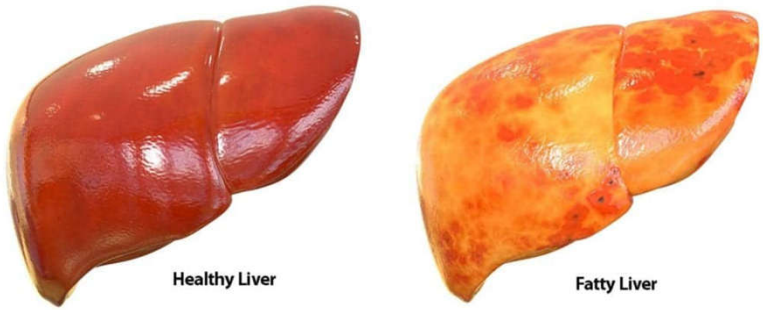
Medic Center

CẬP NHẬT TIẾN BỘ MỚI TRONG CHẨN ĐOÁN & ĐIỀU TRỊ
BỆNH GAN NHIỄM MỠ KHÔNG DO RƯỢU



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07/2023

NỘI DUNG

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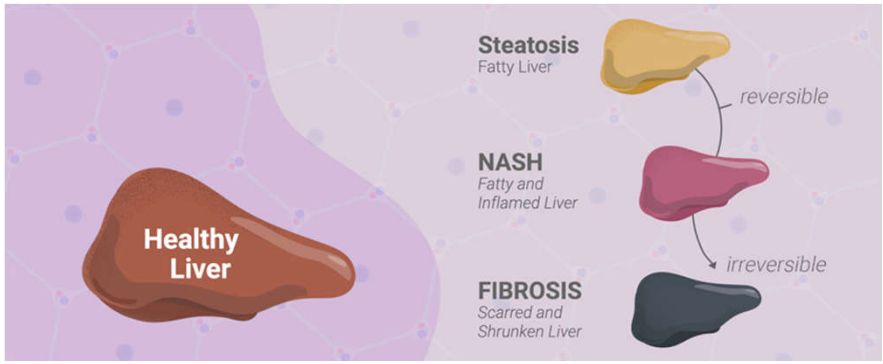
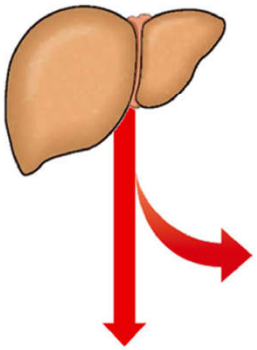


I. Đặt vấn đề.

NAFLD

Hepatic steatosis
Imaging or histology



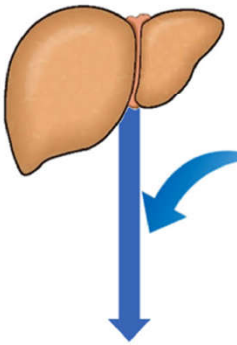
Exclusion criteria
- Alcoholic intake ≥30 g/day for men/ ≥ 20 g/day for women
- Viral hepatitis
- Other etiology of chronic liver disease

NAFLD

- No requirement of metabolic dysfunction
- No combination with other liver diseases
- Moderate/heavy drinkers are excluded
- Liver biopsy is required for diagnosis of NASH

MAFLD

Hepatic steatosis
Imaging, biomarkers or histology



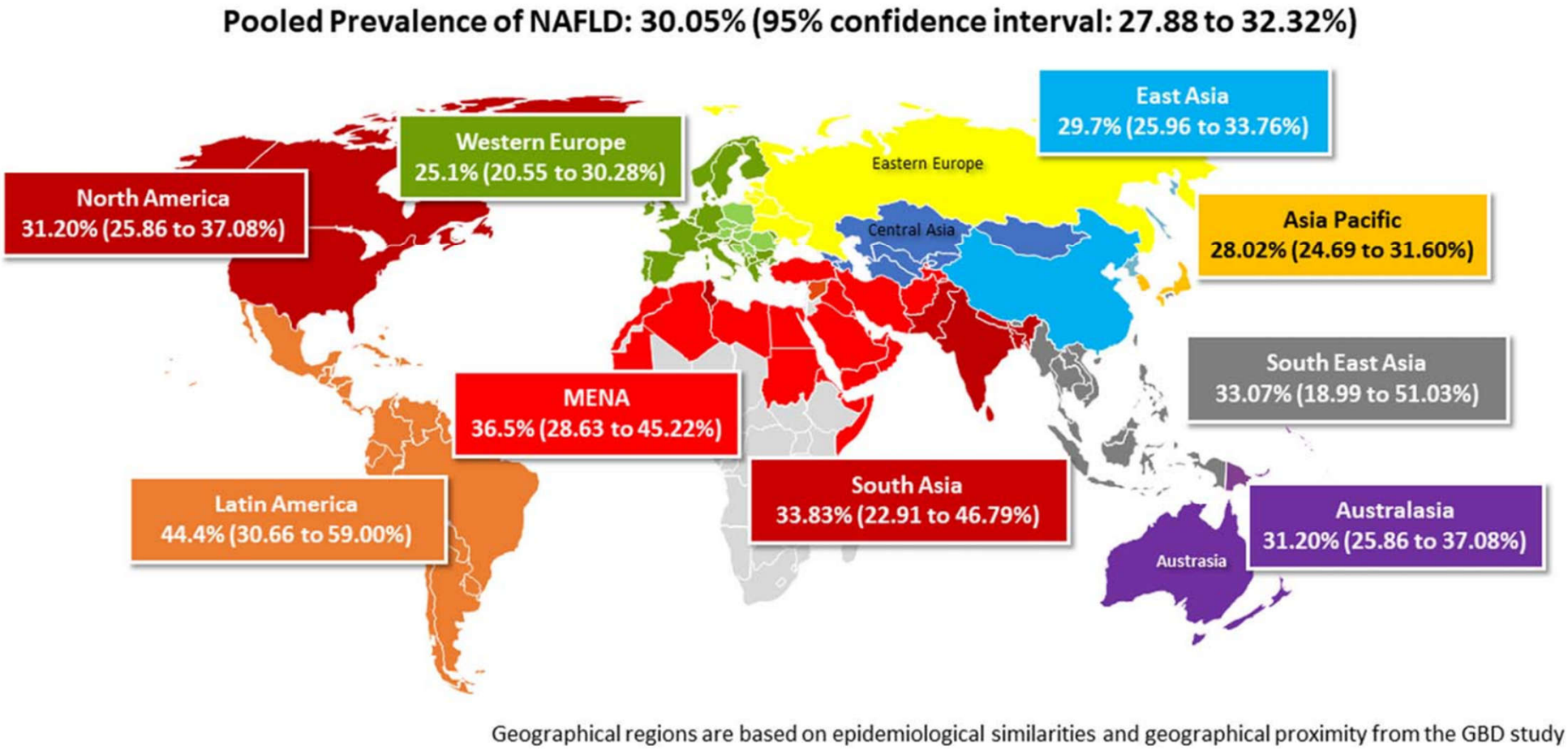
Inclusion criteria
- Overweight/obesity
- Type 2 diabetes mellitus
- Metabolic dysfunctions

MAFLD + **HBV/HCV/ALC/AIH etc.**

- Requirement of metabolic dysfunction
- Combination with other liver diseases
- Independent from alcoholic intake
- No requirement for liver biopsy

Takumi Kawaguchi et al. Hepatology Research – Volume 52, Issue 5 May 2022 Pages 422-432

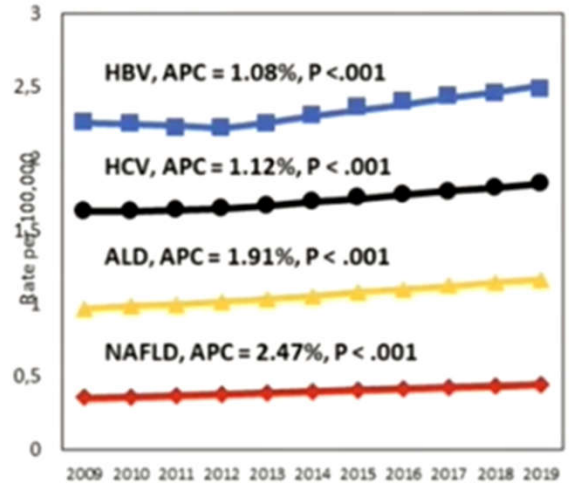
Prevalence of NAFLD According to Global Regions Data Collected 1990–2019



Zobair M. Younossi et al. THE GLOBAL EPIDEMIOLOGY OF NAFLD AND NASH. Hepatology. 2023;77:1335–1347.

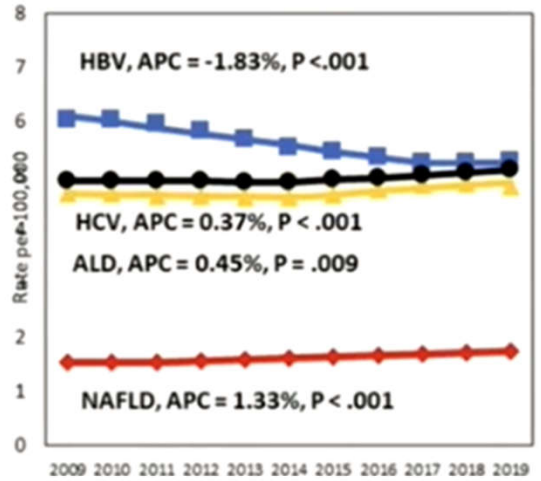
Global Burden of Liver Cancer and Chronic Liver Diseases is Driven by NASH and Alcohol Liver Disease

Global Change in Liver Cancer Death



APC: Annual percentage change

Global Change in Liver disease Death

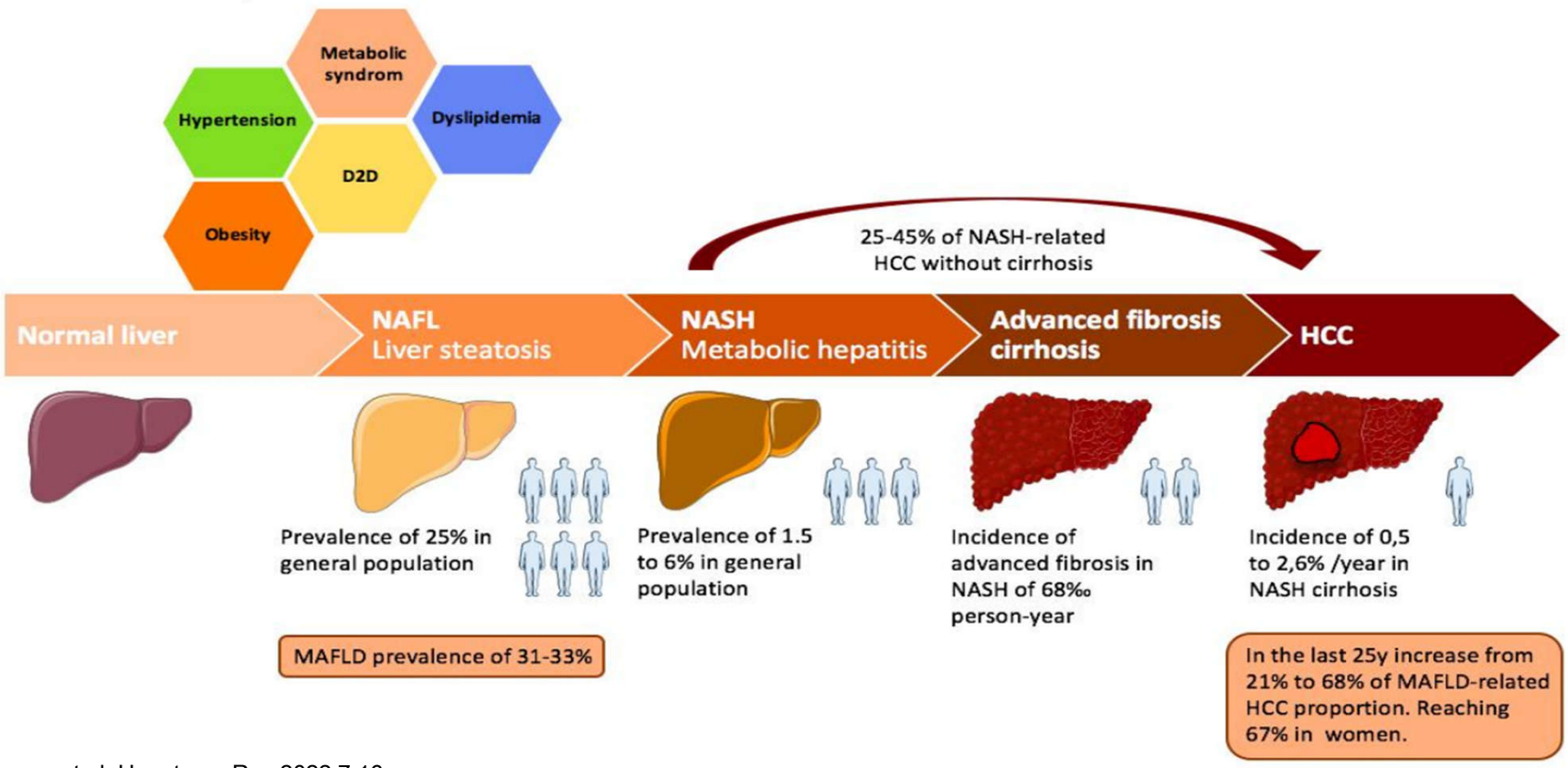


Paik J et al. ILC 2022; OS 044

EASL Highlights

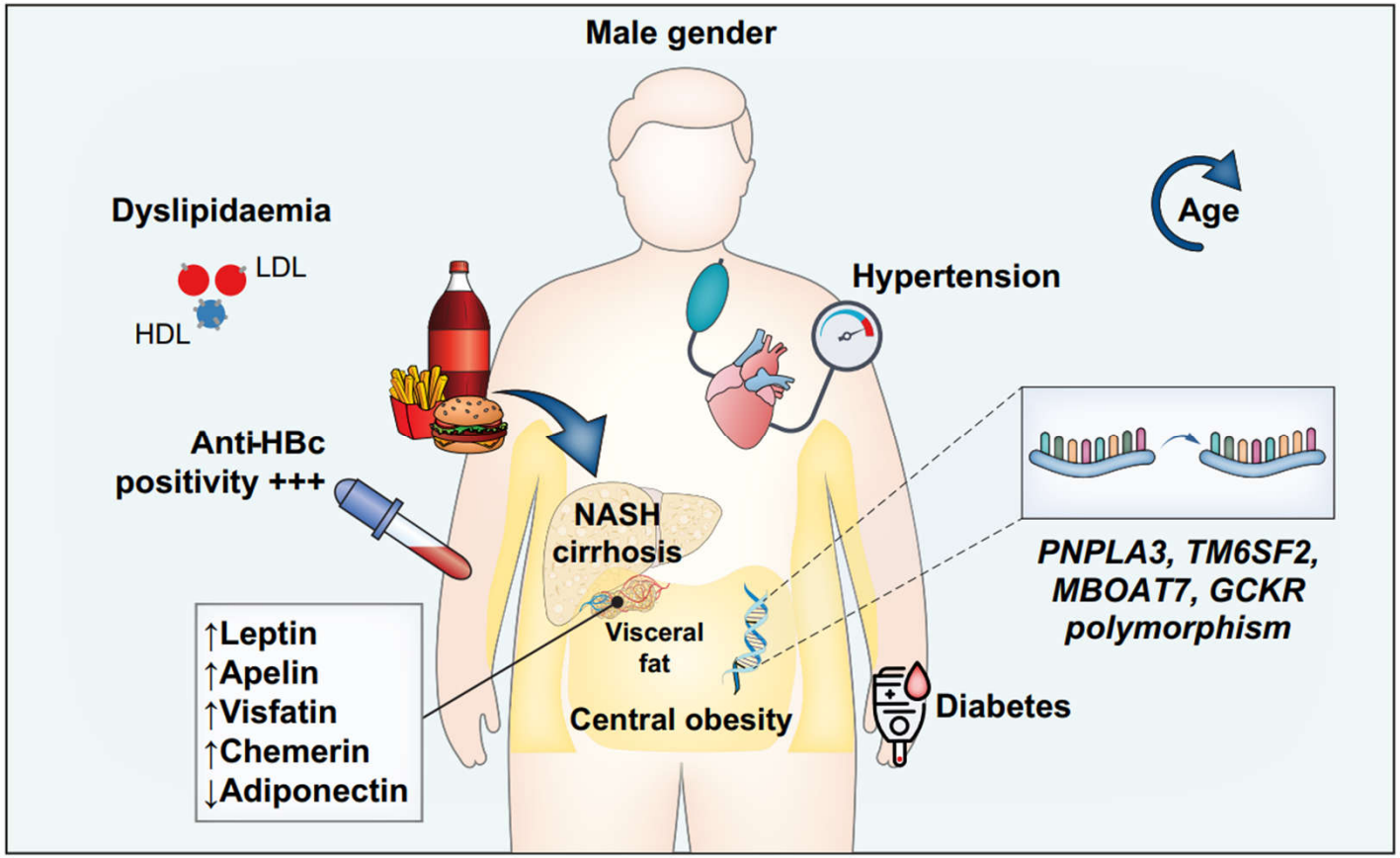
II.Diễn tiến bệnh gan nhiễm mỡ

Natural history of NAFLD: from liver steatosis to HCC



Desjonqueres et al. Hepatoma Res 2022;7:16

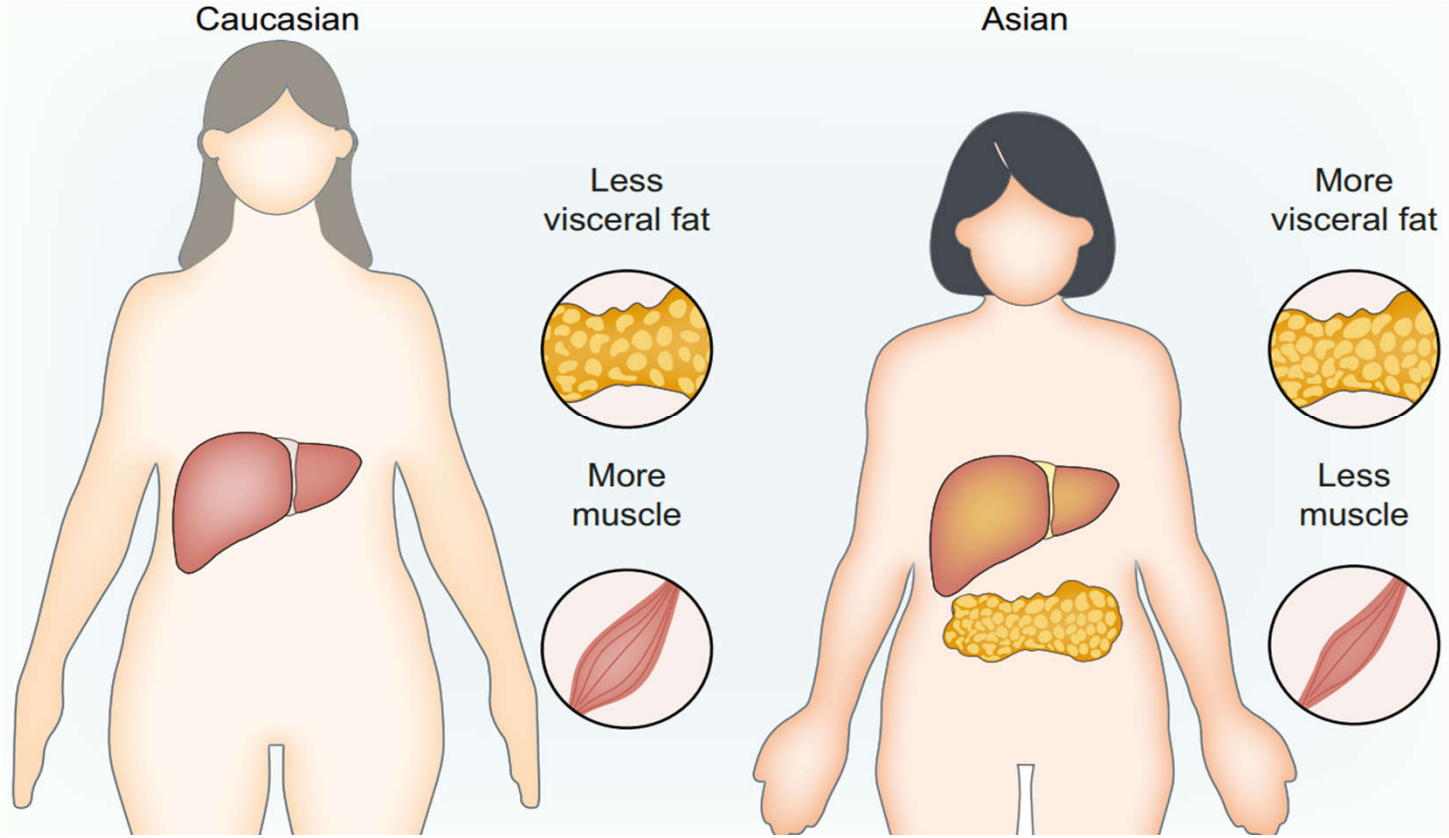
Risk factors for NAFLD-associated HCC in Asia.



HCC, hepatocellular carcinoma;
NAFLD, non-alcoholic fatty liver disease.

Terry Cheuk-Fung Yip et al. Journal of Hepatology 2022 vol. 76 j 726–734

Different body fat distribution in Asians and Caucasians

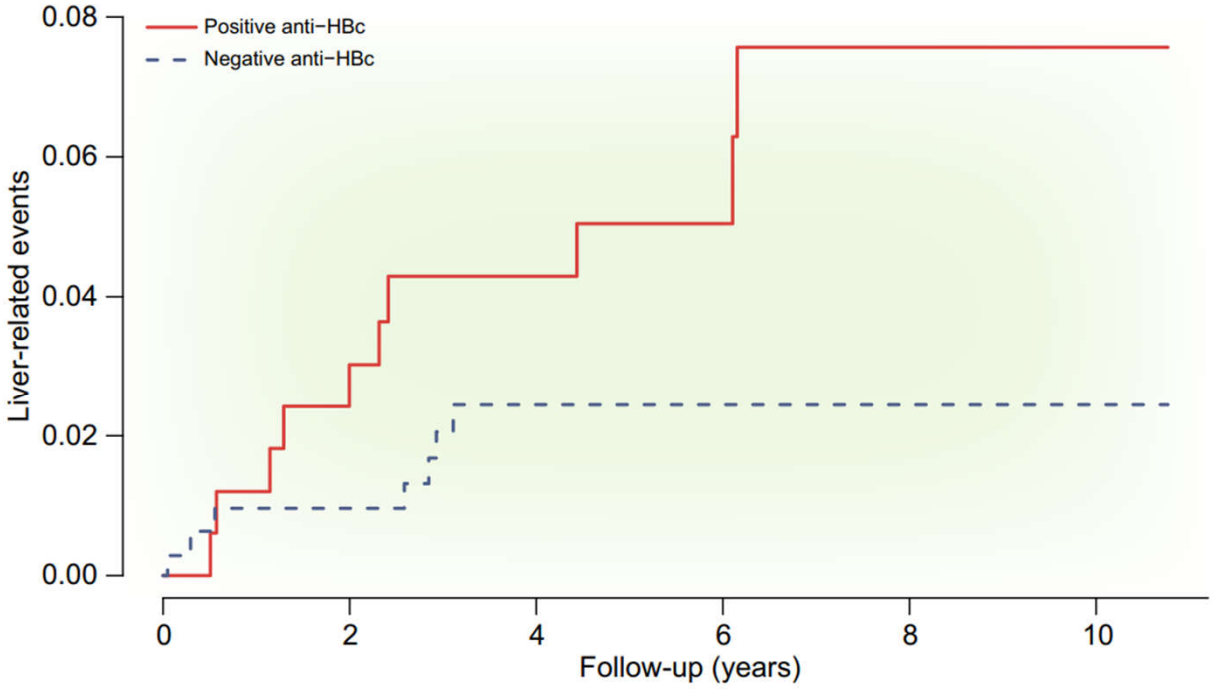


At the same body mass index, Asians tend to have more central fat deposition and visceral adiposity than Caucasians. As a result, Asians start to develop metabolic complications such as diabetes and NAFLD at a lower body mass index

Terry Cheuk-Fung Yip et al. Journal of Hepatology 2022 vol. 76 j 726–734

Increased risk of liver-related events in Asian patients with NAFLD and positive hepatitis B core antibody.

Hepatitis B core antibody is a marker of prior or occult HBV infection. In a study of 489 patients with NAFLD from Hong Kong and Malaysia, 6.5% of those with positive hepatitis B core antibody and 2.2% of those without developed liver-related events (i.e., HCC and cirrhotic complications). All 4 patients who developed HCC had positive hepatitis B core antibody. The figure was reproduced with permission from Chan et al.



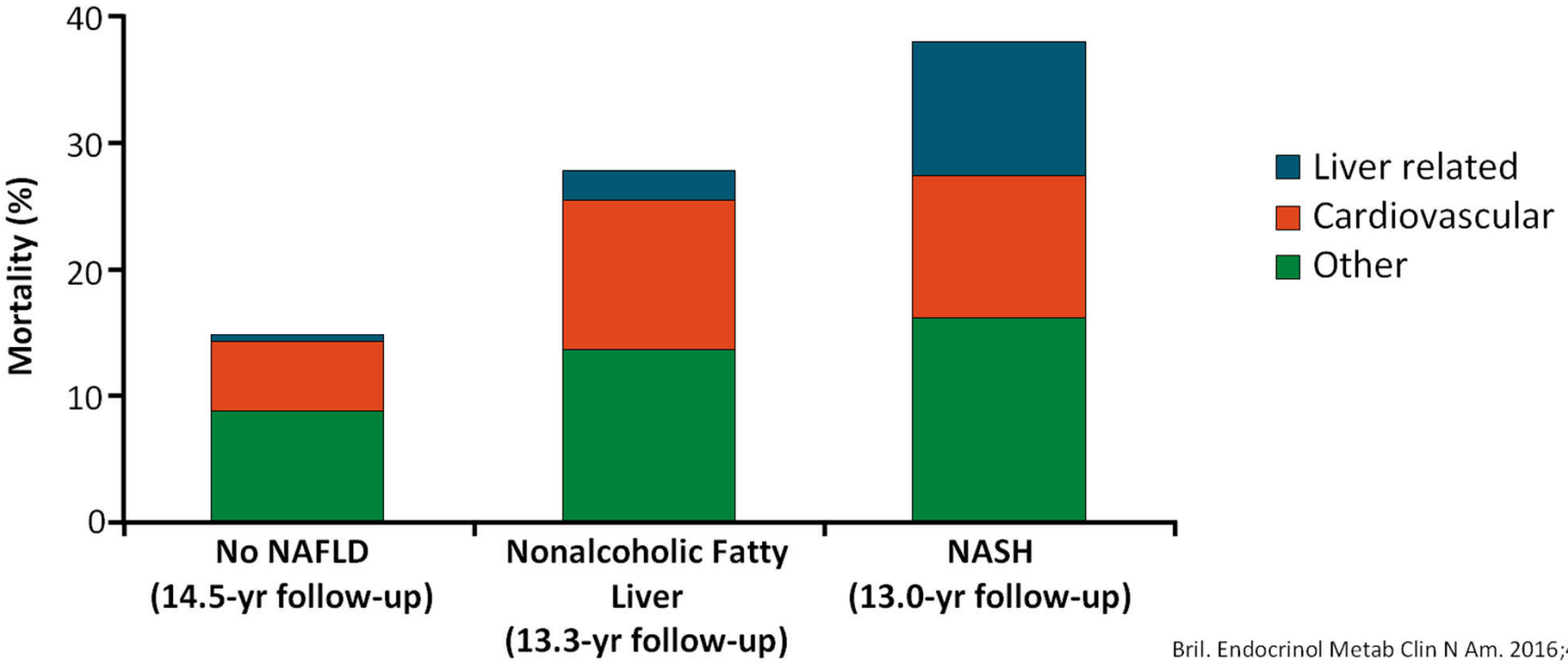
N° at risk						
Positive	170	161	143	81	42	25
Negative	319	311	239	156	69	43

HCC, hepatocellular carcinoma;
NAFLD, non-alcoholic fatty liver disease.

Terry Cheuk-Fung Yip et al. Journal of Hepatology 2022 vol. 76 j 726–734

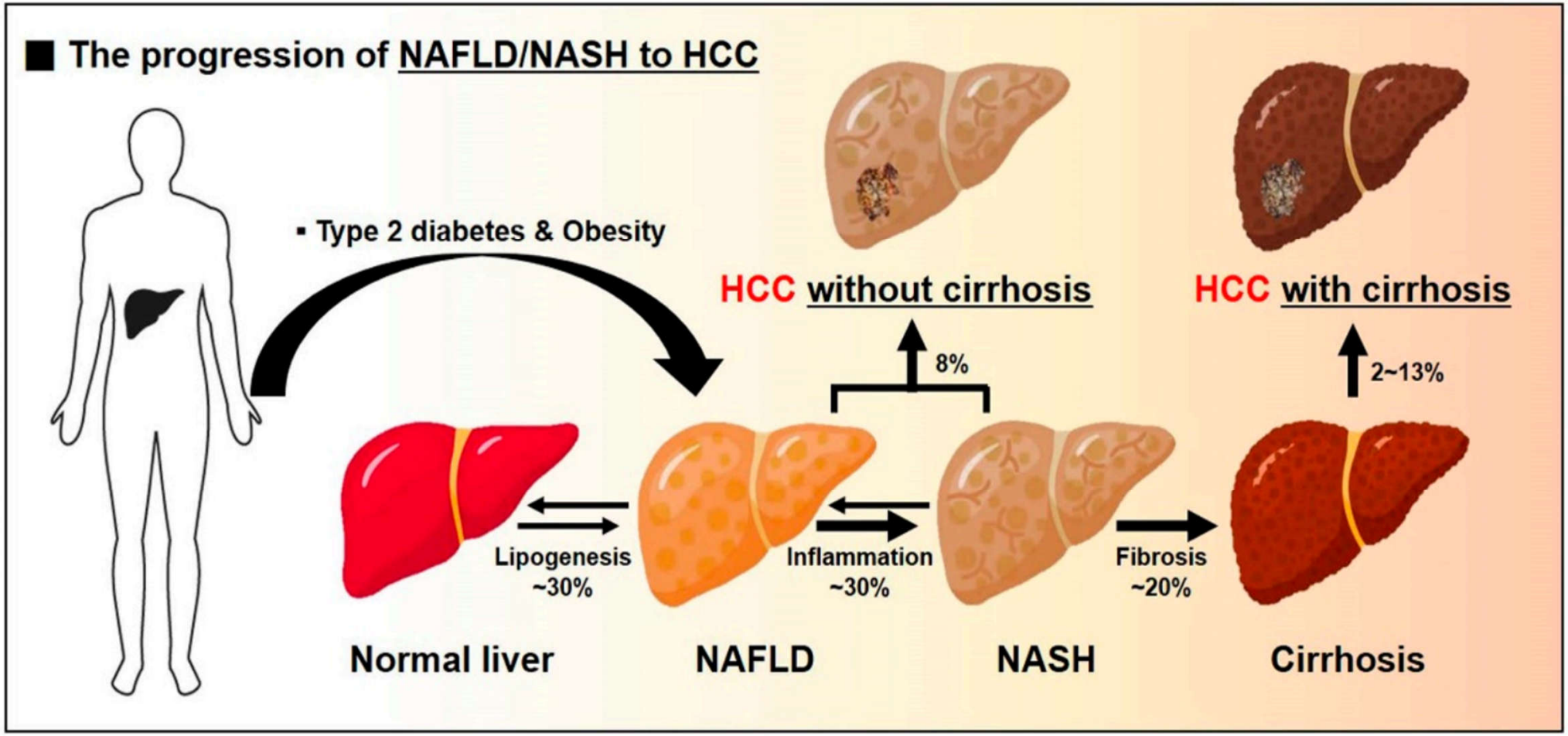
Mortality Risk Associated With Nonalchololic Fatty Liver vs NASH

- Analysis of all-cause mortality in 6 separate studies among patients without NAFLD vs with and without NASH
  - NAFLD determined by ultrasound; NASH determined by liver biopsy



Bril. Endocrinol Metab Clin N Am. 2016;45:765.

Type 2 diabetes and obesity aggravate the progression of NAFLD/NASH to HCC



Hyunmi Kim et al. Int. J. Mol. Sci. 2021, 22, 4495

Prevalence of NAFLD, advanced fibrosis, cirrhosis, and hepatocellular carcinoma in patients with type II diabetes: A prospective study

Aim

To evaluate the prevalence of advanced fibrosis and cirrhosis in a prospectively recruited cohort of adults with type II diabetes mellitus (T2DM).

Methods

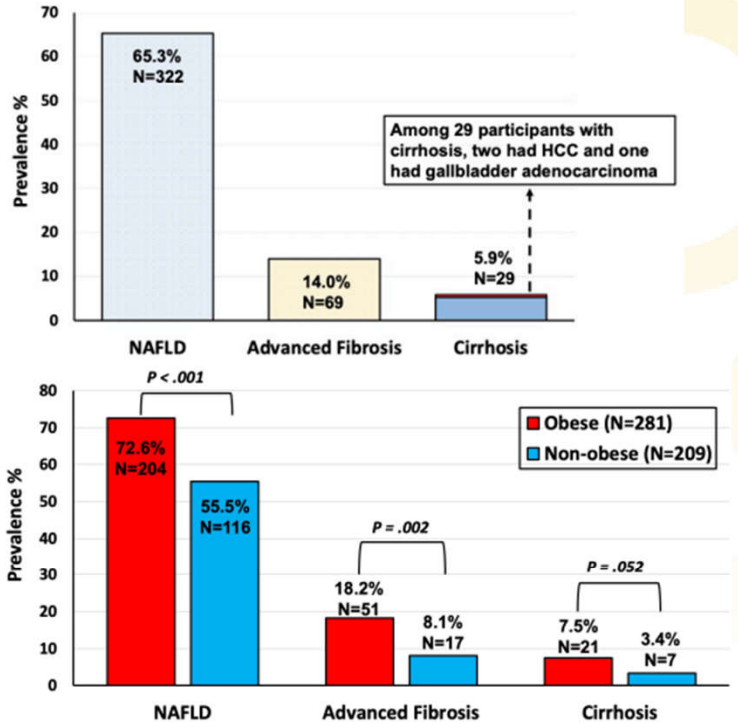
Adults age ≥ 50 years with T2DM recruited from primary care or endocrinology clinics underwent a standardized clinical research visit with MRI-PDFF, MRE, VCTE, and CAP.

Main Findings

- The prevalence of NAFLD, advanced fibrosis, and cirrhosis was 65%, 14% and 6%, respectively.
- In multivariable adjusted models, adjusted for age and sex, obesity and insulin use were associated with increased odds of advanced fibrosis OR=2.50 (95% CI: 1.38-4.54, p=0.003) and OR=2.71 (95% CI: 1.33-5.50, p=0.006), respectively.

Conclusions

The high disease burden in adults with T2DM provide new data to support systematic screening to identify advanced fibrosis or cirrhosis in adults ≥ 50 years with T2DM.



AASLD Nov. 4-8, 2022
The Liver Meeting®
WASHINGTON D.C.

Ajmera V, et al., Abstract 95.

III. Chẩn đoán bệnh gan nhiễm mỡ.

Guideline Recommendations: Who Is at Risk for NASH and Advanced Fibrosis?

AASLD[1]	EASL-EASD-EASO[2]	ADA[3]
In T2D, **suspect NAFLD and NASH** and determine patient's risk of advanced fibrosis	NASH and advanced fibrosis **screening recommended** in persons at high risk (age >50 yrs, T2D, metabolic syndrome)	NASH and fibrosis **screening recommended** in persons with T2D or prediabetes and elevated ALT or fatty liver
Increasing number of metabolic diseases = **increasing risk of progressive liver disease**		

AASLD, EASL, and ADA guidelines call out **patients with T2D** as warranting workup

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. ADA. Diabetes Care. 2019;42:S34.

Commonly Used Noninvasive Tests

Clinical or Laboratory Scores

Simple

- Fibrosis-4 (FIB-4)[1,2]
- NAFLD fibrosis score[1,2]
- AST/platelet ratio index[1]

Proprietary

- Enhanced Liver Fibrosis Test[1] (not available in US)
- NIS4
- ADAPT/Pro-C3[3] (not available in US)
- *FibroSure*[1]
- Hepascore

Imaging

Elastography

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1 (*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- FAST score[8]

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

Liver Enzymes: Inadequate in Assessing NAFLD/NASH

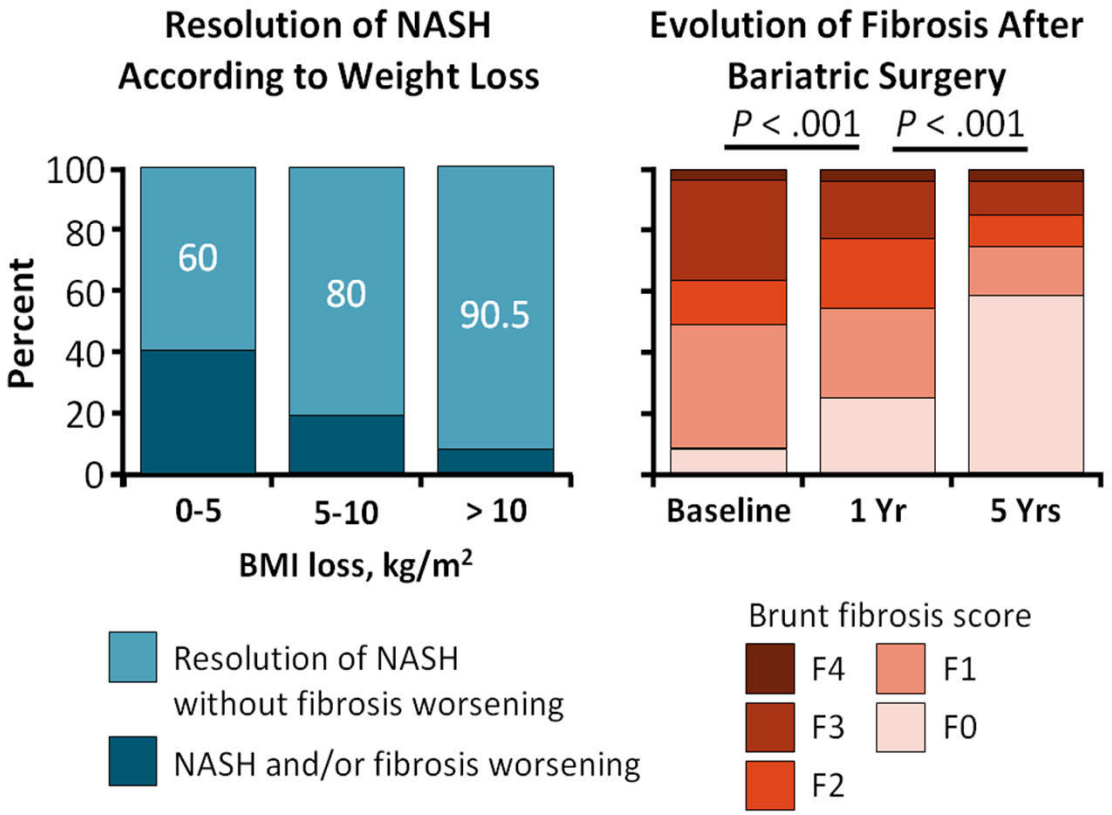
- ALT can be normal in > 50% of individuals with NASH, 80% of individuals with NAFLD[1,2]
- ALT can be elevated in > 50% of individuals with NAFLD but without NASH
- In NAFLD, ALT is neither indicative nor predictive of NASH or fibrosis stage[3]:
  - Normal ALT does not preclude NASH/progressive disease
  - Elevated ALT cannot predict NASH or fibrosis
  - **ALT or AST not sensitive for NAFLD/NASH**

Abnormal ALT may warrant workup for NAFLD,[4]
but is not sensitive to confirm, rule out, or characterize NAFLD

1. Browning. Hepatology. 2004;40:1387. 2. Dyson. Frontline Gastroenterol. 2014;5:211.
3. Mofrad. Hepatology. 2003;37:1286. 4. Younossi. Am J Gastroenterol. 2020;00:1.

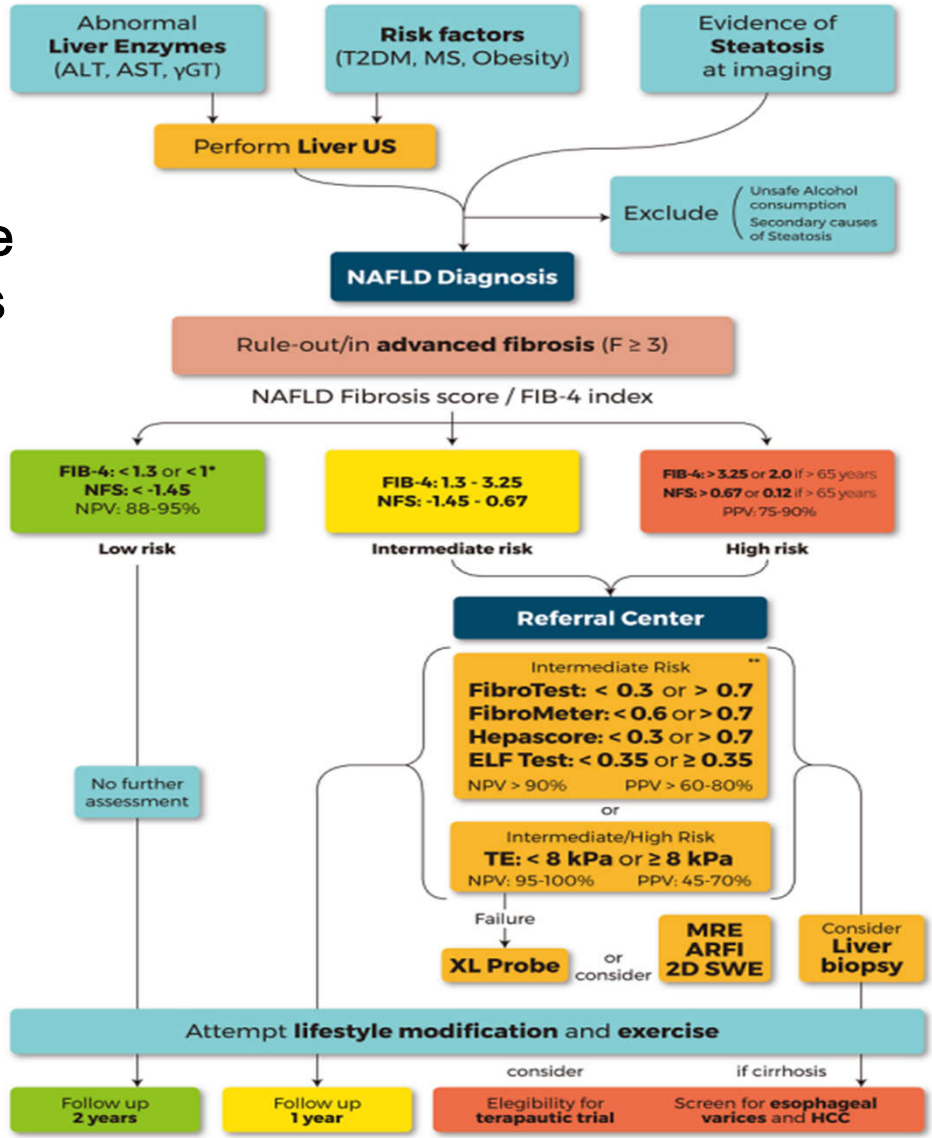
Is NASH Reversible ?

- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yrs post surgery, 64 of 94 patients (84%) had NASH resolution with no worsening of fibrosis
  - NASH improvement correlated with weight loss



Lassailly. Gastroenterology. 2020;159:1290.

A proposed algorithm to be used by clinicians to perform the diagnosis and the risk stratification of patients with steatosis by means of non-invasive tests



Valerio Rosato et al. Explor Med. 2020;1:259-86 | https://doi.org/10.37349/emed.2020.00018

IV. Điều trị bệnh gan nhiễm mỡ.

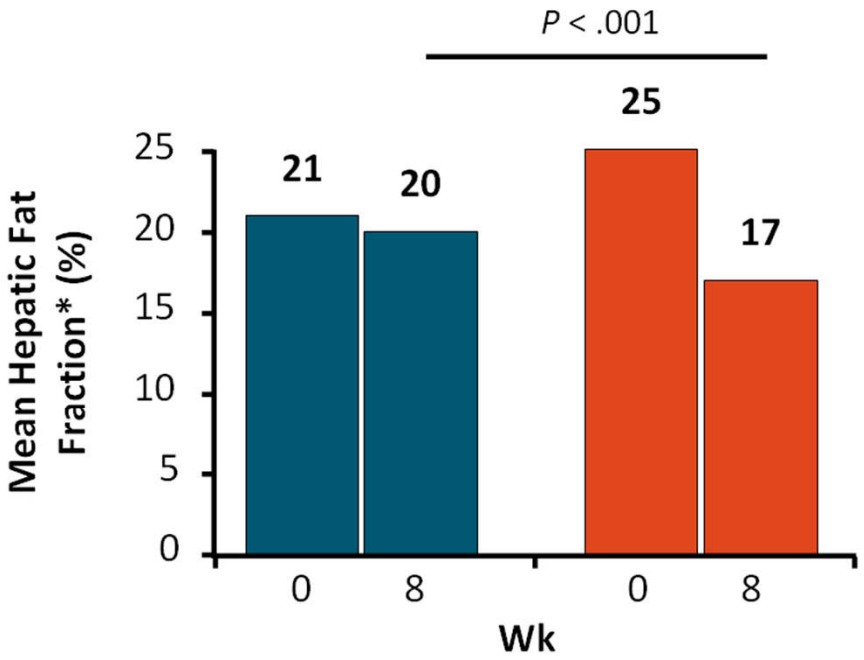
Lifestyle Guidelines in NASH

	AASLD 2018[1]	EASL 2016[2]	APASL 2020[3]
Program	Lifestyle modification including dietary change, weight loss, and structured exercise intervention		
Diet	500-1000 kcal energy deficit to induce a weight loss of 500-1000 g/wk • Prospective trials comparing macronutrient diets in NAFLD are limited	• Exclusion of NAFLD-promoting components (processed food, added fructose) • Mediterranean diet suggested	
Weight Loss	7% to %10% weight loss is the target of lifestyle interventions to improve NASH and fibrosis		
Exercise	• Exercise alone may prevent/ reduce hepatic steatosis – Effect on other aspects of liver histology unknown	• Both aerobic exercise and resistance training reduce liver fat – Tailor to patient preferences	
Bariatric Surgery	• Reduces liver fat, improves histologic lesions of NASH, including fibrosis • Individualize decision in cirrhosis		

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388.
3. Eslam. Hepatol Intern. 2020;14:889.

Low Free Sugar Diet

- Open-label, randomized trial of **low free sugar diet**(< 3% of daily calories) vs **usual diet** in adolescent boys with histologically diagnosed NAFLD



Adjusted mean difference at Wk 8:
-6.23 (95% CI: -9.45 to -3.02)

*Measured by MRI-PDFF.

Schwimmer. JAMA. 2019;321:256.

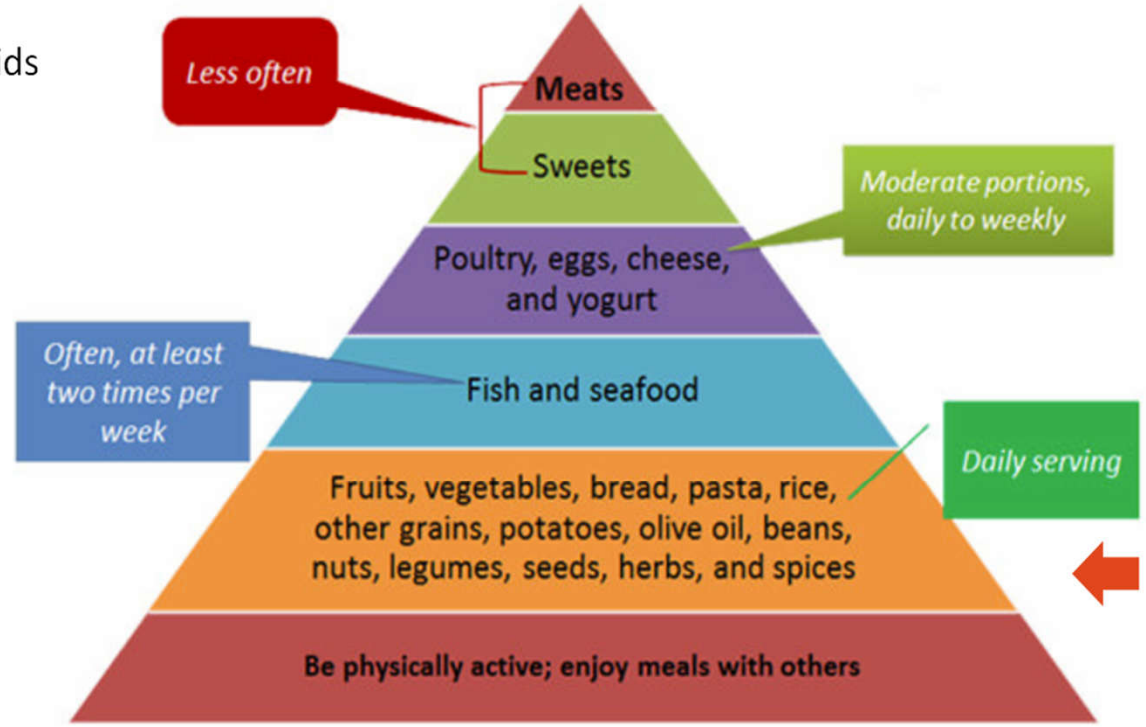
The Mediterranean Diet Pyramid

High in:

- Monounsaturated, omega-3/omega-6 fatty acids
- Polyphenols
- Dietary fiber, prebiotics
- Plant proteins
- Water as drink of choice

Low in:

- Saturated and trans fat
- Animal protein
- Simple sugars



Could be adapted to different cultures but **extra virgin olive oil** is an essential component

Gray. Nutritional Recommendations for Individuals with Diabetes. 2019. endotext.org.

Summary of Weight Loss in NAFLD

- Counsel all patients on healthy lifestyle with **diet, exercise, lifestyle**
- Consider adjunctive **pharmacologic approaches** in all overweight individuals (BMI > 27) and **surgical approaches** in otherwise eligible obese individuals (BMI > 35)



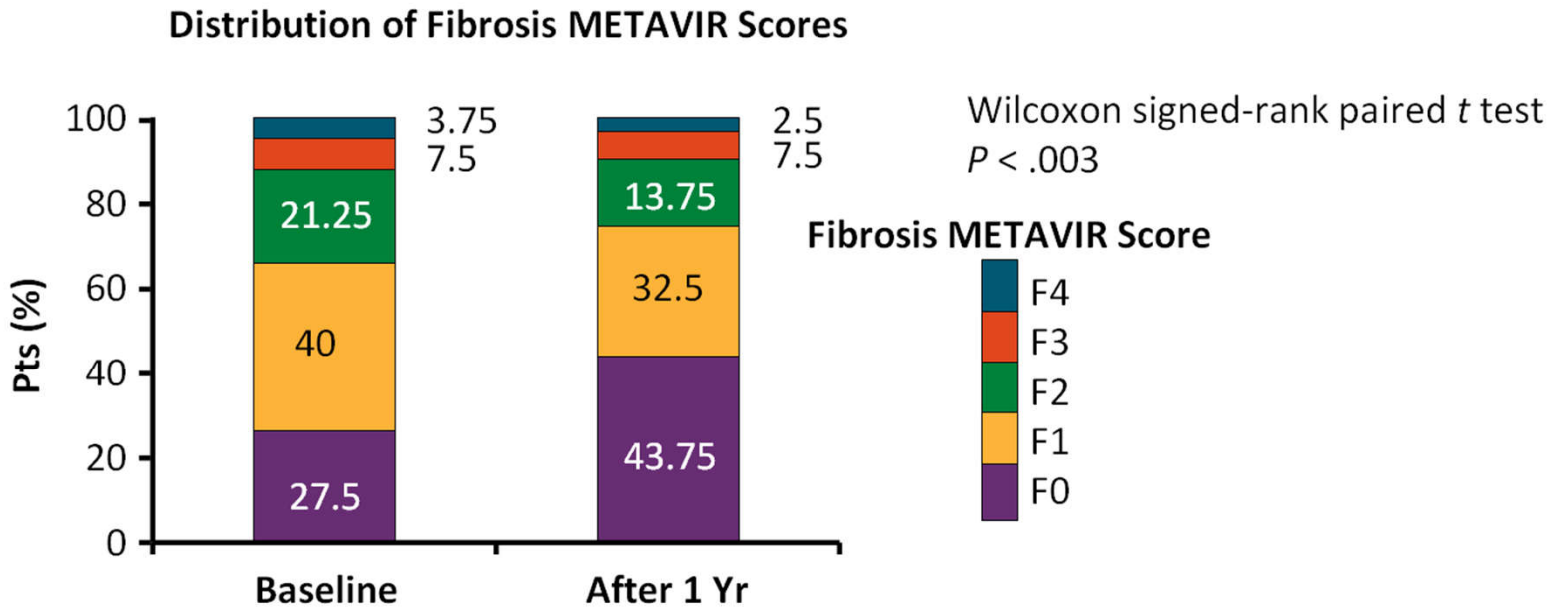
Diet, Exercise, Lifestyle	Pharmacologic Approaches	Bariatric Surgery
~ 5% to 8% weight loss[1]	~ 8% to 10% weight loss[1]	~ 10% to 30% weight loss[2]
Difficult to sustain	Requires continuous use	Sustained over long term

***Degree* of weight loss correlates with NASH improvement, likely regardless of *method* of weight loss**

1. Garvey. Endocr Pract. 2016;(suppl 3):1. 2. Maciejewski. JAMA Surg. 2016;151:1046.

Bariatric Surgery Improves Fibrosis in Pts With NASH

- Prospective study of bariatric surgery in pts who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)



Lassailly G, et al. Gastroenterology. 2015;149:379-388.

Summary of drug agents and benefit in NAFLD

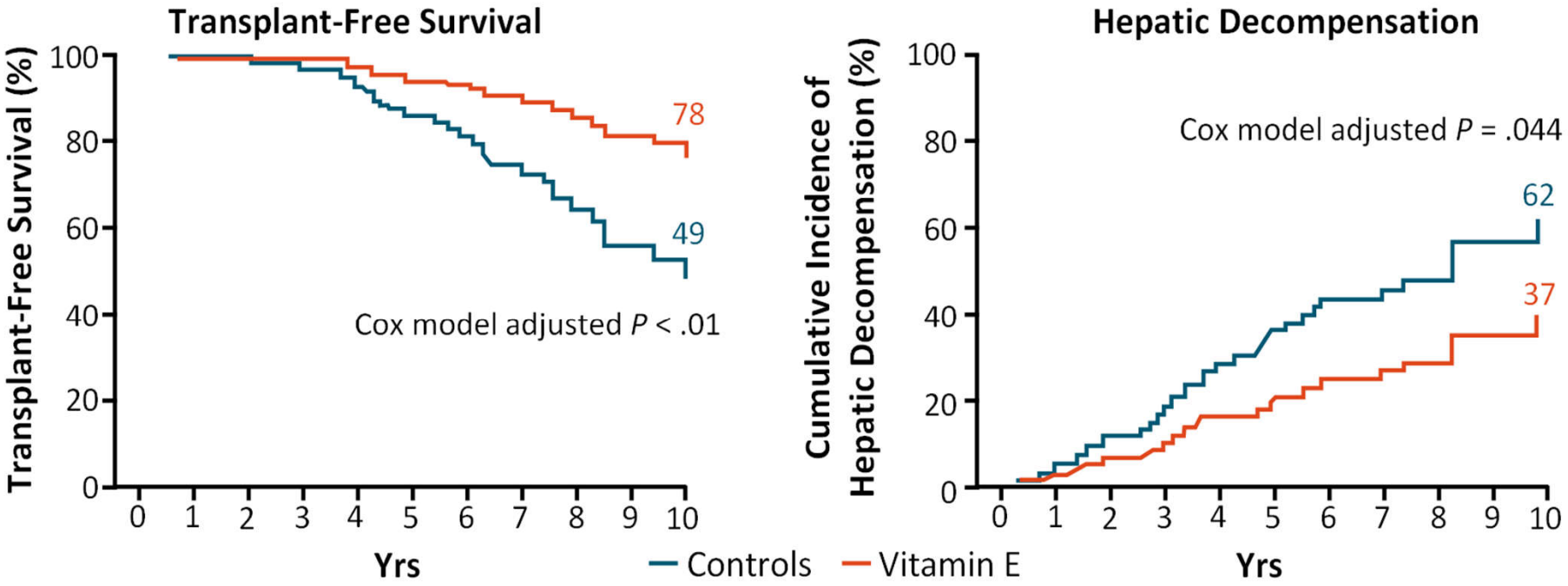
	Medication	EASL 2016	AASLD 2018	APASL 2020
Potential benefit	Vitamin E	Non-DM, ≥F2 non-cirrhosis (liver biopsy-proven cases)	Non-DM, non-cirrhosis (liver biopsy-proven cases)	Non-DM, non-cirrhosis (liver biopsy-proven cases)
	Pioglitazone	With and without DM, ≥F2 (liver biopsy-proven cases)	With and without DM, ≥F2 (liver biopsy-proven cases)	With and without DM, ≥F2 (liver biopsy-proven cases)
No clear benefit	Statin	CVD indication	CVD indication	CVD indication
	Metformin	None	None	None
	n-3 polyunsaturated fatty acids	None	None	None
	Ursodeoxycholic acid	None	None	None
	Pentoxifylline	None	None	None
Unclear benefit	Liraglutide (GLP1 agonist)	None	Premature to consider	Suggested in T2DM
	OCA	None	Should not be used	Wait for study

DM, diabetes mellitus; F, fibrosis; CVD, cardiovascular disease; GLP, glucagon-like peptide-1; OCA, obeticholic acid.

Prasoppokakorn T. et al: Pharmacological therapeutics for MAFLD. Journal of Clinical and Translational Hepatology 2021 vol. 9 | 939–946

Vitamin E Improves Transplant-Free Survival and Hepatic Decompensation in Patients With NASH

- Single-center study of patients with biopsy-proven NASH and bridging fibrosis or cirrhosis (N = 236) followed for median 5.62 yrs



Vilar-Gomez. Hepatology. 2019.

Vitamin D and NAFLD

- Patients with NAFLD often obese, high risk for vitamin D deficiency
  - Endocrine Society guidelines: screen for vitamin D deficiency if BMI ≥ 30 mg/m^2, treat if vitamin D < 20 ng/mL[1]
- Vitamin D receptor highly expressed in hepatic stellate cells, where it is antifibrogenic in preclinical studies

Lack of data in NAFLD/fibrosis

- But studies underway[2]

Data in PCOS

- Randomized, double-blind, placebo-controlled study of vitamin D supplementation in women with PCOS (N = 40) for 3 mos[3]
- Vitamin D significantly decreased ALT

1. Holick. J Clin Endocrinol Metab. 2011;96:1911. 2. Ebrahimpour-Koujan. Trials. 2019;20:153. 3. Javed. Nutrients. 2019;11(1).

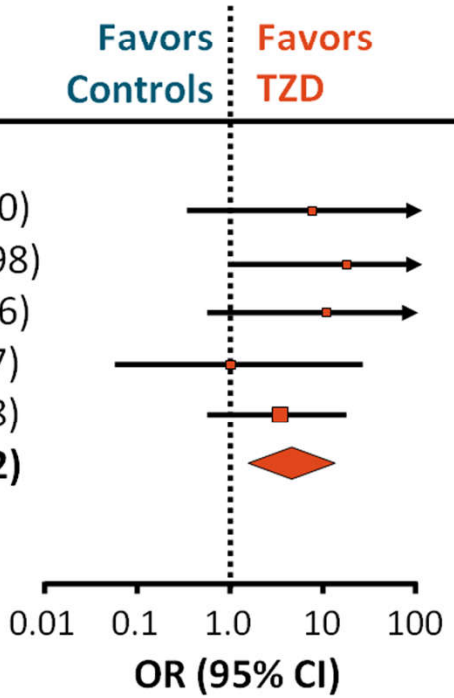
Pioglitazone in NASH Without Diabetes

- Subset of n = 8 TZD studies in systemic review and metanalysis of randomized trials examining outcomes in NAFLD/NASH (N = 516 patients)
- In biopsy-proven NASH, pioglitazone associated with **improvement in advanced fibrosis**

Source	TZD No. of Events	TZD No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)
Pioglitazone					
Aithal 2008	3	31	0	30	7.49 (0.37-151.50)
Belfort 2006	7	26	0	21	16.54 (0.89-308.98)
Cusi 2016	4	50	0	51	9.97 (0.52-190.16)
Sanyal 2004	1	10	1	10	1.00 (0.05-18.57)
Sanyal 2010	6	80	2	83	3.28 (0.64-16.78)
Total (95% CI)	**21**	**197**	**3**	**195**	**4.53 (1.52-13.52)**

Heterogeneity: $T^2 = 0$; $x^{2/2} = 2.39$; $P = .66$; $I^2 = 0\%$

Overall effect: z = 2.71; $P = .007$



Musso. JAMA Intern Med. 2017;177:633.

AASLD Guidance on CV Risk: Statins in Patients With NASH

- "Patients with NAFLD are at high risk for cardiovascular morbidity and mortality. Thus, **aggressive modification of CVD risk factors should be considered** in all patients with NAFLD"

- "Patients with NAFLD or NASH are not at higher risk for serious liver injury from statins. Thus, **statins can be used to treat dyslipidemia in patients with NAFLD and NASH**"

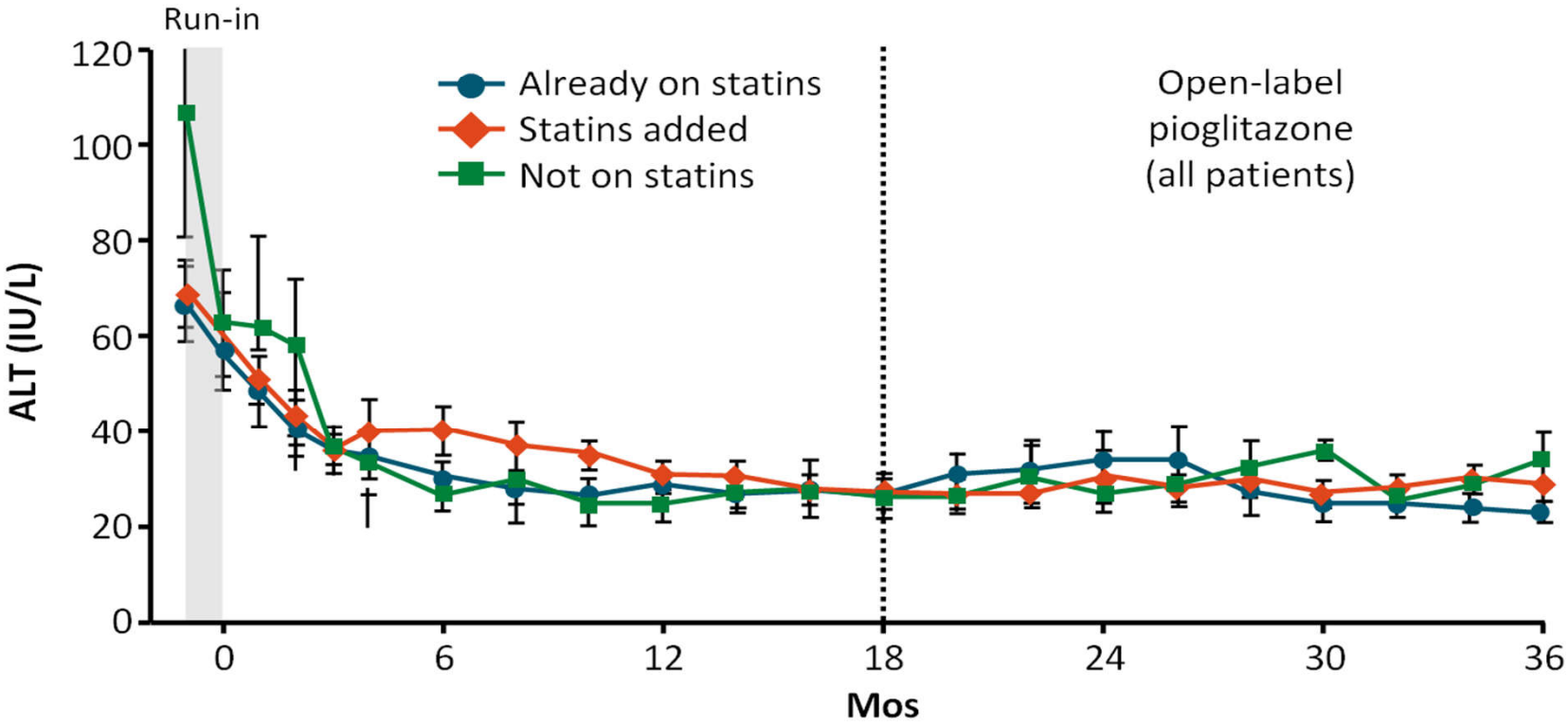
Statins recommended for reducing CV risk, not for resolving NASH

"Clinical trials of statins as treatment for NASH are limited and have shown inconsistent results"

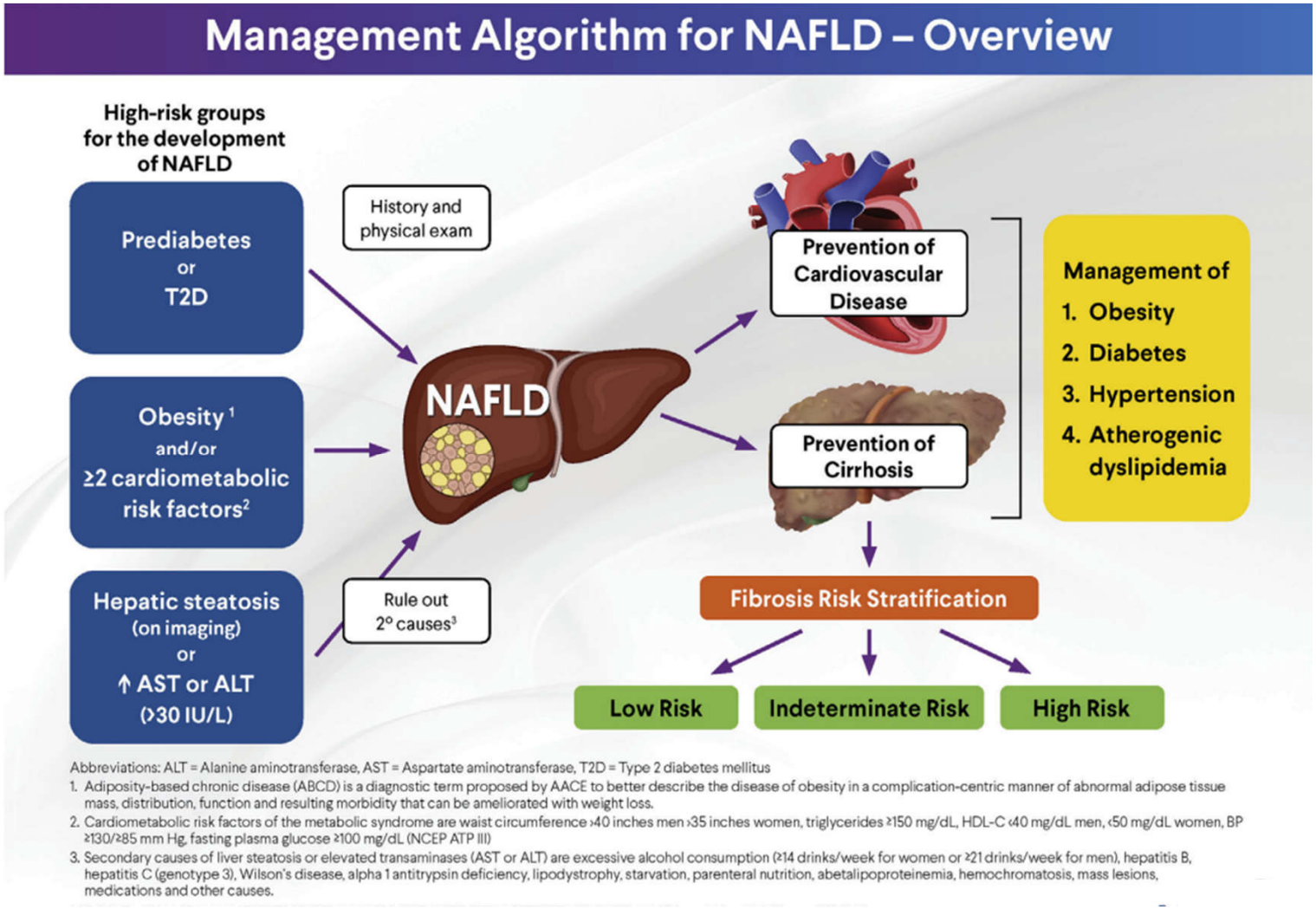
Chalasani. Hepatology. 2018;67:328.

Do Statins Affect ALT in Patients With NASH?

Patients followed prospectively while treated with pioglitazone in a 36-mo clinical trial

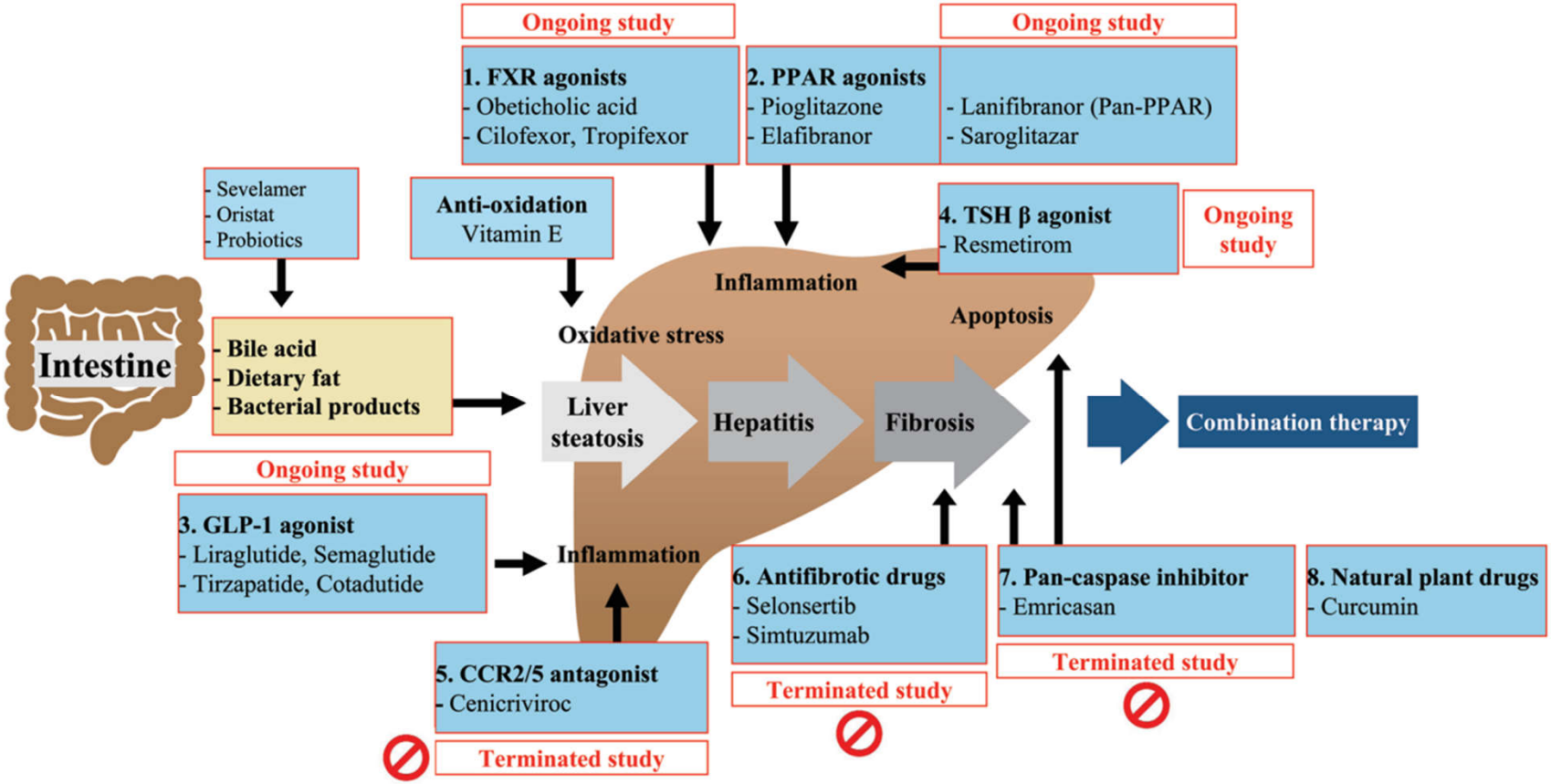


Bril. J Clin Endocrinol Metab. 2017;102:2950.



Kenneth Cusi et el. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. Endocrine Practice 28 (2022) 528-562.

Pharmacological targets of NASH therapy



FXR, Farnesoid X receptor; PPAR, Peroxisome proliferator-activated receptor; CCR, C-C chemokine receptor; GLP-1, Glucagon-like peptide-1; TSH, Thyroid hormone receptor.

Prasoppokakorn T. et al: Pharmacological therapeutics for MAFLD. Journal of Clinical and Translational Hepatology 2021 vol. 9 | 939–946

Efruxifermin (EFX) in nonalcoholic steatohepatitis with fibrosis: Results from a randomized, double-blind, placebo-controlled, phase 2b trial (HARMONY)

Aim

To evaluate the efficacy and safety of efruxifermin (EFX), a long-acting, Fc-FGF21 fusion protein, compared to placebo in patients with fibrosis stage 2 or 3 due to biopsy-confirmed NASH.

Methods

Randomized, placebo-controlled trial evaluating once-weekly 28 mg (n=42) and 50 mg (n=43) EFX compared to placebo (n=43) after 24 weeks.

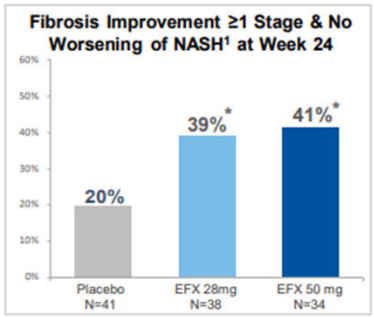
Main Findings

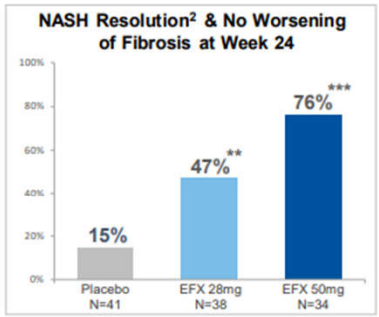
- EFX significantly reduced liver fibrosis and resolved NASH.
- EFX also improved markers of lipid and glucose metabolism.
- The high rates of NASH resolution correlated with normalization of liver fat.
- EFX was well tolerated with the most frequent treatment-emergent adverse events being gastrointestinal, mild-to-moderate in severity.

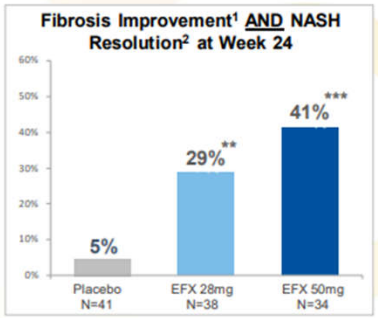
Conclusions

EFX has the potential to be a foundational monotherapy for treating NASH. It reverses fibrosis, resolves NASH, improves liver health, and restores whole body metabolism.

Harrison S, et al., Abstract LO6.







LS Mean Change from Baseline	Placebo (N=40-42)	EFX 28mg (N=35-38)	EFX 50mg (N=34-36)
LFC (%, Relative)	-6	-52***	-64***
% normalized LFC (≤5%)	2	34***	51***
ALT (U/L)	-3.0	-22.4***	-32.9***
Pro-C3 (µg/L)	0.1	-5.1***	-5.2***
ELF Score	0.1	-0.6***	-0.7***
HbA1c (%, Absolute), in T2D (N=82)	-0.0	-0.5*	-0.5*
Triglycerides (%)	+9	-25***	-29***
LDL Cholesterol (%)	+9	-8**	-8**
Body Weight (kg)	-0.6	-0.2	-2.9††
Odds Ratio [95%CI] of achieving NASH resolution	**All patients** (N=112)	**EFX-treated patients only** (N=71)	
LFC normalized (≤5% LFC)	9.3 [3.2, 23.8]****	4.3 [1.3, 11.7]*	

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs. placebo; ††p<0.01 vs. baseline. [1]Improvement in liver fibrosis ≥ 1 stage without increase in NAS for ballooning, inflammation, or steatosis. [2] NAS score of 0 or 1 for lobular inflammation and 0 for ballooning

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PXL065 (Deuterium-stabilized *R*-enantiomer of Pioglitazone) reduces liver fat content and improves liver histology without PPARγ-mediated side effects in patients with NASH: 36-week placebo-controlled phase 2 trial

Objective

To evaluate the effect of 3 doses of PXL065 on liver fat content in a randomized, double-blind, placebo-controlled 36-week study.

Methods

- 117 noncirrhotic NASH (F1-3) patients randomized: placebo vs PXL065 7.5, 15, 22.5 mg QD – 36-week treatment.
- Primary endpoint: liver fat content – LFC, MRI-PDFF.
- Secondary endpoints including paired liver biopsies.

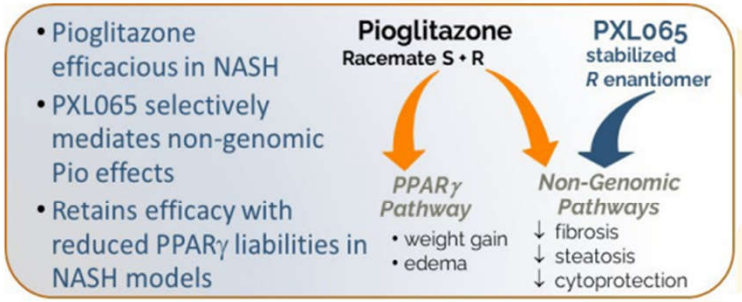
Main Findings

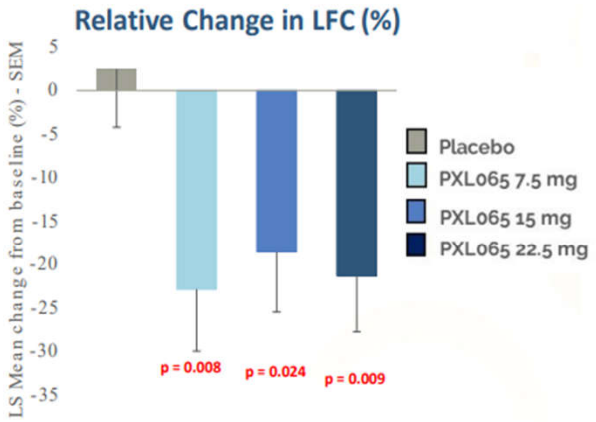
- ↓ LFC – all doses
- ↓ ALT (trend); fibrogenesis, fibrosis risk markers
- ↓ HbA1c; ↑ adiponectin
- Histology improvements (greatest for steatosis, fibrosis)
- No dose-related weight gain; no edema; favorable safety-tolerability
- PK confirms R > S-pioglitazone exposure in NASH patients vs Actos®.

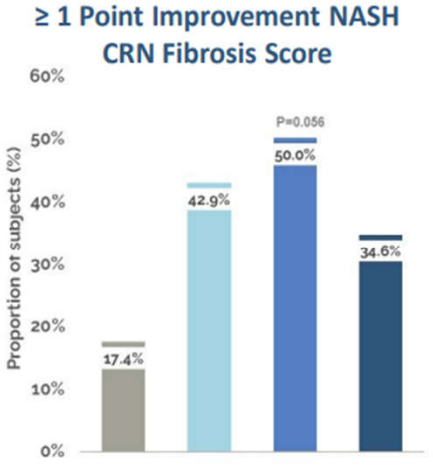
Conclusions

Primary endpoint achieved all doses; improved histology; metabolic benefits; reduced potential for PPARγ side effects; pivotal trial planning ongoing.

Harrison S, et al., Abstract LO10.







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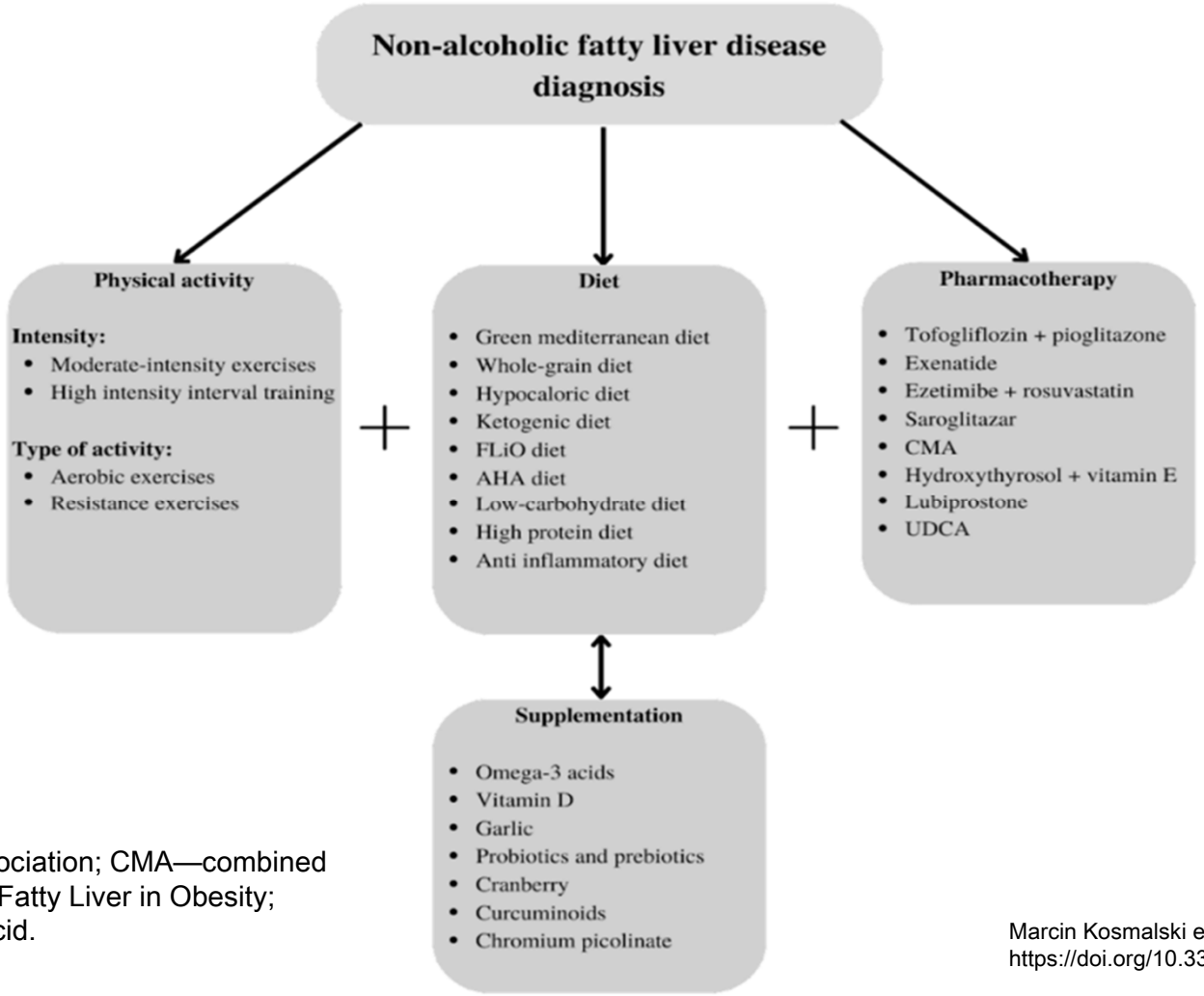
Proposed therapeutic strategies for NAFLD



AHA—American Heart Association; CMA—combined metabolic activator; FLiO—Fatty Liver in Obesity; UDCA—ursodeoxycholic acid.

Marcin Kosmalski et al. J. Clin. Med. 2023, 12, 1852.
https://doi.org/10.3390/jcm12051852

V. Kết luận.

1, Quan tâm chẩn đoán NAFLD, đặc biệt phải đánh giá được độ xơ hóa gan để có phương án theo dõi và điều trị thích hợp.

Chẩn đoán sớm độ xơ hóa giúp điều trị có thể cải thiện được xơ hóa gan.

2, Vai trò ngày càng nổi bật yếu tố "Gene" trong diễn tiến bệnh cũng như phát triển các kỹ thuật chẩn đoán, điều trị bệnh.

3, Điều trị hiệu quả là sự phối hợp của 3 phương cách:

- Chế độ kiêng cử: Ăn kiêng, kiêng rượu bia.

- Tập luyện, thay đổi lối sống để đạt mục tiêu giảm cân, phẫu thuật dạ dày.

- Thuốc: Cho đến hiện nay chưa có 1 thuốc nào được công nhận đặc trị chuyên biệt bệnh viêm gan thoái hóa mỡ / gan nhiễm mỡ không do rượu mà tùy từng tình huống lâm sàng có thể dùng phương pháp phù hợp: vitamine E, thuốc điều trị tiểu đường, mỡ máu, giảm cân …

4, Lưu ý điều trị và xử trí biến chứng của các bệnh đi kèm như đái tháo đường, bệnh mạch vành …

5, Nhiều cơ chế và các nhóm thuốc điều trị gan nhiễm mỡ không do rượu đang được nghiên cứu ở giai đoạn 2 – 3 nhưng cho đến hiện nay chưa có hiệu quả rõ rệt.


Thank
you