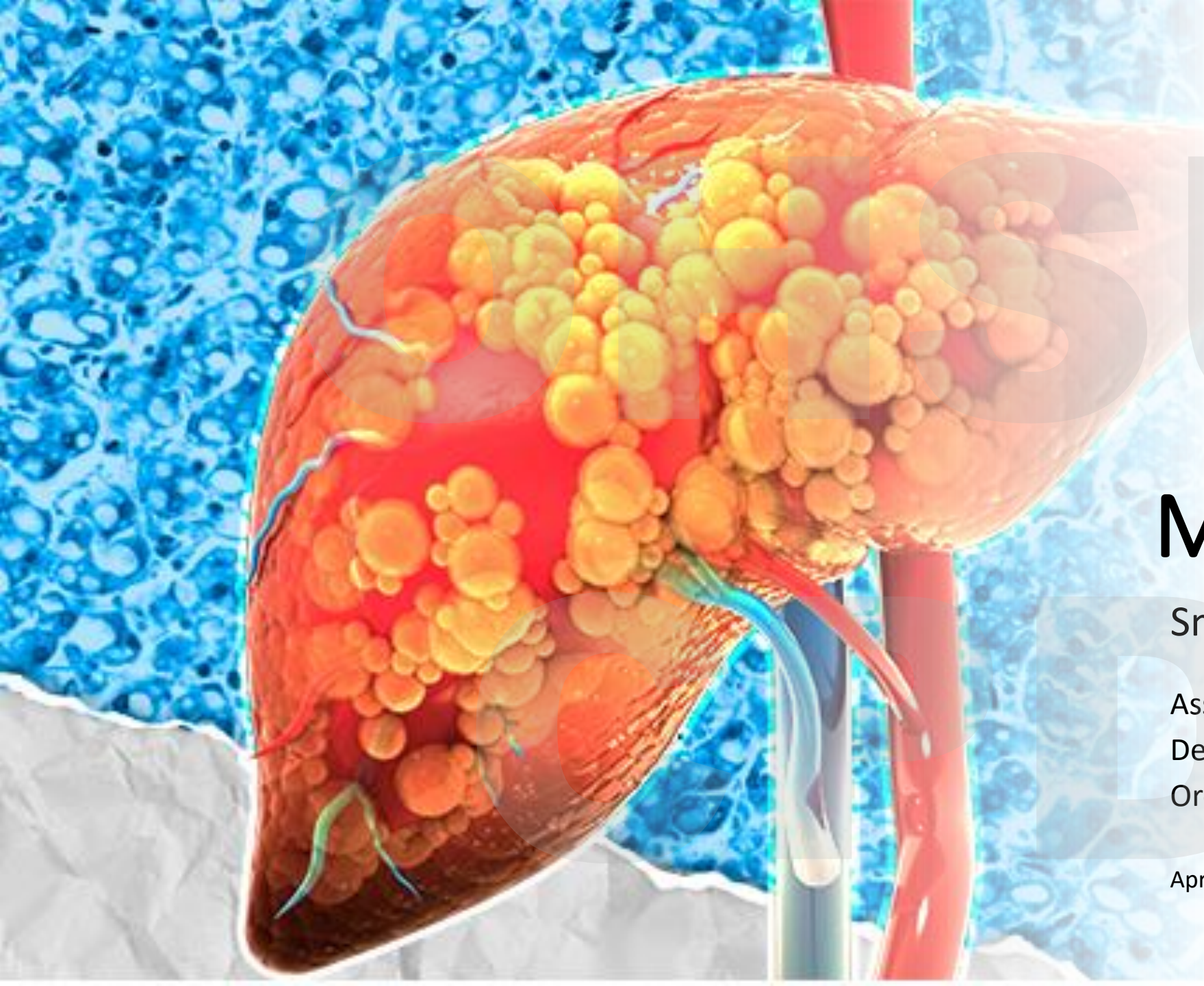

MASLD

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Assoc Professor
Department of Family Medicine
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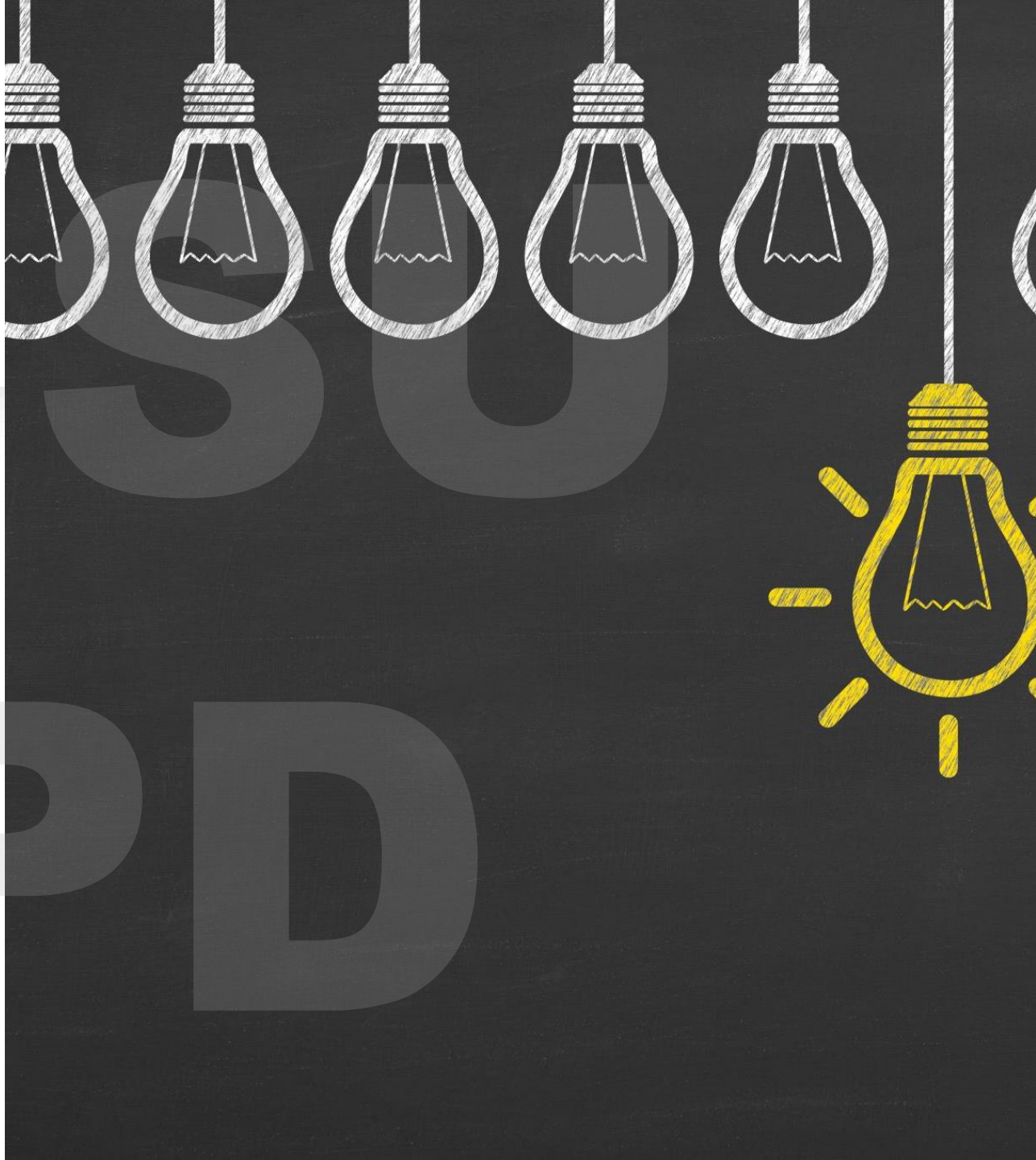
Apr 26, 2024

Objectives

- Define NAFLD and NASH
- Learn new nomenclature
- Review screening for risk of advanced fibrosis
- Apply risk stratification for fibrosis
- Learn management strategies



Case

- 64 y/o cis-F *(she/her)* sees you (PCP) for ED f/u where she had reported fatigue and malaise. Labs in ED: Glu= 185, AST= 54, ALT= 46, rest of CMP normal, TG= 254, rest of the lipid profile normal, HbA1C= 7.9, Plts= 186. ED clinician advised her to f/u with PCP. Has h/o DM2, HTN, dyslipidemia. Meds include: metformin 1000 mg BID, glipizide 10 mg, simvastatin 40 mg, lisinopril/HCTZ 20/12.5 mg once daily. Does not smoke or drink alcohol. PE in clinic: BP= 128/70, HR= 72, RR= 12, BMI= 32. She has truncal obesity and no masses or organomegaly.
- FIB-4= 2.74

Next step?

1. Refer to hepatology
2. Recommend pioglitazone in place of glipizide to help address DM and NASH
3. Recommend GLP-1 in place of glipizide to help with weight loss, DM, reduction in CV risk and NASH
4. Referral to a dietitian and comprehensive weight loss program

NAFL/NASH

- NAFL: Development of hepatic steatosis (triglyceride accumulation in hepatocytes) in the absence of secondary causes (including alcohol).

- NASH: inflammation and hepatocyte injury (ballooning) with or without fibrosis

History of NASH

[Nonalcoholic steatohepatitis (NASH)]: term coined to describe changes in liver pathology similar to that seen in [then called] alcoholic hepatitis but in patients not known to be consuming alcohol.

Considerable skepticism that the entity even existed, assuming alcohol use in these patients had not been detected.

[NASH] entity took years to be accepted by the medical community, with only a few publications on NASH/NAFLD per year through 1990 but with a rapid increase to 5388 publications in 2022.

Prevalence

NASH is among the top causes of HCC (18% of all HCC cases)

NASH is the second most common indication of liver transplant due to HCC in the US (after hep C)

Global prevalence

- NAFLD= 25%
- NASH= 12-14%

Prevalence of NASH in US

- Obesity = 25-30%
- DM= 30-40% → 12-20% with significant fibrosis

Nomenclature

No more NAFLD!

No more NASH!

Updated terms as of June 2023

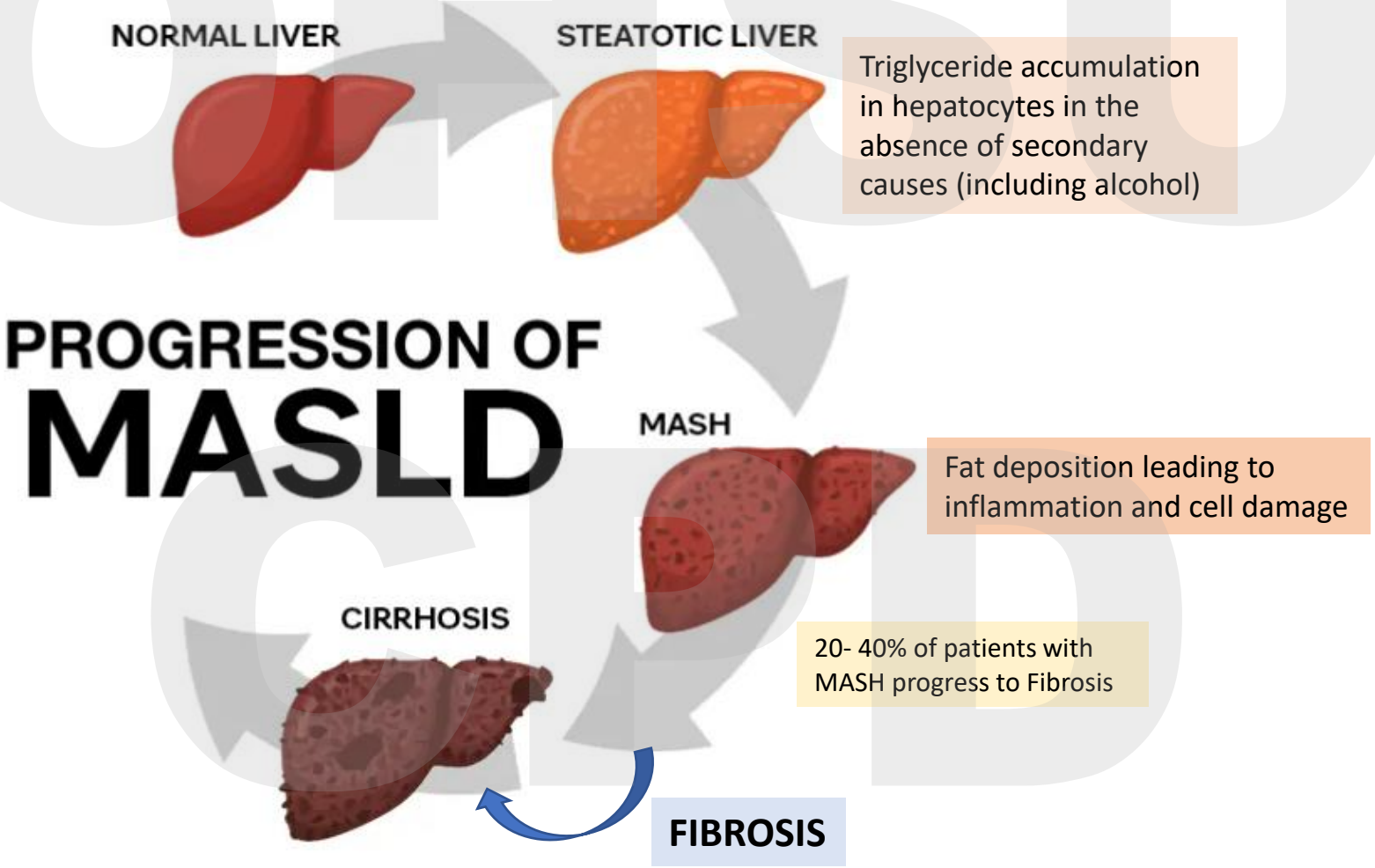
- Fatty Liver Disease: Steatotic Liver Disease (overarching term) **(SLD)**
- NAFLD: Metabolic dysfunction-associated steatotic liver disease **(MASLD)**
- NASH: Metabolic dysfunction-associated steatohepatitis **(MASH)**

Term steatohepatitis: is retained

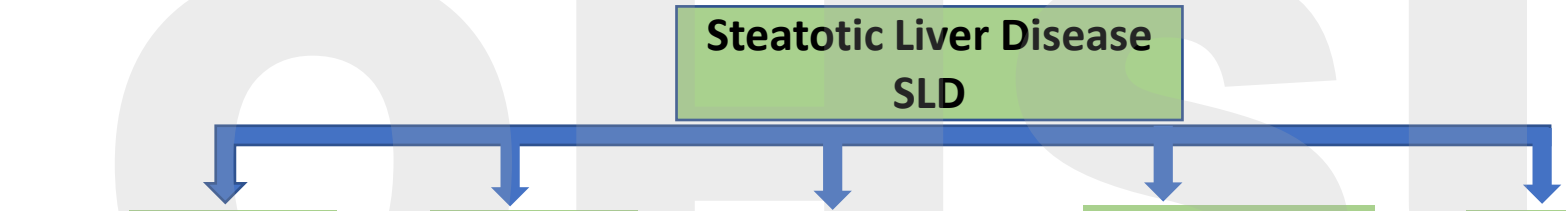
Change to non stigmatizing name

Recognize metabolic dysfunction as the underlying disease pathogenesis

MASLD Spectrum



New nomenclature
Steatotic Liver Disease-overarching term



MASLD

Hepatic steatosis+ at least 1 metabolic risk factor with no or low alcohol use

MetALD

MASLD but with moderate alcohol use

New group-has not been studied but will benefit from being included in clinical trials: recognizing the presence of 2 synergistic driving factors on disease progression

ALD

Alcohol related liver disease

Specific etiology SLD

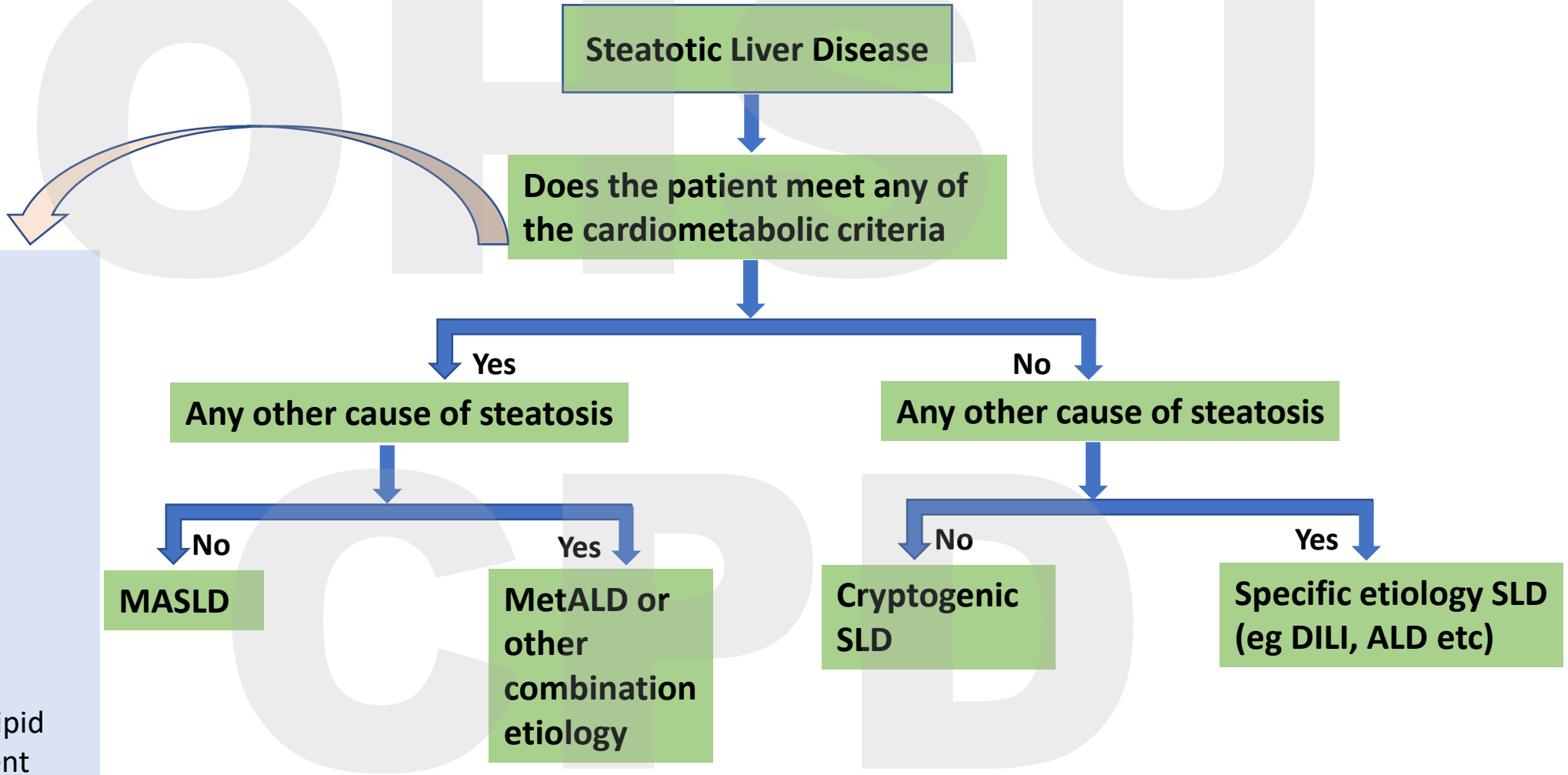
- Drug induced (DILI)
- Hereditary, Wilson's
- Viral hepatitis, Celiac disease, HIV

Cryptogenic SLD

No metabolic cause and no other identified cause: Previously called "lean NAFLD"

Alcohol use	Women (AFAB)	Men (AMAB)
Low	<1 standard drink/day	<2 standard drinks/day
Moderate	2-3 standard drinks/day	3-4 standard drinks/day
Significant	>3 standard drinks/day	>4 standard drinks/day

Steatotic Liver Disease-Evaluation



5 cardiometabolic criteria

1. Increased waist circumference ***or*** increased BMI
2. Increased FPG ***or*** PreDM ***or*** DM2
3. HTN
4. Increased TG ***or*** lipid lowering treatment
5. Decreased HDL ***or*** lipid lowering treatment

Screening: clinically significant fibrosis

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

2023 guidance: Targeted screening of at risk individuals to identify ≥F2 stage

- DM2
- Obesity with cardiometabolic risks
- Family history (first degree relative with cirrhosis due to MASLD/MASH)
- Significant alcohol use

AACE
American Association of Clinical Endocrinology

2022 recommendation: Targeted screening

- DM2 or preDM
- Obesity with cardiometabolic risks
- Hepatic steatosis on any imaging
- Persistently elevated liver enzymes (ALT/AST over 6 months)

American Diabetes Association®

2023 guidelines

- DM2 or preDM specifically with
  - Obesity and cardiometabolic risk
  - ASCVD
- DM1 only when either elevated aminotransferases or hepatic steatosis on imaging

DM and MASLD

- DM2: major risk factor for developing MASLD, disease progression and worse outcomes → hence the rationale for universal screening

- Bidirectional relationship between MASLD and DM2 → presence of one increases the risk and severity of the other.
  - MASLD associated with a 2-5 fold risk of incident DM2 → patients with MASLD should be screened for the presence of DM2

Screening Strategy: Non invasive tests (NITs)

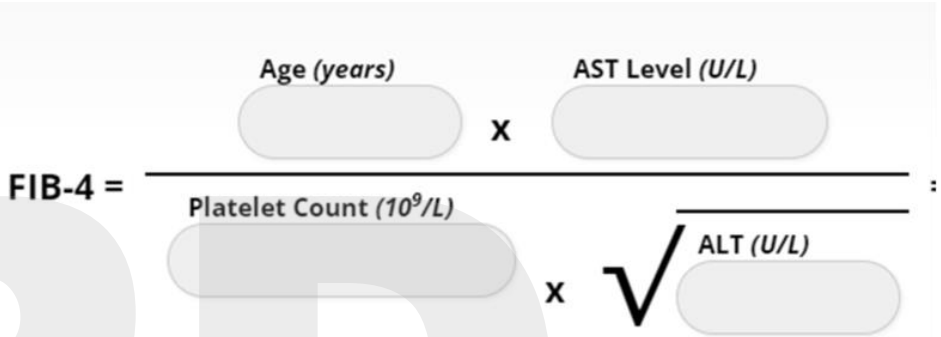
- FIB-4 → Most validated and cost-effective for initial screening in primary care setting
- NAFLD Fibrosis Score (NFS)
- AST Platelet Ratio Index (APRI)

  - Good specificity and negative predictive value → negative result rules out advanced fibrosis
  - Low sensitivity and positive predictive value → positive result requires confirmatory testing
    - Secondary assessment
      - VCTE (Vibration Controlled Transient Elastography)
      - Fibrosis biomarkers- ELF (Enhanced Liver Fibrosis test) *(proprietary)*

Fib-4

- FIB-4 estimates the risk of cirrhosis and predicts changes over time in fibrosis
  - Age
  - Plasma aminotransferases (AST and ALT)
  - Platelets

Fib-4 score	
<1.3	low risk
>2.67	high probability of advanced fibrosis



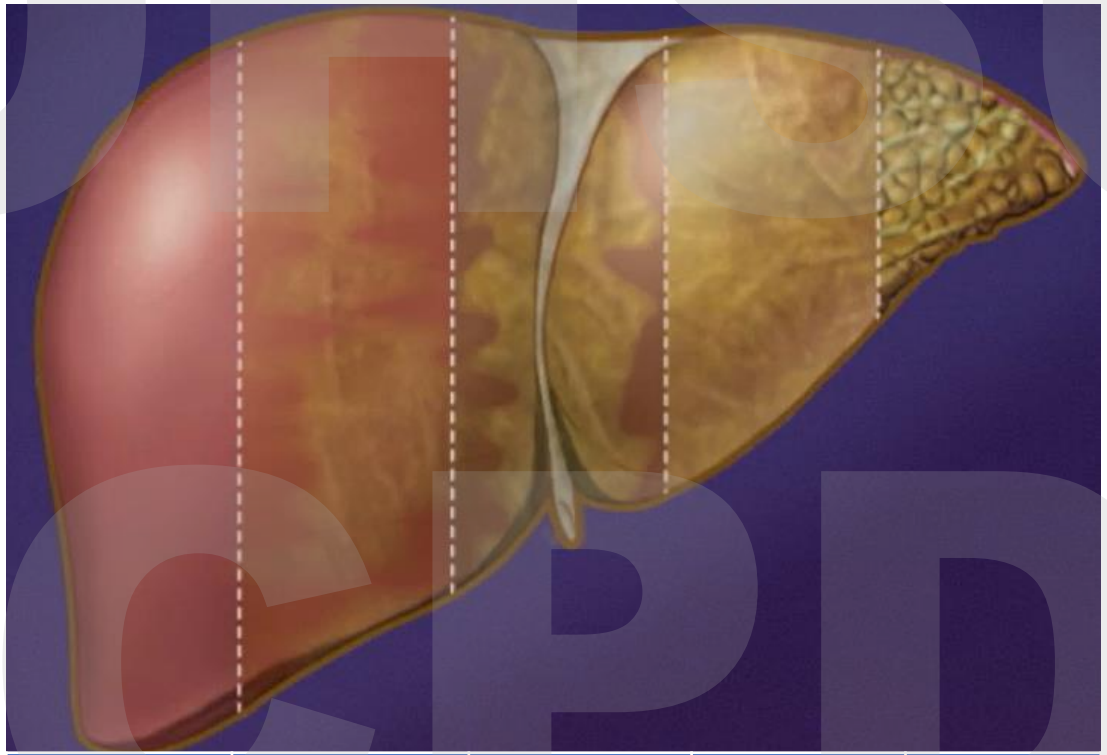
- Patients with DM ≥ 65 y/o → higher cut offs recommended (1.9-2.0 rather than >1.3)
- Not validated for use in patients <35 y/o and is inaccurate in children

Liver enzymes?

- Screening strategy based on liver enzymes would miss most individuals with MASH, because clinically significant fibrosis (≥F2) is frequently observed with levels below the commonly used cutoff of 40.

- ACG: ULN of ALT =29–33 for males (AMAB) and 19–25 for females (AFAB)
- Easy number to remember= 30

Classification of Fibrosis



F0	F1	F2	F3	F4
No fibrosis	Mild	Moderate (Significant)	Severe (Advanced)	Cirrhosis

MASLD management

High risk groups

PreDM or DM

Obesity

[**Term proposed by AACE= ABCD** (Adiposity-based chronic disease]

and/or

≥ 2 metabolic risk factors

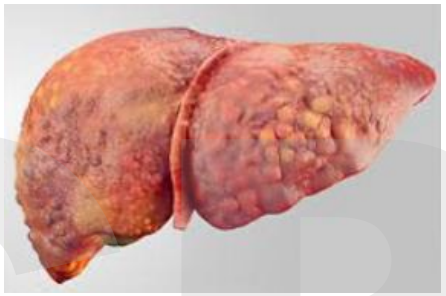
(increased waist circumference, increased TG, decreased HDL, increased BP, elevated FPG)

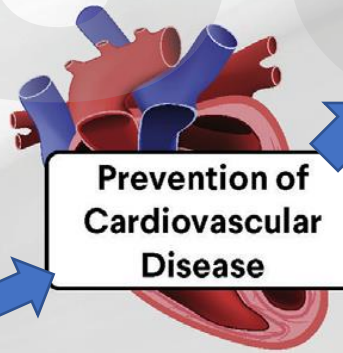
Hepatic Steatosis (on imaging)

or

Increased AST or ALT (>30)

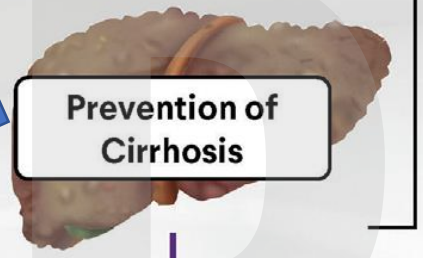
Rule out 2◦ causes





Prevention of Cardiovascular Disease

Leading cause of mortality



Prevention of Cirrhosis

Management of

1. Obesity
2. Diabetes
3. Hypertension
4. Atherogenic dyslipidemia

Fibrosis Risk Stratification

Evaluation: Fibrosis Risk Stratification

Incidental steatotic liver on imaging or clinical suspicion based on metabolic risk factors

Rule out other causes: eg: drug induced, viral hepatitis, celiac disease, autoimmune, hereditary, alcohol

- Hepatitis B and C serology
- ANA, AMA, ASMA
- Ferritin
- Alpha-1 antitrypsin

Primary risk assessment: FIB4

FIB4 ≥ 1.3

Low risk — No

- DM2 *or*
- PreDM *or*
- ≥ 2 metabolic risk factors

No → FIB4 q 2-3 years

Yes → FIB4 q 1-2 years

Yes — **Indeterminate risk 1.3- 2.67**

Secondary risk assessment:

Risk level	VCTE	ELF
Low	<8.0	<7.7
Intermediate	8-12	7.7- 9.8
High	>12	>9.8

High risk

FIB4≥ 2.67

Hepatology referral for additional stratification and potential intervention

Eg may consider MRE, liver biopsy in high risk patients

Management

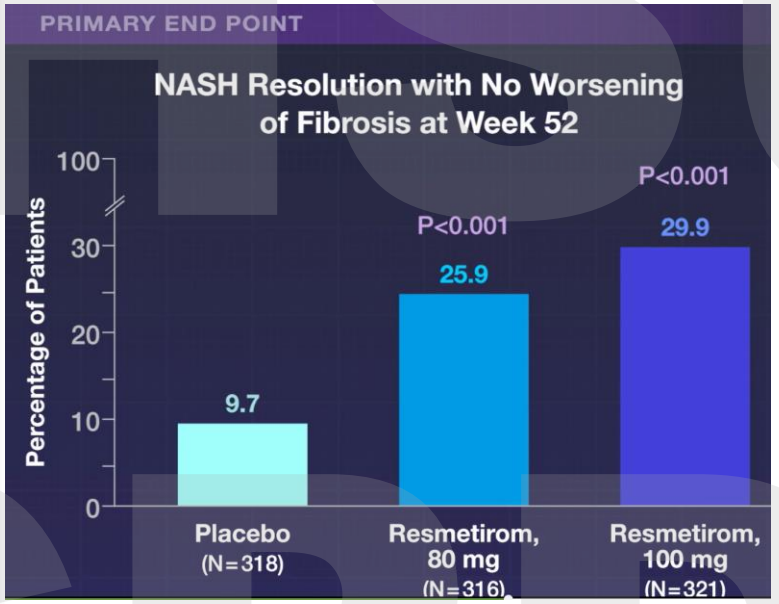
- Despite a high unmet need to prevent, stop or reverse MASH, currently no FDA-approved drugs
- Until….

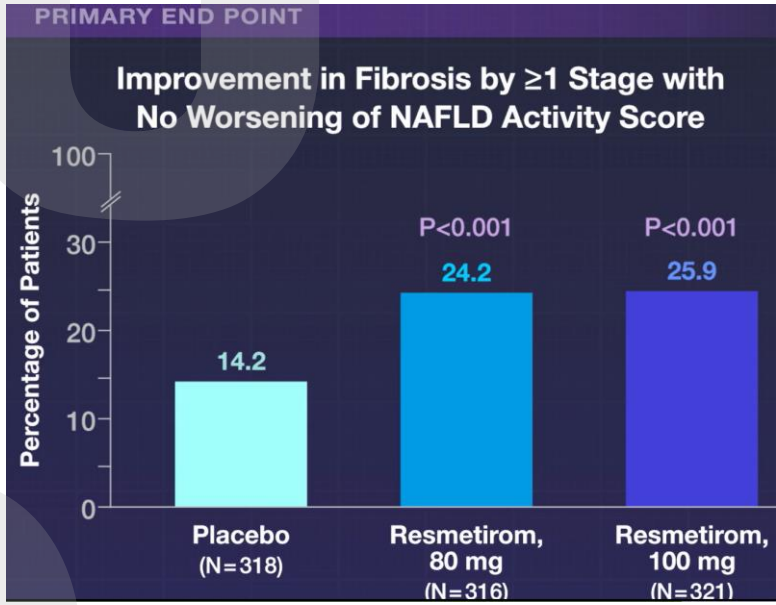
FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease

For Immediate Release: March 14, 2024

MAESTRO-NASH Trial

- Adults with biopsy confirmed NASH with F2-F3 fibrosis, n= 966
- 1:1:1 ratio, in addition to standard care for NASH (counseling for healthy diet and exercise)





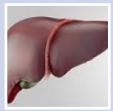
- Adverse effects: diarrhea, nausea, drug-induced liver toxicity, gall bladder related side effects.
- Avoid in patients with decompensated cirrhosis
- Significant drug interactions: STATIN!

N Engl J Med 2024;390:497-509

Resmetirom

Rezdiffra: noncirrhotic MASH with moderate to severe fibrosis (F2-F3), to be used along with diet and exercise.

Mechanism: targets thyroid hormone receptor beta (THR-β)-helps maintain liver homeostasis. THR-β agonists have been shown to improve lipid metabolism

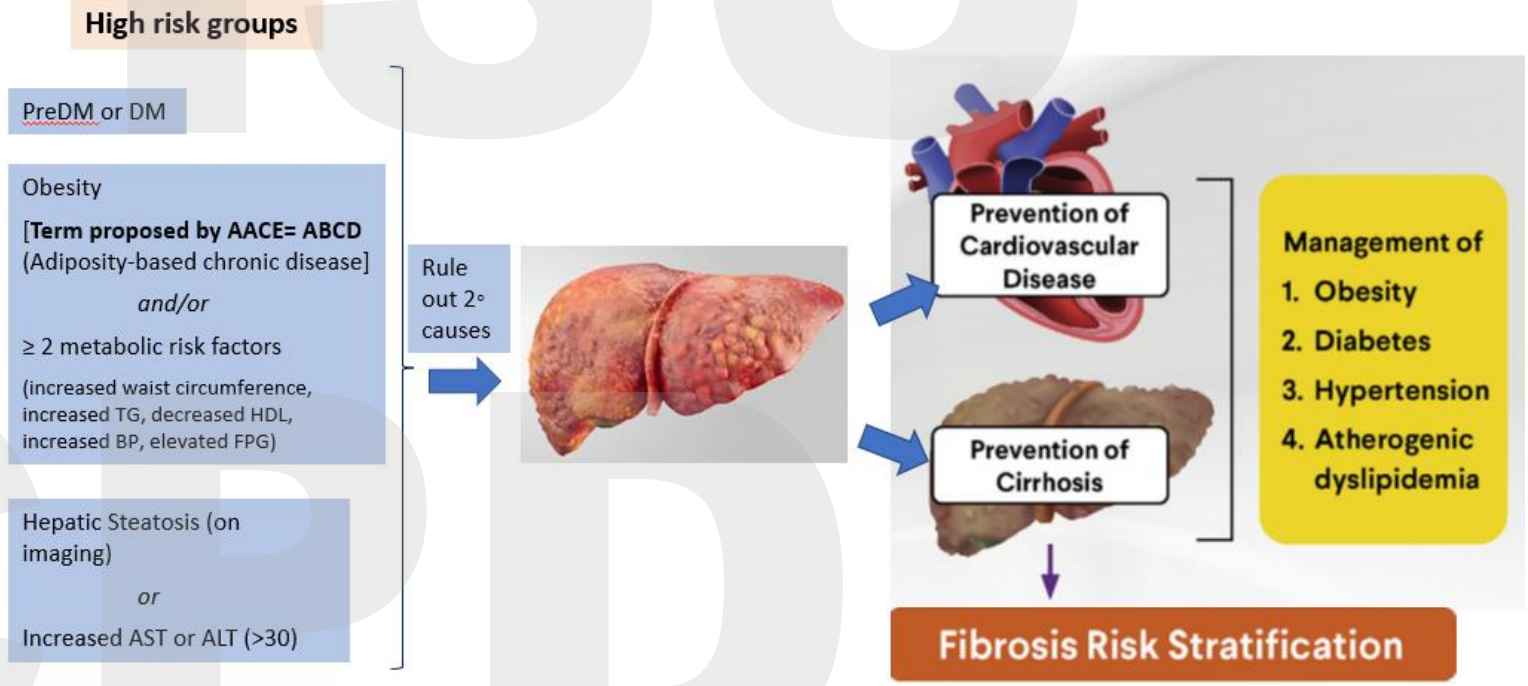


Safety and efficacy: based on surrogate endpoint (liver inflammation and scarring) at month 12 in a 54-month RCT – still ongoing, will be completed

Approved under the accelerated approval pathway, final approval contingent on results

Pharmacological management

- Medications approved for other comorbidities have potential benefits in clinical trials and should be considered in appropriate clinical settings



GLP1 agonists

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Lancet 2016; 387: 679–90

Liraglutide: improved steatosis, resolved NASH, and reduced fibrosis progression compared with placebo

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

N Engl J Med 2021;384:1113-24.

Semaglutide: significantly higher % of patients with NASH resolution than placebo. Though, no significant improvement in fibrosis stage but progression was significantly less with highest dose as compared to placebo

Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

Lancet Diabetes Endocrinol. 2022;10:393–406

Tirzepatide: significant reduction in steatosis compared with insulin degludec in patients with DM2

Though effect on NASH unknown

SGLT2i?

Dapagliflozin Efficacy and Action in NASH (DEAN)

Study completed: Mar 28, 2024

Outcomes of Various Classes of Oral Antidiabetic Drugs on Nonalcoholic Fatty Liver Disease

JAMA Intern Med. 2024;184(4):375-383

Potential benefits in NAFLD regression and lower incidences of adverse liver-related outcomes.

Pioglitazone

A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

N Engl J Med 2006;355:2297-307

Improves glucose and lipids and reverses steatohepatitis in preDM and DM2

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized Trial

Ann Intern Med.2016;165:305-315

Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis

A Meta-analysis

JAMA Intern Med. 2017;177(5):633-640

Improves advanced fibrosis, even in patients without DM

Randomized, Placebo-Controlled Trial of Pioglitazone in Nondiabetic Subjects With Nonalcoholic Steatohepatitis

Gastroenterology 2008;135:1176–1184

Improves metabolic and histologic parameters in NASH even without DM

Side Effects:

- Weight gain – dose dependent
- Osteoporosis in postmenopausal women
- Risk of HF exacerbation
- Increase risk of bladder cancer (controversial)

Vit E

Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: A meta-analysis of randomized controlled trials

Nutrition. 2015;31:923–30.

Vitamin E significantly improved liver function and histologic changes in patients with NAFLD.

NASH CRN Trial

N Engl J Med 2010;362:1675-85

Pioglitazone vs Vit E vs Placebo in NASH **without** DM

Benefits seen with both Vit E and Pioglitazone as compared to Placebo

- Decrease in AST/ALT
- Reduction in hepatic steatosis

- **No reduction in fibrosis**
- **Potential Side Effects:**
  - Hemorrhagic stroke
  - Increased risk of prostate cancer (conflicting data)

Vit E can be considered for treatment of NASH without DM2

NAFLD with Obesity

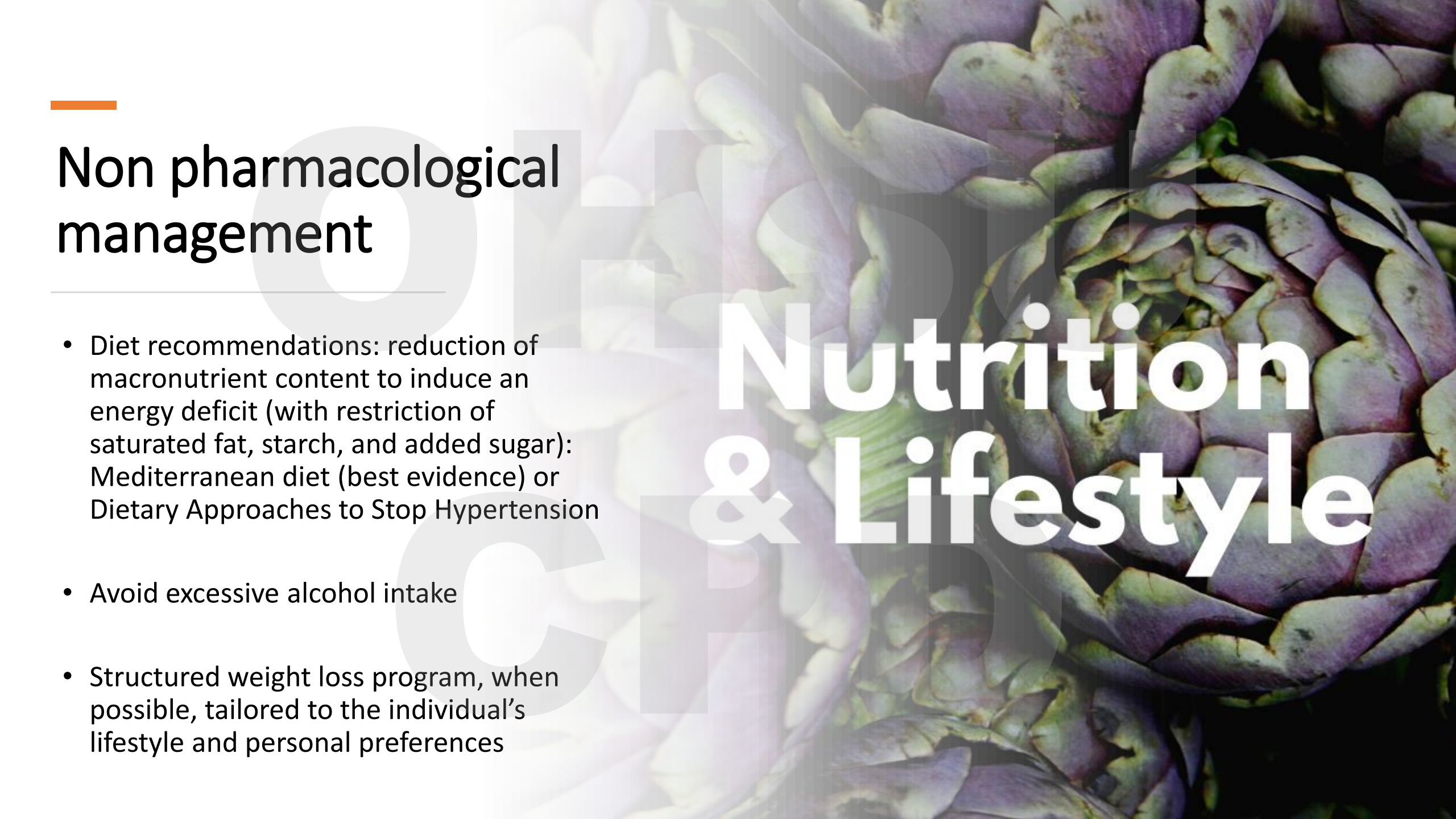
- Lifestyle modification
- Recommend use of obesity pharmacotherapy as an adjunct for obesity + NAFLD or NASH with a goal of at least 5%, preferably 10 %, weight loss, as more weight loss is associated with more liver histologic and cardiometabolic benefit

- Meds currently FDA approved for chronic weight management:
  - orlistat
  - phentermine/topiramate
  - naltrexone/bupropion
  - liraglutide
  - semaglutide

GLP1s: in addition to significant weight loss, role in improving NASH

Non pharmacological management

- Diet recommendations: reduction of macronutrient content to induce an energy deficit (with restriction of saturated fat, starch, and added sugar): Mediterranean diet (best evidence) or Dietary Approaches to Stop Hypertension
- Avoid excessive alcohol intake
- Structured weight loss program, when possible, tailored to the individual's lifestyle and personal preferences



Weight loss

- Most important component for patients who are over-weight or obese
- Weight loss of
  - >5% total body weight (TBW) - reduce hepatic steatosis
  - >7% TBW - improve NASH
  - >10% TBW - fibrosis regression/stability

  Hepatology. 2010;51(1):121e129.

  Gastroenterology. 2015;149(2):367e378

  Metabolism. 2021;115:154455.

- Obesity pharmacotherapies

Metabolic surgery for weight loss

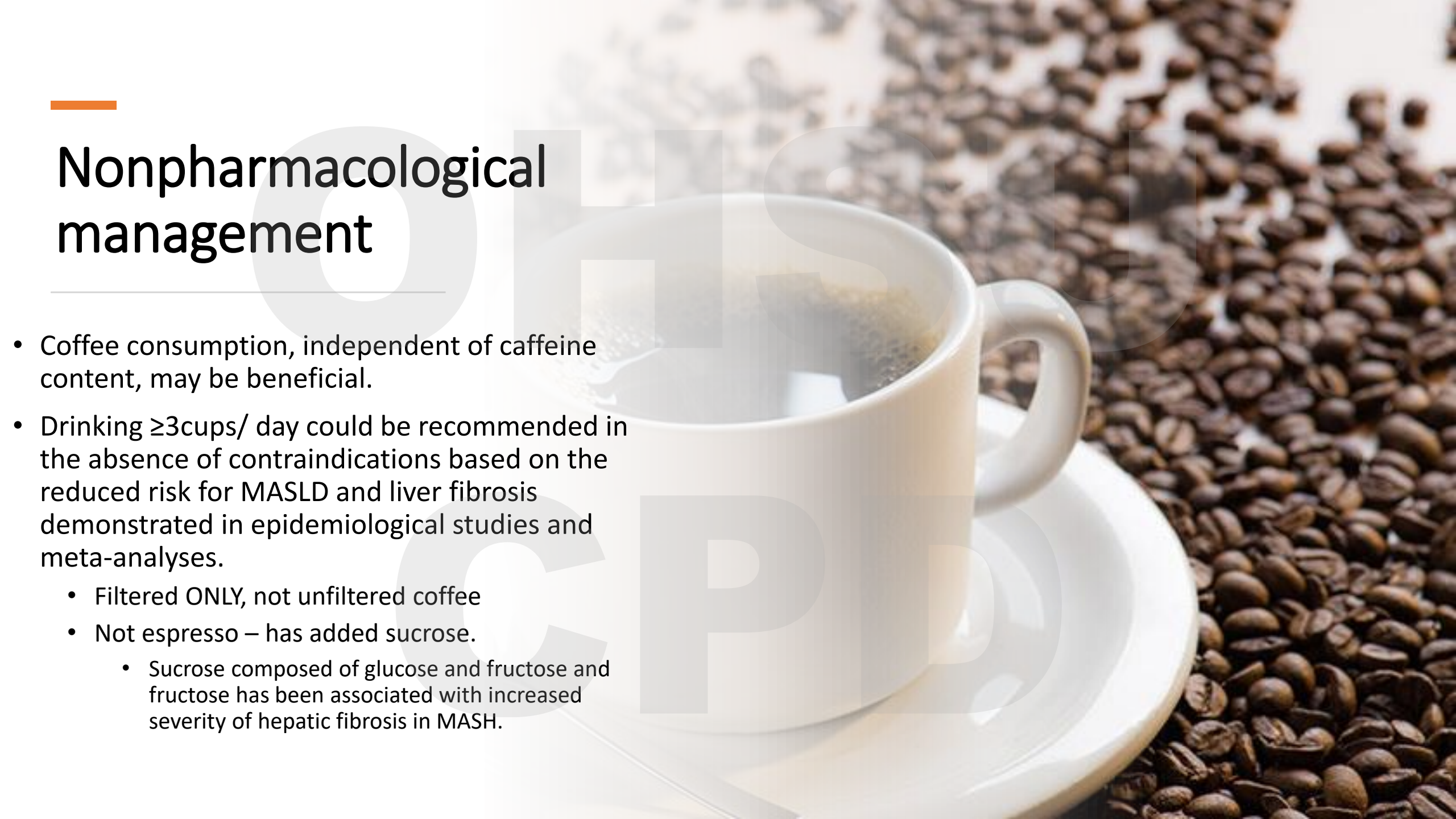
- Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery, as it effectively resolves MASLD or MASH in the majority of patients without cirrhosis and reduces mortality from CVD and malignancy

- MASH with compensated cirrhosis: safety and efficacy not well established

- MASH with decompensated cirrhosis: absolute contraindication to bariatric surgery unless performed in conjunction with liver transplantation

Nonpharmacological management

- Coffee consumption, independent of caffeine content, may be beneficial.
- Drinking ≥3cups/ day could be recommended in the absence of contraindications based on the reduced risk for MASLD and liver fibrosis demonstrated in epidemiological studies and meta-analyses.
  - Filtered ONLY, not unfiltered coffee
  - Not espresso – has added sucrose.
    - Sucrose composed of glucose and fructose and fructose has been associated with increased severity of hepatic fibrosis in MASH.



REVIEW ARTICLE

Impact of coffee on liver diseases: a systematic review

Liver Int. 2014: 34: 495–504

Conclusion:

- Coffee consumption associated with improved serum GGT, AST, ALT in a dose dependent manner in individuals at risk for liver disease.
- Chronic liver disease patients who consume coffee, a decreased risk of progression to cirrhosis, a lowered mortality rate in cirrhosis patients, and a lowered rate of HCC development were observed.
- In chronic hepatitis C patients, coffee was associated with improved virologic responses to antiviral therapy.
- Coffee consumption was inversely related to the severity of steatohepatitis in patients with NAFLD

Coffee consumption and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis

Eur J Gastroenterol Hepatol. 2017;29:e8–12

Significantly decreased risk of NAFLD among coffee drinkers and significantly decreased risk of liver fibrosis among patients with NAFLD who drank coffee on a regular basis.

Meta-analyses

A systematic review and a dose–response meta-analysis of coffee dose and nonalcoholic fatty liver disease

Clin Nutr. 2019;38:2552–7.

Conclusion: Coffee intake level >3 cups was observed with lower risk of NAFLD than <2cups/day.

Future landscape

ENLIGHTEN-Fibrosis study: Pegozafermin- aims to prolong the biological activity of fibroblast growth factor 21 (FGF21), for non-cirrhotic MASH patients with fibrosis stage F2-F3.

ENLIGHTEN-Cirrhosis: Pegozafermin in patients with compensated cirrhosis (F4), expected to begin in the second quarter of 2024.

At least 23 —of the 105 obesity treatments in development or on the market are also being investigated for MASH

“Triple G” drug: targeting GLP1, GIP, glucagon – Ozempic 3.0?

Case

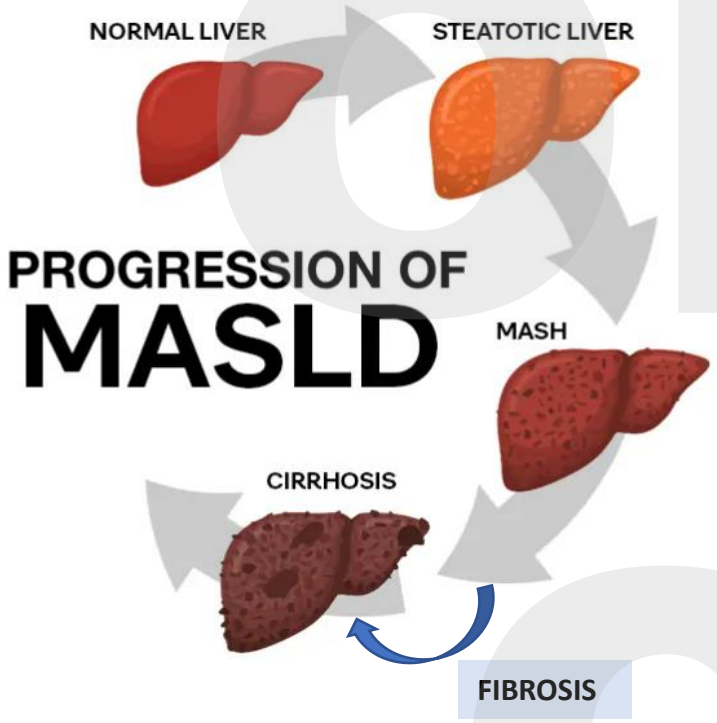
- 64 y/o cis-F *(she/her)* sees you (PCP) for ED f/u where she had reported fatigue and malaise. Labs in ED: Glu= 185, AST= 54, ALT= 46, rest of CMP normal, TG= 254, rest of the lipid profile normal, HbA1C= 7.9, Plts= 186. ED clinician advised her to f/u with PCP. Has h/o DM2, HTN, dyslipidemia. Meds include: metformin 1000 mg BID, glipizide 10, simvastatin 40 mg once daily, lisinopril/HCTZ 20/12.5 mg once daily. Does not smoke or drink alcohol. PE in clinic: BP= 128/70, HR= 72, RR= 12, BMI= 32. She has truncal obesity and no masses or organomegaly.
- FIB-4= 2.74

Next step?

1. Refer to hepatology (multidisciplinary MASLD clinic)
2. Recommendation for pioglitazone in place of glipizide to help address DM and NASH
3. Recommendation for GLP-1 in place of glipizide to help with weight loss, DM, reduction in CV risk and NASH
4. Referral to a dietitian and comprehensive weight loss program

Take Home

MAFLD spectrum



Screen: clinically significant fibrosis

HIGH RISK GROUP

PreDM or DM

Obesity

and/or

≥ 2 metabolic risk factors

(increased waist circumference, increased TG, decreased HDL, increased BP, elevated FPG)

Hepatic Steatosis (on imaging)

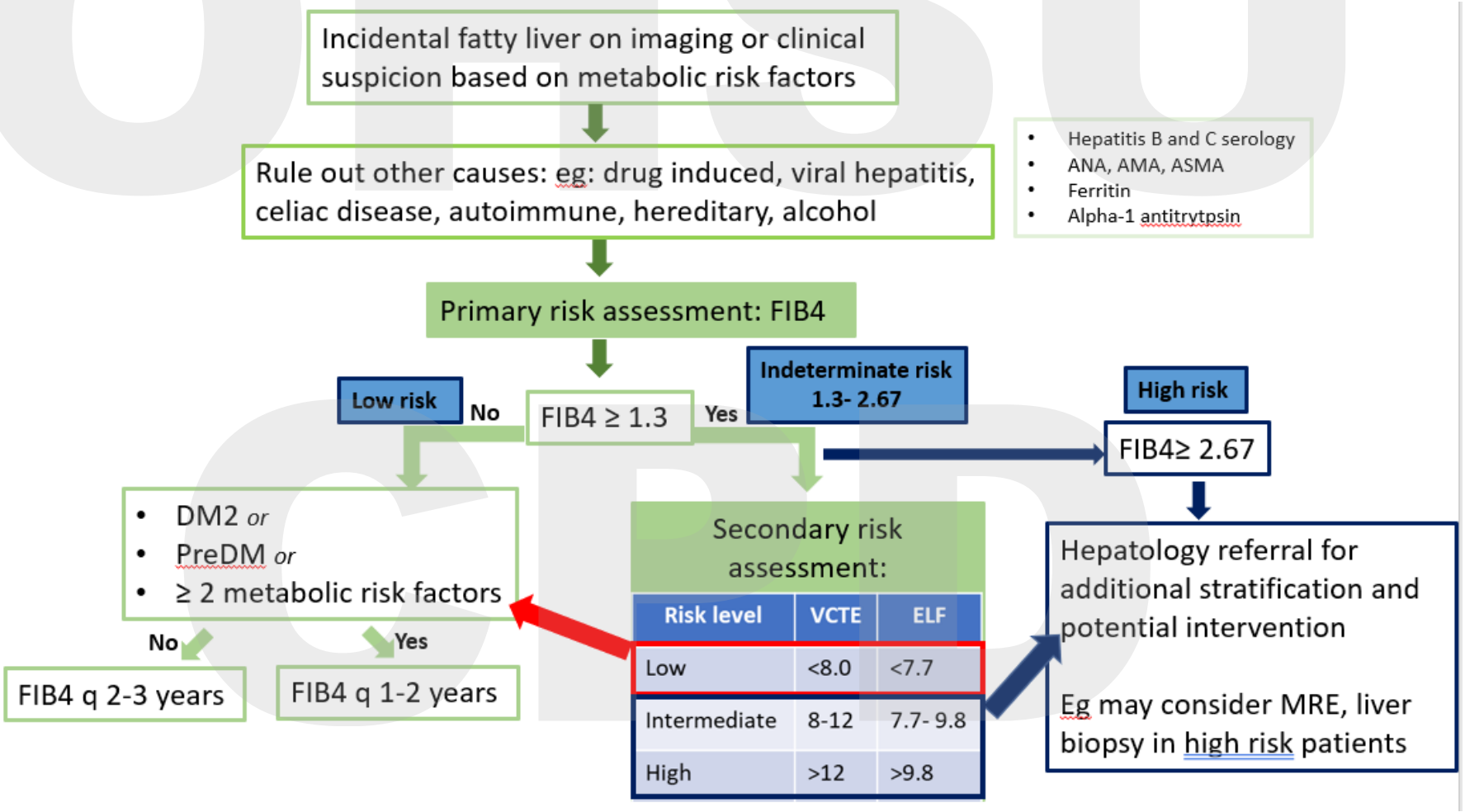
or

Increased AST or ALT (>30)

FIB-4

Most validated and cost-effective

Take home- Fibrosis risk stratification



References

- Metabolic dysfunction–associated steatotic liver disease: Update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease

Hepatology. 2023 Nov 9.

- AASLD Practice Guidance of the clinical assessment and management of NAFLD

Hepatology. 2023;77:1797–1835

- Nonalcoholic fatty liver disease from a primary care perspective

Diabetes Obes Metab.2023;25:1421–1433.

- AACE Clinical Practice Guidelines for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinical Settings

Endocrine Practice 28 (2022) 528-562

- Nonalcoholic Fatty Liver Disease: Review of Management for Primary Care Providers

Mayo Clin Proc. 2022;97(9):1700-1716

- ADA: Standards of Care in Diabetes, 2024