MASLD in Type 2 Diabetes Management – Lifestyle

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Pre-Question – which one answer is most correct

Treatment of MASLD

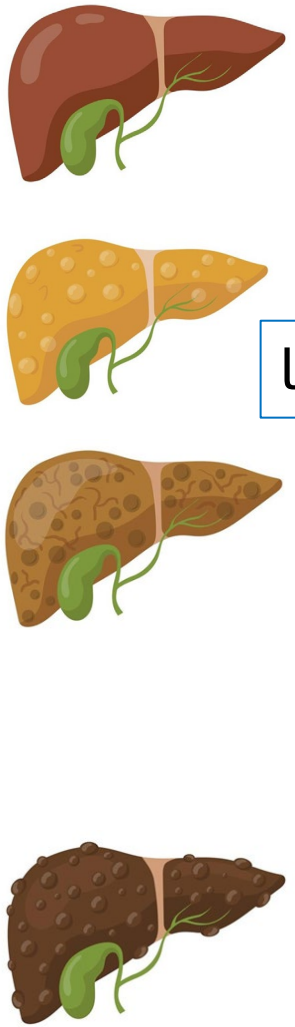
A. Is beneficial only if FIB4 score is elevated (high risk of fibrosis)
B. Can only be done by liver specialists
C. Is primarily needed to prevent liver complications
D. Is beneficial across the entire spectrum of MASLD to reduce CVD, cancer and liver risks

MASLD Recap – Key Points

- MASLD & MASH 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 (CVD is main cause of death in people with MASLD)
- >70% of people with T2D have MASLD and >50% have MASH with 10-20% having significant fibrosis:
  - therefore, the ADA recommends *presuming* the presence of MASLD & *screening for the risk of fibrosis* in all patients (even with normal liver tests) using FIB4 index & secondary NITs
    - Liver Stiffness Measurement (LSM) (e.g., Fibroscan) or ELF score
- Efforts to reverse MASLD are important for all people with MASLD (i.e., most people with T2D) [reduce elevated CVD risk, cancer risk + liver risk]

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

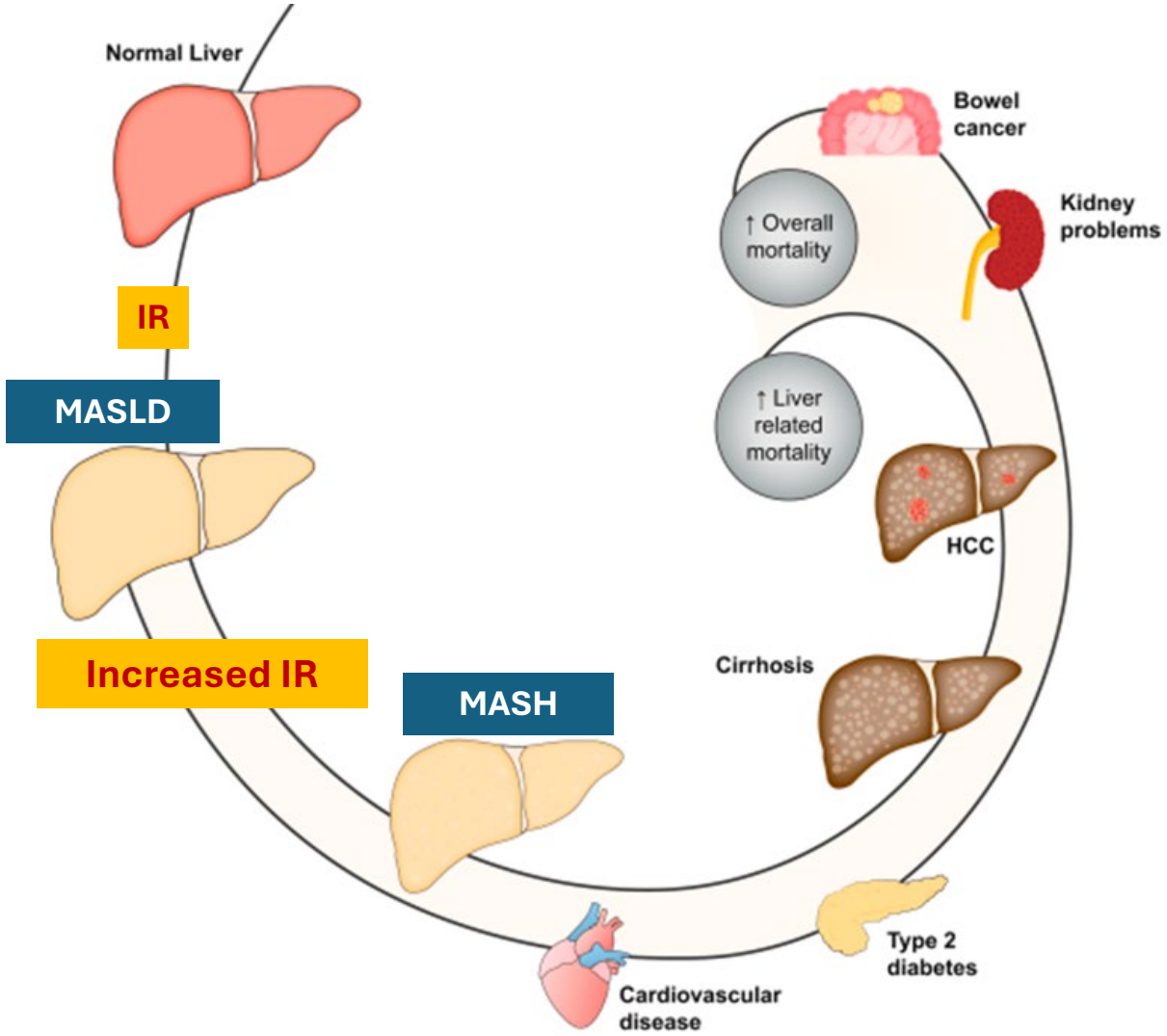
Excess calories, high sat fat, ~high HFCS intake → toxicity:

- 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 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



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

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 Diabetes – weight loss, CVD/renal risk reduction, Steatosis or MASH benefits
  - For Obesity – CVD risk reduction, improvement in MASH parameters/fibrosis
  - Statins – do NOT need to stop
  - For advanced fibrosis F2-F3 – one agent FDA approved – Resmetirom
- **Messaging** & Monitoring

Lifestyle changes are the keystone strategy for managing MASLD

ADA Standards of Care

- 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

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

Lifestyle changes are the keystone strategy for managing MASLD

- *Sustained* lifestyle changes can *prevent MASLD from progressing* and can *reverse* MASLD in the early stages of the disease (even w/ compensated cirrhosis).
  - Need comprehensive, *structured* lifestyle interventions with a dietary, physical, 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
    - ADA: "Obesity pharmacotherapy may assist with weight loss in the context of lifestyle modification if not achieved by lifestyle modification alone"

Diet Composition

- Diets abundant in ***saturated fats, refined carbohydrates, sugar-sweetened beverages, and fructose*** have *been* ***linked to obesity and to MASLD, MASH, and advanced fibrosis***

- Recommend limiting intake of **red & processed meat**
  - Several studies have shown a *harmful* association between high meat intake and MASLD specifically
    - **red** (such as beef, lamb and pork) and
    - **processed meat** (such as hot dogs, salami, sausages)

  High Meat Consumption Is Prospectively Associated with the Risk of Non-Alcoholic Fatty Liver Disease and Presumed Significant Fibrosis - PMC

    - A consistently high consumption of red and/or processed meat was associated with greater odds for **new onset and/or persistence of NAFLD** (OR = 2.12, 95% CI 1.11–4.05, p = 0.022) compared to consistently low consumption.
    - Consistently **high red and/or processed meat consumption** was associated with **4.77-fold** (95% CI 1.36–16.69, p = 0.014) greater odds for **significant fibrosis** compared to consistently low consumption.
    - **Minimizing the consumption of red and/or processed meat may help prevent NAFLD and significant fibrosis.**

Diet Composition continued

- Reducing the intake of **saturated fat** is important - 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** markedly **increased liver fat**, **liver enzymes** and serum lipids

- 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.

Diet Composition continued

- Reducing **refined carbohydrates** & **highly processed foods** is recommended
  - "Higher intake of total *refined carbohydrate* and rice was positively related with MASLD" https://journals.lww.com/ajg/abstract/9900/refined_carbohydrate,_different_staple_foods.1882.aspx
  - *High UPF* intake was associated with an **increased risk of MASLD & higher rates of development of MASH** - incremental in nature, i.e., the more UPF intake, the greater the risk of MASLD
    - Overall poorer diet quality, in addition to high saturated fat and refined grain intake[& added sugars/salt] seem to mediate this association between UPF and MASLD

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

- The intake of **sugar-sweetened beverages** and foods high in **added sugar** should be **reduced** as part of the treatment of MASLD.
  - Evidence from many studies shows an association between added sugars and MASLD, especially added sugar *in the form of sugar-sweetened beverages*
    - **Naturally occurring sugar** refers to the sugar that is an integral constituent of whole fruit, vegetable, and milk products, whereas
    - **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.
      - **Sugar-sweetened beverages** are the leading source of added sugar worldwide.
      - Among children and adolescents, *fructose* consumption was independently associated with NASH (MASH) - reducing sugar consumption in children led to an improvement in liver fat within a few weeks.

Diet Composition continued

- ADA: “Nutrition plans *high in saturated fat and sugar (from sucrose and/or high-fructose corn syrup)* are associated with
  - postprandial hypertriglyceridemia,
  - insulin resistance, and
  - higher risk of MASLD or MASH with fibrosis progression in high-risk individuals.”
- “Increased *fructose* consumption* is associated with *fibrosis severity*, *independent of total caloric intake*” *(Commercial fructose (HFCS) / not fructose in fruit)
- AGA: *“limit or eliminate consumption of commercially produced fructose”*
- 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 metabolized in the liver → lipogenic & increases oxidative stress and inflammation

Diet Composition continued

- **Adequate amounts** of **fruits and vegetables** may *reduce the risk* of MASLD
  - Studies indicate the ***fiber, vitamins and non-vitamin antioxidants*** (such as phenolic compounds, isoflavones, etc.) might protect against MASLD-related liver damage.
  - The best sources of vitamins E and C are **nuts, seeds, plant oils, fruit and vegetables.**
  - Phenolic compounds are abundantly present in foods such as **berries, nuts, coffee, tea and whole grains.**

- **Coffee** (including decaf coffee – most likely the phenols & other compounds that provide benefit – benefits not seen with other caffeinated beverages such as energy drinks)
  - AASLD: Meta-analysis of observational studies suggests that **consuming more than 3 cups of coffee daily may reduce MASLD and liver fibrosis**; however, patients should be advised to avoid adding sweeteners to their coffee.
    - *Clinical Gastroenterology and Hepatology Volume 20, Issue 9, September 2022, Pages 2032-2040.e6*
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC10772480/#sec3 The Influence of Coffee on Reducing Metabolic Dysfunction-Associated Steatotic Liver Disease in Patients With Type 2 Diabetes: A Review. Cureus. 2023 Dec 7;15(12)

And Consider limiting added Salt

published August 2025

- 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.

Dietary Patterns

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

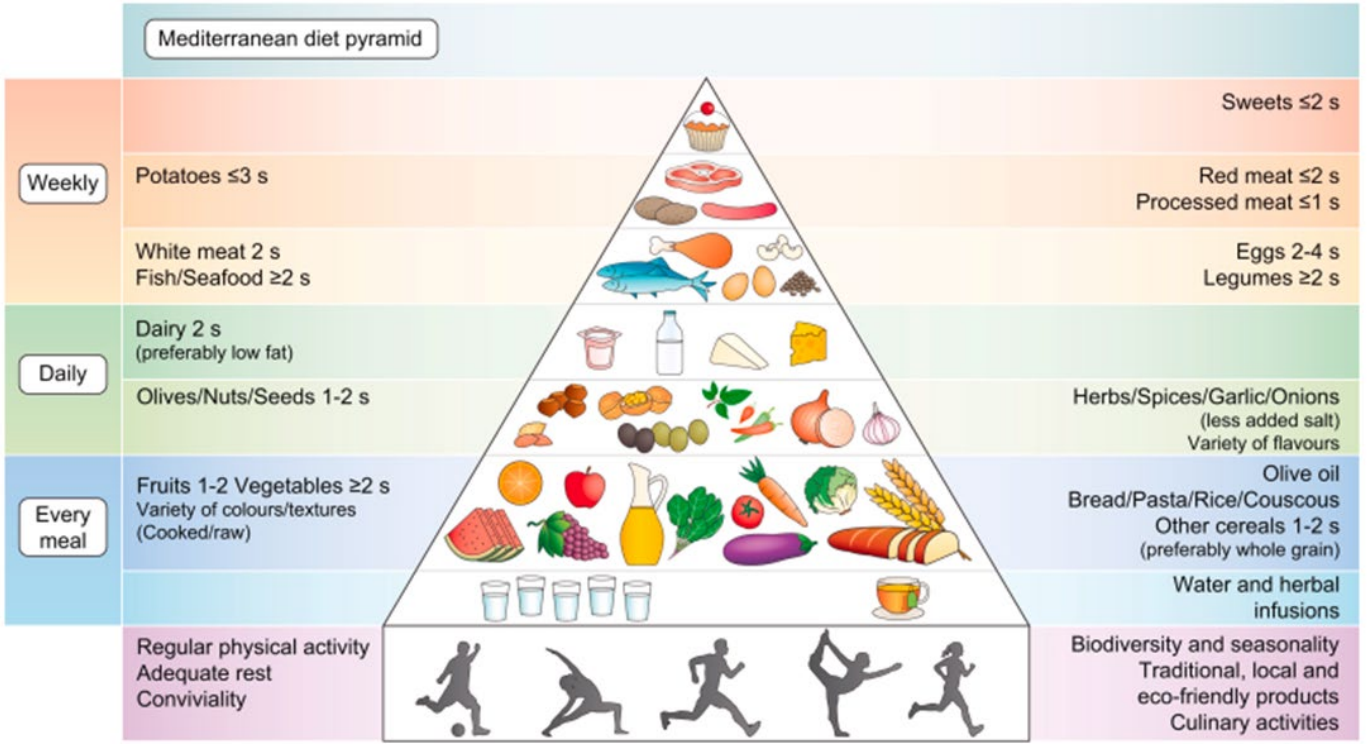
- Dietary patterns represent the overall ***combination of foods*** that can produce ***synergistic* health effects**. One of the most studied dietary patterns is the traditional **Mediterranean diet**
- The Mediterranean diet is frequently recommended due to its beneficial effect on cardiovascular health and on reducing liver fat.
  - In two interventional 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 but limited in refined carbohydrates and saturated fat
  - This diet is 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

ADA Consensus paper on MASLD regarding Eating Patterns

- ADA: “A (*culturally appropriate*) Mediterranean eating pattern (rich in fruits, vegetables, whole grains, and heart healthy fats) is preferred due to the best long-term data on ***beneficial cardiometabolic risk factor reduction*** **and** ***mortality benefit*** and is endorsed in current MASLD guidelines”

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 Plate**] [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.

ADA 2025 Standards of Care: 5.14 In people with prediabetes & diabetes- Eating patterns should emphasize key nutrition principles

inclusion of

- nonstarchy vegetables
- whole fruits
- legumes
- lean proteins
- whole grains
- nuts and seeds
- low-fat dairy or nondairy alternatives

minimize consumption of

- red meat
- sugar-sweetened beverages
- sweets
- refined grains
- processed and ultraprocessed foods

Similar diet changes for diabetes & to help reduce CVD & Non-hepatic Cancer risk – e.g., Colorectal Cancer

Foods to Emphasize Intake of – associated with lower risk of CRC

- Fiber-rich foods: including whole grains and legumes
- Whole grains: such as oatmeal, whole wheat bread, and brown rice
- Calcium-rich dairy products
- Fruits and vegetables: a variety of colorful fruits and vegetables, rich in antioxidants and phytochemicals
- Lean protein: such as fish and poultry, in moderation

Foods to Reduce Intake of – associated with increased risk of CRC

- Red meat: Includes beef, lamb, and pork, especially grilled or high-temperature cooked
- Processed meats: Meats that have been cured, smoked, salted, or preserved with additives. Examples include bacon, lunch meats, hot dogs, and sausages.
- Sugary foods and beverages: Includes sodas, sweetened drinks, and processed foods high in added sugar.
- High-fat diets: saturated and trans fats can contribute to inflammation & cancer risk
- Refined grains: White bread and other refined grains
- Excessive alcohol consumption

The same foods that are “good” or “bad” for MASLD are also related with HCC (liver cancer) risk

Associated with lower risk of liver cancer

- consumption of omega-3 polyunsaturated fat-rich fish
- vegetable intake
- the Mediterranean diet

Associated with increased HCC (liver cancer) risk – high intake of

- red meat
- saturated fat
- cholesterol
- refined sugars
- high-fat dairy products and butter, but not low-fat dairy

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

- Be aware that 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]

Physical Activity/Exercise Recommendations

- Exercise offers **both cardiovascular and hepatic benefits** and should be routinely recommended and tailored to the patient
  - AASLD guidelines recommend that patients be advised *to increase their activity level to the extent possible*
- 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

MASLD Benefits from Weekend Warrior PA Pattern

Weekend warrior and the risk of specific disease: a meta-epidemiology study. BMC Public Health 25, 1414 (2025)

- Conclusion: The WW PA pattern is associated with significant health benefits, including **reduced risks of mortality, cardiovascular diseases, and metabolic syndrome**.
  - This pattern may be a viable alternative for individuals unable to engage in daily physical activity.
- Also shows ***benefit for GI disorders (including MASLD***):
  - At the ***threshold ≥ 150 minutes***, compared with sedentary participants, hazard ratios for any digestive disease were
    - 0.83 for weekend warriors
    - 0.79 for active regulars

"…people should try to get into the habit of doing regular activity; it's more sustainable. But a good alternative, according to this research, is that packing all of that in over the weekend seems to confer benefit. So, all is not lost."

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

- A large retrospective study evaluated the impact of exercise on the development of incident hepatic steatosis and resolution of baseline hepatic steatosis at 5-year follow-up.
- It showed that engaging in **moderate-to-vigorous exercise ≥ 5 times per week (lasting at least 10 min on each occasion)** 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)

- *All levels of physical activity* were *inversely* associated with hepatic fibro-inflammation.
  - Though there appears to be a *dose–response relationship* – more benefit with more activity/exercise

Physical Activity & Exercise

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

- 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 of other comorbid metabolic diseases such as T2D, CVD and obesity.

Research has identified *sedentary behavior* as an independent risk factor for MASLD

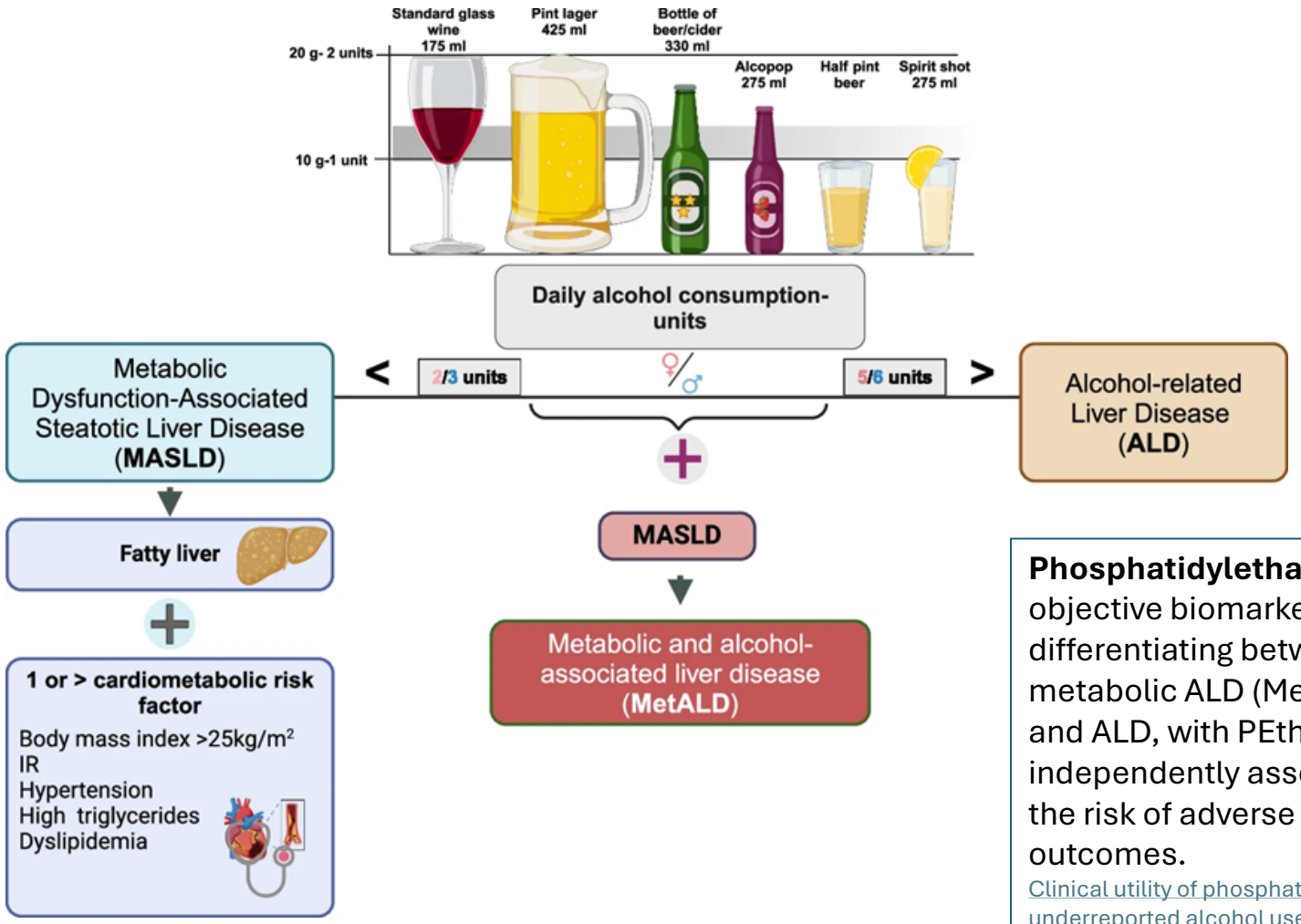
- Sedentary behavior refers to ***"any waking activity characterized by a low level of energy expenditure in a sitting or reclining posture"*** (e.g., watching television, using a computer, travelling by car or bus).
- A 1.15% ***increase in liver fat*** was associated with each additional hour of ***time spent sedentarily*** per day.
  - 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
- 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."*

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

MASLD & Increased Alcohol Intake (MetALD)

Spectrum

- MASLD - <20g (f)- <30g (m) alcohol/day [<2/3 drinks/day]
- **MetALD** (a new category) , describes *individuals with MASLD who consume moderate amounts of alcohol* (between 20-50g/day for females and 30-60g/day for males) - (on spectrum between MASLD & ALD)
- ALD -Alcohol-Associated Liver Disease – in individuals who consume more than 50g/day for females and 60g/day for males [=/> 5/6 drinks/day]



Phosphatidylethanol (PEth) is an objective biomarker capable of differentiating between MASLD, metabolic ALD (MetALD), and ALD, with PEth levels being independently associated with the risk of adverse liver outcomes.

Clinical utility of phosphatidylethanol to detect underreported alcohol use and enhance steatotic liver disease subclassification - Journal of Hepatology

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.

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

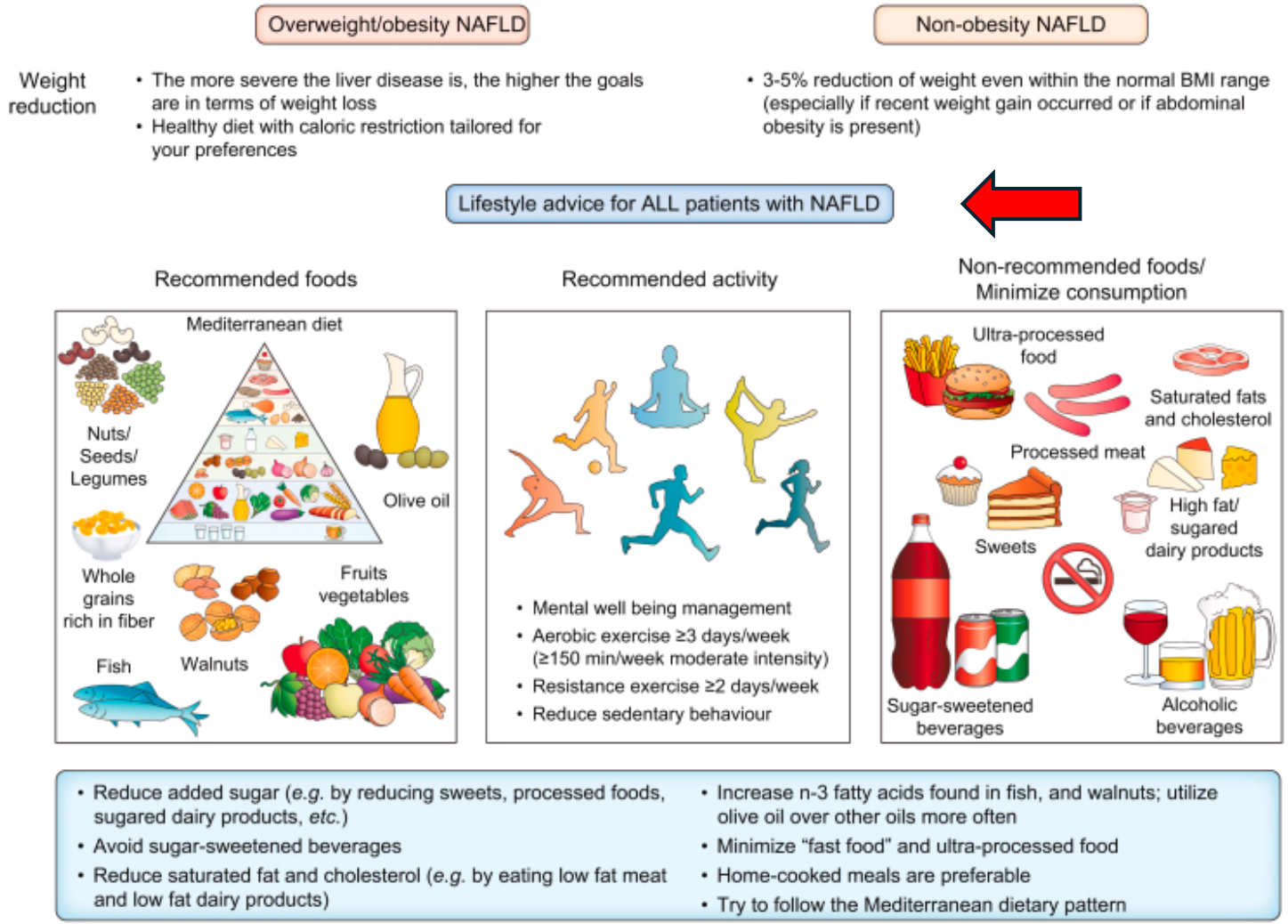
You can check how many units of alcohol you drink per week (and how many calories this adds up to) using the online calculator at (1 unit = 8 g of alcohol):
https://www.drinkaware.co.uk/understand-your-drinking/unit-calculator

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.

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



Summary – Key Points

- Lifestyle interventions are the foundation to preventing & reversing MASLD/MASH & its complications. These include
  - Reducing calorie intake → weight loss
  - 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"
  - Reduce sedentary time & increase physical activity/exercise as much as possible
  - Avoid alcohol consumption & smoking
  - Stress reduction / Sleep

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

The good news →the same lifestyle changes benefit diabetes, CVD risk, cancer risk and liver risk as well as CKD & neuropathy risk

Post-Question – which one answer is most correct

Treatment of MASLD

A. Is beneficial only if FIB4 score is elevated (high risk of fibrosis)
B. Can only be done by liver specialists
C. Is primarily needed to prevent liver complications
D. Is beneficial across the entire spectrum of MASLD to reduce CVD, cancer and liver risks

Post-Question – which one answer is most correct

Treatment of MASLD

A. Is beneficial only if FIB4 score is elevated (high risk of fibrosis)
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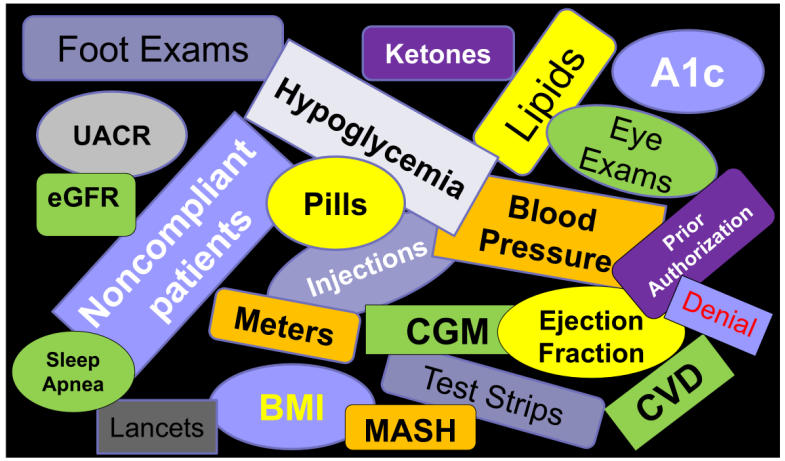
Adding More & More …

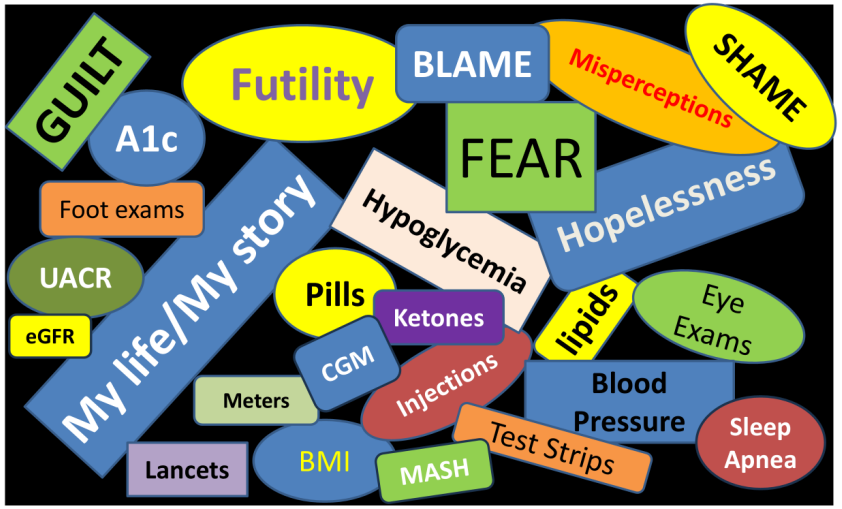
- The ***first American Diabetes Association Standards of Care*** was published in **1989** and provided recommendations based on available evidence at that time.
  - The document was **only four pages long.**
- Since then, it has evolved significantly and now spans **352 pages** in **2025**, covering various aspects of diabetes care

How do we add on addressing & messaging about MASLD without worsening overwhelm?

Diabetes "*Overwhelmus*" – the Care Team Experience



Diabetes Distress – the Patient Experience



Fear of Complications → large contributor to Diabetes Distress
Overwhelm → Distress, Hopelessness, Avoidance, Giving Up

Studies show lack of awareness…

- **Lack of public awareness of MASLD** and how common it is
  - *"When people say, 'I have XYZ cancer,' this has meaning. When people say, 'I have 'NAFLD' ["MASLD"] or 'I have 'NASH'['MASH"], people have no clue what this means"*—80-year-old male with MASH & compensated cirrhosis
- **Lack of awareness among patients at high risk** (such as those with diabetes and obesity)
  - "*Doctor told me 10 years ago I had a little fatty liver, but I never realized it would progress"*
  - In a study examining patients who **received a liver transplant** for **cirrhosis arising from MASLD**, **68.5% were unaware** of their pre-existing MASLD until presenting with new-onset ascites, hepatic encephalopathy, variceal bleeding, and/or thrombocytopenia
- **Lack of awareness among health care professionals**
  - In healthcare records from four large European databases, the estimated prevalence of MASLD (including MASH) was 1.85% in 2015 - noticeably lower than the European prevalence estimate of 23.71% reported in a meta-analysis.
  - Claims data from the US reported an estimated MASLD/MASH prevalence of 5.7% in 2015 - lower than the North American prevalence estimate of 24.13% and NHANES US prevalence estimate of 25.3% [current prevalence is ~40% of adults]

"…even asymptomatic patients can experience more severe forms of MASLD and be at risk of complications. ***Communicating with patients about risk factors for liver disease as well as the risks that can arise from liver disease is therefore essential.***"

The 2025 ADA consensus report aims to address the knowledge gap with a clinical care pathway to manage people with prediabetes or diabetes and MASLD.

"Most individuals and their health care professionals remain unaware of the severe hepatic or extrahepatic health risks associated with MASLD and the need for early identification."

- There is a pressing need for heightened awareness, early diagnosis, and comprehensive management.
  - [MASLD *regression* is most feasible at the earliest stages of fibrosis (i.e. F0-1)]

- Another important consideration is awareness by the health care team about how to best deliver the diagnosis of MASLD as it may affect a person's acceptance of their condition and their ability to manage it.
  - Thus, engaging in a clear, open conversation to explain the clinical implications of MASLD is essential.
  - Understanding and acceptance of their condition often allow for adoption of proactive and problem-solving coping strategies that may reduce psychosocial concerns and support engagement in lifestyle modification and the treatment plan. [Not hopeless – there are things we can do to improve MASLD/reduce risk]

"Literacy [awareness & knowledge] about fibrosis stage and risk of MASLD progression may improve adherence to lifestyle intervention"

Metabolic Dysfunction-Associated Steatotic Liver Disease and Metabolic Dysfunction-Associated Steatohepatitis: The Patient and Physician Perspective. J Clin Med. 2023 Sep 26;12(19)

- Patients at high risk of MASLD, such as those with diabetes and obesity, remain largely unaware of the disease and/or that their conditions are risk factors for MASLD
  - It is important for healthcare professionals to understand that a lack of awareness among patients corresponds with a ***limited level of knowledge of MASLD among the general population.***
  - Also, 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)
- We therefore suggest that when communicating with patients, **clear and simple messages** are critical to help improve their understanding of MASLD.

Challenges for the Care Team regarding MASLD
(based on interviews)

Knowledge:

- Uncertainty regarding
  - screening for MASLD
  - optimal treatment approach
  - dietary recommendations

Hopefully, the updated ADA guidelines & ADA consensus report along with these educational sessions will help –
Please ask for more info as needed
Update of Indian HS SoC in process

Implementation:

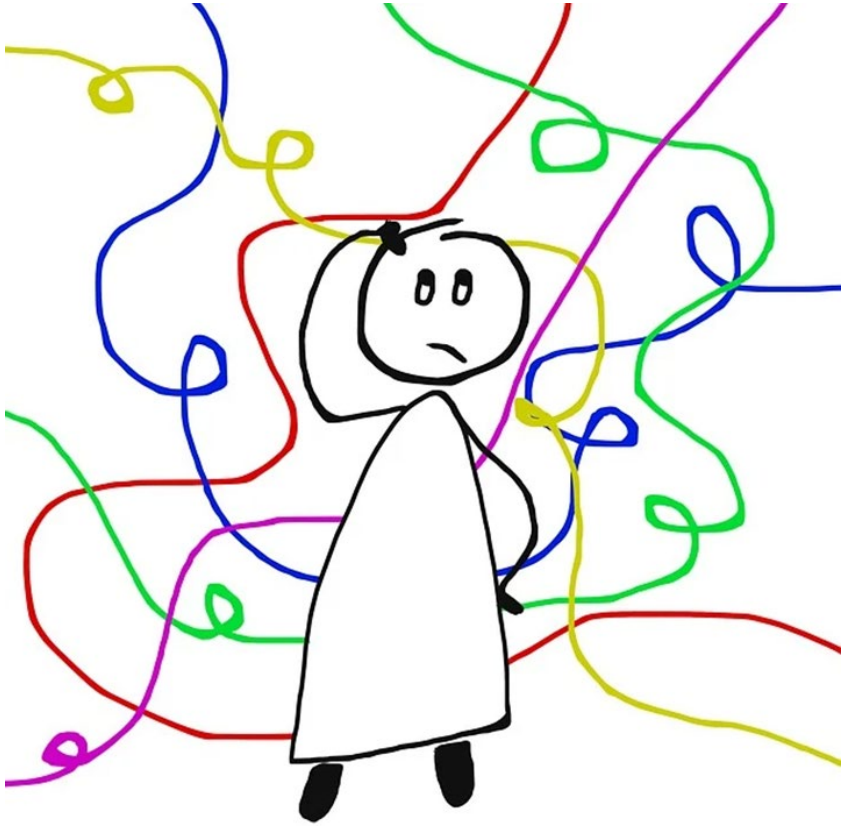
- Need for structured approaches for following-up patients (EMR integration recommended)
- Need for systems in place to provide more standardized care
- Managing and *supporting patients' lifestyle changes* [sustained changes]
  - due to the struggles patients themselves face with adhering to lifestyle interventions
- Lack of support from external services
  - lack of access to dietitians and lifestyle programs
  - lack of access to testing (Fibroscan) & Liver specialty care

ADA 2025 Standards of Care

- “Clinicians *underestimate* the prevalence of at-risk MASH and do not consistently implement appropriate *screening strategies* in people with prediabetes or type 2 diabetes, thus missing a chance to establish an early diagnosis.”
- “This pattern of underdiagnosis is compounded by sparse referral to specialists and inadequate prescription of medications with potential efficacy in MASH.”

- Research shows that 70-80% of PWT2D have MASLD, ~55% have MASH & 10-20% have advanced fibrosis
  - Do you plan to start screening your patients with T2D & Prediabetes for risk of advanced fibrosis?
  - How do you think knowing your patient is at risk for/has MASLD or MASH will impact how you help your patients manage their diabetes?
    - How will you adjust recommendations for lifestyle modifications?
  - How will you explain this to the patient?

Questions, Comments, Clarification



Things to think about:

- How/when will you explain MASLD to patients?
- How will you explain a high-risk score to patients?
- What does your care team need to
  - Add on doing the FIB4 score
  - Do any suggested second step screens (Fibroscan, ELF score)
  - Manage MASLD / MASH

Extra Slides

References

- https://diabetesjournals.org/care/article/48/Supplement_1/S59/157568/4-Comprehensive-Medical-Evaluation-and-Assessment
- Global Consensus Recommendations for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis
- Non-alcoholic fatty liver disease: A patient guideline – PMC
- The Role of Exercise in Steatotic Liver Diseases: An Updated Perspective - Alabdul Razzak - 2025 - Liver International - Wiley Online Library
- https://pmc.ncbi.nlm.nih.gov/articles/PMC11524742/#sec21
- Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) - DynaMedex

References

- Exercise can reduce intrahepatic fat content and serum aminotransferase level even without significant weight loss
- https://www.nature.com/articles/s41598-023-34263-z
- Nam, H. *et al.* Effect of exercise-based interventions in nonalcoholic fatty liver disease: A systematic review with meta-analysis. *Dig. Liver Dis.* https://doi.org/10.1016/j.dld.2022.12.013 (2023).
- Babu, A. F. *et al.* Positive effects of exercise intervention without weight loss and dietary changes in NAFLD-related clinical parameters: A systematic review and meta-analysis. *Nutrients* https://doi.org/10.3390/nu13093135 (2021).

Meat Intake & MASLD

- Several **molecular determinants** might explain the association between meat intake and NAFLD and fibrosis, such as
  - high contents of saturated fats and cholesterol
    - Oxidation of saturated fats and cholesterol induces the production of reactive dialdehydes and isoprostanes, which promote inflammation and fibrogenesis in the liver
  - heme iron, and unfavorable meat products created after specific cooking methods such as advanced glycation end products (AGEs), heterocyclic amines, and other muscle protein oxidation byproducts. Similarly,
    - AGEs and excess iron are also triggers of hepatic stellate cell activation.
  - high meat consumption may promote microbiota dysbiosis, which is implicated in the onset and progression of NAFLD.

High Meat Consumption Is Prospectively Associated with the Risk of Non-Alcoholic Fatty Liver Disease and Presumed Significant Fibrosis - PMC

Studies show patients with NAFLD had significantly higher intake of glucose and fructose than the healthy participants.

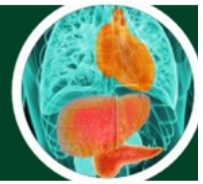
- Fructose is a highly lipogenic substrate mainly because it bypasses the critical regulatory step catalyzed by phosphofructokinase-1 (PFK-1) in glycolysis.
- Fructose intake has been shown to
  - stimulate de novo lipogenesis,
  - block fatty acid oxidation in the liver,
  - increase the synthesis of uric acid from amino acid precursors,
  - induce oxidative stress hypertriglyceridemia, and
  - increase systolic blood pressure, insulin resistance, fibrosis, cirrhosis

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

- Lifestyle changes are currently the keystone strategy for managing MASLD
  - In patients with obesity-associated MASLD, reducing body weight by 5–10% is associated with improvement of MASLD.
  - *Sustained* lifestyle changes can prevent MASLD from progressing and reverse MASLD in the early stages of the disease.
    - In one study of individuals with MASH (33% with type 2 diabetes), lifestyle changes resulting in ≥*10% weight loss* after 52 weeks resolved steatosis in 100% and MASH in 90% and regressed fibrosis in 45% of participants.

- Patients are encouraged to develop methods to control risk factors and implement sustainable lifestyle changes.
  - "*However, comprehensive, structured lifestyle interventions comprising a dietary, physical, and behavioral plan that offer continued support from a multidisciplinary team are critical to helping patients with weight loss and maintenance.*"

Recommended Approaches for the Management of Obesity and T2D in People With MASH



Obesity Management[1]

Weight loss goals	
MASLD with overweight or obesity (BMI 25 to 39.9 kg/m^2)	≥ 5% for steatosis reduction ≥ 7% to 10% for MASH and fibrosis reduction
MASLD with severe obesity (BMI > 40 kg/m^2)	Strongly consider bariatric procedures (also at lower BMI, as per guidelines)
MASLD with healthy BMI (< 25 kg/m^2)	3% to 5% weight reduction, even within the healthy BMI range, to reduce abdominal obesity

→

All individuals—regardless of weight—need a healthy diet and physical activity		
Structured diet and exercise interventions with long-term follow-up	Set achievable goals for increasing activity	Mediterranean diet is the most evidence-based and confers cardiometabolic benefits
Treatment plan tailored to individual preferences, culture, and financial constraints	Minimum of 150 minutes/week of moderate activity	Healthy eating: minimally processed foods
	Combination of aerobic and resistance ("strength") training	

Weight loss

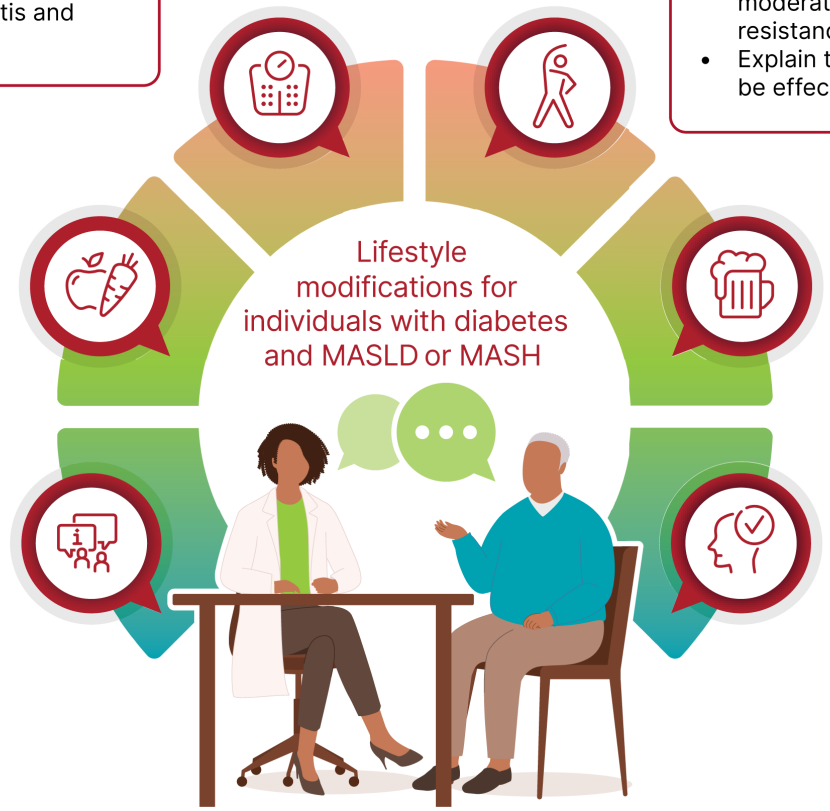
- Encourage calorie deficit that promotes weight loss
- ~5% weight reduction to reduce steatosis
- ~7-10% to reverse steatohepatitis and liver fibrosis

Nutrition (healthy eating)

- Emphasize a high-fiber, whole foods eating pattern with personalized goals, that is low in saturated fat and added sugar
- Individuals should abstain from sugar-containing beverages and minimize consumption of ultraprocessed foods

DSMES

- Support behavior change to address factors complicating diabetes management
- Address lifestyle modification with medical nutrition therapy



Physical activity

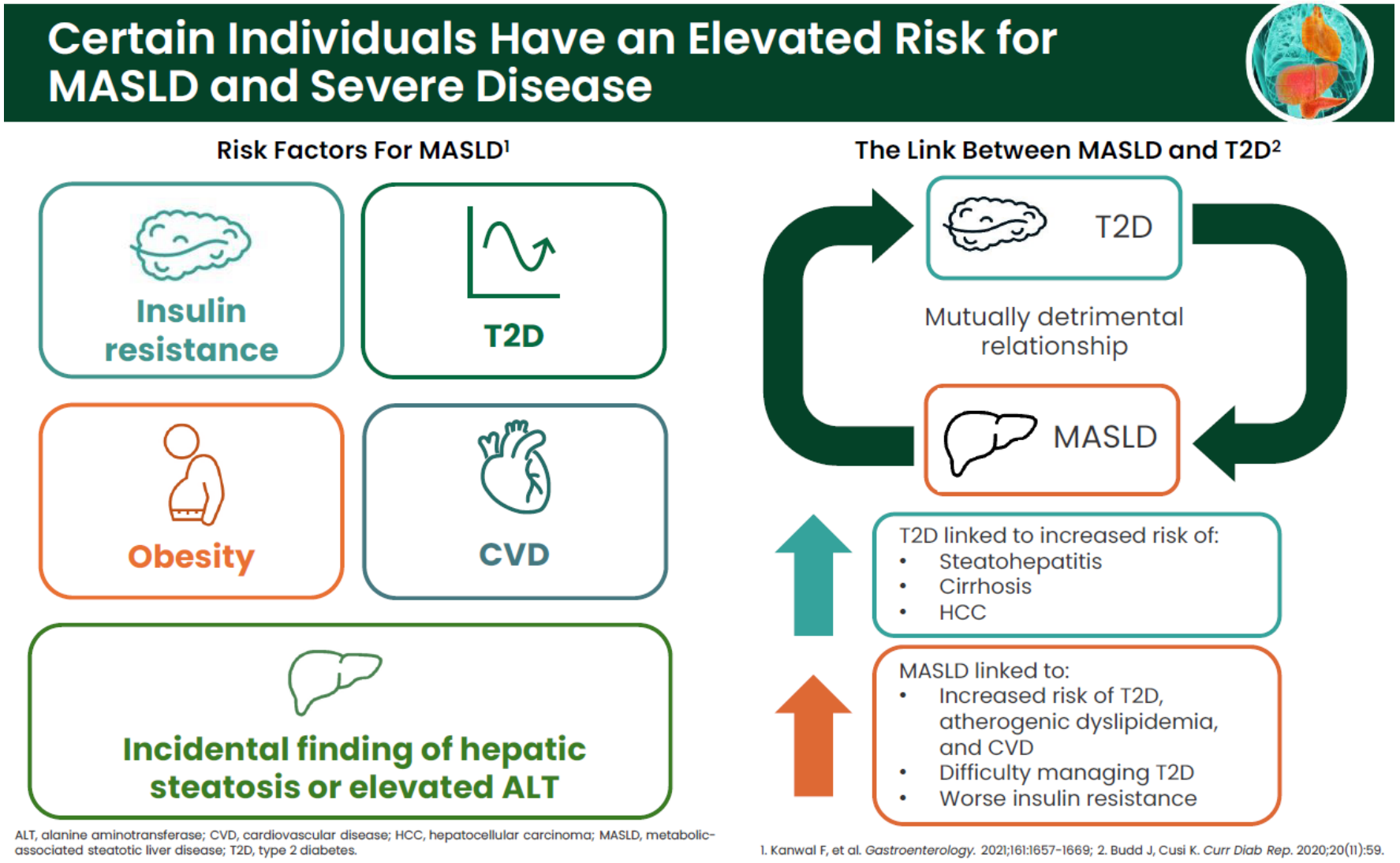
- Discuss goal of performing ≥150 min/week moderate-intensity aerobic activity and resistance activities 2-3 times/week
- Explain that brief sessions (~10 min) can be effective ways to reach goal

Alcohol

- Assess intake at every visit
- Recommend minimizing alcohol intake in MASLD
- Individuals should abstain if moderate fibrosis is present (≥F2)

Behavioral health

- Promote stress reduction via positive health behaviors
- Screen for depression and anxiety at least annually and refer to behavioral health professionals when indicated
- Advise adequate sleep and quitting smoking



ADA 2025 SoC: “Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis.”

Medscape Masters on Alcohol

- Alcohol's True Impact: Rethink Screening and Counseling

Articles on PEth

- Clinical utility of phosphatidylethanol to detect underreported alcohol use and enhance steatotic liver disease subclassification - Journal of Hepatology

- Phosphatidylethanol-guided reclassification of steatotic liver disease subgroups improves prognostic stratification: Greater precision is required - Journal of Hepatology

- Phosphatidylethanol in steatotic liver disease - Journal of Hepatology

Factors affecting PEth formation & measurement following alcohol intake

Diet

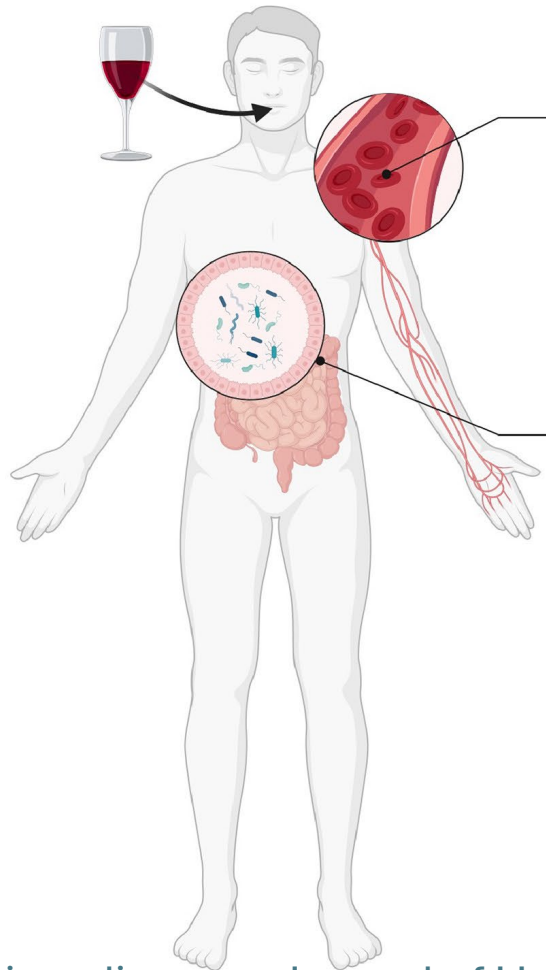
Dietary composition can alter erythrocyte membrane fatty acid content, particularly oleic acid (18:1) and linoleic acid (18:2), subsequently influencing PEth formation.

Body Composition

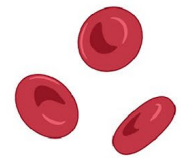
The increased total body water with obesity impacts the peak alcohol blood concentration following alcohol intake and hereby PEth.

Medications

Medication use, notably non-selective beta-blockers such as propranolol, may enhance phospholipase D activity and potentially increase PEth synthesis; however, clinical relevance remains uncertain due to the absence of supportive in vivo data.

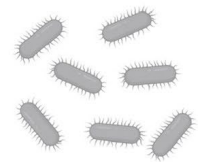


Red Blood Cell Turnover



Variations in red blood cell turnover can affect PEth concentration and assay sensitivity.

Gut Microbiome



Endogenous ethanol production by gut microbiota such as Klebsiella pneumoniae (auto-brewery syndrome) may yield false-positive PEth measurements, though this condition is considered rare.

Genetics

Genetic polymorphism in genes encoding phospholipase D enzymes (PLD1 and PLD2) represent another potential but currently unclarified determinant.

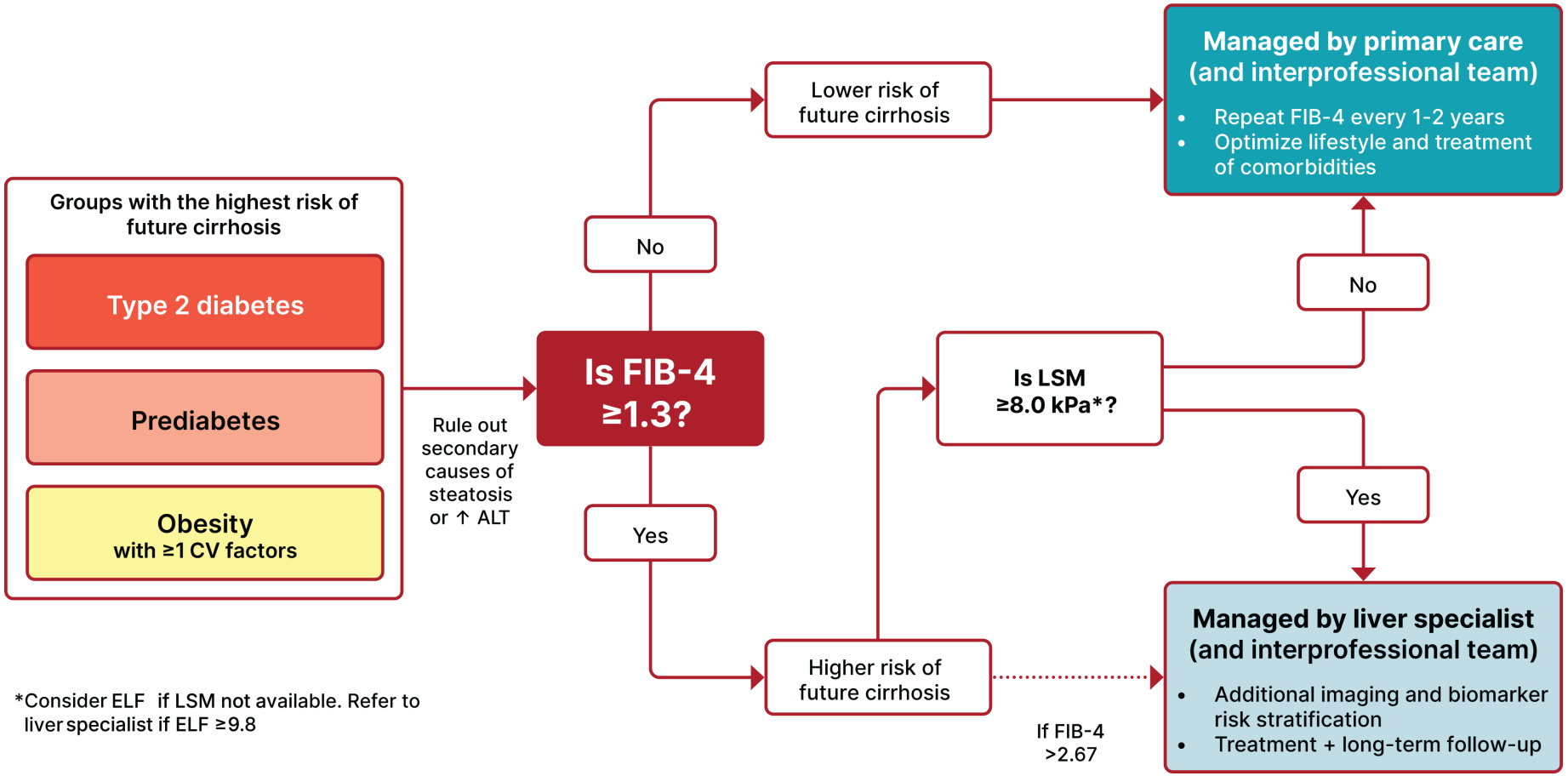
Phosphatidylethanol in steatotic liver disease - Journal of Hepatology

Dr. Richard Johnson -

- Evidence that Obesity and Diabetes are Driven by a Diet-Induced Biological Switch: How it Works and How it Might be Prevented | VuMedi

ADA Recommendations for Referral for Liver

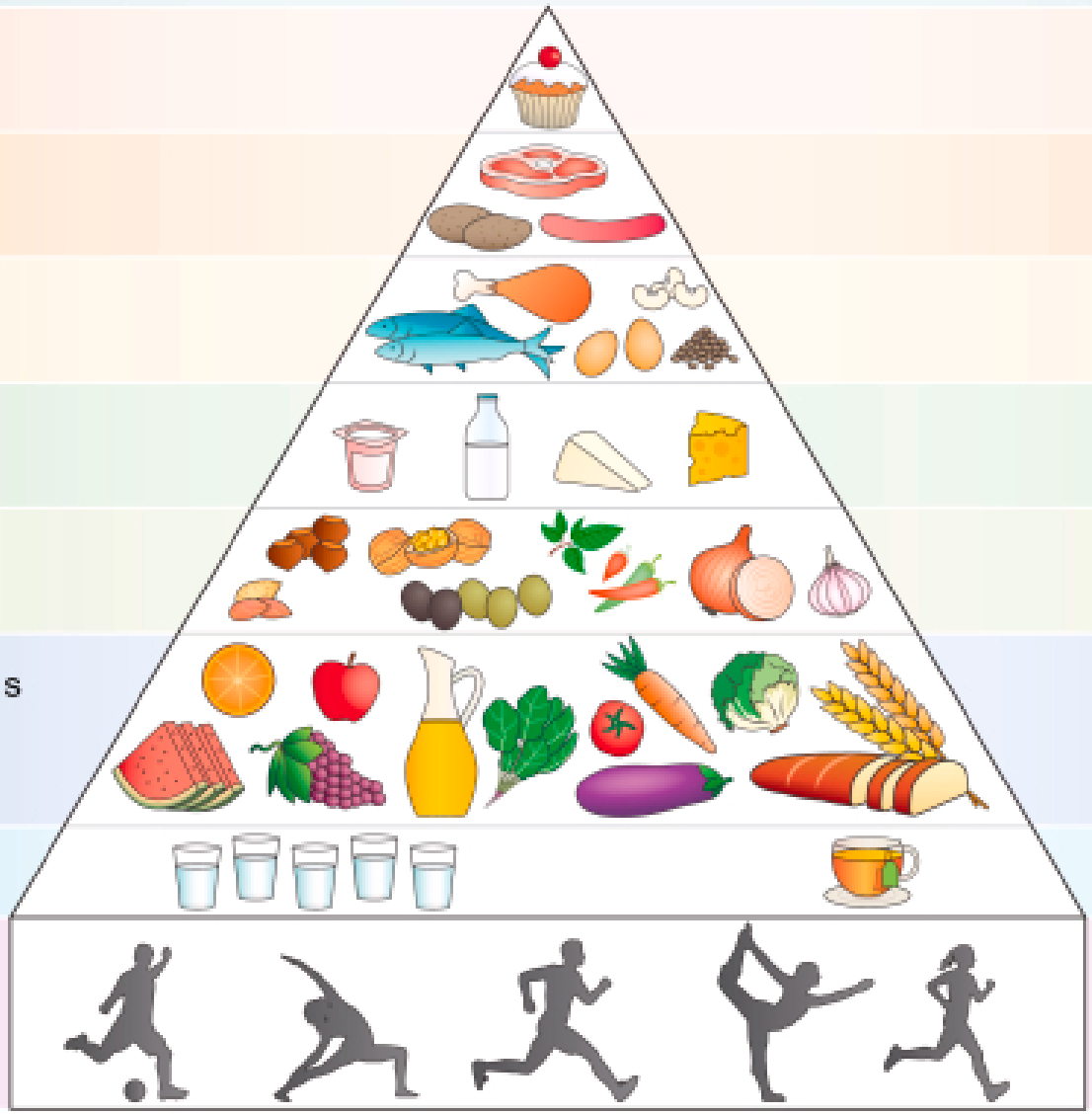
Diagnostic Algorithm for the Prevention of Cirrhosis in People With Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)



Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD). CV, cardiovascular; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement, as measured by vibration-controlled transient elastography. *In the absence of LSM, consider ELF a diagnostic alternative. If ELF ≥9.8, an individual is at high risk of metabolic dysfunction–associated steatohepatitis with advanced liver fibrosis (≥F3–F4) and should be referred to a liver specialist.

American Diabetes Association®

Mediterranean diet pyramid



Weekly

Sweets ≤2 s

Potatoes ≤3 s

Red meat ≤2 s
Processed meat ≤1 s

White meat 2 s
Fish/Seafood ≥2 s

Eggs 2-4 s
Legumes ≥2 s

Daily

Dairy 2 s
(preferably low fat)

Olives/Nuts/Seeds 1-2 s

Herbs/Spices/Garlic/Onions
(less added salt)
Variety of flavours

Every meal

Fruits 1-2 Vegetables ≥2 s
Variety of colours/textures
(Cooked/raw)

Olive oil
Bread/Pasta/Rice/Couscous
Other cereals 1-2 s
(preferably whole grain)

Water and herbal infusions

Regular physical activity
Adequate rest
Conviviality

Biodiversity and seasonality
Traditional, local and eco-friendly products
Culinary activities

Sedentary behaviour refers to any waking activity characterised by a low level of energy expenditure and a sitting or reclining posture (*e.g.* watching the television, using a computer, travelling by car or bus).

Physical activity is any body movement that requires you to use more energy than resting, and it incorporates many of the activities carried out as part of the daily routine *e.g.* housework, walking up/downstairs, gardening.

Exercise is a subcategory of physical activity in which planned, structured and repetitive movements are performed to maintain or improve fitness.

Aerobic exercise ("cardio") strengthens your heart and lungs and improves the way your body uses oxygen. It normally uses the large muscle groups, is rhythmic in nature and can be maintained for at least 10 minutes. Examples include brisk walking, swimming, cycling, dancing.

Resistance exercise strengthens the muscles and improves muscle tone and bulk. It includes any exercise where the muscles contract against a force and can include lifting weights, use of resistance bands or pushing against your body weight.

- Overweight and obesity are important risk factors for NAFLD/NASH, mainly when the calorie overload exceeds the capacity of your fat tissue to store the excess energy you have taken up.

- Lifestyle modification, which includes changes in dietary pattern and composition as well as increasing physical activity levels, is the first step and cornerstone of NAFLD management.

- Achieving sustained weight loss can improve NAFLD across the disease spectrum. The amount of weight loss is the most important determinant of improvement, regardless of the type of diet that has been followed.

- The Mediterranean diet is one of the most studied and beneficial. Even without weight loss, a healthier food pattern, especially the Mediterranean diet, can result in NAFLD improvement.

- Added sugars, especially fructose, play a major role and should be avoided as much as possible. A reasonable fruit consumption of 1-3 fruits per day, should not be further restricted and should be a part of a balanced diet and a source for fiber and vitamins.

- Decreasing overall sedentary time and breaking up sedentary time throughout the day is a useful treatment strategy for all people with NAFLD/NASH.

- Any increase in physical activity is useful, even without weight loss. In order to induce significant changes, over 150 min/week of moderate intensity physical activity over 3-5 sessions including a combination of aerobic ("cardio" *e.g.* brisk walking, cycling, swimming) and resistance ("strength" *e.g.* lifting weights) training are recommended.

- Both the changes in diet and physical activity/exercise levels need to be tailored to your individual needs, preferences and abilities in order to find a way of living that you enjoy and can sustain in the long term.

https://pmc.ncbi.nlm.nih.gov/articles/PMC11058902/#Sec6

- Significantly increased mortality risk over 20 years of follow-up:
  - the presence of steatosis (HR 1.71)
  - MASH without fibrosis (HR 2.14)
  - non-cirrhotic fibrosis (HR 2.44)
  - cirrhosis (HR 3.79)