An Introduction to MASLD in Type 2 Diabetes

Part 1

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Case – Cynthia

- 64-year-old female returns for a follow-up appointment regarding type 2 diabetes (T2D) [dx 10+ years ago after several years of pre-diabetes]
- In the interim she had presented to the local ED with upper GI bleeding and was diagnosed with esophageal varices due to hepatic cirrhosis
  - She is still in disbelief as well as angry – she has never used alcohol and has never had abnormal liver tests. No one ever mentioned a risk of cirrhosis.
  - She has been referred for consideration of liver transplant & needs help with her diabetes management & the preparation for the transplant – she is overwhelmed
  - Her BMI has always been around 24 but she has prominent abdominal/visceral adiposity. Years ago, after having a CT scan for a possible kidney stone she was told she had a "fatty liver" and not to worry about it
  - Her evaluation for transplant reveals a small thyroid cancer in the right thyroid lobe and a renal cell carcinoma in the left kidney – both are resected, and she proceeds to transplant preparation
- Have you had a patient with a similar experience of "cirrhosis out of nowhere"?
  - Is the occurrence of the two cancers related to her condition?

Why the Current Focus on MASLD?
Alarming Impact & Trends

- **Increased awareness of the harms** - not *"just fatty liver"*: MASLD increases the risk of developing ***adverse liver outcomes***, (including cirrhosis, liver failure, and Hepatocellular Carcinoma (HCC) & has become the leading reason for liver transplantation) along with increases in *a broad spectrum of* ***additional comorbidities*** *i*ncluding
  - progression from prediabetes to type 2 diabetes
  - increased Insulin Resistance & more difficulty managing diabetes
  - Increased development of cardiovascular disease (CVD)
  - extrahepatic malignancies (such as colorectal, biliary/pancreatic, endometrial/GU, breast & thyroid)
- MASLD increases the **risk of all-cause [premature] mortality**
  - *the highest risk of mortality with MASLD is in people with* ***type 2 diabetes*** (4.0-fold increased risk)
- **Increased occurrence**: The number of people with MASLD has dramatically increased worldwide, becoming the most common cause of chronic liver diseases –
  - MASLD has increased in parallel with the escalating rates of obesity, type 2 diabetes (T2D), and metabolic syndrome globally
- The global prevalence of MASLD has risen from 25.3% (1990–2006) to 38.2% (2016–2019) to more recent estimates ~45% of individuals
  - In North America, the 2017–2018 NHANES reported an overall prevalence of 56.7%
  - Rates are much **higher in people with type 2 diabetes** with estimated prevalence of >65 - 70% (estimated at > 80% if overweight/obese)
- **Increased options for treatment:** increased understanding what contributes to the development and progression of MASLD and availability of new therapeutics
  - preventing, slowing progression or even reversing – need for action

Learning Objectives

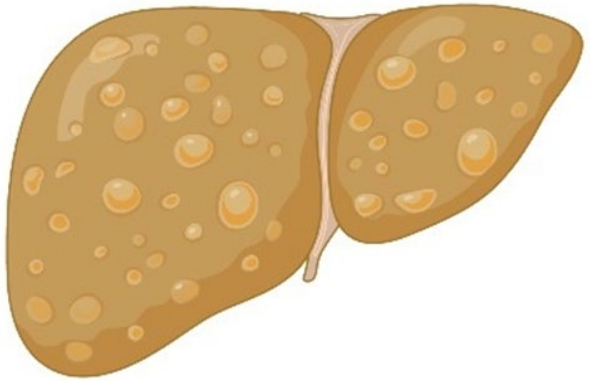
With the focus on people with type 2 diabetes (T2D):

1. Define MASLD & MASH
2. Identify risk factors for developing MASLD & MASH and the risks of MASLD & MASH
3. Apply the updated ADA Standards of Care criteria to screen people with T2D for advanced fibrosis

2023 Terminology Update

Metabolic Dysfunction – Associated Steatotic Liver Disease (**MASLD**) &

Metabolic Dysfunction- Associated Steatohepatitis (**MASH**)



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Nonalcoholic Fatty Liver Disease (**NAFLD**)

& Nonalcoholic Steatohepatitis (**NASH**)

MASLD definition

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined as the presence of **hepatic steatosis** (excess triglyceride storage in the liver) in conjunction **with at least 1 cardiometabolic risk factor***

*cardiometabolic risk factors associated with *insulin resistance*

- obesity/central (visceral) obesity
- prediabetes/diabetes (hyperglycemia)
- hypertension
- atherogenic dyslipidemia (elevated Triglycerides, low HDLc)

- Having multiple risk factors adds risk
- Family history of MASLD is a risk factor

- This is in the ***absence*** *of ongoing or recent consumption of* ***significant amounts of alcohol*** (defined as ingestion of < 21 standard drinks/<210 grams per week in men [<3 drinks/d] and <14 standard drinks/<140 grams per week [<2 drinks/d] in women)

The most common liver disease in the United States & globally
Potentially reversible & preventable

Definitions MASLD, MetALD vs NAFLD

- While NAFLD and MASLD generally refer to the same condition, a key distinction is that a *NAFLD diagnosis excludes other liver diseases*, whereas *MASLD is based on affirmative criteria*.
  - This affirmative method of diagnosis **now allows for the *coexistence of other liver diseases with MASLD***, such as autoimmune or viral hepatitis
    - The evaluation may need to test for other liver diseases, especially if persistent elevated liver tests

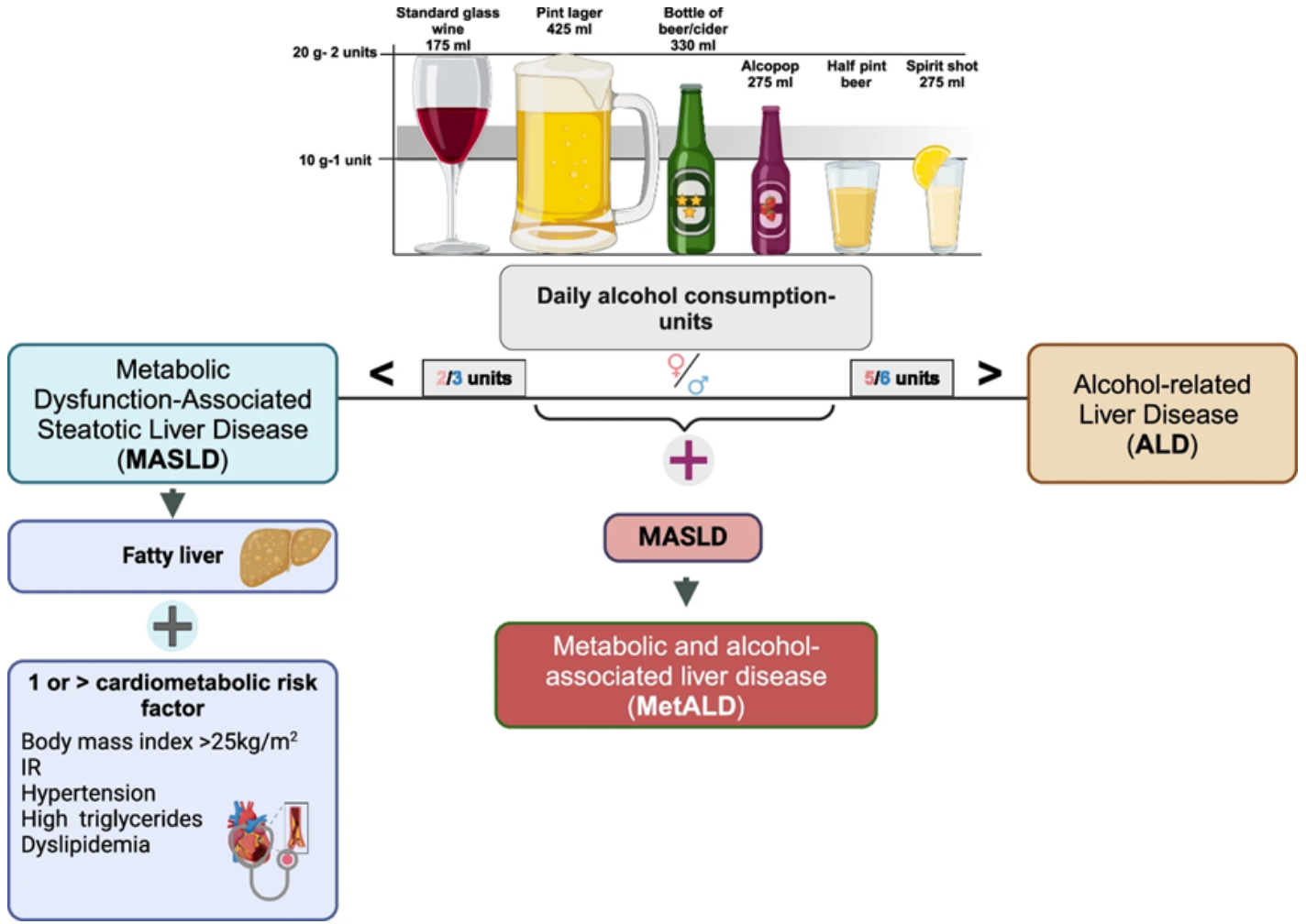
- The new nomenclature also introduces an additional diagnostic category, **Metabolic Dysfunction and Alcohol-associated Liver Disease (MetALD)**, this applies to individuals *meeting MASLD criteria with concurrent excessive alcohol intake*.
  - (MetALD) is defined as steatotic liver disease fulfilling the MASLD criteria in conjunction with an average alcohol intake of 20–50 g/day in women and 30–60 g/day in men (140–350 g/week in women and 210–420 g/week in men)

- **Alcohol-Associated Liver Disease (ALD)-** liver disease when alcohol intake is >50g/d in women or >60g/d in men

MASLD & Increased Alcohol Intake (MetALD)

Spectrum

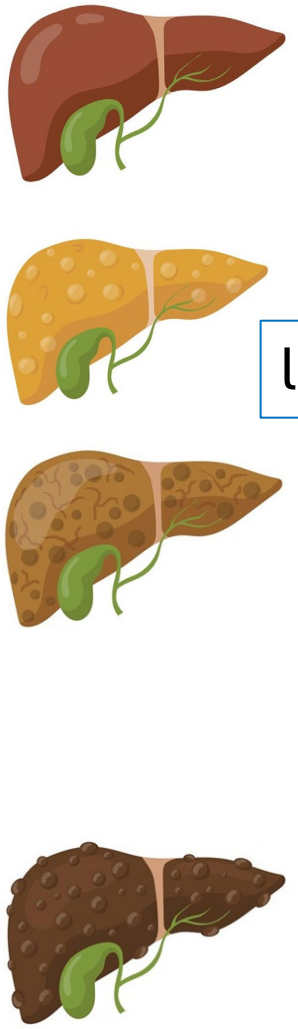
- MASLD - <20g (f)- <30g (m) alcohol/day [<2/3 drinks/day]
- **MetALD** (a new category) , describes *individuals with MASLD who consume moderate amounts of alcohol* (between 20-50g/day for females and 30-60g/day for males) - (on spectrum between MASLD & ALD)
- ALD -Alcohol-Associated Liver Disease –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



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

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

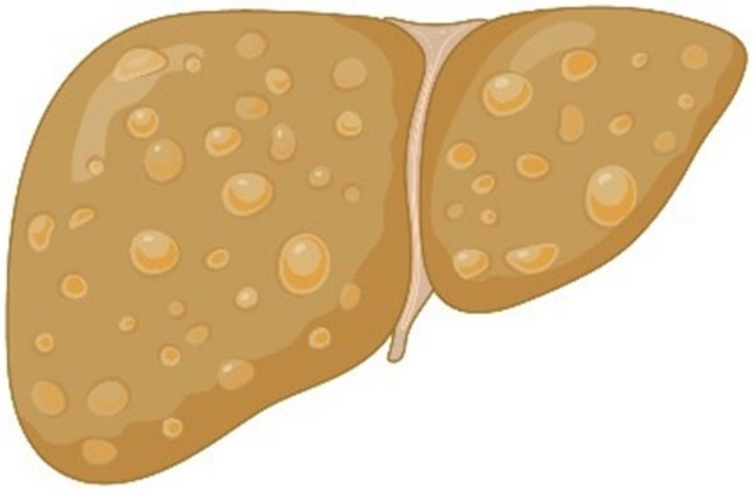


lipotoxicity

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

MASLD is associated with Increased Insulin Resistance & Increased CVD risk



Cardiovascular disease is reported to be the ***most common cause of mortality*** in patients with MASLD

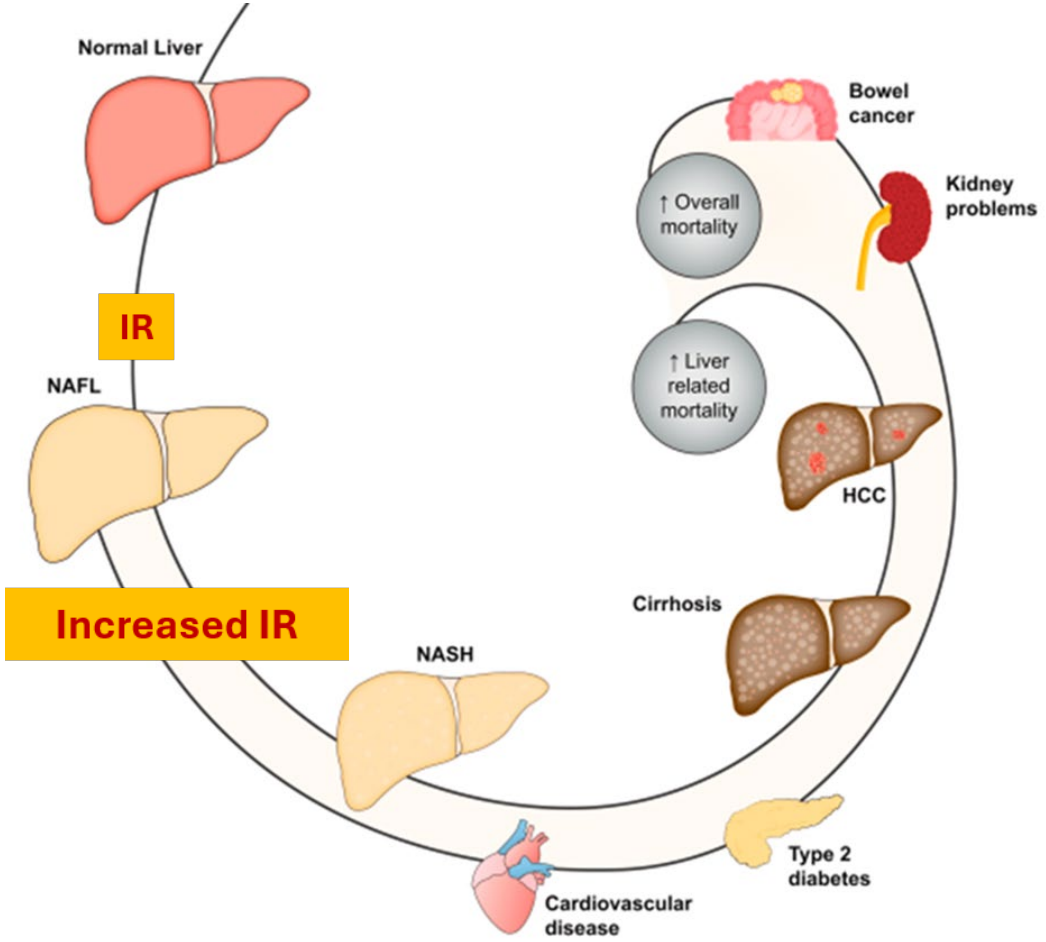
Insulin Resistance

Inflammation
Harmful Cytokines & Chemokines
Oxidate Stress
Endothelial Dysfunction
Plaque Formation

MASLD adds Additional Risk on to Risk

- Individuals with MASLD also are at a greater risk of developing **extrahepatic cancer** including
  - colorectal
  - breast
  - gastric
  - pancreatic & biliary
  - prostate
  - uterine
  - esophageal cancer
  - urinary/kidney
  - thyroid

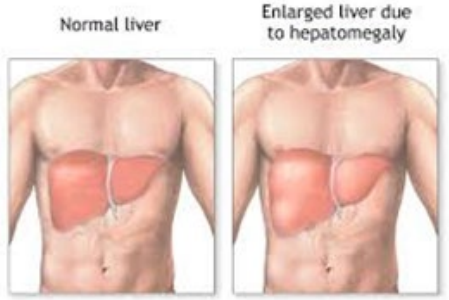
- Emerging evidence suggests that MASLD increases the risk of **CKD** in people with type 2 diabetes, particularly when ***liver fibrosis*** is present



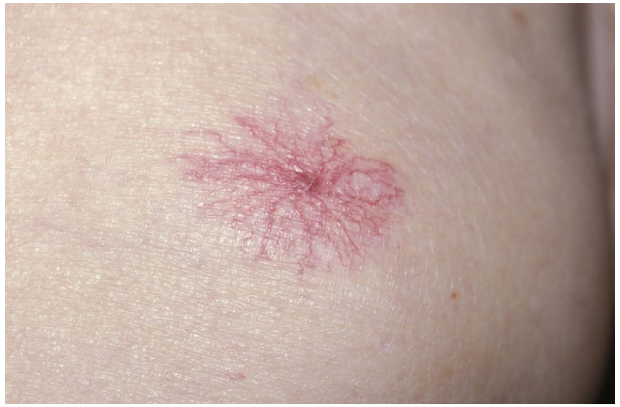
Diagnostics (Basel) 2020 Nov 7;10(11)

MASLD Signs & Symptoms

- Usually NO symptoms (until cirrhosis)
  - Occasional RUQ pain, abdominal fullness
  - *Fatigue* may be more common
- On exam may have an enlarged liver (hepatomegaly)
- Liver tests can be abnormal but are often *normal*
  - Use ALT or AST >30 for men and >20 for women as abnormal
- Fatty infiltration of the liver or “nodular” liver (cirrhosis) might be detected incidentally on other imaging
  - E.g., abdominal US, CT scan or MRI



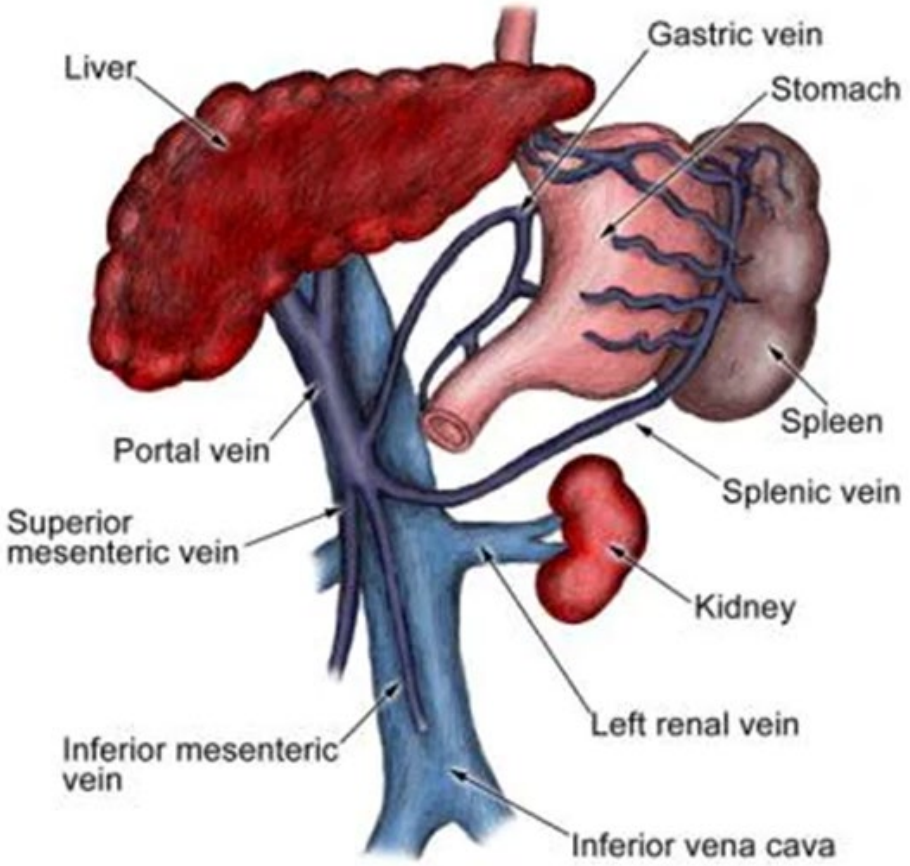
- Cirrhosis & decompensated cirrhosis
  - reduced platelets, AST/ALT ratio >1
  - hepatocellular carcinoma (HCC)
  - portal hypertension & splenomegaly
  - jaundice, spider angiomas, pruritis, sarcopenia
  - ascites, encephalopathy, GI bleeding (varices)



Compensated Cirrhosis

- **Cirrhosis** of the liver is a condition where ***healthy liver tissue is replaced by scar tissue***, hindering the liver's ability to function properly, and can lead to liver failure.
- In compensated cirrhosis, the liver is scarred, but it's ***still functioning at a level that allows the body to cope with the damage***.
  - People with compensated cirrhosis **may not experience any symptoms**, or they might have mild, **non-specific symptoms like fatigue or weight loss**.
  - This stage is characterized by the ***absence of complications*** like ascites (fluid buildup in the abdomen), variceal hemorrhage (bleeding from swollen veins), hepatic encephalopathy (brain dysfunction), or jaundice (yellowing of the skin and eyes).
- While compensated cirrhosis means the liver is still functioning well enough to mask the damage, the primary issue is that it's a **silent stage**, meaning there are no obvious symptoms, which ***can delay diagnosis and treatment until the condition progresses to decompensated cirrhosis***.

Decompensated Cirrhosis "Liver Failure"/ ESLD



- Portal Hypertension
  - Esophageal varices – hemorrhage
  - Splenomegaly – low platelets
  - Ascites / edema
- Reduced liver cell function
  - Manufacturing/clearing functions
    - Jaundice / high bilirubin
    - Low albumin & other proteins
      - Muscle wasting
      - Bruising (clotting factors)
    - Hyperestrogenism /male hypogonadism
    - Reduced thrombopoietin (TPO)
      - Reduced Bone Marrow production of platelets
  - Increased risk Hepatocellular Ca

Hepatocellular Carcinoma

- Cancer that develops from liver cells (hepatocytes) (a primary tumor of the liver)
- Usually develops on background of chronic liver disease and cirrhosis – most patients have cirrhosis
  - **MASLD is now a leading cause of HCC worldwide**, especially in western countries
  - A significant proportion of ***MASLD-related HCC* cases** (around one-third) occur in individuals at ***earlier stages of fibrosis*** **(i.e., without liver cirrhosis)** compared to other causes
- Hepatocellular carcinoma (HCC) is now the fifth most common cause of cancer worldwide & a major cause of cancer death - Five-year survival of HCC is 18%
  - Surgical resection if the tumor is small - high recurrence rate
  - Liver transplantation is associated with the removal of tumors and the potential for cure.
    - requires early detection – recommend every 6-month liver US & AFP level if cirrhosis present
    - MASLD top reason for transplant due to HCC
- Patients with paraneoplastic features of HCC could present with
  - hypoglycemia (not due to extra Insulin – due to tumor glucose consumption/IGF2)
  - hypercalcemia (usually due to PTHrp production – hypercalcemia of malignancy)
  - erythrocytosis

Type 2 Diabetes is a risk factor for MASLD & a risk factor for MASH and Fibrosis

Risk Factors for MASLD

- Elevated body weight, such as with overweight or obesity
- Increased waist circumference
  - Visceral adiposity
- Insulin resistance, such as with:
  - Elevated fasting serum glucose levels
  - Elevated 2-hour post-load glucose levels
  - **Diabetes mellitus type 2**
  - Metabolic syndrome
  - Elevated blood pressure
  - Elevated plasma triglyceride levels

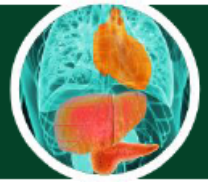
Risk Factors for Fibrosis/Cirrhosis

- Insulin resistance
- **Diabetes**
- Obesity (especially BMI $\geq$ 40)
- Weight gain > 5 kg (11 lbs)
- Hypertension

60 - 70% of people with T2D have MASLD (Higher if also overweight/obese)

~35% of people with T2D have MASH with or without fibrosis

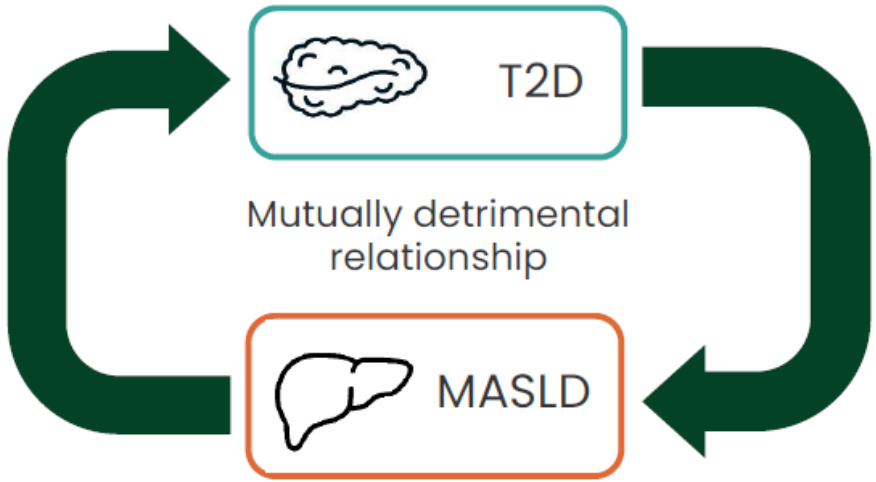
Certain Individuals Have an Elevated Risk for MASLD and Severe Disease



Risk Factors For MASLD[1]

- Insulin resistance
- T2D
- Obesity
- CVD
- Incidental finding of hepatic steatosis or elevated ALT

The Link Between MASLD and T2D[2]



T2D linked to increased risk of:
- Steatohepatitis
- Cirrhosis
- HCC

MASLD linked to:
- Increased risk of T2D, atherogenic dyslipidemia, and CVD
- Difficulty managing T2D
- Worse insulin resistance

ALT, alanine aminotransferase; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; MASLD, metabolic-associated steatotic liver disease; T2D, type 2 diabetes.

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

ADA 2026 SOC
Screen for “at risk” MASH not for MASLD (“fatty liver”)

- *Presume* adult patients with T2D have MASLD – screen for risk of fibrosis
- 4.22a Screen adults with type 2 diabetes or with prediabetes, particularly those with obesity or other cardiometabolic risk factors or established cardiovascular disease, for their ***risk of having or developing cirrhosis*** related to metabolic dysfunction–associated steatohepatitis (MASH) using a calculated **fibrosis-4 index (FIB-4)** (derived from age, ALT, AST, and platelets [mdcalc.com/calc/2200/fibrosis4-fib-4-index-liver-fibrosis]), ***even if they have normal liver enzymes***.

- In the U.S., between 12% and 20% of people with type 2 diabetes have **“at-risk” MASH** (i.e., steatohepatitis with ***clinically significant fibrosis*** [≥F2] and are at risk for cirrhosis)

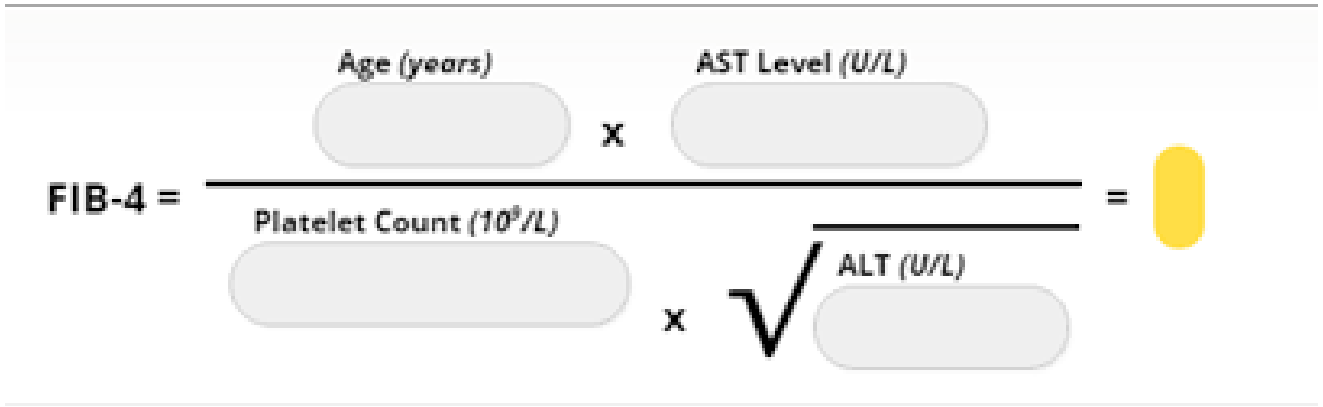
Determine the Risk of Fibrosis

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

- **Liver biopsy** remains the gold standard to evaluate liver fibrosis.
  - Invasive – pain, bleeding & infection risk (sampling of one site in liver)
  - Limited availability

- Use of **non-invasive tests (NITs)** to *estimate risk* of significant or advanced fibrosis (provide a *probability*)
  - FIB4 – Fibrosis 4 Index
  - Liver Stiffness Measurement (LSM)
    - VCTE - Vibration-controlled Transient Elastography (Fibroscan)
  - ELF score - Enhanced Liver Fibrosis score

FIB4 formula



Less reliable at ages <35 or >65

Cut-off values for MASLD

- <1.3 unlikely to have significant fibrosis
  - If age 65+ use < 1.9-2.0*
- >2.67 – high risk of significant (advanced) fibrosis
- >1.3 and <2.67 – additional assessment of risk
  - If age 65+ use >1.9-2.0*

ADA Consensus paper recommends using 1.3 not 2.0 for PwT2D Age ≥ 65

*not all agree with <2.0 – reduces NPV meaning can miss people at risk & in need of additional assessment)

Liver Fibrosis & Low Platelet Count (PTC)

- The liver plays a crucial role in producing **Thrombopoietin (TPO),** a hormone that stimulates the bone marrow to produce platelets.
  - ***In liver fibrosis, the liver's ability to produce TPO is impaired***, leading to a decrease in platelet production in the bone marrow and consequently, to a reduced number of platelets in the peripheral blood of patients with advanced-stage liver disease.

- ***Longitudinal decrease in platelet counts as a surrogate marker of liver fibrosis*** World J Gastroenterol. 2020
  - This study indicates that a ***progressive decline in platelet counts***, within the ***normal range, is associated with a gradual increase in fibrosis scores***, starting up to 15 years before the diagnosis of cirrhosis.
  - The mean PTC decreased from 240,000/μL to 190,000/μL up to 15 years prior to cirrhosis diagnosis compared to controls whose PTC remained stable around the values of 240,000/μL.

- Thrombocytopenia (platelet count < 150,000/μL)
  - Often with cirrhosis, with splenomegaly

If Intermediate FIB-4 Result – Additional Assessment – ADA Standards of Care

- 4.23 Adults with type 2 diabetes or prediabetes with a FIB-4 ≥1.3 should have ***additional risk stratification*** by
  - liver stiffness measurement (LSM) with transient elastography,

    or, if unavailable,
  - the enhanced liver fibrosis (ELF) test. B

- Guidelines:

> A value of >2.67 confers a high risk of having advanced fibrosis (F3–F4), and referral to the liver specialist is warranted without additional testing.

- Practice: Option to obtain additional NIT(s) to expedite care & more accurately stratify risk
  - There usually is a fairly long wait to see a liver specialist and the first thing they will do is order VCTE (e.g., Fibroscan) and/or ELF, so it expedites care to order one or both while awaiting referral

Limitations to Reliability of FIB4 Index

- Age ≤35 – FIB4 underestimates risk of fibrosis
- Age ≥ 65 – FIB4 overestimates risk

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

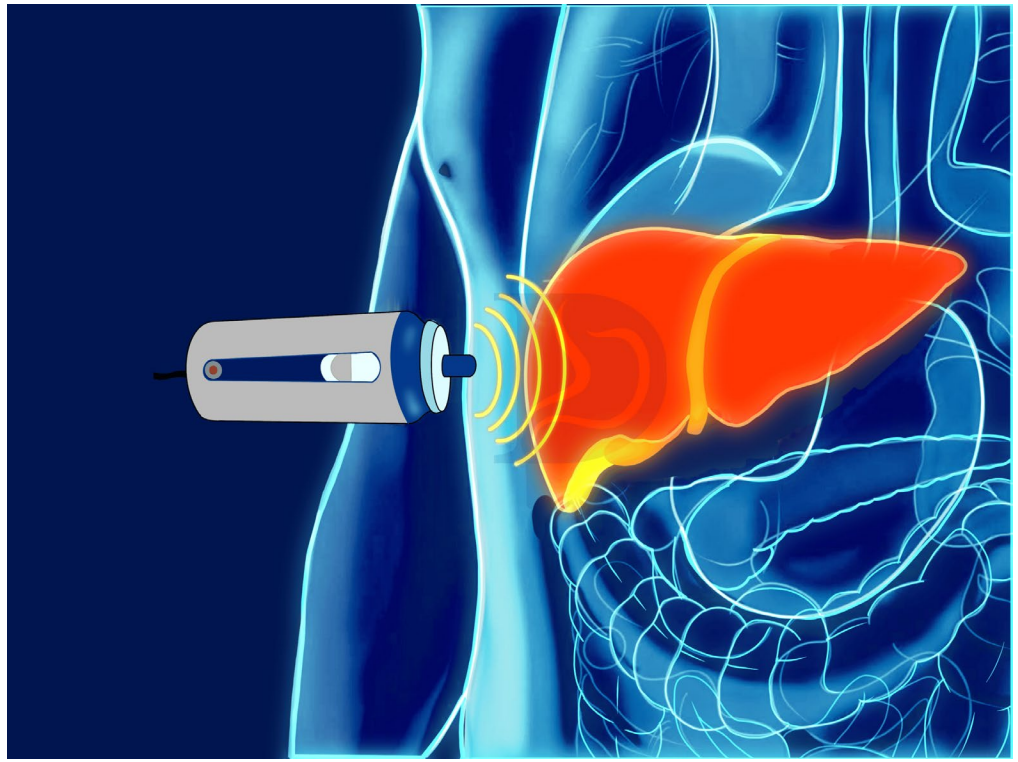
- High alcohol intake (AST>ALT, lower platelets) – overestimate risk of fibrosis

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

Apply Clinical Judgement

- If the FIB4 score is **≥1.0 and ≤1.3** but patient with **T2D has multiple risk factors** – consider checking a secondary assessment test with VCTE or ELF test
  - ADA 2025 MASLD consensus report: ***"Clinically significant fibrosis may be present in some adults with type 2 diabetes and FIB-4 values between 1.0 and 1.3, especially when type 2 diabetes is associated with obesity and multiple cardiometabolic risk factors."***
    - "Therefore, a FIB-4 score cutoff of <1.3 should be taken as a general guidance for assessment of having a lower risk of advanced fibrosis, but it does not replace clinical judgement."
  - Case finding with eventual **additional testing may be justified with a FIB-4 score between 1.0 and 1.3 in people with type 2 diabetes with obesity or other traditional cardiometabolic risk factors.**
    - For these cases transient elastography (Fibroscan) may also be of benefit as part of risk assessment [or ELF test if Fibroscan not available]
    - Refer to liver specialist if FIB4 >1.0 + LSM ≥8 or ELF≥ 9.8 in PWT2D & multiple risk factors

Vibration-controlled transient elastography (VCTE)
Liver Stiffness Measurement (LSM)
Fibroscan (specific brand of device that performs VCTE)



Liver Stiffness Measurement (LSM) in VCTE:

- Normal Range: 2 to 7 kPa.
- Fibrosis: Higher values indicate increased liver stiffness and potential fibrosis.
- Cirrhosis: Values generally >12-14 kPa

- VCTE can also detect steatosis using the controlled attenuation parameter (**CAP score**) - Values >280 dB/m are highly likely indicative of having steatosis.

FIB-4 followed by LSM helps stratify people with diabetes by risk level and minimize specialty referrals ADA 2026 SoC

- Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in MASLD – *ADA Standards of Care suggest cutoff of 8.0 kPa*

- An LSM value of **<8.0 kPa** has a good negative predictive value to *exclude advanced fibrosis (≥F3–F4)* and indicates lower risk for clinically significant fibrosis (F2).
  - Such individuals with prediabetes or type 2 diabetes can be followed in nonspecialty clinics with repeat surveillance testing every ≥2 years (the precise time interval remains to be established).
- If the LSM is **≥8.0 kPa**, the risk for advanced fibrosis (≥F3–F4) is higher and such individuals should be *referred to the hepatologist* within the framework of an interprofessional team

kPa = Pascal or kilopascal - a derived unit of pressure

Different cut off levels for NITs for different liver conditions (e.g., HCV, PBC, autoimmune hepatitis, etc.)

Conditions that can affect Fibroscan results

- Obesity - body mass index (BMI) > 30 (Asian >25)
  - class 3 obesity was strongly linked to the overestimation of fibrosis by at least 2 stages by Fibroscan *Journal of Clinical Gastroenterology*
    - *Among patients with class 3 obesity, Fibroscan suggested the presence of cirrhosis in 57.9%, whereas liver biopsy confirmed cirrhosis in 24.2%.*
    - This could erroneously exclude some people from treatment options that exclude people w/ cirrhosis
    - Consider the XL probe for VCTE or Magnetic Resonance Elastography (MRE) – prefer MRE if BMI >40
- Ascites (fluid build up in the belly)
- Biliary obstruction
- Scar tissue around/outside of the liver
  - Scar tissue from previous surgeries or radiation therapy near the liver can interfere with the ultrasound waves.
- Liver inflammation or congestion:
  - Liver inflammation, either caused by recent liver illness or drinking alcohol, or liver congestion (when the liver is too full of blood or other fluids) can lead to inaccurate readings.
- Liver tumors:
  - Both benign and cancerous tumors in the liver can also affect the accuracy of the test. `

If LSM is not available or accurate → the ELF score

- The Enhanced Liver Fibrosis (ELF) score - A blood sample is taken to measure the levels of three *serum biomarkers*:
  - hyaluronic acid (HA)
  - procollagen III N-terminal peptide (PIIINP)
  - tissue inhibitor of matrix metalloproteinase-1 (TIMP-1)
- Quest, LabCorp, some health system labs, some regional reference labs
  - Often offer reflex test to ELF if FIB4 ≥1.3

- *The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values* J Hepatol. 2013
  - Identified three cut-off values:
    - 7.7 for a high sensitivity exclusion of fibrosis
    - 9.8 for a high specificity identification of fibrosis (sensitivity 69%, specificity 98% for moderate fibrosis),
    - 11.3 to discriminate cirrhosis (sensitivity 83%, specificity 97%)

Given the lack of widespread availability of LSM, the ELF test is a good alternative ADA 2026 Standards of Care

- Individuals with **ELF <9.8** are considered at low risk for adverse liver outcomes.*
- Individuals with **ELF ≥9.8** are considered at high risk of having MASH with advanced liver fibrosis (≥F3–F4) and therefore are at risk for adverse liver outcomes.
  - They should be referred to a gastroenterologist or hepatologist.

- The optimal cutoff for clinical use of ELF in primary care and endocrinology settings is evolving:
  - *An ELF <9.8 suggests an individual is at low risk of advanced liver fibrosis and may be followed in the nonspecialty clinic with repeat testing in ≥2 years but may need repeat testing more often if ELF is between 9.2 and 9.7.

  - No interference by age, diabetes, obesity - males usually measure higher ELF than females

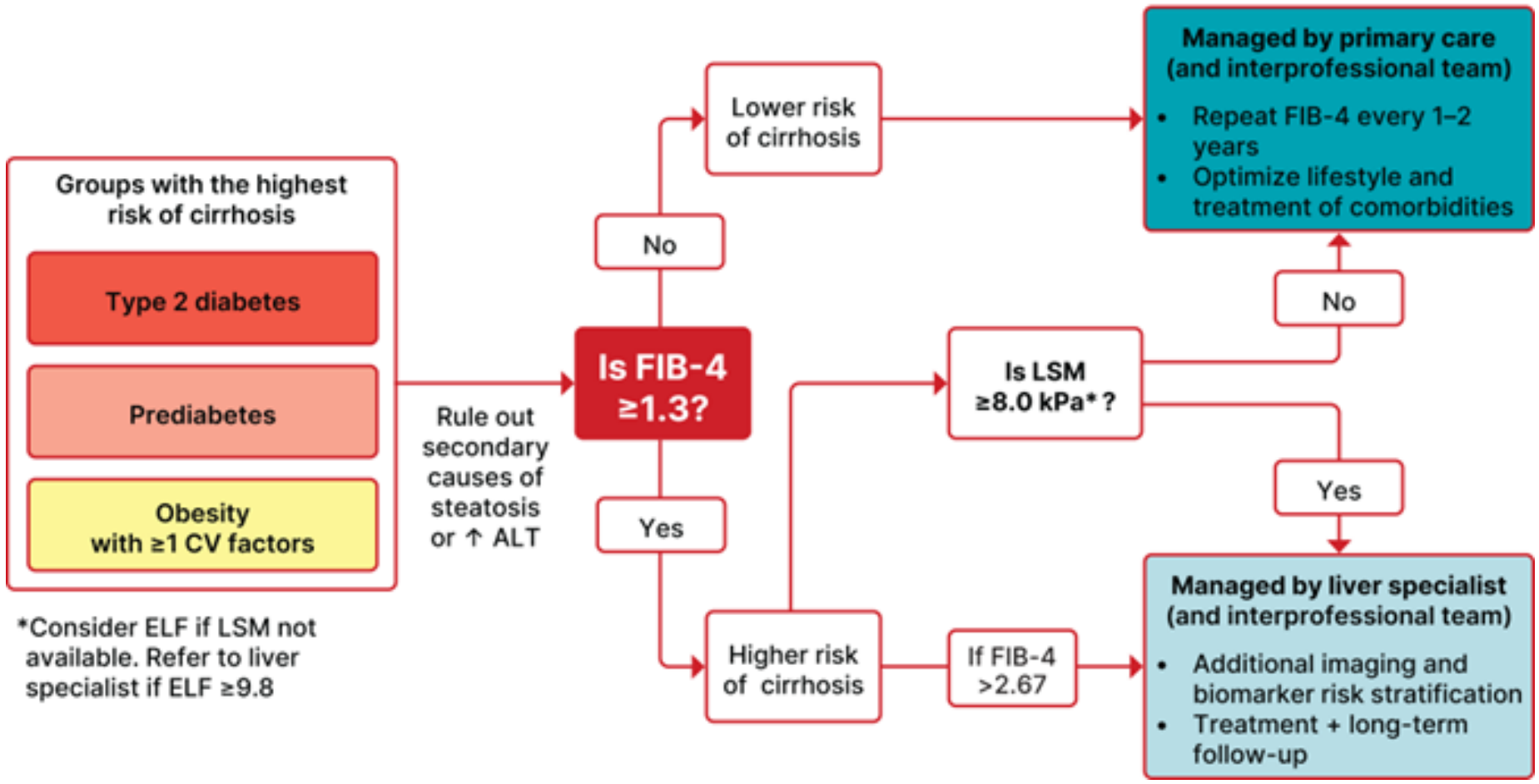
Referral for Further Evaluation & Management

- 4.24 Refer adults with type 2 diabetes or prediabetes at higher risk for significant liver fibrosis (i.e., as indicated by FIB-4, liver stiffness measurement, or ELF) to a gastroenterologist or hepatologist for further evaluation and management. B
  - FIB4 ≥2.67*
  - FIB4 ≥1.3 + LSM ≥ 8
  - FIB4 ≥1.3 + ELF ≥ 9.8

- *Consider ordering a LSM (Fibroscan) and/or ELF test to expedite referral and improve accuracy of risk status

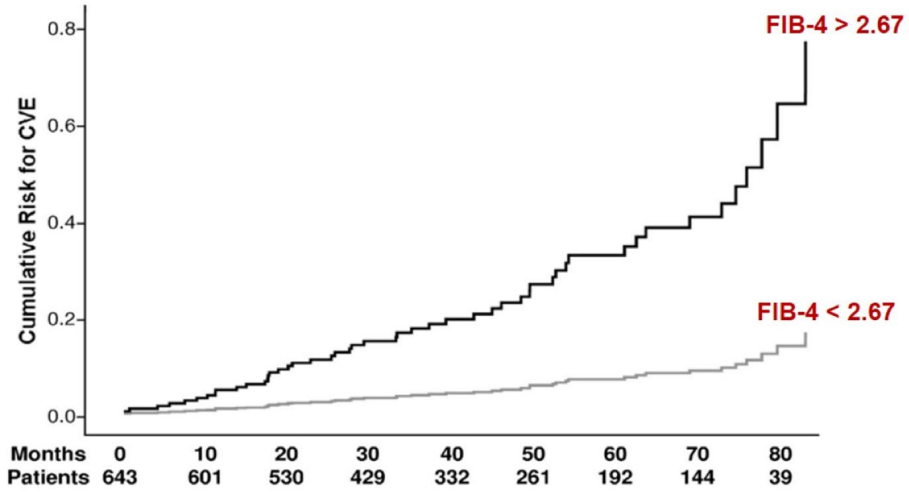
- If FIB4 ≥1.3 but LSM <8.0 or ELF <9.8 – *manage in primary care*

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



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)

Goal of Screening with FIB-4

- FIB4 does *not* tell you who has MASLD – **most people with type 2 diabetes have MASLD** - MASLD is most reversible in earlier phases
  - 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
  - Monitoring liver NITs in PWD with low & intermediate fibrosis risk

Summary - Key Points

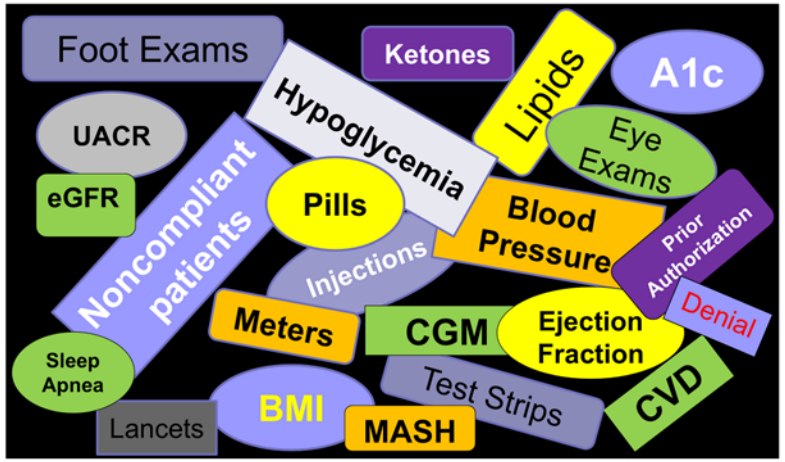
- MASLD & MASH (Metabolic-dysfunction Associated Steatotic Liver Disease & Steatohepatitis) replace the NAFLD & NASH terminology along with some differences to the definition
  - Steatosis with at least one Cardiometabolic risk factor associated with insulin resistance
  - Allows for co-existence of other liver conditions
- MASLD increases the risk of CVD, cancers & CKD as well as the risk of liver complications (CVD is main cause of death in people with MASLD)
  - Liver complications include cirrhosis, liver failure & hepatocellular carcinoma (HCC)
  - Risks increase with increasing fibrosis
- 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 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

Next Steps – Part 2 on Management

- For all patients – even those with low-risk FIB4/NITs & those waiting for referral:
  - Exercise (even 10 minutes) /reduce sedentary time!!
  - Food choices – in addition to reduced calories
    - avoid alcohol
    - avoid/reduce high sugar & High-Fructose Corn Syrup (HFCS) food items
    - reduce saturated fats
    - ample fruits & vegetables
    - encourage coffee intake – 3 to 4 cups/day including both caffeinated and decaffeinated varieties
  - Glycemic management/Weight loss – GLP1 RA or Dual GLP1/GIP RA medications
    - Prefer agents for glycemia that also offer hepatic, CV, renal & other benefits
    - Not if decompensated cirrhosis – only insulin & avoid weight loss
  - Low dose pioglitazone
  - Statins
  - Liver directed therapy

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

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

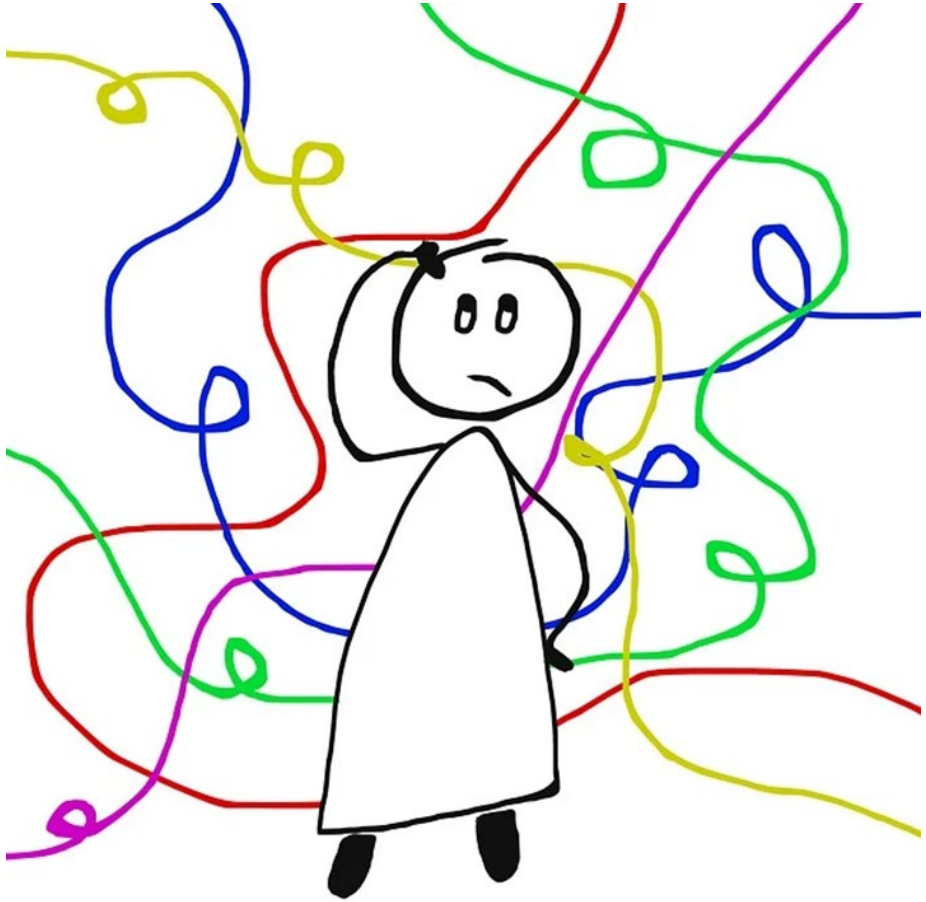
- Patients at high risk of MASLD, such as those with diabetes and obesity, remain largely ***unaware*** of the disease and/or that their conditions are risk factors for MASLD
  - It is important for healthcare professionals to understand that a lack of awareness among patients corresponds with a ***limited 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.

Avoid Scare Tactics – 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.”*

Questions, Comments, Clarification



Are you routinely screening patients with T2D with FIB4 index?
Are you able to get a LSM/Fibroscan result for your patient?

What is your experience of getting patients referred in with a liver team?

Extra Slides

Link to find a Fibroscan near your location

- https://www.echosens.com/en-us/find-a-fibroscan-map/

Diagnosing MASLD / “Fatty Liver”

- Because having obesity and prediabetes or type 2 diabetes is associated with a high pretest probability of hepatic steatosis (>70%), one may proceed directly to fibrosis risk assessment without an ultrasound to confirm steatosis.
- Steatosis can be diagnosed with the controlled attenuation parameter (CAP score) from a vibration-controlled transient elastography (VCTE)(e.g., Fibroscan) examination. Values >280 dB/m are highly likely indicative of having steatosis.
- MRI is the gold standard for confirmation of steatosis
- While a liver ultrasound has in the past been widely used to diagnose hepatic steatosis, the presence of an echogenic liver itself is not highly specific, as its diagnosis is operator dependent and ultrasound has *poor sensitivity* for mild steatosis (not reliably detected until 30% fat or more)

Other causes of elevated liver enzymes which may be differential diagnoses for MASLD:

People with T2D can have an alternative or coexisting (more than one type) liver disease in addition to MASLD/MASH

- **Alcohol-related liver disease (ALD**), which is associated with steatosis and a positive history of excessive alcohol use, may cause elevated liver enzymes. ALD and MASLD are considered overlapping conditions along a continuum across which the contribution of MASLD and ALD will vary, which is called MASLD and increased alcohol intake (MetALD) (see also Determination of Alcohol Consumption in Alcohol-Related Liver Disease) (Hepatology 2020 Jan;71(1):306 and Ann Hepatol 2024 Jan-Feb;29(1):101133).\
- **Autoimmune hepatitis**, which is not associated with steatosis, may have a history of diabetes mellitus type 1, Graves disease, ulcerative colitis, vasculitis, or Sjogren syndrome and may be ruled out by liver biopsy.4
- **Hepatitis B or hepatitis C virus infections** cause elevated liver enzymes, but only hepatitis C genotype 3 is associated with liver steatosis. Risk factors for viral hepatitis include injection drug use, risky sexual behaviors, and blood transfusions (4 and Med Clin North Am 2014 Jan;98(1):1).
- **Drug-induced liver injury** is associated with increased transaminase levels after starting a medication which resolve when the medication is discontinued (Eur J Intern Med 2016 Mar;28:9).
- **Hemochromatosis**, which is not associated with steatosis, may be associated with increased skin pigmentation, hepatomegaly, testicular atrophy, decreased libido, fatigue, and cardiomyopathy. Patients may have elevated transferrin saturation and serum ferritin levels (Hepatology 2011 Jul;54(1):328).

If elevated liver tests/steatosis on imaging – evaluate for Alternative or Co-existing Liver Conditions

- Alcoholic Liver Disease: (AST-ALT ratio often >2), social history
  - Phosphatidylethanol (PEth)
- Hemochromatosis: Ferritin, transferrin saturation test, HFE gene testing
- Chronic viral hepatitis: HCVAb, HBsAg, etc.
- Celiac disease: tTG-IgA (tissue transglutaminase immunoglobulin A) and total IgA.
- Autoimmune liver disease: ANA, anti-smooth muscle AB test
- Alpha 1- Antitrypsin deficiency: alpha 1 Antitrypsin phenotyping
- Drug-induced liver injury: e.g. Methotrexate, amiodarone, tamoxifen, corticosteroids, 5-fluorouracil, Irinotecan, etc.
  - https://www.ncbi.nlm.nih.gov/books/NBK547852/ (Liver Tox)

More details in
"Extra Slides" section

Secondary causes of hepatic fat accumulation which may be differential diagnoses for metabolic dysfunction-associated steatotic liver disease (MASLD):

- Excessive alcohol consumption, such as > 2 drinks/day in female patients and 3 drinks/day in male patients, in the absence of other potential causes of liver injury (see Alcohol-Related Liver Disease)
- Chronic hepatitis C virus (genotype 3)-associated steatotic liver
- Wilson disease
- Disorders of lipid metabolism, including inborn errors of metabolism, such as:
  - Hypobetalipoproteinemia
- Pfeifer-Weber-Christian syndrome, which is an idiopathic disorder with nonsuppurative nodular panniculitis that can affect lipid metabolism and is reported to be associated with MASLD (Clin Med Insights Case Rep 2020;13:117954762091795 8)
- Lysosomal acid lipase deficiency, such as with Wolman disease or cholesteryl ester storage disease
- Lipodystrophy, which is genetically inherited or induced by highly active antiretroviral therapy (HAART)

Secondary causes of hepatic fat accumulation which may be differential diagnoses for metabolic dysfunction-associated steatotic liver disease (MASLD) continued:

- Mauriac syndrome (rare complication of growth failure involving cushingoid appearance and hepatomegaly in young patients with diabetes mellitus type 1 described in Endocrinol Nutr 2013 May;60(5):245)
- Nutrient deficiency/malnutrition, including carnitine or choline deficiency due to anorexia, short bowel syndrome, or bypass surgery
- Parenteral nutrition
- Celiac disease
- Pregnancy associated etiologies such as hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, or acute onset of steatotic liver disease during pregnancy
- Endocrine diseases, such as:
  - Hypothyroidism
  - Polycystic ovary syndrome (PCOS)
  - Growth hormone deficiency (see Growth Hormone Deficiency in Adults and Growth Hormone Deficiency in Children)
  - Panhypopituitarism (primary or secondary)

Medications, that can cause drug-induced liver disease

- 5-fluorouracil (5-FU)
- Acetylsalicylic acid
- Amiodarone
- Amphetamines
- Corticosteroids
- Irinotecan
- Lomitapide
- Methotrexate
- Tamoxifen
- Tetracyclines
- Valproate

Magnetic Resonance Elastography (MRE) - if BMI >40 or need further evaluation

- While MRE may not be the initial choice for risk stratification due to cost and access considerations, it can serve as a valuable tool in specialty clinics, especially in cases of uncertainty or unreliable VCTE results.
  - VCTE-derived LSM >10 kPa and MRE-derived LSM >3.5 kPa suggest advanced fibrosis (i.e., liver fibrosis stages 3 [F3] and 4 [F4])
  - a value >15 kPa and MRE values >4.4 kPa are consistent with a high probability of cirrhosis (i.e., stage F4).\
  - VCTE-derived LSM >25 kPa (99), VCTE-derived LSM >20 kPa with platelet counts ≤150,000/mm3, and MRE-derived LSM >5.7 kPa are all reflective of likely having clinically significant portal hypertension

- Superior Diagnostic Accuracy: MRE has consistently demonstrated higher diagnostic accuracy across all stages of liver fibrosis, particularly in detecting early fibrosis (F0-F2) where VCTE may be less sensitive.
- Effectiveness in Obese Patients: Obesity is a common comorbidity in MASLD, and VCTE's accuracy can be compromised in these patients due to limitations in ultrasound wave transmission. MRE, on the other hand, performs well in assessing liver stiffness even in the presence of obesity.
- Broader Liver Coverage: MRE evaluates the entire liver, unlike liver biopsy which only samples a small portion, according to the Mayo Clinic. This allows for a more comprehensive assessment of fibrosis distribution.

“Apply Clinical Judgement”
ADA 2025 MASLD consensus report

- ADA MASLD 2025 consensus report: *“Clinically significant fibrosis may be present in some adults with type 2 diabetes and FIB-4 values between 1.0 and 1.3, especially when type 2 diabetes is associated with obesity and multiple cardiometabolic risk factors.”*
  - For instance, in a large *phase 3 study* with recruitment of people with MASLD with fibrosis stages F2 and F3, often with obesity and type 2 diabetes, the mean ± SD of the FIB-4 score was 1.4 ± 0.7 .
    - This indicates that for some individuals with at-risk MASH FIB-4 score may be <1.3, especially in the context of obesity and type 2 diabetes.
  - Therefore, a FIB-4 score cutoff of <1.3 should be taken as a general guidance for assessment of having a lower risk of advanced fibrosis, but it does not replace clinical judgement.
- Case finding with eventual additional testing may be justified with a FIB-4 score between 1.0 and 1.3 in people with type 2 diabetes with obesity or other traditional cardiometabolic risk factors.
  - For these cases transient elastography (e.g., Fibroscan) may also be of benefit as part of risk assessment.

Apply Clinical Judgement

- FIB4 has potential for *underestimation of fibrosis severity* in individuals with T2D

- If the FIB4 score is **≥1.0 and <1.3** but patient with ***T2D has multiple risk factors*** – consider checking a secondary assessment test with VCTE or ELF test
  - The risk of developing MASLD, MASH and fibrosis/cirrhosis has been independently associated with
    - insulin resistance
    - weight gain
    - obesity
    - cardiometabolic risk factors
    - family history (genetic risk)

Interpreting/Explaining Non-Invasive Test (NIT) Results

- “Since NITs have significant interindividual variability and overlapping confidence intervals across fibrosis stages, it is best to consider results in the context of having a ***“probability” of a given liver disease stage*** rather than the certainty that only a liver biopsy can provide.”
  - E.g., FIB4 >2.67 has a 60-80% range of a positive predictive value for clinically significant fibrosis in patients with MASLD

- Different cut off levels for NITs for different liver conditions (e.g., HCV, PBC, autoimmune hepatitis, etc.)

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"