1st GLOBAL LIVER HEALTH FORUM

Therapeutic approaches for NAFLD

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Disclosures

- I have nothing to disclose

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Learning objectives

1. Underline the importance of a healthy lifestyle as the cornerstone for the prevention and management of NAFLD
2. Enhance awareness of strategies for managing NAFLD comorbidities, including obesity, diabetes, arterial hypertension and dyslipidemia
3. Understand the place and expectation of hepatoprotective medications
4. Underline the importance of the appropriate choice of liver-directed therapy in biopsy-proven NASH
5. Recognize innovative therapies explored in clinical trials

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

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Why is NAFLD important?

- It is a common disease and its prevalence is increasing[1]
- It has a histologically aggressive form – NASH (10–20% of NAFLD, up to 6% of the general population)[2]
- It is a systemic disease[3]

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

1. Abeysekera K, et al. Lancet Gastroenterol Hepatol 2020;5:295–305; 2. Hashimoto E, et al. JGH 2013;28(Suppl 4):64–70; 3. Fotbolcu H, et al. World J Gastroenterol 2016;22:4079–90

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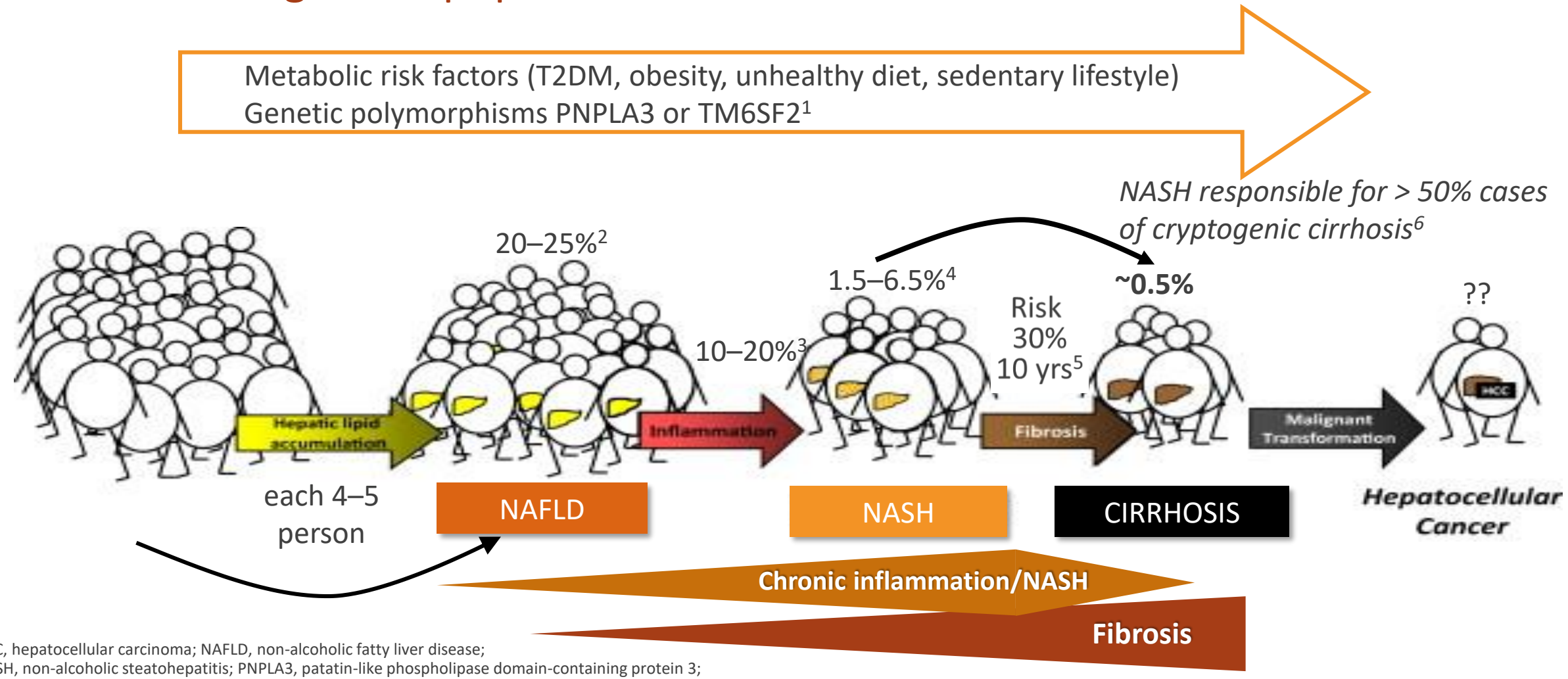
NAFLD in the general population



HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease;
NASH, non-alcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3;
TM6SF2, transmembrane 6 superfamily member 2; T2DM, type 2 diabetes mellitus. 1. Meroni M, et al. Int J Mol Sci 2020;21:2986; 2. Abeysekera K, et al. Lancet Gastroenterol Hepatol 2020;5:295–305; 3. Hashimoto E, et al. JGH 2013;28(Suppl 4):64–70; 4. Younossi ZM, et al. Clin Liver Dis (Hoboken) 2018;11:92–4; 5. Dam-Larsen S, et al. Gut 2004;53:750–5; 6. Golabi P, et al. Medicine 2018;97:e11518

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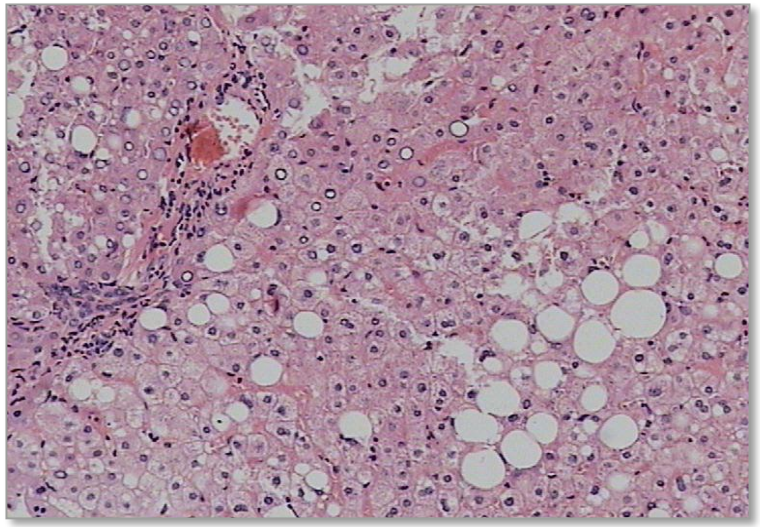
Is it NAFLD or NASH?

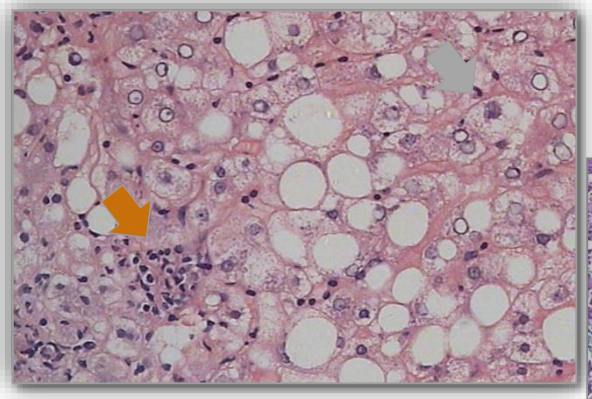
NAFLD (80–90%)

- **Steatosis > 5%**

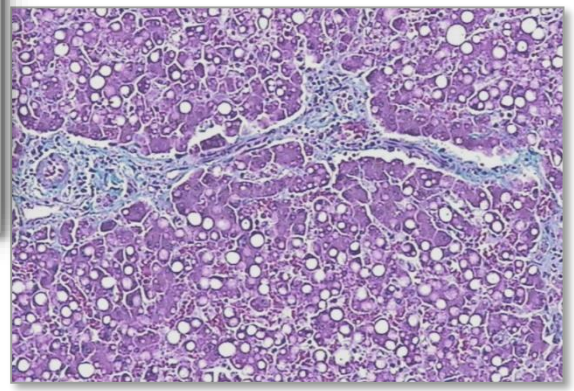


NASH (10–20%)

- **Steatosis > 5%**
- Lobular inflammation
- Hepatocellular ballooning
- Variable degrees of fibrosis



Ballooning and mononuclear inflammatory infiltrate



Fibrosis

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
Images provided by speaker. Hashimoto E, et al. JGH 2013;28(Suppl 4):64–70

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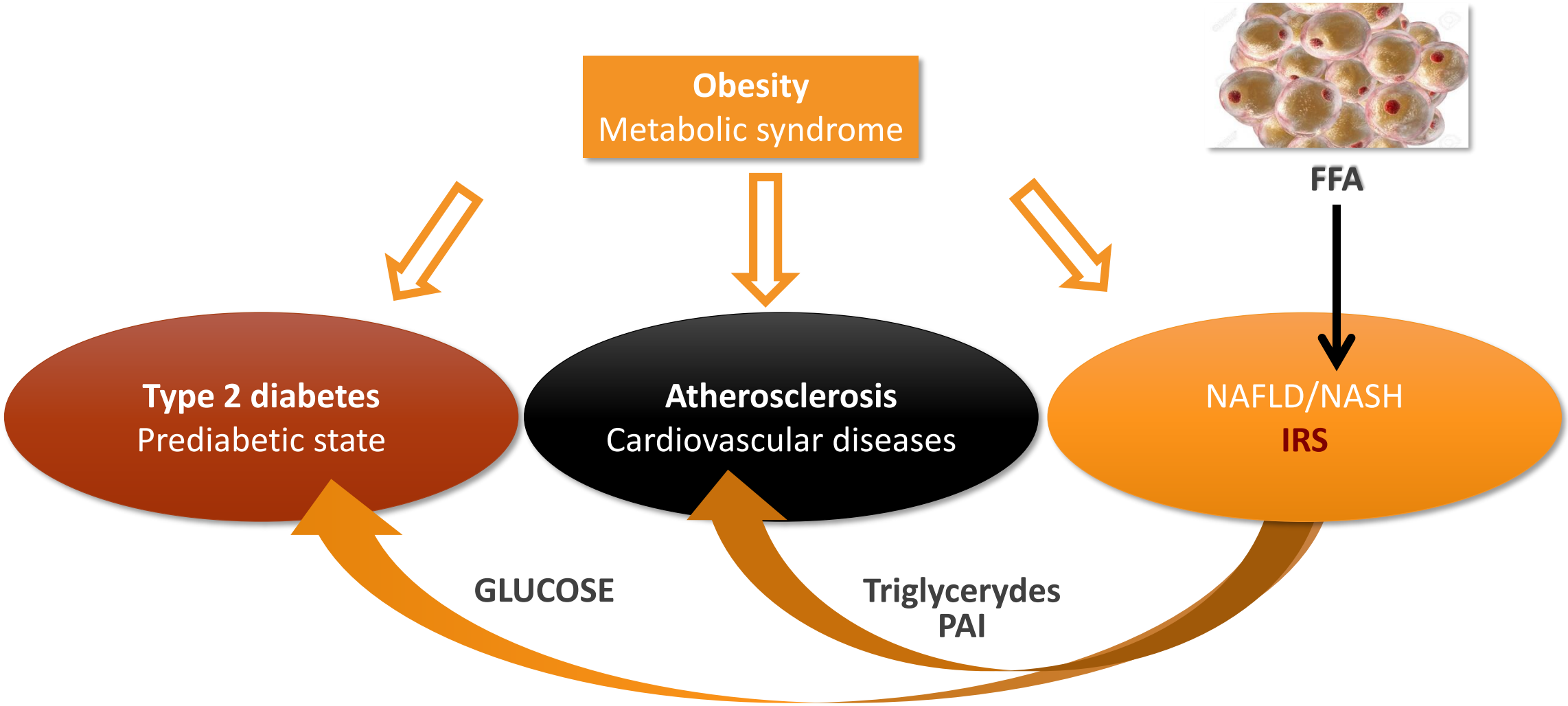

FFA, free fatty acid; IRS, insulin receptor substrate; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PAI, plasminogen activator inhibitor type 1
Meroni M, et al. Int J Mol Sci 2020;21:2986

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Patient heterogeneity in NAFLD

Patient	Liver
Obese/overweight vs lean vs fluctuating BMI	Simple steatosis (NAFL)
T2DM vs no T2DM	NASH w/o fibrosis
Metabolic syndrome vs insulin responsive	NASH + early fibrosis (F1)
Physically active vs leading sedentary lifestyle	NASH + significant fibrosis (≥ F2)
Drinking alcohol vs abstinent	NASH + advanced fibrosis (F3 and F4)
Young vs aged	Cirrhosis ± HCC
Comorbidities affecting the: • Heart • Lungs • Kidneys	

BMI, body mass index; F, fibrosis stage; HCC, hepatocellular carcinoma; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus
Patient phenotypes provided by speaker. Alkhouri N, et al. Gastroenterol Hepatol 2012;8:661–8

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BMI, body mass index

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Dietary causes of NAFLD

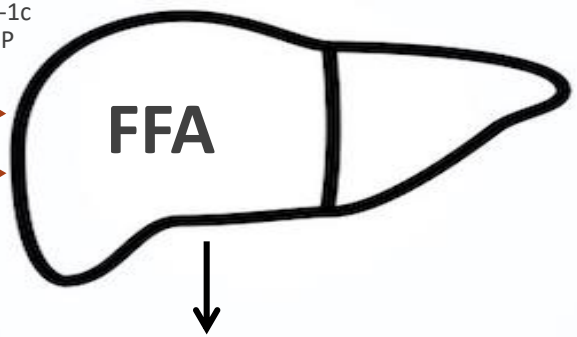
15%

Lipogenesis
de novo
25%

60%

Fructose
+
Glucose
↓
Acetyl CoA

ACC
FAS
SCDs
} SREBP-1c
ChREBP



Circulating FFA ⇧⇧
↑ **IR**
Adipose tissue ⇧
↑
Chylomicrons
Triglycerides

Triglicerides → VLDL
↓
Hypertriglyceridemia

Acetyl CoA, acetyl coenzyme A; ACC, acetyl CoA carboxylase; ChREBP, carbohydrate-response element-binding protein; FFA, free fatty acid; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; SCDs, hepatic stearoyl-CoA desaturases; SREBP-1c, sterol regulatory element-binding protein 1; VLDL, very-low-density lipoprotein. Softic S, et al. Dig Dis Sci 2016;61(5):1282–93

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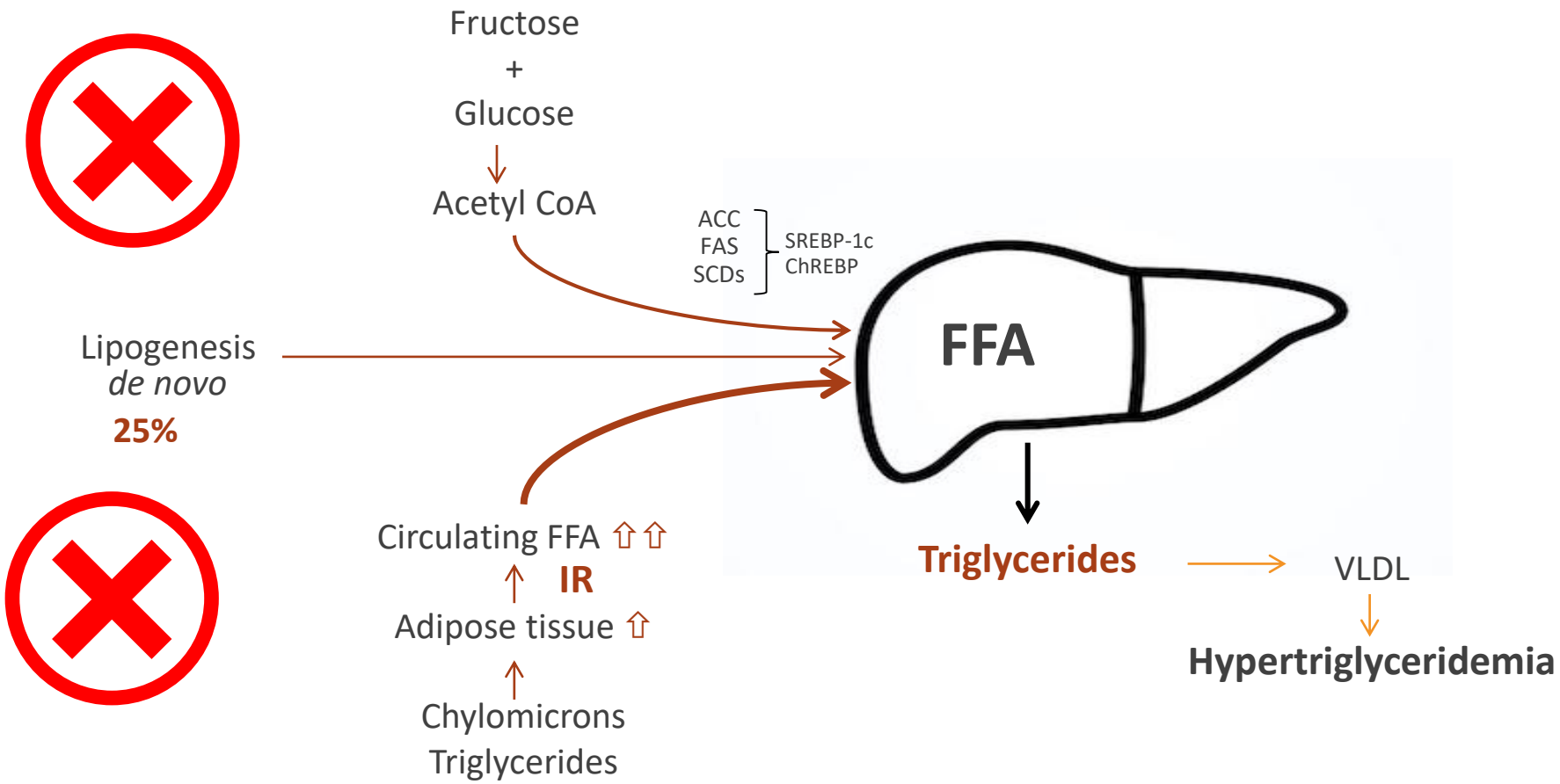
Dietary modifications



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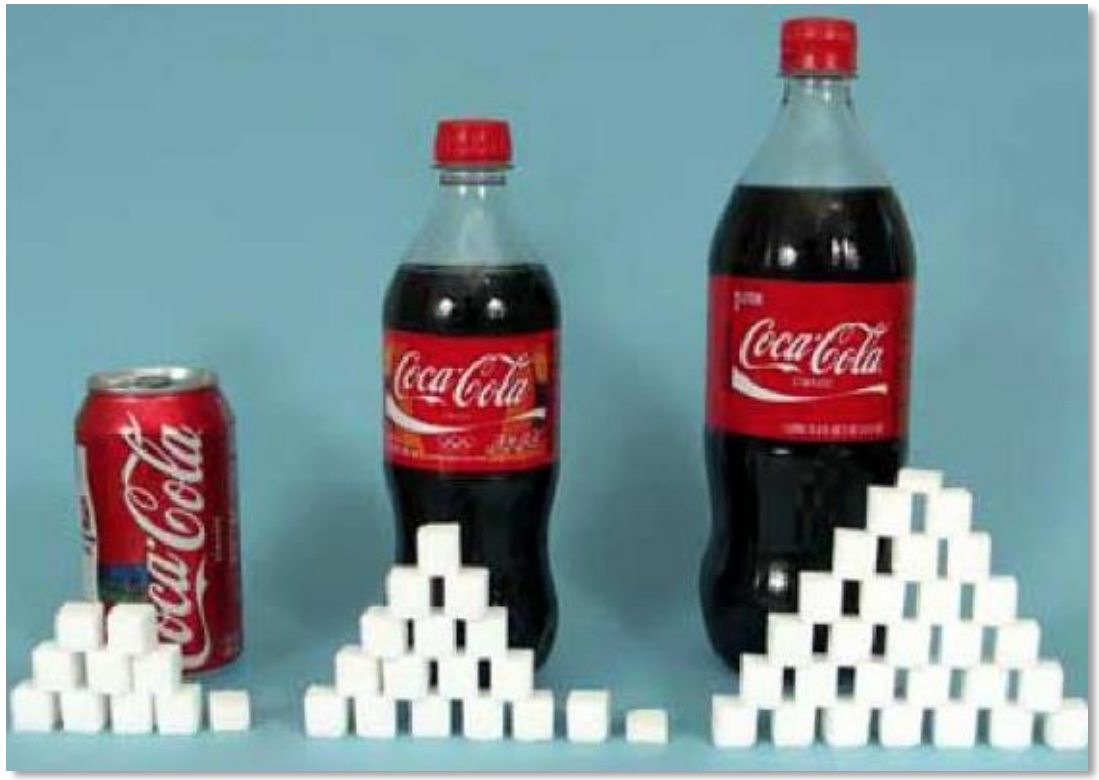
Dietary recommendations

- In overweight/obese patients, decrease caloric intake by 30% in relation to overall energy demand (reduction by 750–1000 kcals daily)[1]
  - Saturated fats (animal origin) and fatty acids trans (avoid fast-food restaurants, cookies)[2]
  - Soft drinks containing simple sugars (fructose, glucose)[2]
  - Alcohol consumption[2]
- More than three cups of coffee daily[2]
- Mediterranean low-caloric diet[1,2]



1. Chalasani N, et al. Hepatology 2018;67:328–57; 2. George ES, et al. Adv Nutr 2018;9:30–40

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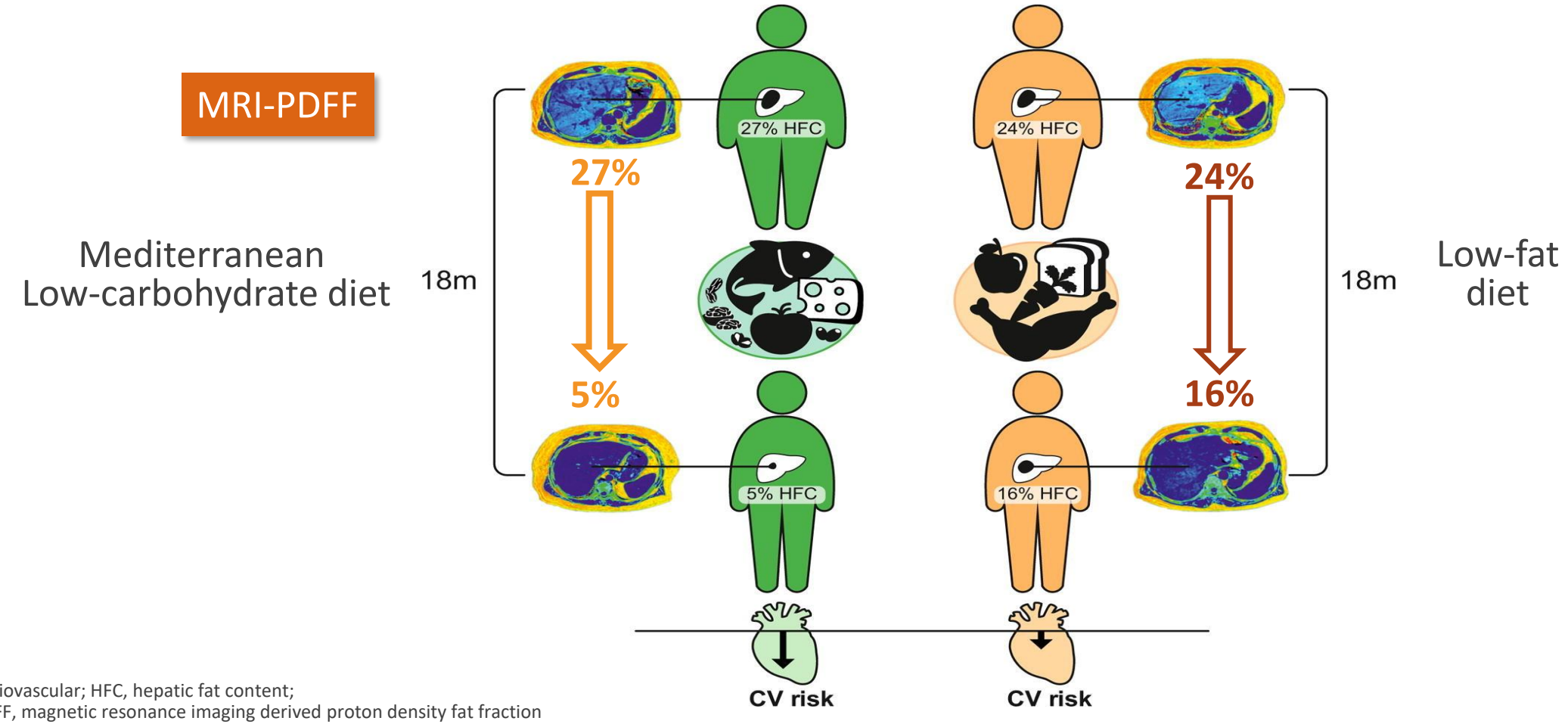
Advantage of the Mediterranean diet vs low-fat diet



CV, cardiovascular; HFC, hepatic fat content;
MRI-PDFF, magnetic resonance imaging derived proton density fat fraction
Gepner Y, et al. J Hepatol 2019;71:39–88

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Regular physical training mobilizes fat from the liver

Systematic review of 8 RCTs conducted in NAFLD patients aged ≥ 18 years (N=433)

Study protocols Training only (6 studies); Training and diet (2 studies)	
Assessment after	8–48 weeks
Frequency	3–7 times/week
Duration of single training	20–60 minutes
Intensity	Medium (45–75% peak VO_2)
Method of assessment	H-MRS or liver biopsy
Reduction of fat content	**30.2%** (training only) **49.8%** (training + diet)

H-MRS, hydrogen-magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; RCTs, randomized controlled trials; VO_2, oxygen consumption

Golabi P, et al. World J Gastroenterol 2016;22:6318–27

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Guidance statements on lifestyle interventions

	EASL[1]	NICE[2]	Asia-Pacific[1]	AISF[1]	AASLD[1]	China[3]	Russia[4]	Poland[5]
Diet	500 to 1,000 kcal deficit Weight loss of 500–1000 g/week (7%–10% total weight loss) Low-to-moderate fat, moderate-to-high CHO, high-protein Mediterranean diet	Reduction of calories by 600 kcal/day Low-calorie, low-fat diet	500–1000 kcal deficit	1200–1,600 kcal/day Low fat (<30% of total calories) Low CHO (<50% of total calories) Mediterranean diet	500–1,000 kcal deficit	Restriction of calorie intake by 25 kcal/kg or by 500–1,000 kcal/day Reduction of fructose and alcohol intake	Increase consumption of MUFA and omega-3 enriched food, vegetable fibre, and low glycemic index food	500 to 1000 kcal deficit In patients with BMI >25 kg/m^2 weight loss of no more than 0.5 kg/week (at least 5% total weight loss)
Physical activity	Aerobic and resistance training (150–200 min/week in 3–5 sessions)	≥30 min of moderate or intensity physical activity on ≥5 days/week	Aerobic and resistance training	Aerobic and resistance training	Aerobic and resistance training (>150 min/week)	150–200 min/week of moderate intensity exercise	Walking for 40 min at a moderate pace ≥5 times/week	Aerobic or resistance training (150 min/week) of medium intensity adjusted to possibilities

AASLD, American Association for the Study of Liver Diseases; AISF, Italian Association for the Study of the Liver; BMI, body mass index; CHO, carbohydrate; EASL, European Association for the Study of the Liver; NICE, National Institute for Health and Care Excellence; MUFA, monounsaturated fatty acids. 1. Leoni S et al. World J Gastroenterol 2018;24:3361–73; 2. NICE. Obesity: identifying, assessing and managing obesity in adults, young people and children. 2014; Available at https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925 (Last accessed: October 2020) 3. Fan JG, et al. J Dig Dis. 2018;1–11; 4. Ivashkin VT, et al. RZHGGK. 2015;6:31-41; 5. Hartleb M, et al. Gastroenterologia Praktyczna. 2019; 11–35

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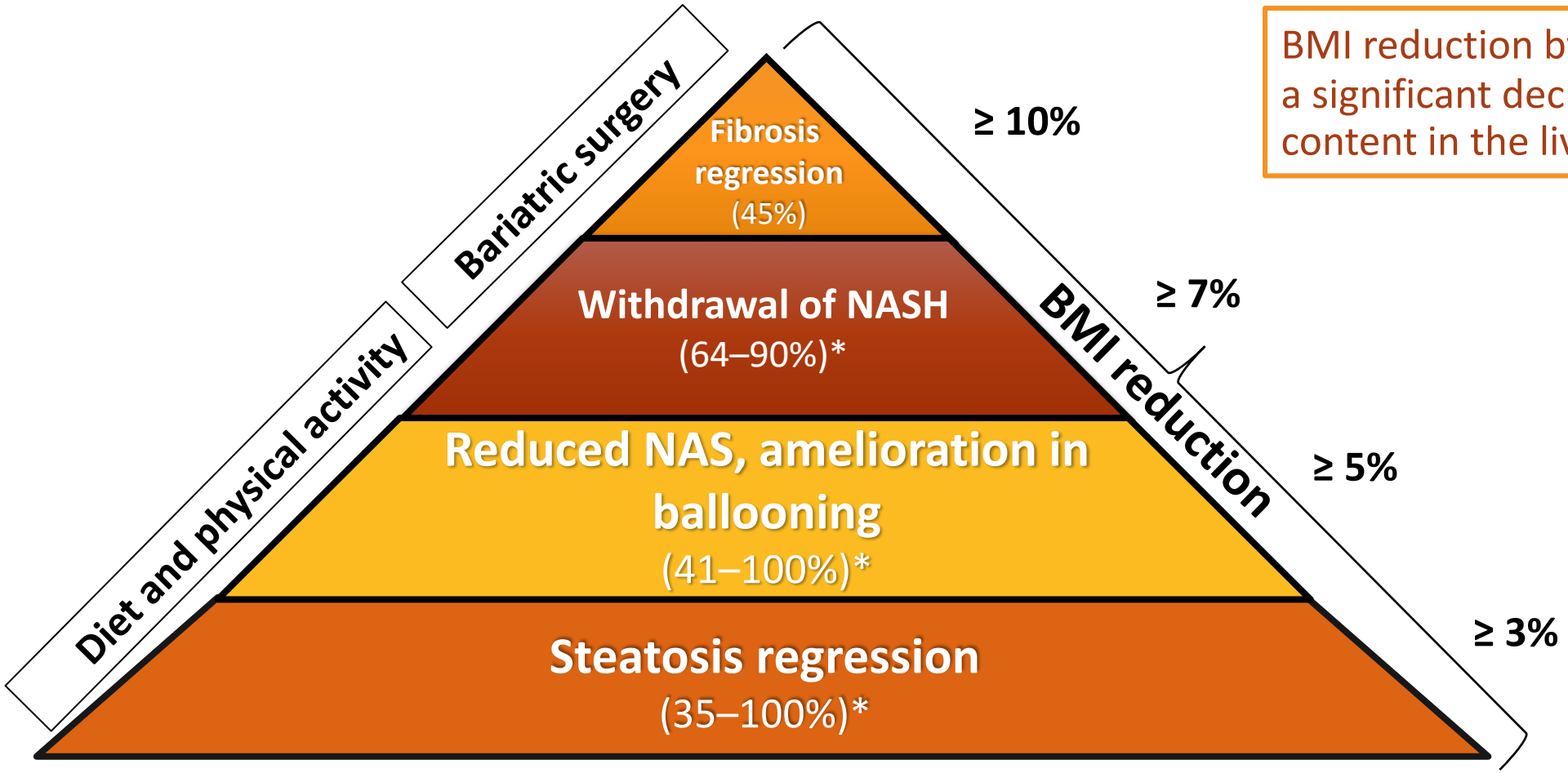
Relationship between magnitude of weight loss and histological improvement

Analysis based on 4 RCTs



BMI reduction by **5%** results in a significant decrease of fat content in the liver

*Depending on the degree of BMI reduction. BMI, body mass index; NASH, non-alcoholic steatohepatitis; NAS, NAFLD Activity Score; RCTs, randomized controlled trials

Hannah WN, et al. Clin Liver Dis 2016;20:339–50

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Bariatric surgery

Prospective study of 109 patients with morbid obesity and NASH who underwent bariatric surgery

	Before surgery		After 1 year
BMI (kg/m²)	49.3	↘	37.4
ALT (IU/l)	52	↘	25
HOMA-IR	3.6	↘	2.9
Histology **Steatosis (%)**	60	↘	10

- Resolution of NASH in 85% of cases (n=70) – 94% with mild and 70% with moderate or severe form
- Improvement in fibrosis in 33.8%* of cases

*Defined by the metavir scale (F0=no fibrosis; F1=enlarged portal tract without septa; F2=enlarged portal tract with rare septa or bridging fibrosis; F3=bridging fibrosis without cirrhosis; F4=cirrhosis)
ALT, alanine aminotransferase; BMI, body mass index; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; NASH, non-alcoholic steatohepatitis
Lassailly G, et al. J Gastroenterol 2015;149:379–88

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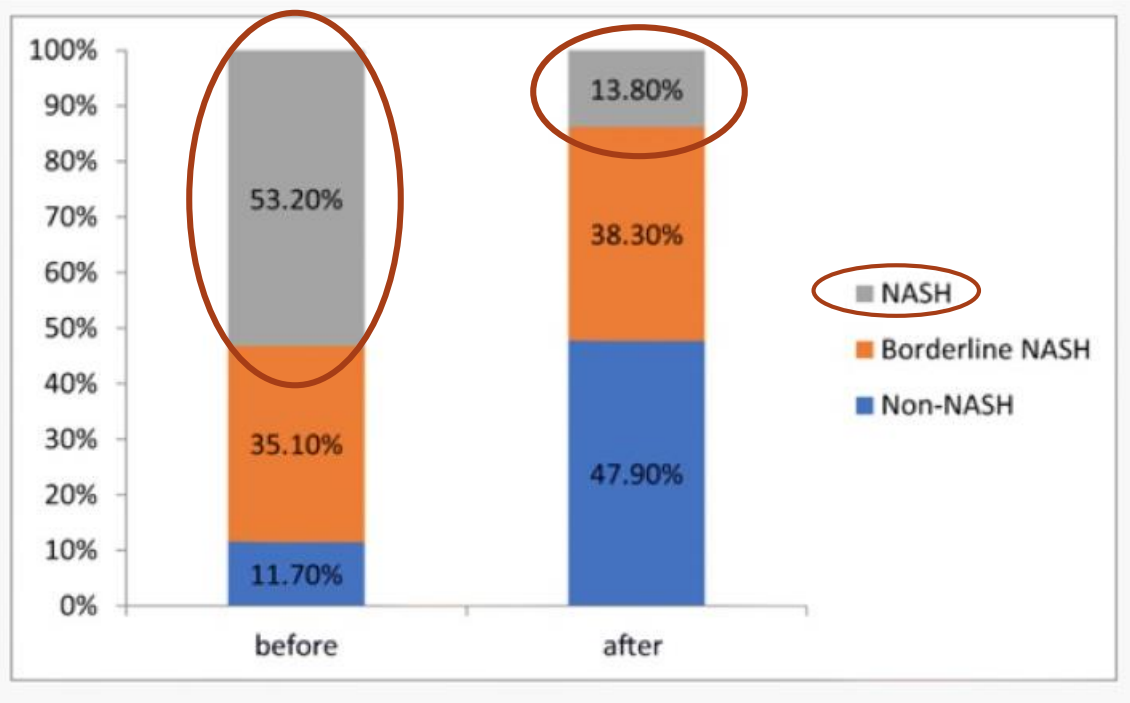
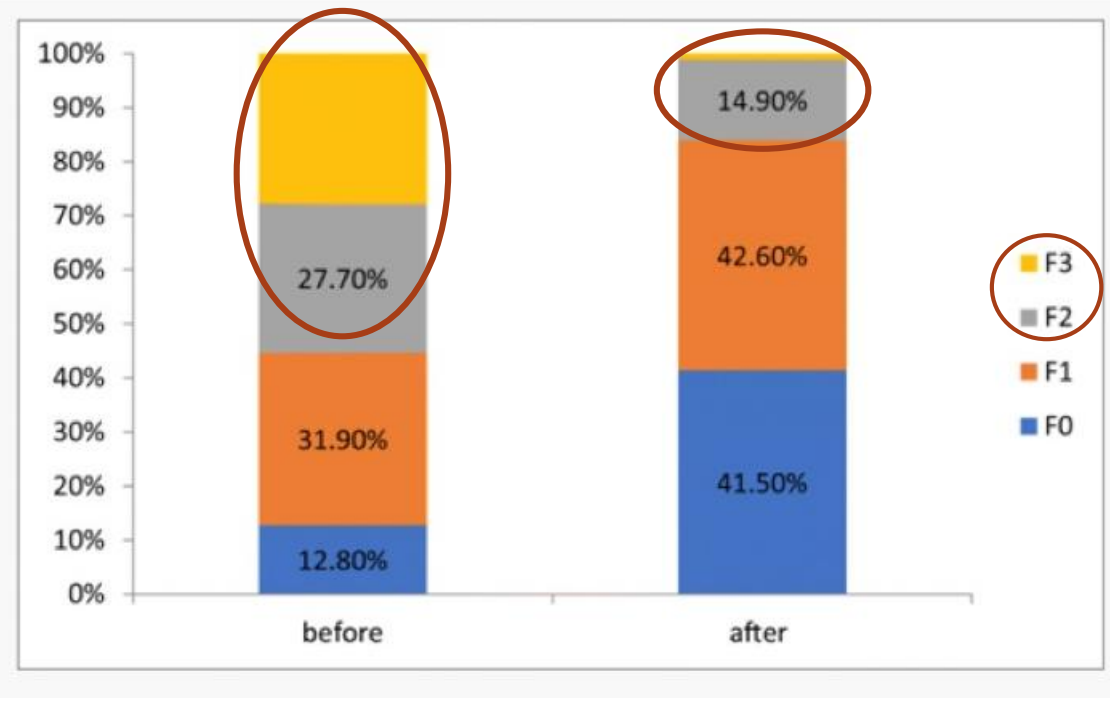
Laparoscopic sleeve gastrectomy: A promising treatment for NASH

Improvement in NASH and fibrosis 12 months after laparoscopic sleeve gastrectomy in obese patients (N=94)

Improvement in NASH at 12-month follow-up after surgery



Improvement of fibrosis stage at 12-month follow-up after surgery



F, fibrosis stage; NASH, non-alcoholic steatohepatitis

Salman MA, et al. Obesity Surgery 2020;30:87–95

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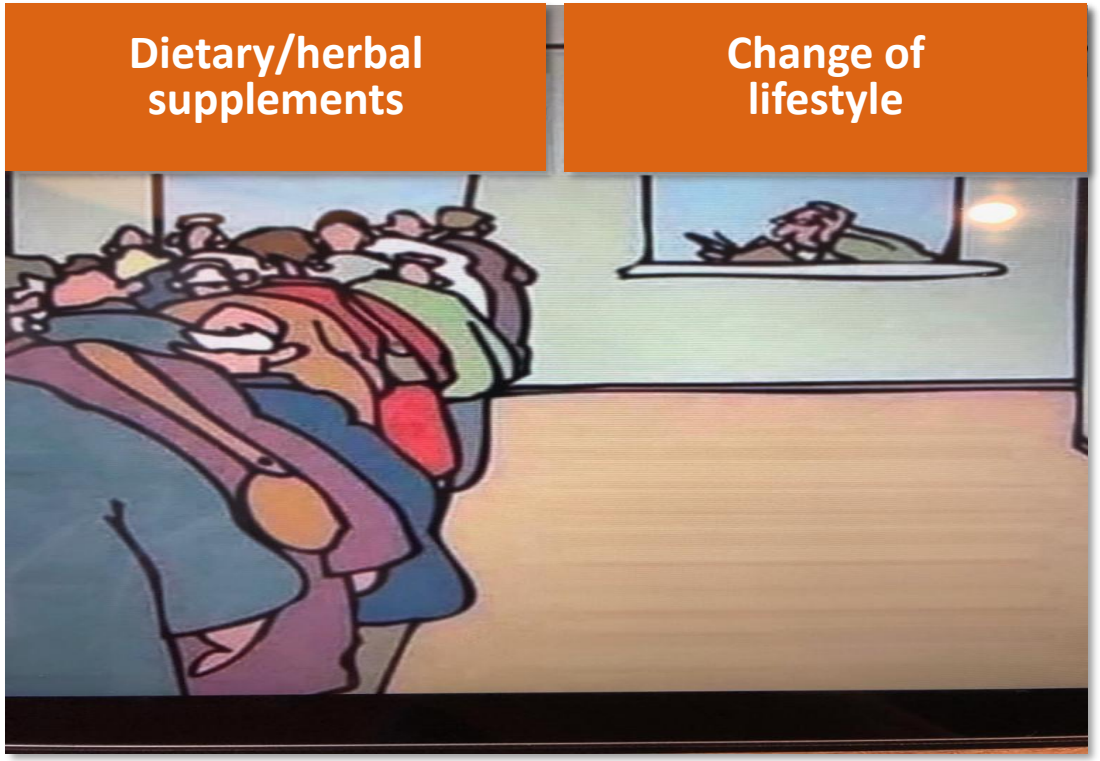
Treatment of NAFLD: The obstacles

- Compulsive eating
- Addictive eating disorder
- Night eating syndrome
- Binge eating ± depressive syndrome



- The population may not having confidence in doctors, but may believe in magic bullets

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BMI, body mass index

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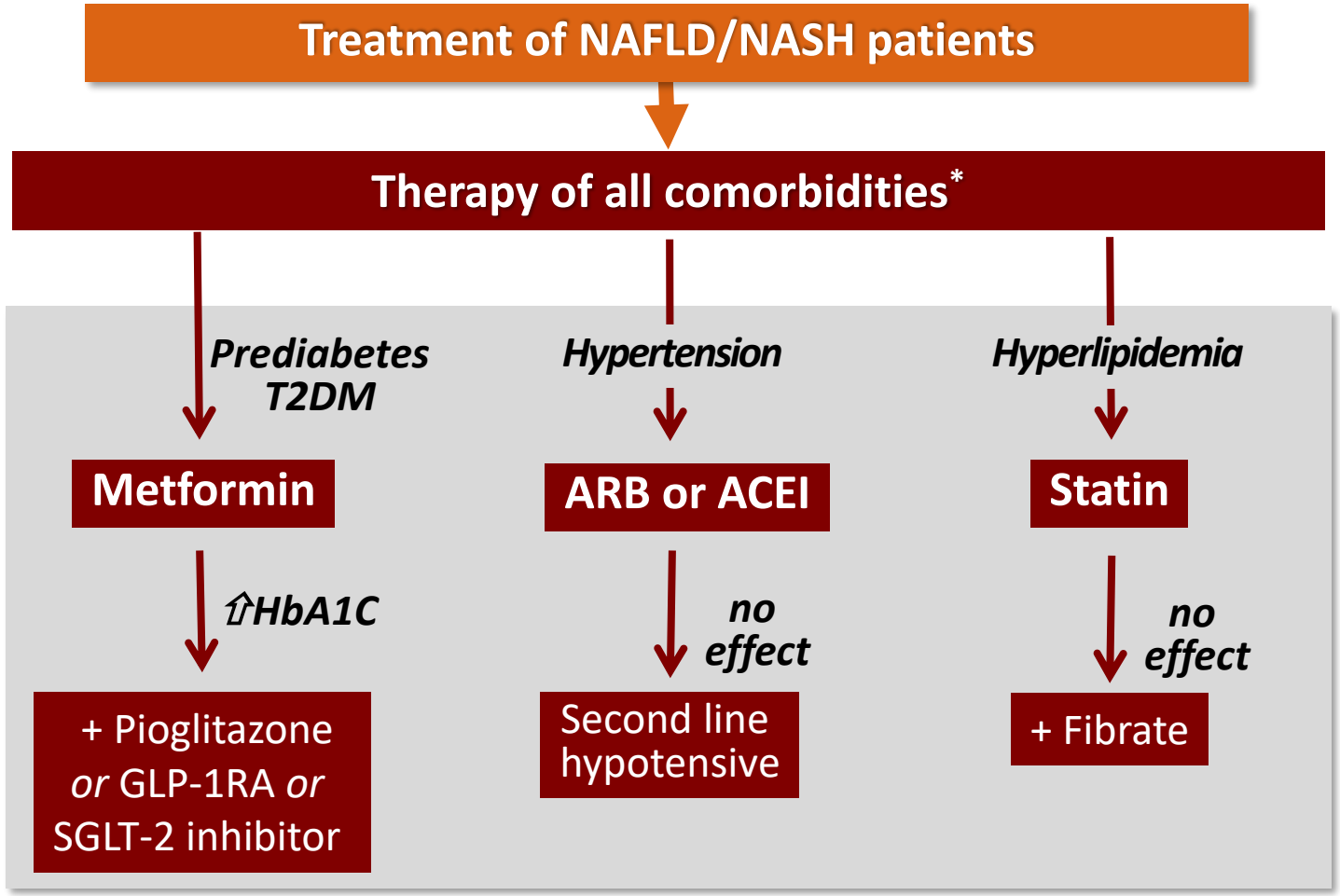
Management of NAFLD and diabetes



*Control of other CV risk factors. CV, cardiovascular; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatoheaptitis; SGLT-2, sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus. Bril F, Cusi K. Diabetes Care 2017;40:419

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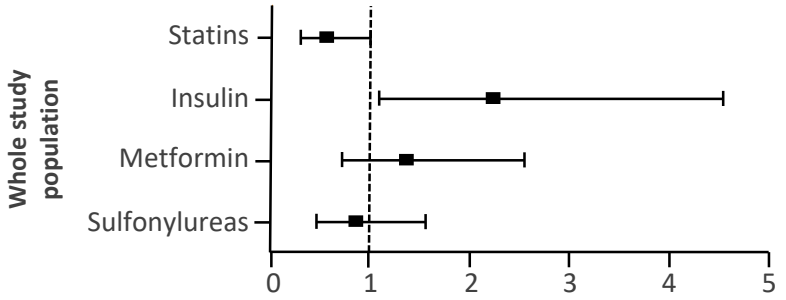
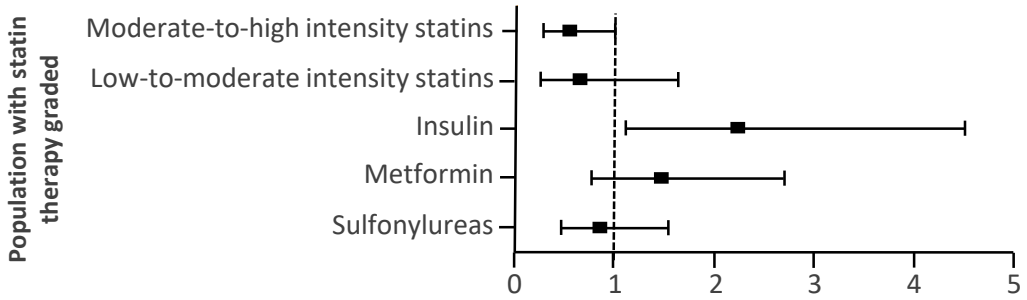
Use of statins in NASH with ≥ F2 fibrosis

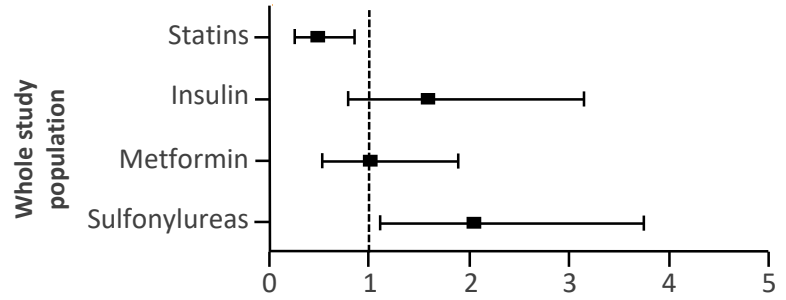
Cross-sectional study of 346 patients with NAFLD and T2DM

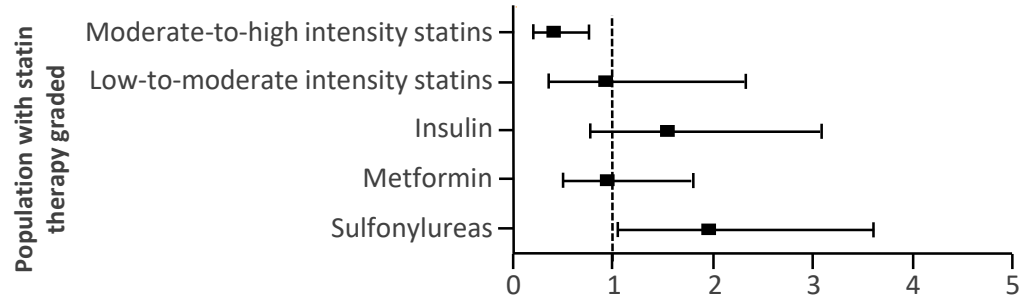
NASH: atorvastatin, rosuvastatin ± ezetymib

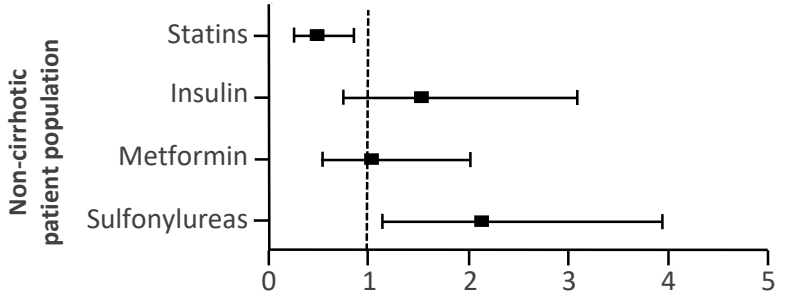


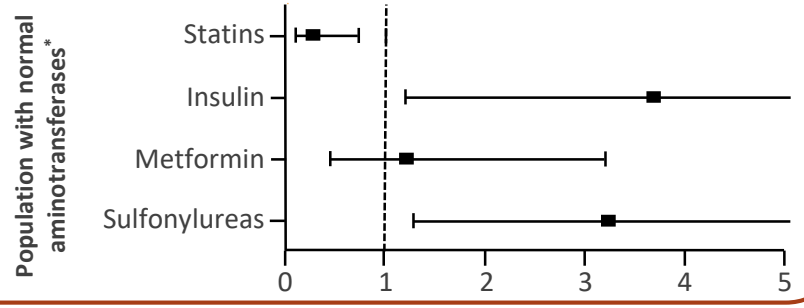


Fibrosis: atorvastatin, rosuvastatin ± ezetymib









Figures represent adjusted odds rations of statins and antidiabetic therapies. *Normal aminotransferases define as ALT <40 U/L and AST <40 U/L. ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus. Nascimbeni F et al. BMJ Open Gastro 2016;3:e000075

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BMI, body mass index

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NAFLD/NASH pathogenesis

15%

Fructose
+
Glucose
↓
Acetyl CoA

Lipogenesis
de novo
25%

60%

Circulating FFA ⇧⇧
↑ IR
Adipose tissue ⇧
↑
Chylomicrons
Triglycerides

Modifying factors
Genes
Intestinal microbiome
Adipokines

"Multi-hit pathogenesis"

Lipotoxic lipids
PNPLA3

RES Stress

Liver injury
↑↓
Apoptosis /Inflammation

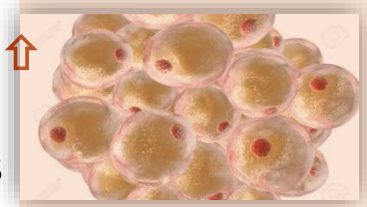
NASH
Fibrosis
HCC

Liver FFA

ROS **ROS**

Mitochondrial ß-oxidation

Triglycerides → VLDL ↓



Hypertriglyceridemia

Cytokines
Adipokines

Acetyl CoA, acetyl coenzyme A; FFA, free fatty acid; HCC, hepatocellular carcinoma; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3; ROS, reactive oxygen species; VLDL, very-low-density lipoprotein Softic S, et al. Dig Dis Sci 2016;61:1282–93; Bril F, et al. Diabetes Care 2019;42:1

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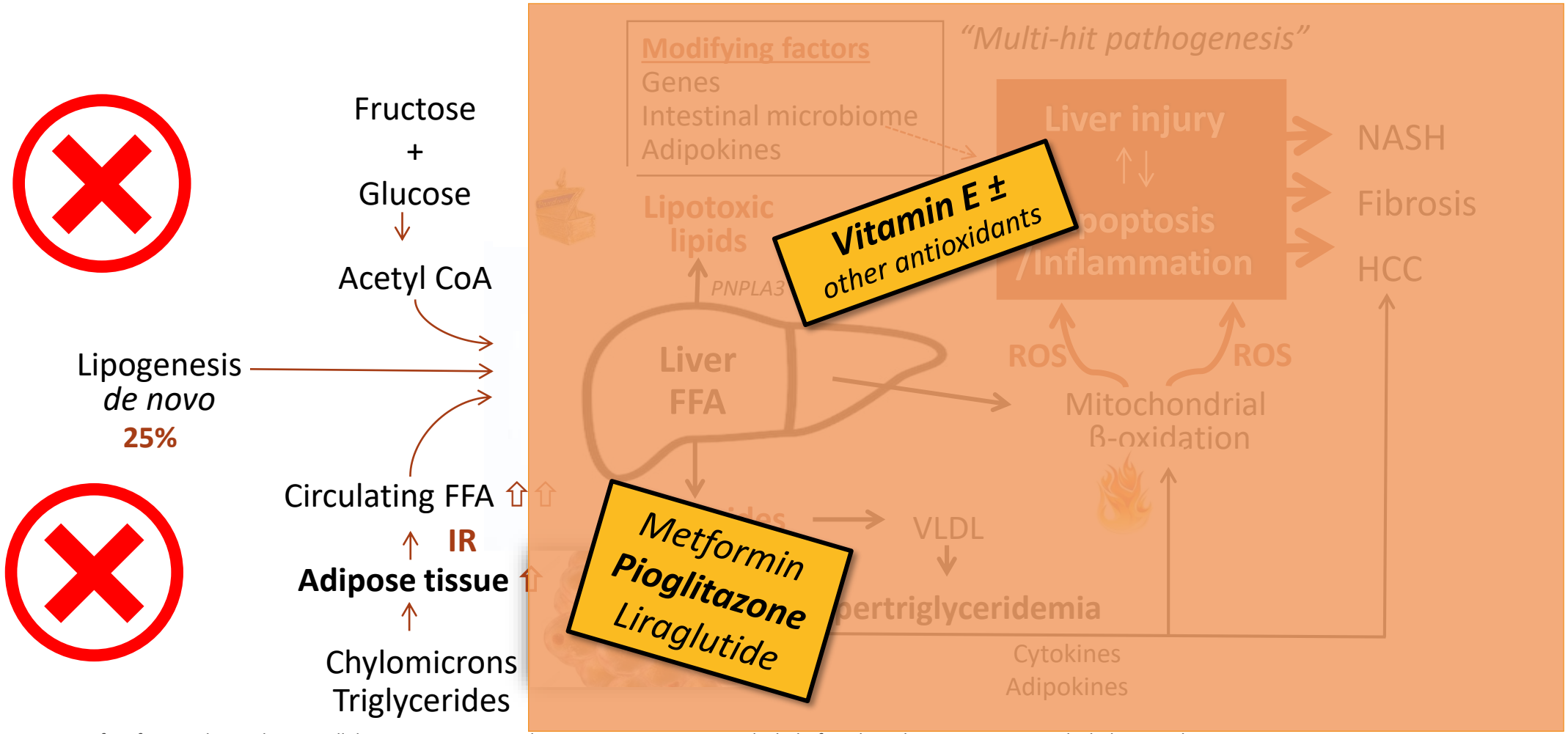
NAFLD/NASH pathogenesis



Acetyl CoA, acetyl coenzyme A; FFA, free fatty acid; HCC, hepatocellular carcinoma; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3; ROS, reactive oxygen species; VLDL, very-low-density lipoprotein Softic S, et al. Dig Dis Sci 2016;61:1282–93; Bril F, et al. Diabetes Care 2019;42:1

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AASLD

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

- Pharmacological liver-directed treatment?
  - May be considered ONLY in patients with histologically confirmed NASH ± hepatic fibrosis
  - AASLD does not recommend ANY drug for NASH-specific treatment

NASH, non-alcoholic steatohepatitis
Chalasani N, et al. Hepatology 2018;67:328–57

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Guidance statements on pharmacological management

	EASL[1]	NICE[1]	Asia-Pacific[1]	AISF[1]	AASLD[1]	China[2]	Russia[3]	Poland[4]
Metformin	Insufficient evidence	Not beneficial	Not beneficial	Not mentioned	Not beneficial	Consider use to improve glucose metabolism	Recommended	Not recommended in NASH Consider use in diabetes with NAFLD Consider use in children with NAFLD
GLP-1 analogues	Insufficient evidence, potentially useful	Insufficient evidence	Insufficient evidence in Asian patients	Insufficient evidence, potentially useful	Insufficient evidence	Not mentioned	Not mentioned	Insufficient evidence
Vitamin E	Insufficient evidence	Consider use regardless of diabetes	Not beneficial	Insufficient evidence	Consider use in nondiabetic, biopsy-proven NASH	Consider use as adjunct therapy	Not mentioned	Consider use in nondiabetic, biopsy-proven NASH
PPAR-gamma agonists	Consider use in selected diabetic patients	Consider pioglitazone in adults regardless of diabetes	Insufficient evidence in Asian patients	Insufficient evidence, potentially useful	Pioglitazone indicated in biopsy-proven NASH (regardless of diabetes)	Consider use of pioglitazone to improve glucose metabolism	Pioglitazone is recommended	Consider pioglitazone in non-obese patients with biopsy-proven NASH and diabetes
Obeticholic acid	Scarce evidence	Not mentioned	Waiting for ongoing RCT results	Waiting for ongoing RCT results	Insufficient evidence	Not mentioned	Not mentioned	Scarce evidence

AASLD, American Association for the Study of Liver Diseases; AISF, Italian Association for the Study of the Liver; EASL, European Association for the Study of the Liver; GLP-1, glucagon-like peptide 1; NAFLD, non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; NICE, National Institute for Health and Care Excellence; PPAR, peroxisome proliferator-activated receptor; RCT, randomized controlled trials

1. Leoni S, et al. World J Gastroenterol 2018;24:3361–-73; 2. Fan JG, et al. J Dig Dis. 2018;1–11; 3. Ivashkin VT, et al. RZHGGK. 2015;6:31-41; 4. Hartleb M, et al. Gastroenterologia Praktyczna. 2019; 11–35

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Pioglitazone and vitamin E for NASH?

American Diabetes Association. Diabetes Care

Therapy vs placebo	Reduced NAS by 2 pts*	Regression of NASH*
Pioglitazone and vitamin E (n=37)	54% vs 19% **p=0.003**	43% vs 12% **p=0.005**
Vitamin E (n=36)	31% vs 19% p=0.26	33% vs 12% **p=0.04**

*vs placebo (n=32). Proof-of-concept, randomized double-blind, placebo-controlled trial in patients with T2DM and biopsy-proven NASH. Primary outcome: Reductions of ≥2 points in NAS without worsening of fibrosis
NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus
Bril F, et al. Diabetes Care 2019;42:1

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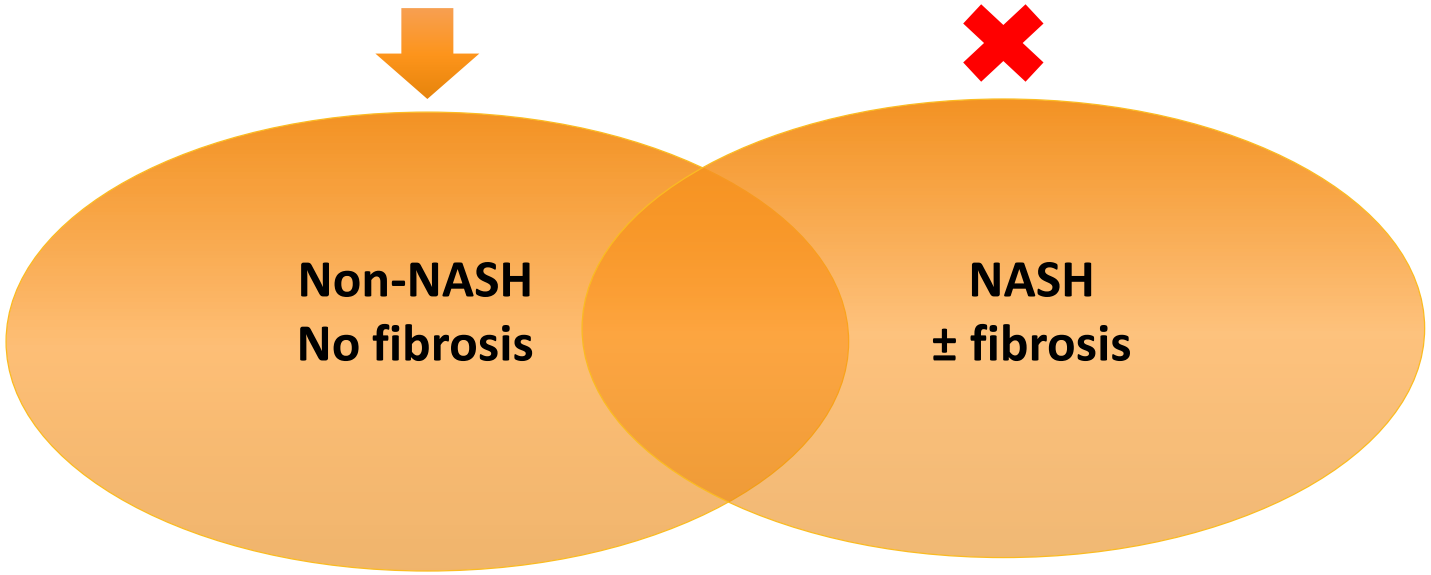
Is there room for hepatoprotective drugs?

Dietary modifications + physical activity

Hepatoprotectants (PPC, UDCA, Sylimarin …)
as adjunctive treatment



NASH, non-alcoholic steatohepatitis; PPC, polyenylphosphatidycholine; UDCA, ursodeoxycholic acid
Schematic developed by speaker

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Polish guidance statements on pharmacological management

	Polish guidance
PUFA	Insufficient evidence
Pentoxifylline	Insufficient evidence
UDCA	Adjunctive treatment in low-risk NAFLD
Silymarin	Insufficient evidence
PPC	Adjunctive treatment in low-risk NAFLD The effects of EPL were assessed in NAFLD patients in 14 RCTs (N=1392) and there was a significant reduction in blood lipids and ALT activity. EPL also appear to have a beneficial effect on the degree of hepatic steatosis; however, this effect has mainly been assessed by non-invasive methods

ALT, alanine aminotransferase; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; PPC, Phosphatidylcholine; PUFA, Polyunsaturated fatty acids; RCT, randomized controlled trial; UDCA, ursodeoxycholic acid. Hartleb M, et al. Gastroenterologia Praktyczna. 2019; 11–35

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Clinical studies evaluating EPL in NAFLD or NASH

Randomized and/or controlled	Other supportive randomized controlled studies	Supportive controlled studies	Supportive observational studies	Real-world evidence studies
• Gonciarz Z et al. 1988 **30** • Yin D et al. 2000 **185** • Arvind N et al. 2006 **40** • Wen-Jin S. 2012 **56** • Li Z et al. 2013 **86** • Sas E et al. 2013 **215** • Dajani A et al. 2015 **324**	• Li JH et al. 2000 **36** • Du Q. 2004 **52** • Liang H et al. 2006 **50** • Qian H et al. 2007 **56** • Sun C et al. 2008 **74** • Guo S. 2008 **108** • Wu Y. 2009 **100** • Li L. 2010 **88** • Sas E et al. 2012 **80** • Wen-Jin S. 2012 **56** • Li Z et al. 2013 **86**	• Watanabe A et al. 1998 • Zeng J et al. 2008 • Buyeverov AO et al. 2008	• Koga S et al. 1991 • Turecký L et al. 1996 • Szántová M et al. 1996 • Dinakaran N. 2003 • Ohbayashi H. 2004 • Poongothai S et al. 2005 • Ohbayashi H et al. 2006 • Dezhou H. 2012 • Padma L et al. 2013	• Maev 2019

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
Gundermann KJ, et al. Clin Exp Gastroenterol 2016;9:105–17

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Clinical evidence for EPL as a supportive treatment in NAFLD


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Original Article

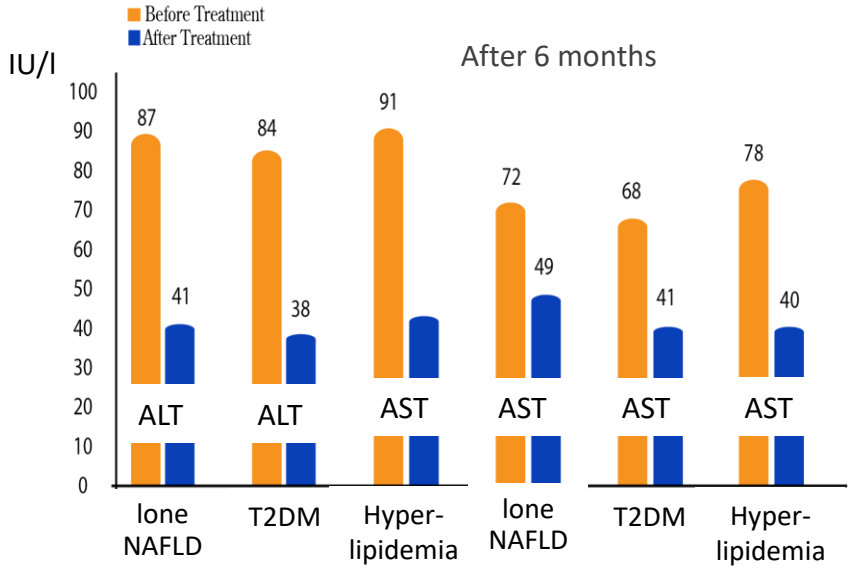
Essential phospholipids as a supportive adjunct in the management of patients with NAFLD

Asad Izziddin Mustafa Dajani [a,*], Adnan M. Abu Hammour [b], Mohammed A. Zakaria [c], Mazen R. Al Jaberi [d], Mohammed A. Nounou [e], Abdul Ilah M. Semrin [f]

Randomized prospective controlled study

Patients (N=324): Lone NAFLD or NAFLD with comorbidities (T2DM, hyperlipidemia)

Treatment: EPL 1,800 mg/d first 6 months, then 900 mg next 48 weeks



After 18 months

Improvement in US in:

- **29.2%** patients with **NAFLD**
- **23.4%** patients with **NAFLD + T2DM**
- **20.2%** patients with **NAFLD + hyperlipidemia**

Improvement of LSM in:

- **14.2%** patients with **NAFLD**
- **26.2%** patients with **NAFLD + T2DM**
- **20.2%** patients with **NAFLD + hyperlipidemia**

ALT, alanine aminotransferase; AST, aspartate transaminase; EPL, essential phospholipids; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus

Gundermann KJ, et al. Clin Exp Gastroenterol 2016;9:105–17

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Drugs investigated in phase 3 trials

Drug	Mechanism	Trial	Endpoint
Obeticholic acid[1]	Agonist FXR	REGENERATE	**Improvement of fibrosis** (≥ 1 stage) w/out worsening of NASH *OR* **NASH resolution** w/out worsening of fibrosis
Cenicriviroc[2]	Antagonist CCR2/CCR5	AURORA	**Improvement of fibrosis** (≥ 1 stage) w/out worsening of NASH
Elafibranor[3]	Agonist PPAR α/δ	RESOLVE-IT	**NASH resolution** w/out worsening of fibrosis
Resmetirom[4]	Selective agonist THR-β	MAESTRO-NASH	**NASH resolution**. Impact on mortality, cirrhosis development and all hepatic complications
Aramchol[5]	Modulator of stearylo-CoA desaturase	ARMOR	**NASH resolution** w/out worsening of fibrosis *OR* **improvement of fibrosis** (≥ 1 stage) w/out worsening of NASH

CCR2, C-C chemokine receptor type 2; CCR5, C-C chemokine receptor type 5; FXR, farnesoid X receptor; NASH, non-alcoholic steatoheaptitis; PPAR, peroxisome proliferator-activated receptors; THR-β, thyroid hormone receptor beta

1. clinicaltrials.gov/ct2/show/NCT02548351; 2. clinicaltrials.gov/ct2/show/NCT03028740; 3. clinicaltrials.gov/ct2/show/NCT02704403; 4. clinicaltrials.gov/ct2/show/NCT03900429; 5. clinicaltrials.gov/ct2/show/NCT04104321

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Conclusions

1. In non-NASH patients, dietary restrictions and physical activity are the most important and usually exclusive mode of treatment
2. NAFLD is a systemic disease, therefore requires a therapeutic approach for all comorbidities, such as T2DM, arterial hypertension and dyslipidemia
3. In patients with NASH ± fibrosis there is a need for liver-directed therapies; however, currently no drug can be recommended due to insufficient evidence of efficacy or an unfavorable safety profile
4. Emergence of an efficacious drug would lead to a surge of NAFLD diagnoses with a concurrent increase in referrals of patients with advanced fibrosis

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

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Considering current evidence and guidance, how likely would you be to consider the use of hepatoprotectants as an adjunctive treatment in early NAFLD?

1. Very likely
2. Likely
3. Neutral
4. Unlikely

NAFLD, non-alcoholic fatty liver disease

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