Hepatic Steatosis (NAFLD/MASLD) and Newer Therapies

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Disclosures

No relevant disclosures for this presentation

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Esperion, Ionis, Kaneka (past), Mirum/Travere/Retrophin, New Amsterdam, Novo Nordisk (past), Regeneron

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Outline

1. **Introduction**
2. Definitions and terminology
3. What is NAFLD/MASLD?
4. Prevalence of NAFLD
5. Etiology of NAFLD
6. Association of NAFLD with ASCVD risk
7. Diagnosis of NAFLD/NASH
8. Potential interventions
9. Summary

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Why Should You Care About Hepatic Steatosis (NAFLD/MASLD)?

It is very common: estimated prevalence 25% worldwide (and increasing)

It is most often undiagnosed

It is a major risk factor for hepatic cirrhosis, hepatocellular carcinoma, and liver failure --> liver transplantation

It is a marker and risk factor for atherosclerotic cardiovascular disease (ASCVD) risk

The leading cause of death is ASCVD

Arterioscler Thromb Vasc Biol. 2022;42:e168–e185. DOI: 10.1161/ATV.0000000000000153

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Definitions and Terminology

"Fatty liver" is not recommended due to the pejorative nature

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NAFLD (Non-alcoholic fatty liver disease) includes everything from simple hepatic steatosis to advanced cirrhosis, excluding "excess" alcohol intake

* **Hepatic steatosis** = excess deposition of triglycerides in the liver
* **NAFL** is defined as ≥ 5% fat content without evidence of hepatic injury
* **NASH** (Nonalcoholic steatohepatitis): ≥ 5% fat content with histological evidence of hepatocellular inflammation + fibrosis stages 0-4

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MAFLD = metabolic-associated fatty liver disease. Consists of hepatic steatosis and one or more of overweight/obesity, type 2 diabetes, or evidence of metabolic dysregulation (not universally adopted)

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Proposed New Terminology 2023

MASLD = metabolic dysfunction-associated steatotic liver disease (AASLD,June 2023)
MetALD = MASLD + alcohol intake> 140 g/wk in women and > 210 g/d in men
MASH = metabolic dysfunction-associated steatohepatitis (new NASH)

Ann Hepatol 2023;29:101133; Hepatology 2023;7:1966-1986, J. Hepatol 2023;79:1542-1556

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What is NAFLD/MASLD?

Refers to abnormal accumulation of triglycerides in the liver (> 5% fat content) in the absence of high intake of alcohol

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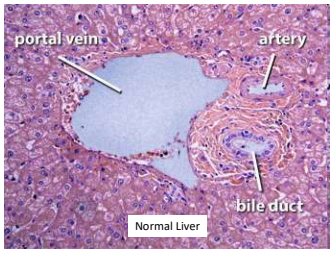
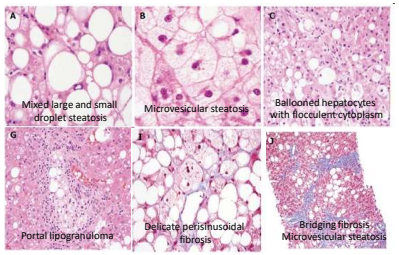
Histology of Hepatic Steatosis

Normal



https://www.hepatitis.va.gov/HEPATITIS/course/

NAFLD/MASLD



World J Gastroenterol. 2014;20(27):9026-9037. doi:10.3748/wjg.v20.i27.9026

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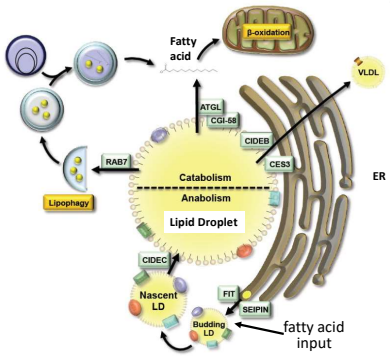
Normal Hepatic Lipid Droplet Biology



Hepatology 2015;62(3):964-967. doi:10.1002/hep.27839

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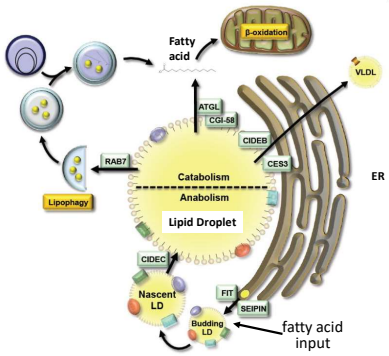

Functions of Lipid Droplets

- Triglyceride storage
- Source of FAs for oxidation
- Substrate for VLDL synthesis
- Membrane trafficking
- Cell signaling
- Steroid metabolism
- *Not* an inert lipid depot

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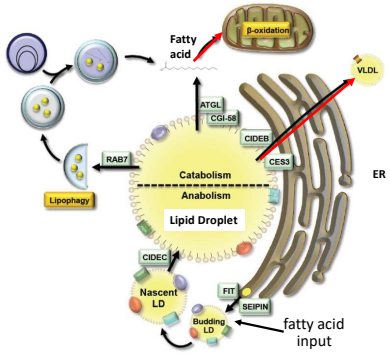

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Key Pathways for Depletion of Lipid Droplets

- Fatty acid oxidation
- VLDL production

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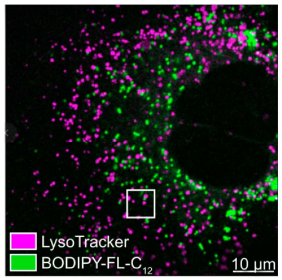
Normal Hepatic Lipid Droplet Biology



Video showing dynamic nature of lipid droplets

Lipid droplet-lysosome interaction in hepatocyte-pnas.2011442117.sm01.mov

8.3 minute recording accelerated to 12 seconds (41.5-fold increase)

Lipid droplets - **green**
Lysosomes - **pink**

PNAS 2020;117(51):32443-32452
https://doi.org/10.1073/pnas.2011442117

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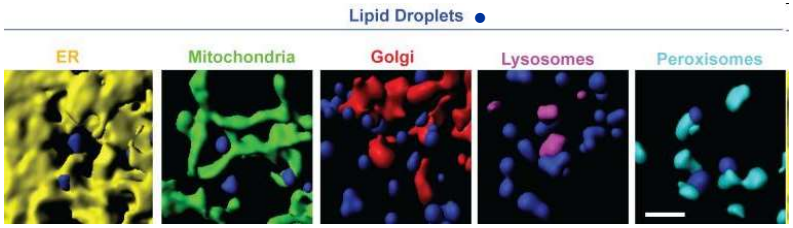
Lipid Droplets Interact with Other Organelles



Int Rev Cell Mol Biol 2018;337:83-110
doi:10.1016/bs.ircmb.2017.12.007

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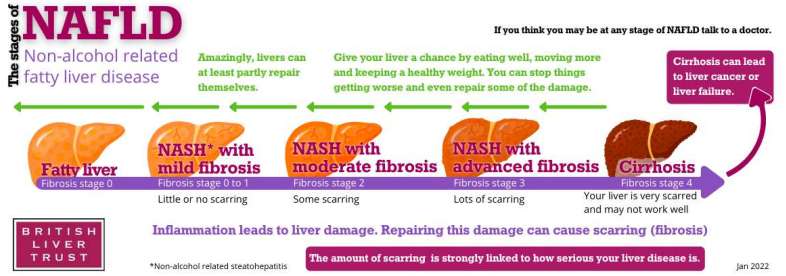
Stages of Fibrosis in NAFLD



https://britishlivertrust.org.uk/

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Prevalence of NAFLD

It is very common: **estimated prevalence 25% worldwide (and increasing)**

More than 50% of patients with type 2 diabetes

Wide geographic and ethnic variation in prevalence (2016 to 2018)
- Africa (13.5%)
- United States (24%)
- Europe (23%)
- East Asia (27%)
- Mexico, Central and South America (31%)
- Middle East (32%)
- **South Asia (33%)**

Arterioscler Thromb Vasc Biol. 2022;42:e168–e185. DOI: 10.1161/ATV.0000000000000153

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Prevalence of NAFLD

Within the United States: 2014 data from MESA study (12.5 to 33%)

Hispanic 21%

- Mexican origin 33%
- Puerto Rican origin 18%
- Dominican origin 16%

White 12.5%

Black 11.6%

World J Gastroenterol. 2014;20:4987–4993. doi: 10.3748/wjg.v20.i17.4987
Arterioscler Thromb Vasc Biol. 2022;42:e168–e185. DOI: 10.1161/ATV.0000000000000153

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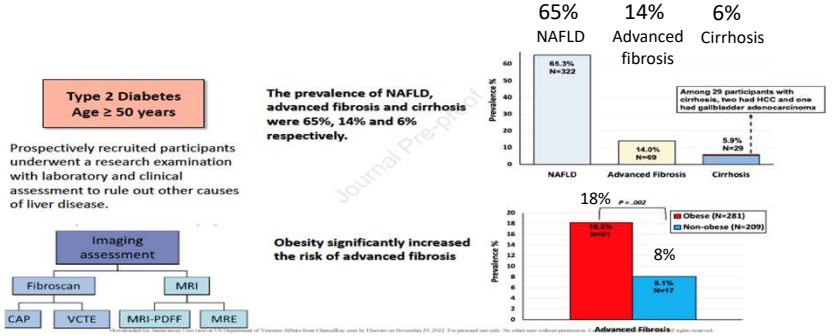
Prevalence of NAFLD, Advanced Fibrosis, Cirrhosis and Hepatocellular Carcinoma in Patients with Type 2 Diabetes: A Prospective Study (n = 501)

65% NAFLD 14% Advanced fibrosis 6% Cirrhosis



J Hepatol. 2023 Mar;78(3):471-478. doi: 10.1016/j.jhep.2022.11.010

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Risk Factors for NAFLD

Metabolic/endocrine
Insulin resistance
Impaired glucose tolerance and diabetes
Hypertriglyceridemia, particularly with imbalance between hepatic triglyceride production and clearance
Visceral adiposity
Metabolic syndrome
Polycystic ovarian syndrome
Chronic kidney disease
Lipodystrophy
Hypobetalipoproteinemia (attributable to defects in apoB)
Lysosomal acid lipase deficiency
Defects in mitochondrial fatty acid oxidation (congenital and acquired)
Drugs
Alcohol
Amiodarone
Aspirin (eg, Reye syndrome)
Corticosteroids
Lomitapide
Mipomersen
Nonsteroidal anti-inflammatory drugs
Reverse transcriptase inhibitors
Tamoxifen
Tetracycline
Valproic acid

Insulin resistance, visceral adiposity, IGT/diabetes, and hypertriglyceridemia are key factors in most cases

Genetic factors	
Family history of NAFLD	
Variants in several genes	
GCKR	
MBOAT7	
PNPLA3	
TM6SF2	
HSD17B13	Protects against NASH

apoB indicates apolipoprotein B; and NAFLD, nonalcoholic fatty liver disease.

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apoB indicates apolipoprotein B; and NAFLD, nonalcoholic fatty liver disease.

Genetic predisposition may explain > 50% of cases

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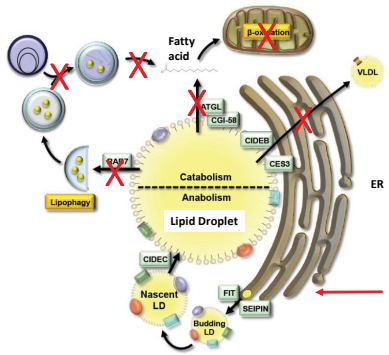
Abnormal Hepatic Lipid Droplet Biology



Increased triglyceride synthesis

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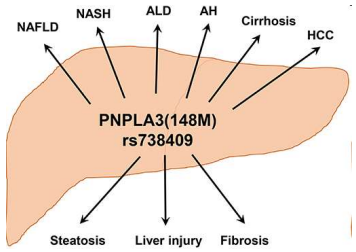
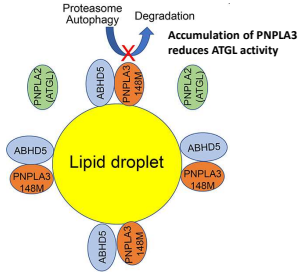
PNPLA3 Gene Variant is Associated with Increased Risk of NAFLD, NASH, Alcohol-Related Liver Disease, Cirrhosis, Liver Cancer





ATGL = adipose triglyceride lipase

Front. Med 17 December 2019 | https://doi.org/10.3389/fmed.2019.00304

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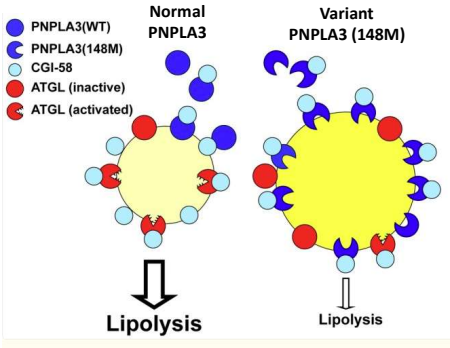
PNPLA3(148M) Gene Variant Inhibits Activation of ATGL in Lipid Droplets



ATGL = adipose triglyceride lipase
CGI-58 is also known as α/ß hydrolase domain-containing 5 (ABHD5)

Hobbs et al. Hepatology 2019;69(6):2427-2441. doi: 10.1002/hep.30583

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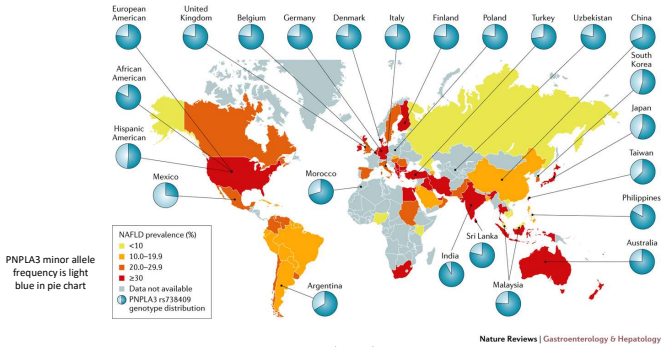
Estimated Prevalence of NAFLD Worldwide is Proportional to the Distribution of *PNPLA3* Genotypes



Nature Reviews | Gastroenterology & Hepatology

Nat Rev Gastroenterol Hepatol 2018;15:11–20
https://doi.org/10.1038/nrgastro.2017.109

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Arteriosclerosis, Thrombosis, and Vascular Biology

AHA SCIENTIFIC STATEMENT

Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association

P. Barton Duell, MD, Chair; Francine K. Welty, MD, Vice Chair; Michael Miller, MD; Alan Chait, MD; Gmerice Hammond, MD, MPH; Zahid Ahmad, MD; David E. Cohen, MD, PhD; Jay D. Horton, MD; Gregg S. Pressman, MD; Peter P. Toth, MD, PhD; on behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease

ABSTRACT: Nonalcoholic fatty liver disease (NAFLD) is an increasingly common condition that is believed to affect >25% of adults worldwide. Unless specific testing is done to identify NAFLD, the condition is typically silent until advanced and potentially irreversible liver impairment occurs. For this reason, the majority of patients with NAFLD are unaware of having this serious condition. Hepatic complications from NAFLD include nonalcoholic steatohepatitis, hepatic cirrhosis, and hepatocellular carcinoma. In addition to these serious complications, NAFLD is a risk factor for atherosclerotic cardiovascular disease, which is the principal cause of death in patients with NAFLD. Accordingly, the purpose of this scientific statement is to review the underlying risk factors and pathophysiology of NAFLD, the associations with atherosclerotic cardiovascular disease, diagnostic and screening strategies, and potential interventions.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ diabetes mellitus ■ hepatocytes ■ hypertriglyceridemia ■ insulin resistance ■ metabolic syndrome ■ nonalcoholic fatty liver disease ■ triglycerides

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Originally published 14 Apr 2022

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Goals of the AHA Scientific Statement on NAFLD and Cardiovascular Risk

Bring attention to the high prevalence and underdiagnosis of NAFLD, a risk factor for ASCVD

Review underlying risk factors and pathophysiology of NAFLD

Highlight the evidence demonstrating associations between NAFLD and ASCVD

Recognize that ASCVD is the principal cause of death in patients with NAFLD

Review potential diagnostic and screening strategies

Discuss potential interventions (but no treatment guidelines)

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Table 2. Summary of Studies That Evaluated the Association Between NAFLD and ASCVD Risk

Reference	NAFLD diagnosis	Patients, n	Type of study	Impact of NAFLD on CVD outcomes or ASCVD compared with control subjects after adjustment for risk factor covariates
Jepsen et al,[34] 2003	Ultrasound	1804	Retrospective	OR, 2.1 for CVD mortality
Targher et al,[35] 2007	Ultrasound	2839	Cross-sectional	OR, 1.49 for CAD, PAD, and cerebrovascular disease in type 2 diabetes
Hamaguchi et al,[36] 2007	Ultrasound	1637	Prospective	HR, 4.1 for nonfatal CVD events
Santos et al,[37] 2007	Ultrasound	505	Cross-sectional	OR, 1.73 for coronary calcification
Haring et al,[38] 2009	Ultrasound	4160	Prospective	HR, 6.22 for all-cause and CVD mortality
Assy et al,[39] 2010	CT	61	Cross-sectional	OR, 2.03 for coronary calcification
Chen et al,[40] 2010	Ultrasound/CT	295	Cross-sectional	OR, 2.46 for CAC >100
Wong et al,[41] 2011	Ultrasound	612	Prospective	OR, 2.31 for significant coronary artery disease (>50% obstruction)
Targher et al,[42] 2012	Ultrasound	343	Cross-sectional	OR, 7.6 for CAD, PAD, and cerebrovascular disease in type 1 diabetes
Kim et al,[43] 2012	Ultrasound	4023	Cross-sectional	OR, 1.32 for CAC >10
Zhou et al,[44] 2012	Ultrasound	3543	Prospective	OR, 3.0 for CVD mortality
Stepanova and Younossi,[45] 2012	Ultrasound	20050	Prospective	OR, 1.23 for CVD events
Ekstedt et al,[46] 2015	Liver biopsy	229	Retrospective	HR, 1.55 for CVD mortality
Mellinger et al,[47] 2015	CT	3014	Cross-sectional	OR, 1.20 for CAC score >90th percentile for age
Mantovani et al,[48] 2016	Ultrasound	286	Retrospective	OR, 6.73 for incident cardiovascular events in type 1 diabetes
Pais et al,[49] 2016	Fatty Liver Index	5671	Retrospective	NAFLD severity correlates with CIMT and carotid plaque severity
Yoshitaka et al,[50] 2017	Ultrasound	1647	Prospective	HR, 10.4 in nonoverweight, 3.1 in overweight for incident cardiovascular events
Mahfood Hadad et al,[51] 2017	Ultrasound	25837 (11 studies)	Meta-analysis	RR, 1.77 for incident CVD, 1.43 for cardiovascular mortality
Zhou et al,[52] 2018	Ultrasound/CT	8346 (6 studies)	Meta-analysis	OR, 2.20 for incident CVD in patients with diabetes
Kapuria et al,[53] 2018	Ultrasound/CT	42410 (12 studies)	Meta-analysis	OR, 1.64 for higher CAC scores
Sinn et al,[54] 2019	Ultrasound	111 492	Retrospective	HR, 1.54 for myocardial infarction
Pais et al,[55] 2019	Fatty Liver Index	2554	Retrospective	NAFLD correlated with CIMT, CAC, and carotid plaque

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CIMT, carotid intima-media thickness; CT, computed tomography; CVD, cardiovascular disease; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PAD, peripheral artery disease; and RR, relative risk.

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NAFLD is associated with risk of:
- MI
- CVD events
- CVD mortality
- CAC
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- CIMT
- Carotid plaque

NAFLD is probably an independent risk factor for ASCVD (despite many risk factors in common)

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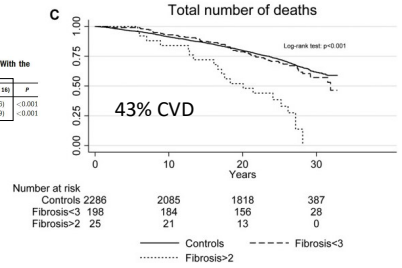
Fibrosis Stage Predicts CVD Risk and Mortality in Biopsy Proven NAFLD After up to 33 Years

Table 4. Hazard Ratios for Causes of Death in the Entire Cohort and in Histopathological Subgroups Compared With the Reference Population [HR (95% CI)]

Cause of Death	Entire Cohort (n = 229)	P	NAS 0-4, F0-2 (n = 76)	P	NAS 5-8, F0-2 (n = 57)	P	NAS 0-8, F3-4 (n = 16)	P
Overall mortality	1.29 (1.04-1.59)	0.020	1.13 (0.79-1.60)	0.511	1.41 (0.97-2.06)	0.072	3.28 (2.27-4.76)	<0.001
Cardiovascular disease	1.55 (1.11-2.15)	0.01	1.19 (0.65-2.20)	0.557	1.38 (0.72-2.65)	0.335	4.36 (2.29-8.29)	<0.001



Hepatology 2015 May;61(5):1547-54. doi: 10.1002/hep.27368

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Outline

1. Introduction
2. Definitions and terminology
3. What is NAFLD/MASLD?
4. Prevalence of NAFLD
5. Etiology of NAFLD
6. Association of NAFLD with ASCVD risk
7. **Diagnosis of NAFLD/NASH**
8. Potential interventions
9. Summary

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Diagnosis of NAFLD/NASH

Diagnostic Tools

AST/ALT useful if elevated

NAFLD fibrosis score (online tool)
Fibrosis-4 index (FIB-4)
(age, BMI, glucose, platelets, albumin, AST/ALT ratio)
Enhanced liver fibrosis (ELF) score

Liver biopsy (gold standard)

Imaging Tools

Hepatic ultrasonography
(requires > 20% fat content)
Vibration-controlled transient elastography
(discriminates grades of steatosis)
Hepatic CT imaging
(quantitative assessment of fat content in mod. to severe disease)
MRI imaging - Best modality/expensive
(distinguishes histological grades of stenosis)

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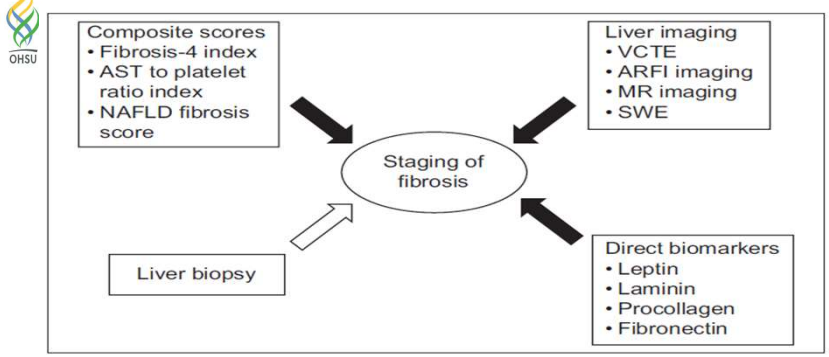

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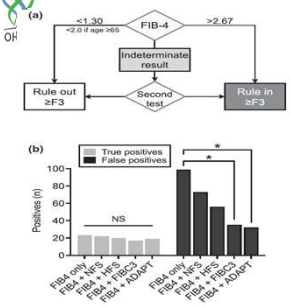
FIB-4 Composite Scoring for Hepatic Fibrosis



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

0.00 - 1.29 Low risk for advanced liver fibrosis
1.30 - 2.67 Indeterminate risk for advanced liver fibrosis
>2.67 High risk for advanced fibrosis and for developing of other liver related events

The relatively low diagnostic accuracy of Fib-4, mandates the use of 2 cutoff points to rule in (> 2.67) or rule out (< 1.30) advanced fibrosis and leaves up to 50% of all patients in an indeterminate gray area.

J Clin Endocrinol Metab 2022;107,e2008–e2020

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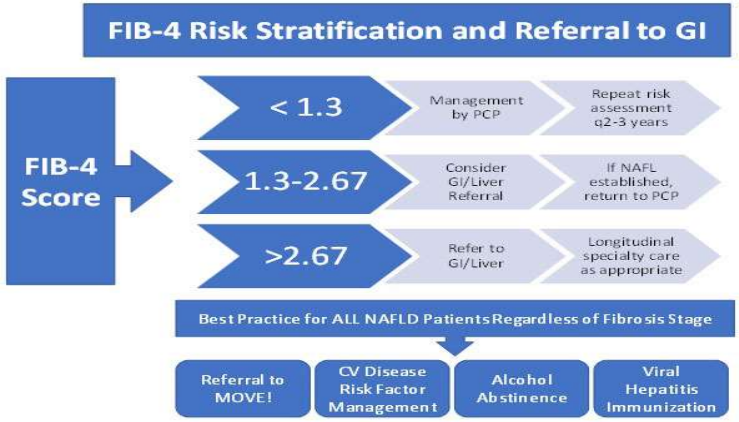

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The Fibrosis-4 Index (FIB-4) can be Incorporated into the EMR

A simple test such as FIB-4 that is embedded within electronic medical records together with a clinical care pathway to refer to hepatology can efficiently screen and risk-stratify patients and prevent future cirrhosis in many people with obesity or T2DM—within seconds.

The Journal of Clinical Endocrinology & Metabolism, 2022, 107, e3076–e3077
https://doi.org/10.1210/clinem/dgac186
Advance access publication 25 March 2022
Commentary

A Simple Test to Identify the Risk of NASH and Cirrhosis in People With Obesity or Diabetes: The Time to Screen Is Now

Kenneth Cusi[1]
[1]Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, FL, USA

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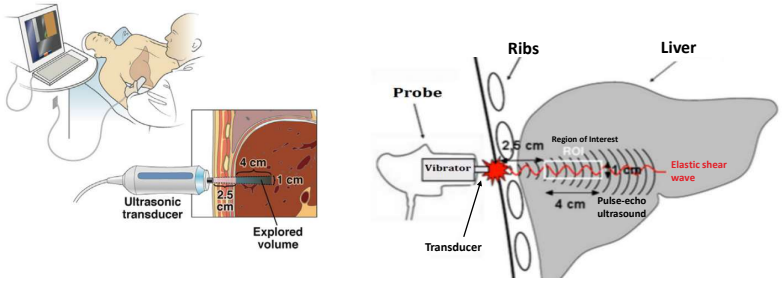
Non-Invasive Assessment of Liver Fibrosis by Vibration-Controlled Transient Elastography (VCTE)



Stiffer, less elastic tissue increases the speed of shear wave propagation

Clin Gastroenterol Hepatol. 2015;13:27-36. doi: 10.1016/j.cgh.2014.04.039
Diagn Interv Imaging. 2013;94:515-34. doi: 10.1016/j.diii.2013.02.005

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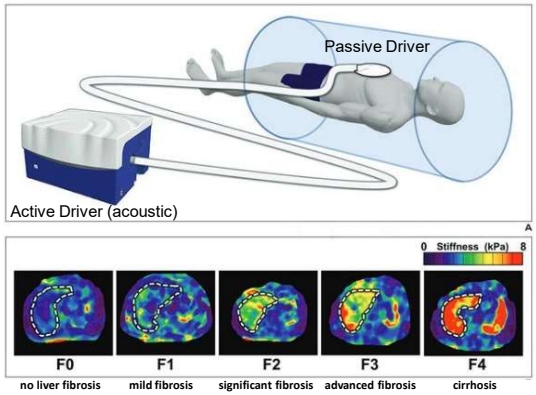
Magnetic Resonance Elastography



AJR Am J Roentgenol 2024;222:e2329437. doi: 10.2214/AJR.23.29437

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Potential Interventions for NAFLD(MASLD)/NASH(MASH)

Key Interventions (all are challenging!)

Dietary modification (reduce hyperglycemia, reduce hypertriglyceridemia, reduce insulin resistance, reduce caloric intake, reduce intake of high-fructose foods, simple carbohydrates).

Alcohol avoidance (even modest intake can aggravate NAFLD)

Increase physical activity

Weight loss > 5-10%

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Potential Interventions for NAFLD(MASLD)/NASH(MASH)

Weight loss >10% over one year was associated with
- NASH resolution in 90%
- Regression of hepatic fibrosis in 45%

Gastroenterology. 2015;149:367–378. e365

Bariatric surgery (well proven intervention for MASLD/MASH):
- Absolute 10-year risk in 1158 pts (650 surgery, 508 control) with biopsy-proven fibrotic nonalcoholic steatohepatitis without cirrhosis :
- 12.4% decrease in major liver outcomes (progression to cirrhosis, diagnosis of HCCa, liver transplantation or liver-related death)
- 13.9% decrease in MACE

JAMA. 2021 Nov 23;326(20):2031-2042. doi: 10.1001/jama.2021.19569

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Potential Pharmacologic Interventions for NAFLD(MASLD)/NASH(MASH)

Drug Therapy

Diabetes-related medications: metformin (not recommended for NAFLD), pioglitazone (variable effects), **GLP-1 RAs,** saroglitazar (PPAR- α/γ agonist)?, GLP-1/GIP dual RAs?, **pemafibrate**.
Vitamin E 800 IU/d can be considered for biopsy-proven NASH
Leptin in lipodystrophy
Sebelipase alpha in lysosomal acid lipase deficiency (LALD)
FXR agonists: obeticholic acid (CDCA-derivative for biliary cirrhosis). Ongoing trials in NASH
Many experimental agents: many too toxic or ineffective
- Pentoxifyline: ↓ TNF-α production. ↓ NAFLD activity score, AST/ALT. Steatosis unchanged
- Lanifibranor. Phase 3 PPAR-$\alpha/\delta/\gamma$ agonist. Top dose ↓ NASH and fibrosis stage 48-49%
- Arachidyl amido cholanoic acid: FA-bile acid conjugate, downregulates hepatic stearoyl-CoA desaturase 1 activity, granted fast-track designation by FDA for NASH, phase 3

Bempedoic acid?? **Thyroid receptor agonists**

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Potential Pharmacologic Interventions for NAFLD(MASLD)/NASH(MASH)

Drug Therapy

Diabetes-related medications without proven benefit
- metformin
- sulfonylureas
- DPP4 inhibitors
- SGLT-2 inhibitors
- insulin

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Potential Pharmacologic Interventions for NAFLD(MASLD)/NASH(MASH)

Drug Therapy

GLP-1 and GLP-1/GIP receptor agonists: some are effective for weight loss (all SQ), prevention of ASCVD (liraglutide, semaglutide, dulaglutide), and treatment of NAFLD/MASLD (liraglutide, semaglutide, tirzepatide, exenatide, dulaglutide)

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Potential Pharmacologic Interventions for NAFLD(MASLD)/NASH(MASH)

Drug Therapy

GLP-1 and GLP-1/GIP receptor agonists: effective for weight loss and benefit for MASLD

The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

Authors: Philip N. Newsome, M.B., Ch.B., Ph.D., Kristine Buchholtz, M.D., Ph.D., Kenneth Cusi, M.D., Martin Linder, M.Sc., Takeshi Okanoue, M.D., Ph.D., Vlad Ratziu, M.D., Ph.D., Arun J. Sanyal, M.D., Anne-Sophie Sejling, M.D., Ph.D., and Stephen A. Harrison, M.D., for the NN9931-4296 Investigators* Author Info & Affiliations

Published November 13, 2020 | N Engl J Med 2021;384:1113-1124 | DOI: 10.1056/NEJMoa2028395
VOL. 384 NO. 12

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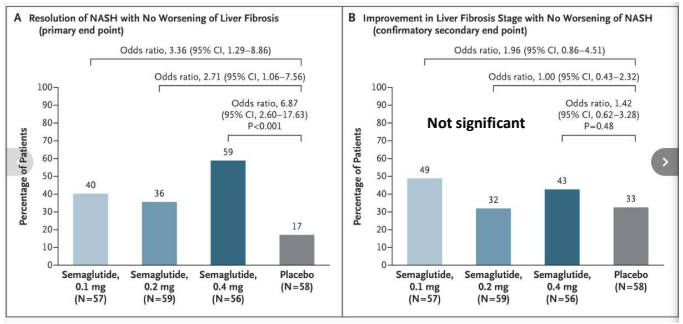
A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

320 patients with biopsy-confirmed NASH and liver fibrosis stage F1, F2, or F3 treated for 72 weeks with semaglutide 0.1, 0.2, or 0.4 mg SQ **daily** vs placebo



N Engl J Med 2021;384:1113-1124. DOI: 10.1056/NEJMoa2028395

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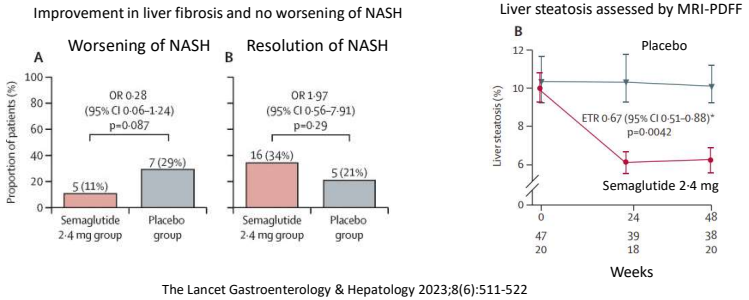
No Benefit on NASH from Semaglutide 2.4 mg SQ Weekly for 48 wks in Patients with NASH-F4

71 patients with biopsy-confirmed **NASH-related cirrhosis** (fibrosis stage 4) and BMI ≥ 27 kg/m2



The Lancet Gastroenterology & Hepatology 2023;8(6):511-522

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 24, 2022 VOL. 387 NO. 21

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

A. Das Pradhan, R.J. Glynn, J.-C. Fruchart, J.G. MacFadyen, E.S. Zaharris, B.M. Everett, S.E. Campbell, R. Oshima, P. Amarenco, D.J. Blom, E.A. Brinton, R.H. Eckel, M.B. Elam, J.S. Felicio, H.N. Ginsberg, A. Goudev, S. Ishibashi, J. Joseph, T. Kodama, W. Koenig, L.A. Leiter, A.J. Lorenzatti, B. Mankovsky, N. Marx, B.G. Nordestgaard, D. Pall, K.K. Ray, R.D. Santos, H. Soran, A. Susekov, M. Tendera, K. Yokote, N.P. Paynter, J.E. Buring, P. Libby, and P.M Ridker, for the PROMINENT Investigators*

ABSTRACT

BACKGROUND

High triglyceride levels are associated with increased cardiovascular risk, but whether reductions in these levels would lower the incidence of cardiovascular events is uncertain. Pemafibrate, a selective peroxisome proliferator–activated receptor α modulator, reduces triglyceride levels and improves other lipid levels.

METHODS

RESULTS

Among 10,497 patients (66.9% with previous cardiovascular disease), the median

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Das Pradhan can be contacted at apradhan@bwh.harvard.edu and Dr. Ridker can be contacted at pridker@bwh.harvard.edu or at the Center for Cardiovascular Disease Prevention, Brigham

Pemafibrate

Selective PPARα modulator with multiple activities

N Engl J Med 2022;387:1923-1934
DOI: 10.1056/NEJMoa2210645

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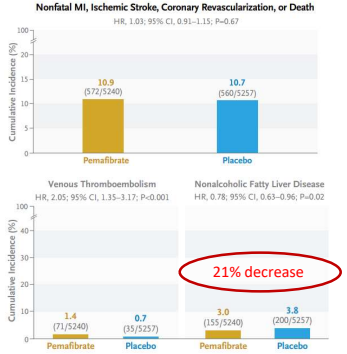
RESEARCH SUMMARY

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

Das Pradhan A et al. DOI: 10.1056/NEJMoa2210645



N Engl J Med 2022;387:1923-1934
DOI: 10.1056/NEJMoa2210645

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Daily aspirin associated with a reduced risk of hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: a population-based cohort study

Teng-Yu Lee,[a,b] Yao-Chun Hsu,[c,d,e,f] Hsiu J. Ho,[f] Jaw-Town Lin,[c] Yi-Ju Chen,[f,g,h,i] and Chun-Ying Wu[f,j,k,l,*]

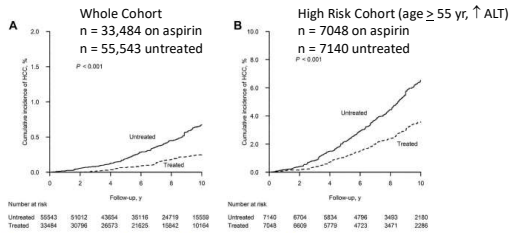

Fig. 2: **Cumulative incidence of hepatocellular carcinoma development after inverse probability of treatment weighting, accounting for patient mortality or liver transplantation as a competing risk** (A) The whole patient cohort; (B) The high-risk patient cohort. Follow-up from the 90th day after daily aspirin therapy in the treated group and the matched index date in the untreated group. Treated patients were those who continuously received daily aspirin therapy for 90 days or more; untreated patients were those who had not received antiplatelet therapy cumulatively ≥90 days.

EClinicalMedicine (Lancet) 2023 Jun 29;61:102065. doi: 10.1016/j.eclinm.2023.102065

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Resmetirom is FDA-Approved for NASH with Moderate to Advanced Liver Fibrosis

U.S. FOOD & DRUG ADMINISTRATION

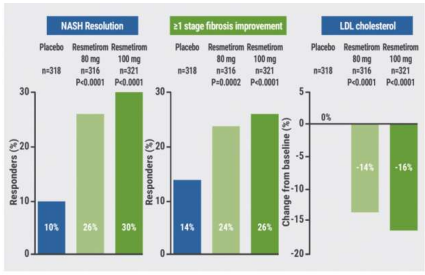
FDA NEWS RELEASE

FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease

March 14, 2024

Today, the U.S. Food and Drug Administration approved Rezdiffra

Liver-targeted thyroid hormone receptor-ß (THR-ß) agonist



N Engl J Med 2024;390:497-509

AEs: diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, dizziness, possible hepatotoxicity, gallstones

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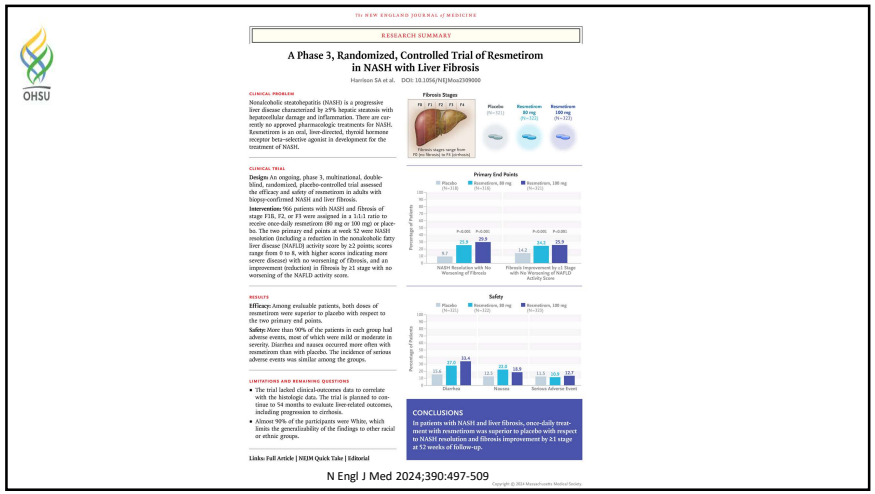

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

CLINICAL PROBLEM

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease characterized by ≥5% hepatic steatosis with hepatocellular damage and inflammation. There are currently no approved pharmacologic treatments for NASH. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH.

CLINICAL TRIAL

Design: An ongoing, phase 3, multinational, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

Intervention: 966 patients with NASH and fibrosis of stage F1B, F2, or F3 were assigned in a 1:1:1 ratio to receive once-daily resmetirom (80 mg or 100 mg) or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by ≥1 stage with no worsening of the NAFLD activity score.

RESULTS

Efficacy: Among evaluable patients, both doses of resmetirom were superior to placebo with respect to the two primary end points.

Safety: More than 90% of the patients in each group had adverse events, most of which were mild or moderate in severity. Diarrhea and nausea occurred more often with resmetirom than with placebo. The incidence of serious adverse events was similar among the groups.

LIMITATIONS AND REMAINING QUESTIONS

- The trial lacked clinical-outcomes data to correlate with the histologic data. The trial is planned to continue to 54 months to evaluate liver-related outcomes, including progression to cirrhosis.
- Almost 90% of the participants were White, which limits the generalizability of the findings to other racial or ethnic groups.

Links: Full Article | NEJM Quick Take | Editorial

CONCLUSIONS

In patients with NASH and liver fibrosis, once-daily treatment with resmetirom was superior to placebo with respect to NASH resolution and fibrosis improvement by ≥1 stage at 52 weeks of follow-up.

N Engl J Med 2024;390:497-509

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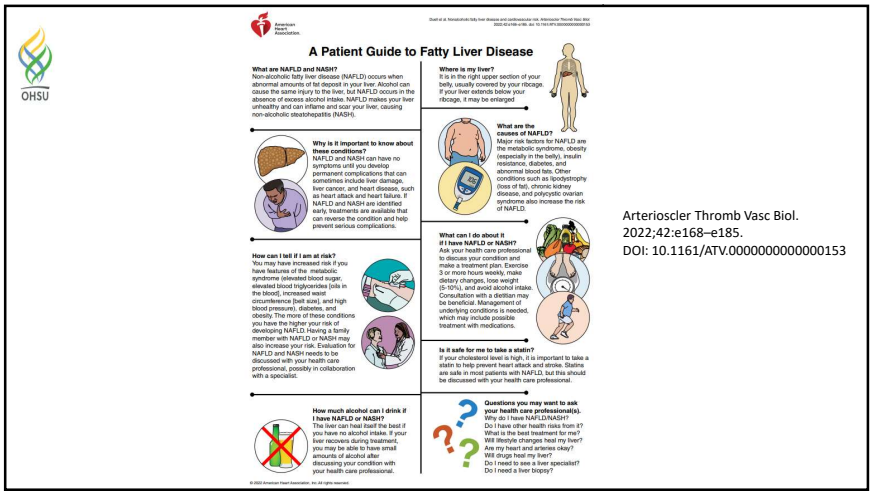

A Patient Guide to Fatty Liver Disease

What are NAFLD and NASH?
Non-alcoholic fatty liver disease (NAFLD) occurs when abnormal amounts of fat deposit in your liver. Alcohol can cause the same injury to the liver, but NAFLD occurs in the absence of excess alcohol intake. NAFLD makes your liver unhealthy and can inflame and scar your liver, causing non-alcoholic steatohepatitis (NASH).

Where is my liver?
It is in the right upper section of your belly, usually covered by your ribcage. If your liver extends below your ribcage, it may be enlarged

Why is it important to know about these conditions?
NAFLD and NASH can have no symptoms until you develop permanent complications that can sometimes include liver damage, liver cancer, and heart disease, such as heart attack and heart failure. If NAFLD and NASH are identified early, treatments are available that can reverse the condition and help prevent serious complications.

What are the causes of NAFLD?
Major risk factors for NAFLD are the metabolic syndrome, obesity (especially in the belly), insulin resistance, diabetes, and abnormal blood fats. Other conditions such as lipodystrophy (loss of fat), chronic kidney disease, and polycystic ovarian syndrome also increase the risk of NAFLD.

How can I tell if I am at risk?
You may have increased risk if you have features of the metabolic syndrome (elevated blood sugar, elevated blood triglycerides [oils in the blood], increased waist circumference [belt size], and high blood pressure), diabetes, and obesity. The more of these conditions you have the higher your risk of developing NAFLD. Having a family member with NAFLD or NASH may also increase your risk. Evaluation for NAFLD and NASH needs to be discussed with your health care professional, possibly in collaboration with a specialist.

What can I do about it if I have NAFLD or NASH?
Ask your health care professional to discuss your condition and make a treatment plan. Exercise 3 or more hours weekly, make dietary changes, lose weight (5-10%), and avoid alcohol intake. Consultation with a dietitian may be beneficial. Management of underlying conditions is needed, which may include possible treatment with medications.

Is it safe for me to take a statin?
If your cholesterol level is high, it is important to take a statin to help prevent heart attack and stroke. Statins are safe in most patients with NAFLD, but this should be discussed with your health care professional.

How much alcohol can I drink if I have NAFLD or NASH?
The liver can heal itself the best if you have no alcohol intake. If your liver recovers during treatment, you may be able to have small amounts of alcohol after discussing your condition with your health care professional.

Questions you may want to ask your health care professional(s).
Why do I have NAFLD/NASH?
Do I have other health risks from it?
What is the best treatment for me?
Will lifestyle changes heal my liver?
Are my heart and arteries okay?
Will drugs heal my liver?
Do I need to see a liver specialist?
Do I need a liver biopsy?

Arterioscler Thromb Vasc Biol. 2022;42:e168–e185.
DOI: 10.1161/ATV.0000000000000153

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Summary
Key Take-Home Messages

*NAFLD is common, occurring in about 25% of individuals worldwide. Rates are increasing everywhere
*Most NAFLD is undiagnosed. Normal AST/ALT do not r/o NAFLD. Hepatic U/S is useful if positive. Liver biopsy gold standard.
*Noninvasive diagnostic options such as FIB-4 and vibration-controlled transient elastography (VCTE) are available
*Risk factors include insulin resistance, IGT/diabetes, obesity (especially visceral adiposity), metabolic syndrome, and dyslipidemia (hypertriglyceridemia, increased free fatty acids)
*Genetic factors (monogenic or polygenic) modulate the risk of development of NAFLD and progression to NASH
*Most patients with hepatic steatosis do not progress to NASH, cirrhosis, or hepatocellular carcinoma, but a subgroup will
*NASH contributes to increased ASCVD risk, due in part to risk factors in common.
*NAFLD is a risk enhancer when ASCVD risk is assessed in patients
***Key Interventions: Dietary modification, increased exercise, weight loss 5-10%, alcohol avoidance**, treat risk factors (e.g. increased TG)
*GLP-1 receptor agonists modestly improve NAFLD in association with improved glycemia, weight loss, and reduced risk of ASCVD events (liraglutide, semaglutide, dulaglutide)
*Novel experimental drug therapies are in development, but most have modest efficacy. Toxicity is a problem for some.
* Resmetirom is the first FDA-approved treatment for MASH 3/14/2024

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