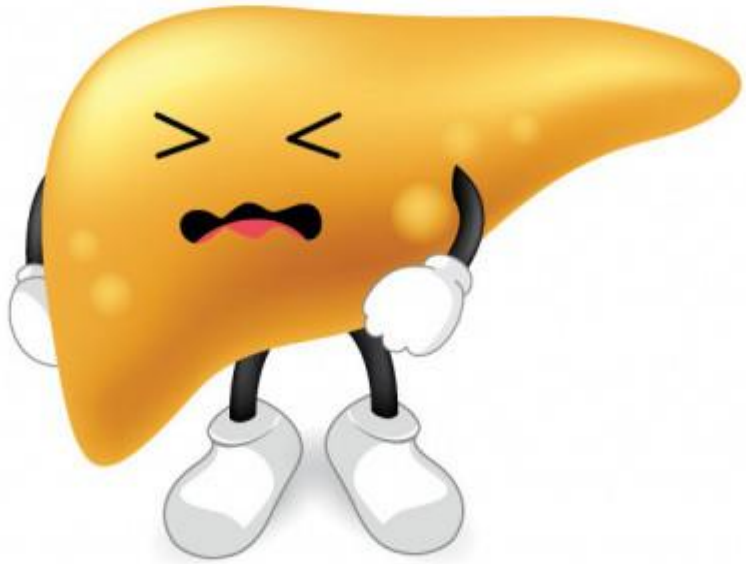

بسم الله الرحمن الرحیم

تغذیه درمانی پزشکی در کبد چرب

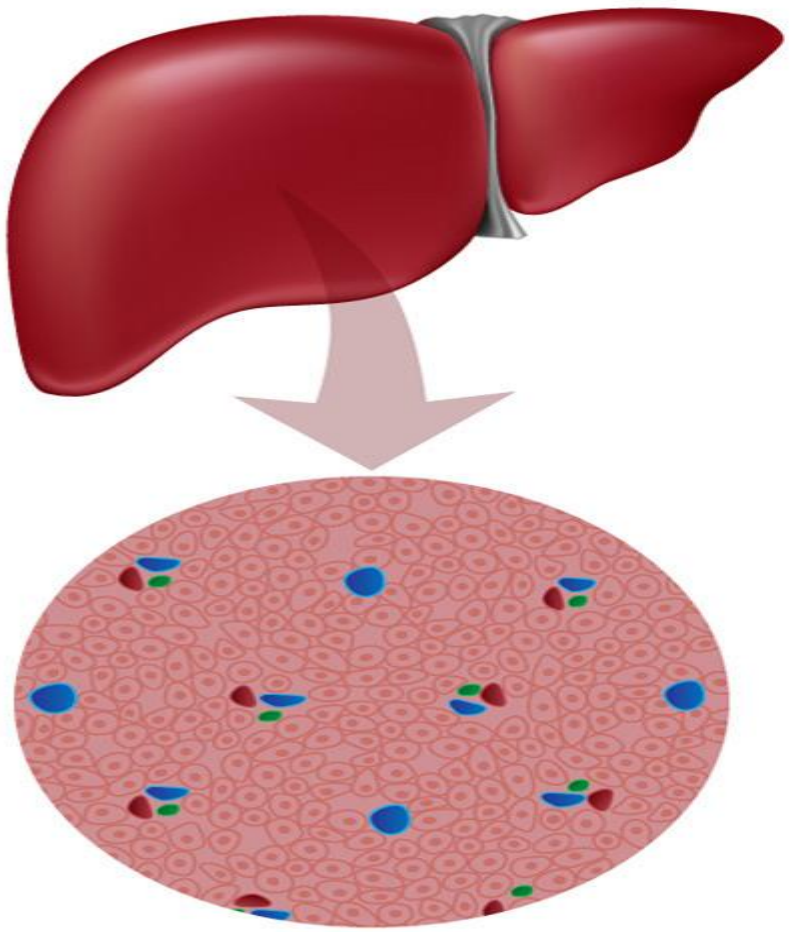
دکتر مهدیه گل زرند

استادیار مرکز تحقیقات تغذیه در بیماری های غدد درون ریز

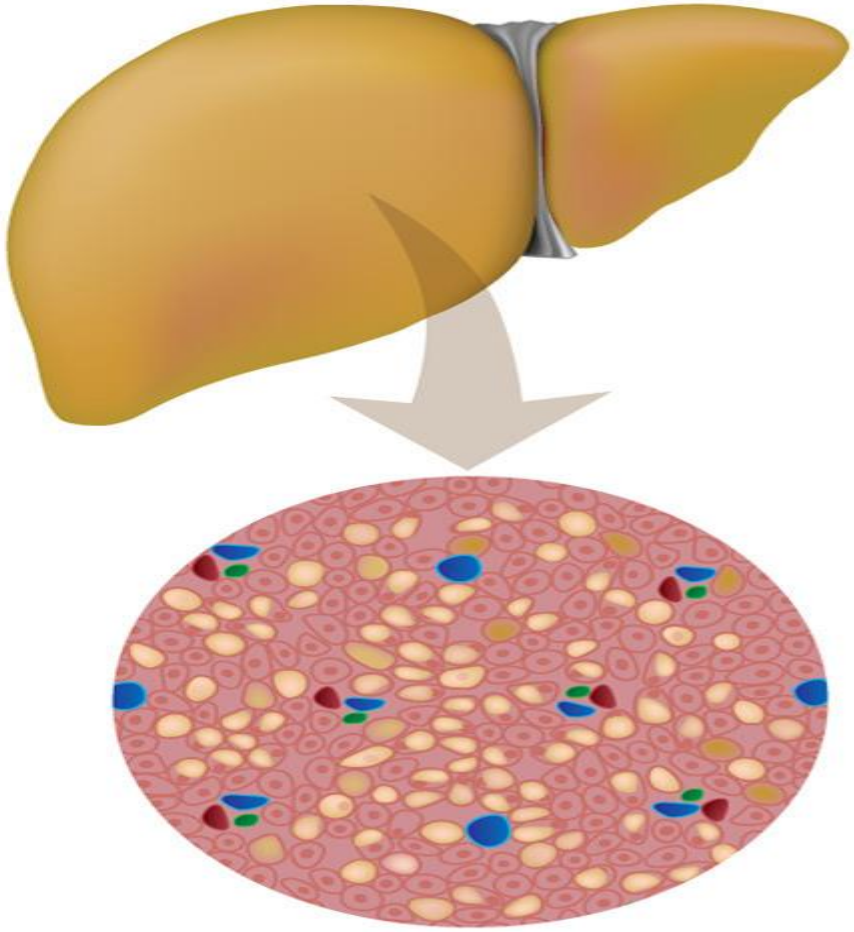
دانشگاه علوم پزشکی شهیدبهشتی



Healthy liver



Fatty liver



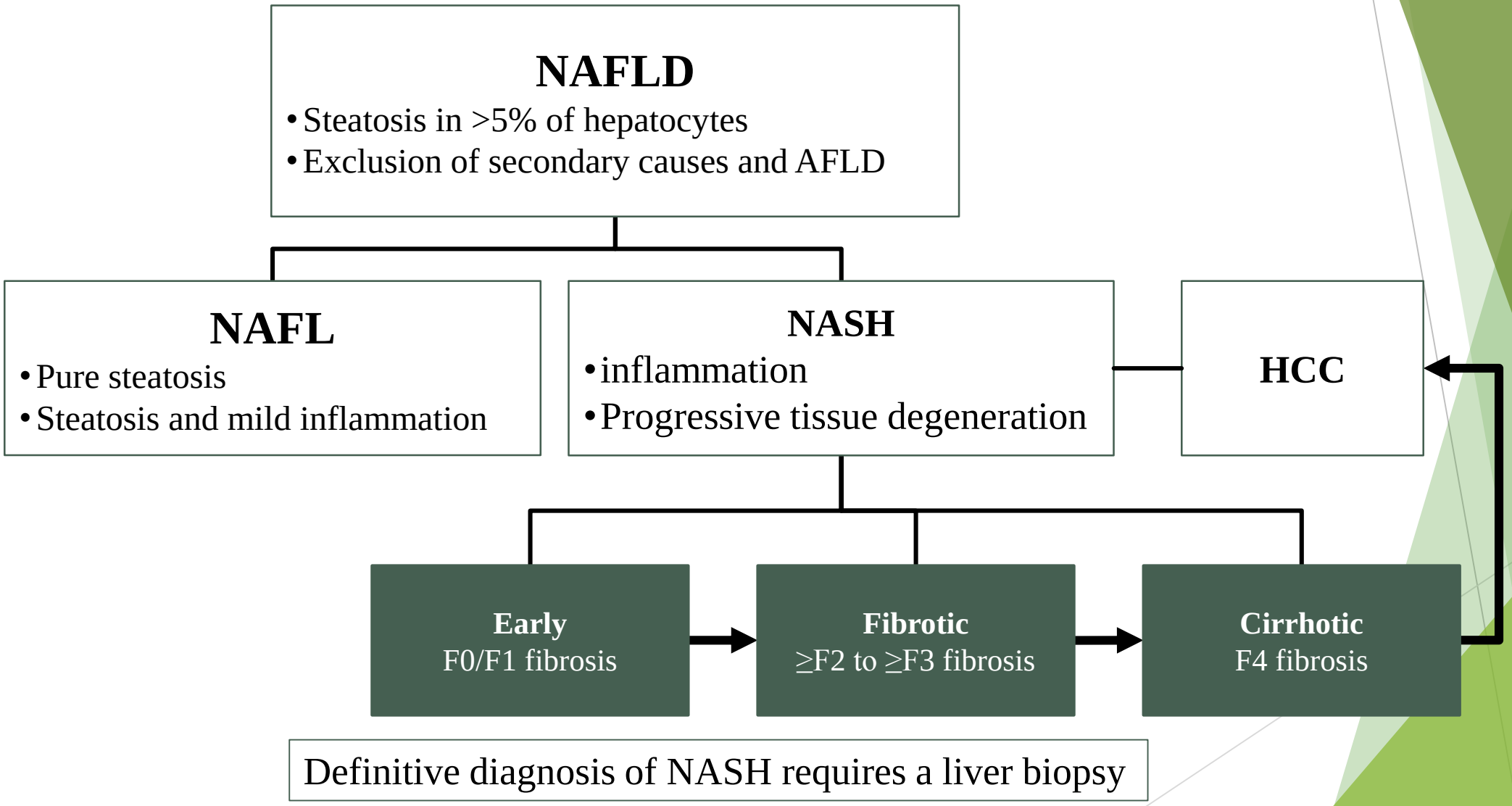
Most common concurrent diseases

Alcoholic fatty liver disease (AFLD)
Drug-induced fatty liver disease
HCV-associated fatty liver disease
Others

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

J Hepatol 2016;64:1388–402

Definitions of NAFLD, NAFL and NASH



Global NAFLD prevalence:

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

The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023; 77(4):1335-1347.

- **NAFLD** prevalence in overweight: 70%
- **NAFLD** prevalence in obesity: 75%
- **NASH** prevalence in overweight: 33.5%
- **NASH** prevalence in obesity: 33.6%

- **NAFL** prevalence in T2D: 65%
- The NAFLD prevalence was in Middle East 71% (after Eastern Europe)
- **NASH** 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 NASH

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 NAFLD

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 ⟶ NASH

Non-Alcoholic Fatty Liver Disease: From Pathogenesis to Clinical Impact. Processes 2021; 9: 135.

Diagnosis: protocol for evaluation of NAFLD

- Usually asymptomatic; majority discovered by chance
- Fatigue frequently present
- Right upper quadrant discomfort
- Abnormal LFTs

- ALT / AST not sensitive tool for diagnosis NAFLD/NASH

- 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

- **Ultrasound essential**
- Identify steatosis
- Cannot distinguish type of NAFLD

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)

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

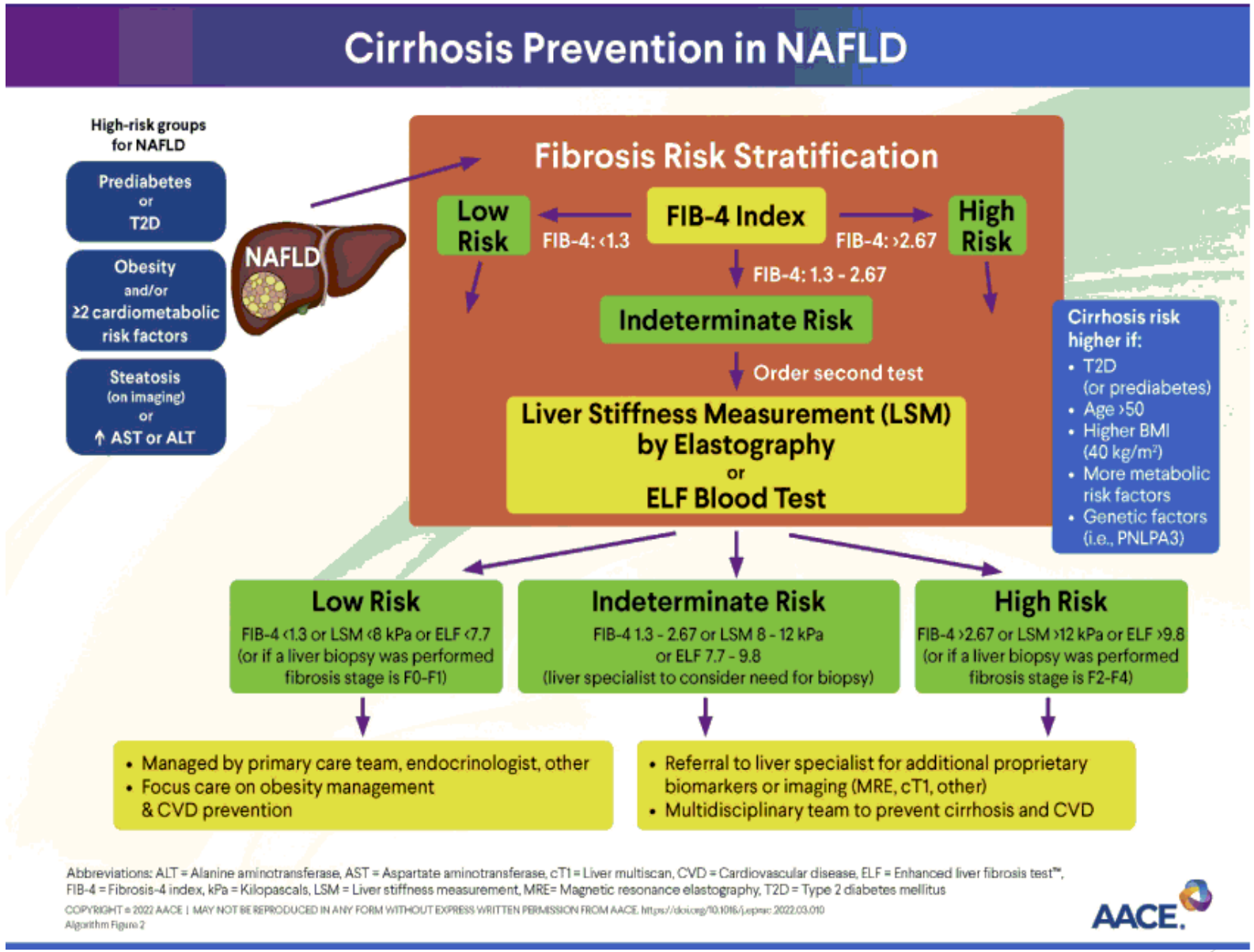
NAFLD fibrosis score
Online calculator

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

Age (years)
BMI (kg/m²)
IGF/diabetes ☐
AST
ALT
Platelets (x10³/l)
Albumin (g/l)
calculate score

BMI: body mass index
IGF: impaired fasting glucose

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

Algorithm Figure 2

AACE

2- Imaging including: Fibroscan

Advantage:

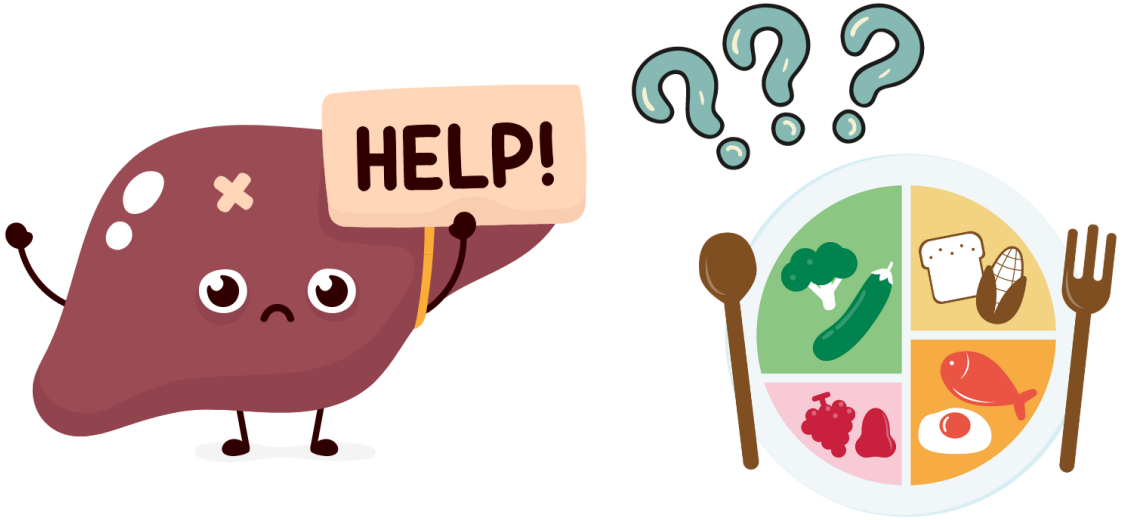
High performance for fibrosis and cirrhosis

- **Limitations:**
- Morbid obesity
- Ascites
- Extra-hepatic cholestasis
- Pregnancy

Liver Biopsy: Gold Standard for fibrosis

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

Treatment: diet and lifestyle changes



Aims:

- Improvement of liver histology including regression of fibrosis or resolution of NASH
- 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 cession
- 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.

Results of a meta-analysis:

- WL ≥ 5% ⟶ hepatic steatosis
- WL ≥ 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

Weight loss

- **EASL 2016:** 7%-10% total WL
- **AASLD 2018:** ≥5% for steatosis improvement, ≥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

Overall recommendation for weight loss:

- ≥5% to reduce liver fat
- 7-10% to improve liver inflammation
- ≥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

The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: A systematic review and meta-analysis. Metabolism. 2021;115:154455.
Lifestyle changes in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis. PLoS One. 2022;17(2):e0263931.

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

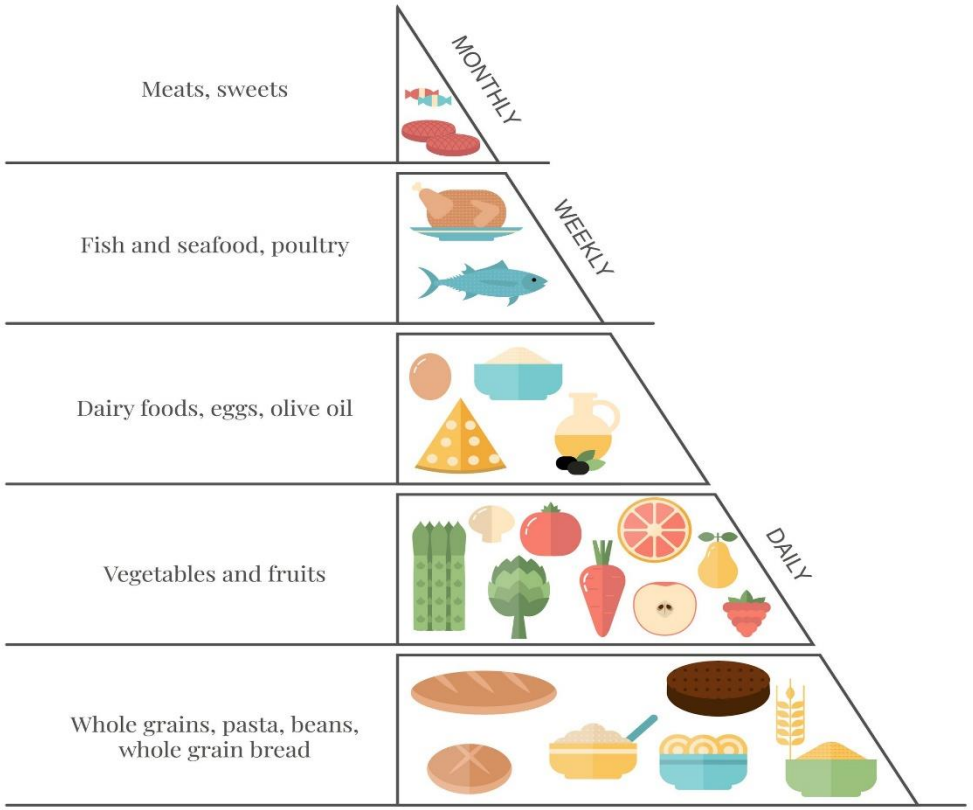
Dietary carbohydrates and fats in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2021;18(11):770–86.
EASL-EASD-EASO Clinical Practice Guidelines on the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Obes Facts 2024; 17(4):374–444.

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

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.

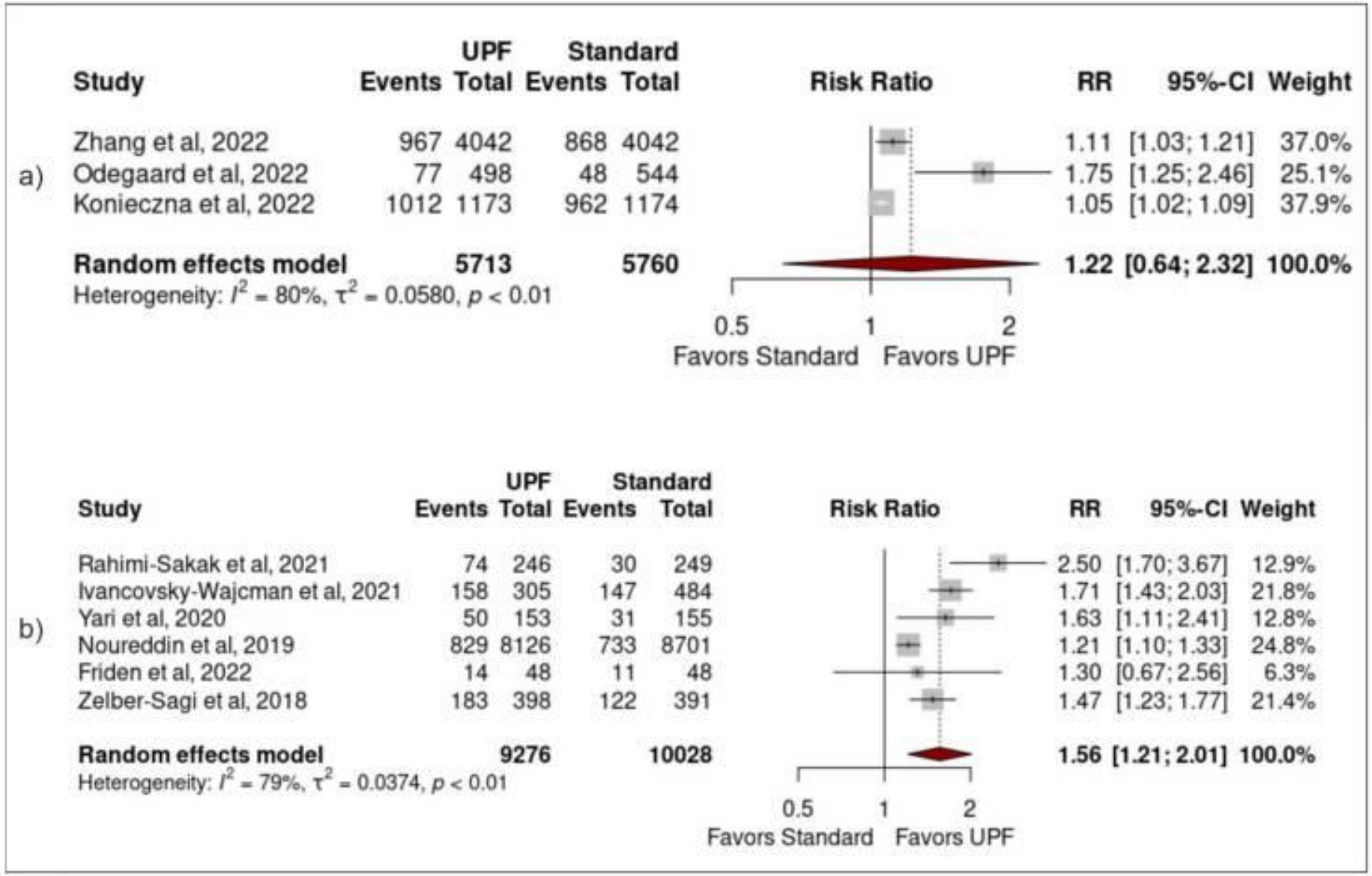
Processed food and Fructose

- **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

Important Food Sources of Fructose-Containing Sugars and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of Controlled Trials. Nutrients. 2022 Jul 12;14(14):2846.

- **SSB** ⟶ higher NAFLD prevalence, NASH 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%

Important Food Sources of Fructose-Containing Sugars and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of Controlled Trials. Nutrients. 2022 Jul 12;14(14):2846.



Ultra-Processed Food Intake Is Associated with Non-Alcoholic Fatty Liver Disease in Adults: A Systematic Review and Meta-Analysis. Nutrients. 2023; 15 (10): 2266.

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 NAFLD)
- 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 NAFLD incident

✓ A 33% lower risk of liver fibrosis in NAFLD patients

Although there are some controversy

The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis of 11 epidemiological studies. Ann Hepatol. 2021 Jan-Feb;20:100254.

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 NAFLD) indicated:

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

✓ High-intensity interval training ⟶ decrease of liver fat

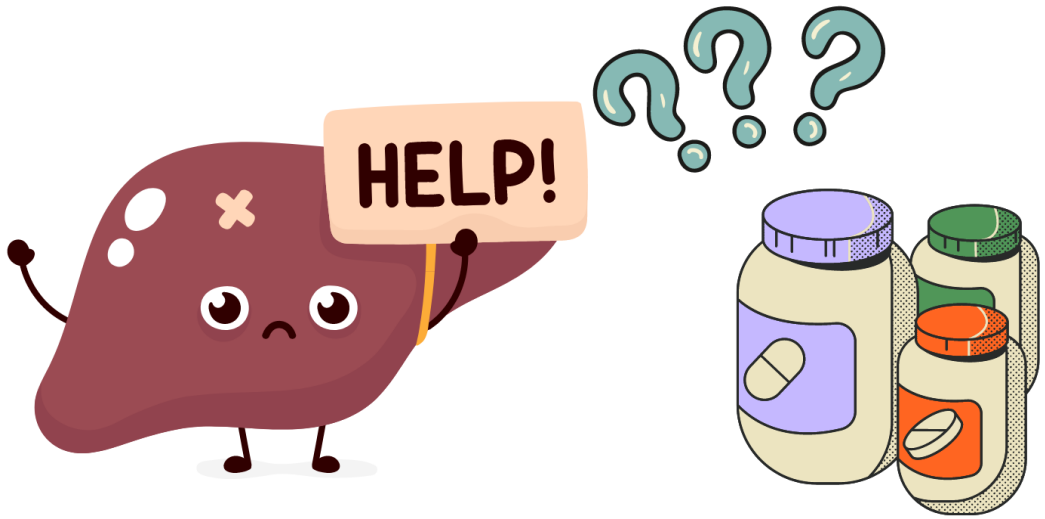
Does aerobic exercise reduce NASH and liver fibrosis in patients with non-alcoholic fatty liver disease? A systematic literature review and meta-analysis. Front Endocrinol (Lausanne). 2022 Nov 3;13:1032164.

Meta-analysis on 10 studies (316 individuals who had NAFLD) 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

Positive Effects of Exercise Intervention without Weight Loss and Dietary Changes in NAFLD-Related Clinical Parameters: A Systematic Review and Meta-Analysis. Nutrients. 2021 Sep 8;13(9):3135.

Treatment: pharmacotherapy



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

No drugs are approved for NASH
No specific therapy can be recommended
Any drug treatment is off label

Resmetiron (Thyroid Hormone Receptor Agonists)

- **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

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med. 2024;390(6):497–509.

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

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med. 2024;390(6):497–509.

Pioglitazone (PPARγ agonist)

- Reduction of > 2 points NAS
- Improved all histological features
- Achieved resolution of NASH more often

Withdrawn in several European countries

- New generation pan-PPAR is on going: improvement of steatohepatitis and fibrosis

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med. 2016;165(5):305–15.
Treating NASH by targeting peroxisome proliferator-activated receptors. J Hepatol. 2023;79(5):1302–16.

Vitamin E (800 IU/d)

- Improve steatosis, inflammation and ballooning
- (histological improvement ≥ 2 point reduction in NAS)
- Resolution of NASH
- No improvement in fibrosis scores
- Concerns about long-term safety exist

    * incidence of prostate cancer and

    * hemorrhagic stroke

- **The optimal duration of therapy is unknown → up 6 months**

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. N Engl J Med. 2010;362(18):1675–85.

Three new drugs:

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

- *Dapagliflozin*
- *Empagliflozin* ⟹ *Reductions in ALT*

FDA indication: Diabetes with NAFLD

2- Dual GLP1-GIP (**Tirzepatide)**

FDA indication: Diabetes/obesity with NAFLD

In a RCT: steatohepatitis resolution

Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial). Diabetes Care. 2018;41(8):1801–8.
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 202; 10(6):393-406.

3- GLP-1 analogue

- *Liraglutide*
- *Semaglutide*

FDA indication: NASH without cirrhosis

In RCT:

- ✓ Resolution of steatohepatitis
- ✓ No fibrosis improvement

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679–90.
A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med. 2021;384(12):1113–24.

Synbiotics and probiotics:

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

Use of probiotics, prebiotics, and synbiotics in non-alcoholic fatty liver disease: A systematic review and meta-analysis. J Gastro Hepatol 2023 July.

- Results are inconsistent
- Effective strains: Bifidobaceria, Lactobacili, S.thermophiles
- **Safe & well tolerated**

Co-administartion 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???

Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial
No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. Gastroenterology. 2014;147(2):377–84 e1

Possible Interaction:

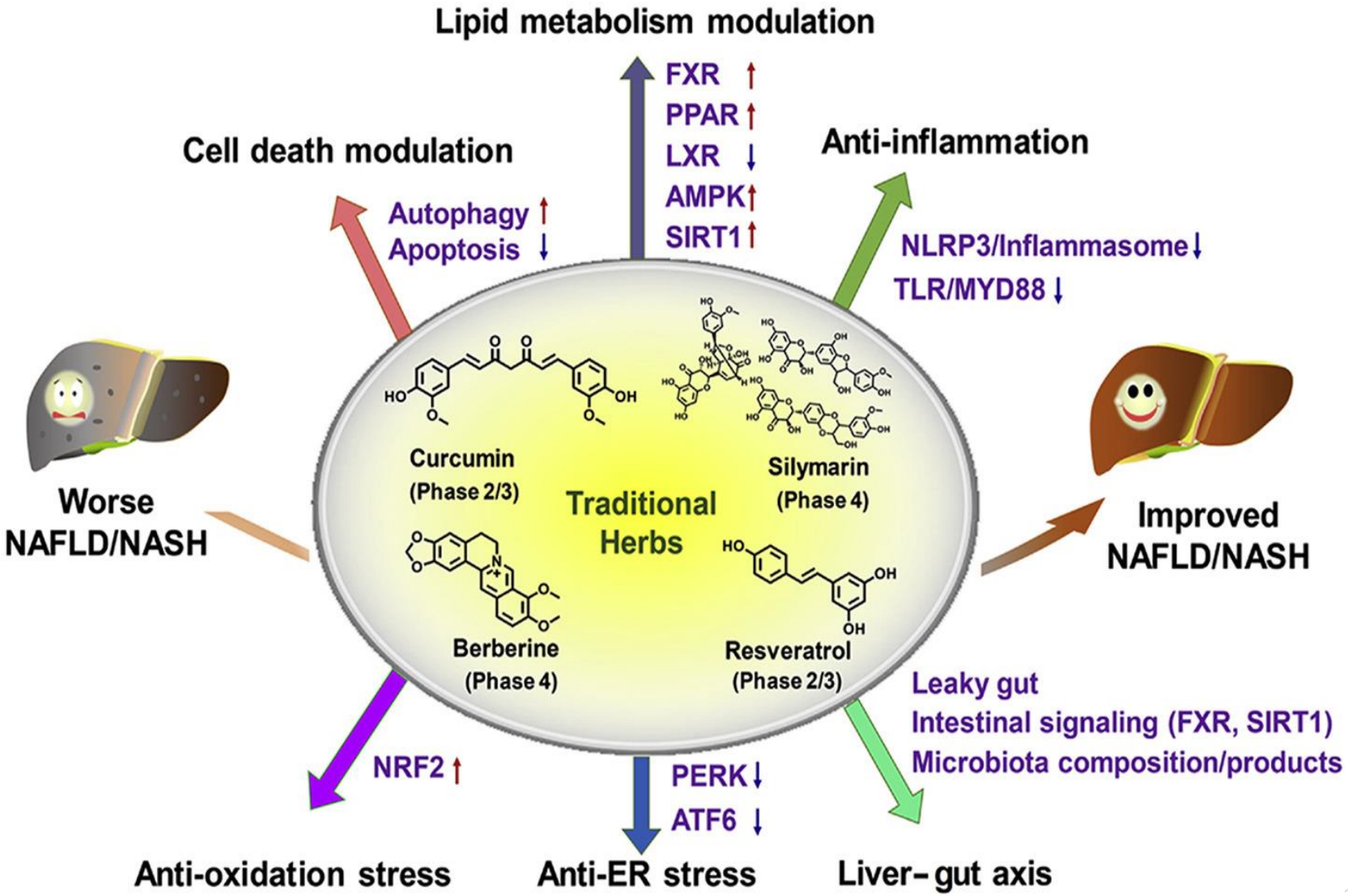
- Anticoagulant and antiplatelet drugs, herbs and supplements
- Blood pressure drugs, herbs and supplements
- Contraceptive drugs
- Orlistat
- Vitamin E

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 NAFLD (> 1000 mg/d)
- Maybe mitigating NASH 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**

Treatment: surgery

Bariatric surgery:

- ✓ In adults with non-cirrhotic NAFLD **with an approved indication**
- ✓ In adults with NAFLD-related compensated advanced chronic liver disease/compensated cirrhosis **with an approved indication**

- ▶ Reduces liver fat and reduce NASH progression
- ▶ Histological resolution of NASH without worsening of fibrosis in 55%
- ▶ Fibrosis improvement by ≥1 stage without worsening of NASH after one-year was achieved in 37%

Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial. Lancet 2023; 401: 1786-97.

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

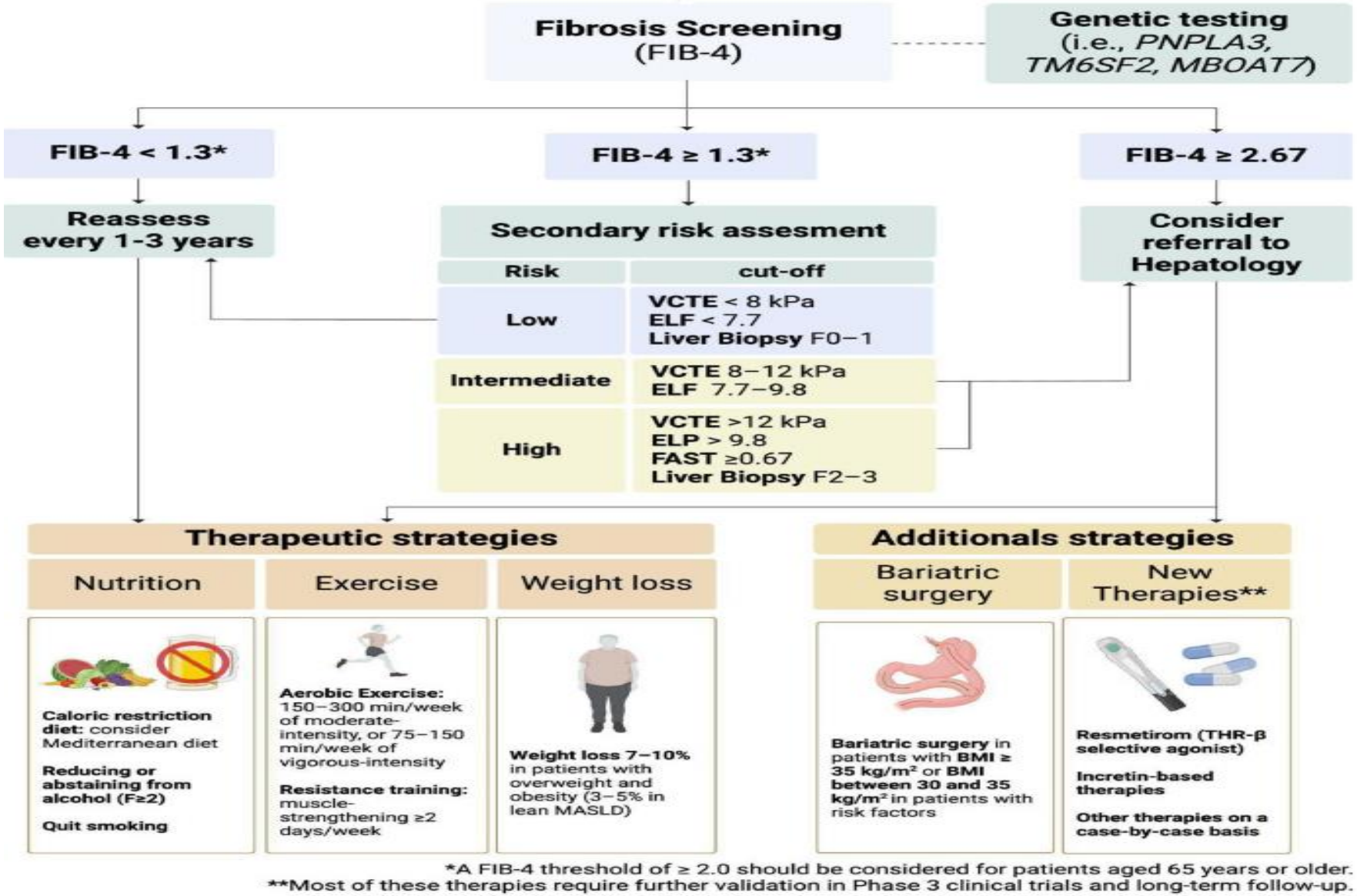
In meta-analysis improvement in:

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

Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. Gastroenterology 2020; 159(4):1290-1301.e5.
Bariatric Surgery Improves Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis. Obes Surg 2022; 32(6):1872-1883.

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 NASH and liver failure and/or HCC**



Updated recommendations for the management of metabolic dysfunction–associated steatotic liver disease (MASLD) by the Latin American working group. Annals of Hepatology 2025; 30: 101903.

Thank you for your time.

Any questions?