FATTY LIVER IN DIABETES AND OBESITY

Moderator: Alireza Esteghamati, MD

Panelists:

Manouchehr Nakhjavani,MD

Soghra Rabizadeh,MD

Farhad Hossein panah,MD

Hamidreza Zakeri,MD

Mohsen Rajabnia,MD

CASE PRESENTATION

Mohsen Rajabnia,MD

1-WHAT IS THE MOST LIKELY CAUSE OF HER RAISED LIVER FUNCTION TESTS?

2-CAN FATTY LIVER BE PRESENT IN THE ABSENCE OF RAISED LFTS?

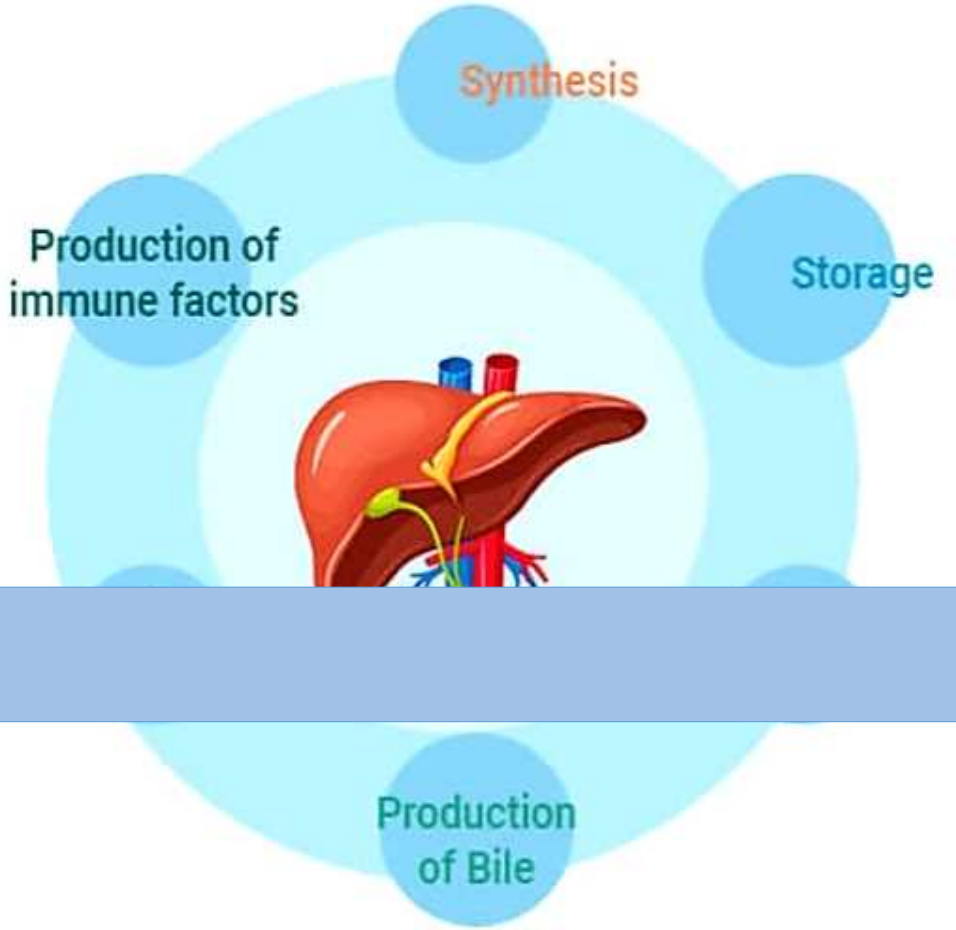
Obesity, Diabetes Mellitus, and Fatty Liver

Mohsen Rajabnia M.D.

Assistant Professor of Gastroenterology and Hepatology

ABZUMS

FUNCTIONS OF Liver



The most common
Causes Of liver disorders

- Chronic Alcoholism
- Chronic viral infections of the liver
- Autoimmunity
- Metabolic
- Fatty liver associated with obesity and diabetes
- Insufficient blood circulation in the liver due to various causes

DIAGNOSIS

Medical History

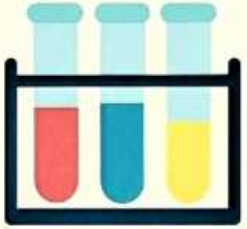
Medical History

Physical Examination

Physical Examination

Imaging Tests

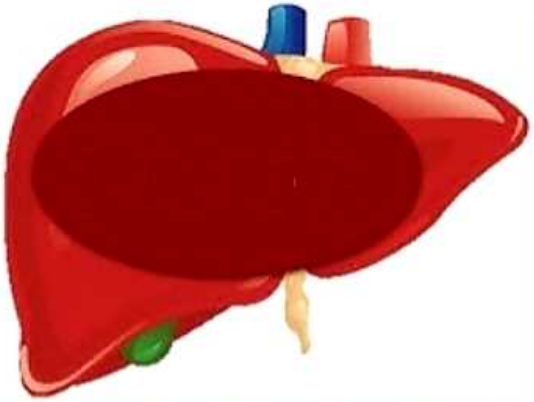
Laboratory Tests



Liver function tests

Tests of Hepatic excretory functions

- **Serum** — **Bilirubin**
  - Total
  - Direct (C)
  - Indirect (UC)
- **Urine**
  - Bile pigments
  - Bile salts
  - Urobilinogen



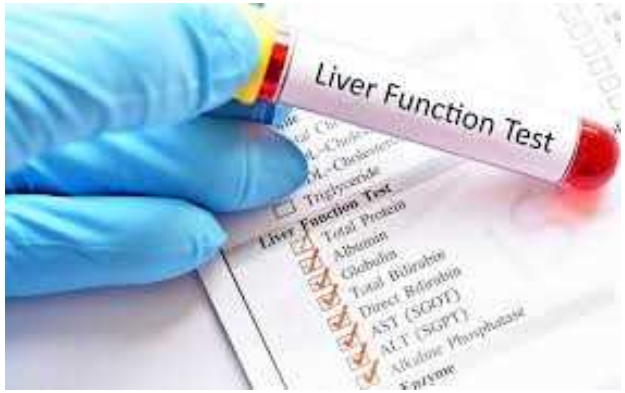
Serum proteins, A/G ratio, PT

Liver enzyme panel

- **AST**
- **ALT**
- **ALP**
- **GGT**
- **5'Nucleotidase**

Liver enzymes that are commonly measured in the serum include:

- Serum aminotransferases: ALT and AST
- Alkaline phosphatase
- Gamma-glutamyl transpeptidase
- 5'-nucleotidase
- Lactate dehydrogenase (LDH)

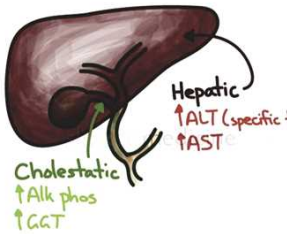


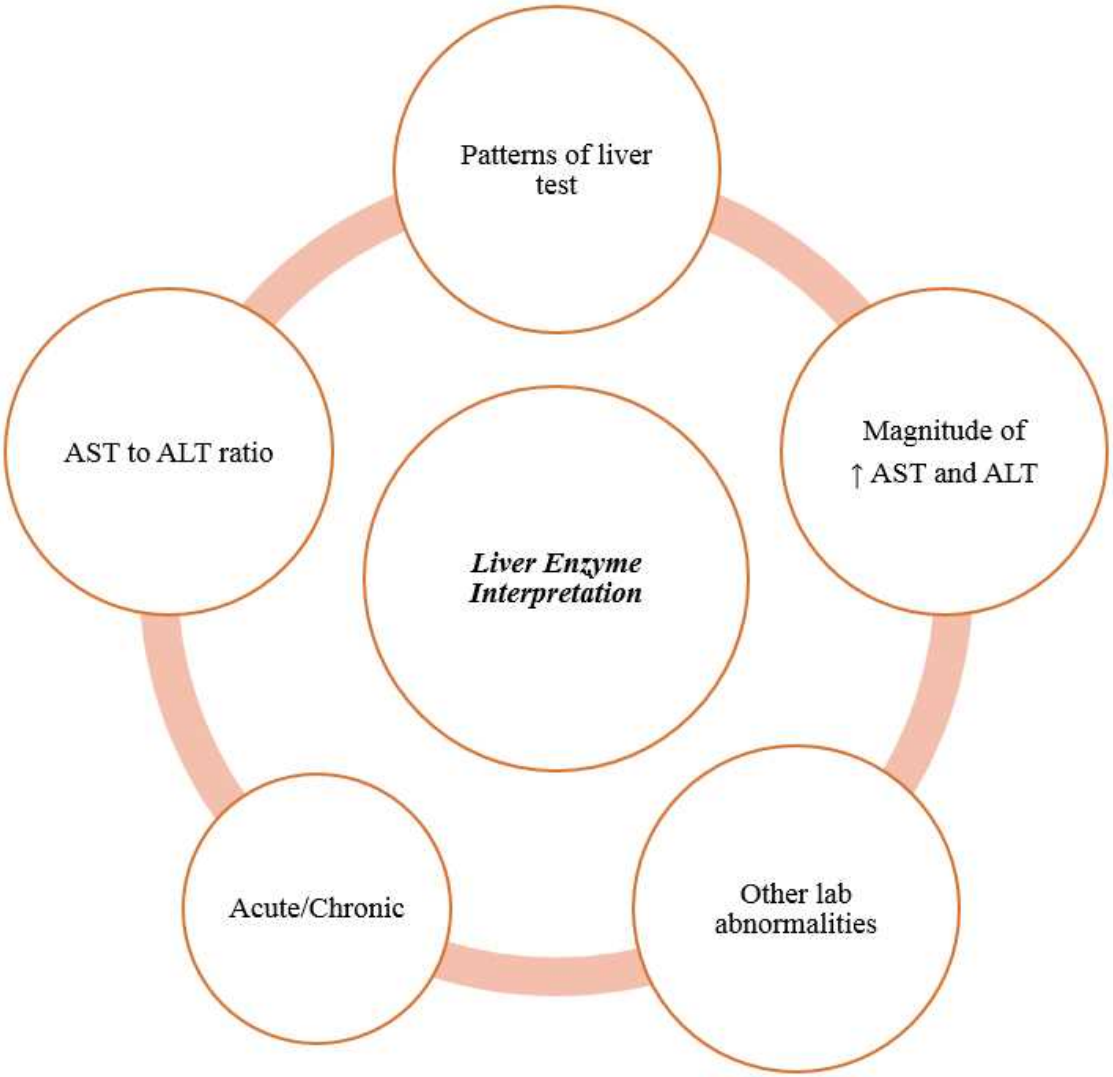
Tests of hepatic synthetic function include:

- Serum albumin
- Prothrombin time/international normalized ratio

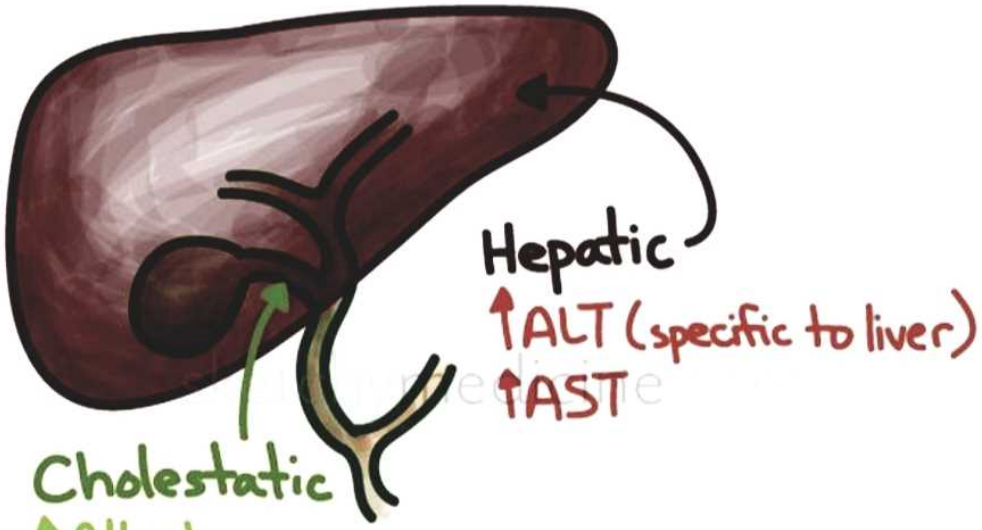
ALT, AST, alkaline phosphatase, and bilirubin are biochemical markers of liver injury.

Albumin, bilirubin, and prothrombin time are markers of synthetic function.


Hepatic
↑ALT (specific
↑AST
Cholestatic
↑Alk phos
↑GGT


Patterns of liver test
Magnitude of ↑ AST and ALT
Other lab abnormalities
Acute/Chronic
AST to ALT ratio
Liver Enzyme Interpretation

Liver Enzymes



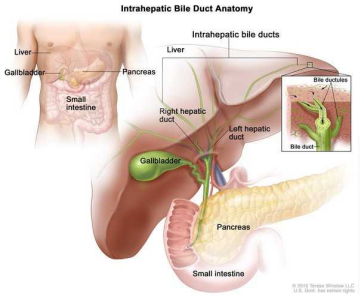
AST>ALT 2:1 - 3:1, AST>300: alcohol

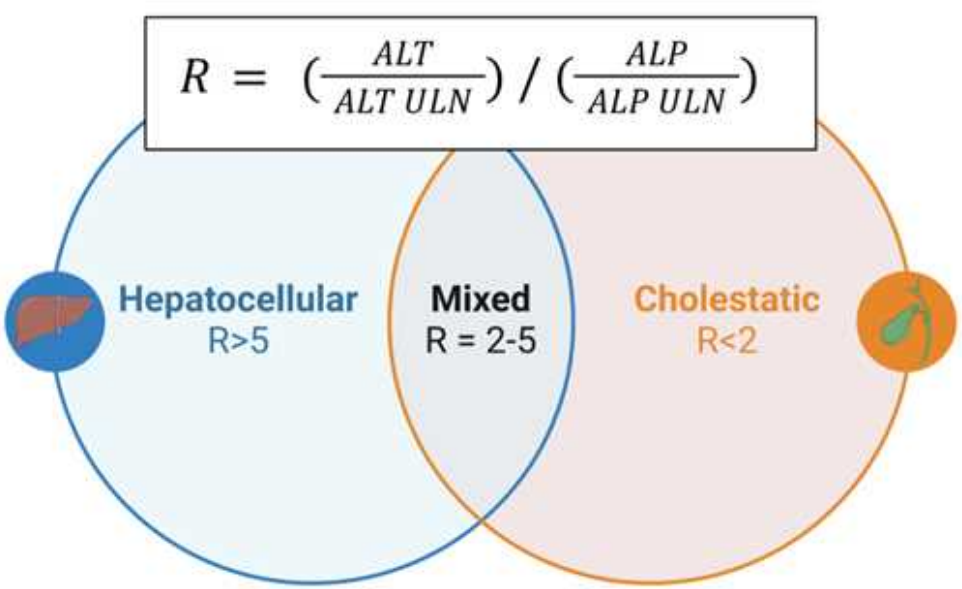
ALT>AST in fatty liver disease

ALT>AST by 1000x: acute viral hepatitis, ischemia, toxins, autoimmune, Wilson's disease

*AST can also come from muscle

*ALP has 5 minor sources (liver, blue duct, kidney, bone, , ...a)


Intrahepatic Bile Duct Anatomy
Intrahepatic bile ducts
Liver
Gallbladder
Pancreas
Small intestine
Right hepatic duct
Left hepatic duct
Bile ductules
Bile duct
Gallbladder
Pancreas
Small intestine


$R = (\frac{ALT}{ALT\ ULN}) / (\frac{ALP}{ALP\ ULN})$
Hepatocellular
R>5
Mixed
R = 2-5
Cholestatic
R<2

GAMMA-GLUTAMYL TRANSPEPTIDASE

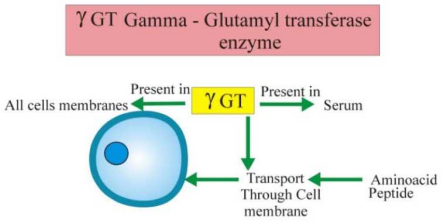
Function and source

GGT is present in hepatocytes and biliary epithelial cells and the cell membranes in many tissues,

including the kidneys, pancreas, liver, spleen, heart, brain, and seminal vesicles .

Isolated elevation or disproportionate elevation

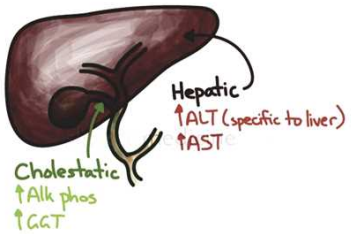
— Elevation in serum GGT is not completely specific for hepatobiliary disease. High serum GGT values have been associated with the use of barbiturates or phenytoin or ingestion of large quantities of alcohol .

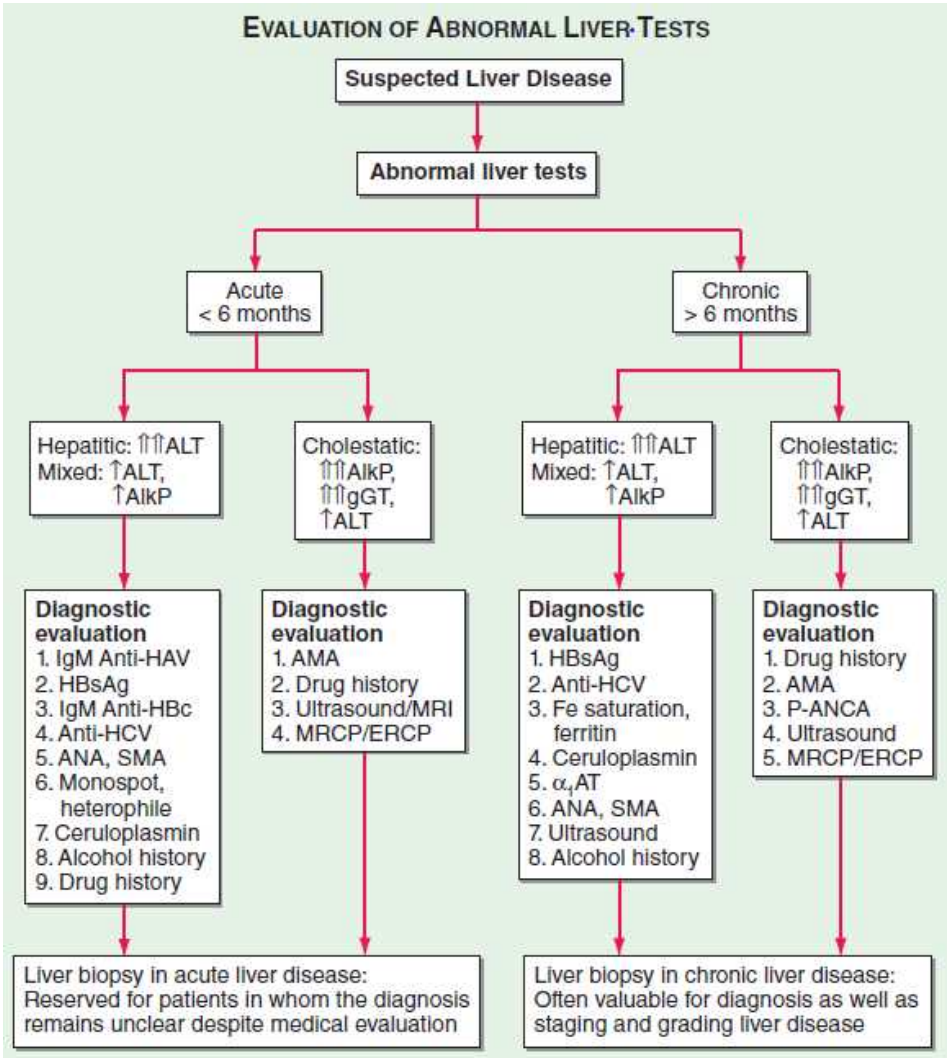


Magnitude of AST and ALT elevations

- Alcohol-associated fatty liver disease – AST <8 times the upper limit of normal; ALT <5 times the upper limit of normal.
- Metabolic dysfunction-associated steatotic liver disease – AST and ALT <4 times the upper limit of normal.
- Acute viral hepatitis or toxin-related hepatitis with jaundice – AST and ALT >25 times the upper limit of normal.
- Ischemic hepatitis (ischemic hepatopathy, shock liver, hypoxic hepatitis) – AST and ALT >50 times the upper limit of normal.

- Chronic hepatitis C virus infection – Wide variability, typically normal to less than twice the upper limit of normal, rarely more than 10 times the upper limit of normal.
- Chronic hepatitis B virus infection – Levels vary; the AST and ALT may be normal in inactive carriers, whereas most patients with chronic hepatitis B have mild to moderate elevations (approximately twice the upper limit of normal); with exacerbations, levels are more than 10 times the upper limit of normal.

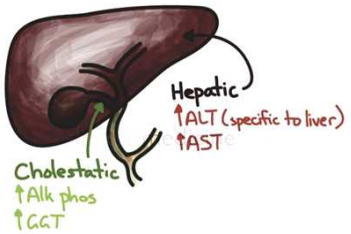



EVALUATION OF ABNORMAL LIVER TESTS
Suspected Liver Disease
Abnormal liver tests
Acute
< 6 months
Chronic
> 6 months
Hepatitic: ⇑⇑ALT
Mixed: ↑ALT,
↑AlkP
Cholestatic:
⇑⇑AlkP,
⇑⇑gGT,
↑ALT
Hepatitic: ⇑⇑ALT
Mixed: ↑ALT,
↑AlkP
Cholestatic:
⇑⇑AlkP,
⇑⇑gGT,
↑ALT
Diagnostic evaluation
1. IgM Anti-HAV
2. HBsAg
3. IgM Anti-HBc
4. Anti-HCV
5. ANA, SMA
6. Monospot, heterophile
7. Ceruloplasmin
8. Alcohol history
9. Drug history
Diagnostic evaluation
1. AMA
2. Drug history
3. Ultrasound/MRI
4. MRCP/ERCP
Diagnostic evaluation
1. HBsAg
2. Anti-HCV
3. Fe saturation, ferritin
4. Ceruloplasmin
5. α_1AT
6. ANA, SMA
7. Ultrasound
8. Alcohol history
Diagnostic evaluation
1. Drug history
2. AMA
3. P-ANCA
4. Ultrasound
5. MRCP/ERCP
Liver biopsy in acute liver disease: Reserved for patients in whom the diagnosis remains unclear despite medical evaluation
Liver biopsy in chronic liver disease: Often valuable for diagnosis as well as staging and grading liver disease

AST to ALT ratio

An AST to ALT ratio of 2:1 or greater is suggestive of alcohol-associated liver disease, particularly in the setting of an elevated GGT.

A pattern of elevated AST greater than ALT with a ratio less than two may be observed in patients with cirrhosis due to viral hepatitis and acute Wilson disease.



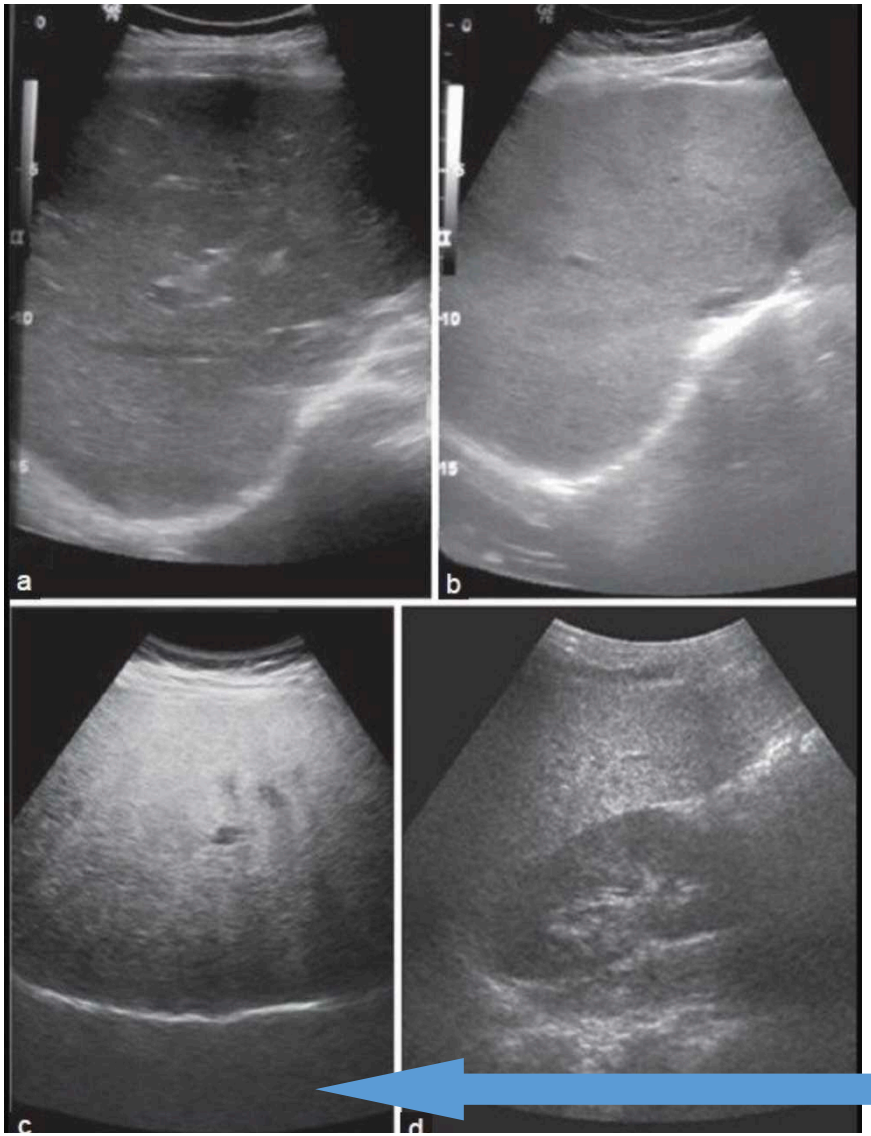
Differential diagnosis of mildly and moderately elevated serum aminotransferases (< 15 times upper limit of normal)

Hepatic disease	
ALT predominant (AST/ALT < 1)	**AST predominant (AST/ALT ≥ 1)**
Drug-induced liver injury	Alcohol-associated hepatitis
Chronic viral hepatitis (HBV, HCV)	Cirrhosis due to viral hepatitis or NAFLD
Occupational, toxin-related hepatocellular damage	Wilson disease
Autoimmune hepatitis	
NAFLD	
Genetic disorders ■ Wilson disease ■ Hemochromatosis ■ Alpha-1 antitrypsin deficiency	
Congestive hepatopathy	
Malignant infiltration of the liver	

Evaluation of isolated mild elevation of serum aminotransferases*

Step 1: Initial evaluation
Review possible links to medications, herbal therapies, or recreational drugs
Screen for alcohol abuse (history, screening instruments, AST/ALT ratio >2:1)
Obtain serology for hepatitis B and C (HBsAg, anti-HBs, anti-HBc, anti-HCV)
Screen for hemochromatosis (Fe/TIBC >45%)
Evaluate for fatty liver (AST/ALT usually <1, obtain RUQ ultrasonography)

* Mild is defined as between 2 and 10 times the upper limit of normal



Ultrasound showed a grade 2 fatty liver

Liver Enzyme in Fatty Liver

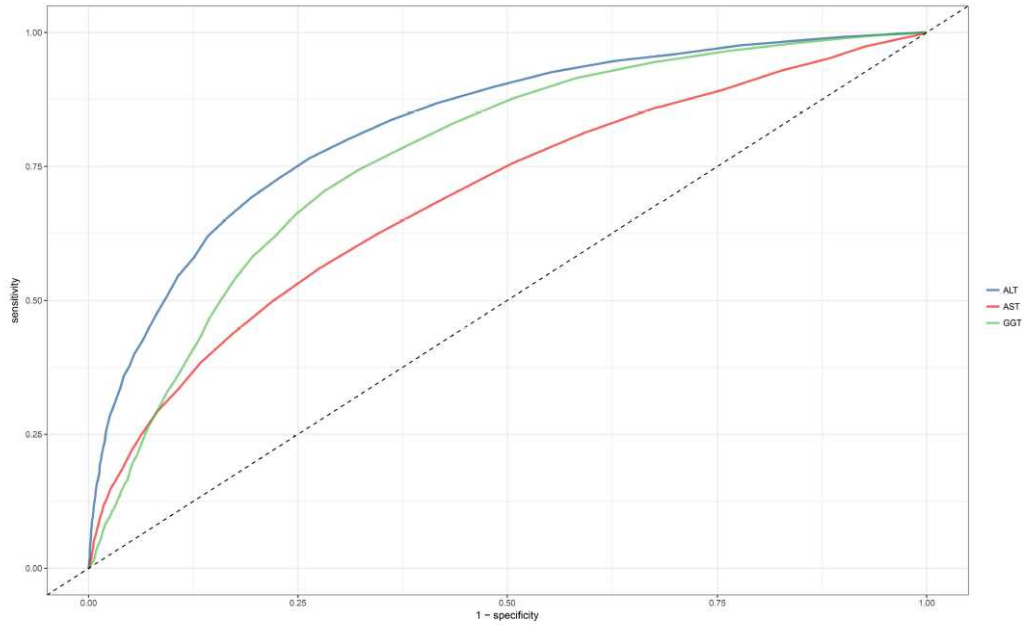
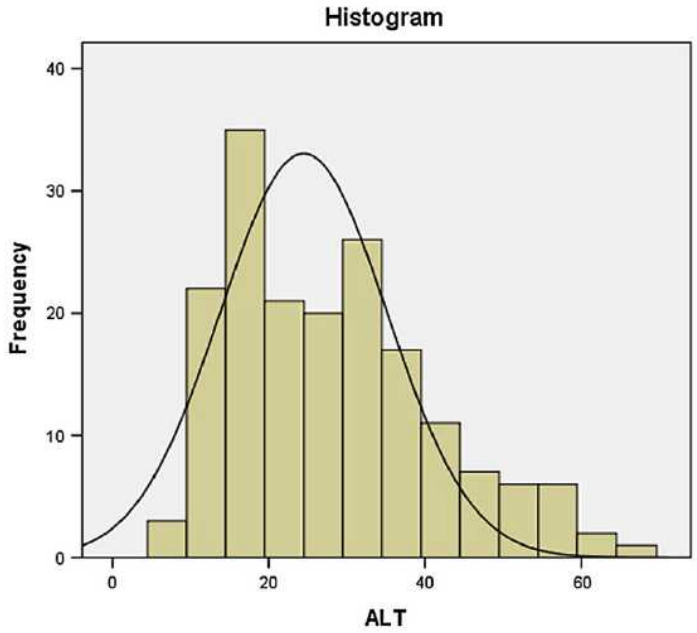


FIGURE 2
Area under the receiver operating characteristic curve for ALT, AST, and GGT for identification of NAFLD in the entire population. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NAFLD, Nonalcoholic fatty liver disease.



ALT values in 177 overweight patients undergoing bariatric surgery. Mean = 28.16; standard deviation = 13.091.

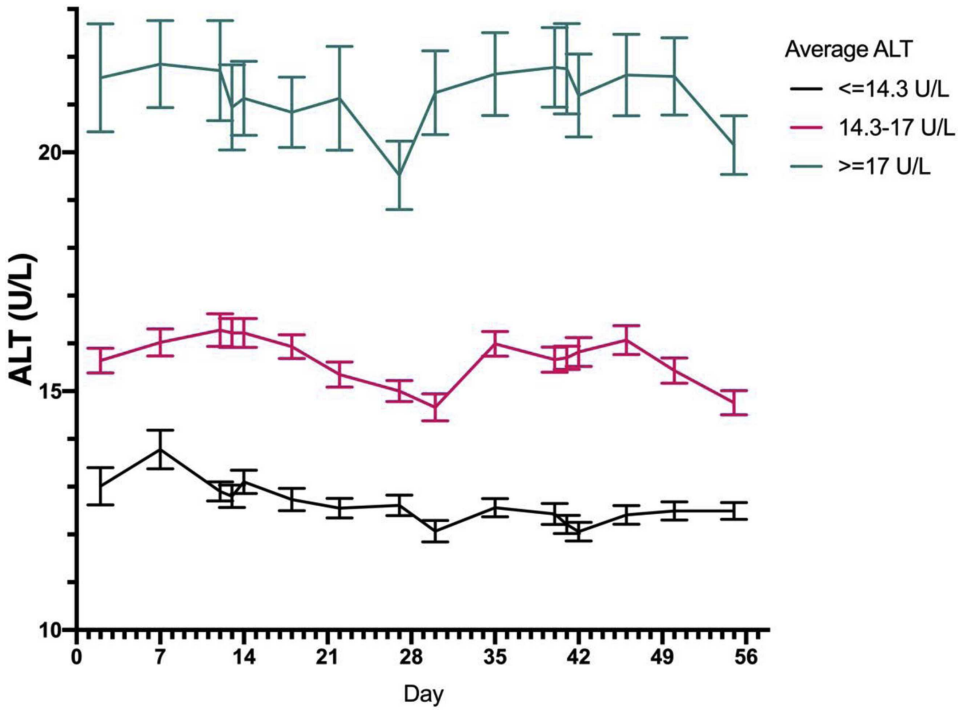
ELSEVIER

Journal of Hepatology 41 (2024) 751–757

Journal of Hepatology

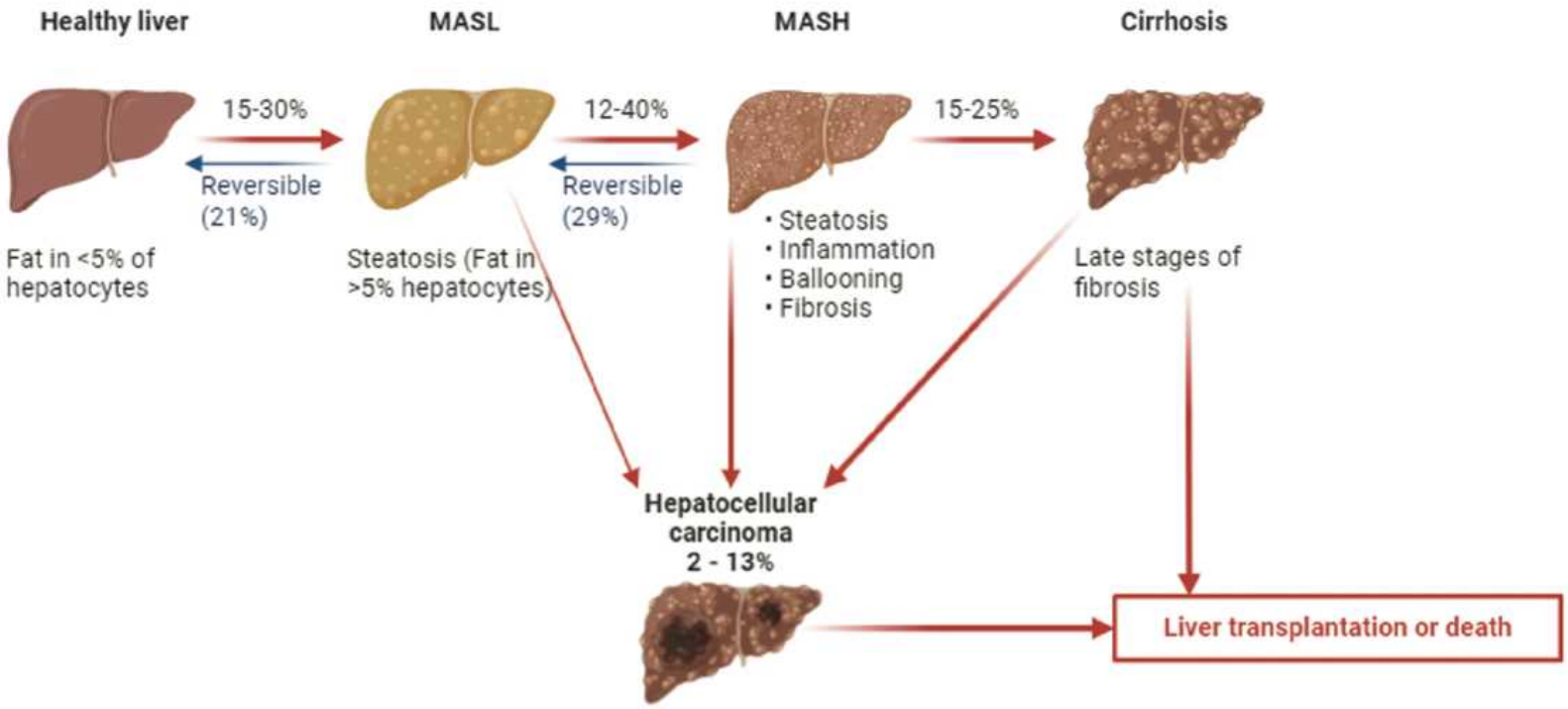
Silent non-alcoholic fatty liver disease—a clinical–histological study

Results: **Fifty-eight of the 80 patients enrolled had varying degrees of non-alcoholic steatohepatitis, of these 26 had fibrosis and 8 silent cirrhosis. The association of metabolic-syndrome, female-sex, a long-history of obesity and body mass index > 45 were considered to be independent risk-factors for fibrosis.**

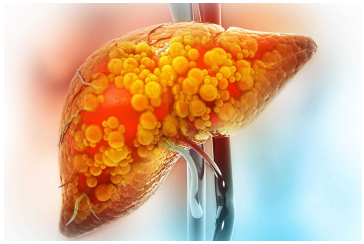


Rhythmic Fluctuations in Levels of Liver Enzymes During Menstrual Cycles

Metabolic dysfunction-associated steatotic liver disease (MASLD) spectrum



Natural history of metabolic dysfunction-associated steatotic liver disease (MASLD)



Fatty Liver Screening

When to suspect MASLD

— MASLD may be suspected in patients who fulfill any of the following criteria :

- Liver steatosis on imaging
- Unexplained elevation in liver enzymes
- Two or more metabolic risk factors (eg, obesity, dyslipidemia, pre- or established type 2 diabetes mellitus, hypertension)
- First-degree relative of a patient with MASLD cirrhosis

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Recommendations

- General population-based screening for SLD is not advised (**LoE 3, strong recommendation, strong consensus**).

Should a policy of screening for MASLD at risk of fibrotic disease (or fibrosis progression) in primary care or at the non-hepatology specialist level be implemented in the general population or only in individuals with cardiometabolic risk factors?

- Healthcare providers should look for MASLD with liver fibrosis either in individuals with (A) type 2 diabetes or (B) abdominal obesity and ≥1 additional metabolic risk factor(s) (Table 3) or (C) abnormal liver function tests (**LoE 3, strong recommendation, consensus**).

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Guidance statements:

9. General population-based screening for NAFLD is not advised.

10. All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4.

11. High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis.

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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Recommendations

4.22a Screen adults with type 2 diabetes or with prediabetes, particularly those with obesity or other cardiometabolic risk factors or established cardiovascular disease, for their risk of having or developing cirrhosis related to metabolic dysfunction–associated steatohepatitis (MASH) using a calculated fibrosis-4 index (FIB-4) even if they have normal liver enzymes.

4.22b Adults with diabetes or prediabetes with persistently elevated plasma aminotransferase levels for >6 months and low FIB-4 should be evaluated for other causes of liver disease.

4.23 Adults with type 2 diabetes or prediabetes with a FIB-4 ≥1.3 should have additional risk stratification by liver stiffness measurement with transient elastography, or, if unavailable, the enhanced liver fibrosis (ELF) test.

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

2025 American Diabetes Association.

WHAT IS THE PREVALENCE AND INCIDENCE OF FATTY LIVER IN DIABETIC PATIENTS AND OBESE INDIVIDUALS?

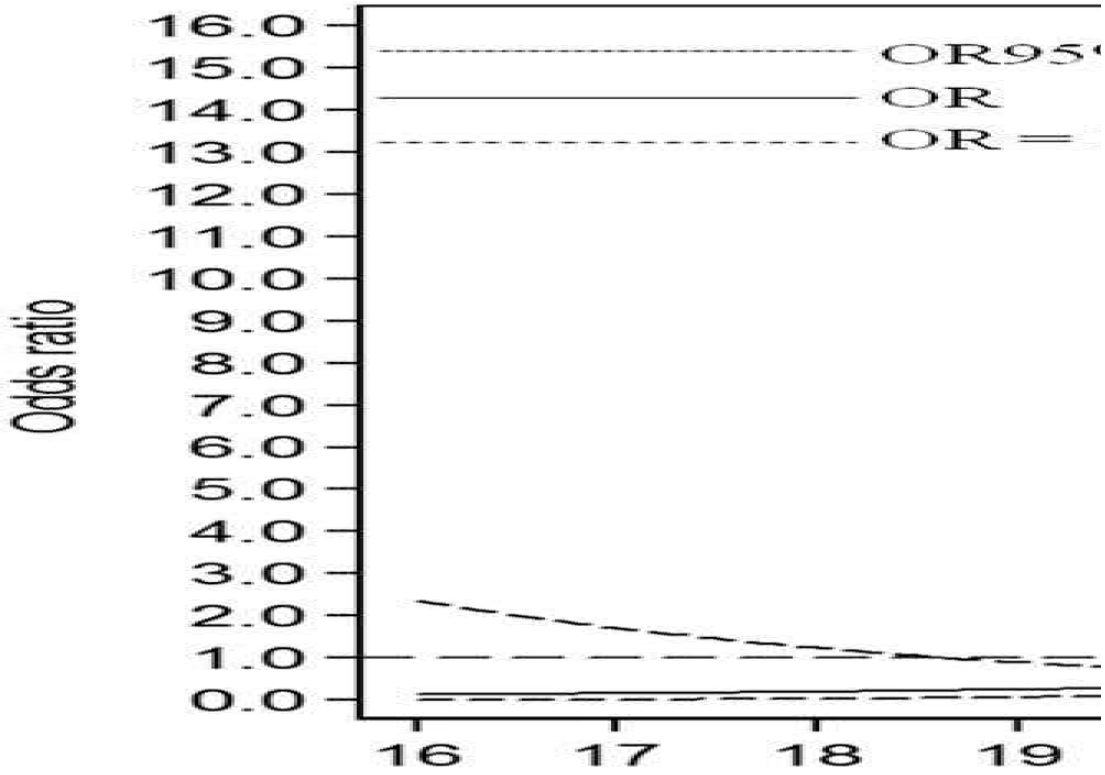
Hamidreza Zakeri,MD

Prevalence and incidence of fatty liver in diabetes and obesity

Prevalence in Diabetes

Obesity as a Key Driver

Association between BMI and fatty liver risk



Sci Rep 8, 15273 (2018).

Synergy of Diabetes and Obesity

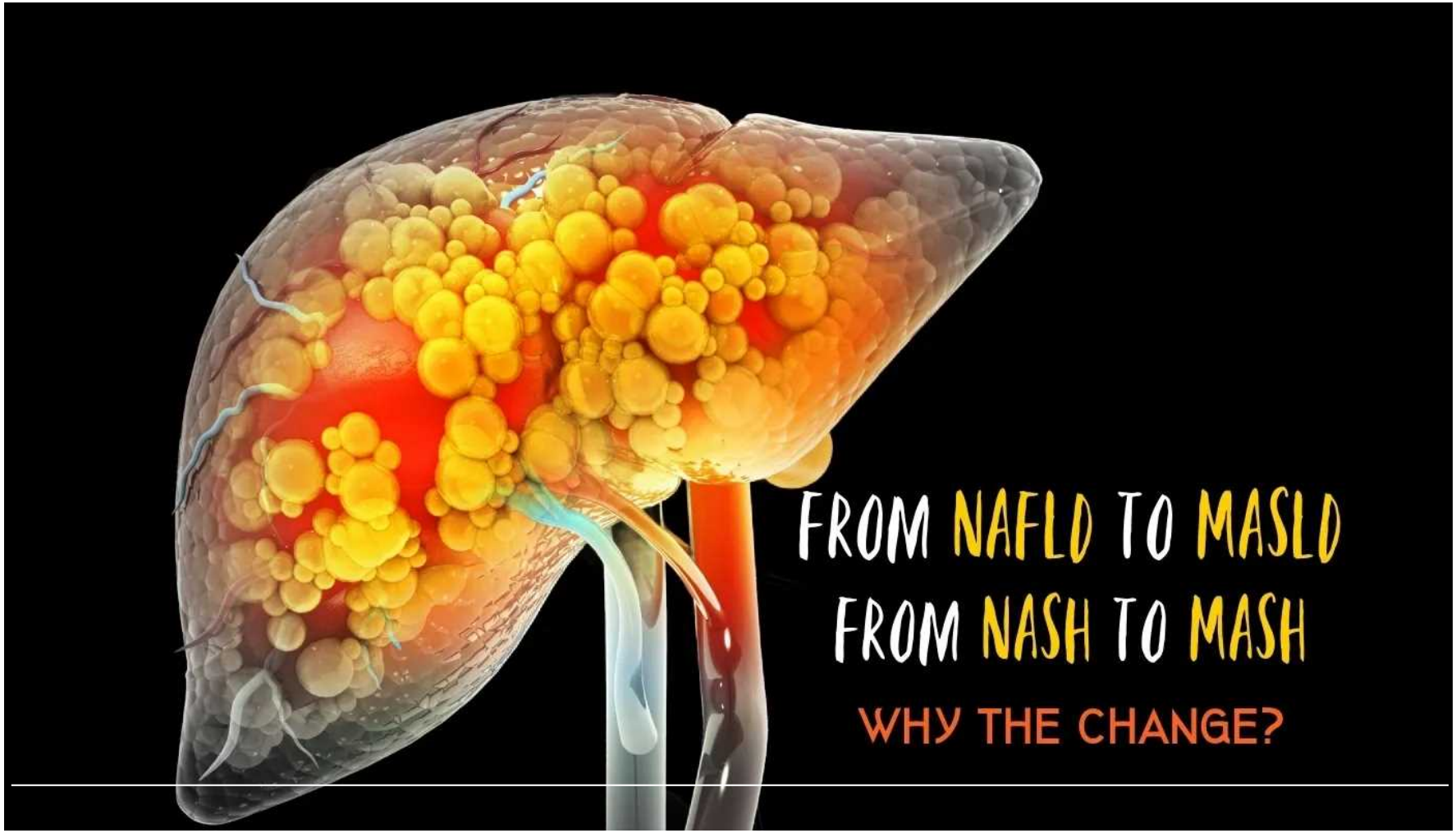
Fibrosis and Cirrhosis Risks

Public Health Implications

CASE PRESENTATION

WHAT IS THE DEFINITION OF MASLD?
ROLE OF ALCOHOL USE

Mohsen Rajabnia,MD


FROM NAFLD TO MASLD
FROM NASH TO MASH
WHY THE CHANGE?

ON

DISEASES OF THE LIVER.

BY

GEORGE BUDD, M.D. F.R.S.,

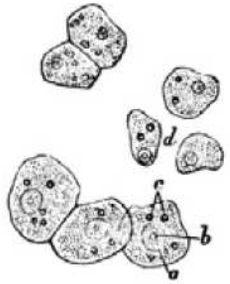
PROFESSOR OF MEDICINE IN KING'S COLLEGE, LONDON; AND FELLOW OF CAIUS COLLEGE, CAMBRIDGE.

LONDON:

JOHN CHURCHILL, PRINCES STREET, SOHO.

MDCCCXLV.

Nucleated cells, from a liver in a state of fatty degeneration: *a*, nucleus; *b*, nucleolus; *c*, *c*, *c*, fatty globules. (Bowman.)



Nucleated cells of the liver; *a*, the nucleus; *b*, the nucleolus; *c*, fat-globules; *d*, cells of small size, detached.

George Budd. On diseases of the liver (1857).

CELLULAR PATHOLOGY

AS BASED UPON

PHYSIOLOGICAL AND PATHOLOGICAL HISTOLOGY.

TWENTY LECTURES

DELIVERED IN THE

PATHOLOGICAL INSTITUTE OF BERLIN

DURING THE

MONTHS OF FEBRUARY, MARCH, AND APRIL, 1858.

BY

RUDOLF VIRCHOW,

PUBLIC PROFESSOR IN ORDINARY OF PATHOLOGICAL ANATOMY, GENERAL PATHOLOGY AND THERAPEUTICS, IN THE UNIVERSITY OF BERLIN; DIRECTOR OF THE PATHOLOGICAL INSTITUTE, AND PHYSICIAN TO THE CHARITÉ HOSPITAL, ETC. ETC.

TRANSLATED FROM THE SECOND EDITION OF THE ORIGINAL,

BY

FRANK CHANCE, B.A., M.B. CANTAB.

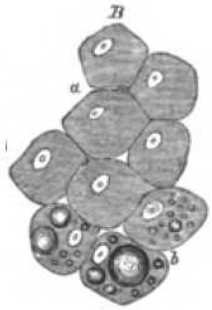
LICENTIATE OF THE ROYAL COLLEGE OF PHYSICIANS; PHYSICIAN TO THE SHEFFIELD PUBLIC DISPENSARY AND INFIRMARY.

WITH

NOTES AND NUMEROUS EMENDATIONS, PRINCIPALLY FROM MS. NOTES OF THE AUTHOR,

AND

ILLUSTRATED BY 144 ENGRAVINGS ON WOOD.



Diagrams of hepatic cells. with accumulation of fat (fatty degeneration, fatty liver).

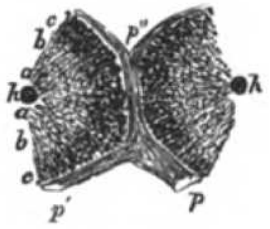
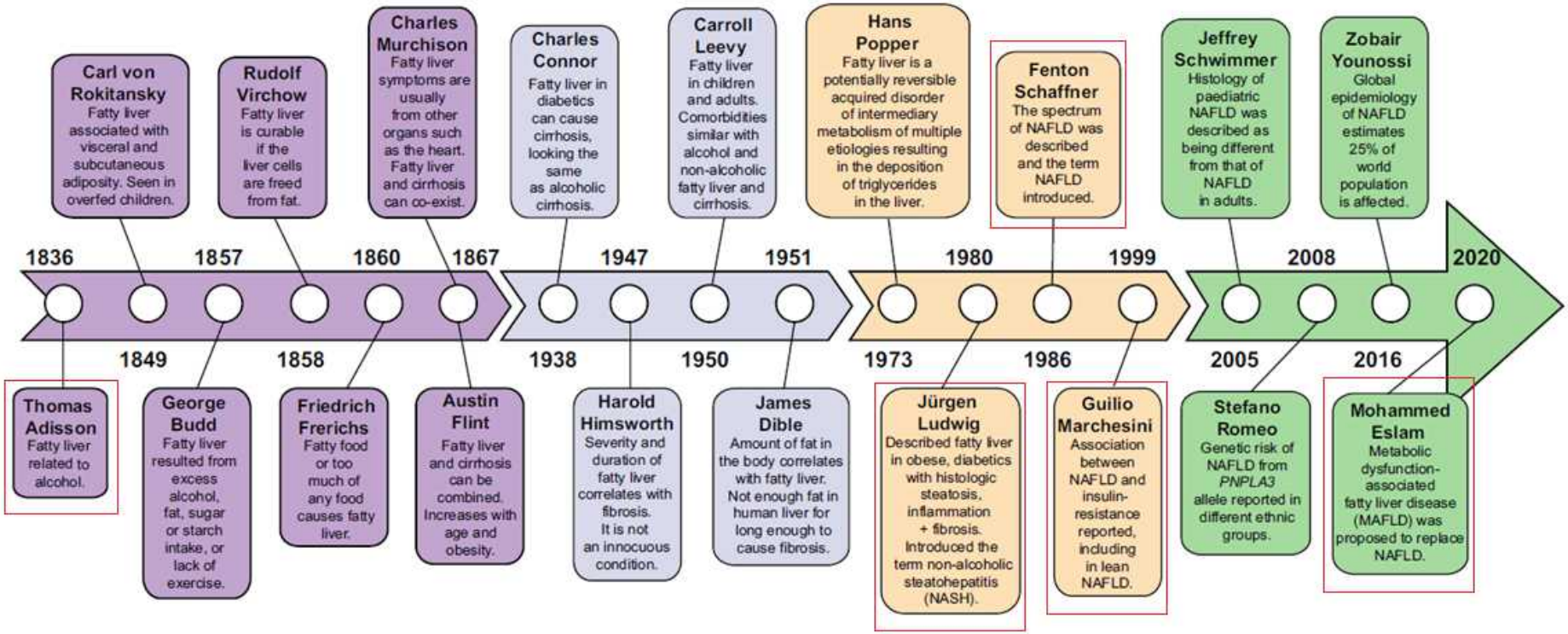


Fig. 110. The adjoining halves of two hepatic acini. *p*. A branch of the portal vein with branches *p' p''*, corresponding to the interlobular veins. *h, h*. Transverse sections of the intralobular, or hepatic, vein. *a*. The pigment zone, *b* the amyloid zone, *c* the fat zone. 20 diameters.

Virchow R, Chance F. Cellular Pathology as based upon physiological and pathological histology (1858).



Timeline summarising the evolution of fatty liver knowledge.

Review > Prog Liver Dis. 1986:8:283-98.

Nonalcoholic fatty liver disease

F Schaffner, H Thaler

PMID: 3086934

Expert Opinion

JOURNAL OF HEPATOLOGY

A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement

Mohammed Eslam[1,*,†], Philip N. Newsome[2,*,†], Shiv K. Sarin[3], Quentin M. Anstee[4], Giovanni Targher[5], Manuel Romero-Gomez[6], Shira Zelber-Sagi[7], Vincent Wai-Sun Wong[8], Jean-François Dufour[9], Jörn M. Schattenberg[10], Takumi Kawaguchi[11], Marco Arrese[12], Luca Valenti[13], Gamal Shiha[14], Claudio Tiribelli[15], Hannele Yki-Järvinen[16], Jian-Gao Fan[17], Henning Grønbæk[18], Yusuf Yilmaz[19], Helena Cortez-Pinto[20], Claudia P. Oliveira[21], Pierre Bedossa[22], Leon A. Adams[23], Ming-Hua Zheng[24], Yasser Fouad[25], Wah-Kheong Chan[26], Nahum Mendez-Sanchez[27], Sang Hoon Ahn[28], Laurent Castera[29], Elisabetta Bugianesi[30], Vlad Ratziu[31,*,‡], Jacob George[1,*,‡]

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DOI: 10.1097/HEP.0000000000000520

AASLD

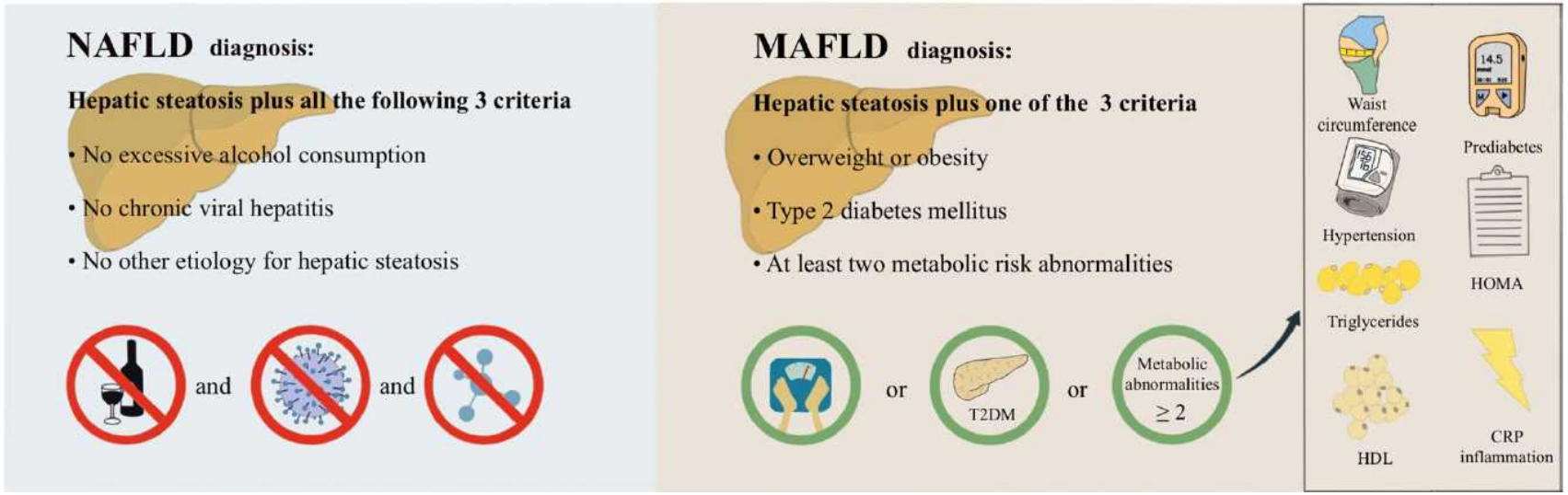
SPECIAL ARTICLE

OPEN

A multisociety Delphi consensus statement on new fatty liver disease nomenclature

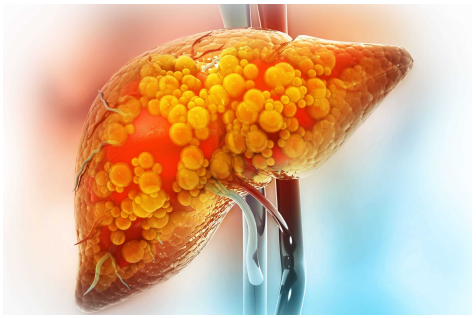
Hepatology. 2023;78:1966–1986

***NAFLD* (1986) → *MAFLD* (2020) → *MASLD* (2023)**


NAFLD diagnosis:
Hepatic steatosis plus all the following 3 criteria
• No excessive alcohol consumption
• No chronic viral hepatitis
• No other etiology for hepatic steatosis
and
and
MAFLD diagnosis:
Hepatic steatosis plus one of the 3 criteria
• Overweight or obesity
• Type 2 diabetes mellitus
• At least two metabolic risk abnormalities
or
T2DM
or
Metabolic abnormalities ≥ 2
Waist circumference
Prediabetes
Hypertension
HOMA
Triglycerides
HDL
CRP inflammation

What was the impetus for the name change?

- "non-alcoholic" → not accurately reflect the current understanding of ~~**disease drivers**~~.
- "***alcohol***" intake is common in many cultures → left many patients outside the NAFLD diagnostic category
- ***Poor categorization*** and heterogeneous (lean NAFLD, secondary, etc)
- **Lower awareness** even in patients with metabolic risk factor
- **Stigmatization** from names including "alcoholic" or "Fatty"



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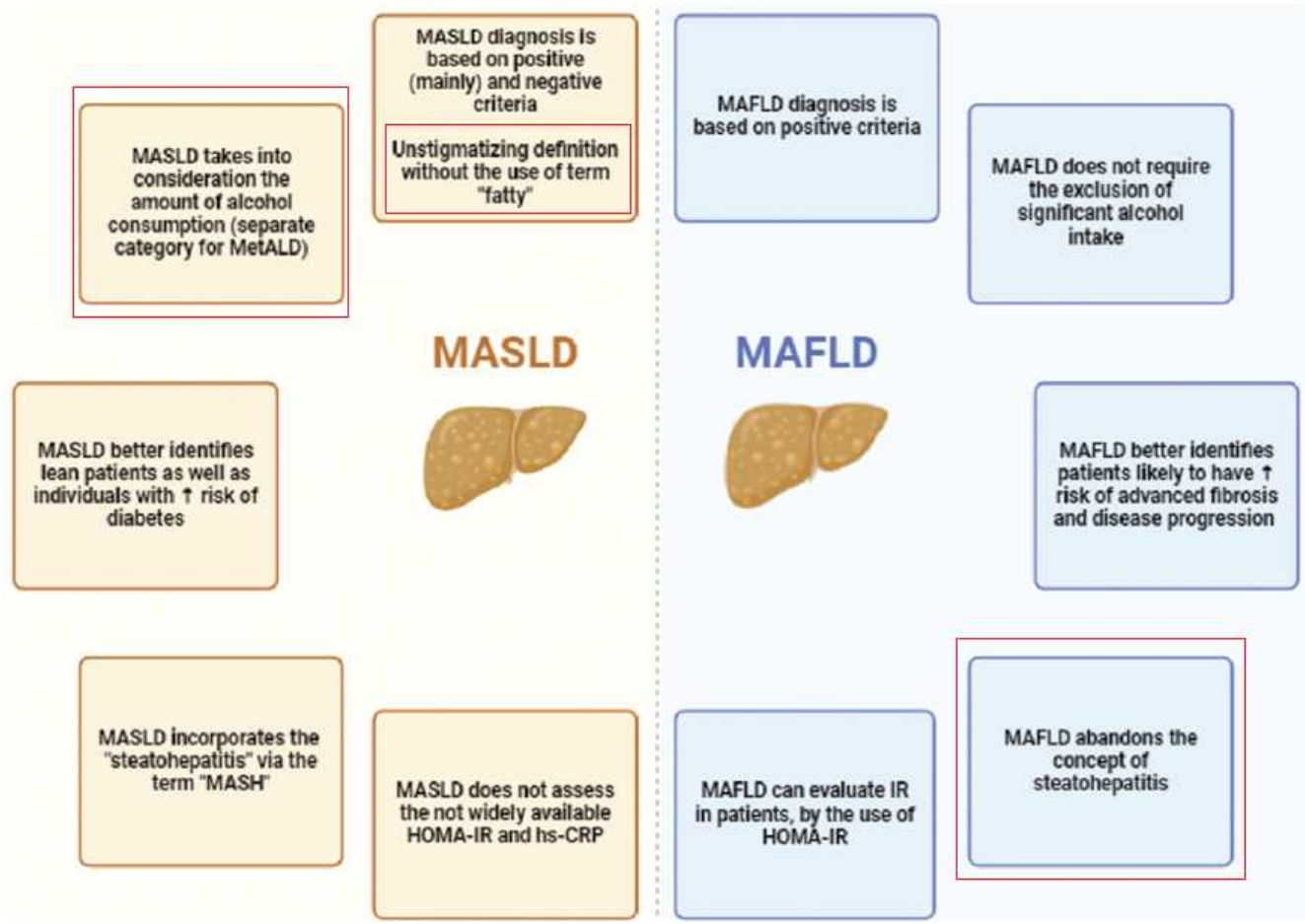
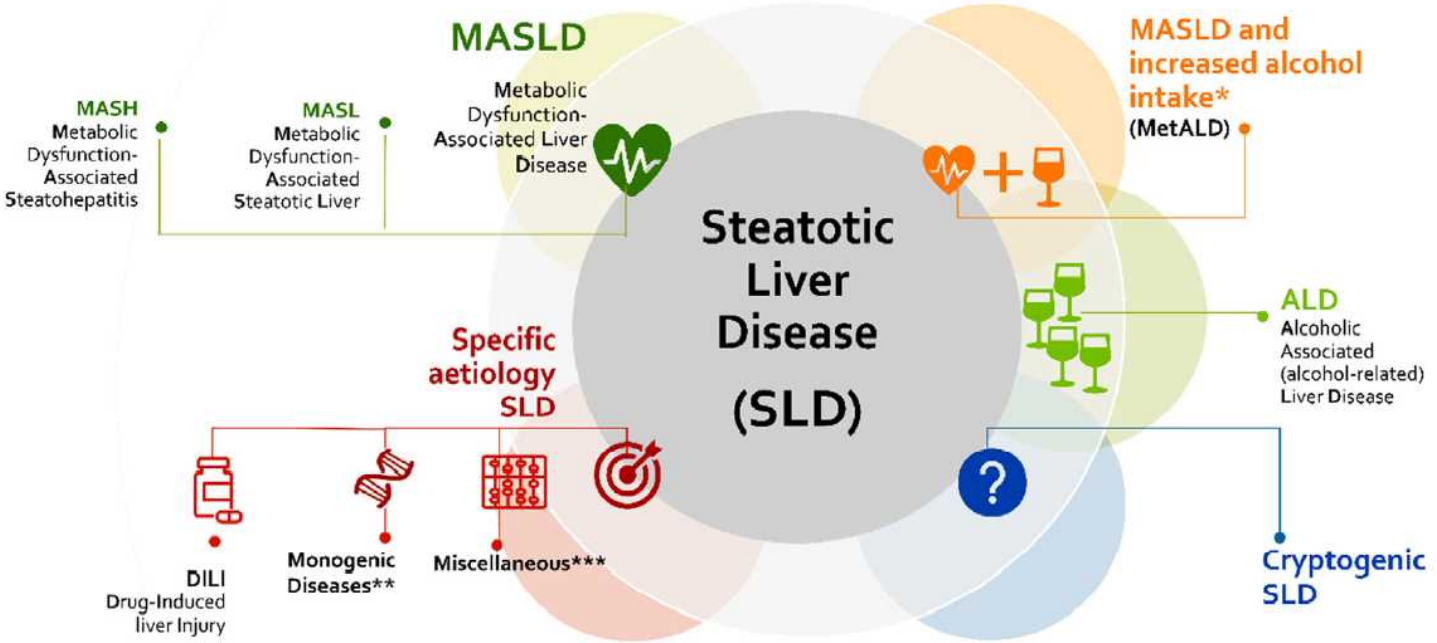
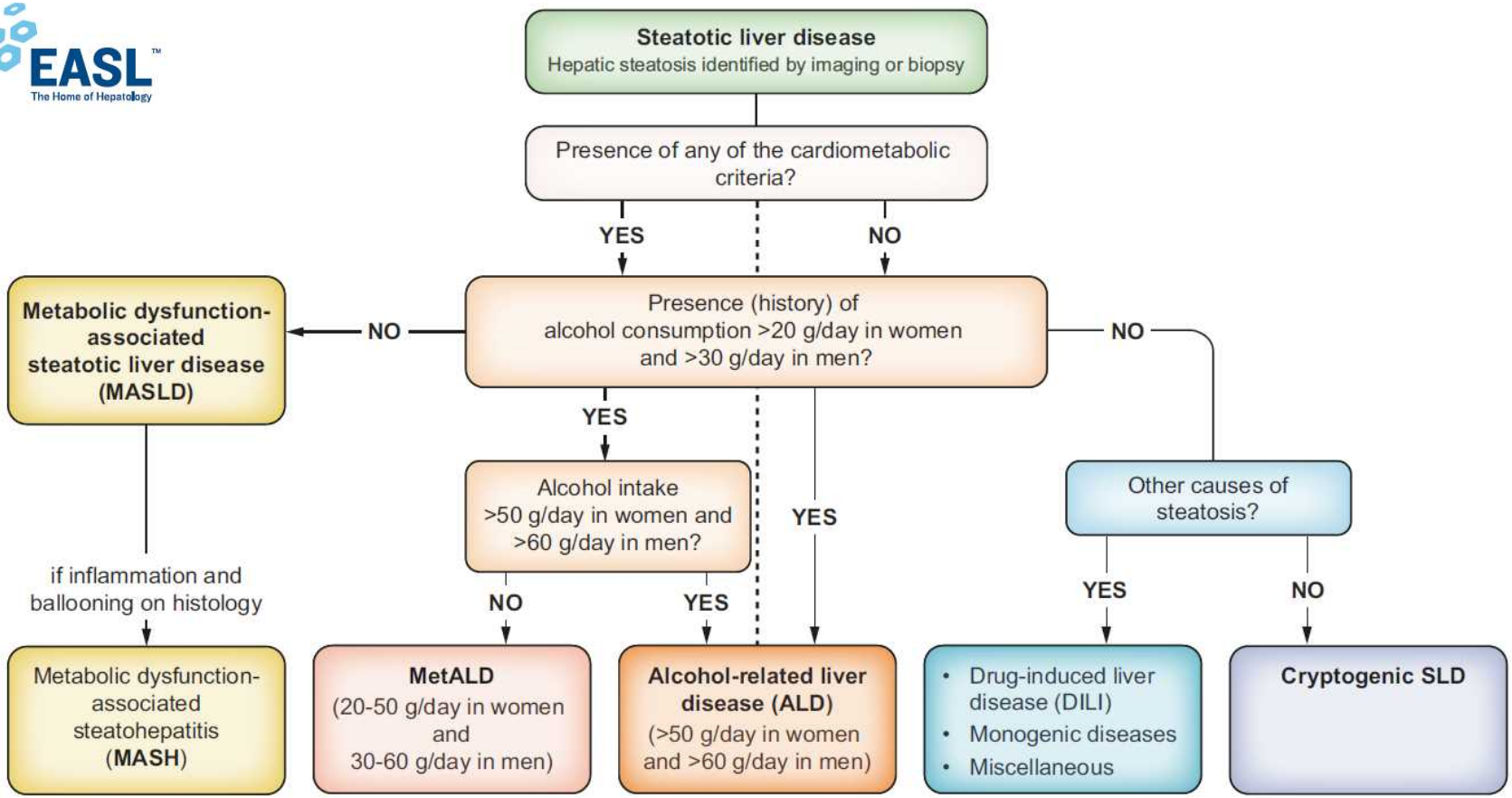
A multisociety Delphi consensus statement on new fatty liver disease nomenclature

Hepatology. 2023;78:1966–1986



Comparison of the main characteristics and advantages of MASLD and MAFLD


MASLD
MASH
Metabolic Dysfunction-Associated Steatohepatitis
MASL
Metabolic Dysfunction-Associated Steatotic Liver
Metabolic Dysfunction-Associated Liver Disease
MASLD and increased alcohol intake*
(MetALD)
Steatotic Liver Disease
(SLD)
ALD
Alcoholic Associated (alcohol-related) Liver Disease
Specific aetiology SLD
DILI
Drug-Induced liver Injury
Monogenic Diseases**
Miscellaneous***
Cryptogenic SLD

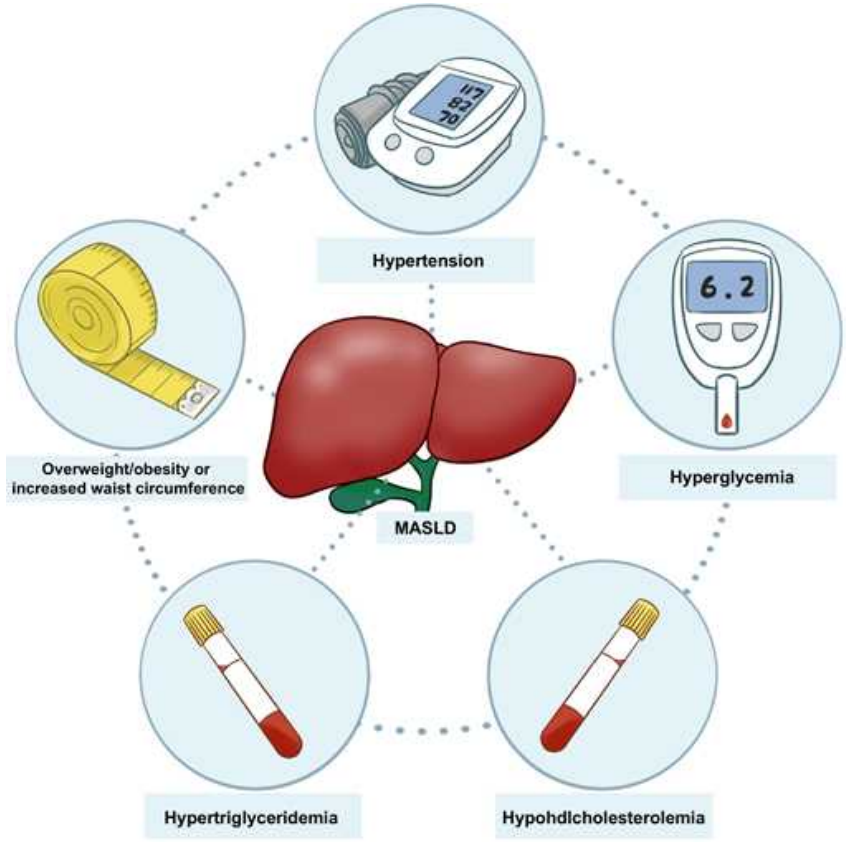


Flow-chart for SLD and its sub-categories.

Adult Criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

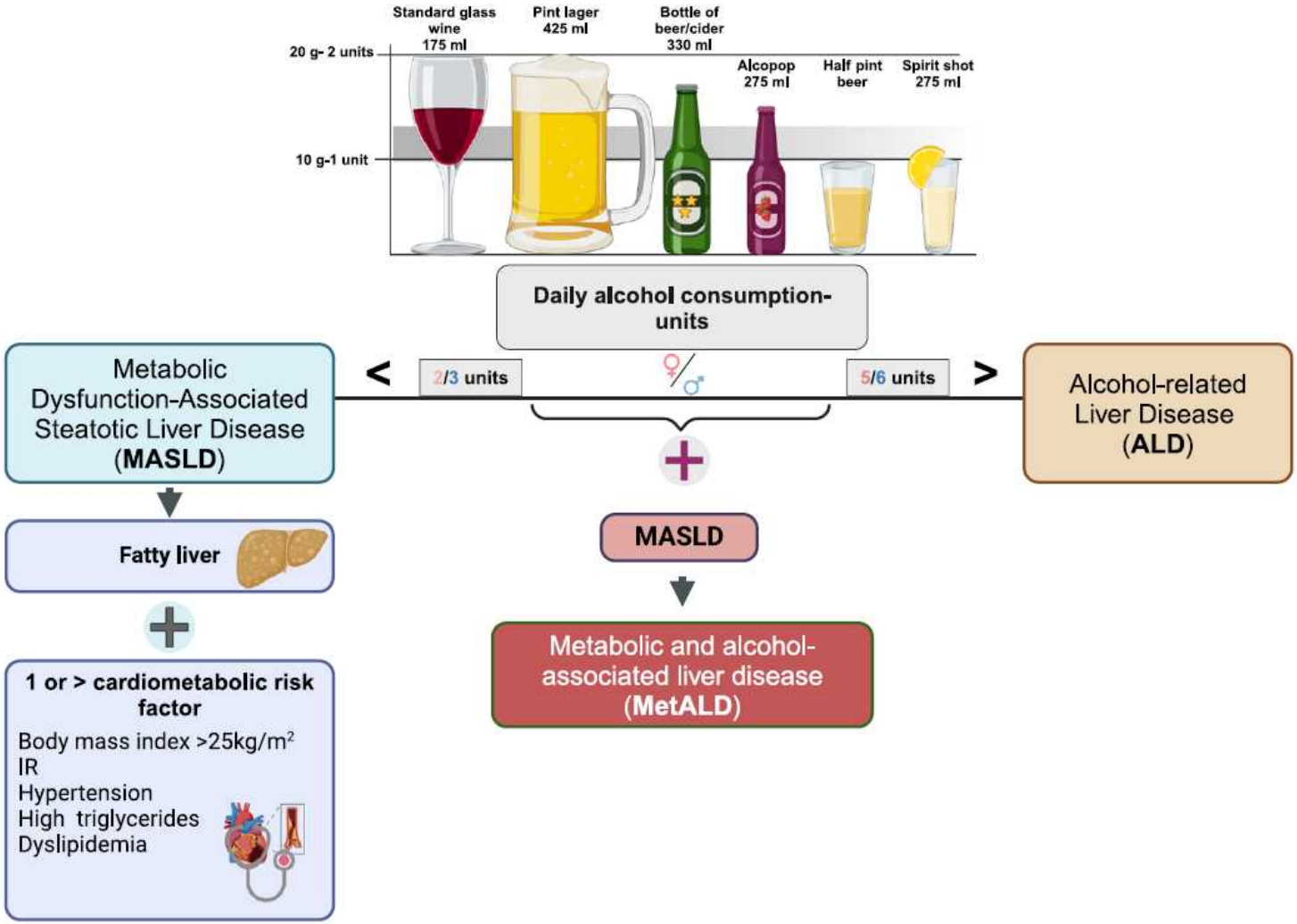


Alternative Causes of Hepatic Steatosis

- Alcoholic liver disease
- Hepatitis C (particularly genotype 3)
- Inborn errors of metabolism
  - Abetalipoproteinemia
  - Cholesterol ester storage disease
  - Galactosemia
  - Glycogen storage disease
  - Hereditary fructose intolerance
  - Homocystinuria
  - Systemic carnitine deficiency
  - Tyrosinemia
  - Weber-Christian syndrome
  - Wilson's disease
  - Wolman's disease
- Medications
- Miscellaneous
  - Industrial exposure to petrochemical
  - Inflammatory bowel disease
  - Lipodystrophy
  - Bacterial overgrowth
  - Starvation
  - Parenteral nutrition
- Surgical procedures
  - Bilopancreatic diversion
  - Extensive small-bowel resection
  - Gastric bypass
  - Jejunoileal bypass
- Reye's syndrome
- Acute fatty liver of pregnancy
- HELLP syndrome (*h*emolytic anemia, elevated *l*iver enzymes, *l*ow *p*latelet count)

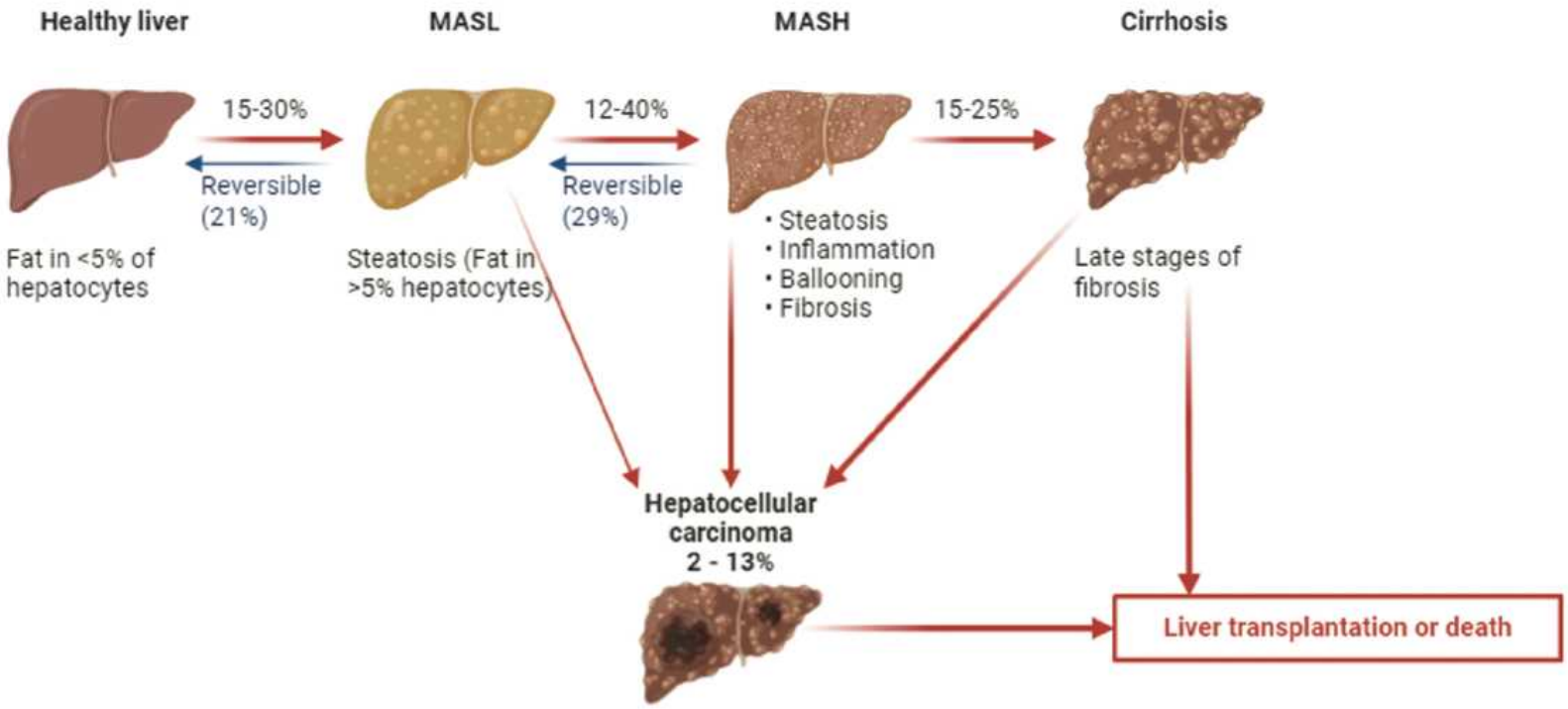
Medications Associated with Hepatic Steatosis

- Cytotoxic and cytostatic drugs
  - L-Asparaginase
  - Azacitidine
  - Azaserine
  - Bleomycin
  - Methotrexate
  - Puromycin
  - Tetracycline
  - Doxycycline
- Metals
  - Antimony
  - Barium salts
  - Chromates
  - Phosphorus
  - Rare earths of low atomic number
  - Thallium compounds
  - Uranium compounds
- Other drugs and toxins
  - Amiodarone
  - 4,4′-Diethylaminoethoxyhexesterol
  - Ethionine
  - Ethyl bromide
  - Estrogens
  - Glucocorticoids
  - Highly active antiretroviral therapy
  - Hydralazine
  - Hypoglycin
  - Orotate
  - Perhexiline maleate
  - Safrole
  - Tamoxifen


Standard glass wine 175 ml
Pint lager 425 ml
Bottle of beer/cider 330 ml
Alcopop 275 ml
Half pint beer
Spirit shot 275 ml
20 g- 2 units
10 g-1 unit
Daily alcohol consumption-units
Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
<
2/3 units
♀/♂
5/6 units
>
Alcohol-related Liver Disease (ALD)
Fatty liver
MASLD
1 or > cardiometabolic risk factor
Body mass index >25kg/m²
IR
Hypertension
High triglycerides
Dyslipidemia
Metabolic and alcohol-associated liver disease (MetALD)

		Cardiometabolic criteria	Alcohol intake effect
1		BMI ≥ 25 kg/m2 [23 Asia] OR WC> 94 cm (M) 80 cm (F) OR ethnicity adjusted	Weight gain due to its high caloric content and its ability to alter fat metabolism
2		Fasting serum glucose ≥ 5.6 mmol/L OR 2-hour post-load glucose levels ≥ 7.8 mmol/L OR HbA1c ≥ 5.7% OR type 2 diabetes OR treatment for type 2 diabetes	Acute consumption can cause hyperglycemia. Overall effect on A1c is unclear and may depend on genetic and epigenetic factors
3		Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug treatment	Increase in blood pressure due to vasoconstriction, which raises peripheral vascular resistance.
4		Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] OR lipid lowering treatment	Increases triglyceride synthesis in the liver and reduces its degradation, contributing to hypertriglyceridemia
5		Plasma HDL-cholesterol ≤ 1.0 mmol/L (M) and ≤ 1.3 mmol/L (F) OR lipid lowering treatment	In the long term, it leads to an increase in HDL but also other atherogenic lipoproteins

Metabolic dysfunction-associated steatotic liver disease (MASLD) spectrum



Natural history of metabolic dysfunction-associated steatotic liver disease (MASLD)

Farhad Hosseinpanah, MD

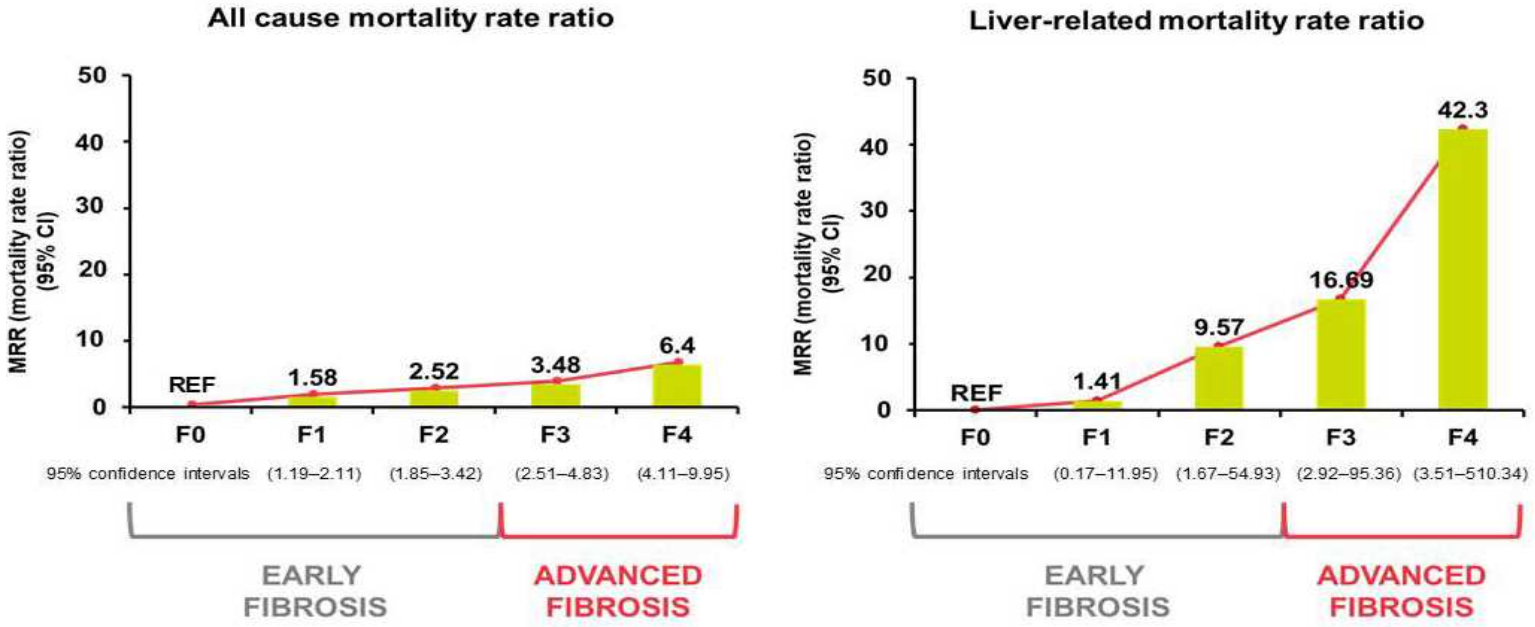
WHAT ARE THE DIAGNOSTIC METHODS OF MASLD?

Non-invasive Assessment of SLD

Hosseinpanah F, MD
Professor of Endocrinology and Metabolism
Shahid Beheshti University of Medical Sciences

The risk of liver-related mortality increases exponentially with increasing fibrosis stage

Impact of fibrosis stage on liver-related mortality in a meta-analysis of five multinational cohorts (17,452 PYF)



Dulai PS, et al. Hepatology 2017

Noninvasive Assessment of NSH and Advanced Fibrosis in NAFLD

- Liver biopsy is currently the most reliable approach for identifying the presence of steatohepatitis (SH) and fibrosis in patients with NAFLD

- But it is generally acknowledged that biopsy is limited by cost, sampling error, and procedure-related morbidity and mortality

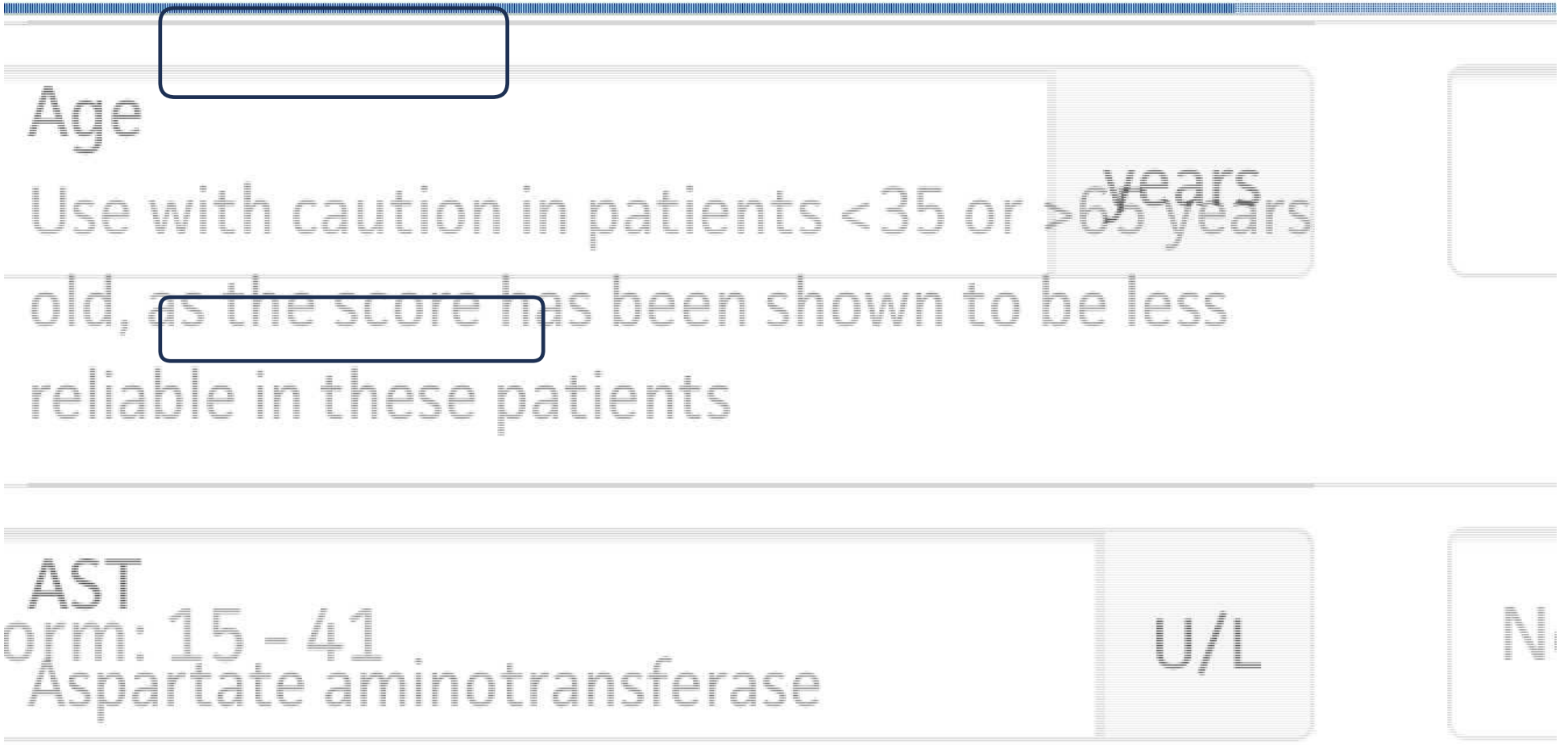
- Therefore, there has been significant interest in developing clinical prediction rules and noninvasive biomarkers for identifying SH in patients with NAFLD

	Components and calculation	Rule out cut-point	Rule in cut-point	Limitations	Strengths
Indirect serum fibrosis biomarkers					
FIB-4					
Direct serum fibrosis biomarkers					
FibroSpect NASH	Proprietary algorithm combining HA, TIMP-1, and α2-macroglobulin	<16	Not reported	Proprietary test; lower NPV	Easy to interpret results
FIB-C3	−5·939 + (0·053 × age) + (0·076 × BMI) + (1·614 × T2DM) − (0·009 × platelet count) + (0·071 × PRO-C3)	<−0·4	>−0·4	Requires non-routine clinical data; lower NPV	Uses a single threshold for risk stratification
ELF	−7·412 + [ln(HA) × 0·681) + [ln(PIIINP × 0·775] + [ln(TIMP) × 0·494)	<7·7	>9·8	Send-out testing; cost	High NPV
Imaging fibrosis biomarkers					
VCTE	kPa	<8	>12	Multiple potential confounders; requires experienced operator	Point of care; high NPV
MRE	kPa	<2·5	>3·6	High cost; not widely available	Highly accurate; few confounders

NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. FIB-4=Fibrosis-4 index. AST=aspartate aminotransferase. ALT=alanine aminotransferase. PPV=positive predictive value. NPV=negative predictive value. HA=hyaluronic acid. TIMP-1=tissue inhibitor of metalloproteinase-1. T2DM=type 2 diabetes. PIIINP=procollagen III-peptide. ELF=enhanced liver fibrosis. VCTE=vibration controlled transient elastography. MRE=magnetic resonance elastography.

Lancet Gastroenterol Hepatol. 2023 Apr 12;S2468-1253

https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis



Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

When to Use | Pearls/Pitfalls | Why Use

Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients	55	years
AST Aspartate aminotransferase	35	U/L
Platelet count	450	× 10⁹/L
ALT Alanine aminotransferase	56	U/L

0.57 points

	Components and calculation	Rule out cut-point	Rule in cut-point	Limitations	Strengths
Indirect serum fibrosis biomarkers					
FIB-4					
Direct serum fibrosis biomarkers					
FibroSpect NASH	Proprietary algorithm combining HA, TIMP-1, and α2-macroglobulin	<16	Not reported	Proprietary test; lower NPV	Easy to interpret results
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ELF	−7·412 + [ln(HA) × 0·681) + [ln(PIIINP) × 0·775] + [ln(TIMP) × 0·494)	<7·7	>9·8	Send-out testing; cost	High NPV
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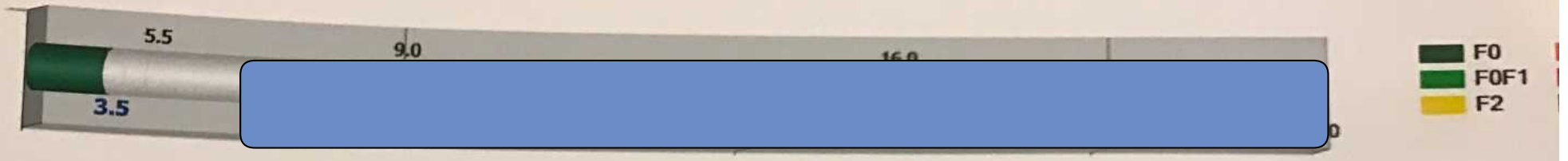
Lancet Gastroenterol Hepatol. 2023 Apr 12;S2468-1253

Vibration-controlled transient elastography (VCTE

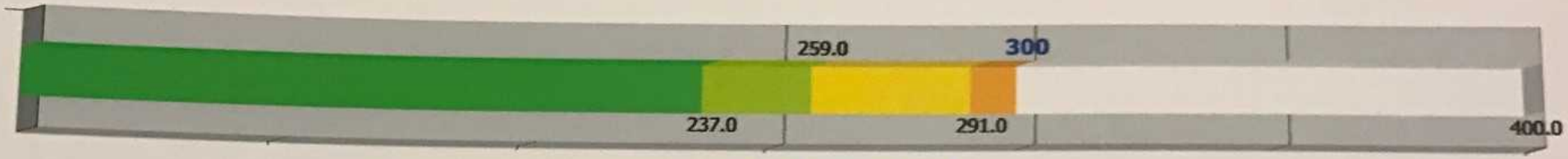
- Measures the speed of a mechanically generated shear wave across the liver to derive a liver stiffness measurement (LSM), a marker of hepatic fibrosis.

- Measuring the attenuation of ultrasound signal through the liver is used to derive the controlled attenuation parameter (CAP), which is as a marker of hepatic steatosis

Diagnosis: None Alcohol Fatty Liver Disease



Fibro Score = 3.5



CAP Score = 300

Fibroscan

Patient Score: **3.5 (kPa)**

Metavir Score: **F0**

CAP

Patient Score **300 (dB/m)**

Steatosis Percent **70%**

Steatosis Stage: **S3**

Fibrosis Staging

- LSM ≥7.0–8.1 kPa, mild fibrosis (F1)
- LSM ≥8.2–9.6 kPa, moderate fibrosis (F2)
- LSM ≥9.7–13.5 kPa, advanced fibrosis (F3)
- LSM ≥13.6 kPa, cirrhosis (F4)

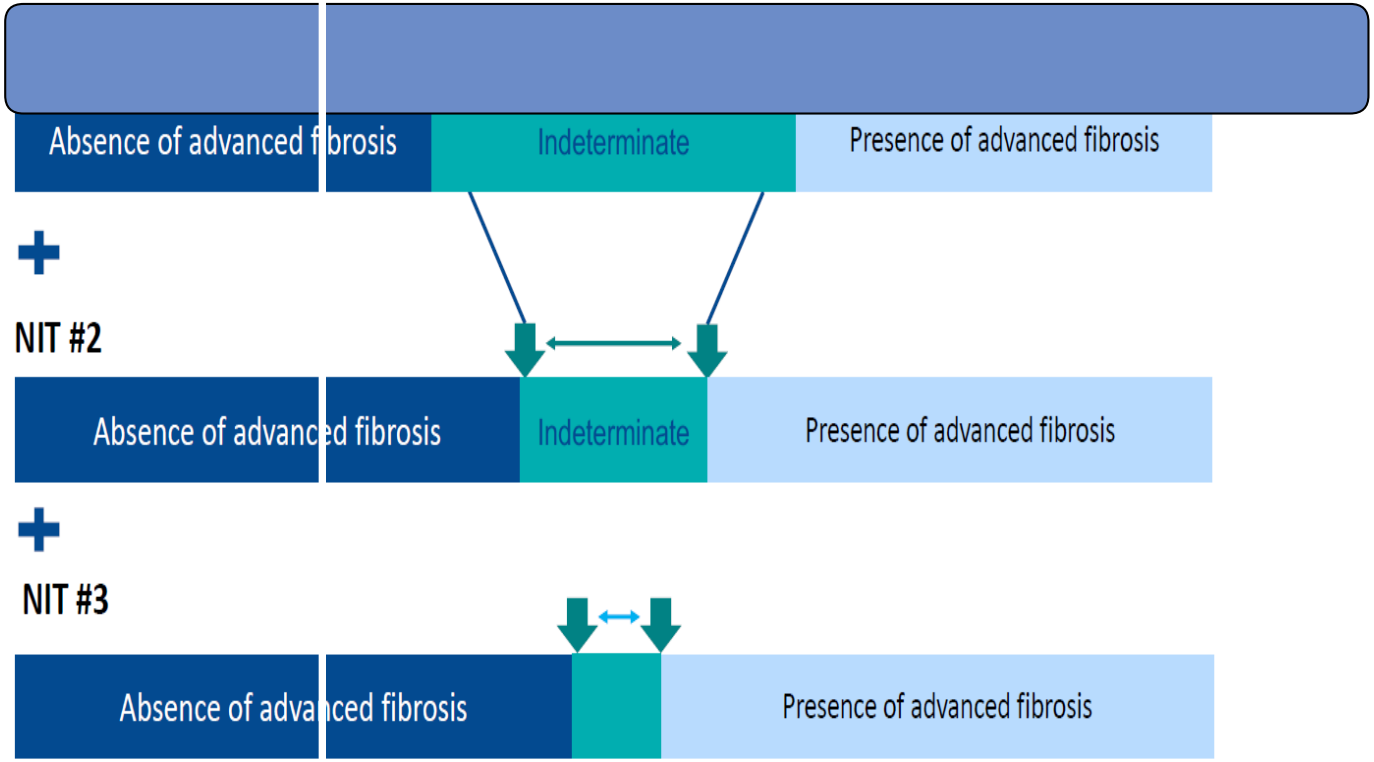
Gastroenterology 2019;156:1717–1730

Steatosis Staging

- CAP 274–289 dB/m (S1 = mild)
- CAP 290–301 dB/m (S2= moderate)
- CAP ≥ 302 dB/m (S3=severe)

Gastroenterology 2019;156:1717–1730

Combining NITs to Improve Detection of Fibrosis



- Anstee QM, et al. *Hepatology.* 2019;70:1521-1530.

key points to remember

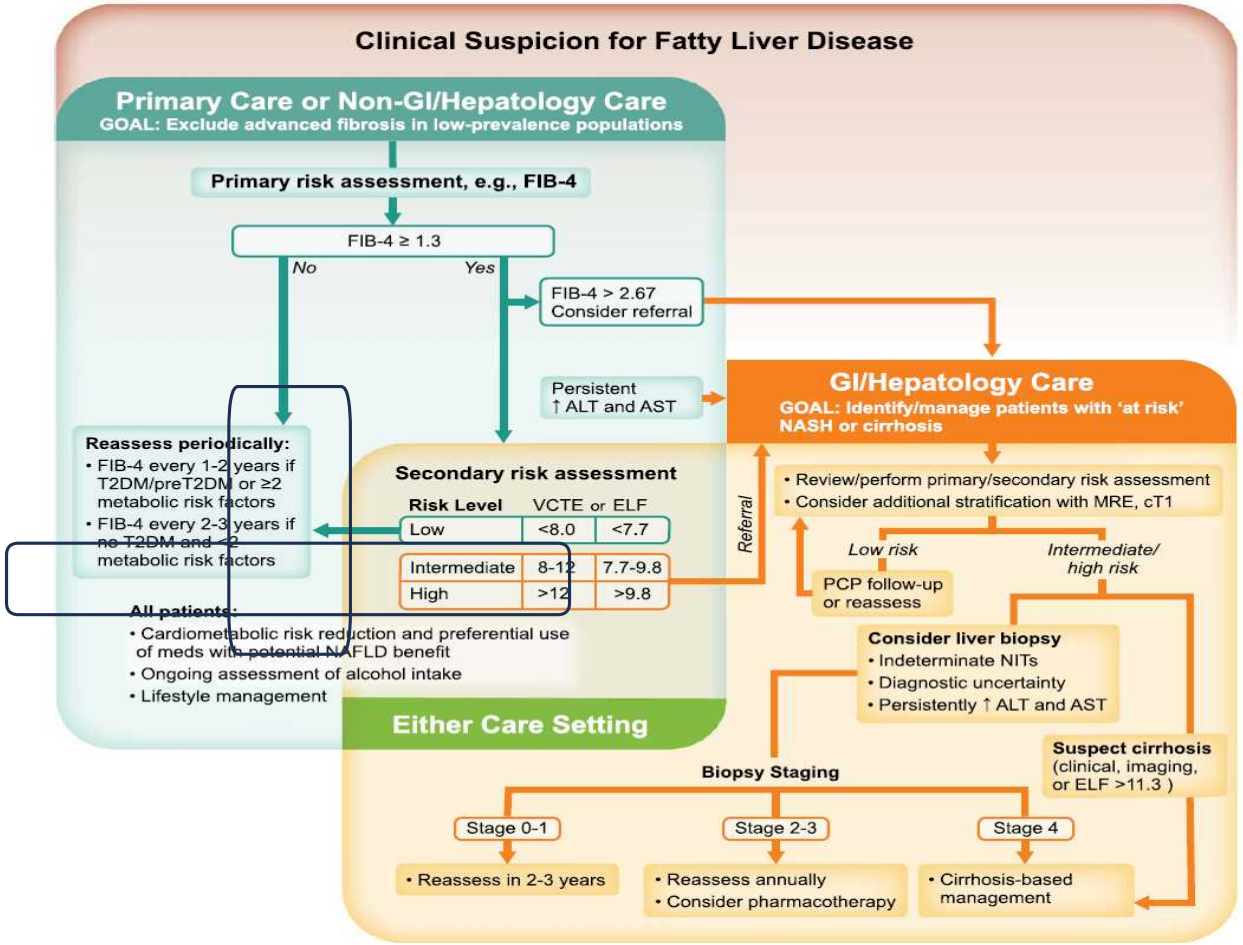
- All non-invasive tests for liver fibrosis are better at excluding advanced fibrosis than diagnosing it

- They have only modest positive predictive value for advanced fibrosis, but a much stronger negative predictive value

Modality type	Cut point: Likely	Cut point: Unlikely	Strengths/limitations, references/caveats
Detection of advanced fibrosis			
Ser[redacted]			
Fl[redacted]			threshold among high-risk individuals who have high pretest probability
NFS	≥0.672	<−1.44	No added cost; not accurate in age <35 y, people with obesity and/or type 2 diabetes[117,329,330]
ELF	≥9.8	<7.7	Blood test sent to a reference laboratory[331]; cost
FIBROSpect II	≥17	<17	Blood test sent to a reference laboratory[332]; cost
Imaging			
VCTE	≥12 kPa	<8 kPa	Point of care[4]
ARFI	≥1.34	<1.3	Cut points not well validated[333]
SWE	≥12 kPa	<8 kPa	Cut points not well validated[488]
MRE	≥3.63 kPa	<2.55 kPa	MRE LSM ≥3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)[334]

Modality	Cut point		
Identification of hepatic steatosis			
Imaging			
Ultrasound	"Detected"	NA	Semiquantitative assessment: mild/moderate/severe; low sensitivity with less severe steatosis[322]; steatosis can have similar echo characteristics as advanced fibrosis
FibroScan: CAP	≥288 dB/min		Limited accuracy for quantification[323]
MRI-PDFF	≥5%	<5%	Most sensitive across spectrum of steatosis; accurate to assess dynamic change[324]

Modality type	Cut point: Likely	Cut point: Unlikely	Strengths/limitations, references/caveats
Diagnosis of cirrhosis (rule-in or rule-out)	Rule-in	Rule-out	
CPR			
FIB-4	≥3.48	<1.67	90% specificity cut point for ruling-in and 90% sensitivity for ruling out cirrhosis, respectively[4,335]
ELF	≥11.3	<7.7	ELF ≥11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis[331]
Imaging			
VCTE	≥20 kPa	<8 kPa	LSM by VCTE ≥20 kPa is associated with cirrhosis, but for ruling out, cirrhosis optimal cut point is <8 kPa[4]
MRE	≥5 kPa	<3 kPa	LSM by MRE ≥5 kPa has a very good (approaches 95%) specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation[334,336]



Hepatology. 2023;77:1797–1835.

Diagnostic Algorithm for the Prevention of Cirrhosis in People With Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

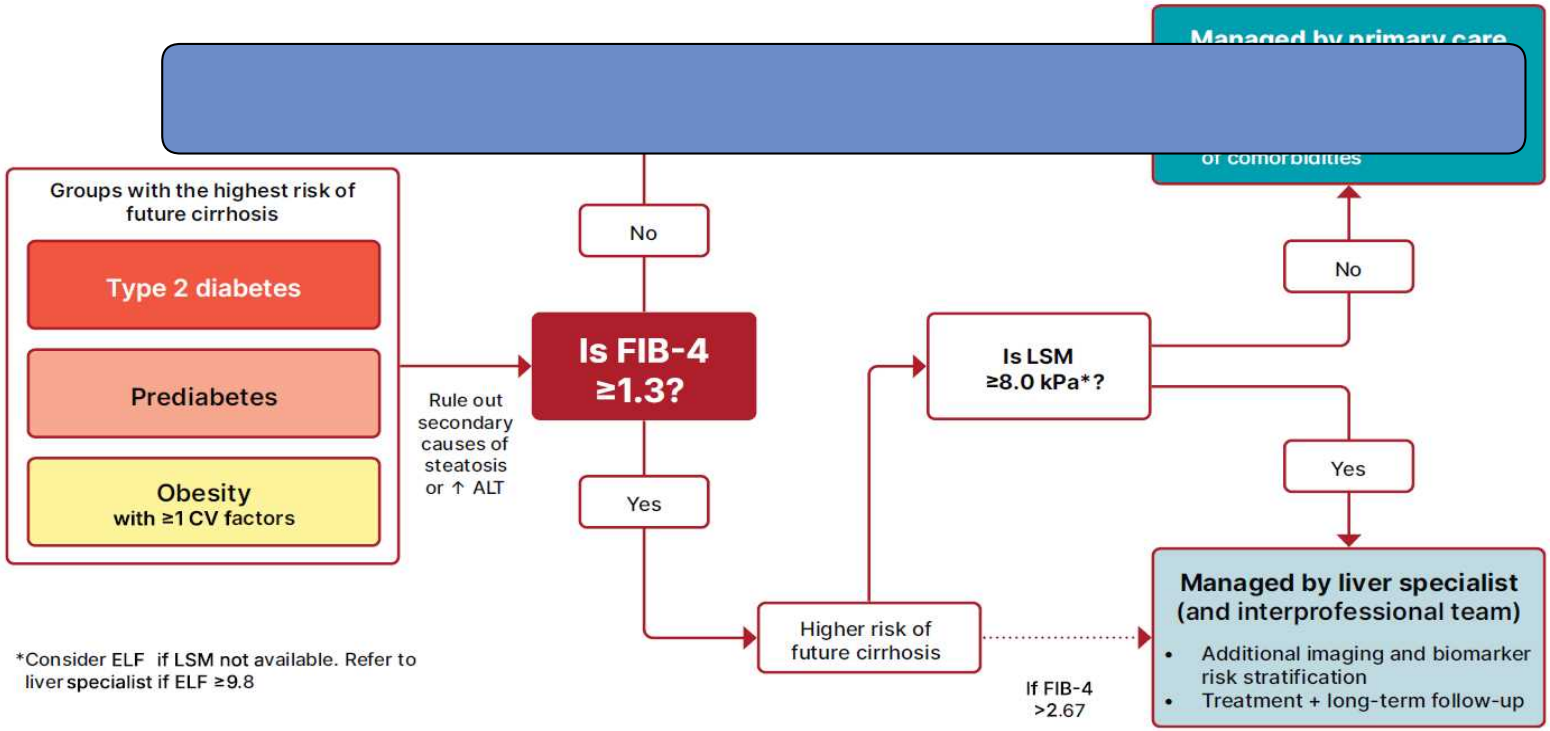


Figure 4.2—Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD). CV, cardiovascular; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement, as measured by vibration-controlled transient elastography. *In the absence of LSM, consider ELF a diagnostic alternative. If ELF ≥9.8, an individual is at high risk of metabolic dysfunction–associated steatohepatitis with advanced liver fibrosis (≥F3–F4) and should be referred to a liver specialist.

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Care in Diabetes - 2025. *Diabetes Care* 2025;48(Suppl. 1):S59-S85

ADA 2025

Recommendations

4.22a Screen adults with type 2 diabetes or with prediabetes, particularly those with obesity or other cardiometabolic risk factors or established cardiovascular disease, for their risk of having or developing cirrhosis related to metabolic dysfunction–associated steatohepatitis (MASH) using a calculated fibrosis-4 index (FIB-4) (derived from age, ALT, AST, and platelets [mdcalc.com/calc/2200/fibrosis4-fib-4-index-liver-fibrosis]), even if they have normal liver enzymes. **B**

4.22b Adults with diabetes or prediabetes with persistently elevated plasma aminotransferase levels for >6 months and low FIB-4 should be evaluated for other causes of liver disease. **B**

4.23 Adults with type 2 diabetes or prediabetes with a FIB-4 ≥1.3 should have additional risk stratification by liver stiffness measurement with transient elastography, or, if unavailable, the enhanced liver fibrosis (ELF) test. **B**

4.24 Refer adults with type 2 diabetes or prediabetes at higher risk for significant liver fibrosis (i.e., as indicated by FIB-4, liver stiffness measurement, or ELF) to a gastroenterologist or hepatologist for further evaluation and management. **B**

BP: 148/92 mmHg

BMI: 33.1 kg/m2 Waist circumference: 94 cm.

CASE PRESENTATION

HbA1c: 7.4%

Cholesterol: 224 mg/dl

Triglycerides: 131.5 mg/dl

HDL: 34.8 mg/dl, Non-HDL:189.2

WHY IS IT IMPORTANT TO ESTABLISH WHETHER OR NOT PATIENT HAS MAFLD/MASLD ?

IS THERE ANY LINK TO CARDIOVASCULAR COMPLICATIONS?

WHAT ABOUT MANAGEMENT OF DYSLIPIDEMIA?

Manouchehr Nakhjavani, MD

MASLD and Cardiovascular Complications

M. Nakhjavani, MD,
Endocrinology and Metabolic Disease
MAY 2025

Epidemiological data on MASLD and the risk of CVD complications

A systematic review and meta-analysis of population-based studies published between 1990 and 2019

Younossi ZM, Golabi P, Paik JM, et al.
The global epidemiology of Nonalcoholic fatty liver disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH): a systematic review.
Hepatology 2023;77:1335–47.

Epidemiological data on MASLD and the risk of CVD complications

- Pooled mortality rate 12.6 per 1000 person-years (95% CI 6.7 to 23.7)
- Cardiac specific mortality; 4.2 per 1000 person-years (95% CI 1.3 to 7.0)
- Extrahepatic cancer-specific mortality; 2.8 per 1000 person-years (95% CI 0.8 to 4.9)
- Liver specific mortality; 0.92 per 1000 person-years (95% CI 0.0 to 2.2).

Younossi ZM, Golabi P, Paik JM, et al. The global epidemiology Nonalcoholic fatty liver disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH): a systematic review.
Hepatology 2023;77:1335–47.

All-cause and cause-specific mortality rate among NAFLD patients

	Studies with ultrasound or FLI (n = 3)	Studies with ultrasound, FLI, or biopsy (n = 5)
	Rate per 1000 person-years (95% CI)	
Total NAFLD cases	8153	19,340
Total person-years	104,470	263,947
All-cause mortality	12.6 (6.68–23.67)	17.05 (10.31–28.05)
Cause-specific death		
Cardiac specific	4.20 (1.34–7.05)	5.54 (2.72–8.35)
Extrahepatic cancer specific	2.83 (0.78–4.88)	4.21 (1.94–6.48)
Liver specific	0.92 (0.00–2.21)	1.75 (0.58–2.91)

Abbreviation: FLI, fatty liver index.

DOI: 10.1097/HEP.0000000000000004
Hepatology. 2023;77:1335–1347

Nonalcoholic Fatty Liver Disease as a Potential Risk Factor for Cardiovascular Disease in Patients with Type 2 Diabetes: A Prospective Cohort Study

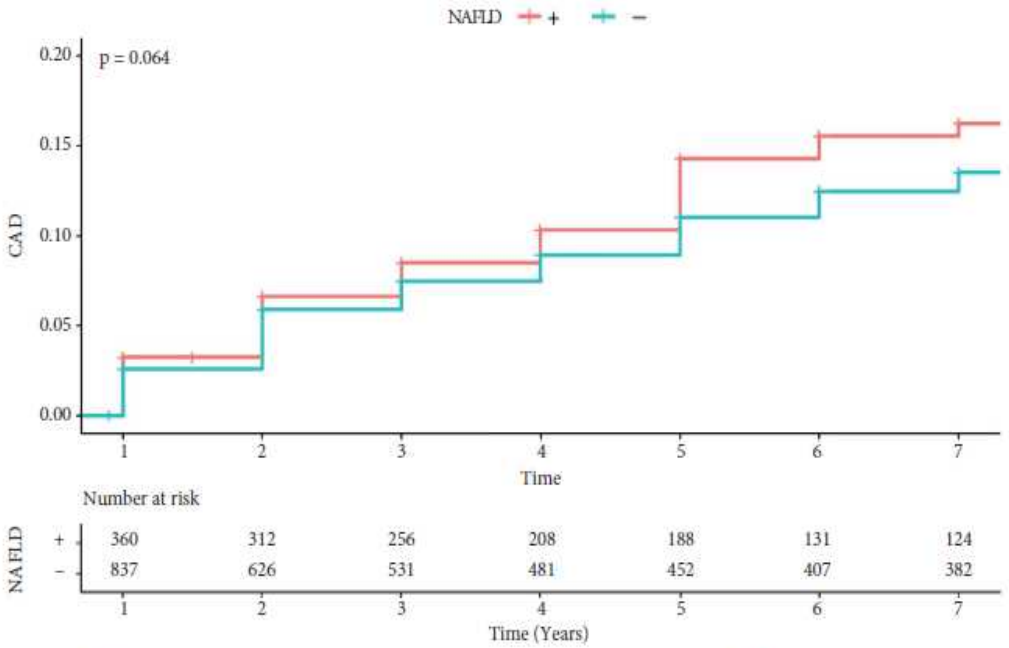


FIGURE 2: The Kaplan–Meier CAD incidence analysis of patients with and without NAFLD.

Dehghani Firouzabadi M. et al,
International Journal of Endocrinology
Volume 2024, Article ID 5328965, 10 pages https://doi.org/10.1155/2024/5328965

Epidemiological data on MASLD and the risk of CVD complications: Fatal and nonfatal CVD events

Author	Study characteristics	Study outcomes	Random-effects HRs(95% CI)
Mantovani et al, 2021	36 longitudinal studies involving 5.8 million individuals, median follow-up 6.5 years	Any fatal or nonfatal CVD events, n=36 studies	1.45 (1.31 to 1.61)
		Fatal CVD events, n=12 studies	1.30(1.08 to 1.56)
		Nonfatal CVD events=13 studies	1.40(1.20 to 1.64)

Mantovani A, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis.
The Lancet Gastroenterology & Hepatology 2021;6:903–13.

Epidemiological data on MASLD and the risk of CVD complications: Permanent atrial fibrillation

Author	Study characteristics	Study outcomes	Random-effects HRs(95% CI)
Cai et al, 2020	6 longitudinal cohort studies involving 614673 individuals, median follow-up 10years	Incident atrial fibrillation, n=6 studies	1.19 (1.04 to 1.31)
	Subgroup analyses in patients with more severe MASLD	Not enough data available for analysis	

Cai X, Zheng S, Liu Y, et al. Nonalcoholic fatty liver disease is associated with increased risk of atrial fibrillation. Liver Int 2020;40:1594–600.

Epidemiological data on MASLD and the risk of CVD complications: Heart Failure

Author	Study characteristics	Study outcomes	Random-effects HRs(95% CI)
Mantovani et al, 2022	**11 longitudinal cohort studies involving 12.2 million individuals, median follow-up 10years**	**Incident heart failure, n=11 studies**	**1.50 (1.34 to 1.67)**
	Subgroup analyses in patients with more severe MASLD	Incident heart failure, n=2 studies	1.76(0.75 to 4.36)

Mantovani A, et al. Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals.
Gut 2023;72:372–80.

Meta-analytical quantification of the excess risk of developing extrahepatic cancers in middle-aged individuals with MASLD

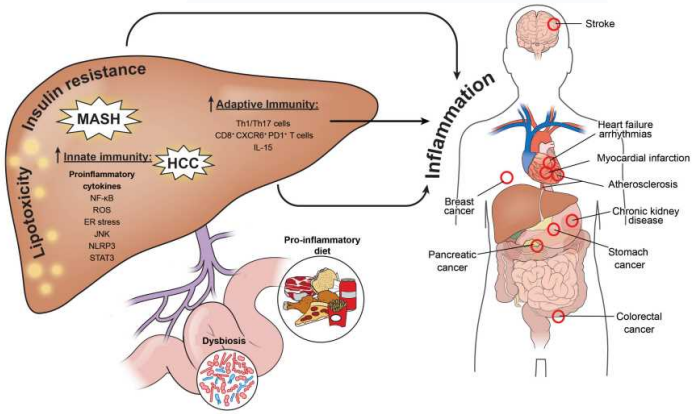
Extrahepatic cancers			
Mantovani *et al*, 2022[30]	10 longitudinal cohort studies involving a total of 182 202 individuals; median follow-up of 5.8 years	Incident oesophagus cancer, n=5 studies	1.93 (1.19 to 3.12)
		Incident stomach cancer n=6 studies	1.81 (1.19 to 2.75)
		Incident pancreas cancer, n=3 studies	1.84 (1.23 to 2.74)
		Incident colorectal cancer, n=8 studies	1.64 (1.24 to 2.19)
		Incident thyroid cancer, n=2 studies	2.63 (1.27 to 5.45)
		Incident lung cancer, n=5 studies	1.30 (1.14 to 1.48)
		Incident urinary system cancer, n=4 studies	1.33 (1.04 to 1.70)
		Incident breast cancer, n=4 studies	1.39 (1.13 to 1.71)
		Incident female genital organ cancer, n=4 studies	1.62 (1.13 to 2.32)
		Incident prostate cancer, n=5 studies	1.16 (0.82 to 1.64)
		Incident haematological cancers, n=2 studies	1.47 (0.69 to 3.12)
	Subgroup analyses in patients with 'more severe' MASLD	Not enough data available for analysis	Not available

- Mantovani A, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. Gut 2022;71:778–88.

Pathophysiology of MASLD and its Relationship with CVD Complications

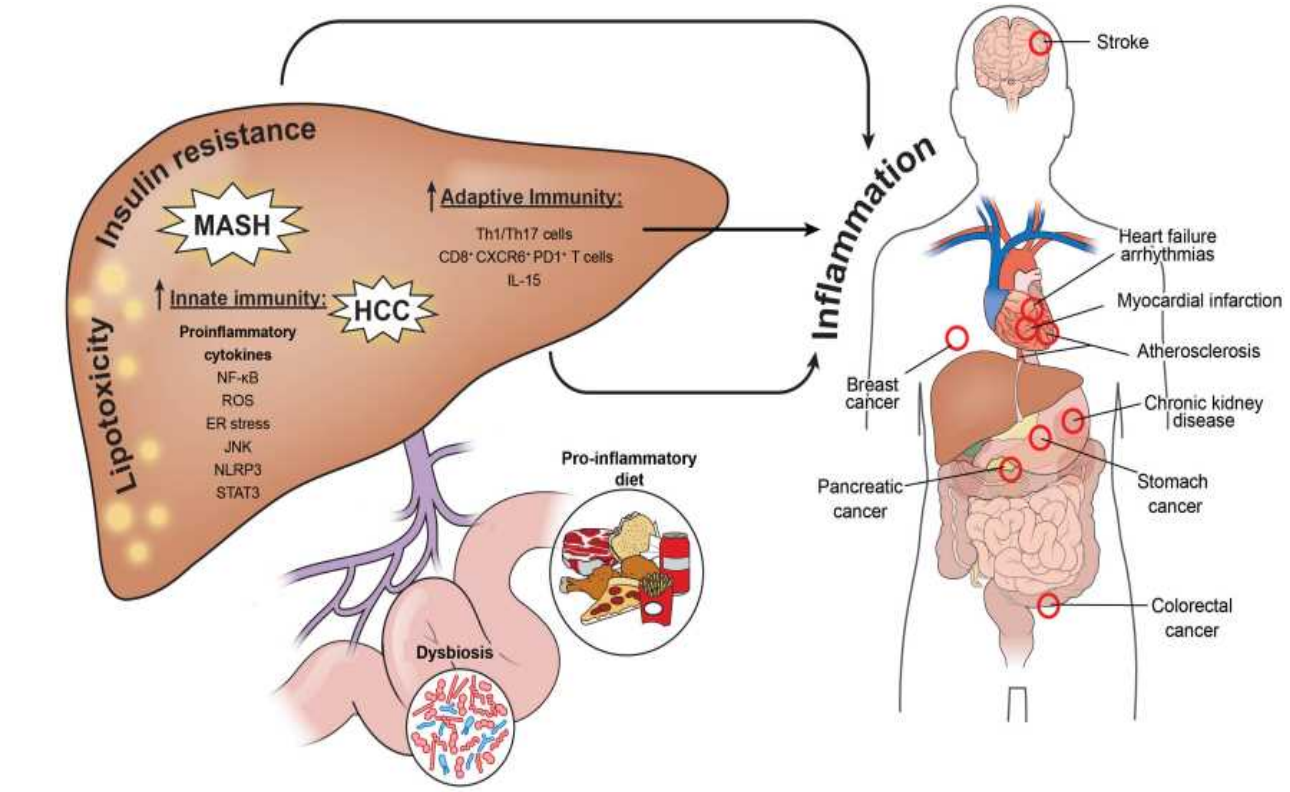
Pathophysiological aspects contributing to cardiovascular and malignant complications in people with MASLD

Chronic liver inflammation is a major driver of liver fibrosis and further complications of MASLD, both inside and outside of the liver.



It is also well established that low-grade systemic inflammation, such as that observed in MASLD and many other associated diseases, may promote CVD outcomes and tumorigenesis.

Pathophysiological aspects contributing to cardiovascular and malignant complications in people with MASLD

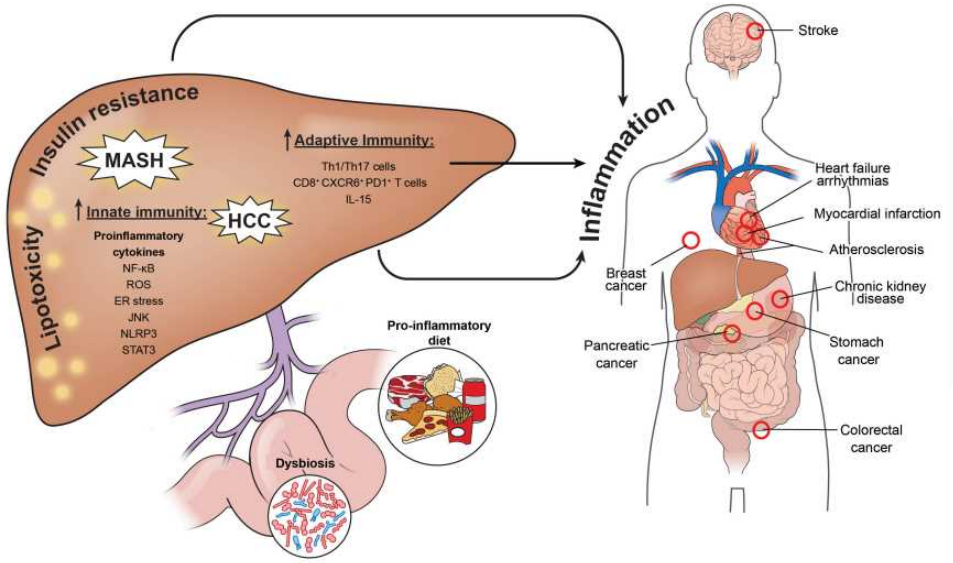


Pathophysiological aspects contributing to cardiovascular and malignant complications in people with MASLD

- **Multiple parallel Hits Theory**

With respect to

- **hepatic and extrahepatic inflammation and their driving forces, it remains unclear which 'hits' come first and take the lead.**



Pathophysiological aspects contributing to cardiovascular and malignant complications in people with MASLD

- **Multiple parallel Hits Theory**

Various pathophysiological factors can adversely act in parallel, such as

lipotoxicity,

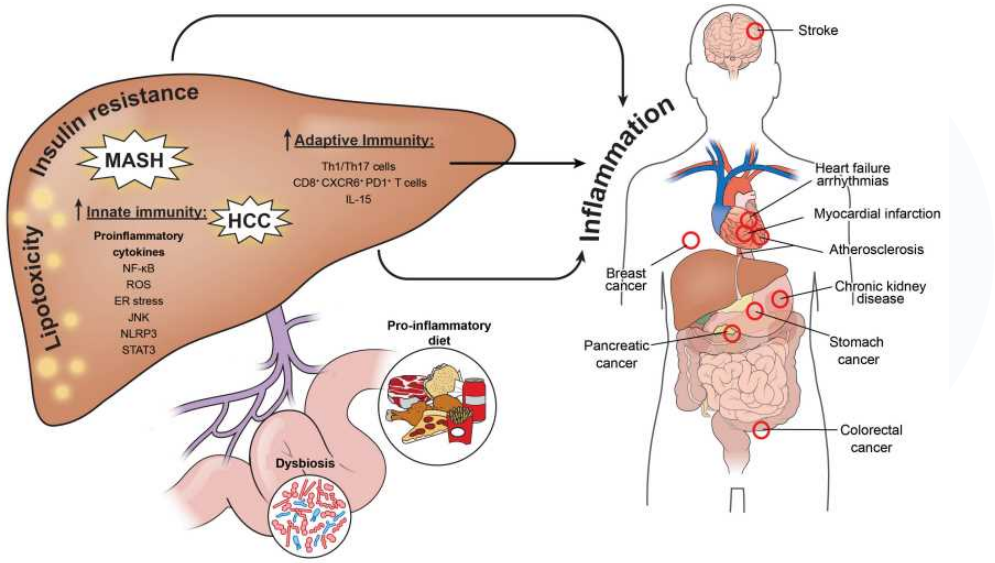
insulin resistance,

obesity,

proinflammatory diets

or intestinal dysbiosis,

causing hepatic and extrahepatic chronic

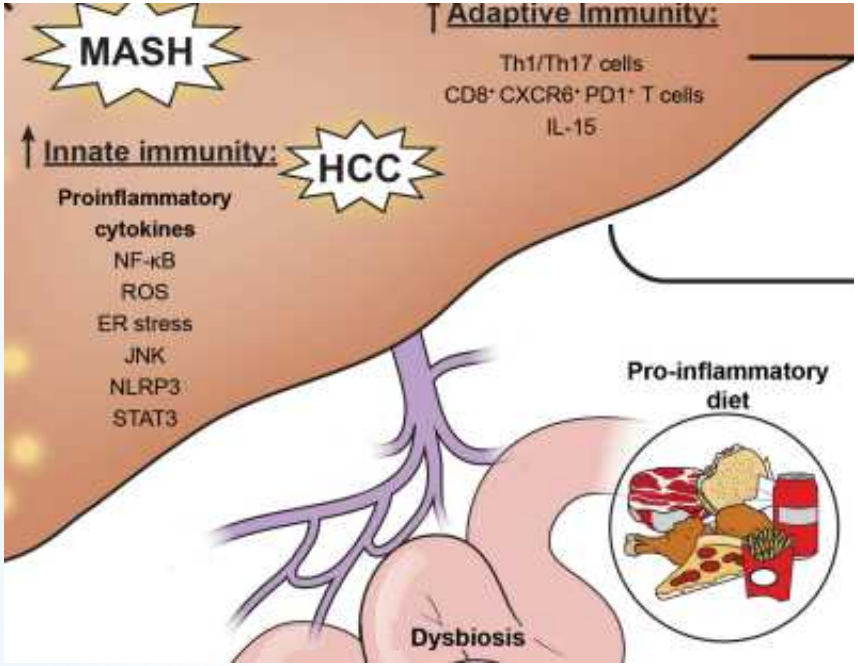


Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

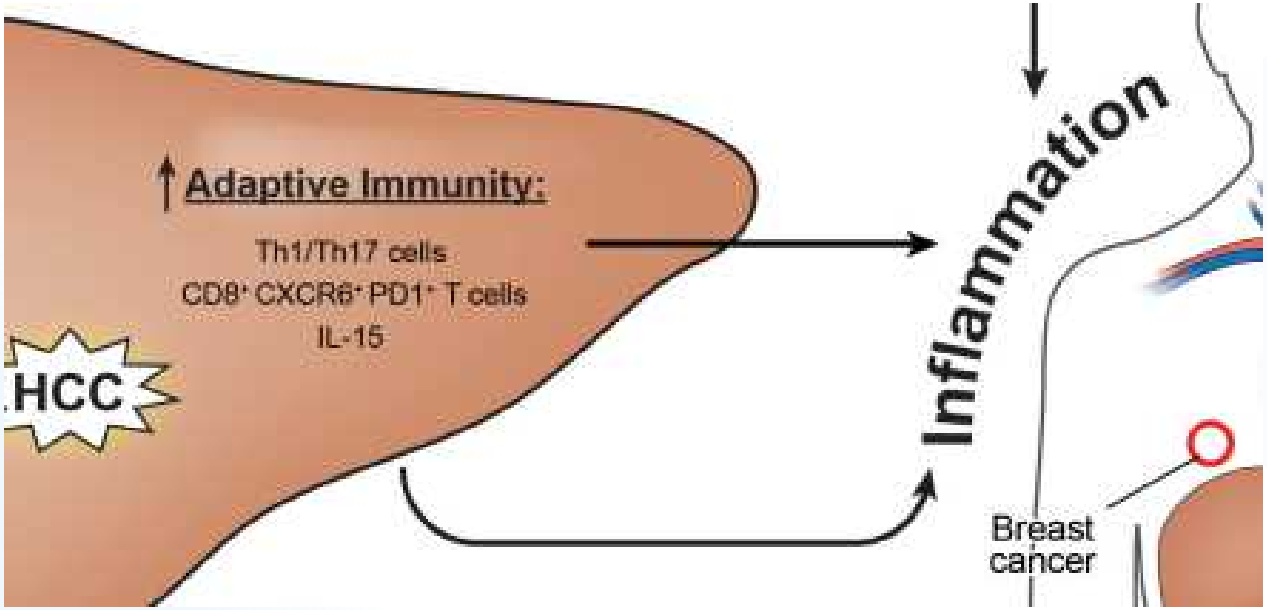
- Patients with MASH show evidence of low-grade systemic inflammation as the circulating levels of hsCRP and IL-1 receptor antagonist (IL-1RA), another sensitive marker of systemic inflammation, are increased.

- Interestingly, plasma hsCRP concentrations correlate with all-cause mortality in MASLD patients, as well as malignancy-related and CVD mortality.
-

Pathophysiological aspects contributing to cardiovascular and malignant complications in people with MASLD



Pathophysiological aspects contributing to cardiovascular and malignant complications in people with MASLD



Chronic inflammation in MASLD and alteration of gut microbiota.

- MASLD and especially advanced stages of the disease process are commonly accompanied by substantial gut dysbiosis and the evolution of certain pathobionts.

Chronic inflammation in MASLD and alteration of gut microbiota.

- A profound gut dysbiosis in MASLD was demonstrated in patients with advanced liver fibrosis and dysbiosis was accompanied by the appearance of Proteobacteria and pathobionts such as Escherichia coli.

- Loomba R, Seguritan V, Li W, et al. Gut Microbiome-based Metagenomic signature for non-invasive detection of advanced fibrosis in human Nonalcoholic fatty liver disease. Cell Metab 2017;25:1054–62.

Chronic inflammation in MASLD and alteration of gut microbiota.

- Several mouse MASH models have shown protective and anti-inflammatory effects using probiotics such as Faecalibacterium prausnitzii.

- Aron-Wisnewsky et al. Nonalcoholic fatty liver disease: Modulating gut Microbiota to improve severity.
- Gastroenterology 2020;158:1881–98.

Chronic inflammation in MASLD and alteration of gut microbiota.

- A gut dysbiosis might increase hepatic and systemic lipopolysaccharide (LPS) concentrations in patients with MASLD.

- Besides LPS, increased circulating levels of various proinflammatory metabolites, such as gut microbiome-derived lactate, ethanol or trimethylamine oxide (TMAO), characterize MASLD.

Chronic inflammation in MASLD and alteration of gut microbiota.

- Furthermore, MASLD is accompanied by decreased total bile acid pool size, especially secondary bile acids or short-chain fatty acids.

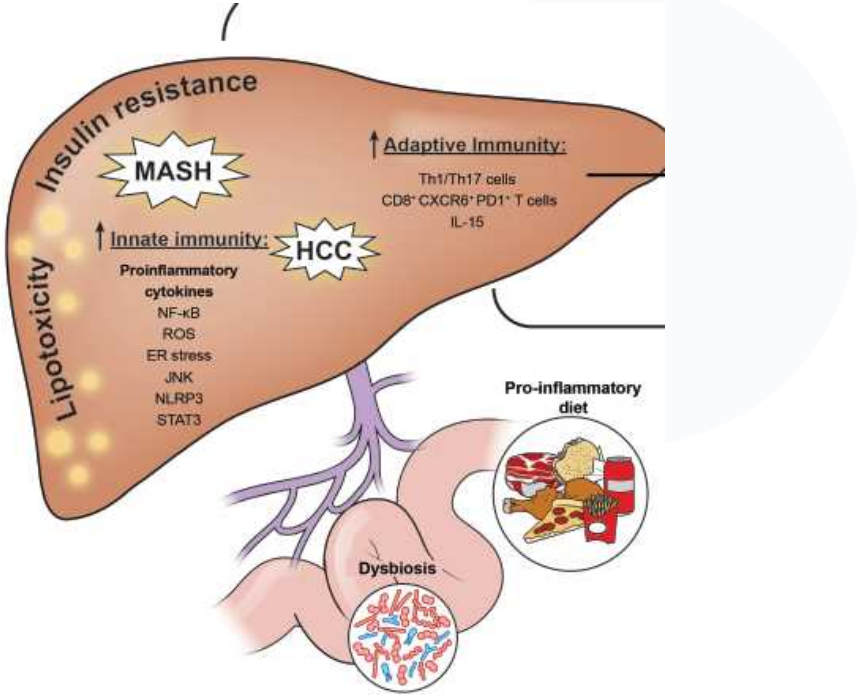
- Aron-Wisnewsky et al. Gut Microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat Rev
- Gastroenterol Hepatol 2020;17:279–97.

Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

- Metabolic dysfunction and
- Atherogenic dyslipidemia
- are key pathophysiological components of MASLD.

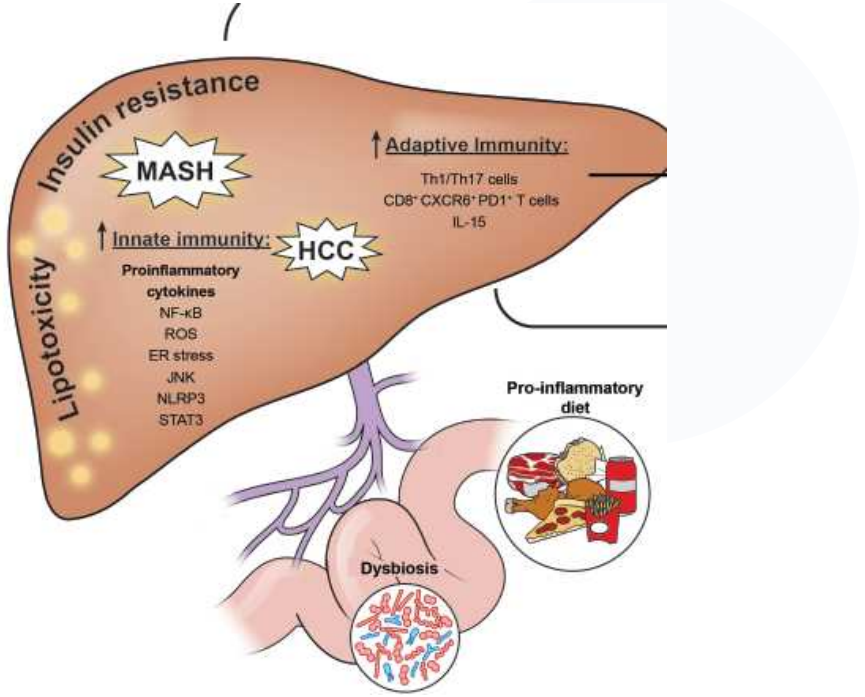
Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

- **Hepatic insulin resistance** characterizes most patients with MASLD and is commonly associated with an increased influx of free fatty acids into the liver, which is also aggravated by **systemic insulin resistance.**



Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

- **Insulin resistance may be closely associated with the development and progression of MASLD..**



Lipotoxicity

Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for development of MASLD.

- Hepatic entry of increased fatty acids released from adipose tissue
- Increase in fatty acid synthesis
- Reduced fatty acid oxidation
- Hepatic overproduction of TG-rich- lipoproteins

Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

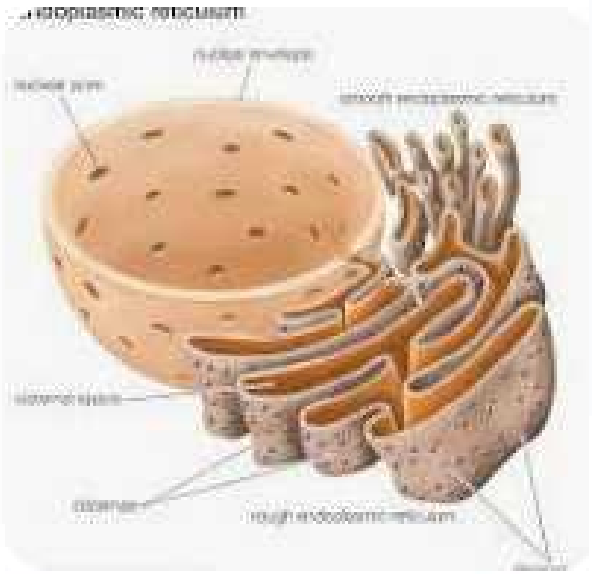
- Lipotoxicity reflects an important aspect of MASLD pathogenesis as specific lipids may exert :
- Proinflammatory effects
- Promote the release of several proinflammatory mediators and the
- Accumulation of inflammatory leucocytes within the liver.

Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

- Diverse lipid species, such as
- Sphingolipids,
- Ceramides,
- Trans fatty acids
- Free cholesterol
- can also induce liver inflammation, including upregulation of multiple proinflammatory cytokines and nuclear factor kappa B (NF-

- Inflammatory signals cause insulin resistance or may further exacerbate existing insulin resistance, and NF-kB has been crucially linked to the generation of hepatic insulin resistance.

Inflammation-driven insulin resistance also involves other important pathways in MASLD, such as endoplasmic reticulum stress (ER stress).



Endoplasmic reticulum (ER) | ...

Obesity

Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

- Obesity, present in about 80%–90% of MASLD patients, is also associated (independently of MASLD) with low-grade systemic inflammation (‘metaflammation’), ER stress dysregulation or lipotoxicity.
- A very high rate of MASLD is observed in obese individuals, further strengthening the pathophysiological link between obesity and MASLD

Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

- Genetic factors might also contribute to
- CVD outcomes as studies have observed a link between certain
- PNPLA3 genotypes and CVD, including carotid atherosclerosis or coronary heart disease.

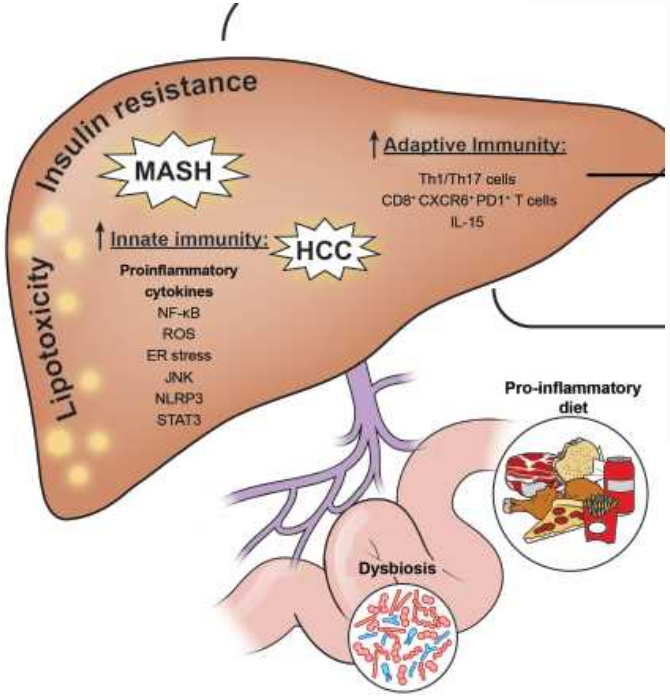
CVD Risk Assessment

CVD risk assessment in MASLD
Common risk factors

- Obesity
- Impaired glucose metabolism
- Hypertension
- Atherogenic dyslipidemia

Pathophysiological aspects contributing to cardiovascular complications in people with MASLD- Starting points for disease.

- **Since insulin resistance induces atherosclerosis, the leading cause for death in MASLD patients is cardiovascular disease.**



CVD risk assessment in MASLD

- Assess risk factors
- (a) non-modifiable: age, gender, family history of premature CVD, ethnicity, early menopause
- (b) modifiable: smoking, increased LDL-cholesterol, sedentary life, unhealthy diet, obesity, hypertension, atherogenic dyslipidemia, and T2D

CVD risk assessment in MASLD

- Assess risk factors
- Further amplification of CVD risk when associated comorbidities such as CKD also occur.
- Although increased plasma LDL-C concentration is a common risk factor in middle-aged subjects (and occurs independently of MASLD), an increased plasma LDL-C concentration will further increase the risk of CVD in people with MASLD.

CVD risk assessment in MASLD data on MASLD and the risk of CVD complications

- The first consideration is how CVD risk should be assessed in patients with MASLD? Most patients with MASLD are likely to be middle-aged, and although there are exceptions, women with MASLD are most likely to be perimenopausal or postmenopausal.

CVD risk assessment in MASLD data on MASLD and the risk of CVD complications

- Because of the age demographic of patients with MASLD, this patient group should be considered for a CVD health check as most patients will be >40 years old.

CVD risk assessment in MASLD data on MASLD and the risk of CVD complications

- A more common dyslipidaemia frequently occurring with MASLD is the atherogenic lipoprotein phenotype, comprising increased small dense LDL particles, low HDL-cholesterol and high triglyceride concentrations.

- Although subjects with MASLD with atherogenic dyslipidaemia may have normal plasma LDL-C concentrations, it is in this situation that treatment with a statin will decrease CVD risk

Sample of published articles from Iran

Samimi *et al.*
European Journal of Medical Research (2022) 27:112
https://doi.org/10.1186/s40001-022-00731-x

European Journal of Medical Research

RESEARCH Open Access

Atherogenic index of plasma is an independent predictor of metabolic-associated fatty liver disease in patients with type 2 diabetes

Sahar Samimi[1], Sahar Rajabzadeh[1], Soghra Rabizadeh[1], Manouchehr Nakhjavani[1], Pooria Nakhaei[1], Foroogh Alborzi Avanaki[2] and Alireza Esteghamati[1*]

Results: Out of 2547 patients with T2D, 824 (32.4%) had MAFLD. The multivariate logistic regression analysis showed a significant difference in female-to-male ratio (1.11 vs. 1.33, OR = 0.347, *P*-value < 0.001), ALT (42.5 ± 28.1 vs. 22.4 ± 11.1, OR = 1.057, *P*-value < 0.001), and AIP (0.6 ± 0.3 vs. 0.5 ± 0.3, OR = 5.057, *P*-value < 0.001) between MAFLD and non-MAFLD groups, respectively. According to the AIP quartile, the prevalence of MAFLD increased significantly in patients with higher AIP quartiles (*P*-value < 0.001). Also, we found a cut-off of 0.54 for AIP in predicting MAFLD in patients with T2D (sensitivity = 57.8%, specificity = 54.4%).

Namakchian *et al. Diabetology & Metabolic Syndrome* (2023) 15:57
https://doi.org/10.1186/s13098-023-01031-y

Diabetology & Metabolic Syndrome

RESEARCH Open Access

Fibrosis score 4 index has an independent relationship with coronary artery diseases in patients with metabolic-associated fatty liver disease

Maryam Namakchian[1], Soghra Rabizadeh[1], Sara Seifouri[1], Hassan Asadigandomani[1], Melika Arab Bafrani[1], Kiana Seifouri[1], Foroogh Alborzi Avanaki[2], Armin Rajab[1], Manouchehr Nakhjavani[1] and Alireza Esteghamati[1*]

Result Among the 1644 patients (all have MAFLD), 364(21.4%) had CAD. Patients with MAFLD and CAD were more probable to be hypertensive, have longer duration of diabetes and be older (with p-values < 0.001). After adjustment for confounding factors, in a multivariable logistic regression model, FIB4 showed a significant independent relationship with concomitant MAFLD and CAD. Upper Tertile FIB-4 had an odds ratio of 3.28 (P-value = 0.002) to predict CAD. Furthermore, in Receiver Operating Characteristic (ROC) Curve analysis with the maximum Youden Index, a FIB-4 cut-off of 0.85 (AUC = 0.656, 95% CI 0.618–0.693, P < 0.001) noted to predict CAD in patients with MAFLD.

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 05 June 2023
DOI 10.3389/fendo.2023.1147458

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Deravi N, Dehghani Firouzabadi F, Moosaie F, Asadigandomani H,

Non-alcoholic fatty liver disease and incidence of microvascular complications of diabetes in patients with type 2 diabetes: a prospective cohort study

Niloofar Deravi[1,2], Fatemeh Dehghani Firouzabadi[3], Fatemeh Moosaie[1], Hassan Asadigandomani[1], Melika Arab Bafrani[1], Niyoosha Yoosefi[1], Amirhossein Poopak[1], Mohammad Dehghani Firouzabadi[1], Mohadeseh Poudineh[1,4], Soghra Rabizadeh[1], Ibrahim Kamel[1], Manouchehr Nakhjavani[1] and Alireza Esteghamati[1*]

Wiley
International Journal of Endocrinology
Volume 2024, Article ID 5328965, 10 pages
https://doi.org/10.1155/2024/5328965

WILEY

Research Article

Nonalcoholic Fatty Liver Disease as a Potential Risk Factor for Cardiovascular Disease in Patients with Type 2 Diabetes: A Prospective Cohort Study

Mohammad Dehghani Firouzabadi,[1] Amirhossein Poopak,[1] Ali Sheikhy,[1,2] Fatemeh Dehghani Firouzabadi,[1,2] Fatemeh Moosaie,[1] Soghra Rabizadeh,[1] Sara Momtazmanesh,[1] Manouchehr Nakhjavani,[1] and Alireza Esteghamati[1]

CASE PRESENTATION

1- HOW DOES NAFLD IMPACT ON GLYCEMIC CONTROL?

2- DOES HER MOTHER'S DIET DURING PREGNANCY HAVE ANYTHING TO DO WITH HER FATTY LIVER? DEVELOPMENTAL ORIGIN OF FATTY LIVER

Soghra Rabizadeh,MD

HOW DOES MAFLD IMPACT ON GLYCAEMIC CONTROL?

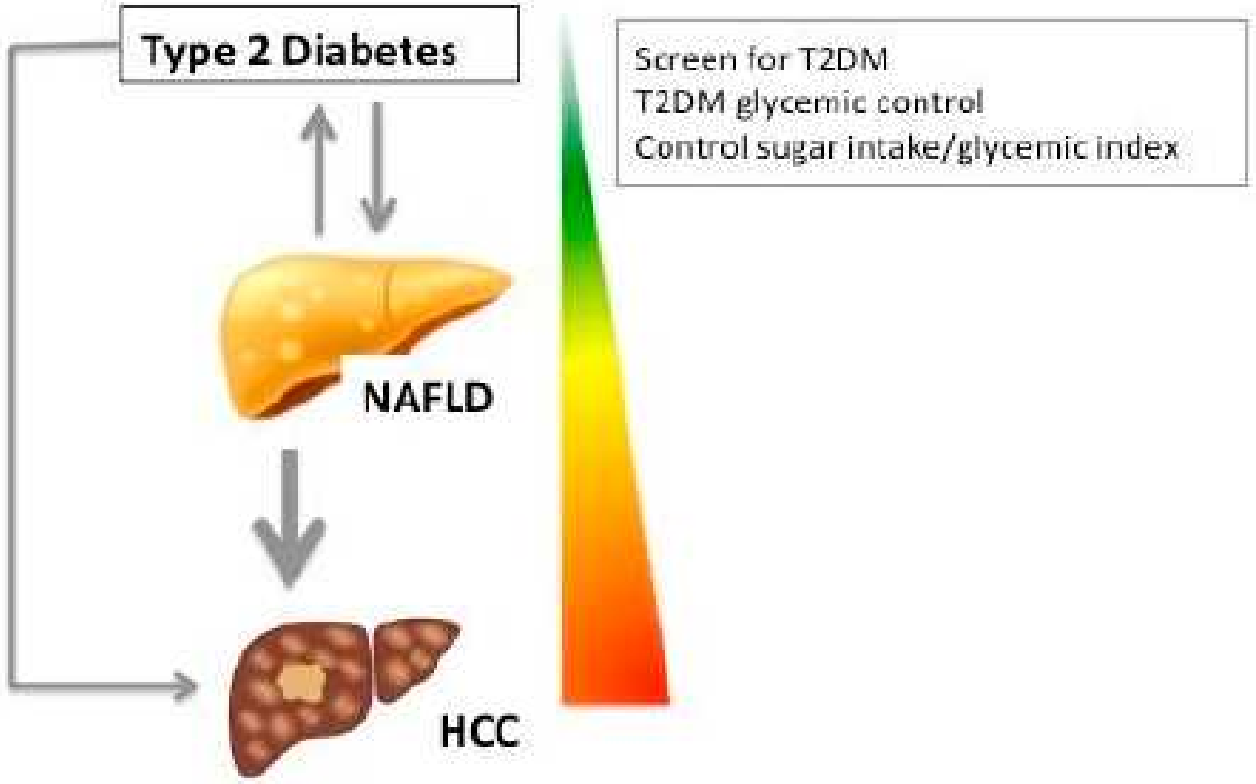
S.Rabizadeh, Endocrinologist,

Tehran University of Medical Sciences

INTRODUCTION

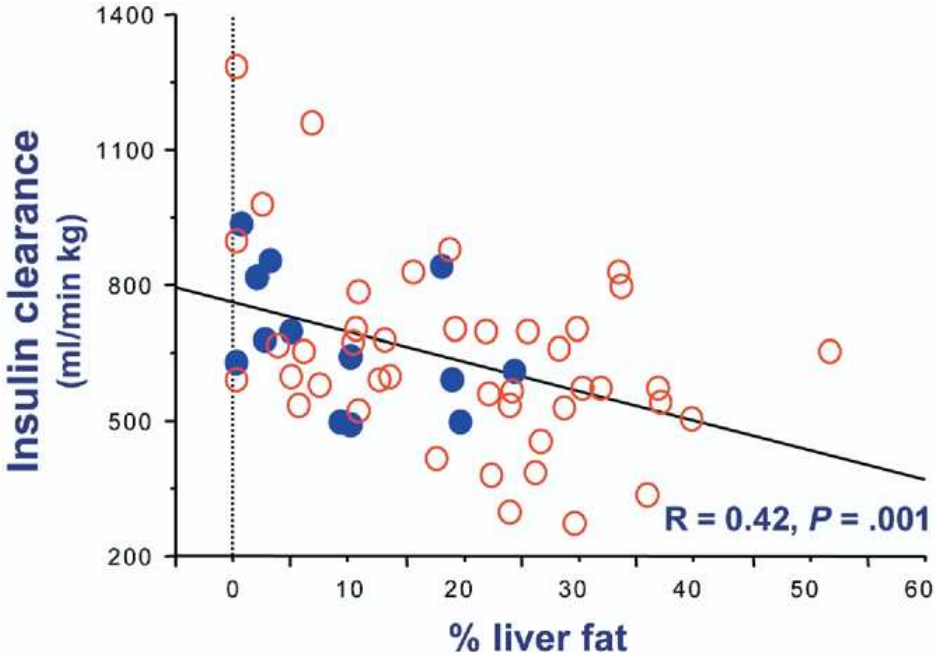
- Accumulation of fat in the liver is responsible for increased hepatic insulin resistance so that glucose release from the liver is less well controlled in the presence of NAFLD AND glycaemic control to be more challenging.

Byrne CD et al (2018). *BMJ* **362**: 74–7
Paris R, Maurel T (2021) *J Clin Med* **10**: 1161



T2DM and NAFLD are linked through a bidirectional relationship: NAFLD increases the risk of T2DM occurrence and T2DM is a risk factor for NAFLD development and fibrosis progression.

Diabetic subjects with NAFLD have increased fasting insulin concentrations and are significantly more insulin-resistant than their diabetic counterparts without NAFLD



Amalia Gastaldelli et al. Gastroenterology. 2007

SEVERITY OF FATTY LIVER AND WORSENING OF GLYCEMIC CONTROL

Table 3. Association between the severity of NAFLD at baseline and risk of developing worsening of glycaemic control at follow-up in postmenopausal women with type 2 diabetes.

Logistic Regression Models	Odds Ratios (95% CI)	*p*-Value
Unadjusted model		
NAFLD and clinically significant fibrosis §	4.66 (1.07–20.3)	0.041
Adjusted model 1		
NAFLD and clinically significant fibrosis	4.72 (1.07–20.7)	0.040
Age (years)	0.98 (0.91–1.06)	0.678
BMI (kg/m^2)	0.99 (0.88–1.12)	0.866

Alessandro Mantovani, Int. J. Mol. Sci. **2022**

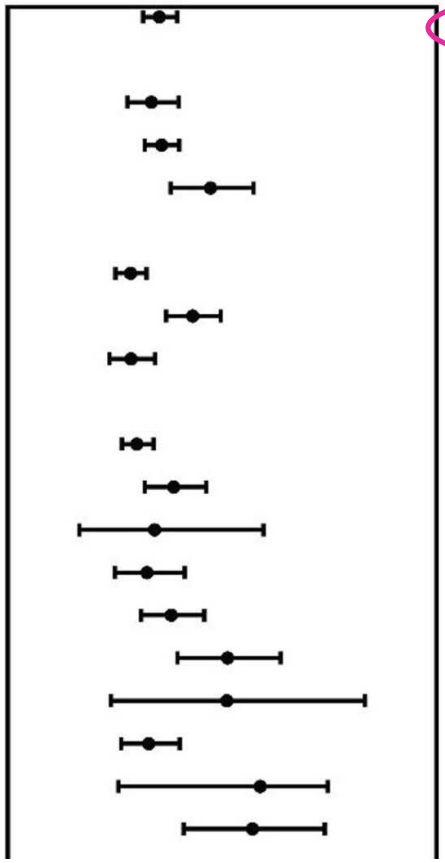
KEY MECHANISM NAFLD CONTRIBUTES TO HYPERGLYCEMIA

Mechanism	Effect on Glycemic Control
Hepatic insulin resistance	↑ Gluconeogenesis, ↓ Glucose uptake
Systemic inflammation	Impaired peripheral insulin sensitivity
Fibrosis-related adipokine changes	Dysregulated glucose homeostasis
Mitochondrial dysfunction	Oxidative stress → Insulin resistance

fatty liver is not just a consequence of diabetes, but also a factor that can make diabetes harder to control and increase the risk of diabetes-related complications

PREVALENCE OF TYPE 2 DIABETES AMONG PATIENTS WITH NAFLD

	Study (n)	Prevalence (95% CI)	I^2
Global	340	28.3 (25.2-31.6)	100.0%
Study design			
Cross-sectional	185	26.8 (22.3-31.9)	100.0%
Cohort	129	28.7 (25.6-32.0)	100.0%
Case-control	26	37.8 (30.4-45.9)	100.0%
Average age, years old			
<50.6	165	22.9 (20.1-25.9)	100.0%
≥50.6	169	34.5 (29.6-39.7)	100.0%
NA	6	23.0 (19.0-27.5)	100.0%
Region			
East Asia	102	24.1 (21.3-27.2)	100.0%
South Asia	16	31.0 (25.6-37.0)	98.7%
Southeast Asia	7	27.4 (13.4-47.7)	99.8%
West Asia	27	26.0 (20.0-33.0)	99.8%
North America	92	30.5 (24.9-36.7)	100.0%
South America	12	41.0 (31.7-50.9)	99.1%
Australia	7	40.9 (19.3-66.7)	99.7%
Europe	65	26.3 (21.2-32.1)	100.0%
Africa	4	47.1 (20.6-59.7)	95.1%
Mixed	8	45.7 (32.8-59.2)	99.8%

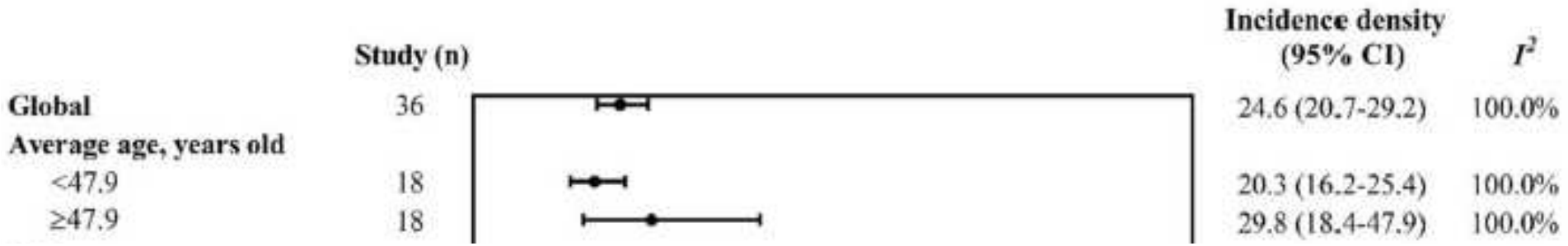


PREVALENCE OF TYPE 2 DIABETES AMONG PATIENTS WITH NAFLD

West Asia		
Iran	4	21.5 (13.4-32.6)
Israel	7	24.1 (11.8-42.9)
Pakistan	6	24.1 (17.4-32.5)
Saudi	5	36.3 (25.6-48.6)
Turkey	5	25.4 (18.3-34.1)

Cao *et al. BMC Medicine (2024*

INCIDENCE DENSITY OF TYPE 2 DIABETES AMONG PATIENTS WITH NAFLD OR MAFLD



Cao *et al. BMC Medicine (2024*

INCIDENCE DENSITY OF TYPE 2 DIABETES AMONG PATIENTS WITH NAFLD OR MAFLD

	Studies, n	Incidence density (95% CI)	I^2
East Asia			
China	12	27.0 (21.5-33.8)	99.9%
Japan	9	19.5 (16.5-23.2)	99.9%
Korea	6	17.0 (11.2-25.9)	100.0%
West Asia			
Iran			
North America			
USA	3	81.6 (57.5-114.6)	99.5%
Australia			
Australia	1	17.0 (16.1-18.0)	-
Europe			
UK	1	8.79 (8.78-8.81)	-
Sweden	3	30.8 (26.5-35.7)	95.1%

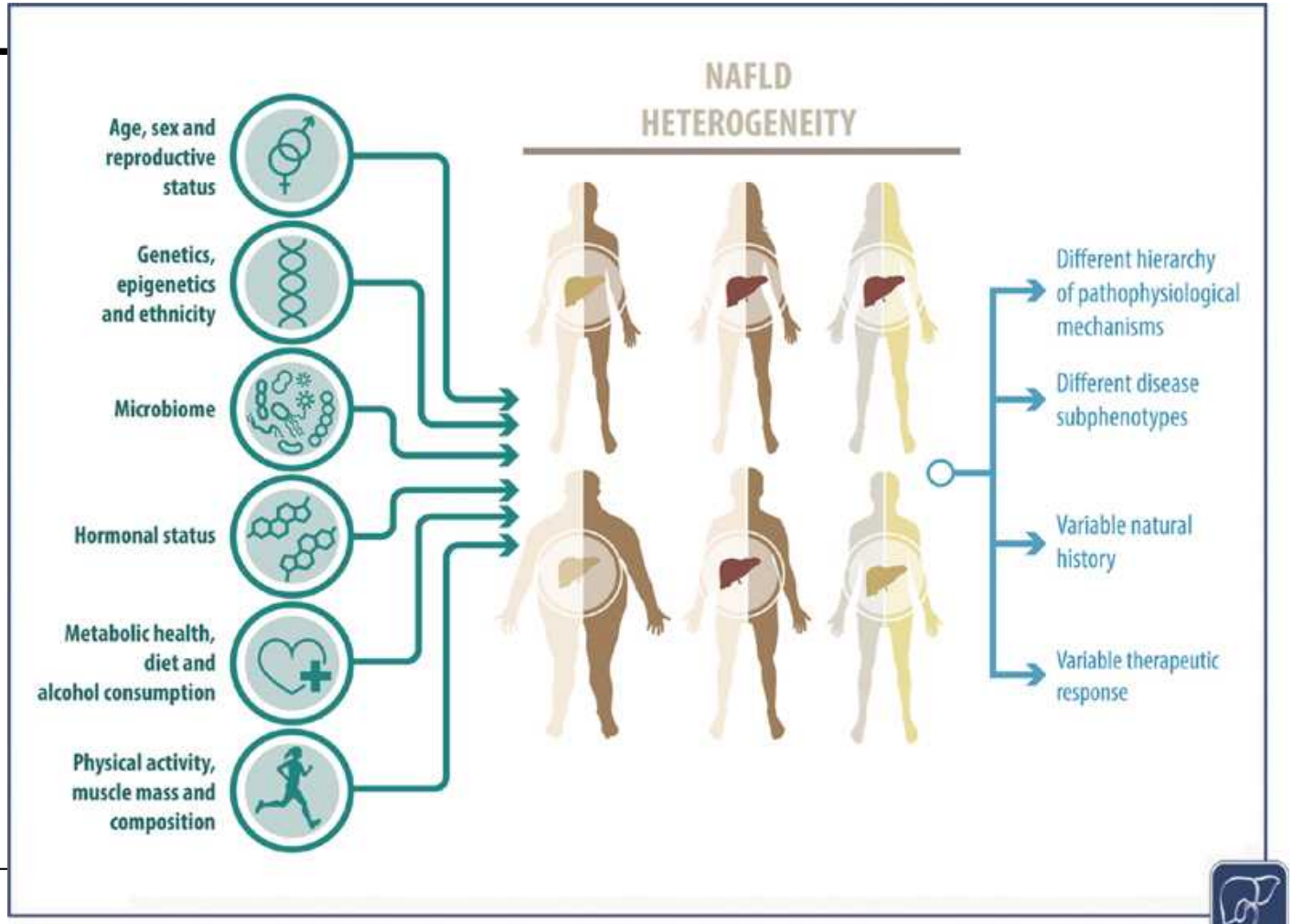
Cao *et al. BMC Medicine (2024*

RISK OF DEVELOPING **TYPE2 DM** IN NAFLD

Country	Population	NAFLD assessment	Duration follow up	T2DM risk
Japan	3189* -802 NAFLD -2387 normal	US	4	5.5 HR
Korea	5372 -1790 NAFLD -3582 normal	US	5	1.51 RR
Australia	358 -109 NAFLD -249 normal	ALT	11	NS
France	863 -277 NAFLD -594 normal	FLI <20 FLI ≥70	5	Men: 4.71 OR Women: 22.71 OR
Japan	12,375 NAFLD/normal not reported	US	5	1.91 OR men 2.15 OR women
Korea	11,091 -8120 NAFLD - 2971 normal	US	5	2.05 OR
Korea	8849 - 2292 NAFLD -5557 normal	US	4	1.33 HR
Korea	1161* -107 NAFLD -1054 normal	US	4	7.63 OR
Korea	12,853 -3555 NAFLD	US	5	2.42 OR

Jonathan M. Hazlehurst,et al , Metabolism. 2016

- NAFLD AND DIABETES : CHICKEN OR EGG?



Arrese, sem Liv Dis. 2021

There is additional evidence that the **genetic setup** of NAFLD can influence the profile of extrahepatic organ damage and the response to therapy

INSIGHTS INTO NONALCOHOLIC FATTY-LIVER DISEASE HETEROGENEITY

- **Group of patients** defined by the presence of high genetic risk of obesity and insulin resistance in the absence of specific risk determinants of liver injury ("insulin-resistant fatty-liver disease").
- **Group of genetic** variants including those in glucokinase regulator (GCKR) at high risk of dyslipidemia.
- Insulin-resistant patients carrying GCKR variants may possibly benefit from approaches reducing lipogenesis, such as statins and omega-3 fatty acids.

Marco Arrese,et al. Semin Liver Dis 2021

INSIGHTS INTO NONALCOHOLIC FATTY-LIVER DISEASE HETEROGENEITY

- **Genetic variants**, including those in PNPLA3, TM6SF2, MBOAT7, and APOB favoring lipotoxicity.
- High risk of liver-related complications, including HCC before cirrhosis development.
- They develop type-2 diabetes.
- **From a therapeutic point of view**:

➢ They respond well to weight loss

➢ when they carry the PNPLA3 variant do not benefit from statins

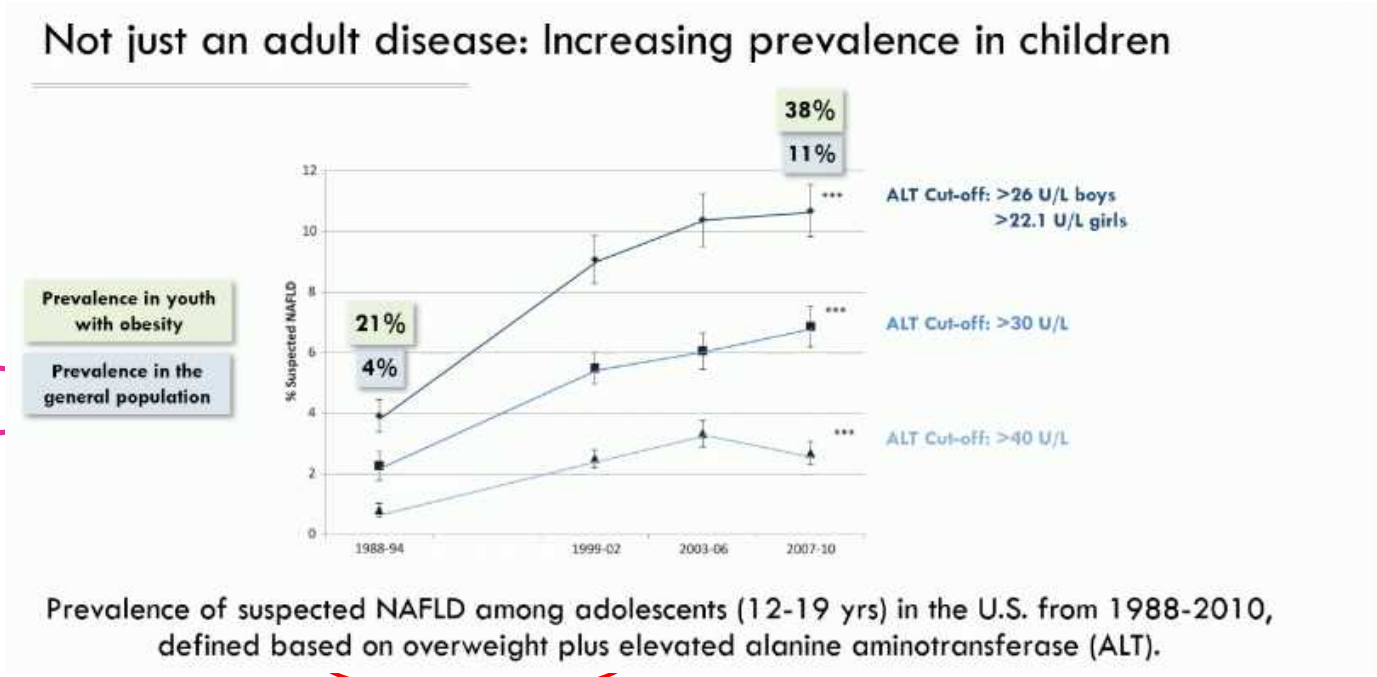
➢ They are at increased risk of liver injury due to enhanced hepatic lipid accumulation during insulin therapy.

Marco Arrese,et al. Semin Liver Dis 2021

DEVELOPMENTAL ORIGIN OF FATTY LIVER

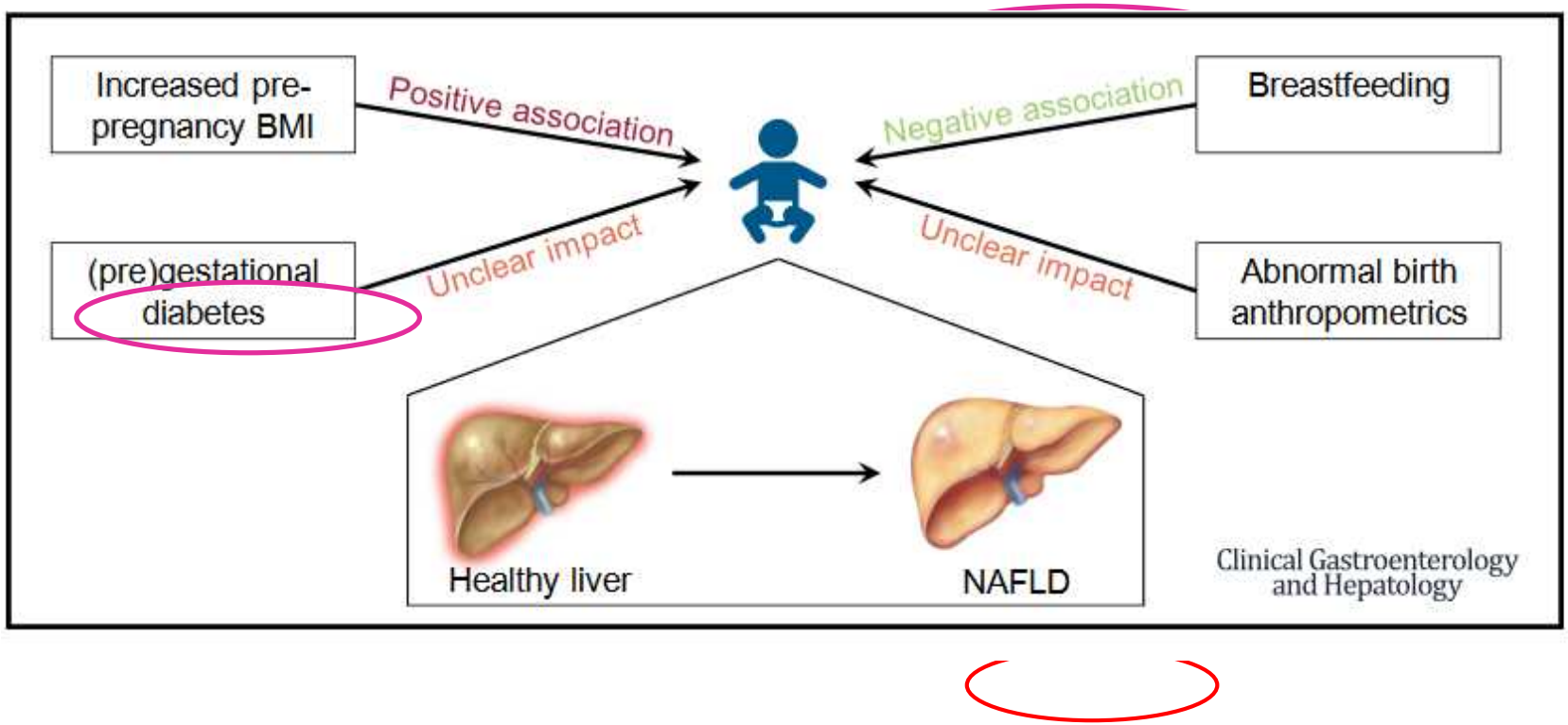
S.Rabizadeh, Endocrinologist, Tehran University of Medical Sciences

Not just an adult disease: Increasing prevalence in children



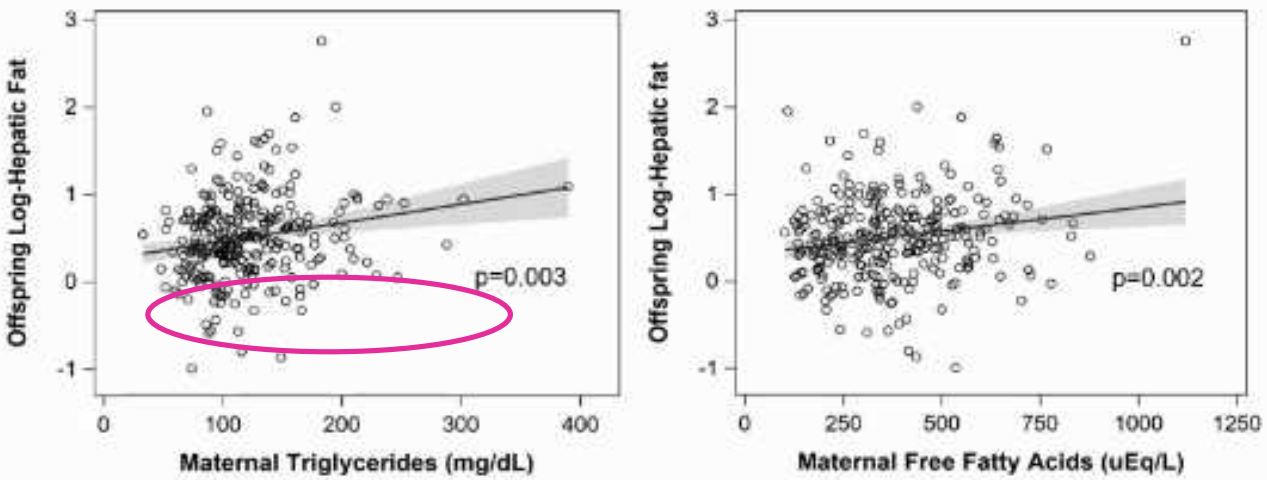
Prevalence of suspected NAFLD among adolescents (12-19 yrs) in the U.S. from 1988-2010, defined based on overweight plus elevated alanine aminotransferase (ALT).

MATERNAL OVERNUTRITION



Ilya Querter, et al. Clinical Gastroenterology and Hepatology 2022

Maternal lipids during pregnancy and childhood hepatic fat



- ↑Maternal lipids associated with higher offspring hepatic fat, independent of obesity, aligning with animal studies[2].
- Null association for maternal glucose may be due to sample characteristics, and/or a nonlinear relationship[3].

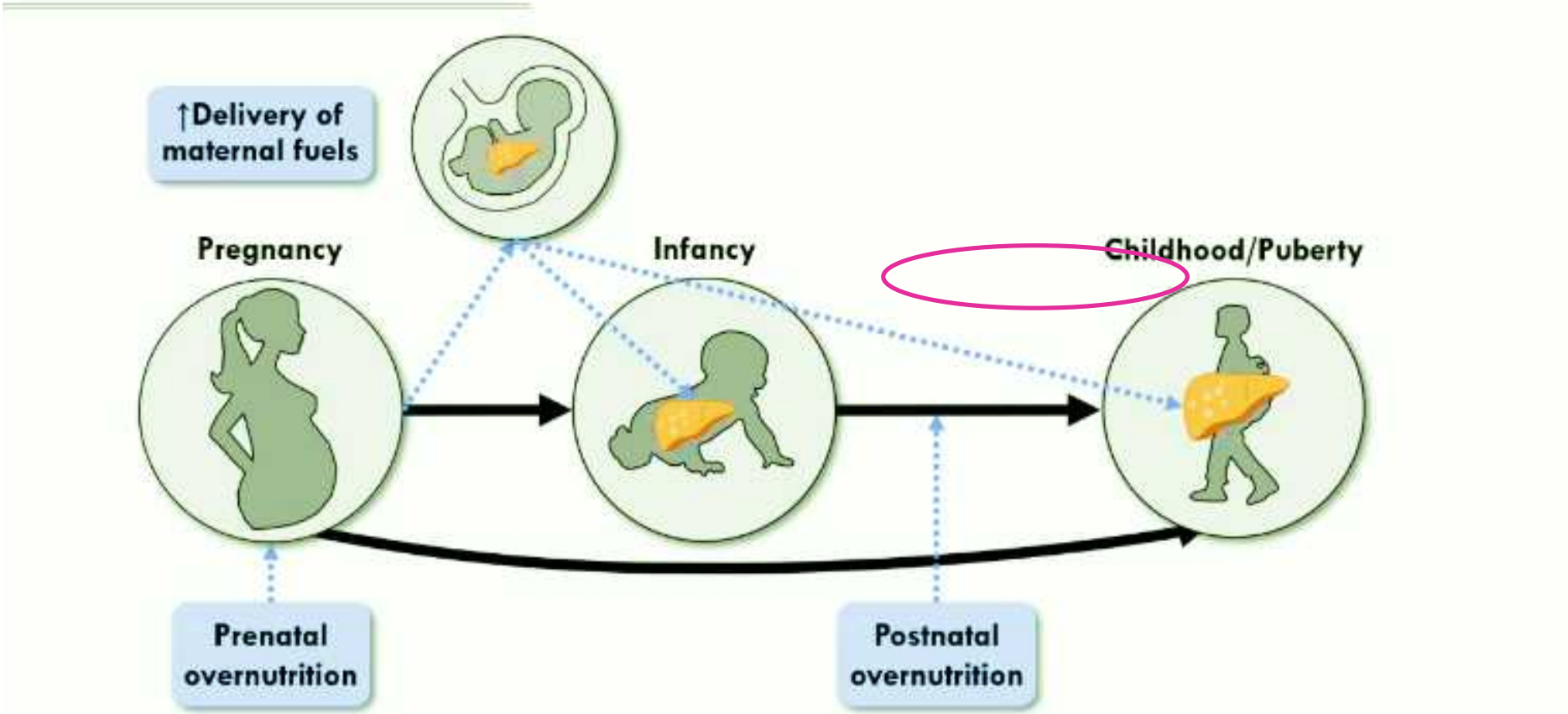
N=286 mother-child pairs in the longitudinal Healthy Start Study (Colorado, USA)[1].

- Maternal metabolic markers assessed by fasting blood draws in pregnancy (~17 and 27 weeks)
- Offspring hepatic fat assessed by MRI in early childhood (~5 years)

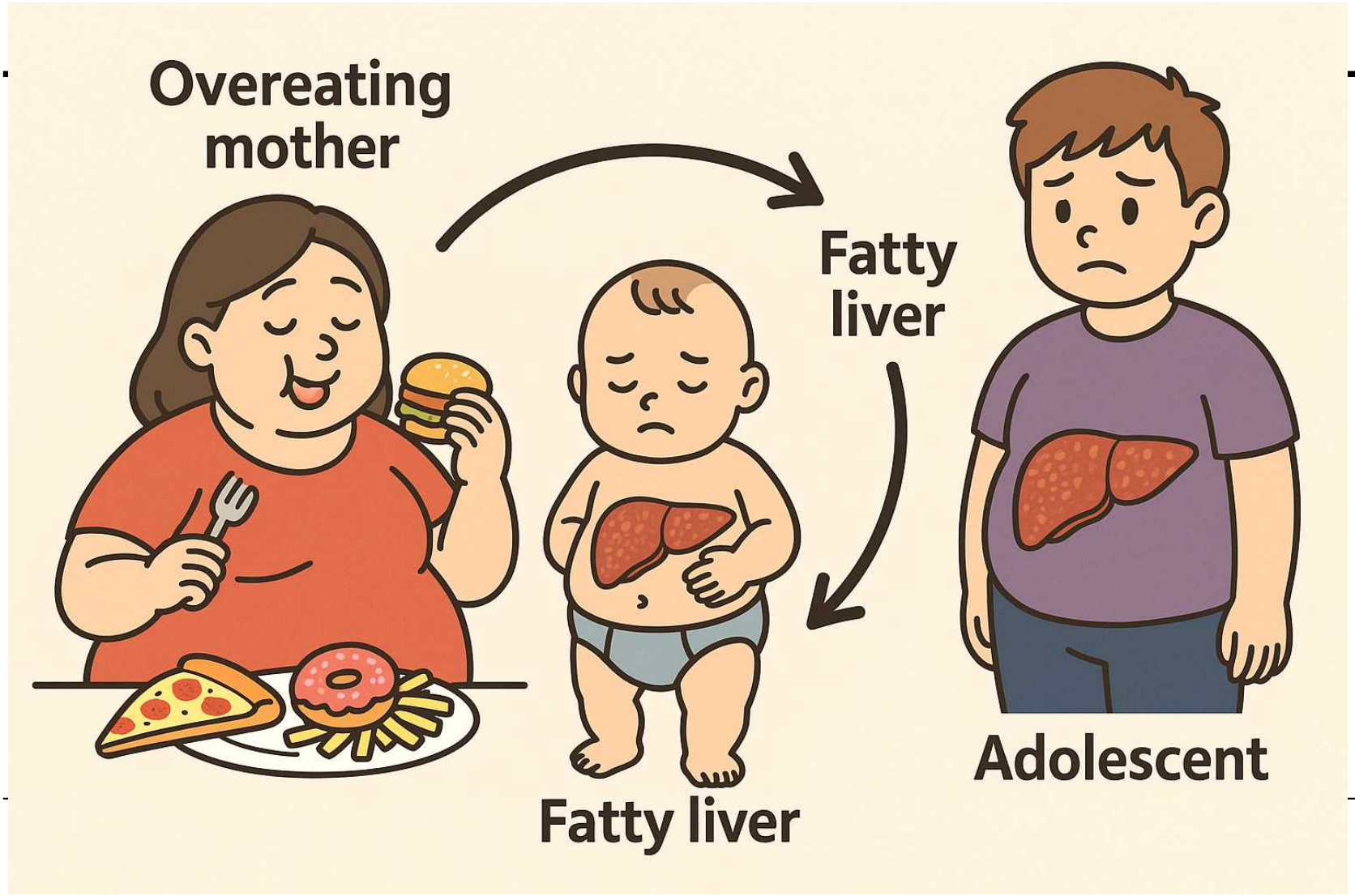
*P-values from linear regression models adjusted for child sex, age, race/ethnicity, maternal age, income, parity, pre-pregnancy BMI, smoking, physical activity, diet quality (HEI-2010), and gestational age during pregnancy.

[1]Cohen CC et al. *Pediatr Obes.* 2022;17(7). [2]McCurdy CE et al. *J Clin Investig.* 2009. [3]Geurtsen ML et al. *Hepatol.* 2021.

Developmental overnutrition as a risk factor for NAFLD



Mechanism	Effect on Child's Liver
Bile Acid Toxicity	Excess fetal bile acids damage liver cells, promoting fibrosis.
Insulin Resistance	Maternal high-fat diets impair offspring glucose regulation, worsening lipid accumulation.
Inflammation	Pro-inflammatory cytokines (e.g., IL-6) disrupt lipid metabolism and liver function.
Epigenetic Changes	Altered gene expression (e.g., Scd1) persists postnatally, driving NAFLD


Overeating mother
Fatty liver
Fatty liver
Adolescent

WHAT ADVICE WOULD YOU OFFER TO THIS PATIENT TO MANAGE HER FATTY LIVER DISEASE?

WHAT'S **NEW IN THE TREATMENT** OF FATTY LIVER?

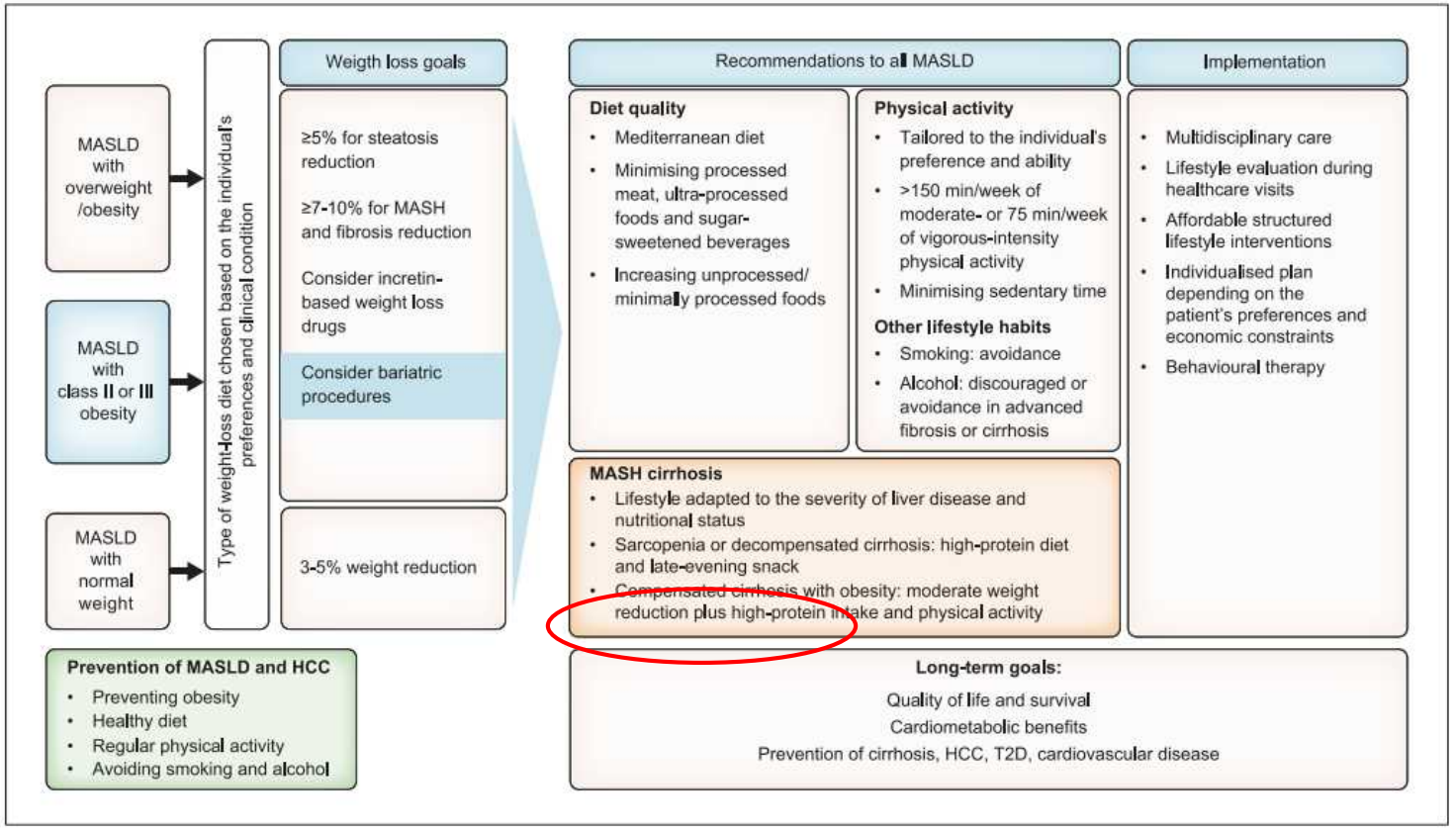
Alireza Esteghamati, MD

Management of Metabolic Associated Steatotic Liver Disease

AR. Esteghamati,MD
Professor of Endocrinology
Tehran University of Medical Sciences

Agenda

Lifestyle management algorithm for MASLD



Question

Diet quality?

- In adults with MASLD, is changing diet **quality** effective in **reducing histologically**/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared with no intervention?

Recommendation

Improving diet quality

In adults with MASLD:

1. Improving diet quality (like the Mediterranean dietary pattern)
2. limiting the consumption of ultra-processed food (rich in sugars and saturated fat)
3. Avoiding sugar sweetened beverages

Should be recommended to improve histologically or non-invasively assessed liver injury (LoE 2, strong recommendation, strong consensus).

nutrients

MDPI

Review

Does the Mediterranean Diet Have Any Effect on Lipid Profile, Central Obesity and Liver Enzymes in Non-Alcoholic Fatty Liver Disease (NAFLD) Subjects? A Systematic Review and Meta-Analysis of Randomized Control Trials

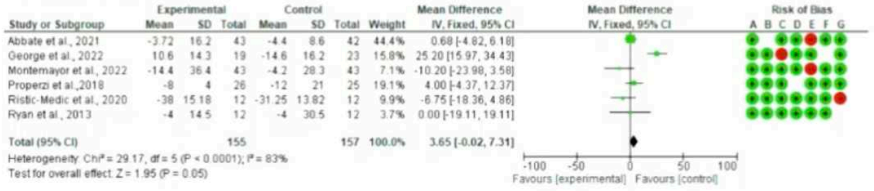
Cristian Del Bo' [1], Simone Perna [1,*], Sabika Allehdan [2], Ayesha Rafique [2], Sara Saad [2], Fahad AlGhareeb [2], Mariangela Rondanelli [3,4], Reema F. Tayyem [5], Mirko Marino [1], Daniela Martini [1] and Patrizia Riso [1]

Metaanalysis: Effects of Mediterranean Diets in MASLD

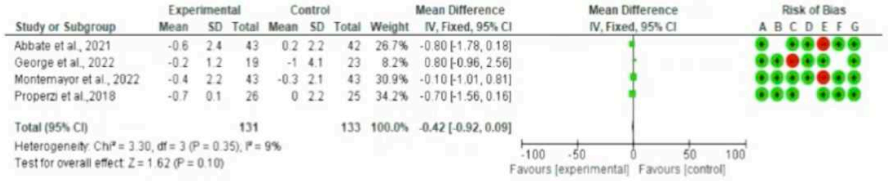
DDZ German Diabetes Center

10 RCTs (out of 107 articles), 737 adults with NAFLD

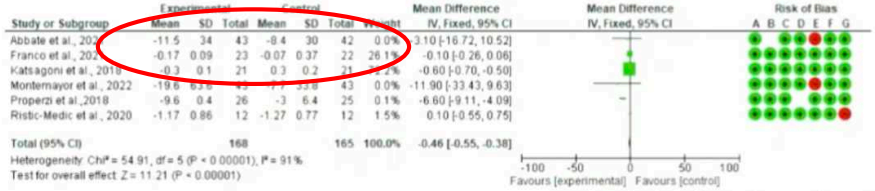
No significant effect on liver enzymes (ALT, GGT)



No significant effect on liver stiffness



Significant reduction of total cholesterol (-0.46 mg/dl)



Del Bo´ et al. *Nutrients* 15:2250,2023

Statement

- There is **little evidence** that improving diet quality beneficially impacts **clinical liver-related outcomes** (LoE 3, consensus).

Question
Physical activity?

- In adults with MASLD, are physical activity and exercise effective at reducing histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared with no intervention

Recommendation

- In adults with MASLD, physical activity and exercise should be recommended **to reduce steatosis**

- Tailored to the individual's preference and ability (preferably >150 min/ week of moderate or 75 min/week of vigorous-intensity physical activity)

(LoE 1, strong recommendation, strong consensus).

Statement

- In comparison to the well-documented cardiometabolic benefits

- There is less robust evidence for benefits of physical activity and exercise on histological outcomes, non-invasively assessed liver damage/ fibrosis and liver-related clinical outcomes (LoE 5, strong consensus).

Question?

- In adults with MASLD who are normal weight, are diet and exercise interventions effective in reducing histologically/non-invasively assessed liver damage/ fibrosis and liver-related outcomes in comparison with no intervention?

Recommendation

- In normal-weight adults with MASLD, diet and exercise interventions should be recommended to **reduce liver fat** (LoE 3, strong recommendation, strong consensus).

Statement

- In normal-weight adults with MASLD, there is currently **no** evidence regarding the beneficial effect of diet and/or exercise on **liver histology, fibrosis** and liver related clinical outcomes (LoE 5, consensus).

Question
Nutraceuticals?

- In adults with MASLD, are nutraceuticals (food supplements, herbal products, gut microbiota-modifying agents) effective to reduce histologically/non-invasively assessed **liver damage/fibrosis** and liver-related outcomes compared with no intervention?

Recommendation

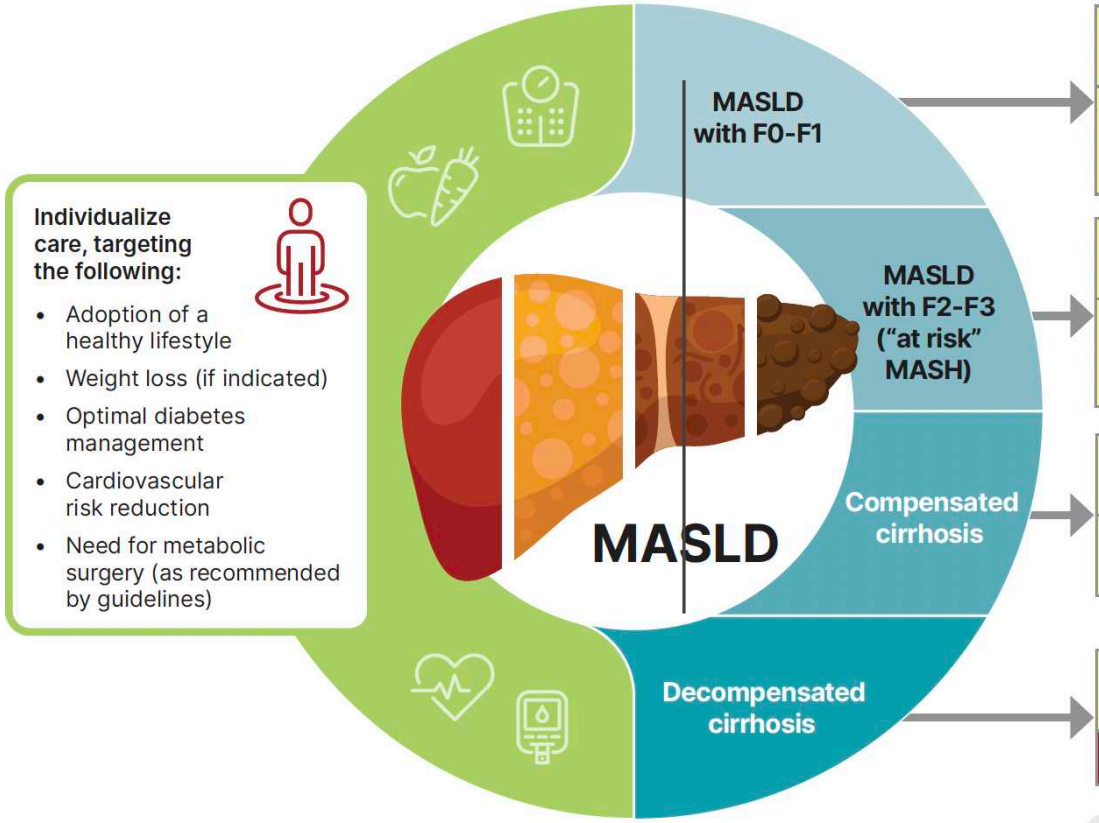
- In adults with MASLD, nutraceuticals **cannot be recommended** since there is insufficient evidence of their effectiveness in reducing histologically/non-invasively assessed **liver damage/fibrosis** and liver-related outcomes in MASLD, **nor of their safety** (LoE 2, open recommendation, strong consensus).

Statement

- In adults with MASLD, coffee consumption has been associated with improvements in liver damage and reduced liver-related clinical outcomes in observational studies (LoE 4, strong consensus).

Pharmacological treatment

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) Treatment Algorithm



Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, SGLT2i	Not indicated

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone	Resmetirom

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
As with F2-F3 with caution*	As with F2-F3 with caution*	ⓘ AVOID

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
ⓘ AVOID	Only use insulin	ⓘ AVOID

Metformin effects on mortality in compensated cirrhosis

DDZ German Diabetes Center

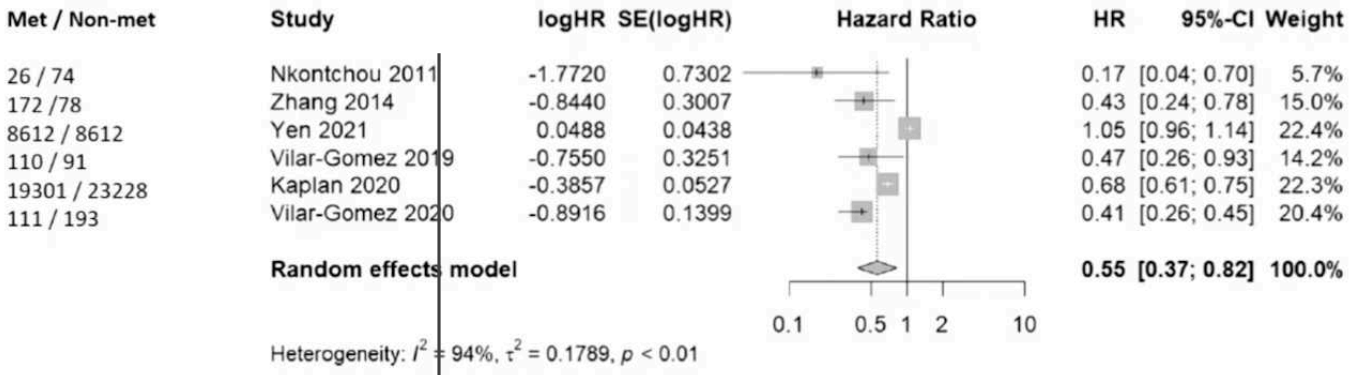


Fig. 2. Forest plot depicting the meta-analysis performed using multivariate-adjusted hazard ratios of all-cause mortality or liver transplantation in metformin users versus non-users. CI, confidence interval; HR, hazard ratio; SE, standard error.

Peppas et al. *Eur J Gastroenterol Hepatol* 36:674,2024

- NO relevant effects on steatosis or MASH
- Prevention of hepatic decompensation in cirrhosis: HR: 0.97; 95% [0.77–1.22]
- Reduction in all-cause mortality or LTX: HR: 0.50; 95% [0.38–0.65] in MASH cirrhosis (subgroup)
- NO CONTROLLED trials in cirrhosis, (direct) mechanisms of possible benefit unclear

Question
Non-glucose lowering drugs?

- In adults with MASH, is there sufficient evidence to recommend **non-glucose lowering drugs** to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes

Resmetirom

Thyromimetics that are selective for the β subtype (liver expressed)

Resmetirom is, an orally active

- Liver-directed
- Thyroid hormone receptor agonist
- **With high selectivity for the β 1 receptor**

Recommendations

- If approved locally, adults with non-cirrhotic MASH with significant liver fibrosis (stage ≥2) should be considered for treatment with **resmetirom as a MASH-targeted therapy**

- As this treatment demonstrated histological efficacy on steatohepatitis and fibrosis in a large phase III registrational trial with an acceptable safety and tolerability profile (LoE 2, strong recommendation, consensus).

Resmetirom

- Treatment with resmetirom, if approved locally, may be considered for individuals with MASLD who are non-cirrhotic and with documentation of either:

A) advanced fibrosis

B) at-risk steatohepatitis with significant fibrosis (by liver biopsy, or by non-invasive panels validated for that purpose); or

C) risk of adverse liver-related outcom y elastography- or biomarker-defined
(LoE 3, open recommendation, consensus).

Cirrhotic stage

- No MASH-targeted pharmacotherapy can currently be recommended for adults with MASH at the cirrhotic stage (LoE 5, weak recommendation, strong consensus).

Statement

long term data

- For individuals with MASLD undergoing therapy with resmetirom, data on sustainability of histological benefits, individual prediction of response, liver-related outcomes and long-term safety are not currently available (LoE 5, strong consensus)

Liver-directed thyroid hormone receptor agonists

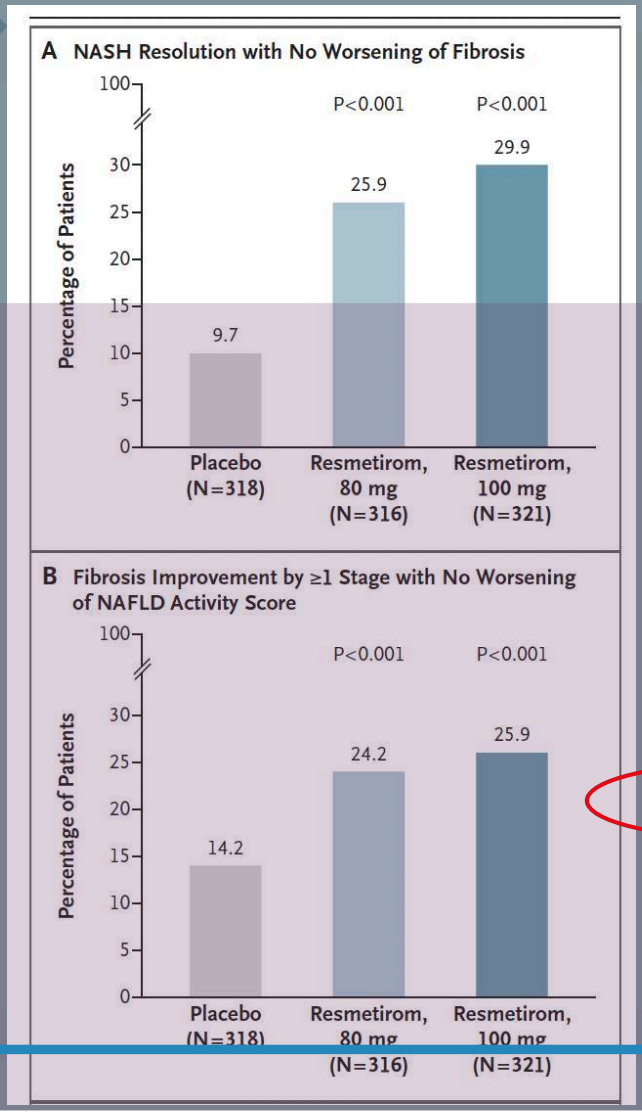
- The incidence of clinical and subclinical hypothyroidism appears to be higher in individuals with MASLD or MASH relative to age-matched controls, and low thyroid function is associated with more severe outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

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

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*



resolution of NA

worsening of fibr

Currently, resme

with positive resu

Resmetirom

- Resmetirom performed better than placebo as it **improved both disease activity (resolution of steatohepatitis) and fibrosis.**

- Progression of fibrosis in individuals with stage 2 fibrosis was lower than in the placebo arm

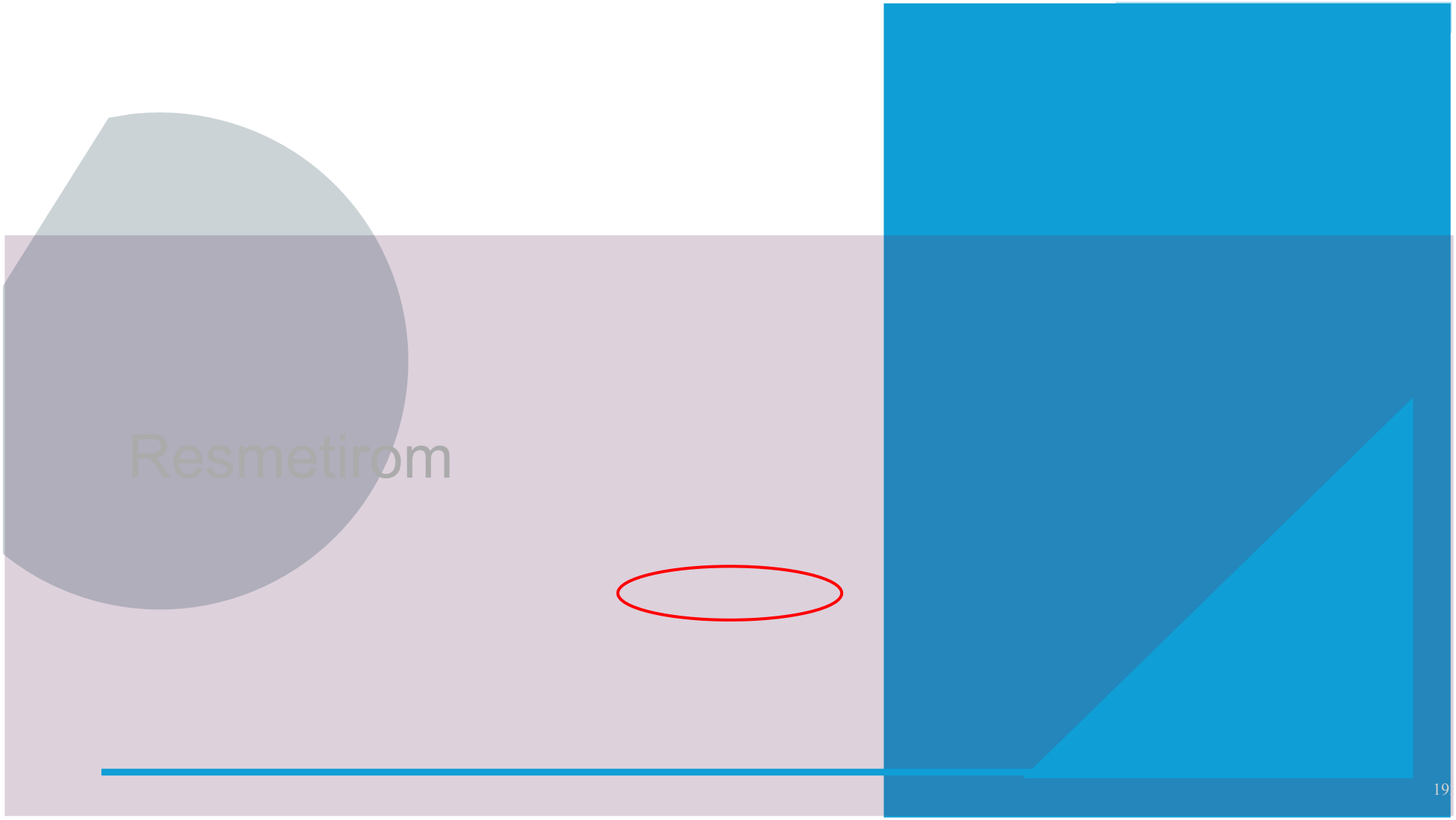
Resmetirom- Side effects

Nausea, vomiting, and diarrhea occurred more often with res

GI side effects are dose dependent and improve with continu

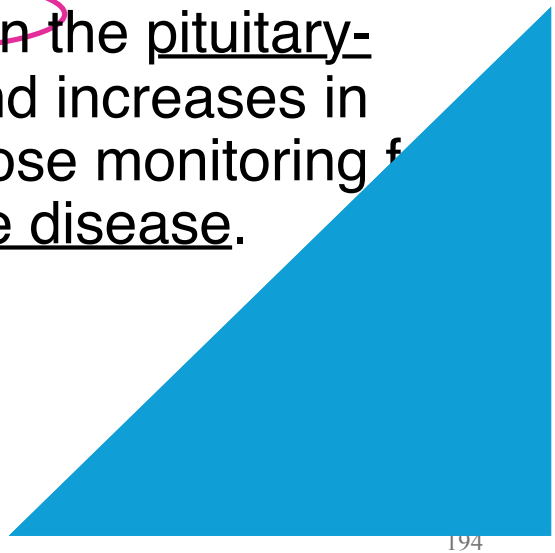
Resmetirom decreased FT4 levels by 20% and increased SH

Although a recent review of the data concluded that there is l
long-term post marketing data must be collected


Resmetirom

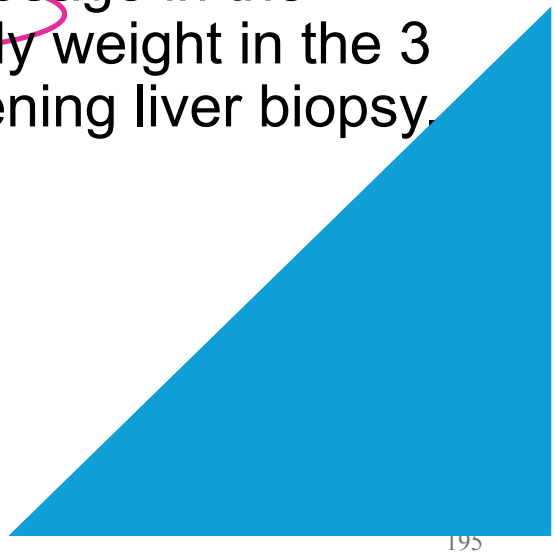
Resmetirom

- Linked to the lack of long-term data, there is uncertainty regarding long-term safety and effectiveness of resmetirom.
- Particularly the effects on the pituitary-thyroid hormone axis and increases in SHGB levels warrant close monitoring f thyroid, gonadal or bone disease.



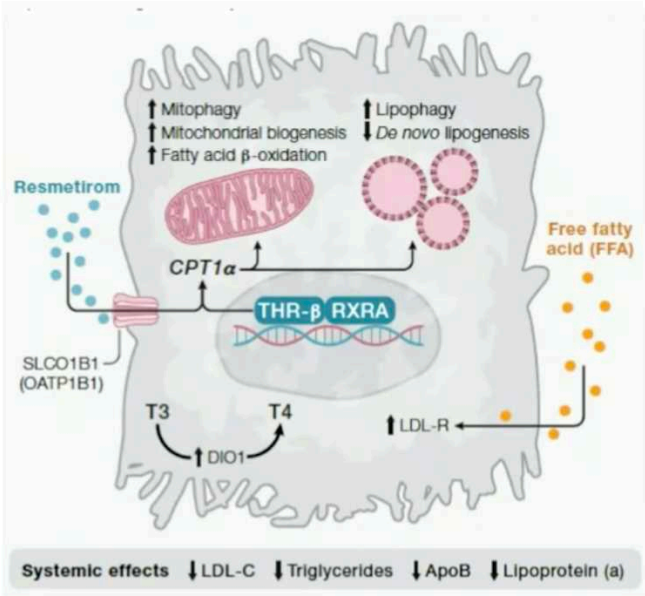
Resmetirom plus GLP-1RA

- About 14%of participants in the MAESTRO-NASH trial were on **GLP1RA** treatment, with stable dosage in the 6months and stable body weight in the 3 months preceding screening liver biopsy.



Addressing energy metabolism: Liver-selective THRß agonists

DDZ German Diabetes Center



Sookoian & Pirola. *Cell* 187, June 6, 2024

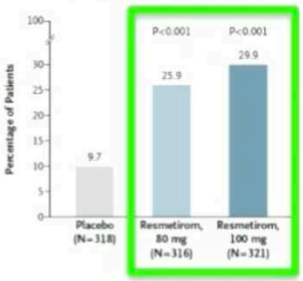
MAESTRO-NASH:

52-w db, pc phase 3 RCT; 1:1:1

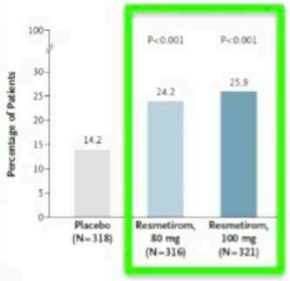
resmetirom 80, 100 mg or PLC

n=966, **NASH F1B-F3, 65-70% T2D**

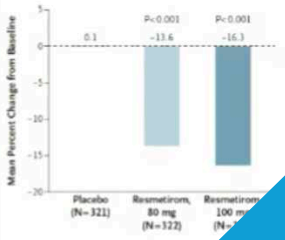
NASH resolution



Fibrosis reduction



Change in LDL



Side effects:

- **Decrease in fT4 and TSH**
- **Increases in estradiol and testosterone (mal**
- **Diarrhea (initially), nausea**
- **No effects on heart rate, BW, glycemia**

Harrison et al. *N Engl J Med*

What about Vitamin E?

- Given the lack of robust demonstration of histological efficacy on steatohepatitis and liver fibrosis derived from large phase III trials and
- potential long-term risks
- **Vitamin E cannot be recommended** as a MASH-targeted therapy (LoE 2, weak recom , strong consensus).

Question
Glucose-lowering drugs?

- In adults with MASH, is there sufficient evidence to recommend prescription of existing glucose-lowering drugs to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared to no pharmacological intervention?

Recommendations

- In the absence of a formal demonstration of histological improvement in large, well conducted, phase III trials, **GLP1RA cannot currently be recommended as MASH-targeted therapies**

(LoE 5, strong recommendation, strong consensus)

Recommendations

- GLP1RAs **are safe to use in MASH** (including compensated cirrhosis) and should be **used for their respective indications**, namely type 2 diabetes and obesity, as their use improves cardiometabolic outcomes (LoE 2, strong recommendation, strong consensus)

Recommendations

- **Pioglitazone is safe to use in adults with non-cirrhotic MASH**

- But given the **lack of robust** demonstration of histological efficacy on steatohepatitis and liver fibrosis in large phase III trials, pioglitazone ca recommended as a **MASH-targeted therapy** (LoE 2, weak recommendation, c

Recommendations

- Pioglitazone reverses steatohepatitis in people with prediabetes or type 2 diabetes and even in individuals without diabetes.

- Fibrosis also improved in some trials.

- A meta-analysis concluded that pioglitazone treatment results in resolution of MASH and may improve fibrosis

Recommendations

- There is insufficient evidence to recommend the use of sodium-glucose cotransporter-2 **(SGLT2) inhibitors or metformin** as MASH-targeted therapies;

- However, they are safe to use in MASLD and should be used for their respective indications, namely type 2 diabetes, heart failure and chronic kidney disease (LoE 3, strong recommendation, strong consensus).

scientific reports

Check for updates

OPEN

Efficacy of sodium glucose cotransporter 2 inhibitors on hepatic fibrosis and steatosis in non-alcoholic fatty liver disease: an updated systematic review and meta-analysis

Albert Macaire C. Ong Lopez[1]✉ & Janine Audrei T. Pajimna[2]

Scientifc Reports | (2024) 14:2122 |
https://doi.org/10.1038/s41598-024-52603-5

Conclusion

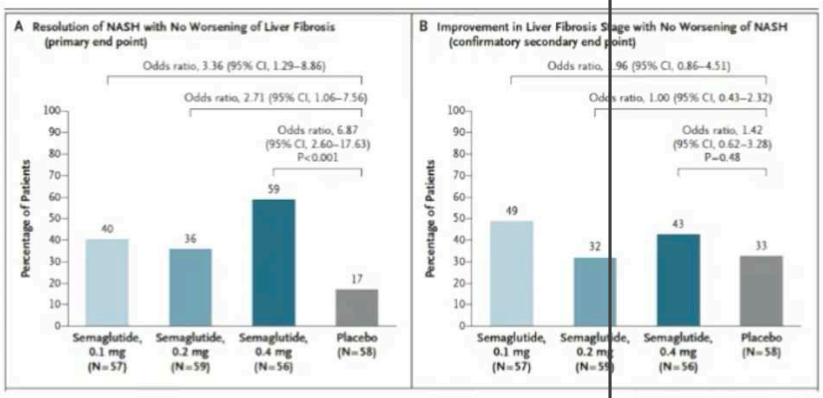
- The pooled meta-analysis suggests that SGLT2 inhibitors **slightly improve hepatic steatosis and fibrosis** as compared to controls in adult patients with NAFLD and T2DM **with low to moderate certainty of evidence**

RCTs of GLP-1RA semaglutide for

DDZ German Diabetes Center

RCT, n=320, 72 w

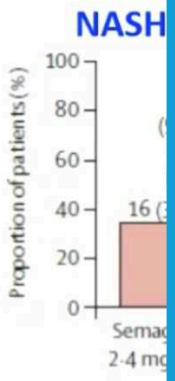
BMI 36 kg/m², 62% T2DM, HbA1c 7.3%, **50% F3**



Newsome et al. *NEJM* 384:1113,2021

RCT, n=6

BMI 35 k



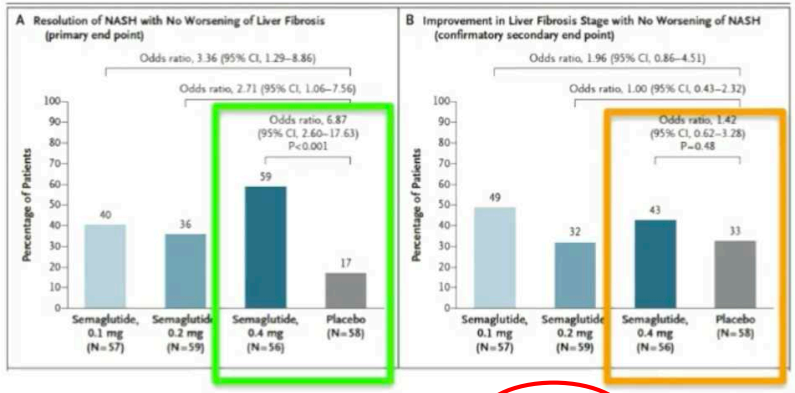
Loomba et

RCTs of GLP-1RA semaglutide for

DDZ German Diabetes Center

RCT, n=320, 72 w

BMI 36 kg/m², 62% T2DM, HbA1c 7.3%, **50% F3**



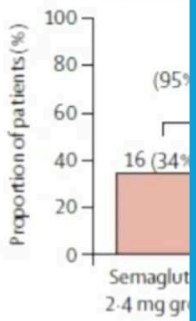
- NASH resolution: Yes
- Fibrosis improvement: No

Newsome et al. *NEJM* 384:1113,2021

RCT, n=67,

BMI 35 kg/

NASH r



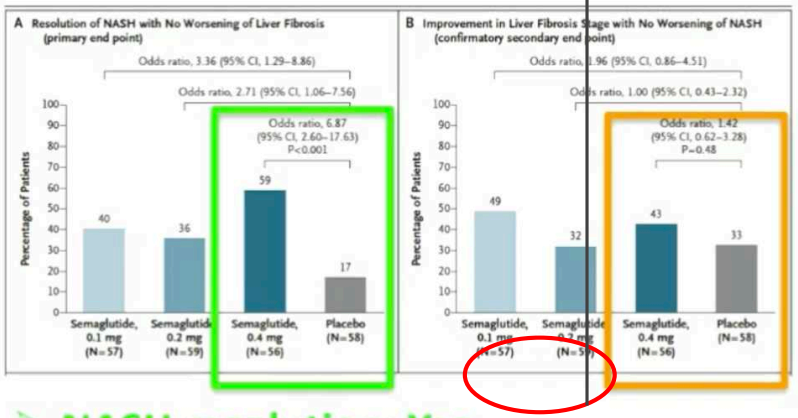
Loomba et al

RCTs of GLP-1RA semaglutide for MASH +/-fibrosis

DDZ German Diabetes Center

RCT, n=320, 72 w

BMI 36 kg/m², 62% T2DM, HbA1c 7.3%, **50% F3**

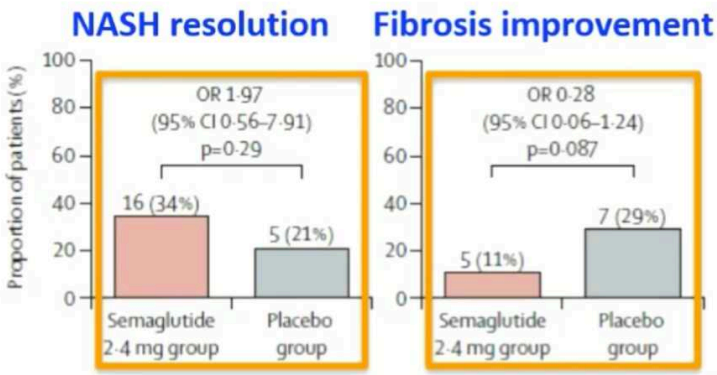


- NASH resolution: Yes
- Fibrosis improvement: No

Newsome et al. *NEJM* 384:1113,2021

RCT, n=67, 48 w

BMI 35 kg/m², 75% T2D, HbA1c 7.2%, **all F4**



- Loss of BW and liver fat: Yes
- NASH resolution: No
- Fibrosis improvement: No

Loomba et al. *Lancet Gastroenterol Hepatol* 8:511,2023

Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial

Rohit Loomba, Manal F Abdelmalek, Matthew J Armstrong, Maximilian Jara, Mette Skalshøi Kjær, Niels Krarup, Eric Lawitz, Vlad Ratziu, Arun J Sanyal, Jörn M Schattenberg, Philip N Newsome*, on behalf of the NN9931-4492 investigators†*

71 patients

49 (69%) patients were female and 22 (31%) were male
Mean age of 59·5 years
Mean BMI of 34·9 kg/m²
53 (75%) patients had diabetes.
47 patients were randomly assigned to the semaglutide group and 24 to the placebo group.

After 48 weeks, there was no statistically significant difference between the two groups in the proportion of patients with an improvement in liver fibrosis of one stage or more without worsening of NASH
(five [11%] of 47 patients in the semaglutide group vs seven [29%] of 24 in the placebo group; odds ratio 0·28 [95% CI 0·06–1·24; p=0·087).

There was also no significant difference between groups in the proportion of patients v achieved NASH resolution (p=0·29).

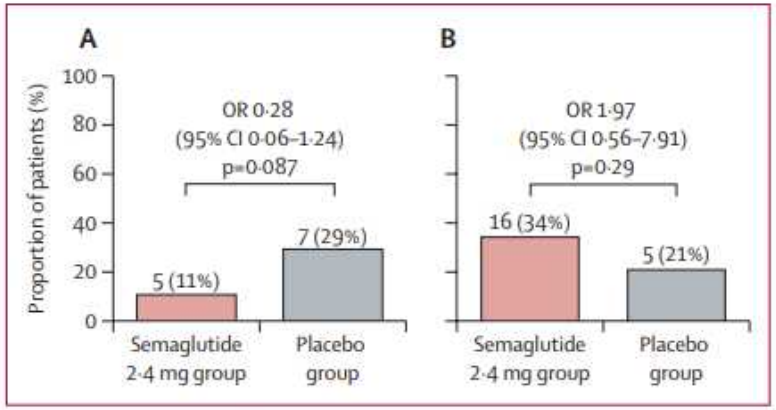
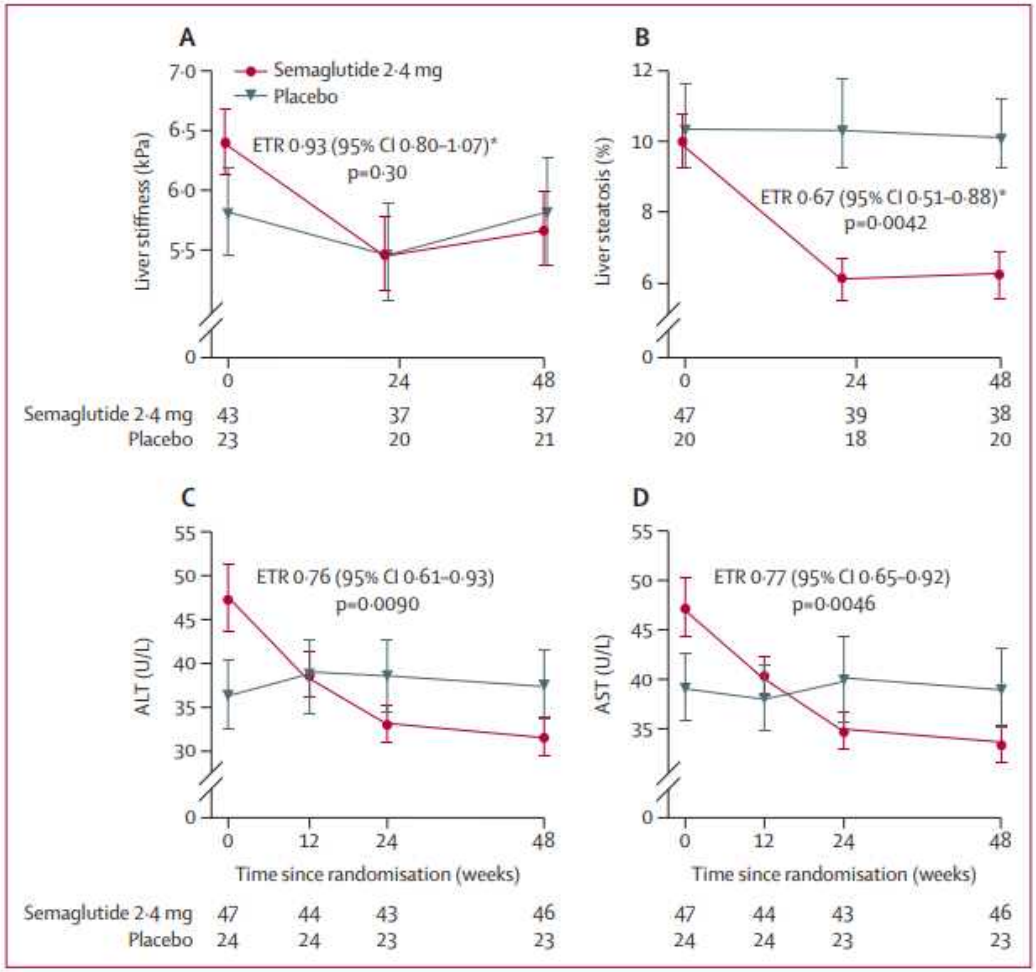


Figure 2: **Improvement in liver fibrosis and no worsening of NASH (A) and resolution of NASH (B) at 48 weeks**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

320 patients (of whom 230 had stage F2 or F3 fibrosis) randomly assigned to receive semaglutide

0.1 mg (80 patients)
0.2 mg (78 patients)

0.4 mg (82 patients)

placebo (80 patients)

72-week, double-blind phase 2 trial

The primary end point was resolution of NASH with no worsening of fibrosis.

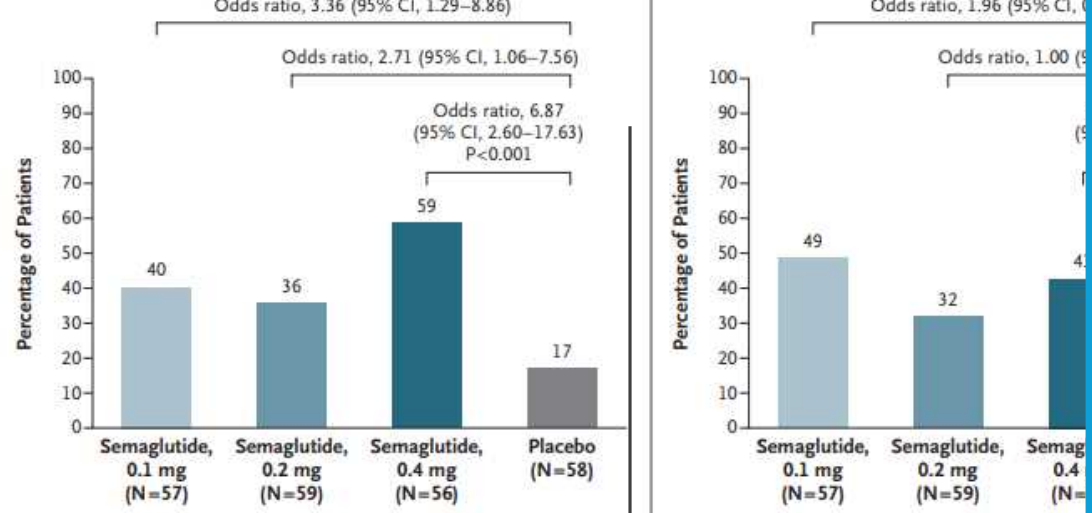


Figure 1. Primary and Secondary Confirmatory End Points.

Panel A shows the observed percentages of patients with stage F2 or F3 fibrosis in whom resolution of nonalcoho
(NASH) was achieved by week 72 with no worsening of liver fibrosis (with worsening defined as an increase of one
lution was defined by the NASH Clinical Research Network as no more than mild residual inflammatory cells [scor
hepatocyte ballooning [score of 0]). Panel B shows the observed percentages of patients with stage F2 or F3 fibrosis
ment of at least one fibrosis stage by week 72 with no worsening of NASH (with worsening defined as an increase
the lobular inflammation score or the hepatocyte ballooning score according to the NASH Clinical Research Networ
analyzed with the use of a Cochran–Mantel–Haenszel test stratified according to baseline diabetes status and bas
Data from the in-trial observation period (from randomization until the last study-related procedure) were include
come data were imputed as nonresponse.

published on April 30, 2025, at NEJM.org.

New

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

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Patients and methods

- In this ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled trial
- 1197 patients with biopsy-defined MASH and fibrosis stage 2 or 3
- in a 2:1 ratio to receive once-weekly S/C semaglutide at a dose of 2.4 mg or placebo for 240 weeks.

Patients and methods

The results of a planned interim analysis conducted at week 72 involving the first 800 patients are reported here (part 1).

The primary end points for part 1 were the resolution of steatohepatitis without worsening of liver fibrosis and reduction in liver fibrosis without worsening of steatohepatitis.

Results

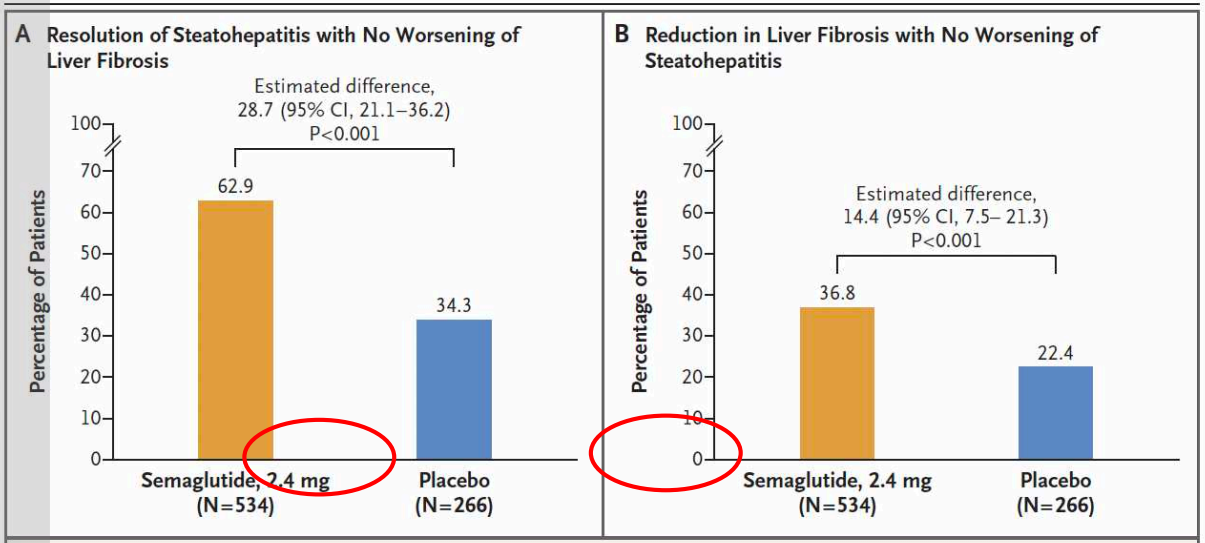

Figure 1. Primary End Points.

The figure shows the percentage of patients with fibrosis stage 2 or 3 who had resolution of steatohepatitis with no worsening of liver fibrosis (Panel A) and reduction in liver fibrosis with no worsening of steatohepatitis (Panel B) after 72 weeks, with the estimated difference expressed in percentage points.

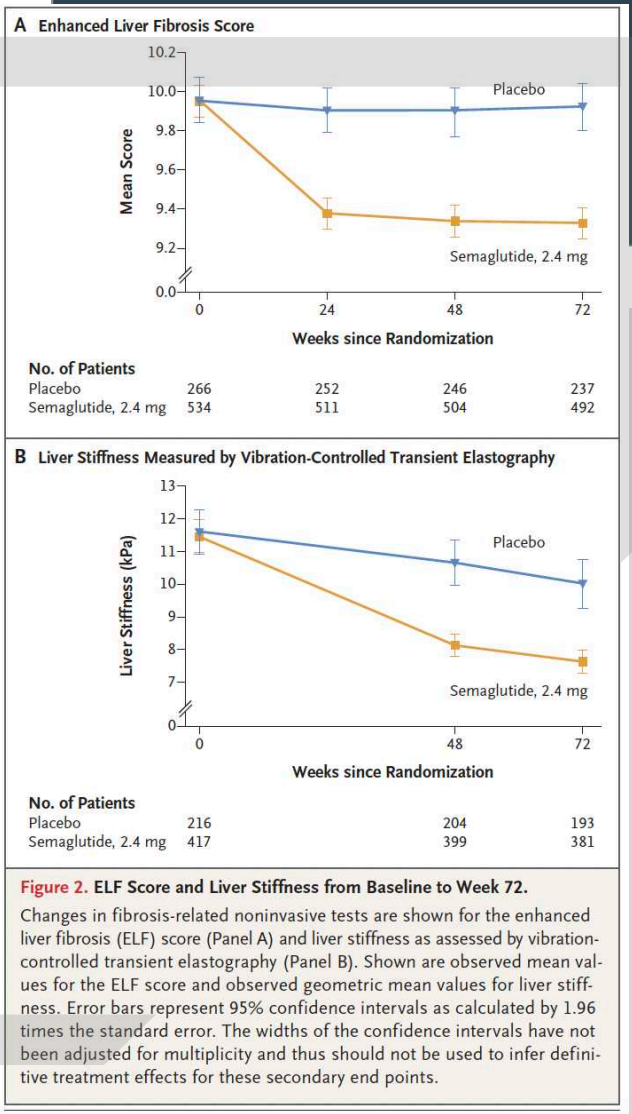

Figure 2. ELF Score and Liver Stiffness from Baseline to Week 72.

Changes in fibrosis-related noninvasive tests are shown for the enhanced liver fibrosis (ELF) score (Panel A) and liver stiffness as assessed by vibration-controlled transient elastography (Panel B). Shown are observed mean values for the ELF score and observed geometric mean values for liver stiffness. Error bars represent 95% confidence intervals as calculated by 1.96 times the standard error. The widths of the confidence intervals have not been adjusted for multiplicity and thus should not be used to infer definitive treatment effects for these secondary end points.

RESULTS

- Results for the three secondary outcomes

- **<u>Combined resolution of steatohepatitis and reduction in liver fibrosis was reported in</u>**
- 32.7% of the patients in the semaglutide group
- 16.1% of those in the placebo group

- (estimated difference, 16.5 percentage points; 95% CI, 10.2 to 22.8; P<0.001).

CONCLUSIONS

- In patients with MASH and moderate or advanced liver fibrosis, once-weekly semaglutide at a dose of 2.4 mg improved liver histologic results.

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Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

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Phase 2, dose-finding, multicenter, double-blind, RCT involving participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis

once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks

The primary end point was resolution of MASH without worsening of fibrosis at 52 weeks.

A key secondary end point was an improvement (decrease) of at least one fibrosis stage without worsening of MASH

190 participants who had undergone randomization,
157 had liver-biopsy results at week 52 that could be evaluated

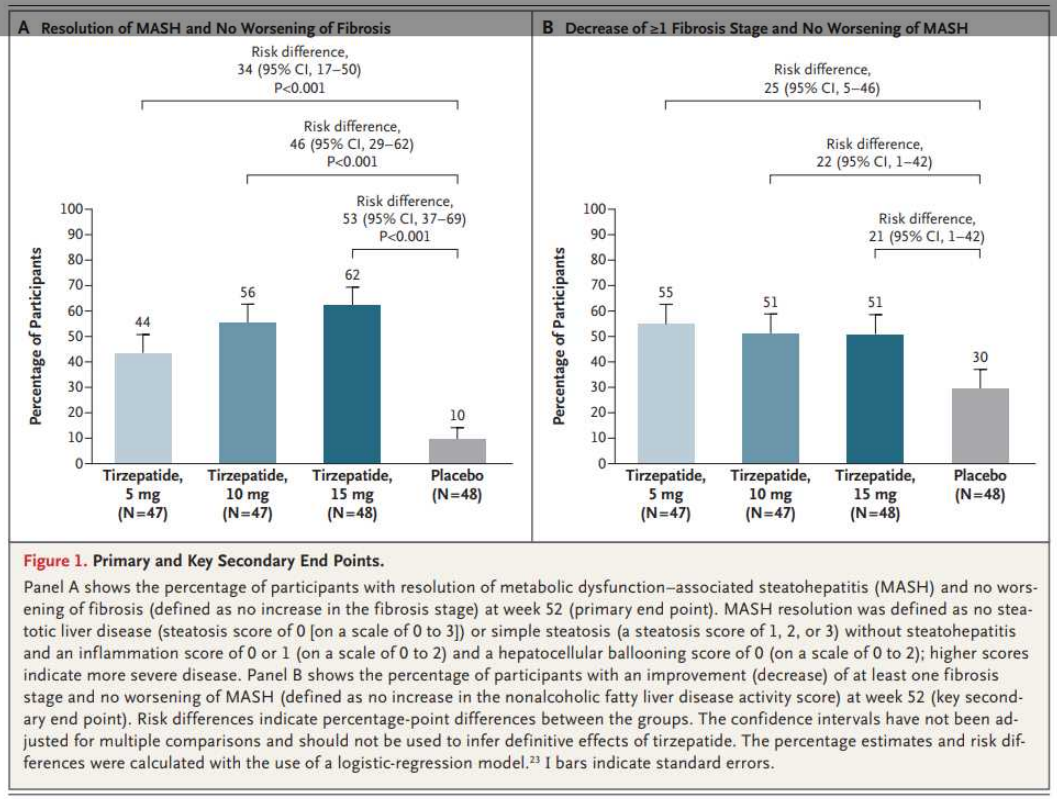


Figure 1. Primary and Key Secondary End Points.

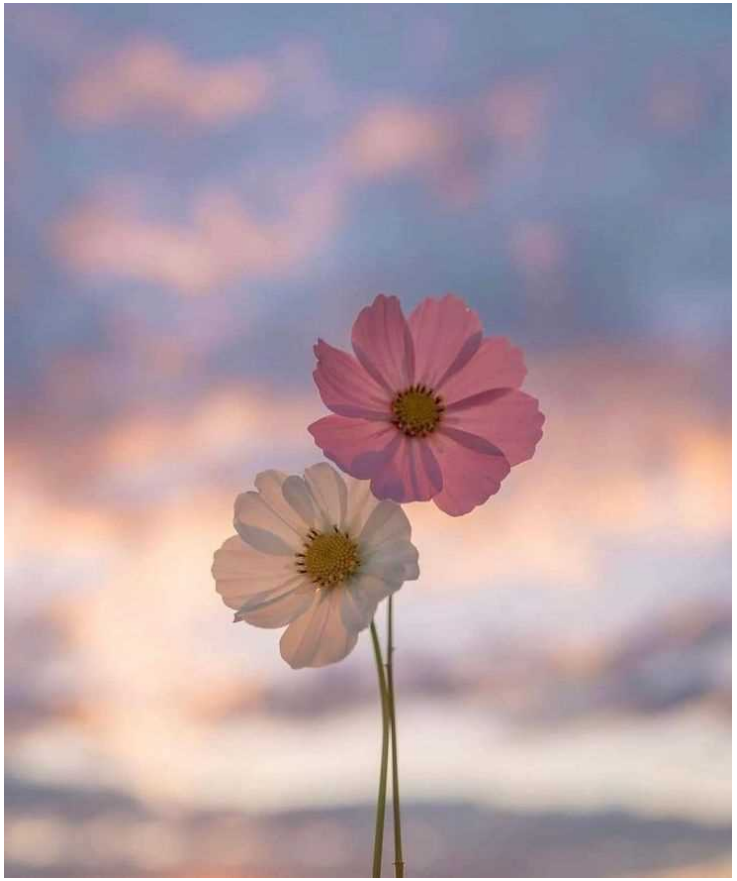
Panel A shows the percentage of participants with resolution of metabolic dysfunction–associated steatohepatitis (MASH) and no worsening of fibrosis (defined as no increase in the fibrosis stage) at week 52 (primary end point). MASH resolution was defined as no steatotic liver disease (steatosis score of 0 [on a scale of 0 to 3]) or simple steatosis (a steatosis score of 1, 2, or 3) without steatohepatitis and an inflammation score of 0 or 1 (on a scale of 0 to 2) and a hepatocellular ballooning score of 0 (on a scale of 0 to 2); higher scores indicate more severe disease. Panel B shows the percentage of participants with an improvement (decrease) of at least one fibrosis stage and no worsening of MASH (defined as no increase in the nonalcoholic fatty liver disease activity score) at week 52 (key secondary end point). Risk differences indicate percentage-point differences between the groups. The confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive effects of tirzepatide. The percentage estimates and risk differences were calculated with the use of a logistic-regression model.[23] I bars indicate standard errors.

CONCLUSIONS

- In this phase 2 trial involving participants with MASH and moderate or severe fibrosis, treatment with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis.

- Larger and longer trials are needed to further assess the efficacy and safety of tirzepatide for the treatment of MASH.

(Funded by Eli Lilly; SYNERGY-NASH ClinicalTrials.gov number, NCT04166773.)



Thank you