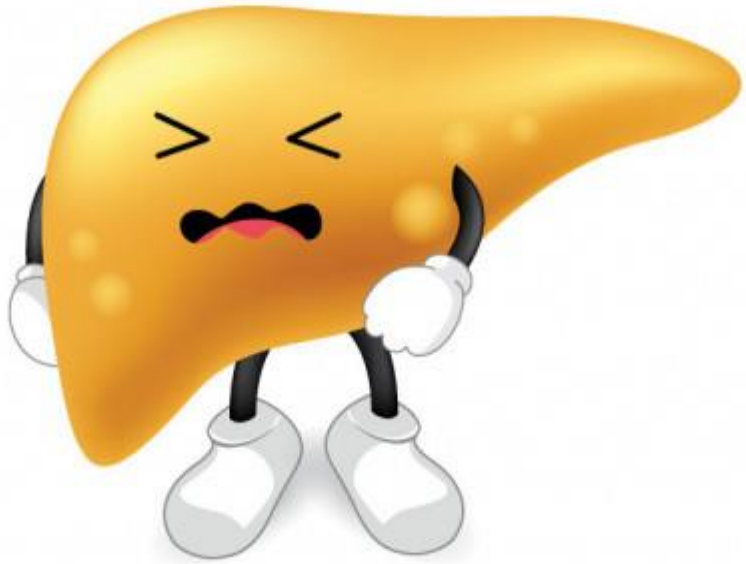

بسم الله الرحمن الرحیم

تغذیه درمانی در کبد چرب

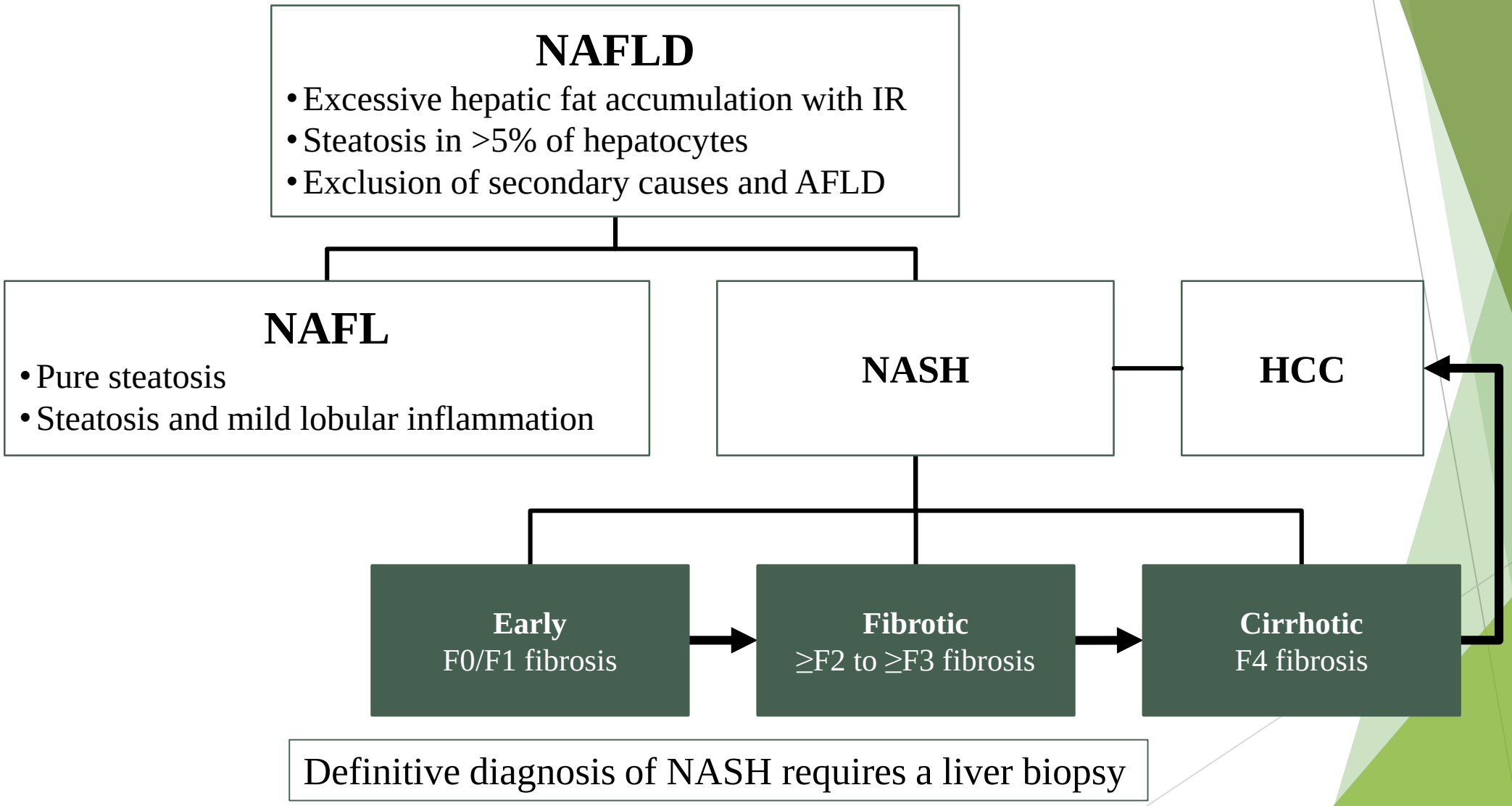
دکتر مهدیه گل زرند

استادیار مرکز تحقیقات تغذیه در بیماری های غدد درون ریز

دانشگاه علوم پزشکی شهیدبهشتی



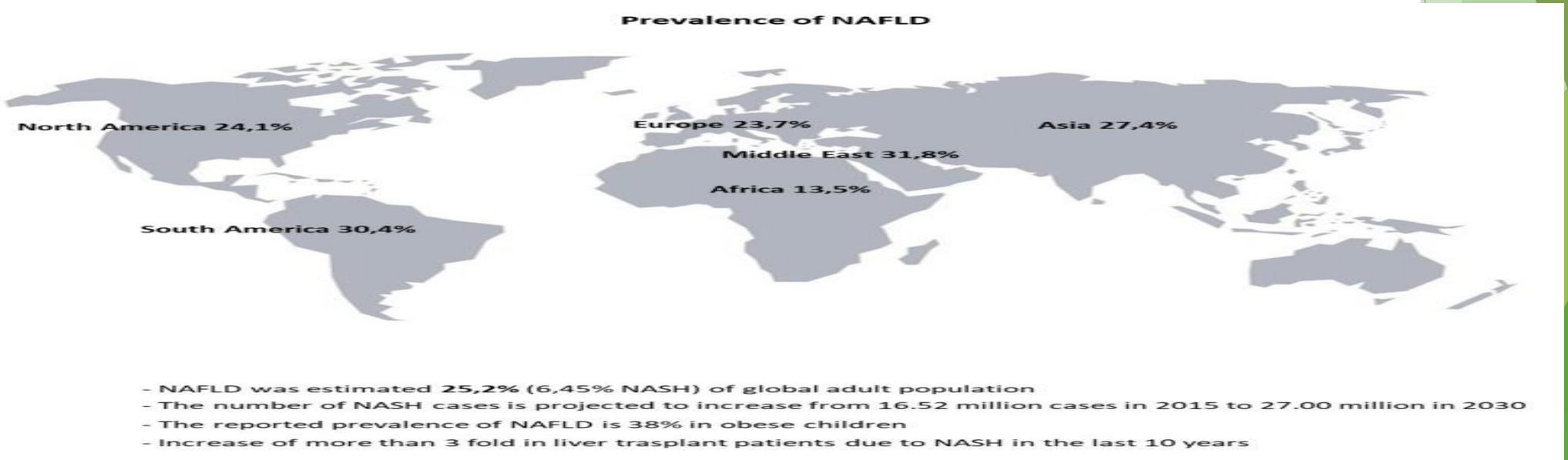
Definitions of NAFLD, NAFL and NASH



Spectrum of NAFLD and concurrent disease

Sub-classification of NAFLD	Most common concurrent diseases
NAFL • Pure steatosis • Steatosis and mild lobular inflammation	**AFLD**† **Drug-induced fatty liver disease** **HCV-associated fatty liver disease** **Others** • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism – Wolman disease (lysosomal acid lipase deficiency)
NASH • Early NASH (no or mild fibrosis) • Fibrotic NASH (significant/advanced fibrosis) • NASH cirrhosis	
HCC	

- NAFLD ⟶ 32.4% of general population
- NAFLD ⟶ 7% of normal-weight
- Prevalence increased from 25·5% in or before 2005 to 37·8% (32·4-43·3) in 2016 or later.
- NAFLD was significantly higher in men than in women (39·7% vs 25·6%).



Pathogenesis: lifestyle and genes

- **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

- **Genes:**

1- PNPLA3 I148M

2- TM6SF2 E167K

- Associated with risk of NASH

Genotyping is not recommended routinely

Other risk factors

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

Diagnosis: protocol for evaluation of NAFLD

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

Patients with IR and/or metabolic risk factors (i.e. obesity or MetS) should undergo procedures for the diagnosis of NAFLD

Level	Variable
Initial evaluation	1. Alcohol intake: <20 g/day (women), <30 g/day (men) 2. Personal and family history of diabetes, hypertension and CVD 3. BMI, waist circumference, change in body weight 4. Hepatitis B/hepatitis C virus infection 5. History of steatosis-associated drugs 6. Liver enzymes (ALT, AST, GGT) 7. Fasting blood glucose, HbA1c, OGTT, (fasting insulin [HOMA-IR]) 8. Complete blood count 9. Serum total and HDL cholesterol, triacylglycerol, uric acid 10. Ultrasonography (if suspected for raised liver enzymes)
Extended* evaluation	1. Ferritin and transferrin saturation 2. Tests for coeliac and thyroid diseases, polycystic ovary syndrome 3. Tests for rare liver diseases (Wilson, autoimmune disease, AATD)

- ALT / AST not sensitive tool for diagnosis NAFLD/NASH: **Ultrasound essential**

- **Ultrasound:**
- 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 (x10⁹/l)
Albumin (g/l)
calculate score

BMI: body mass index
IGF: impaired fasting glucose

2- Imaging including: Fibroscan

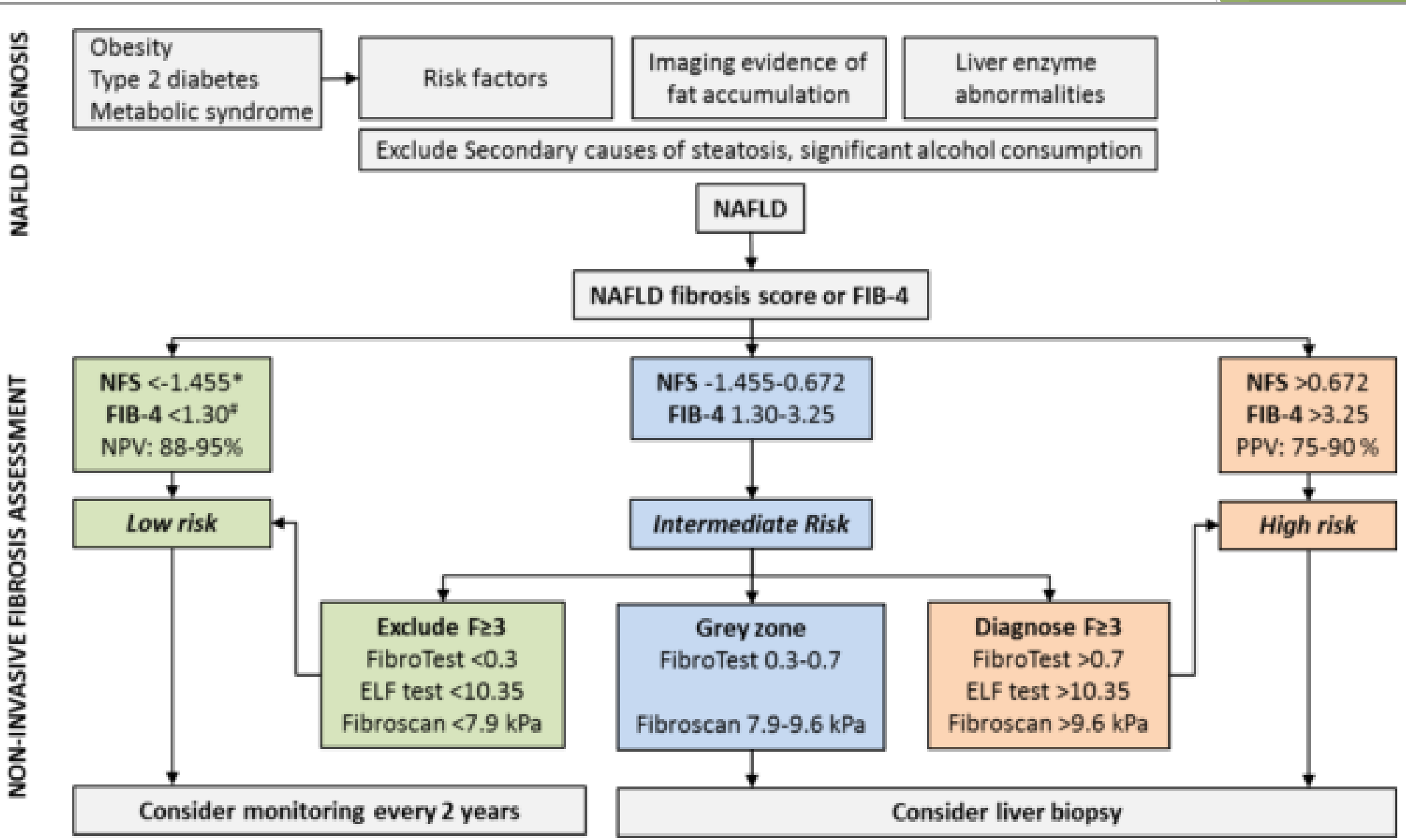
Advantage:

High performance for fibrosis and cirrhosis

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

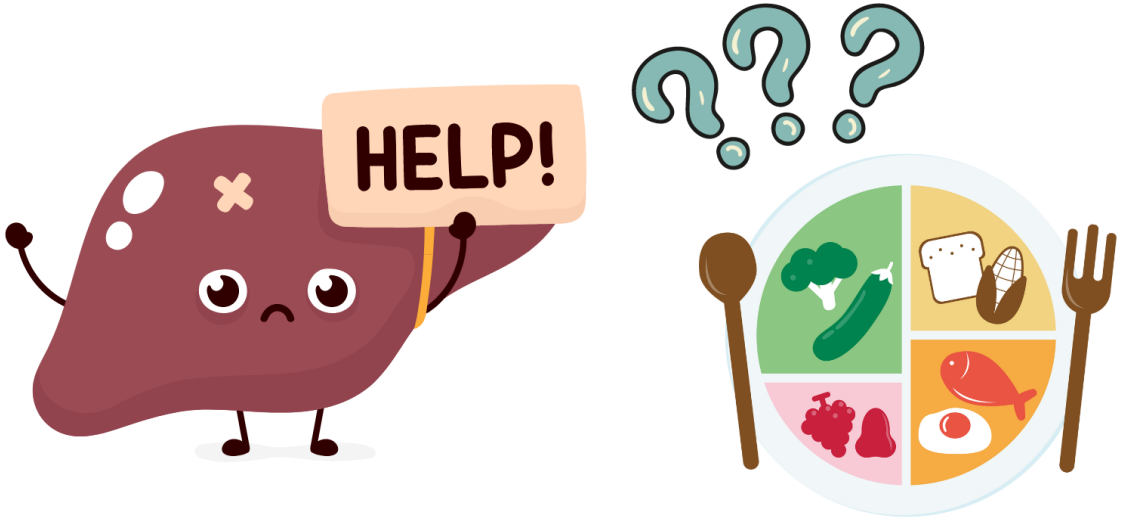
Liver Biopsy: Gold Standard for fibrosis

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



https://www.bsg.org.uk/web-education-articles-list/nafld-diagnosis-assessment-and-management/

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 and habitual physical activity
- No pharmacotherapy

	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

- Every 1 kg of weight lost was associated with:
- A 0.83-unit reduction in ALT
- A 0.56-unit reduction in AST
- A 0.77% point in steatosis assessed by radiology or histology
- Limited evidence of a dose-response relationship with fibrosis or NAFLD activity score.

The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: A systematic review and meta-analysis. Metabolism. 2021 Feb;115:154455.

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

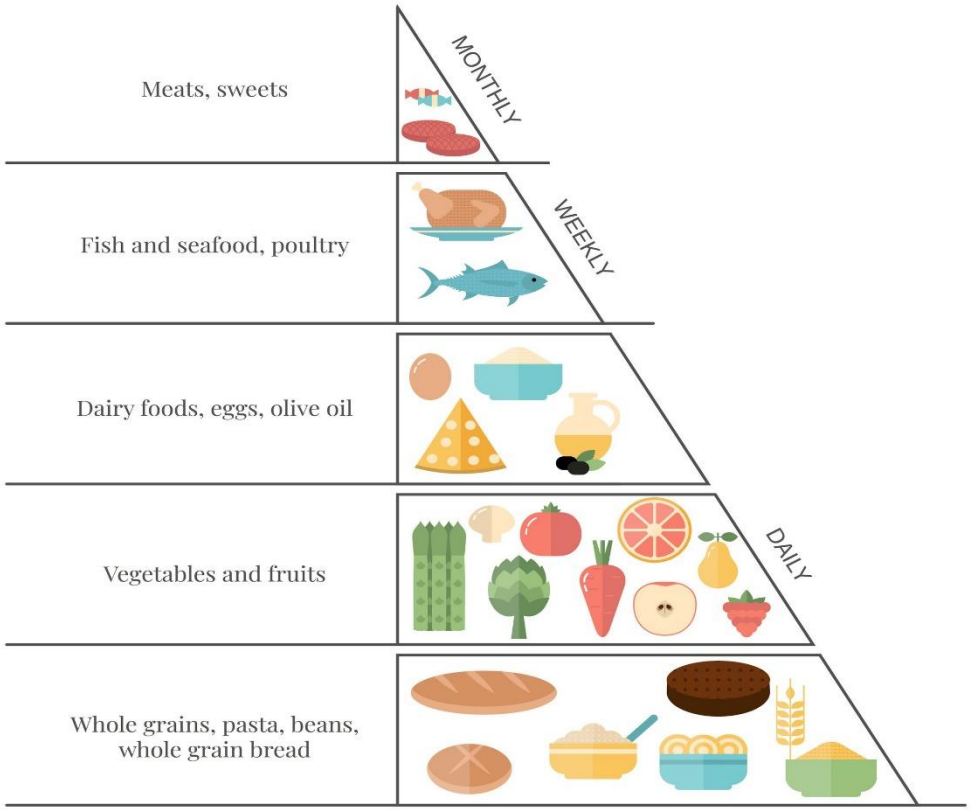
- **Low carbohydrate diet (LCD):** reduction in intrahepatic lipid content
- Hypocaloric LCD is more effective than hypocaloric LFD
- **VLCD contains 5-10% carbohydrate:** very effective in short-term
- **Intermittent calorie restriction:** reduced LFTs but long-term feasibility and safety is controversial

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

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.

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

- 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

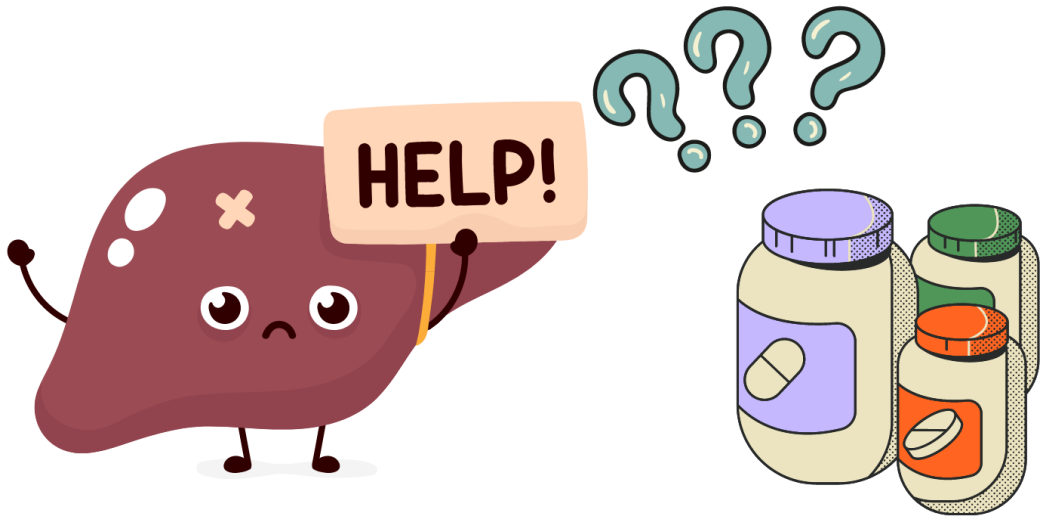
✓ High-intensity interval training ⟶ decrease of liver fat

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:
  - Progressive NASH
  - Early-stage NASH with risk of fibrosis progression*
  - Active NASH with high necroinflammatory activity

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

Vitamin E (800 IU/d)

- Improve steatosis, inflammation and ballooning
- (histological improvement ≥ 2 point reduction in NAS)
- Resolution of NASH
- Concerns about long-term safety exist

    * incidence of prostate cancer and

    * hemorrhagic stroke

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

Pioglitazone (PPARγ agonist)

- Improved all histological features
- Achieved resolution of NASH more often

- **A meta-analysis of eight RCTs found pioglitazone is efficacious for:**
- NASH resolution (OR: 3.22)
- Improvement of advanced fibrosis (OR: 3.15)
- Reversal of fibrosis (OR: 1.66)

Two new drugs:

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

- *Dapagliflozin*
- *Empagliflozin*

2- GLP-1 analogue

- *Liraglutide*

3- Dipeptidyl peptidase-4 (DPP-4) inhibitor

- *Sitagliptin*

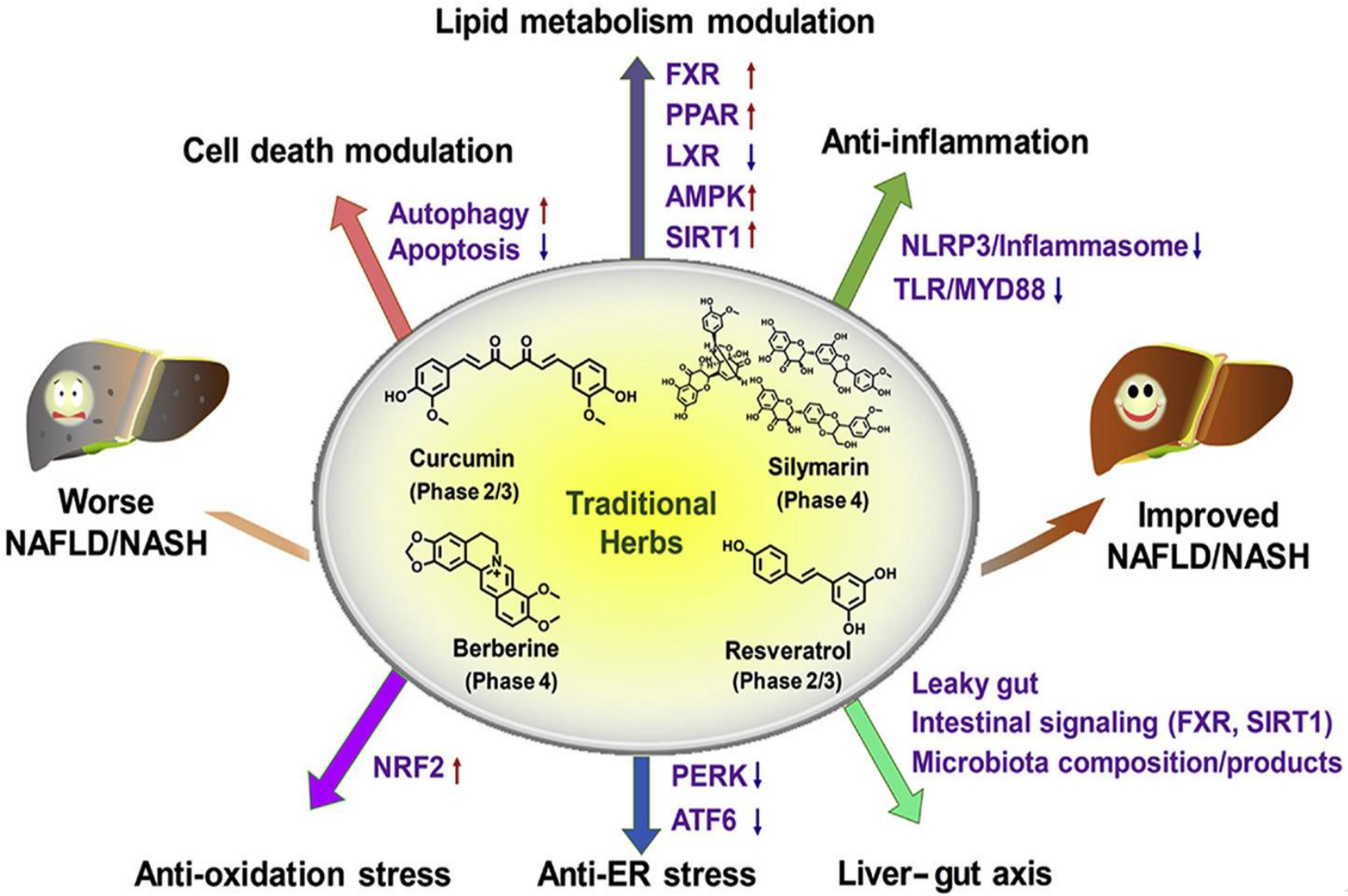
Synbiotics and probiotics

- Improved hepatic steatosis
- Decreased hepatic enzymes
- No beneficial effects on fibrosis
  - *Probiotics marginally are effective*

- **Prebiotics showed no effectiveness**

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

Herbal Medicine



Silymarin:

- Improving fatty liver
- Improving insulin resistance
- Improving glucose and lipid metabolism
- In NASH, improves fibrosis and liver stiffness

- **safe and well tolerated**

Resveratrol:

- Improving liver enzymes
- Reduced hepatic steatosis
- Improved liver damages

- **safe and well tolerated**
- No long-term results

Treatment: surgery

Bariatric surgery:

- Reduces liver fat and is likely to reduce NASH progression
- **Prospective data have shown an improvement in all histological lesions of NASH, including fibrosis**

- **A meta-analysis of 32 studies:**
- Resolution of steatosis in 66%
- Fibrosis in 40% of patients
- Worsened in 12% of these patients

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**

Thank you for your time.

Any questions?