

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

تغذیه درمانی پزشکی در کبد چرب

دکتر مهدیه گل زرند

استادیار مرکز تحقیقات تغذیه در بیماری های غدد درون ریز

دانشگاه علوم پزشکی شهید بهشتی



- ▶ MASLD = Metabolic dysfunction-associated steatotic liver disease
- ▶ Current terminology that largely replaced NAFLD (non-alcoholic fatty liver disease) in 2023
- ▶ MASH = Metabolic dysfunction-associated steatohepatitis
- ▶ MASH is a more active form of MASLD:
- ▶ hepatic steatosis plus inflammation and hepatocellular injury, with or without fibrosis

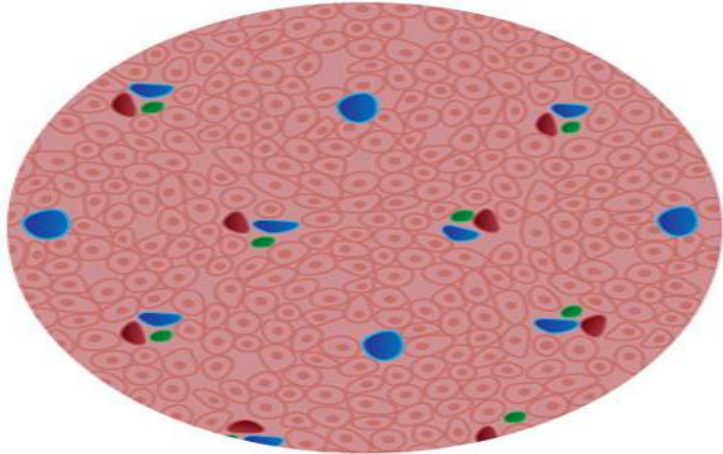
MASLD is characterized by:

- ▶ Hepatic steatosis (fat accumulation in the liver)

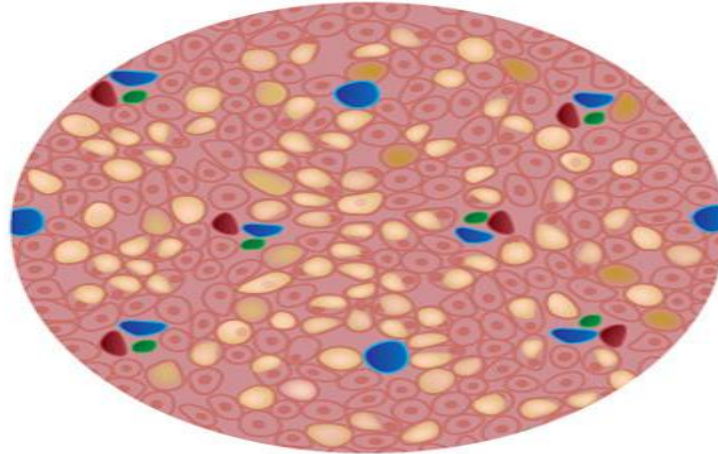
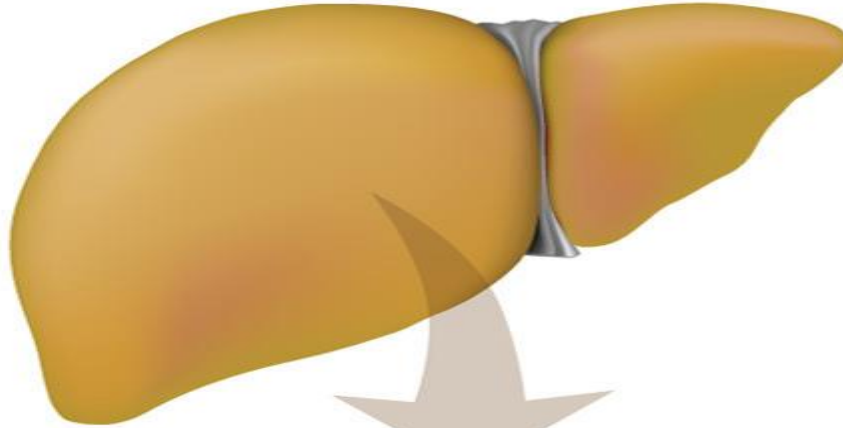
And at least one cardiometabolic risk factor, such as:

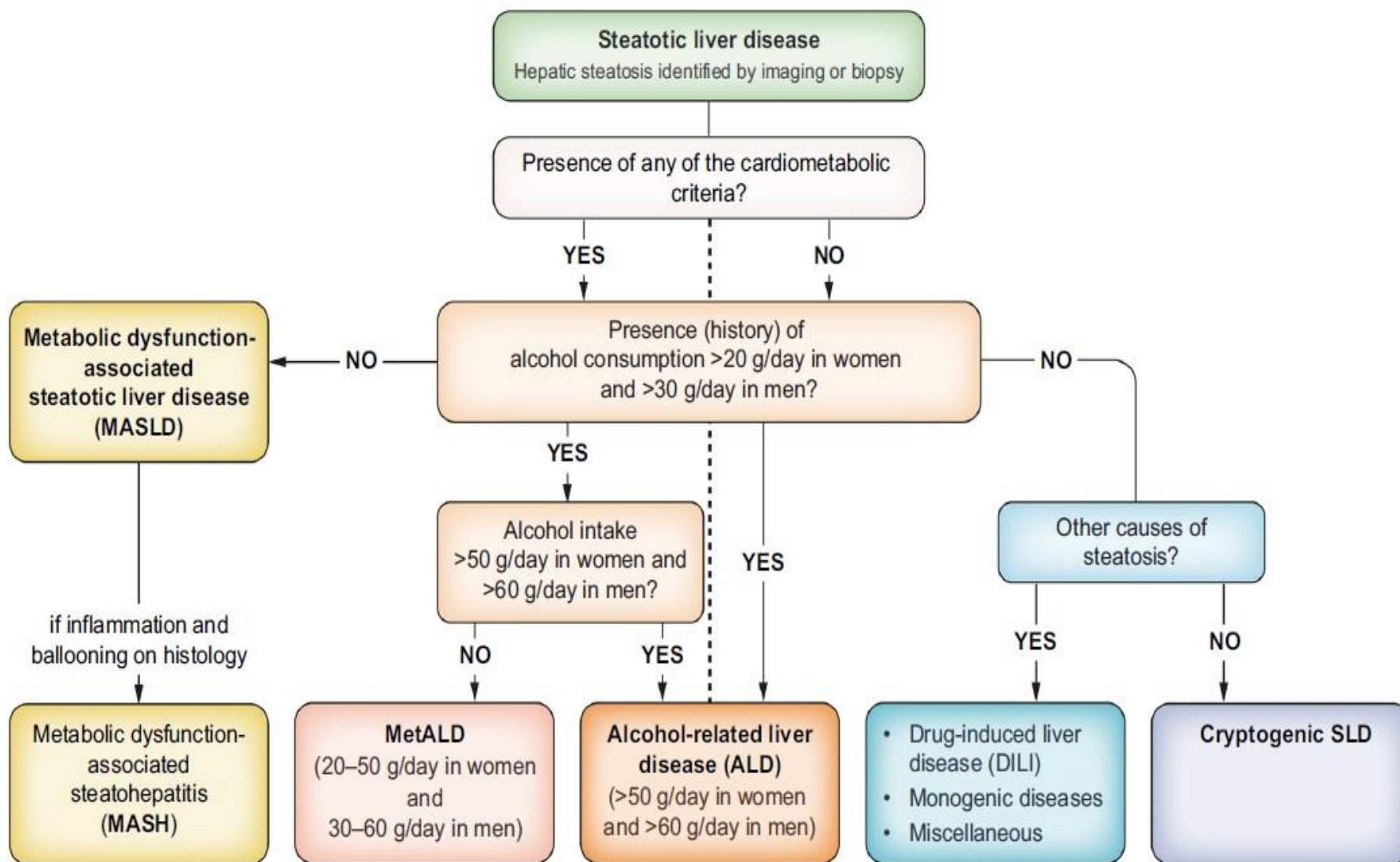
- ▶ Overweight or obesity
- ▶ Type 2 diabetes
- ▶ Hypertension
- ▶ Elevated triglycerides
- ▶ Low HDL cholesterol
- ▶ Other evidence of metabolic dysfunction

Healthy liver



Fatty liver





Most common concurrent diseases

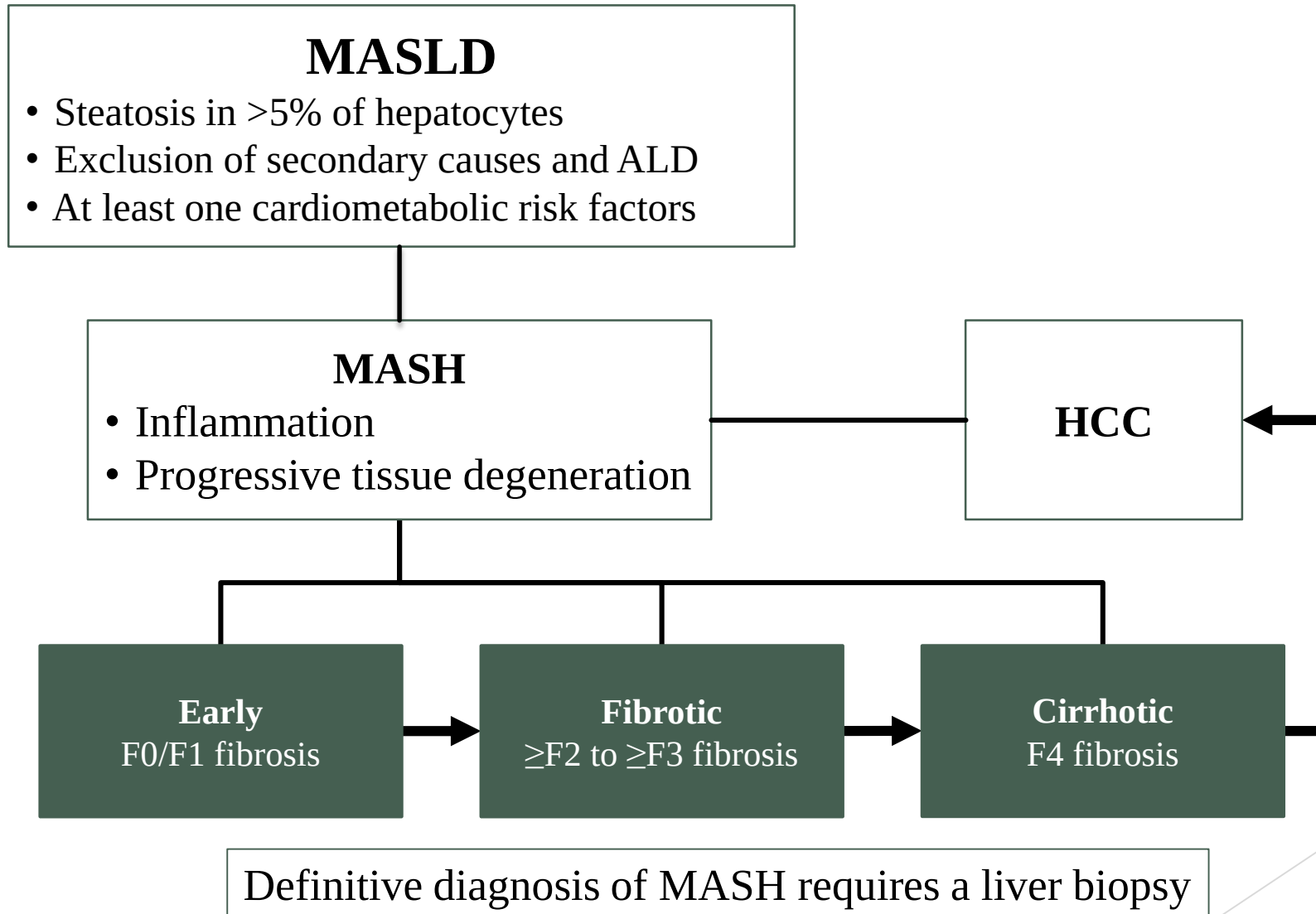
Drug-induced fatty liver disease

HCV-associated fatty liver disease

Others

- Haemochromatosis
- Autoimmune hepatitis
- Celiac disease
- Wilson disease
- A/hypo-betalipoproteinaemia lipodystrophy
- Hypopituitarism, hypothyroidism
- Starvation, parenteral nutrition
- Inborn errors of metabolism
 - Wolman disease (lysosomal acid lipase deficiency)

Disease spectrum and the clinical priority



Global MASLD prevalence:

- ▶ From 1990-2006 to 2016-2019 (meta-analysis)
- ▶ By 50% from 25% to 38%
- ▶ The MASLD prevalence was in Middle East 36.5% (after Latin America)
- ▶ **Global MASH prevalence: 5.3%**
- ▶ In the Middle East 5.8%

- ▶ **MASLD** prevalence in overweight: 70%
- ▶ **MASLD** prevalence in obesity: 75%
- ▶ **MASH** prevalence in overweight: 33.5%
- ▶ **MASH** prevalence in obesity: 33.6%

- ▶ **MASH** prevalence in T2D: 65%
- ▶ **MASH** prevalence in T2D: 66%

Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. The Lancet 2023; 8(1): 20-30.

The Global Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among Patients With Type 2 Diabetes. Clin Gastroenterol Hepatol 2024; 22(10): 1999-2010.

Pathogenesis: xenobiotic factors and genes

► **Genes:**

1- PNPLA3 I148M

2- TM6SF2 E167K

3- GCKR

► Associated with risk of MASH

Genotyping is not recommended routinely

► **Unhealthy lifestyles including:**

- 1- High calorie intake
- 2- Excess (saturated) fat
- 3- High fructose intake
- 4- Sedentary behaviour



Unhealthy lifestyles → **development and progression of MASLD**

Other risk factors

- ▶ Obesity especially abdominal obesity
- ▶ Type 2 diabetes
- ▶ Hyperlipidemia
- ▶ Metabolic syndrome
- ▶ Older people > 50 years
- ▶ Smoking

Gut microbiota

- ▶ Fermentation resistant starch and non-starch polysaccharides in SCFA → absorption by the intestinal epithelium
- ▶ **Obese microbiota** absorb higher energy from the diet and higher increase in total body fat than **lean microbiota**
- ▶ Dietary choline metabolism → produce TMAO
- ▶ Promote inflammation → MASH

Diagnosis: protocol for evaluation of MASLD

- ▶ Usually asymptomatic; majority discovered by chance
- ▶ Fatigue frequently present
- ▶ Right upper quadrant discomfort
- ▶ Abnormal LFTs
- ▶ ALT / AST not sensitive tool for diagnosis MASLD/MASH

- ▶ **Ultrasound essential**
- ▶ Identify steatosis
- ▶ Cannot distinguish type of MASLD

**To establish the degree of inflammation and fibrosis
non-invasive tools is warranted**

► Non-invasive tools:

1- Hepatic fibrosis markers: Fibrosis Score (NFS) and Fibrosis 4 (FIB-4)

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}}$$

NAFLD fibrosis score Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 [doi:10.1002/hep.21496](https://doi.org/10.1002/hep.21496)

Age (years)

BMI (kg/m²)

IGF/diabetes ☐

AST

ALT

Platelets (x10⁹/l)

Albumin (g/l)

BMI: body mass index
IGF: impaired [fasting glucose](#)

2- Imaging including: Fibroscan

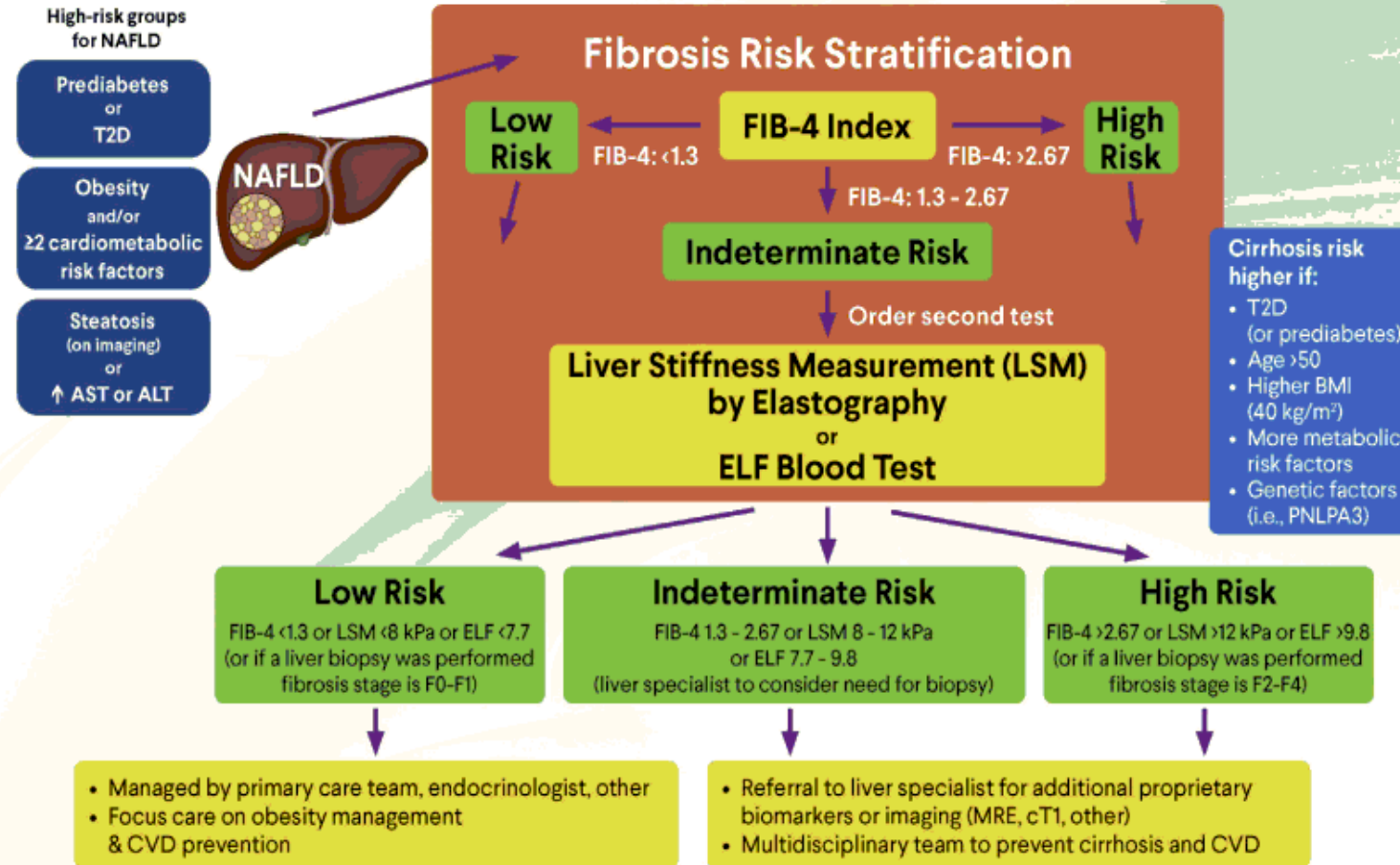
Advantage:

High performance for fibrosis and cirrhosis

▶ **Limitations:**

- ▶ Morbid obesity
- ▶ Ascites
- ▶ Extra-hepatic cholestasis
- ▶ Pregnancy

Cirrhosis Prevention in NAFLD



Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, cT1 = Liver multiscan, CVD = Cardiovascular disease, ELF = Enhanced liver fibrosis test™, FIB-4 = Fibrosis-4 index, kPa = Kilopascals, LSM = Liver stiffness measurement, MRE = Magnetic resonance elastography, T2D = Type 2 diabetes mellitus

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Algorithm Figure 2

Liver Biopsy: Gold Standard for fibrosis

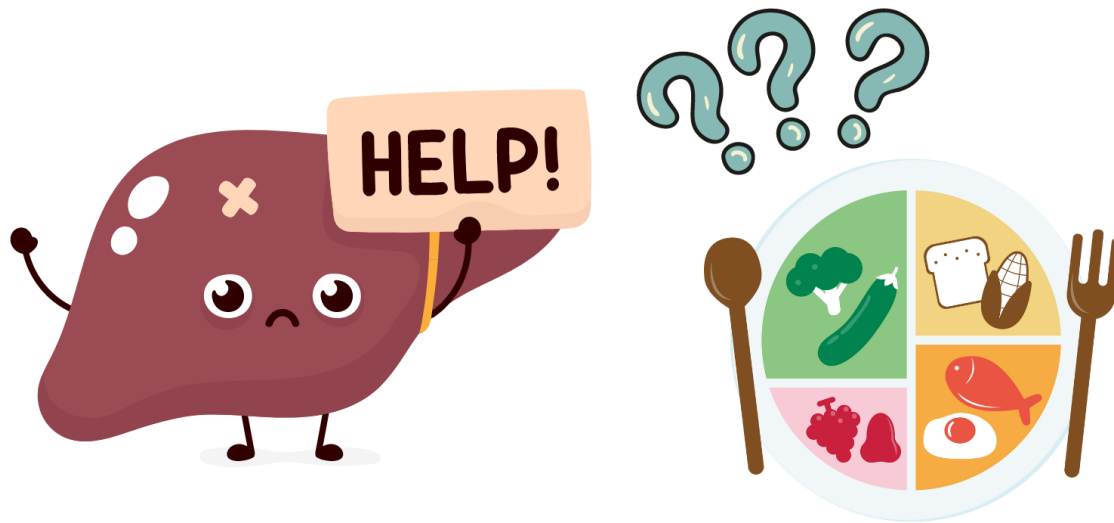
- ▶ Sampling errors
- ▶ Expensive
- ▶ Need hospitalization
- ▶ Dependent of observers interpretation

- ▶ Screening is **not recommended** in the general population

❖ **Recommended in individuals with:**

- ▶ Abnormal liver biochemistries
- ▶ Radiological signs of hepatic steatosis
- ▶ Type 2 diabetes mellitus
- ▶ Excess weight
- ▶ Aged over 50 years old

Treatment: diet and lifestyle changes



Aims:

- ▶ Improvement of liver histology including regression of fibrosis or resolution of MASH
- ▶ Changes in quantitative parameters assessing liver fat content
- ▶ Changes in quantitative assessment of liver fibrosis
- ▶ Changes in transaminases (ALT/AST) as a surrogate for hepatic inflammation
- ▶ Changes in metabolic parameters

Recommendations

- ▶ Healthy diet
- ▶ Smoking cessation
- ▶ Physical activity

	EASL-EASD-EASO 2016 ⁸	AASLD 2018 ⁹	ESPEN 2019 ¹⁰	APASL 2020 ¹¹
Energy restriction	500-1000 kcal energy deficit/day to induce a weight loss of 500-1000 g/week	Decrease caloric intake by at least 30% or by approximately 750-1000 kcal/day	Hypocaloric diet	Hypocaloric diet (500-1000 kcal deficit/day).
Weight loss	7%-10% total weight loss target	≥5% for steatosis improvement, ≥7% for histological improvement	7%-10% in overweight/obese patients >10% to improve fibrosis	7%-10% weight loss, gradual weight loss (up to 1 kg/week)
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein	NS	• Irrespective of macronutrient composition • Mediterranean diet to improve steatosis and insulin sensitivity	• No strong evidence to support a particular dietary approach. • Plans should encourage low-carbohydrate, low-fat and Mediterranean-type diets
Fructose	Avoid fructose-containing beverages and foods	NS	NS	Exclusion of beverages high in added fructose
Alcohol	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women) • Moderate alcohol intake (namely, wine) below the risk threshold is associated with lower prevalence of NAFLD, NASH and even lower fibrosis	• Should not consume heavy amounts of alcohol. • Insufficient data on nonheavy consumption of alcohol	Abstain	• The "cut-off" values of alcohol intake in MAFLD should be set lower than the apparent "threshold levels". • Patients with MAFLD should be advised to avoid alcohol and if that is not possible, to consume the lowest amount possible.
Coffee	No liver-related limitations.	NS	More likely to benefit health than harm	NS
Physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise	• Physical activity more than 150 minutes/week • Moderate intensity exercise	Increase physical activity	• Aerobic exercise and resistance training effectively should be tailored based on patient preferences to ensure long-term adherence. • Resistance exercise may be more feasible than aerobic exercise for patients with poor fitness.

Weight loss

- ▶ **EASL 2016:** 7%-10% total WL
- ▶ **AASLD 2018:** $\geq 5\%$ for steatosis improvement, $\geq 7\%$ for histological improvement
- ▶ **ESPEN 2019:** 7%-10% in overweight/obese patients, $>10\%$ to improve fibrosis
- ▶ **APASL 2020:** 7%-10% total WL
- ▶ Weight reduction not exceed approximately 1.6 kg/week

Results of a meta-analysis:

- ▶ $WL \geq 5\%$ ➡ hepatic steatosis
- ▶ $WL \geq 7\%$ ➡ improvement in the NAFLD Activity Score (NAS)
- ▶ **Results of a recent study: $WL > 10\%$**
- ▶ 45% regression of fibrosis
- ▶ 90% resolution of steatohepatitis
- ▶ 100% improvements in NAS

Overall recommendation for weight loss:

- ▶ $\geq 5\%$ to reduce liver fat
- ▶ 7-10% to improve liver inflammation
- ▶ $\geq 10\%$ to improve fibrosis

Weight reduction with or without physical activity improvements in:

- ▶ Liver enzymes
 - ▶ Steatosis
 - ▶ NASH
 - ▶ Fibrosis
-
- ▶ Evidence for advanced fibrosis or cirrhosis is insufficient

Energy restriction

- ▶ **EASL 2016:** 500-1000 kcal/day
- ▶ **AASLD 2018:** 750-1000 kcal/day
- ▶ **ESPEN 2019:** Hypocaloric diet
- ▶ **APASL 2020:** 500-1000 kcal/day

Macronutrient composition

- ▶ **EASL 2016:** low-carbohydrate ketogenic diets or high-protein
- ▶ **AASLD 2018:** NS
- ▶ **ESPEN 2019:** Mediterranean diet
- ▶ **APASL 2020:** low-carbohydrate, low-fat and Mediterranean-type diets

- ▶ **Low-carbohydrate diet (LCD):** reduction in intrahepatic lipid content
- ▶ Hypocaloric LCD is more effective than hypocaloric LFD
- ▶ **VLCD contains 5-10% carbohydrate:** very effective in short-term
- ▶ **VLKD (<20-50 g/day):** insufficient evidence on the efficacy or safety
- ▶ **Intermittent calorie restriction:** reduced LFTs but long-term

feasibility and safety is controversial

High protein diet → decrease intrahepatic lipid content

▶ animal protein or plant protein???

▶ Animal proteins → increase Met, Hcy and Cys

▶ Plant proteins → increase BCAAs

▶ **Controversy ???**

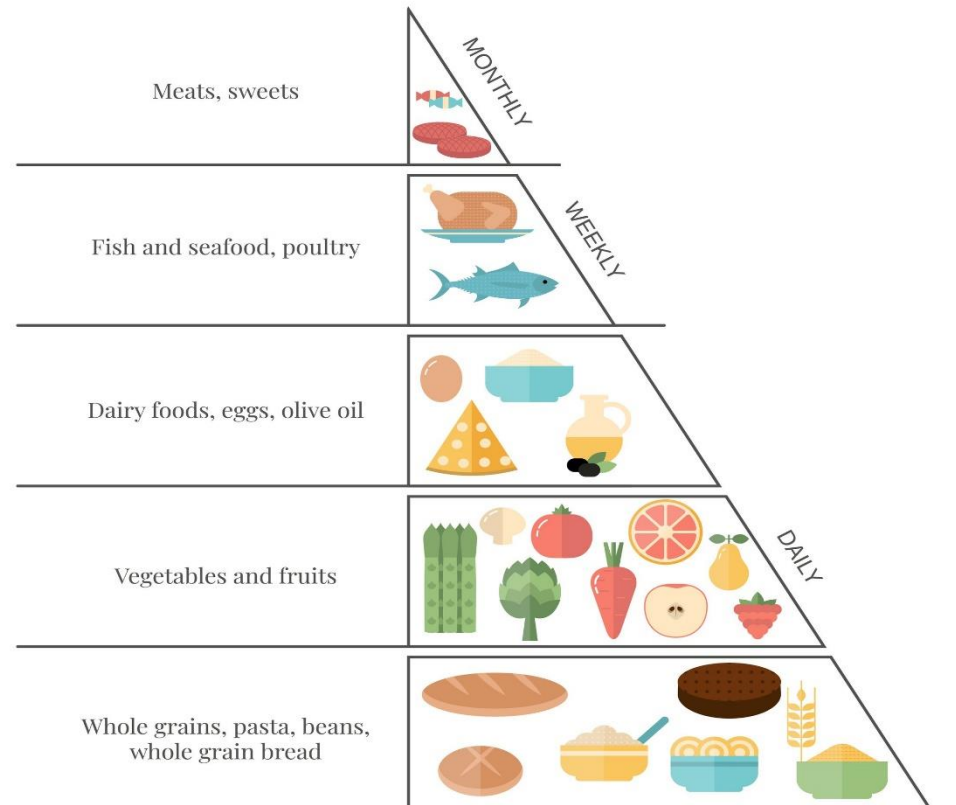
- ▶ **The Mediterranean diet**

- ▶ Fruit and vegetables

- ▶ Whole grains

- ▶ Nuts and legumes

- ▶ Fish and olive oil



- ▶ Reduces hepatosteatosis and liver stiffness measurement (LSM)

- ▶ Reduced risk of HCC or liver-related death

► A systematic review and meta-analysis of 13 interventions reduced:

✓ ALT (-6.59)

✓ Fatty Liver Index (FLI) (-15.6)

✓ Liver stiffness (-0.75)

✓ No effect on AST and hepatic steatosis

❖ In children & adolescent: improve LFTs and liver function

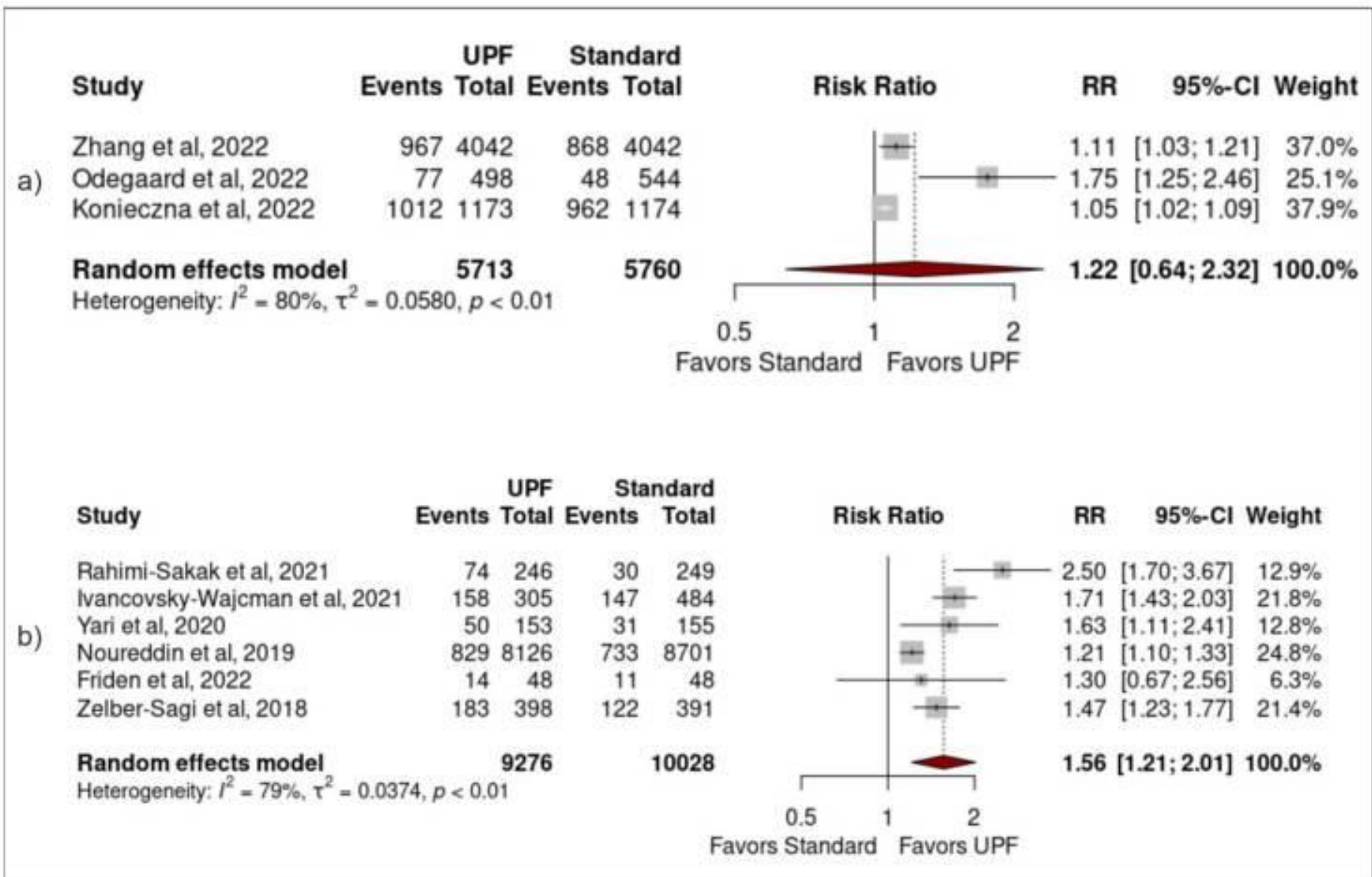
The effectiveness and acceptability of Mediterranean diet and calorie restriction in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis. Clin Nutr. 2022 Sep;41(9):1913-1931.

Efficacy of the Mediterranean diet in treating metabolic dysfunction-associated steatotic liver disease (MASLD) in children and adolescents: a systematic review and meta-analysis. BMC Public Health 2024; 24(1):2701.

Processed food and Fructose

- ▶ **EASL 2016:** Avoid processed foods and fructose-containing beverage and foods
- ▶ **AASLD 2018:** NS
- ▶ **ESPEN 2019:** NS
- ▶ **APASL 2020:** Exclusion of processed foods and beverages high in added fructose
- ▶ Based on a meta-analysis, total fructose-containing sugars  increased intrahepatocellular lipid (IHCL) by %10

- ▶ **SSB** —→ higher MASLD prevalence, MASH presence and fibrosis
- ▶ **Fructose-** but not **glucose-SSB** have been associated with:
 - ▶ increased *de novo* lipogenesis
 - ▶ dyslipidemia
 - ▶ visceral adiposity
 - ▶ impaired insulin sensitivity
- ▶ SSBs providing 27% to 30% excess energy led to a moderate increased IHCL by 10% and ALT by 11%



Alcohol

- ▶ **EASL 2016:** <30 g for men and 20 g for women
- ▶ **AASLD 2018:** Not consume heavy amounts of alcohol
- ▶ **ESPEN 2019:** Abstain
- ▶ **APASL 2020:** Lower than “threshold levels” in MAFLD should be set

Coffee

- ▶ **EASL 2016:** No limitations
- ▶ **AASLD 2018:** NS
- ▶ **ESPEN 2019:** Benefit health more than harm
- ▶ **APASL 2020:** NS

Based on some studies:

- ▶ Increasing antioxidant capacity
- ▶ Suppressing inflammation
- ▶ Decreasing hepatic lipid accumulation (improve MASLD)
- ▶ Regulating gut Microbiota
- ▶ Improving liver damage
- ▶ Reduced liver-related clinical outcomes

► Results of a meta-analysis of 11 epidemiological studies indicated regular coffee consumption leads to:

- ✓ A 23% lower risk of MASLD incident
- ✓ A 33% lower risk of liver fibrosis in MASLD patients

Although there are some controversy

Exercise

- ▶ **EASL 2016:** 150-200 min/wk of moderate intensity aerobic PA (3-5 sessions)
and resistance training is also effective
- ▶ **AASLD 2018:** > 150 min/wk moderate intensity PA
- ▶ **ESPEN 2019:** Increase physical activity
- ▶ **APASL 2020:** Aerobic exercise and resistance training

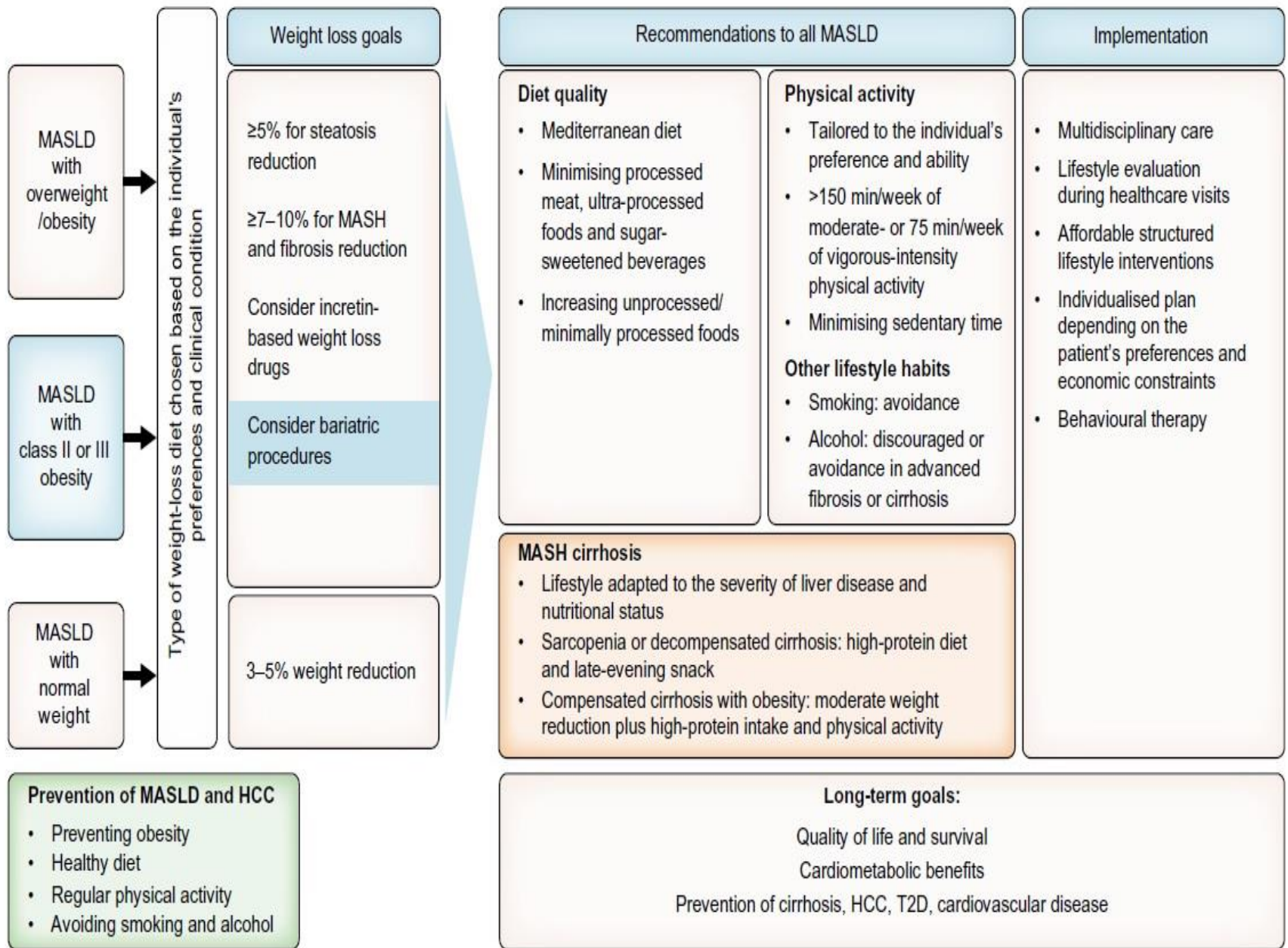
► Result of a meta-analysis including 24 studies (18 RCTs and six non-RCTs, encompassing 1014 patients with MASLD) indicated:

✓ Moderate-intensity continuous training ➡ decrease of liver enzymes and liver fat

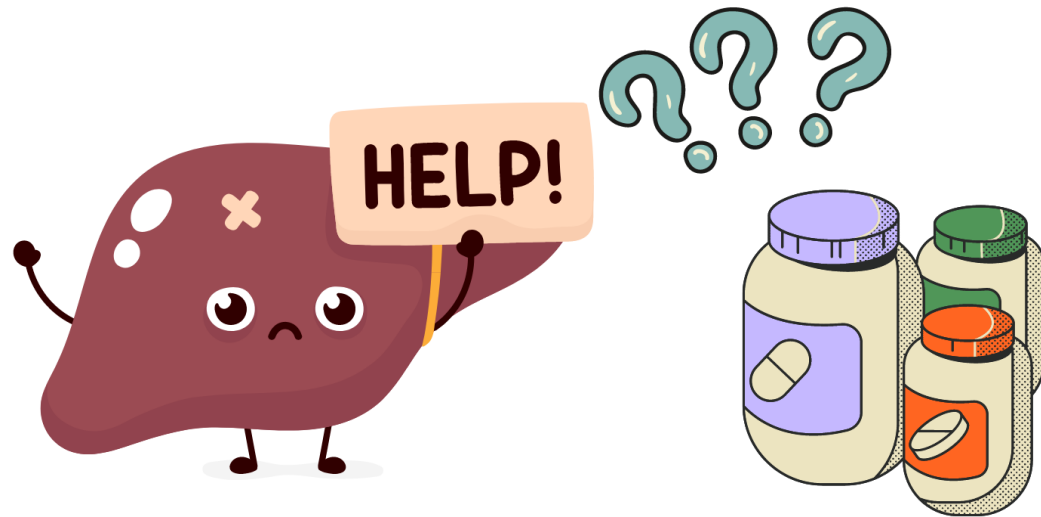
✓ High-intensity interval training ➡ decrease of liver fat

Meta-analysis on 10 studies (316 individuals who had MASLD) has shown:

- ▶ Exercise without significant weight loss significantly reduced the intrahepatic lipid (IHL) content and ALT, AST
- ▶ Aerobic exercise alone significantly reduced IHL, ALT, and AST
- ▶ Resistance training alone significantly reduced TC and TG
- ▶ A combination of both exercise types significantly reduced IHL



Treatment: pharmacotherapy



- 
- ▶ Treatment should be indicated in:
 - ▶ Non-cirrhotic MASH with significant fibrosis (stage ≥ 2)
 - ▶ Non-cirrhotic MASH at-risk significant fibrosis
 - ▶ No for MASH at the cirrhotic stage

Resmetirom (Thyroid Hormone Receptor Agonists)

First FDA-approved for noncirrhotic MASH with F2–F3 fibrosis

- ▶ **Hepatic steatosis:** stimulating hepatic lipophagy and mitochondrial biogenesis / inhibiting hepatic lipogenesis
- ▶ **Fibrosis:** by inhibiting TGF- β signaling

In a RCT:

- ▶ Resolution of steatohepatitis and fibrosis
- ▶ Lower progression of fibrosis in stage 2 fibrosis
- ▶ Reduced liver enzymes

Daily dose of in US:

- ▶ 80 mg in <100 kg / 100 mg in ≥ 100 kg
- ▶ **Common side effects:** diarrhoea, nausea, pruritus and vomiting
- ▶ **Monitoring:** gastrointestinal side effects and thyroid hormone function
- ▶ **Contraindication:** CYP2C8 inhibitors such as Clopidogrel & Gemfibrozil

Pioglitazone (PPAR γ agonist)

- ▶ Reduction of > 2 points NAS
 - ▶ Improved all histological features
 - ▶ Achieved resolution of MASH more often
 - ▶ Safe but not recommended for MASH therapy
- Withdrawn in several European countries
- ▶ New generation pan-PPAR is on going: improvement of steatohepatitis and fibrosis

Vitamin E (800 IU/d)

- ▶ Improve steatosis, inflammation and ballooning
- ▶ (histological improvement ≥ 2 point reduction in NAS)
- ▶ Resolution of MASH
- ▶ No improvement in fibrosis scores
- ▶ Concerns about long-term safety exist
 - * incidence of prostate cancer
 - * hemorrhagic stroke
- ▶ **The optimal duration of therapy is unknown** → **up 6 months**

Three new drugs:

1- GLP-1 analogue

▶ *Liraglutide*

▶ *Semaglutide*

FDA indication: MASH without cirrhosis

In RCT:

✓ Resolution of steatohepatitis

✓ **No fibrosis improvement**

2- Dual GLP1-GIP (Tirzepatide)

- ▶ FDA indication: Diabetes/obesity with MASLD
- ▶ In a RCT: steatohepatitis resolution
- ▶ Safe but **not** recommended for MASH therapy

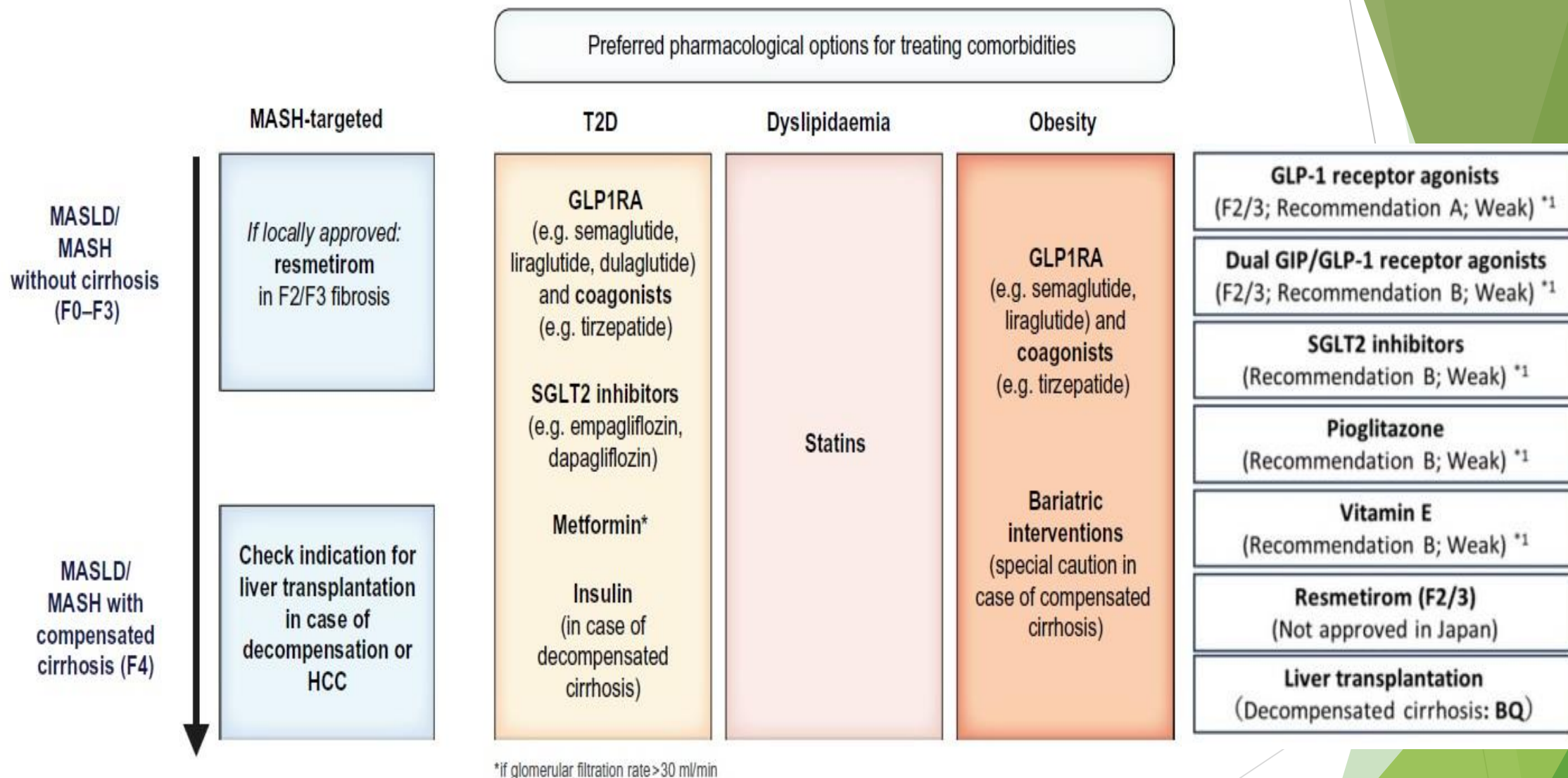
3- Sodium glucose co-transporter 2 (SGLT2) inhibitor

- ▶ *Dapagliflozin*

- ▶ *Empagliflozin* → *Reductions in ALT*

FDA indication: Diabetes with MASLD

- ▶ Safe but **not** recommended for MASH therapy



Synbiotics and probiotics:

- ▶ Improving insulin resistance
- ▶ Improving hepatic steatosis
- ▶ Decreased hepatic enzymes
- ▶ Reducing MASLD progression
- ▶ No beneficial effects on fibrosis
- *Probiotics marginally are effective*

- 
- The background of the slide features abstract, overlapping green geometric shapes, primarily triangles and polygons, in various shades of green, creating a modern and dynamic visual effect.
- ▶ Results are inconsistent
 - ▶ Effective strains: Bifidobacteria, Lactobacili, S.thermophiles
 - ▶ **Safe & well tolerated**

Co-administration of prebiotics:

- ▶ Improving lipid profile
- ▶ Improving insulin resistance
- ▶ Improving liver enzymes
- ▶ Improving hepatosteatosis
- ▶ **Prebiotics alone showed no effectiveness**

Omega 3:

- ▶ Reduced circulating TG levels (2 g/day)
- ▶ Reduced inflammatory markers
- ▶ Reduced AST & ALT
- ▶ **No histological efficacy**
- ▶ **Safe up to 4 g/d & tolerated (occasional abdominal discomfort)**
- ▶ may atrial fibrillation???

Possible Interaction:

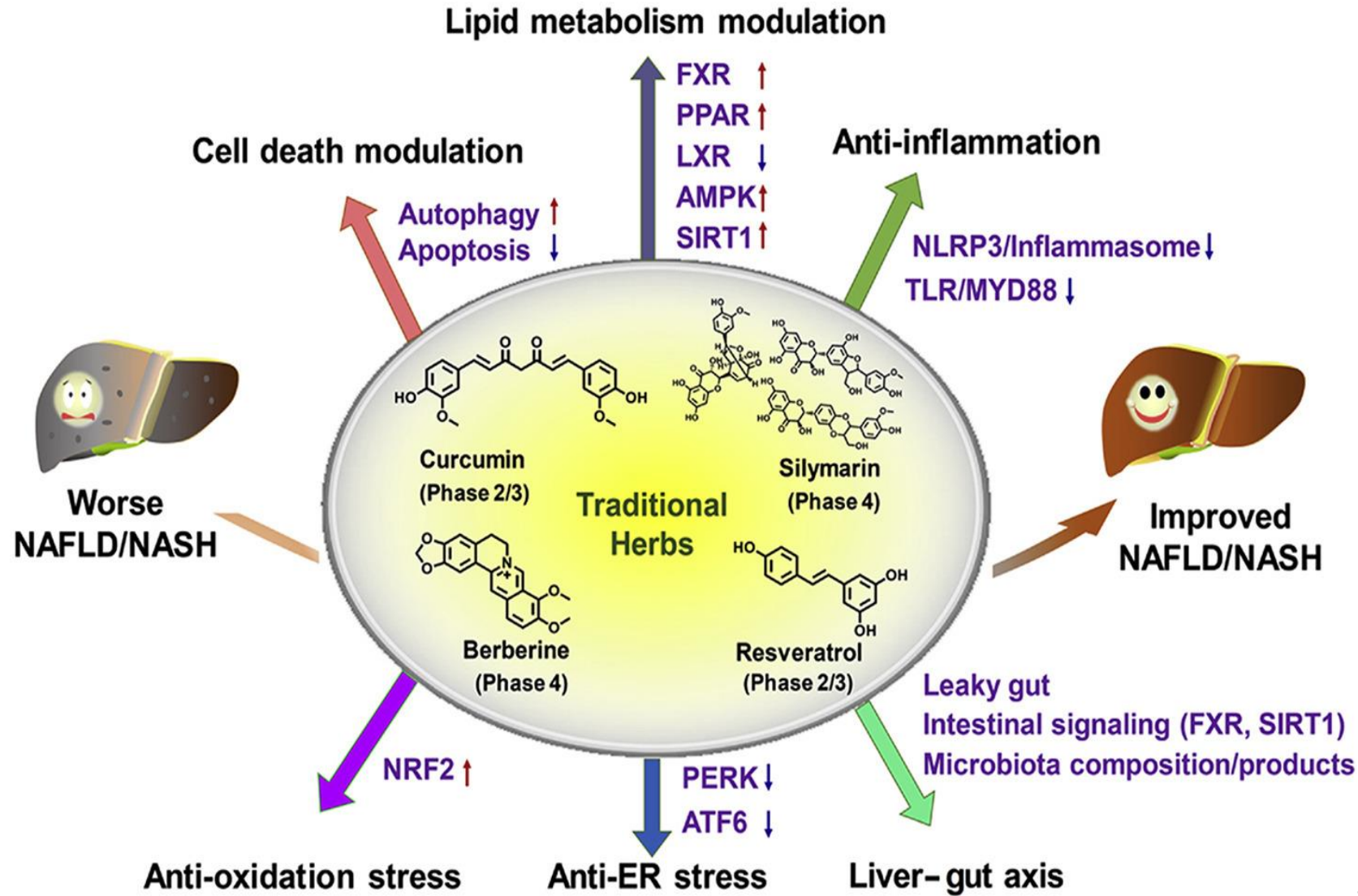
- ▶ Anticoagulant and antiplatelet drugs, herbs and supplements
- ▶ Blood pressure drugs, herbs and supplements
- ▶ Contraceptive drugs
- ▶ Orlistat
- ▶ Vitamin E

Vitamin D3:

- ▶ Improving of insulin sensitivity
- ▶ Reducing production of inflammatory markers
- ▶ Reducing hepatic inflammation
- ▶ Inhibiting of liver fibrosis

- ▶ **Safe and well tolerated**

Herbal Medicine



Silymarin:

- ▶ Improving hepatostatosis and fatty liver enzymes
- ▶ Improving insulin resistance
- ▶ Improving glucose and lipid metabolism
- ▶ In NASH, improves fibrosis and liver stiffness
- ▶ In cirrhosis, reduced mortality (420 mg/d)
- ▶ **Safe (short-term) & well tolerated**

Interaction:

- ▶ Diazepam
- ▶ Warfarin
- ▶ Diabetes medications
- ▶ Raloxifene
- ▶ Simeprevir
- ▶ Sirolimus

Resveratrol:

- ▶ Improving most of inflammatory indices
- ▶ Improving liver enzymes
- ▶ Reducing hepatic steatosis
- ▶ Improving liver damages
- ▶ **Safe & well tolerated up to 1 g/d (no > 2.5 g/d)**

Curcumin:

- ▶ Improved inflammation and metabolic markers
- ▶ Improved gut microbiota
- ▶ Reducing liver enzymes
- ▶ Improving MASLD (> 1000 mg/d)
- ▶ Maybe mitigating MASH progression
- ▶ **Safe & well tolerated but maybe low adherence**

Possible Interaction:

- ▶ Anticoagulant / Antiplatelet drugs
- ▶ Diabetes medications
- ▶ Antitumor drugs
- ▶ Hepatotoxic drugs (methotrexate)

Berberine:

- ▶ Improved oxidative stress and inflammatory markers
- ▶ Improved glucose, lipid profile, and insulin resistance
- ▶ Reducing liver fat content

- ▶ **Safe & well tolerated up to 1 g/d**

Results of new network meta-analysis:

- ▶ **ALT:** Artichoke leaf, Cinnamon, Chicory
- ▶ **AST:** Cinnamon, Berberine, Artichoke leaf
- ▶ **GGT:** Cinnamon, Garlic + Silymarin, Berberine, Silymarin
- ▶ **Stiffness:** Silymarin, Hesperidin + flaxseed, Pomegranate, Curcumin
- ▶ **Steatosis:** Fenugreek seeds, Curcumin, N. stavia

Treatment: surgery

Bariatric surgery:

- ✓ In adults with non-cirrhotic MASLD **with an approved indication**
 - ✓ In adults with MASLD -related compensated advanced chronic liver disease/compensated cirrhosis **with an approved indication**
-
- ▶ Reduces liver fat and reduce MASH progression
 - ▶ Histological resolution of MASH without worsening of fibrosis in 55%
 - ▶ Fibrosis improvement by ≥ 1 stage without worsening of MASH after one-year was achieved in 37%

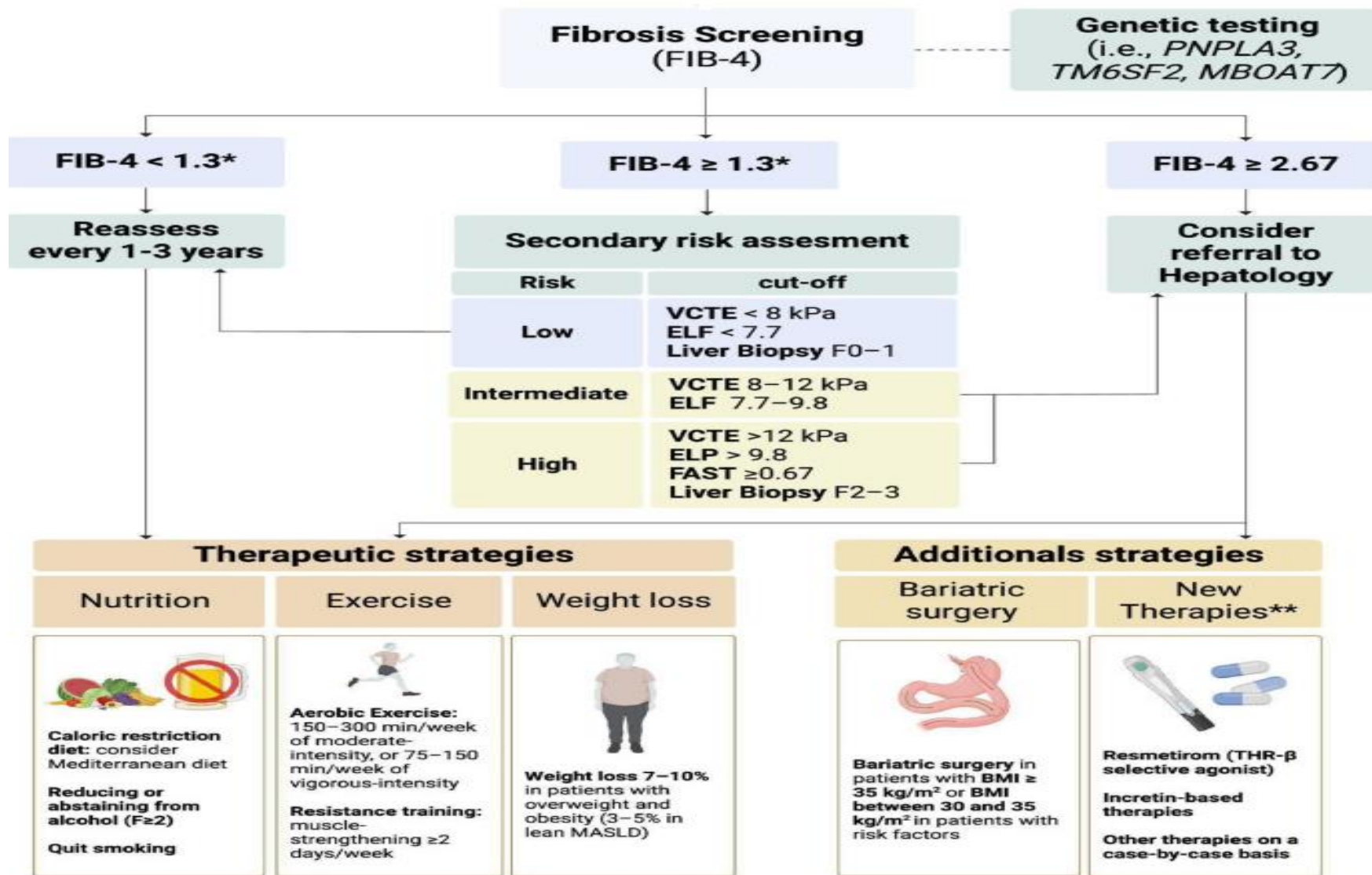
- ▶ At 5 years: NASH was resolved, without worsening fibrosis: 84%
- ▶ Fibrosis decreased, compared with baseline: 70%
- ▶ Fibrosis disappeared: 56%

In meta-analysis improvement in:

- steatosis in 56%
- ballooning degeneration in 49%
- inflammation in 45%
- fibrosis in 25%
- ALT and AST

Liver transplantation:

- ▶ An accepted procedure in patients with NASH and end-stage liver disease.
Overall survival is comparable to other indications, despite a higher cardiovascular mortality.
- ▶ **Only for patients with MASH and liver failure and/or HCC**



*A FIB-4 threshold of ≥ 2.0 should be considered for patients aged 65 years or older.

**Most of these therapies require further validation in Phase 3 clinical trials and long-term follow-up.



Thank you for your
time.

Any questions?



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