~~NAFLD~~

OBESITY AND MASLD

~~MAFLD~~

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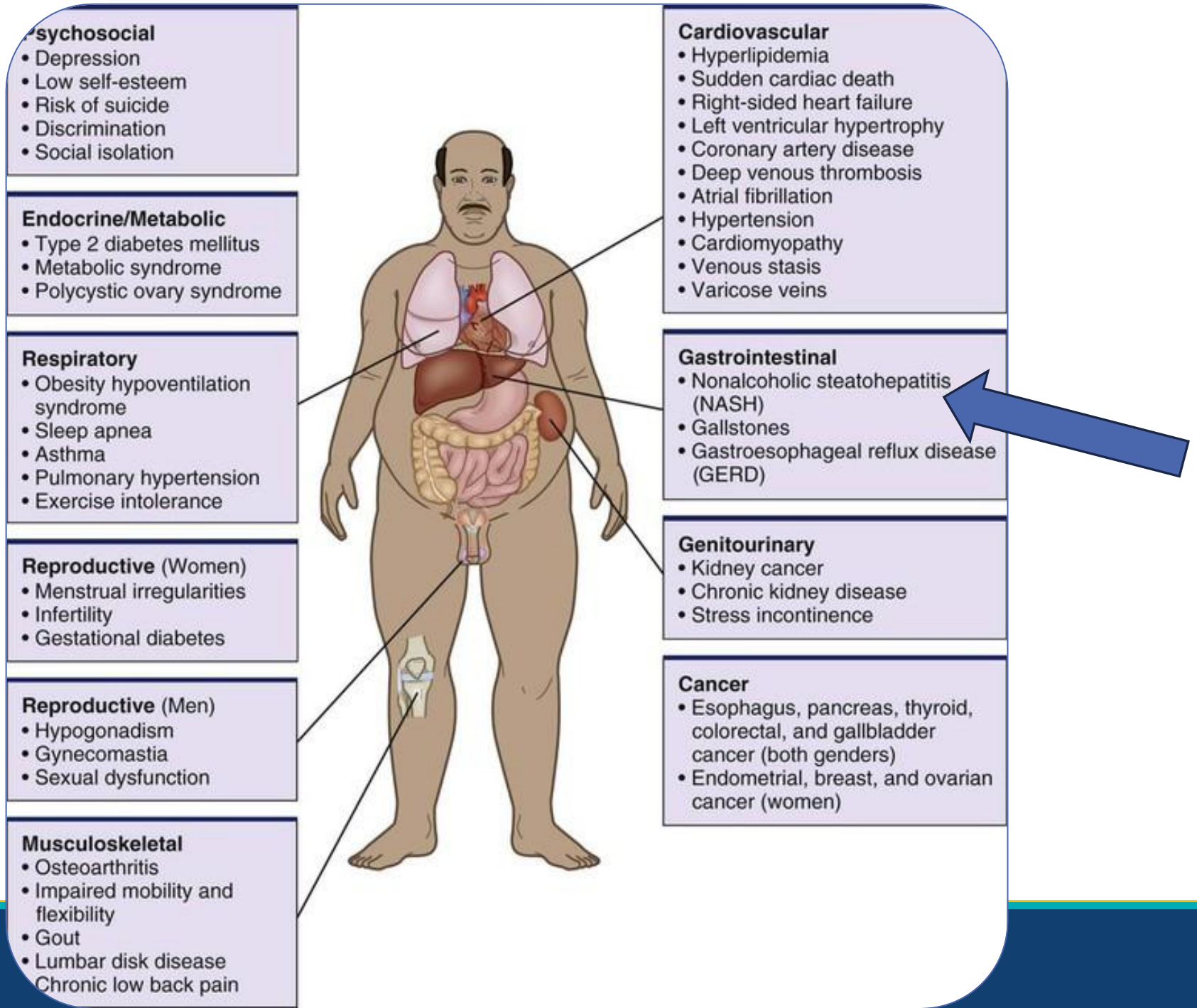
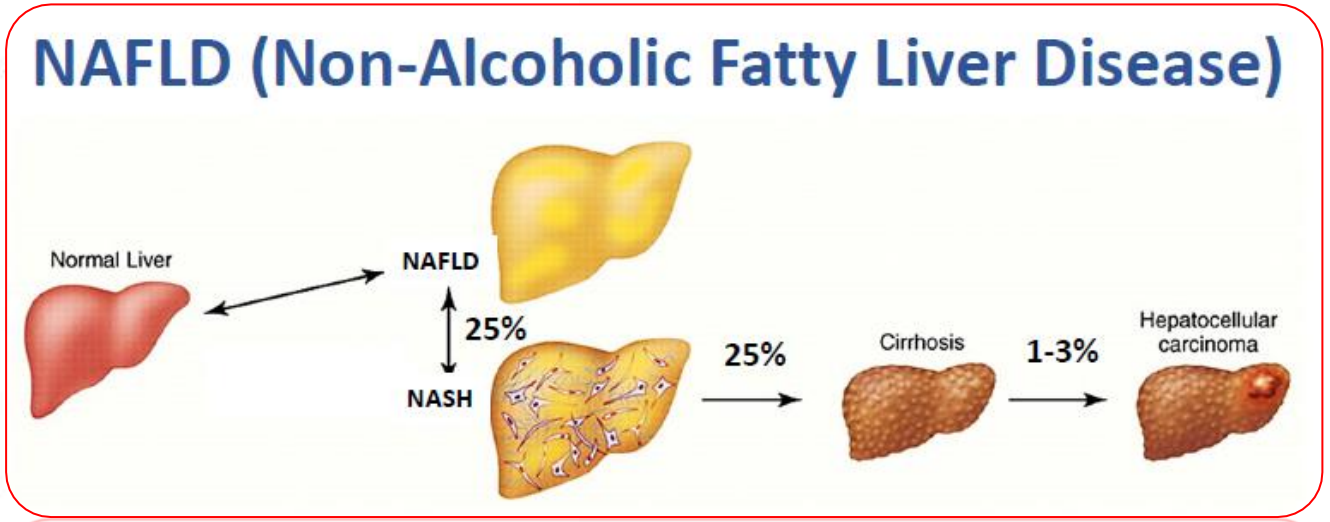
Direct link to 60- 200 comorbidites





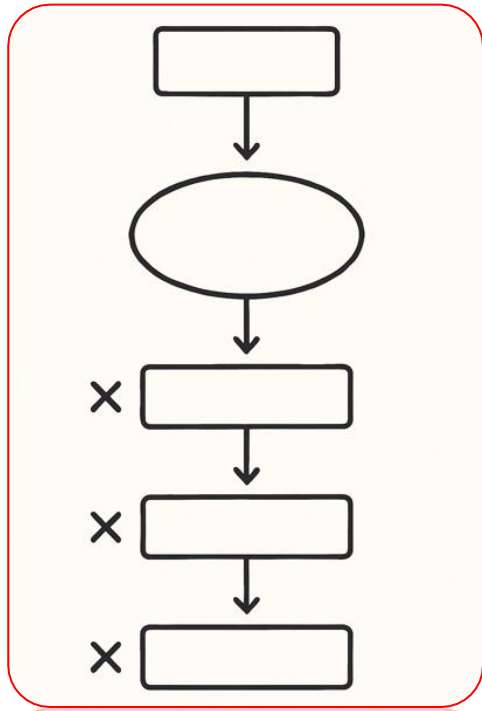
91% of pts...OBESE!

Characteristics

Accumulation of triglycerides in hepatocytes (> 5% of the total liver weight)

Reduced (/NO) alcohol intake (less than 20g/day for women and 30g/day for men)

(Excluded diagnosis of viral infection, toxicity, selfimmunity etc)



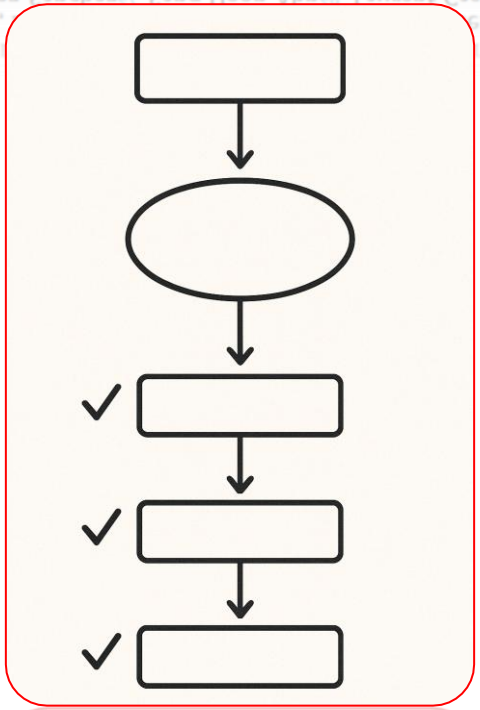
Expert Opinion

JOURNAL OF HEPATOLOGY

2020

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,*,‡]



Hepatic steatosis in adults
(detected either by imaging techniques, blood biomarkers/scores or by liver histology)

Overweight or obesity
(defined as BMI ≥25 kg/m² in Caucasians or BMI ≥23 kg/m² in Asians)

Lean/normal weight
(defined as BMI <25 kg/m² in Caucasians or BMI <23 kg/m² in Asians)

Type 2 diabetes mellitus
(According to widely accepted international criteria)

***If* presence of <u>at least</u> two metabolic risk abnormalities:**

- Waist circumference ≥102/88 cm in Caucasian men and women (or ≥90/80 cm in Asian men and women).
- Blood pressure ≥130/85 mmHg or specific drug treatment.
- Plasma triglycerides ≥150 mg/dL (≥1.70 mmol/l) or specific drug treatment .
- Plasma HDL-cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment.
- Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dL (5.6 to 6.9 mmol/L), or 2-hour post-load glucose levels 140 to 199 mg/dL (7.8 to 11.0 mmol) or HbA1c 5.7% to 6.4% (39–47 mmol/mol)).
- Homeostasis model assessment (HOMA)-insulin resistance score ≥2.5
- Plasma high-sensitivity C-reactive protein (hs-CRP) level >2 mg/L

MAFLD
(Metabolic associated fatty liver disease)

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https://doi.org/10.1042/CS20220572

2022

PORTLAND PRESS

Review Article

Molecular mechanisms of metabolic associated fatty liver disease (MAFLD): functional analysis of lipid metabolism pathways

Olufunto O. Badmus[1], Sarah A. Hillhouse[1], Christopher D. Anderson[2], Terry D. Hinds Jr[3] and David E. Stec[1]

[1]Department of Physiology and Biophysics, Cardiorenal, and Metabolic Diseases Research Center, University of Mississippi Medical Center, Jackson, MS 39216, U.S.A.; [2]Department of Surgery, University of Mississippi Medical Center, Jackson, MS 39216, U.S.A.; [3]Department of Pharmacology and Nutritional Sciences, Barnstable Brown Diabetes Center, Markey Cancer Center, University of Kentucky, Lexington, KY 40508, U.S.A.

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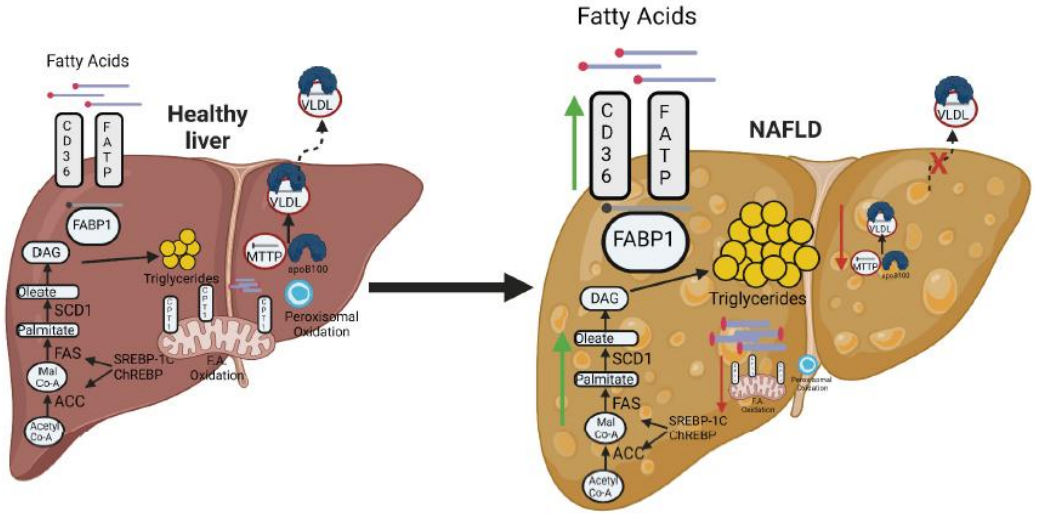
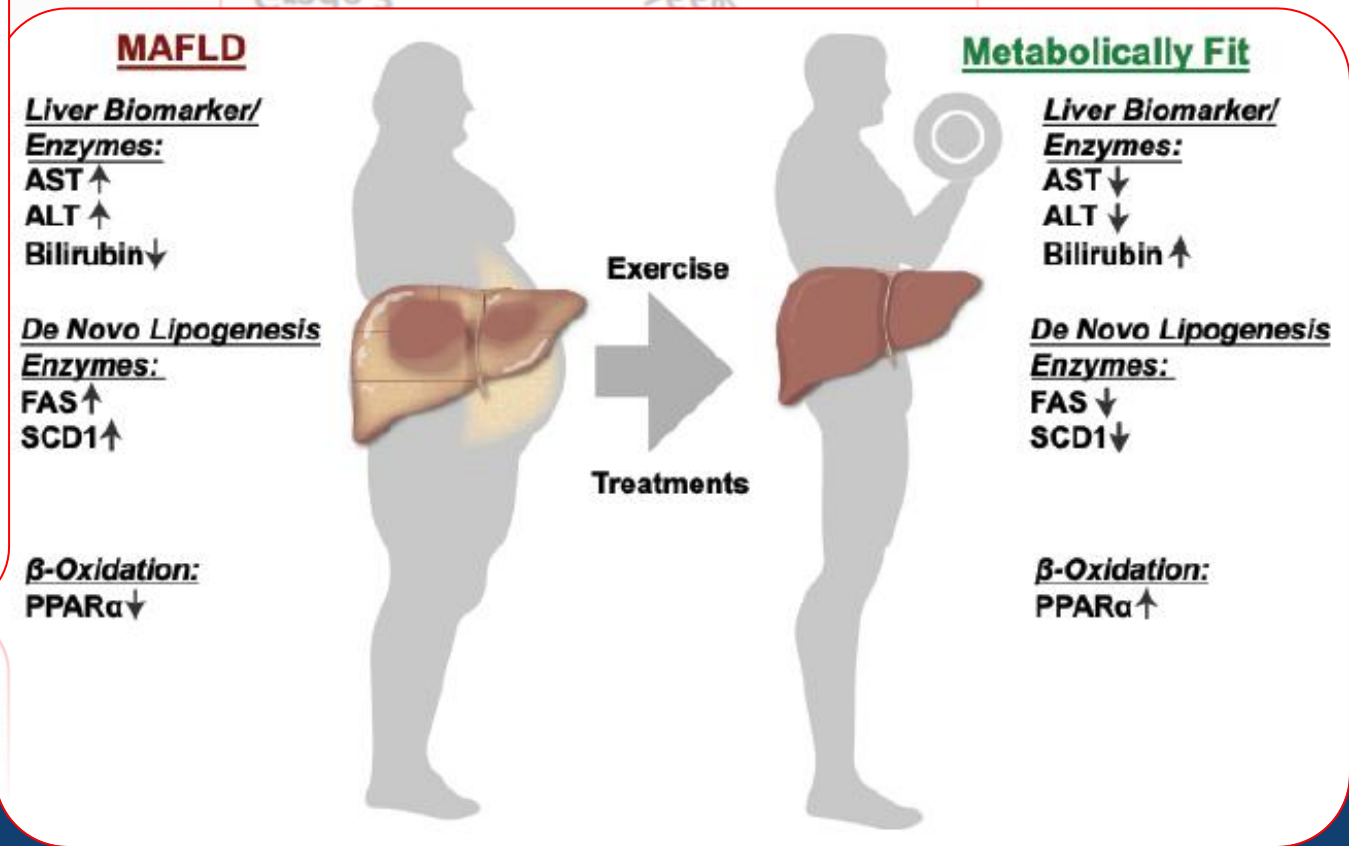


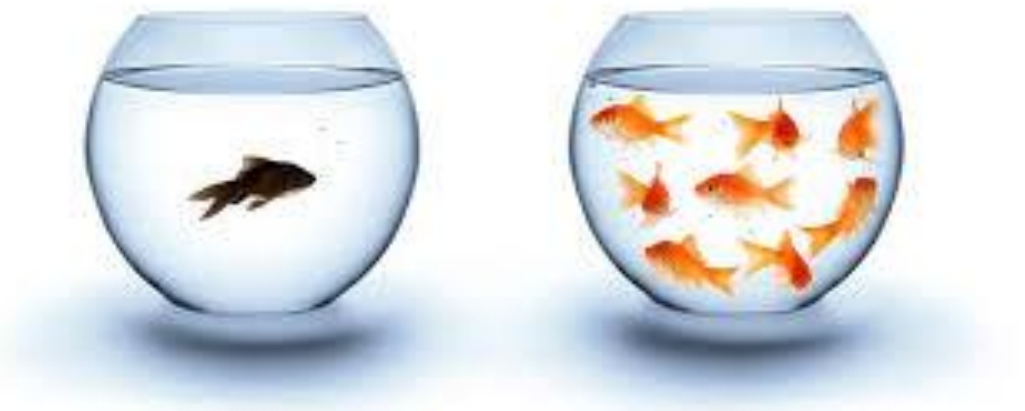
Figure 3. Pathways governing lipid accumulation in the liver

Fatty acid uptake and *de novo* lipogenesis can be up-regulated in MAFLD (green arrows), while fatty acid export and oxidation of fatty acids by the mitochondria and peroxisomes are decreased in MAFLD (red arrows); ACC, acetyl-CoA carboxylase; DAG, diacylglycerol; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase-1; VLDL, very-low-density lipoprotein. Created with Biorender.com

Grade	Percent Fat
Grade 0	<5%
Grade 1	5-33%
Grade 2	34-66%
Grade 3	>66%



NAFLD (Nonalcoholic Fatty Liver Disease)	MAFLD (Metabolic Associated Fatty Liver Disease)
Hepatic steatosis (detected by imaging methods, serum biomarker scores, or histology)	Hepatic steatosis (detected by imaging methods, serum biomarker scores, or histology)
No excessive alcohol consumption (a threshold of 20 g/day for women and 30 g/day for men is conventionally adopted)	One of the following metabolic criteria: • Overweight/obesity • Type 2 diabetes • Metabolic dysregulation[§]
No other causes of hepatic steatosis (e.g., HBV, HCV, drugs, hemochromatosis, autoimmunity, Wilson's disease, alpha 1 anti-trypsin deficiency, rapid weight loss)	[§]At least *two* features amongst: • increased waist circumference (i.e., ≥102/88 cm in Caucasian men and women or ≥90/80 cm in Asian men and women), • arterial hypertension (i.e., blood pressure ≥130/85 mmHg or drug treatment), • hypertriglyceridemia (i.e., plasma triglycerides ≥150 mg/dl or specific drug treatment), • low HDL-cholesterol (i.e., plasma HDL <40 mg/dl for men and <50 mg/dl for women or specific drug treatment), • prediabetes (i.e., fasting plasma glucose from 100 to 125 mg/dl or 2 hour post-load glucose levels from 140 to 199 mg/dl or HbA1c from 39 to 47 mmol/mol Hb), • insulin resistance (i.e., Homeostatic Model Assessment of Insulin Resistance [HOMA-IR] ≥2.5) • subclinical inflammation (i.e., high sensitivity C-reactive protein [hs-CRP] >2 mg/L)



Sports Medicine (2023) 53:2347–2371
https://doi.org/10.1007/s40279-023-01918-w

REVIEW ARTICLE

Exercise in the Management of Metabolic-Associated Fatty Liver Disease (MAFLD) in Adults: A Position Statement from Exercise and Sport Science Australia

Shelley E. Keating[1] · Angelo Sabag[2,3,4] · Kate Hallsworth[5,6,7] · Ingrid J. Hickman[8,9] · Graeme A. Macdonald[9,10] · Jonathan G. Stine[11,12,13,14] · Jacob George[15] · Nathan A. Johnson[2,3]

biomedicines
MDPI

Review

From NAFLD to MAFLD: Definition, Pathophysiological Basis and Cardiovascular Implications

Andrea Boccatonda [1,†], Lorenzo Andreetto [2,†], Damiano D'Ardes [3,*,†], Giulio Cocco [4], Ilaria Rossi [3], Susanna Vicari [1], Cosima Schiavone [4], Francesco Cipollone [3] and Maria Teresa Guagnano [3]

frontiers | Frontiers in Endocrinology

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Advancements in the treatment of non-alcoholic fatty liver disease (NAFLD)

Li Rong[1†], Junyan Zou[2,3†], Wei Ran[3], Xia
Yaokai Chen[3], Hongjuan Cui[2] and Jinju

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International Journal of
Molecular Sciences
MDPI

Review

Role of Insulin Resistance in MAFLD

Yoshitaka Sakurai [1], Naoto Kubota [1,2,3,*], Toshimasa Yamauchi [1] and Takashi Kadowaki [4,*]

International Journal of
Molecular Sciences
MDPI

Review

Pathophysiological Molecular Mechanisms of Obesity: A Link between MAFLD and NASH with Cardiovascular Diseases

Jorge Gutiérrez-Cuevas [1,*], Arturo Santos [2] and Juan Armendariz-Borunda [1,2,*]

2020-2023

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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

EASL™
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34 other members to ensuring broad geographic representation.

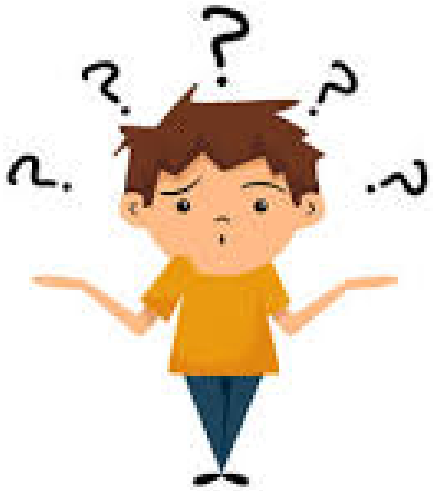
June 2023

SPECIAL ARTICLE

A multi-society Delphi consensus statement on new fatty liver disease nomenclature

Rinella, Mary E.[1]; Lazarus, Jeffrey V.[2,3]; Ratziu, Vlad[4]; Francque, Sven M.[5,6]; Sanyal, Arun J.[7]; Kanwal, Fasiha[8,9]; Romero, Diana[2]; Abdelmalek, Manal F.[10]; Anstee, Quentin M.[11,12]; Arab, Juan Pablo[13,14,15]; Arrese, Marco[15,16]; Bataller, Ramon[17]; Beuers, Ulrich[18]; Boursier, Jerome[19]; Bugianesi, Elisabetta[20]; Byrne, Christopher[21,22]; Castro Narro, Graciela E.[16,23,24]; Chowdhury, Abhijit[25]; Cortez-Pinto, Helena[26]; Cryer, Donna[27]; Cusi, Kenneth[28]; El-Kassas, Mohamed[29]; Klein, Samuel[30]; Eskridge, Wayne[31]; Fan, Jiangao[32]; Gawrieh, Samer[33]; Guy, Cynthia D.[34]; Harrison, Stephen A.[35]; Kim, Seung Up[36]; Koot, Bart[37]; Korenjak, Marko[38]; Kowdley, Kris[39]; Lacaille, Florence[40]; Loomba, Rohit[41]; Mitchell-Thain, Robert[42]; Morgan, Timothy R.[43,44]; Powell, Elisabeth[45,46,47]; Roden, Michael[48,49,50]; Romero-Gómez, Manuel[51]; Silva, Marcelo[52]; Singh, Shivaram Prasad[53]; Sookoian, Silvia C.[15,54,55]; Spearman, C. Wendy[56]; Tiniakos, Dina[11,57]; Valenti, Luca[58,59]; Vos, Miriam B.[60]; Wong, Vincent Wai-Sun[61]; Xanthakos, Stavra[62]; Yilmaz, Yusuf[63]; Younossi, Zobair[64]; Hobbs, Ansley[2]; Villota-Rivas, Marcela[65]; Newsome, Philip N[66,67]; on behalf of the NAFLD Nomenclature consensus group

..FROM MAFLD TO MASLD



MAFLD limits

No endorsement

No clear exclusion of different causes

No rigorous scientific definition

*Cardiometabolic criteria

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
- ☐ 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

Pediatric Criteria

At least 1 out of 5:

- ☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

Diagnostic tools

Blood Tests:

- *Liver function tests (LFTs) are checked to assess liver enzymes like ALT and AST.*
- *Blood tests also evaluate for other conditions like diabetes, high cholesterol, and metabolic syndrome.*
- *Tests can also rule out other causes of liver disease, such as viral hepatitis.*

Imaging Studies:

- *Ultrasound, CT scans, or MRI can show fat accumulation in the liver.*
- *Transient elastography (FibroScan) or MR elastography can measure liver stiffness and estimate fibrosis, helping assess the severity of the disease.*

Liver Biopsy:

- *Although not always necessary, a liver biopsy is the gold standard for diagnosis and can help differentiate MASLD from MASH (Metabolic Dysfunction-Associated Steatohepatitis).*
- *It involves taking a small tissue sample and examining it under a microscope.*

REVIEW OPEN ACCESS

Accuracy of Non-Invasive Imaging Techniques for the Diagnosis of MASH in Patients With MASLD: A Systematic Review

Jennifer Cathcart[1,2] | Rachael Barrett[1] | James S. Bowness[3,4] | Ashis Mukhopadhya[2] | Ruairi Lynch[1] | John F. Dillon[1]

[1]Division of Molecular and Clinical Medicine, University of Dundee, Dundee, UK | [2]Gastroenterology Department, Aberdeen Royal Infirmary, Aberdeen, UK | [3]University College London Hospitals NHS Foundation Trust, London, UK | [4]Department of Targeting Intervention, University College London, London, UK

Summary

- There is no clear imaging tool or score currently available to diagnose MASH.
- The most promising imaging tools are MRI techniques or ultrasound-based scores.
- More independent validation studies are needed; this will reduce bias.
- Future work should build on these studies with validation.

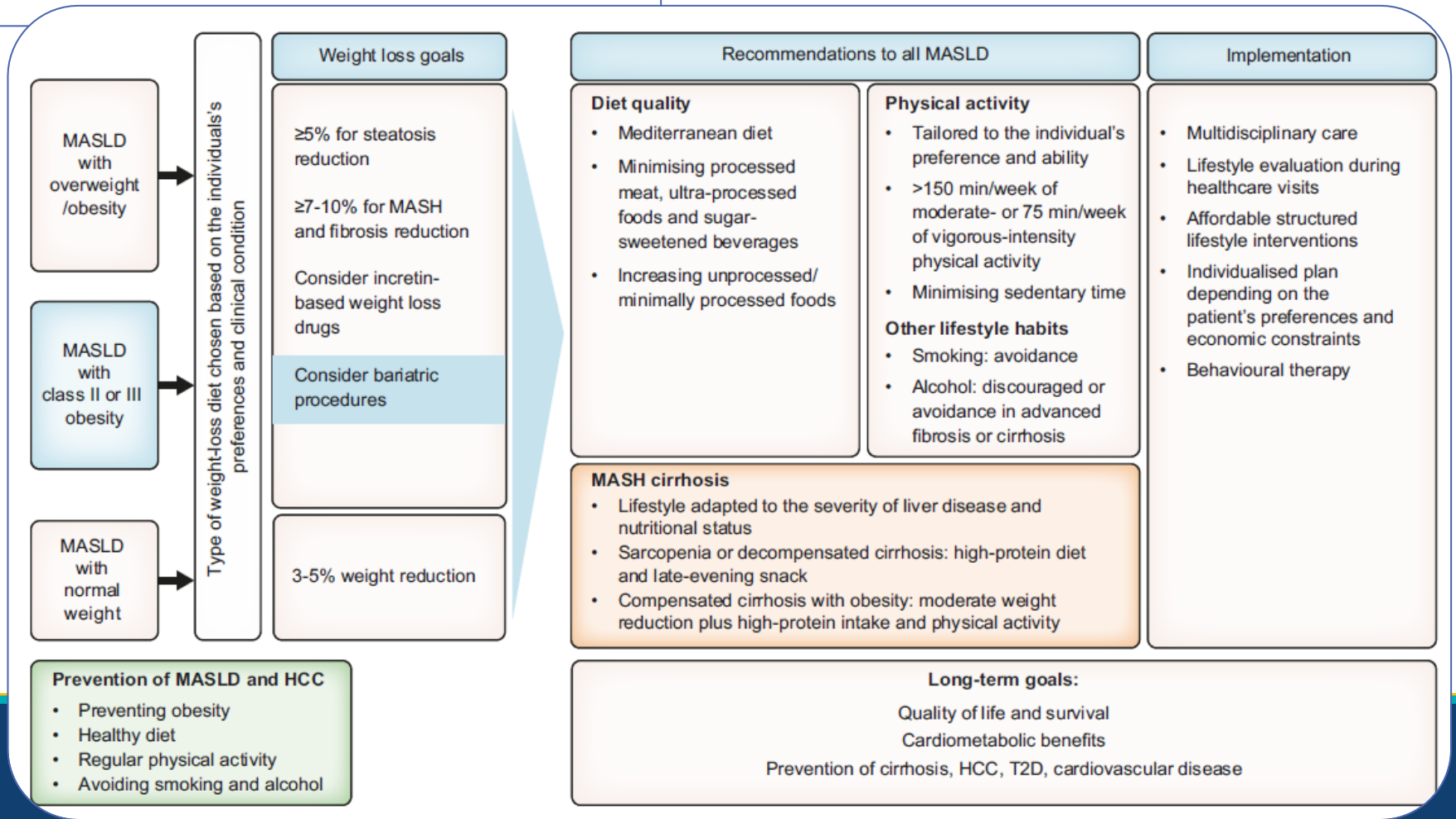
Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

2024

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO)



>10% weight loss through lifestyle modification cures NASH and fibrosis

Paired biopsies from 261 NASH patients at 0 and 52 weeks; BMI= 31,3; T2D= 33%; men= 41%

WEIGHT LOSS GOAL

% Weight loss (WL)	5%	7%	10%
NASH resolution	10%	26%	64%	90%
FIBROSIS regression	45%	36%	50%	81%
STEATOSIS improvement	35%	65%	76%	100%
% Patients achieving WL	70%	12%	9%	10%

Vilar-Gomez E et al; Gastroenterology 2015; 149: 367-378

Integrated treatment

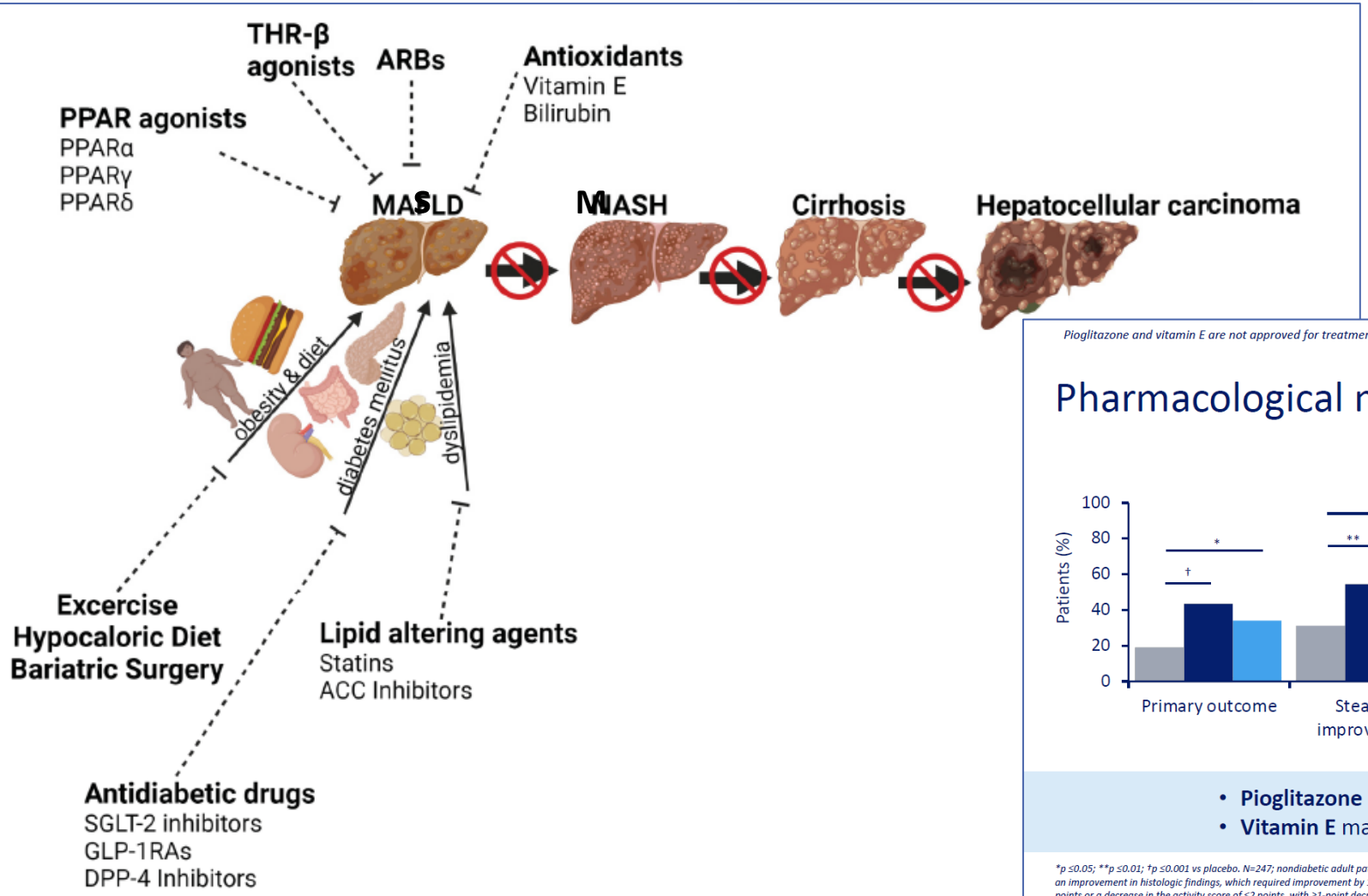
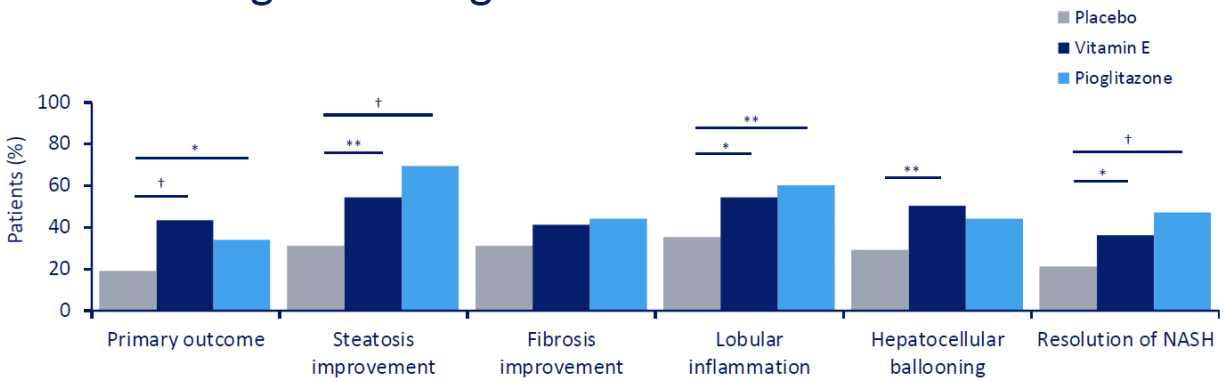


Figure 5. Influence of current and emerging therapies on MAFLD

Risk factors such as obesity, diet, diabetes mellitus, dyslipidemia, oxidative stress, inflammation, and apoptosis stimulate MAFLD, which can progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma. Lifestyle intervention (diet and exercise) and therapeutic interventions inhibit fatty liver diseases; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; FGF, fibroblast growth factor; GLP-1RAs, glucagon-like peptide-1 receptor agonists; PPAR, peroxisome proliferator-activated receptor; SGLT-2, sodium-glucose cotransporter-2; THR-β, thyroid hormone receptor-β. Created with Biorender.com

Pioglitazone and vitamin E are not approved for treatment of NASH

Pharmacological management of NASH



- **Pioglitazone** may improve NASH histology other than fibrosis
- **Vitamin E** may improve histology

**p ≤0.05; **p ≤0.01; †p ≤0.001 vs placebo. N=247; nondiabetic adult patients with biopsy-proven NASH were randomized to pioglitazone 30 mg/day, vitamin E 800 IU/day, or placebo for 96 weeks. The primary outcome was defined as an improvement in histologic findings, which required improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the activity score for NAFLD to a score of ≤3 points or a decrease in the activity score of ≤2 points, with ≥1-point decrease in either the lobular inflammation or steatosis score.*
NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
Sanyal AJ et al. N Engl J Med. 2010;362:1675–85.

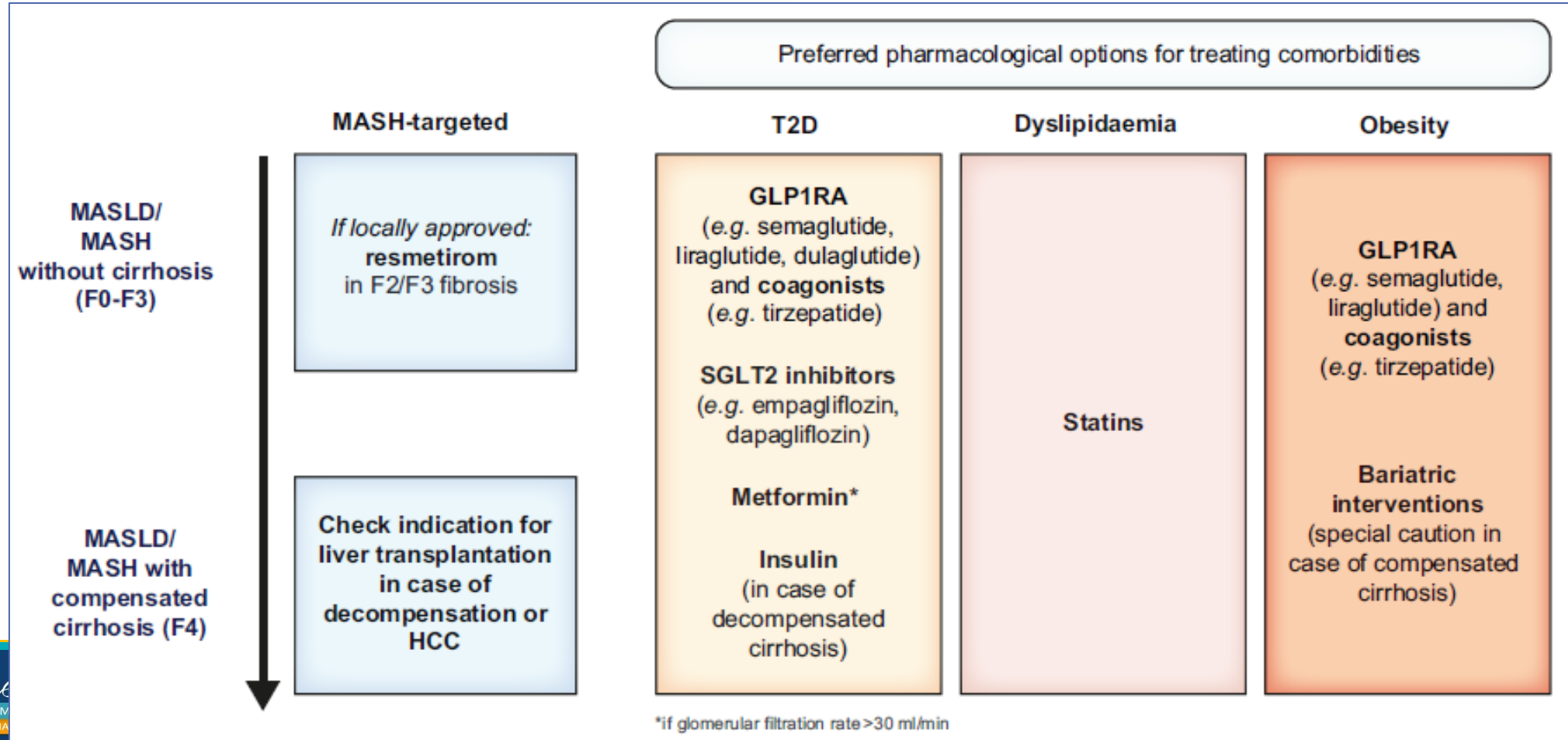
Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO)

2024



OBESITY AND MASLD

Grazie

- ***THANK YOU!***
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