., ≥30 g/d in men and ≥20 g/d in women). Dietary intake was assessed using a validated diet history questionnaire. NAFLD was diagnosed from abdominal ultrasonography results. The association between quartiles of fruit or vegetable consumption and NAFLD prevalence was assessed using logistic regression analysis, with lowest category as reference.
- Results: The prevalence of NAFLD was 34.9% in men and 11.7% in women. Adjusted for age and lifestyle factors, **fruit intake was inversely associated with NAFLD in both sexes.** However, these associations disappeared after further adjustment for body mass index. Consumption of total vegetables was not associated with NAFLD. In women, a linear inverse association was demonstrated between green and yellow vegetable intake and NAFLD in the final model (Ptrend = 0.04), but odds ratios for any intake category did not reach significance.
- Conclusions: No obesity-independent association was found between fruit or vegetable intake and NAFLD. According to the findings of this study, Japanese do not need to restrict fruit consumption to limit fructose intake as a means of preventing NAFLD.

Additional References

- Comparative Efficacy of Herbal Products on Metabolic Parameters in MASLD: A Systematic Review and Network Meta-Analysis - Gastro Hep Advances
- Foods That Trigger Fatty Liver — Hint: It's Not Fat
- https://www.medscape.com/viewarticle/dapagliflozin-cuts-heart-risk-t2d-advanced-fibrosis-2026a1000mwf?ecd=WNL_mdpls_260707_mscpedit_diab_etid8485865&uac=224091BN&spon=22&impID=8485865

Diet Composition

- Adding salt to foods increases the risk of metabolic dysfunction-associated steatotic liver disease | Communications Medicine
  - Background: Animal studies suggest that excessive salt intake contributes to the onset and progression of MASLD and its related metabolic disorders.
    - In mice, high salt consumption has been shown to exacerbate hepatic steatosis, inflammation, and fibrosis, likely through mechanisms involving oxidative stress, insulin resistance, and lipid metabolism dysregulation
  - This longitudinal study using data from the UK Biobank, found that a higher frequency of adding salt (table salt) to foods is associated with ***increased MASLD risk in a dose-dependent manner***.
    - This association is partially mediated by increased IR & inflammation (increased metabolic and inflammatory biomarkers, including C-reactive protein, triglycerides, and urate)
  - Among individuals with existing MASLD, frequent salt addition is associated with a threefold ***higher risk of advanced liver fibrosis***.
  - These findings suggest that **reducing table salt use represents a simple, modifiable dietary intervention for MASLD prevention**, particularly for genetically susceptible individuals.

Newer Criteria for Alcohol Ingestion – US Dietary Guidelines

https://www.niaaa.nih.gov/alcohols-effects-health/alcohol-drinking-patterns

Decompensated Cirrhosis