

OBESITY AND MASLD MAFLD

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Direct link to 60- 200 comorbidites



- Depression
- · Low self-esteem
- · Risk of suicide
- Discrimination
- Social isolation

Endocrine/Metabolic

- Type 2 diabetes mellitus
- Metabolic syndrome
- Polycystic ovary syndrome

Respiratory

- Obesity hypoventilation syndrome
- · Sleep apnea
- Asthma
- Pulmonary hypertension
- Exercise intolerance

Reproductive (Women)

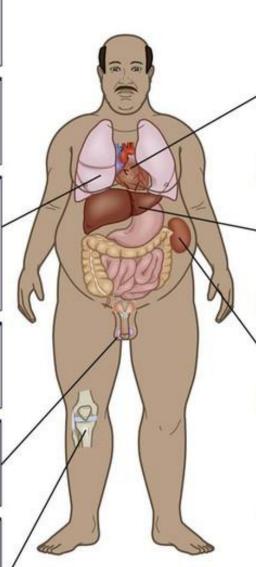
- · Menstrual irregularities
- · Infertility
- · Gestational diabetes

Reproductive (Men)

- Hypogonadism
- Gynecomastia
- · Sexual dysfunction

Musculoskeletal

- Osteoarthritis
- Impaired mobility and flexibility
- Gout
- Lumbar disk disease
 Chronic low back pain



Cardiovascular

- Hyperlipidemia
- · Sudden cardiac death
- · Right-sided heart failure
- · Left ventricular hypertrophy
- · Coronary artery disease
- Deep venous thrombosis
- · Atrial fibrillation
- Hypertension
- Cardiomyopathy
- Venous stasis
- Varicose veins

Gastrointestinal

- Nonalcoholic steatohepatitis (NASH)
- Gallstones
- Gastroesophageal reflux disease (GERD)

Genitourinary

- · Kidney cancer
- Chronic kidney disease
- Stress incontinence

Cancer

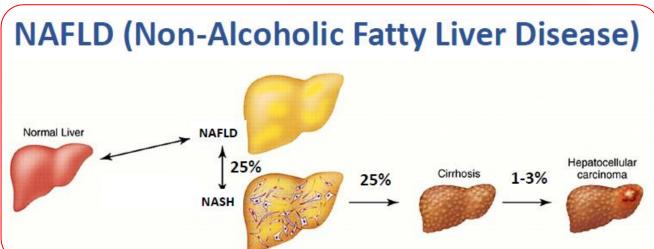
- Esophagus, pancreas, thyroid, colorectal, and gallbladder cancer (both genders)
- Endometrial, breast, and ovarian cancer (women)











91% of pts...OBESE!

Characteristics

Accumulation of triglycerides in hepatocytes (> 5% of the total liver weight) Reduced (/NO) alcohol intake (less than 20q/day for women and 30q/day for men)

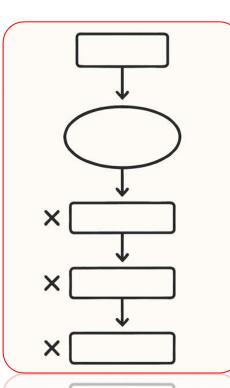
(Excluded diagnosis of viral infection, toxicity, selfimmunity etc)

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r men,









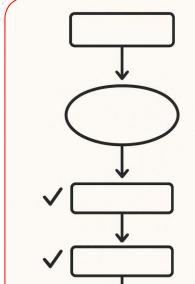
2020

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. Sarin³, Quentin M. Anstee⁴, Giovanni Targher⁵, Manuel Romero-Gomez⁶, Shira Zelber-Sagi⁷, Vincent Wai-Sun Wong⁸, Jean-François Dufour⁹, Jörn M. Schattenberg¹⁰, Takumi Kawaguchi¹¹, Marco Arrese¹², Luca Valenti¹³, Gamal Shiha¹⁴, Claudio Tiribelli¹⁵, Hannele Yki-Järvinen¹⁶, Jian-Gao Fan¹⁷, Henning Grønbæk¹⁸, Yusuf Yilmaz¹⁹, Helena Cortez-Pinto²⁰, Claudia P. Oliveira²¹, Pierre Bedossa²², Leon A. Adams²³, Ming-Hua Zheng²⁴, Yasser Fouad²⁵, Wah-Kheong Chan²⁶, Nahum Mendez-Sanchez²⁷, Sang Hoon Ahn²⁸, Laurent Castera²⁹, Elisabetta Bugianesi³⁰, Vlad Ratziu^{31,*,‡}, Jacob George^{1,*,‡}

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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 at least 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)

Clinical Science (2022) **136** 1347–1366 https://doi.org/10.1042/CS20220572

2022



Review Article

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

Olufunto O. Badmus¹, Sarah A. Hillhouse¹, Christopher D. Anderson², Terry D. Hinds Jr³ and o David E. Stec¹

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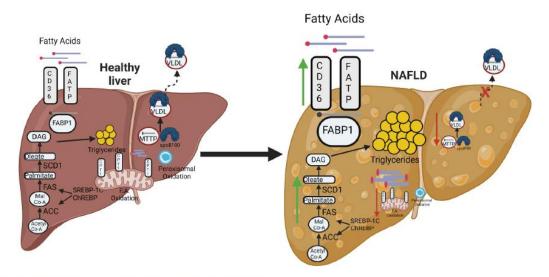


Figure 3. Pathways governing lipid accumulation in the liver

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

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, diacylglycerol; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase-1; VLDL, very-low-density lipoprotein. Created with

of fatty acids by the mitochondria and peroxisomes are decreased in MAFLD (red arrows); ACC, acetyl-CoA carboxyl





		$\overline{}$
Grade	Percent Fat	
Grade 0	<5%	
Grade 1	5-33%	
Grade 2	34-66%	
Grade 3	>66%	

>00%

Exercise

Treatments

MAFLD

Grade 3

Liver Biomarker/

Enzymes:

AST ↑

ALT ↑

Bilirubin∳

De Novo Lipogenesis

Enzymes:

FAS↑ SCD1↑

β-Oxidation: PPARα∳

Metabolically Fit

Liver Biomarker/ Enzymes:

AST ↓ ALT ↓

Bilirubin **↑**

De Novo Lipogenesis

Enzymes:

FAS ∜ SCD1∜

β-Oxidation: PPARα∱

NAFLD

(Nonalcoholic Fatty Liver Disease)

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)

No other causes of hepatic steatosis (e.g., HBV, HCV, drugs, hemochromatosis, autoimmunity, Wilson's disease, alpha 1 anti-trypsin deficiency, rapid weight loss)







(Metabolic Associated Fatty Liver Disease)

Hepatic steatosis (detected by imaging methods, serum biomarker scores, or histology)

One of the following metabolic criteria:

- Overweight/obesity
 - Type 2 diabetes
- Metabolic dysregulation⁶

⁵At 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)

protein [hs-CRP] >2 mg/L)

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- mg/dl or HbA1c from 39 to 47 mmol/mol Hb),
 insulin resistance (i.e., Homeostatic Model Assessment of







REVIEW ARTICLE



biomedicines



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 10 · 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

Review

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

Andrea Boccatonda 1,† D. Lorenzo Andreetto 2,†, Damiano D'Ardes 3,*,† D. Giulio Cocco 4 D. Ilaria Rossi 3 D. Susanna Vicari 1, Cosima Schiavone 4, Francesco Cipollone 3 and Maria Teresa Guagnano 30



Frontiers Frontiers in Endocrinology

PUBLISHED 16 January 2023 DOI 10.3389/fendo.2022.1087260





Review

Role of Insulin Resistance in MAFLD

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

Check for updates

Andrea Dalbeni, Verona University Hospital, Italy

Hua-Tian Gan. Sichuan University, China

Chongqing General Hospital, China

quojinjun1972@163.com

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

Li Rong^{1†}, Junyan Zou^{2,3†}, Wei Ran³, Xiao Yaokai Chen³, Hongjuan Cui² and Jinju

¹Department of Gastroenterology, Bishan Hospital of Chongo Hospital of Chongging, Chongging, China, 2Medical Research Chongging, China, 3 Medical Research Institute, Southwest Un Affiliated to Southwest University, Chongqing, China, ⁴Departr People's Hospital of Yunnan Province, Baoshan, Yunnan, Chin



International Journal of Molecular Sciences



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,*











34 other members to ensuring broad geographic representation.

SPECIAL ARTICLE

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

in Rinella, Mary E.¹; in Lazarus, Jeffrey V.²,³; in Ratziu, Vlad⁴; in Francque, Sven M.⁵,⁶; in Sanyal, Arun J.²; in Kanwal, Fasiha^{8,9}; in Romero, Diana²; in Abdelmalek, Manal F.¹0; in Anstee, Quentin M.¹¹,¹²; in Arab, Juan Pablo¹³,¹⁴,¹⁵; in Arrese, Marco¹⁵,¹⁶; in Bataller, Ramon¹²; in Beuers, Ulrich¹³; in Boursier, Jerome¹³; in Bugianesi, Elisabetta²⁰; in Byrne, Christopher²¹,²²; in Castro Narro, Graciela E.¹⁶,²³,²⁴; in Chowdhury, Abhijit²⁵; in Cortez-Pinto, Helena²⁶; in Cryer, Donna²²; in Cusi, Kenneth²³; in El-Kassas, Mohamed²³; in Klein, Samuel³⁰; in Eskridge, Wayne³¹; in Fan, Jiangao³²; in Gawrieh, Samer³³; in Guy, Cynthia D.³⁴; in Harrison, Stephen A.³⁵; in Kim, Seung Up³⁶; in Koot, Bart³³; in Korenjak, Marko³³; in Kowdley, Kris³³; in Lacaille, Florence⁴⁰; in Loomba, Rohit⁴¹; in Mitchell-Thain, Robert⁴²; in Morgan, Timothy R.⁴³,⁴⁴; in Powell, Elisabeth⁴⁵,⁴⁶,⁴ñ,* in Roden, Michael⁴³,⁴ð,⁴⁵, in Romero-Gómez, Manuel⁵¹; in Silva, Marcelo⁵²; in Singh, Shivaram Prasad⁵³; in Sookoian, Silvia C.¹⁵,⁵⁴,⁵⁵; in Spearman, C. Wendy⁵⁶; in Tiniakos, Dina¹¹,⁵⁵; in Valenti, Luca⁵³,⁵⁵; in Hobbs, Ansley²; in Villota-Rivas, Marcela⁶⁵; in Newsome, Philip N⁶⁶,⁶⁵; on behalf of the NAFLD Nomenclature consensus group

Kowdley, Kris²⁴; Lacaille, Florence²⁴; Loomba, Rohit²; Rohert-Thain, Robert²²; Morgan, Timothy R.^{43,44}; Powell, Elisabeth^{45,46,43}; Roden, Michael^{48,49,50}; Romero-Gómez, Manuel²³; Silva, Marcelo²²; Singh, Shivaram Prasad²³; Sookoian, Silvia C.^{15,54,25}; Spearman, C. Wendy²⁶; Tiniakos, Dina^{11,57}; Walenti, Luca^{58,59}; Vos, Miriam B.⁶⁰; Wong, Vincent Wai-Sun⁶³; Xanthakos, Stavra⁶²; Yilmaz, Yusuf⁶³; Younossi, Zobair⁶⁴; Hobbs, Ansley²; Villota-Rivas, Marcela⁶⁵; Newsome, Philip N^{66,67}; on behalf of the NAFLD Nomenclature consensus group

June 2023

..FROM MAFLD TO MASLD









MAFLD limits

No endorsement
No clear exclusion of different causes
No rigorous scientific definition

No rigorous scientific definition

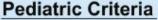






*Cardiometabolic criteria

Adult Criteria At least 1 out of 5: At least 1 out of 5: Metaboli BMI $\geq 25 \text{ kg/m}^2 [23 \text{ Asia}] \text{ OR WC} > 94 \text{ cm (M) } 80 \text{ cm}$ Associa (F) OR ethnicity adjusted Live 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 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



- BMI $\geq 85^{th}$ percentile for age/sex [BMI z score $\geq +1$] 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
- 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





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.



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

Jennifer Cathcart^{1,2} | Rachael Barrett¹ | James S. Bowness^{3,4} | Ashis Mukhopadhya² | Ruairi Lynch¹ | John F. Dillon¹

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

UK | ³University College Lond 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.

validation

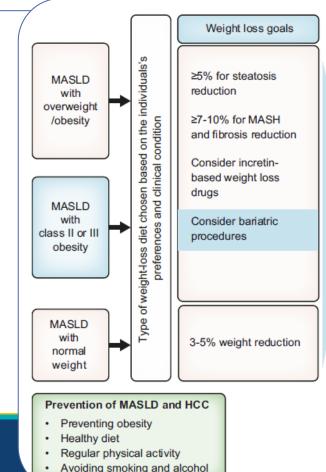
Future work should build on these studies with





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)



Recommendations to all MASLD

Diet quality

- · Mediterranean diet
- Minimising processed meat, ultra-processed foods and sugarsweetened beverages
- Increasing unprocessed/ minimally processed foods

Physical activity

- Tailored to the individual's preference and ability
- >150 min/week of moderate- or 75 min/week of vigorous-intensity physical activity
- · Minimising sedentary time

Other lifestyle habits

- Smoking: avoidance
- Alcohol: discouraged or avoidance in advanced fibrosis or cirrhosis

Implementation

- Multidisciplinary care
- Lifestyle evaluation during healthcare visits
- Affordable structured lifestyle interventions
- Individualised plan depending on the patient's preferences and economic constraints
- Behavioural therapy

MASH cirrhosis

- Lifestyle adapted to the severity of liver disease and nutritional status
- Sarcopenia or decompensated cirrhosis: high-protein diet and late-evening snack
- Compensated cirrhosis with obesity: moderate weight reduction plus high-protein intake and physical activity

Long-term goals:

Quality of life and survival Cardiometabolic benefits

Prevention of cirrhosis, HCC, T2D, cardiovascular disease







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

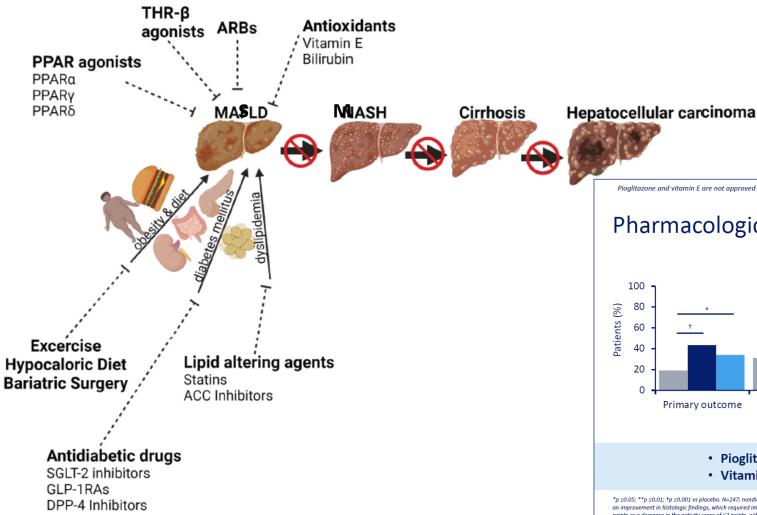
Paired biopsies from 261 NASH patients at 0 and 52 weeks; BMI= 31,3; T2D= 33%; men= 41%

% Weight loss (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%

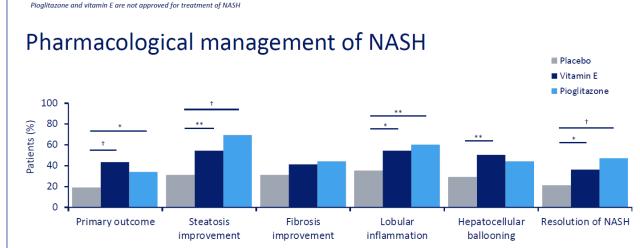
WEIGHT LOSS GOAL







Integrated treatment



- 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 ballooming score; no increase in the fibrosis score; and either a decrease in the activity score of \$2\$ points, with 21-points, with 21-points, either the lobular inflammation or steatosis score.

NAFLD, non-alcoholic fotty liver disease; NASH, non-alcoholic steatohepatitis.

Sanyal Al et al. Nefall IMed. 2010;36:21:675-82.

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





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)

Preferred pharmacological options for treating comorbidities

MASH-targeted

MASLD/ MASH without cirrhosis (F0-F3)

> MASLD/ MASH with compensated cirrhosis (F4)

If locally approved: resmetirom in F2/F3 fibrosis

Check indication for liver transplantation in case of decompensation or HCC T2D

GLP1RA

(e.g. semaglutide, liraglutide, dulaglutide) and coagonists (e.g. tirzepatide)

SGLT2 inhibitors

(e.g. empagliflozin, dapagliflozin)

Metformin*

Insulin

(in case of decompensated cirrhosis) Dyslipidaemia

Statins

GLP1RA

Obesity

(e.g. semaglutide, liraglutide) and coagonists (e.g. tirzepatide)

Bariatric interventions special caution in

(special caution in case of compensated cirrhosis)



*if glomerular filtration rate >30 ml/min

OBESITY AND MASLD









Grazie



THANK YOU!



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