CẬP NHẬT ĐIỀU TRỊ
BỆNH GAN NHIỄM MỠ KHÔNG DO RƯỢU

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Trung Tâm Y Khoa MEDIC, TP. Hồ Chí Minh

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NỘI DUNG

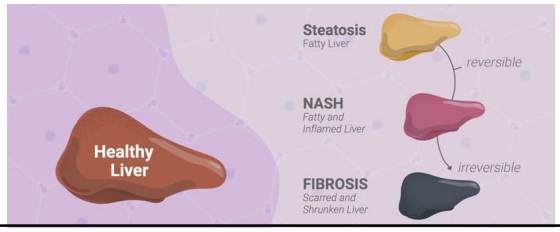
I, Đặt vấn đề.

II, Diễn tiến bệnh gan nhiễm mỡ.

III, Chẩn đoán bệnh gan nhiễm mỡ.

IV, Điều trị bệnh gan nhiễm mỡ.

V, Kết luận.



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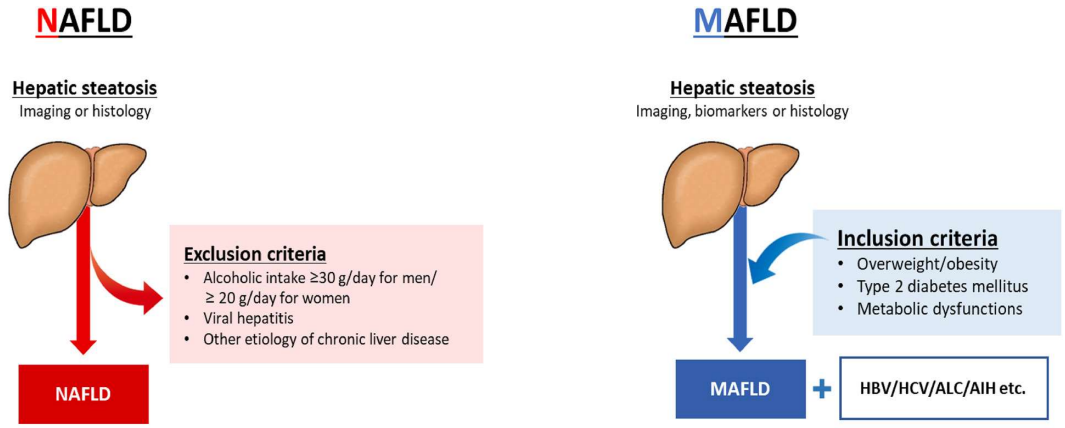
I, Đặt vấn đề.



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

- 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

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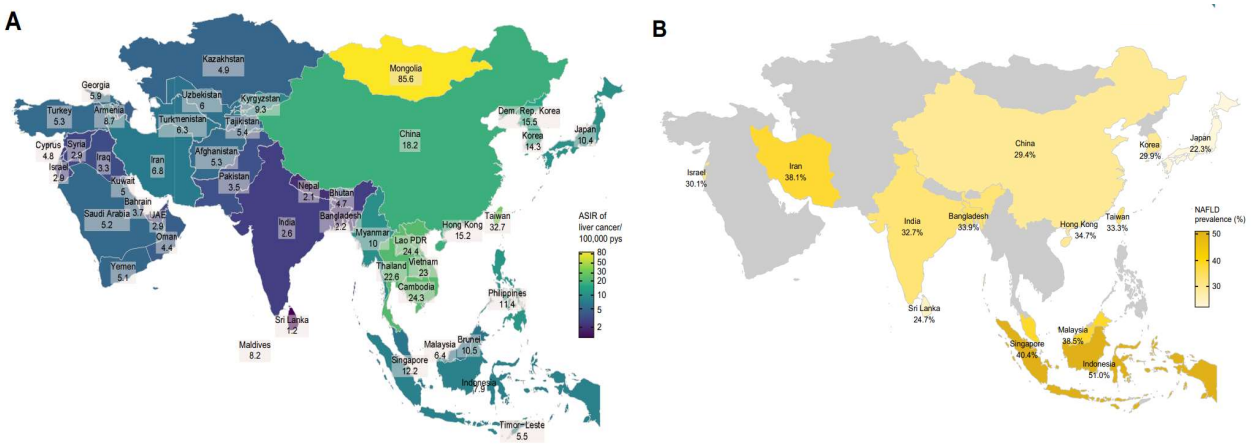
Map of primary liver cancer and NAFLD in Asia



(A) ASIR of primary liver cancer, and (B) prevalence of NAFLD. Hepatocellular carcinoma accounts for 75- 85% of primary liver cancer. Data were obtained from GLOBOCAN 2020 (https://gco.iarc.fr/today/home). The prevalence of NAFLD by any diagnostic modality was based on the study by Li et al.

ASIR, age-standardised incidence rate;
NAFLD, non-alcoholic fatty liver disease.

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

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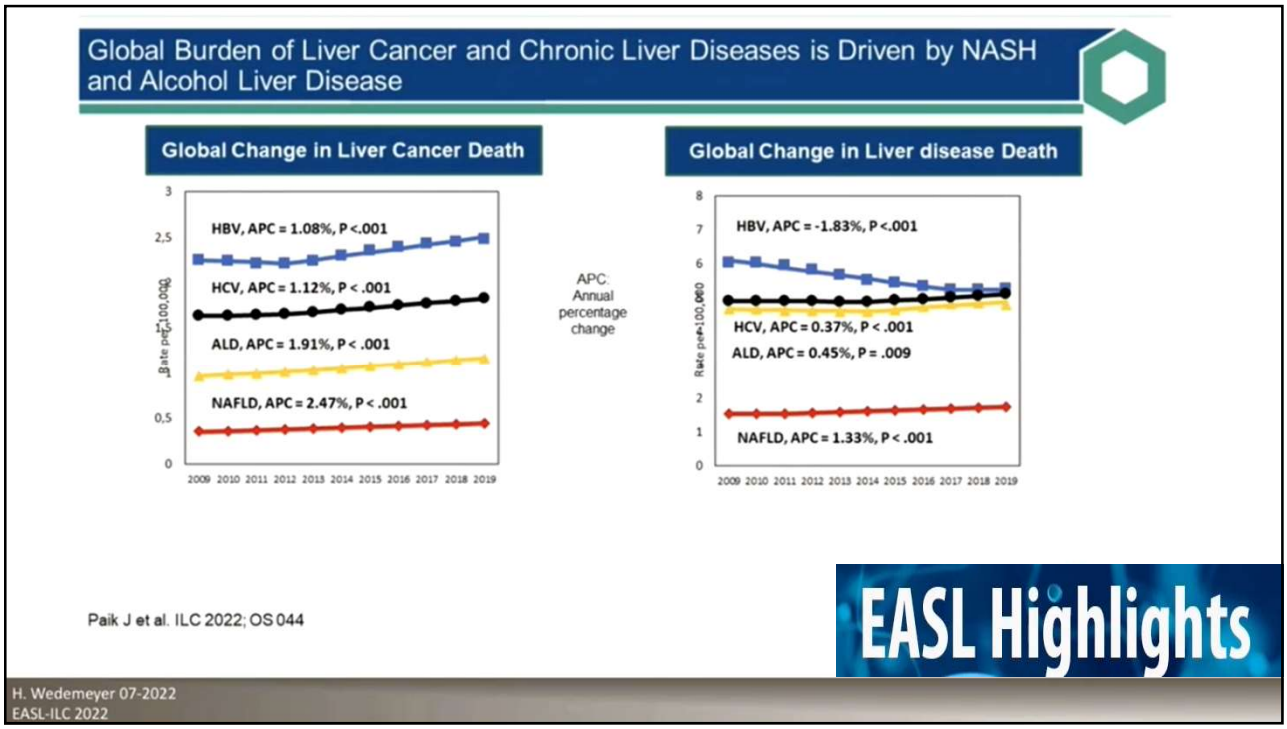

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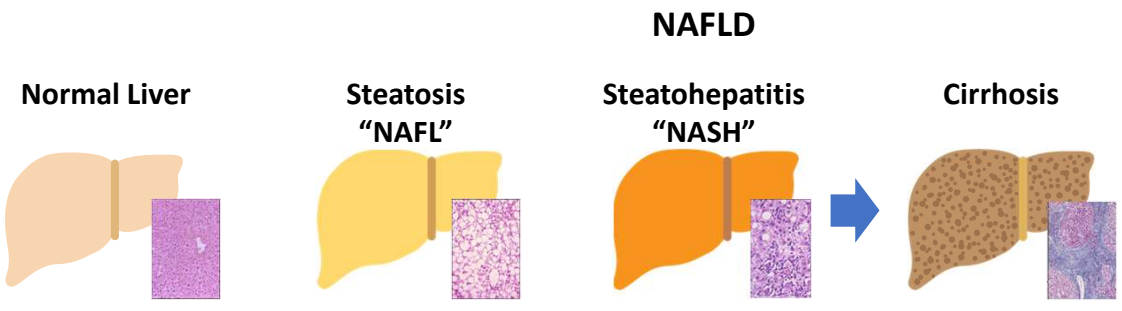
II, Diễn tiến bệnh gan nhiễm mỡ.

Worldwide Prevalence of NAFLD and NASH



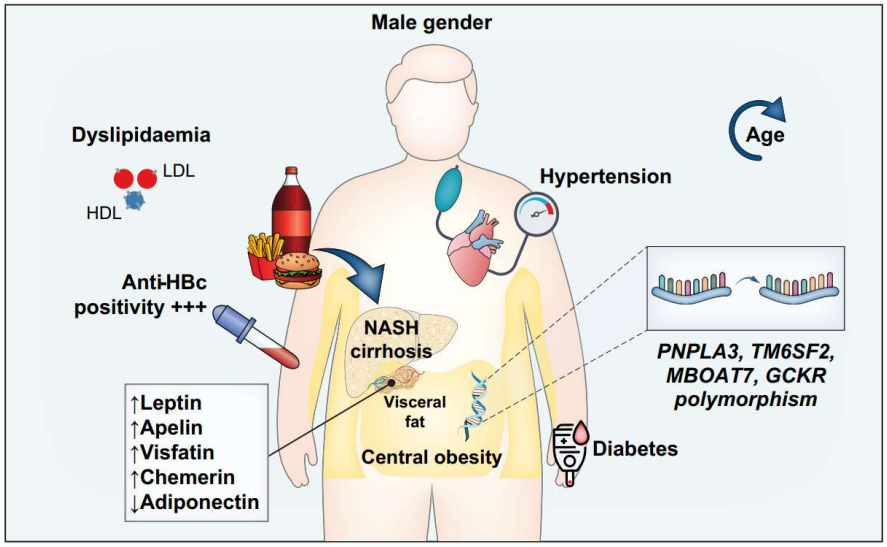
Worldwide prevalence:	25%[1]	3% to 5%[1]	1% to 2% at risk*

*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis[2]

1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.

6

Risk factors for NAFLD-associated HCC in Asia.



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

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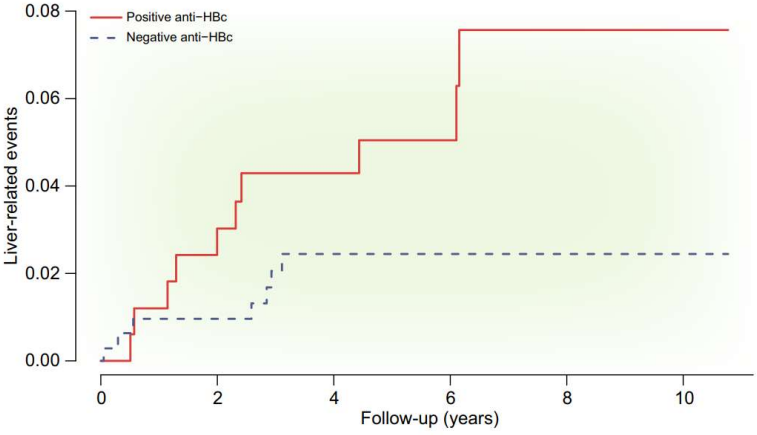
Increased risk of liver-related events in Asian patients with NAFLD and positive hepatitis B core antibody.

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

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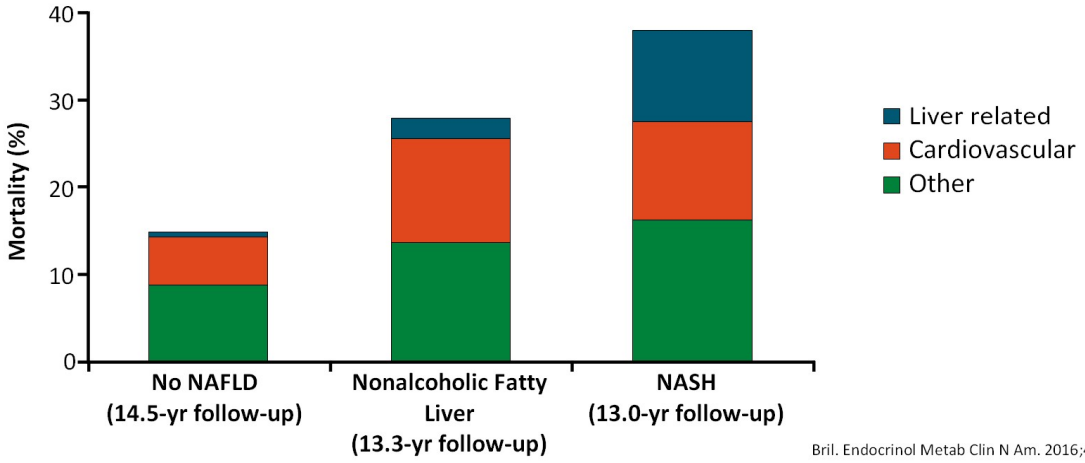
Mortality Risk Associated With Nonalchololic Fatty Liver vs NASH

- 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.

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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.

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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].

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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.

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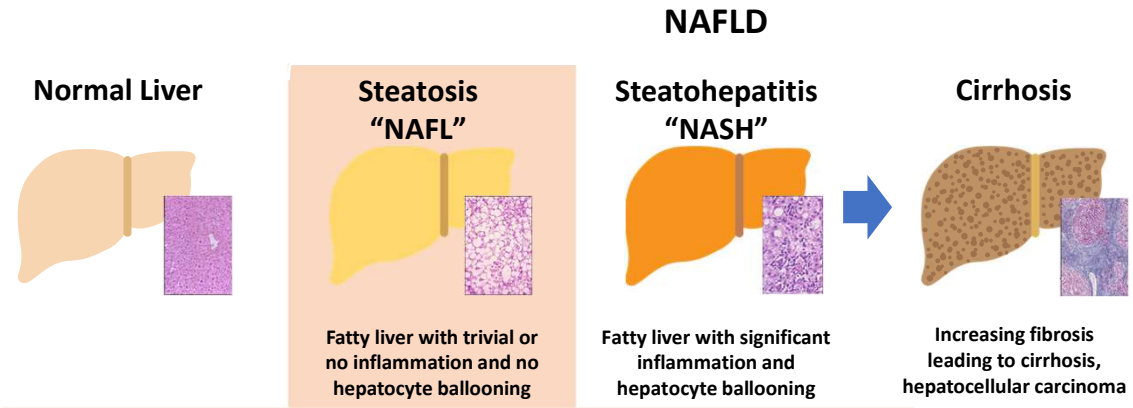
Identifying NAFL: Ultrasound



Ultrasound can identify fatty liver (steatosis),
but cannot distinguish steatosis vs NASH vs fibrosis/early cirrhosis

Younossi. J Hepatol. 2019;70:351. Kabbany. Am J Hepatol. 2017;112:581.

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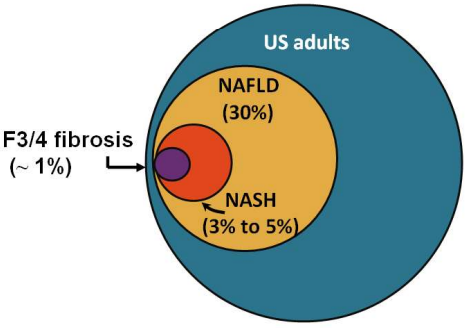
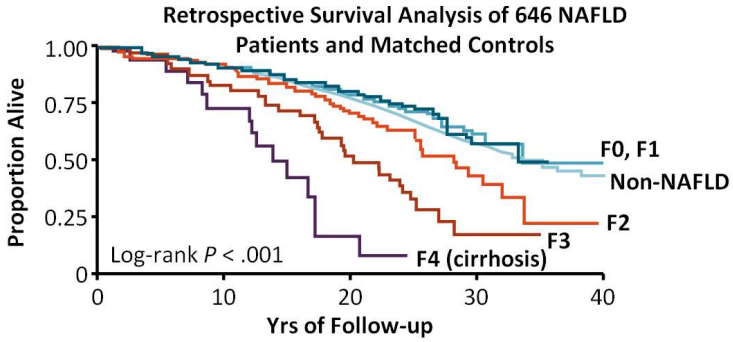
Importance of Diagnosing NASH and Advanced Fibrosis

- Goal 1: Identify those with NASH
  - **Having NASH increases the risk of progression of fibrosis**
  - Identify treatment candidates
- Goal 2: Identify those at risk for progressing to cirrhosis
  - Having **any fibrosis, and particularly significant fibrosis ≥ F2,** associated with increased mortality





Stål. World J Gastroenterol. 2015;21:11077. Hagström. J Hepatol. 2017;67:1265. Le. PLoS ONE. 2017;12:e0173499.

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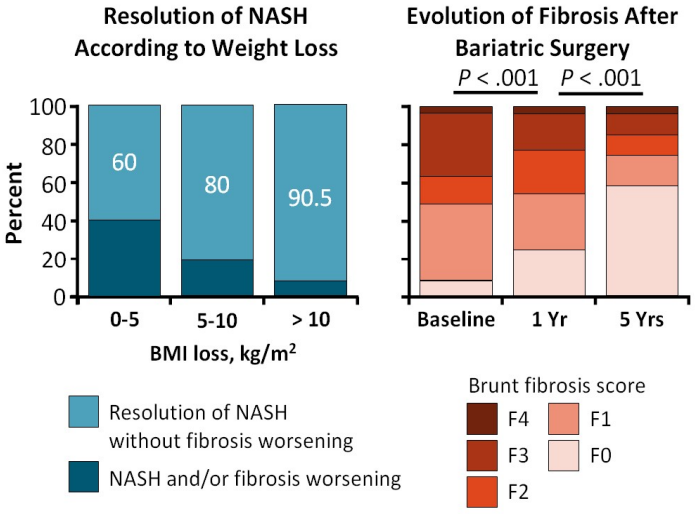
Is NASH Reversible ?

- 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.

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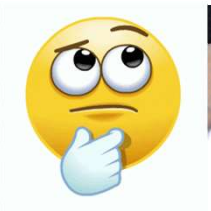
IV, Điều trị bệnh gan nhiễm mỡ.



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Lifestyle Guidelines in NASH

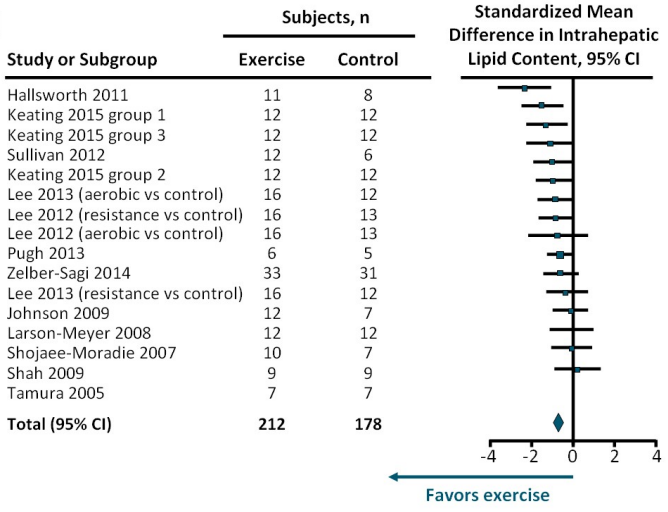
	AASLD 2018[1]	EASL 2016[2]	APASL 2020[3]
Program	Lifestyle modification including **dietary change**, **weight loss**, and structured **exercise** intervention		
Diet	500-1000 kcal energy deficit to induce a weight loss of 500-1000 g/wk • Prospective trials comparing macronutrient diets in NAFLD are 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.

17

Exercise in NAFLD: Effect on Liver Fat and ALT

- 28 randomized trials of exercise-based interventions in patients with NAFLD and underlying metabolic disorders (N = 1644)
- Reduction in **intrahepatic lipid content**
  - Standardized mean difference: -0.69 (95% CI: -0.90 to -0.48)
- Reduction in **ALT**
  - Weighted mean difference: -3.30 IU/L (95% CI: 5.57 to -1.04)



Orci. Clin Gastroenterol Hepatol. 2016;14:1398.

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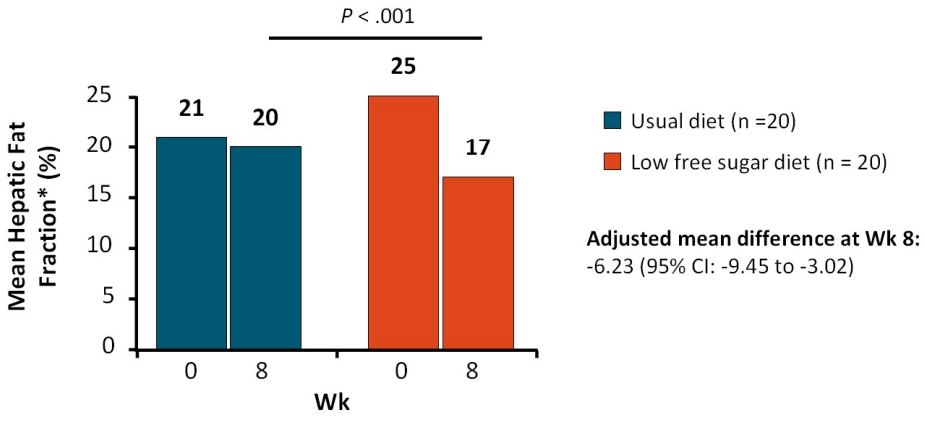
Low Free Sugar Diet

- 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.

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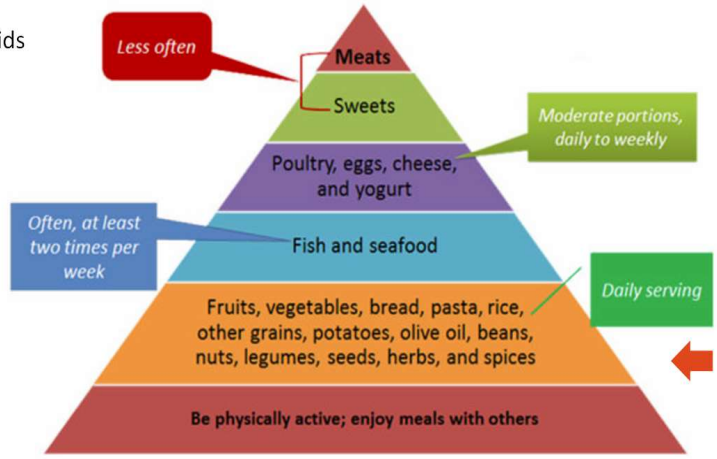
The Mediterranean Diet Pyramid

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.

20

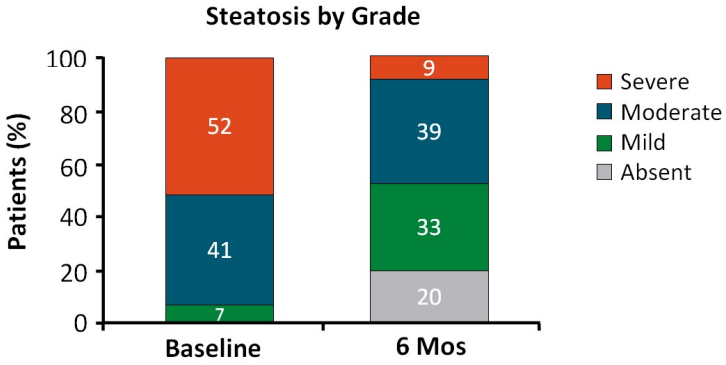
Mediterranean Diet in NAFLD: Observational Study

Design

- 6-mo observational study of **Mediterranean diet** intervention with monthly nutrition counseling in patients with NAFLD (N = 46)

Results

- Frequency of grade ≥ 2 steatosis decreased in > 80%, with resolution in 20%

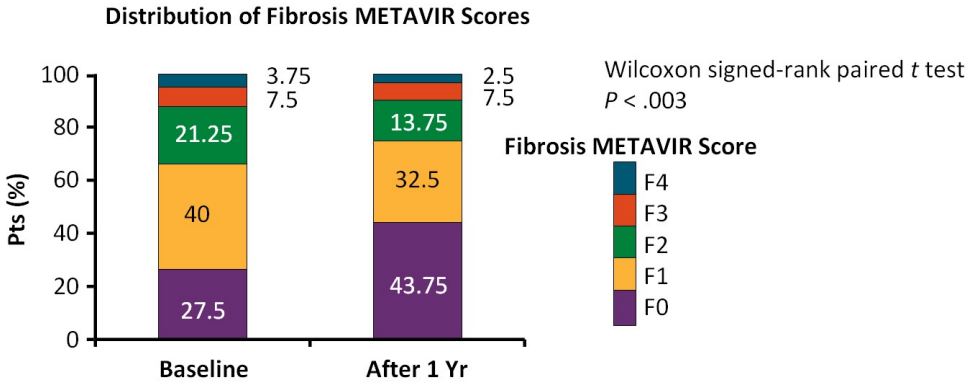


Gelli. World J Gastroenterol. 2017;23:3150.

21

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.

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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.

23

Pharmacotherapy in NAFLD and NASH

	AASLD 2018[1]	EASL-EASD-EASO 2016[2]	APASL 2020[3]
Vitamin E	**Recommended** in nondiabetic patients with biopsy-proven NASH (800 IU/day)	**Recommended** (800 IU/day)	Insufficient evidence, no firm recommendation
Pioglitazone	**Recommended** in patients with and without T2D and biopsy-proven NASH	**Recommended** in patients with T2D and biopsy-proven NASH	
Metformin	Not recommended		
Statin	▪ Can be used to treat dyslipidemia, not NASH ▪ No higher risk for serious liver injury		Reduce cardiovascular mortality, consider in all NAFLD patients with hyperlipidemia
UDCA	Not recommended		Not mentioned
Omega-3 Fatty Acids	▪ Not a specific treatment of NAFLD ▪ Consider to treat hypertriglyceridemia		Not mentioned
Obeticholic Acid	Further data needed		
GLP-1 RAs	Further data needed		Improve fibrosis, weight
SGLT2 Inhibitors	Not mentioned		Further data needed

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

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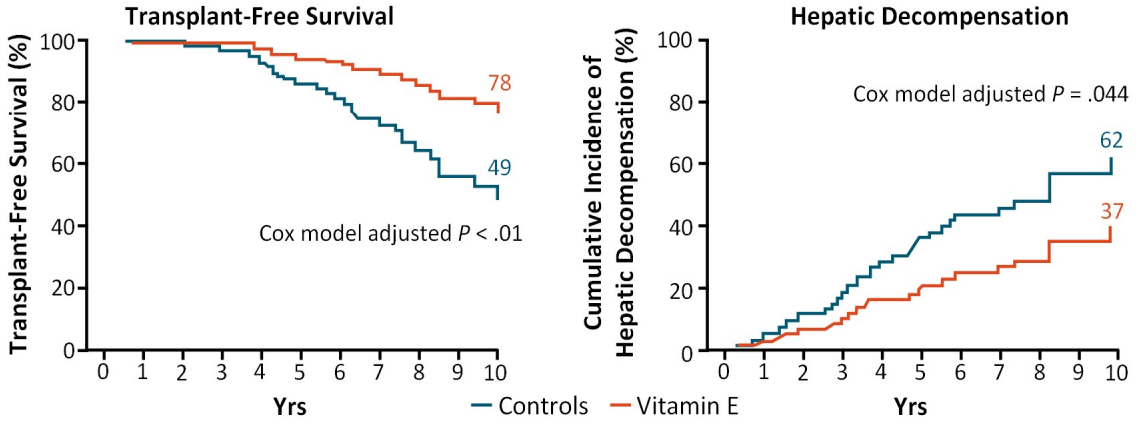
Vitamin E Improves Transplant-Free Survival and Hepatic Decompensation in Patients With NASH

- 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.

25

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).

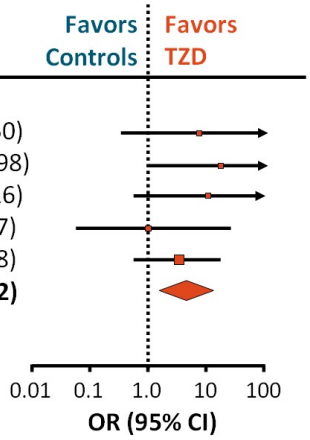
26

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.

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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.

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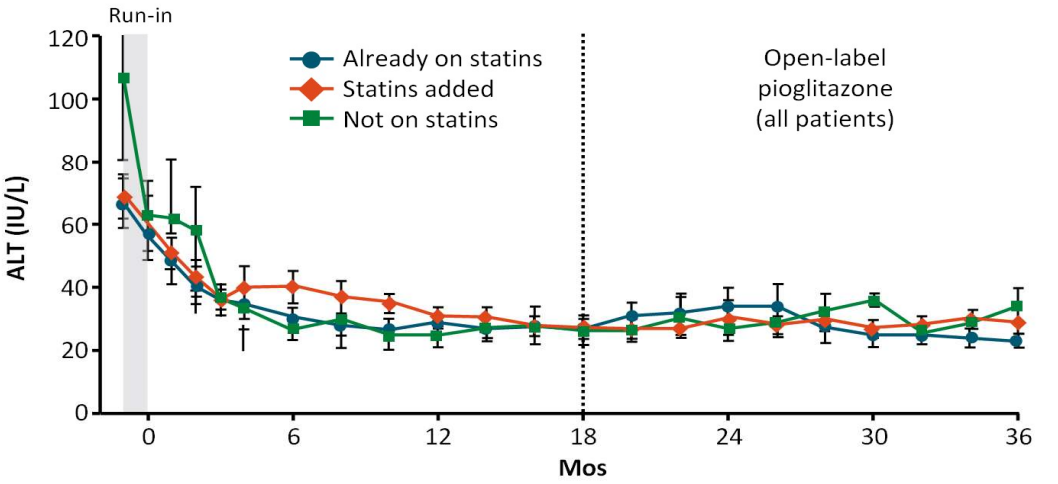
Do Statins Affect ALT in Patients With NASH?

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



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

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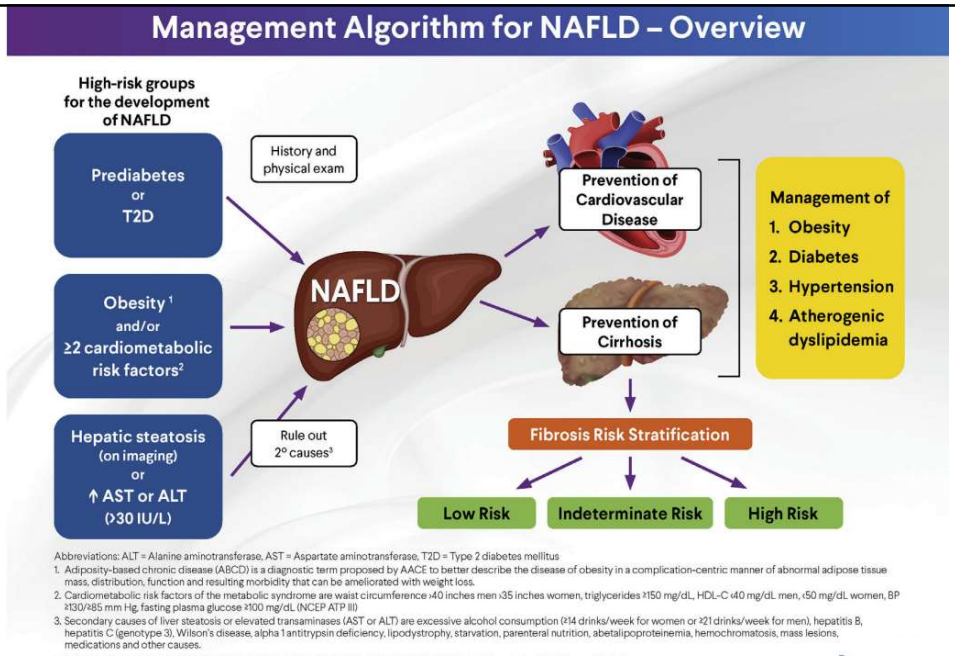

Kenneth Cusi et el. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. Endocrine Practice 28 (2022) 528-562.

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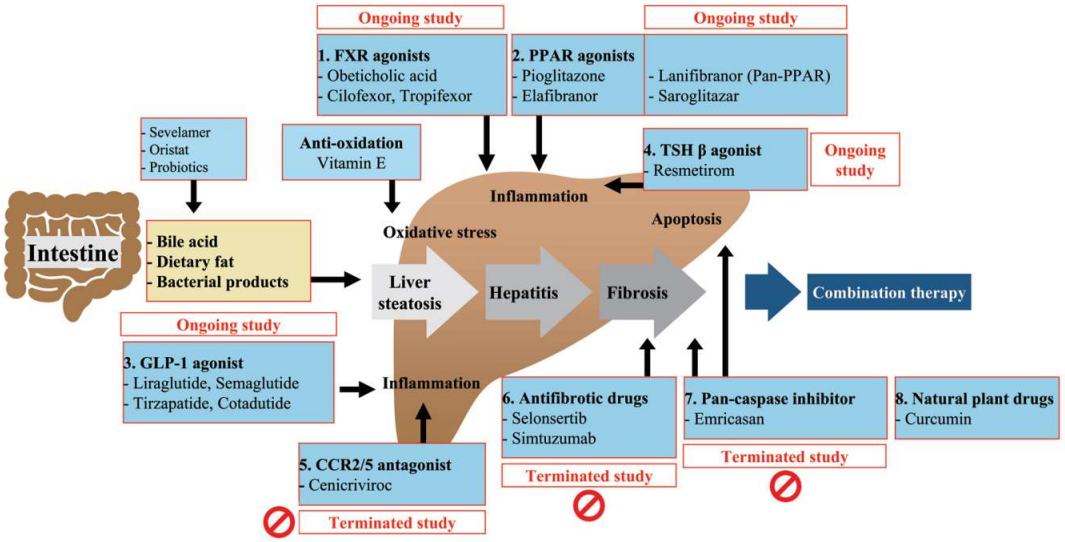
Pharmacological targets of NASH therapy



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

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

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

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

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

3, Lưu ý điều trị và xử trí biến chứng của các nhóm bệnh đi kèm như tiểu đường, bệnh mạch vành …

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

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