METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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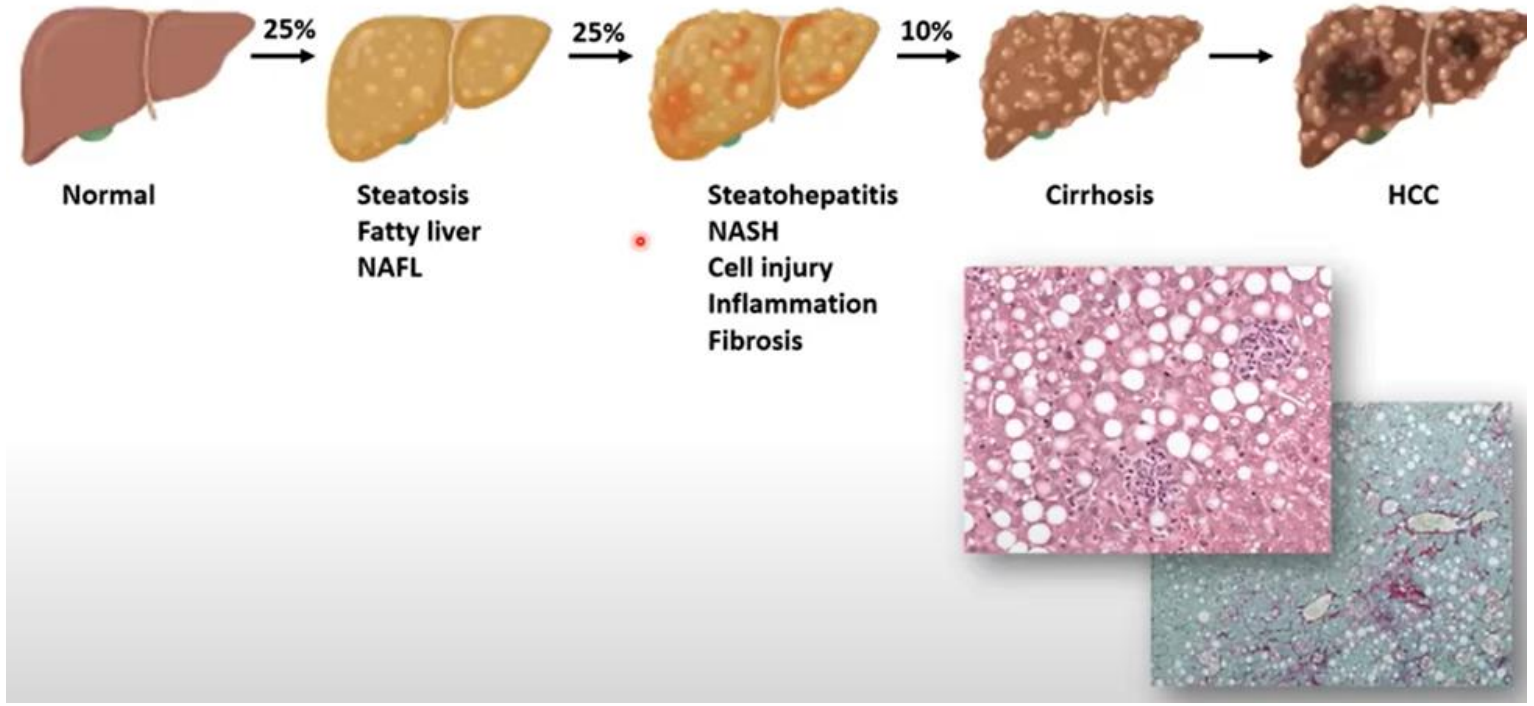
CMJAH

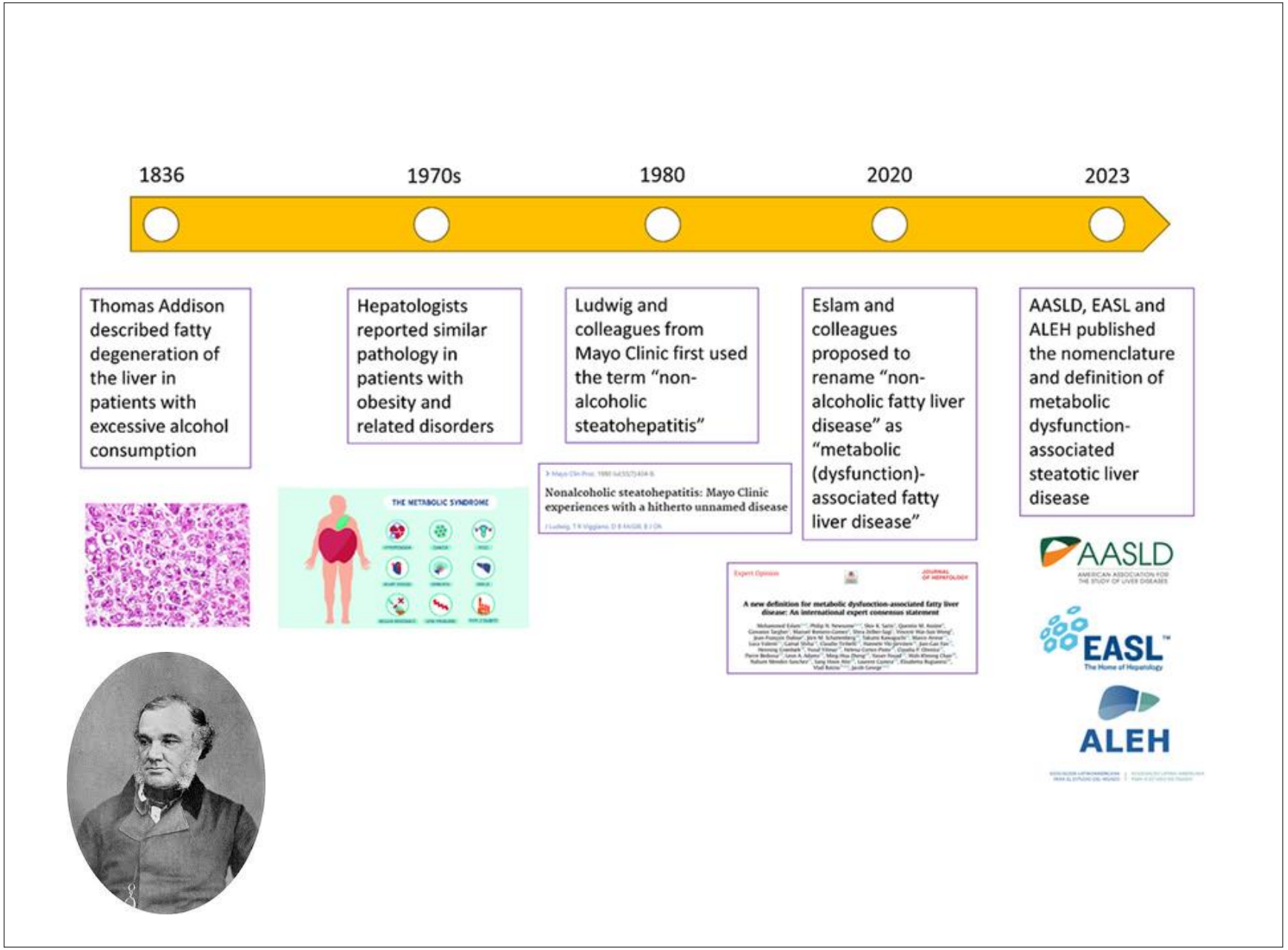
03/2025

Progression of fatty liver disease



Loomba, Rohit & Wong, Vincent. (2023). Implications of the new nomenclature of steatotic liver disease and definition of metabolic dysfunction-associated steatotic liver disease. Alimentary Pharmacology & Therapeutics. 59. 150-156. 10.1111/apt.17846.

MASLD



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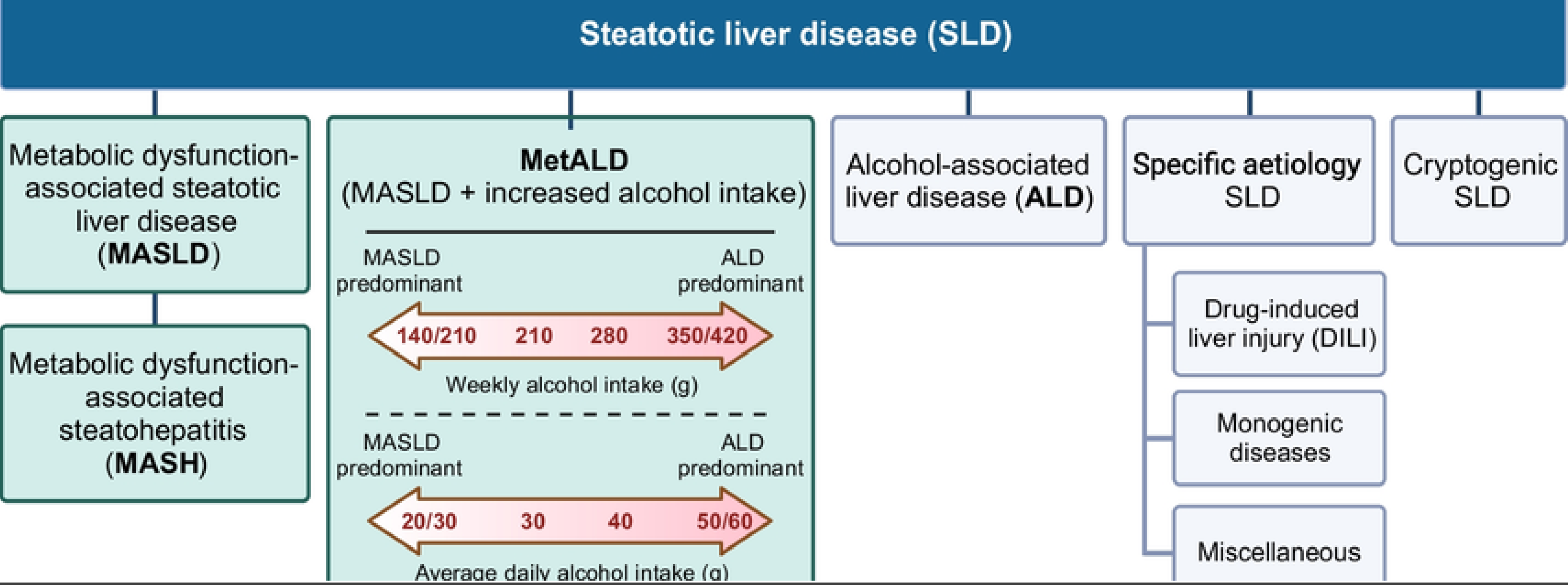
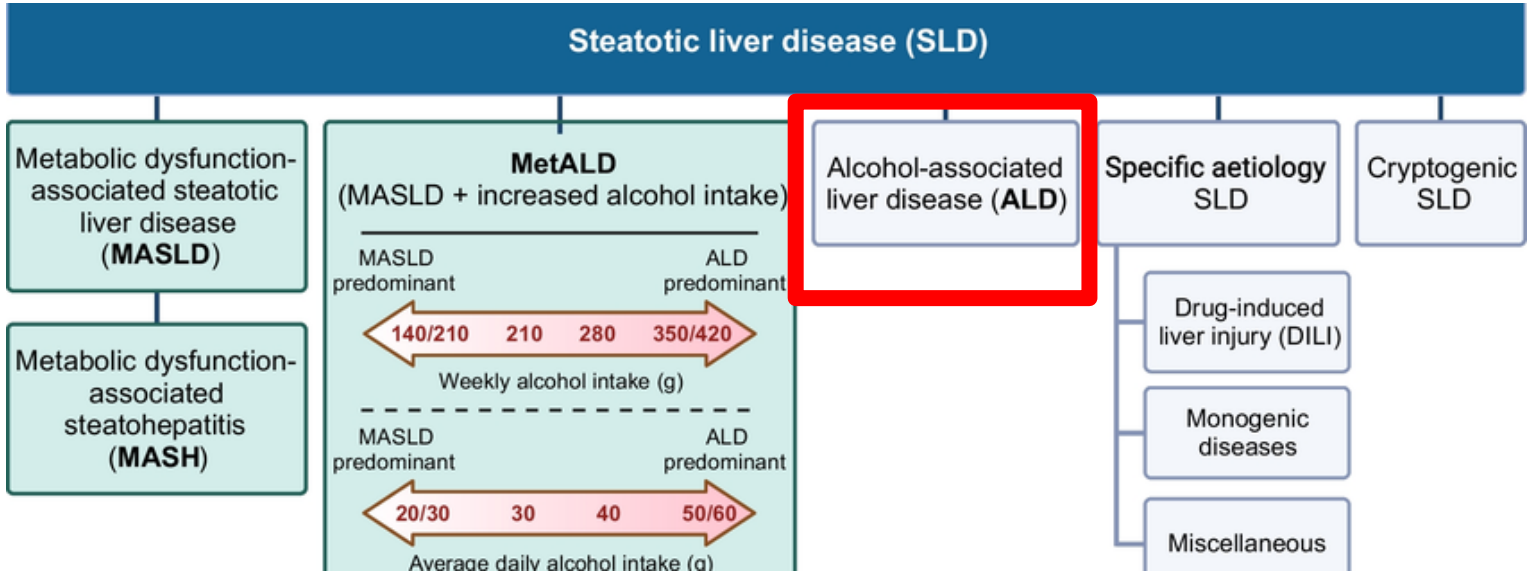


STEATOTIC LIVER DISEASE

Qadri, Sami & Yki-Järvinen, Hannele. (2024). Surveillance of the liver in type 2 diabetes: important but unfeasible?. Diabetologia. 67. 1-13. 10.1007/s00125-024-06087-7.

- ALD (Alcohol-related Liver Disease)-Alcohol intake of >50g/daily in female and >60g/daily in male



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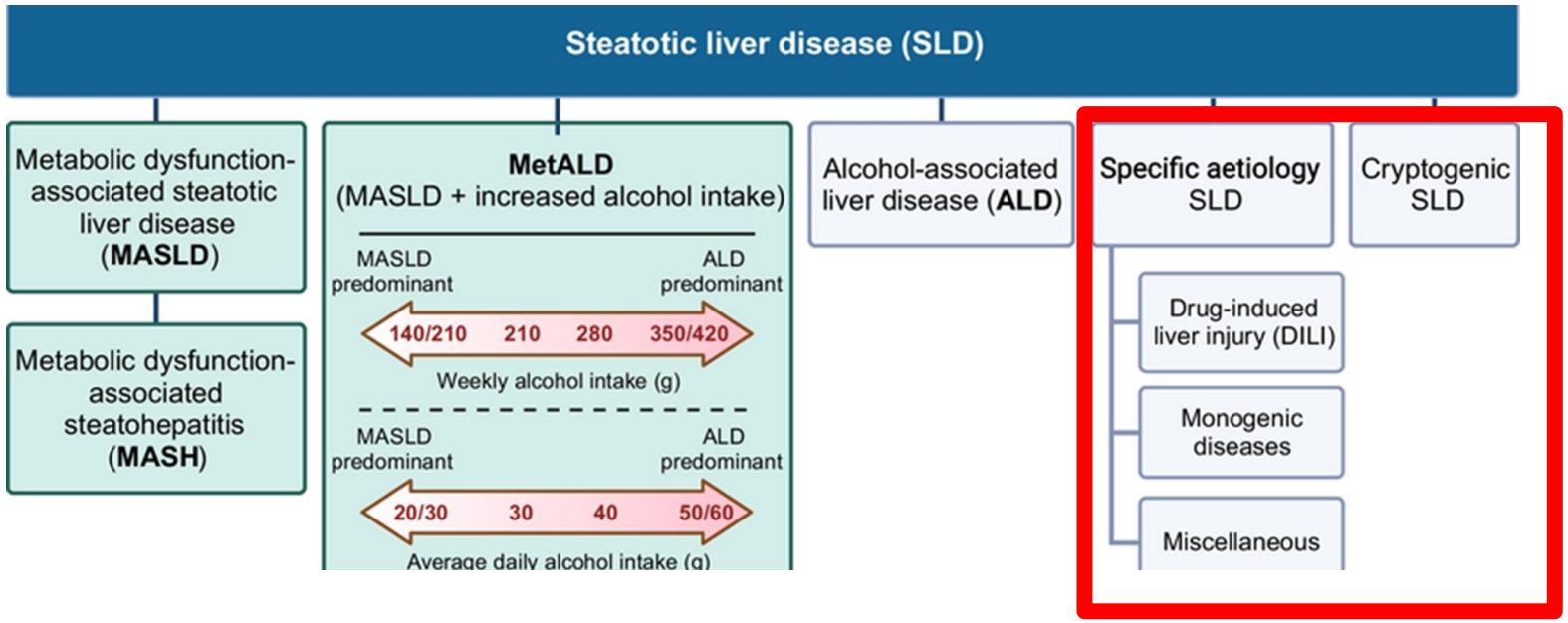
Specific Aetiology SLD

Cryptogenic SLD



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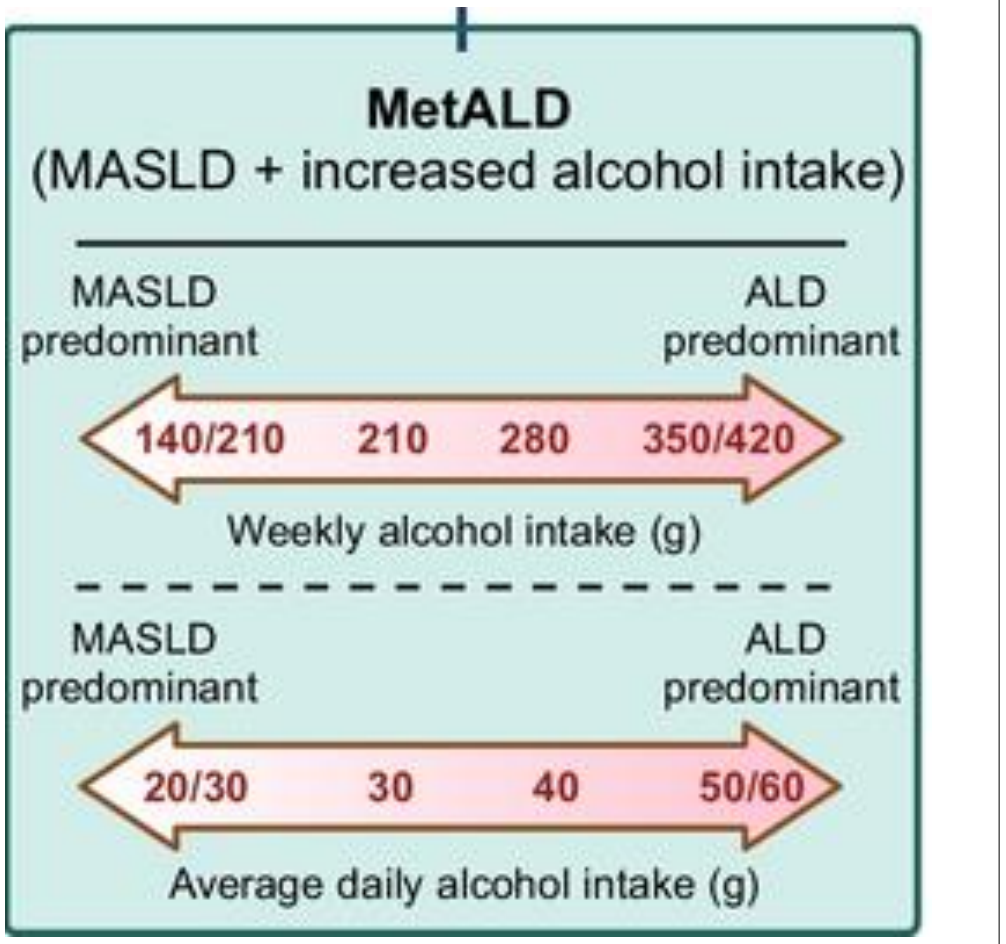

- Combination of MASLD and alcohol consumption of >20-50g/daily for female and >30-60g/daily for male BUT do not meet criteria for ALD

- Qadri, Sami & Yki-Järvinen, Hannele. (2024). Surveillance of the liver in type 2 diabetes: important but unfeasible?. Diabetologia. 67. 1-13. 10.1007/s00125-024-06087-7.

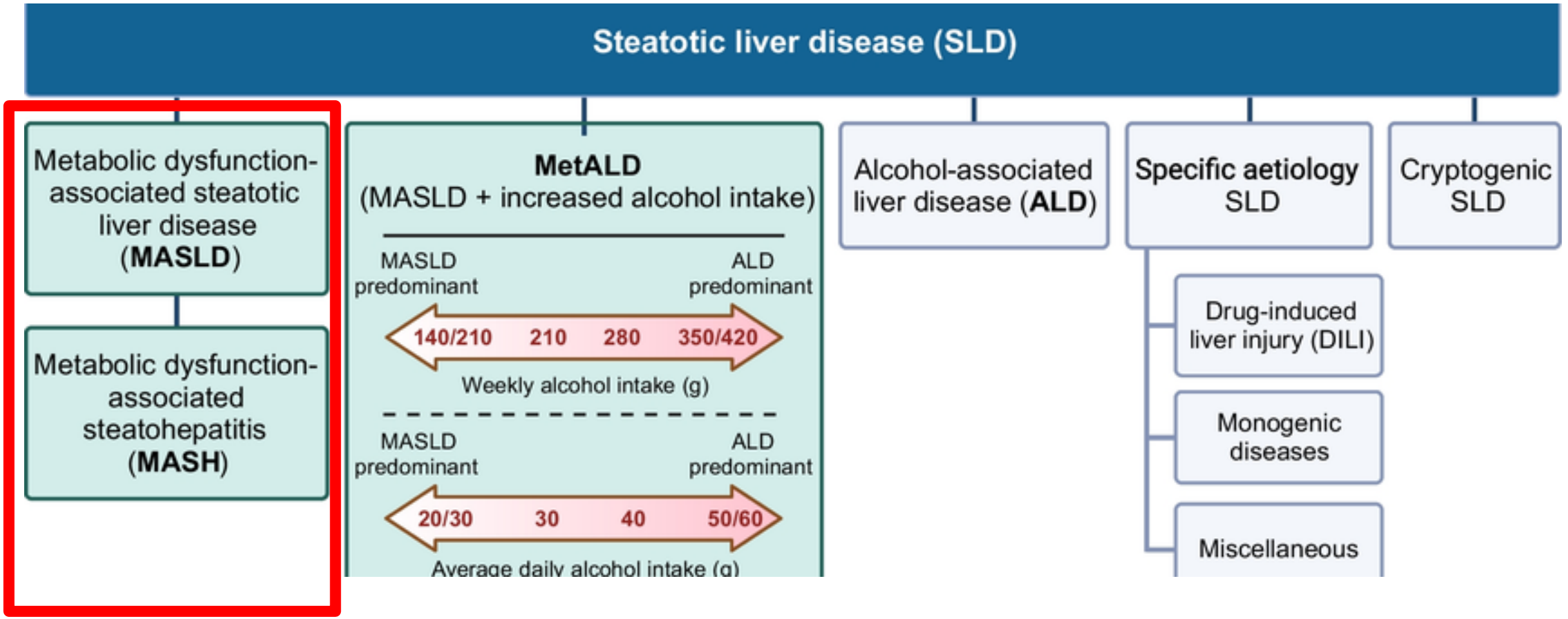

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Table 3. Cardiometabolic risk factors in the definition of MASLD.[2]

Metabolic risk factor	Adult criteria
Overweight or Obesity	Body mass index ≥25 kg/m^2 (≥23 kg/m^2 in people of Asian ethnicity) Waist circumference • ≥94 cm in men and ≥80 cm in women (Europeans) • ≥90 cm in men and ≥80 cm in women (South Asians and Chinese) • ≥85 cm in men and ≥90 cm in women (Japanese)
Dysglycaemia or type 2 diabetes	Prediabetes: HbA_{1c} 39-47 mmol/mol (5.7-6.4%) or fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dl) or 2-h plasma glucose during OGTT 7.8-11 mmol/L (140-199 mg/dl) *or* Type 2 diabetes: HbA_{1c} ≥48 mmol/mol (≥6.5%) or fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dl) or 2-h plasma glucose during OGTT ≥11.1 mmol/L (≥200 mg/dl) *or* Treatment for type 2 diabetes
Plasma triglycerides	≥1.7 mmol/L (≥150 mg/dl) *or* lipid-lowering treatment
HDL-cholesterol	≤1.0 mmol/L (≤39 mg/dl) in men and ≤1.3 mmol/L (≤50 mg/dl) in women *or* lipid-lowering treatment
Blood pressure	≥130/85 mmHg *or* treatment for hypertension

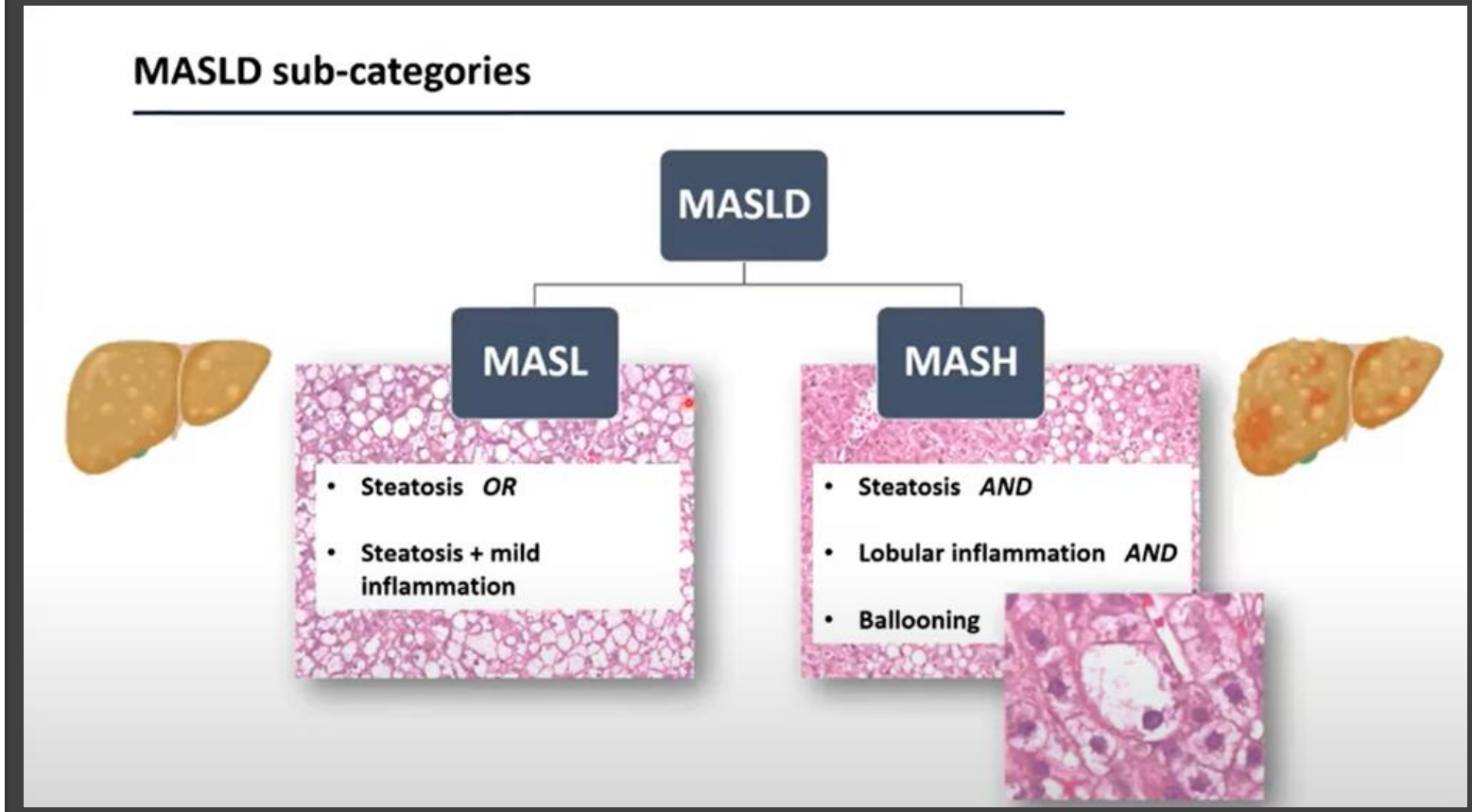
HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test.

MASLD

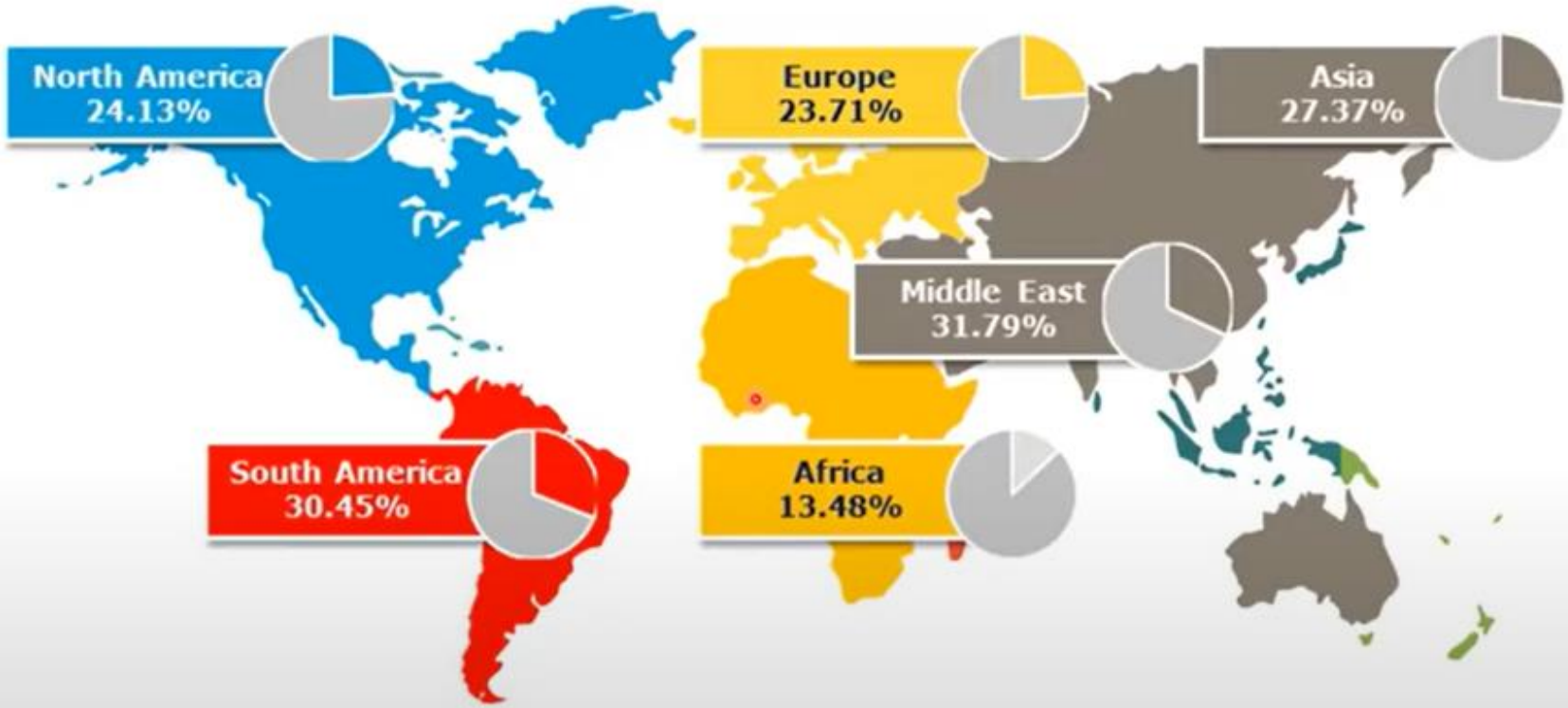
- Presence of hepatic steatosis in conjunction with at least ONE cardiometabolic risk factor
- AND no other discernible cause

Tacke, Frank et al. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD), Journal of Hepatology, Volume 81, Issue 3, 492 - 542

MASLD SUB-CATEGORIES

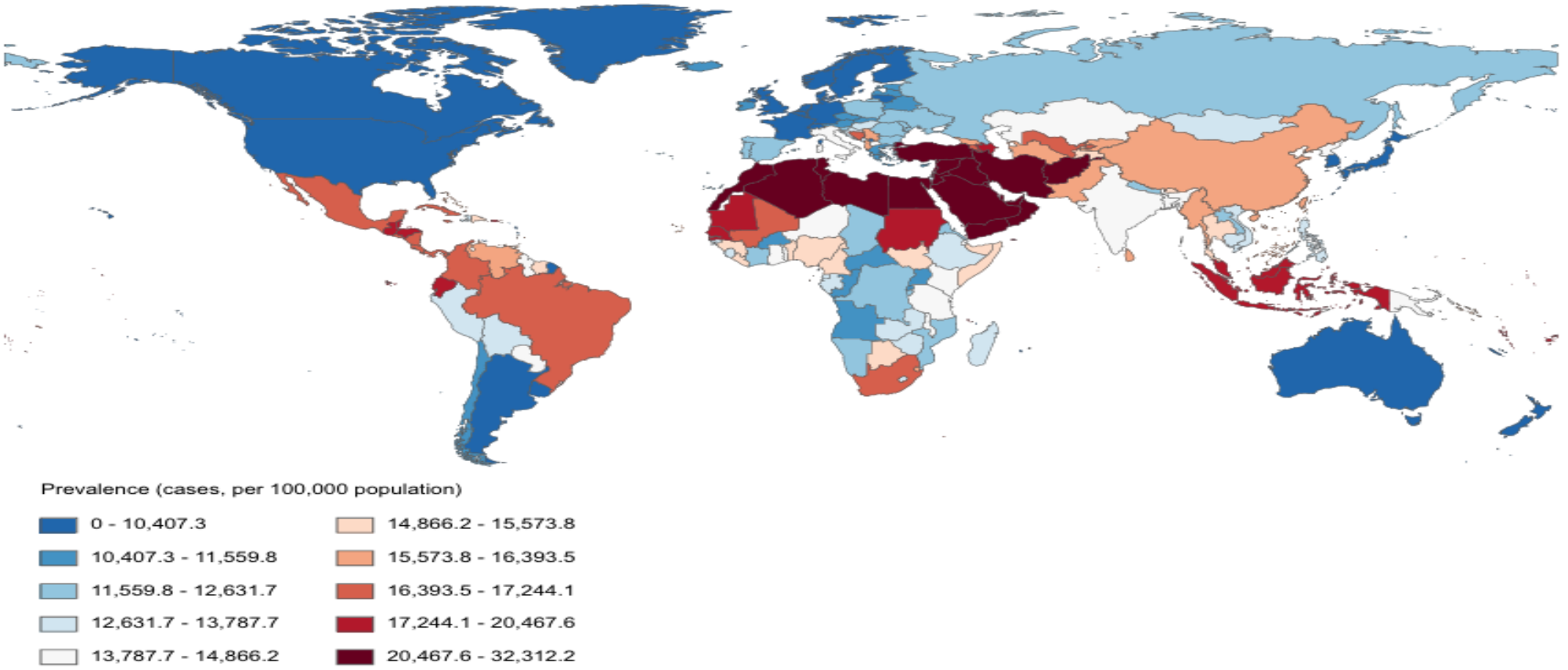


MASLD is a global health problem



Younossi et al, Hepatology 2019;69:2672-2682.

Age-standardized point prevalence rates of MASLD per 100,000 population in 2021 by country



Gong Feng et al. Global burden of metabolic dysfunction-associated steatotic liver disease, 2010 to 2021,mJHEP Reports,Volume 7, Issue 3,2025,101271,. ISSN 2589-5559,.https://doi.org/10.1016/j.jhepr.2024.101271, (https://www.sciencedirect.com/science/article/pii/S2589555924002751)

Natural Course

- Accelerates the progression of liver disease
- Induce cirrhosis or HCC development
- Type 2 DM increases the risk to advanced liver disease much faster
- Presence of steatosis in the general population is not linked to clinical meaningful increase in liver related outcomes. THEREFORE-no need for population-based screening
- Elevated liver enzymes (ALT M >33 and F >25) associated liver related mortality
- Risk of extrahepatic outcomes:
  - Risk increases the more cardiometabolic factors there are
- MASLD not associated with overall cancer mortality but increased risk for HCC and certain extrahepatic cancers (Thyroid and gastrointestinal)

Tacke, Frank et al. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD), Journal of Hepatology, Volume 81, Issue 3, 492 - 542

Risk Factors and Comorbidities

- Obesity
- Type 2 Diabetes Mellitus
- Hypertension and dyslipidemia
- Obstructive sleep apnoea and polycystic ovarian syndrome
- Menopause
- Ethnicity
- Smoking

Tacke, Frank et al. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD), Journal of Hepatology, Volume 81, Issue 3, 492 - 542

Risk Factors and Comorbidities

Obesity

- Presence, duration and severity are associated with increased risk of disease progression
- BMI, visceral fat distribution with waist circumference
- Prospective studies of liver biopsies showed->5 kg weight gain, higher insulin resistance and more pronounced hepatic steatosis→ during follow up were associated with progression of fibrosis
- Obesity in individuals with compensated cirrhosis at baseline are associated with a higher risk of clinical decompensation
- Association of the development of HCC with obesity

Ekstedt, M. · Franzen, L.E. · Mathiesen, U.L. Long-term follow-up of patients with NAFLD and elevated liver enzymes *Hepatology (Baltimore, Md).* 2006; 44:865-873

Risk Factors and Comorbidities

Type 2 Diabetes Mellitus

- Increased risk of fibrosis and HCC development
- Many studies available to confirm the association
- Study showed biopsy proven MASH and compensated cirrhosis over 5 year period
  - Confirmed poor outcomes with 4 fold increased risk of death and 2 fold increase in liver outcomes

Kanwal, F. · Kramer, J.R. · Li, L.Effect of metabolic traits on the risk of cirrhosis and hepatocellular cancer in non-alcoholic fatty liver disease *Hepatology (Baltimore, Md)*. 2020; 71:808-819
Yang, J.D. · Ahmed, F. · Mara, K.C. .Diabetes is associated with increased risk of hepatocellular carcinoma in patients with cirrhosis from nonalcoholic fatty liver disease *Hepatology (Baltimore, Md)*. 2020; 71:907-916

Risk Factors and Comorbidities

Hypertension and dyslipidaemia

- MASLD has a high rate of dyslipidaemia and hypertension
- Associated with fibrosis progression
- Large retrospective study with 271906 individuals had a 1.8 fold higher risk of progression to cirrhosis or HCC; compared to those with no cardiometabolic risk factors

Yang, J.D. · Ahmed, F. · Mara, K.C. .Diabetes is associated with increased risk of hepatocellular carcinoma in patients with cirrhosis from nonalcoholic fatty liver disease *Hepatology (Baltimore, Md)*. 2020; 71:907-916

Risk Factors and Comorbidities

Obstructive Sleep Apnoea and Polycystic Ovarian Syndrome

- Several studies suggest OSA associated with more advanced MASLD/MASH histology
- Only one study PCOS and MASH; increase severity/advanced fibrosis

Menopausal Status

- 2.4 fold higher risk of MASLD
- Women >50 have increased risk of advanced fibrosis due to MASLD

Sarkar, M. · Terrault, N. · Chan, W.Polycystic ovary syndrome (PCOS) is associated with NASH severity and advanced fibrosis *Liver Int.* 2020; 40:355-359

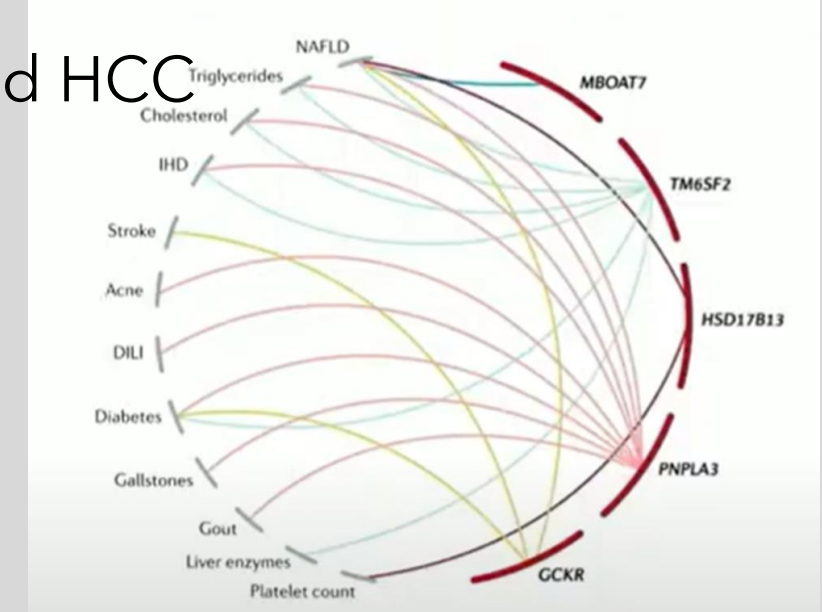
Asfari, M.M. · Niyazi, F. · Lopez, R. The association of nonalcoholic steatohepatitis and obstructive sleep apnea *Eur J Gastroenterol Hepatol*. 2017; 29:1380-1384

Yoneda, M. · Thomas, E. · Sumida, Y. The influence of menopause on the development of hepatic fibrosis in nonobese women with nonalcoholic fatty liver disease *Hepatology (Baltimore, Md).* 2014; 60:1792

Risk Factors and Comorbidities

Ethnicity

- Hispanic population has the highest prevalence of steatohepatitis
- Number of genes associated with steatohepatitis
- PNPLA3 gene associated with MASLD, cirrhosis and HCC



Rich, N.E. · Oji, S. · Mufti, A.R. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the United States: a systematic review and meta-analysis *Clin Gastroenterol Hepatol*. 2018; 16:198-210 e2

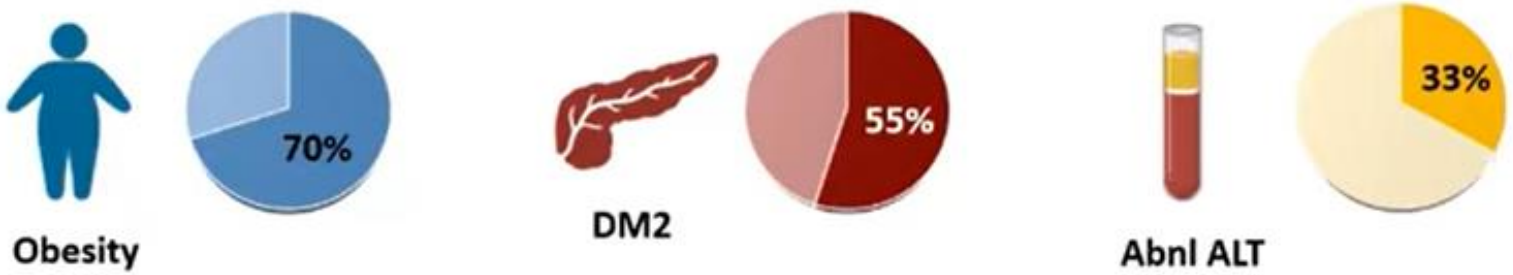
Risk Factors and Comorbidities

Smoking

- Increased risk of HCC independent of aetiology as well as in MASLD specifically

Yoo, J.J. · Park, M.Y. · Cho, E.J. Smoking increases the risk of hepatocellular carcinoma and cardiovascular disease in patients with metabolic-associated fatty liver disease *J Clin Med.* 2023; 12

Pre-test probability of MASLD based on common comorbidities



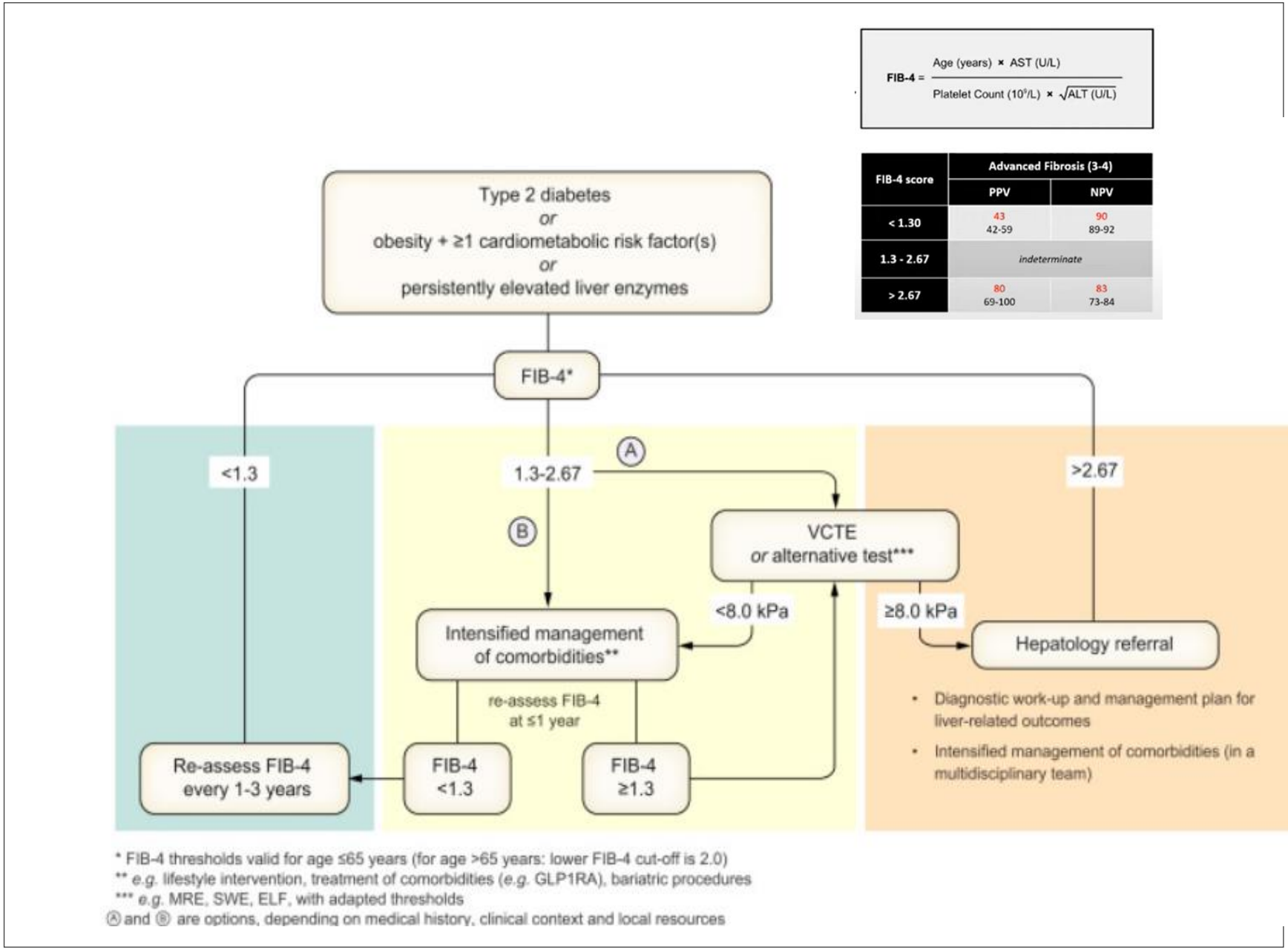
Younossi et al, J Hepatol 2019;71:793-801.
Nabi et al, Gastroenterology 2020;159:791-793.
Noureddin et al, Hepatol Commun 2022;6:1537-1548.
Quek et al, Lancet Gastro Hep 2023;8:20-30.

Screening of MASLD

Screening:

- Type 2 Diabetes
- Abdominal obesity and one or more additional risk factors
- Abnormal liver function tests

Proposed non-invasive assessment



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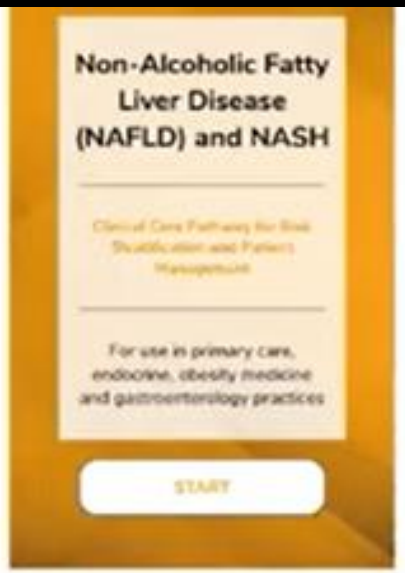


Find AGA's NASH Clinical Care Pathway App for iOS and Android mobile devices at nash.gastro.org. Scan this QR code to be taken directly to the website.

MANAGEMENT

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Kanwal et al, Gastroenterology 2021;161:1657-166

General Measures

Abstain from alcohol

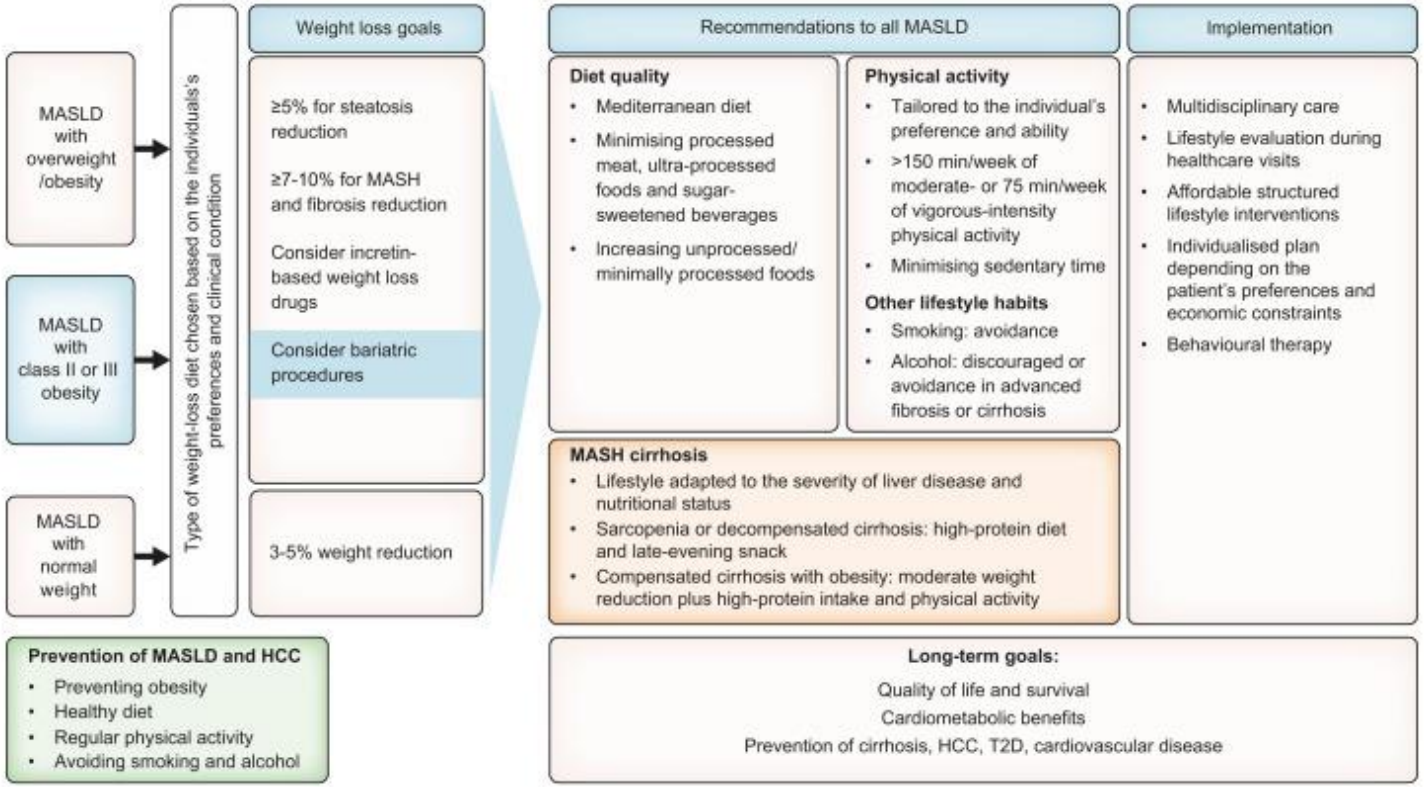
- Refrain from alcohol use (especially heavy alcohol use)

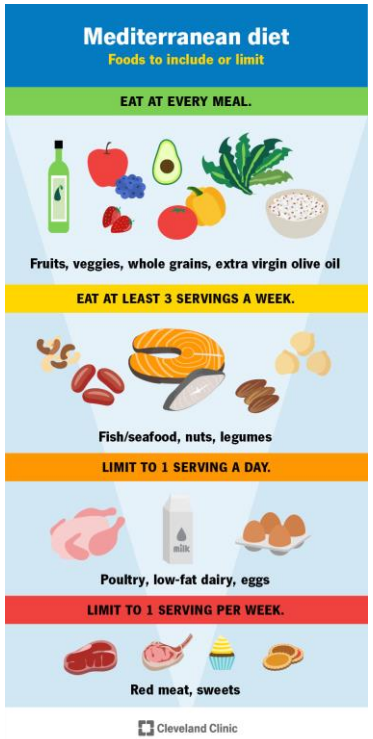
Immunisations

- Vaccinations Hepatitis A and B to be given to patients without serological evidence of immunity
- Additional vaccines: pneumococcal, influenza, diphtheria and tetanus

https://www.uptodate.com/contents/immunizations-for-adults-with-chronic-liver-disease?sectionName=VACCINES%20IN%20CHRONIC%20LIVER%20DISEASE&topicRef=3600&anchor=H8&source=see_link#

1.https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics (Accessed on December 26, 2022).





WEIGHT LOSS

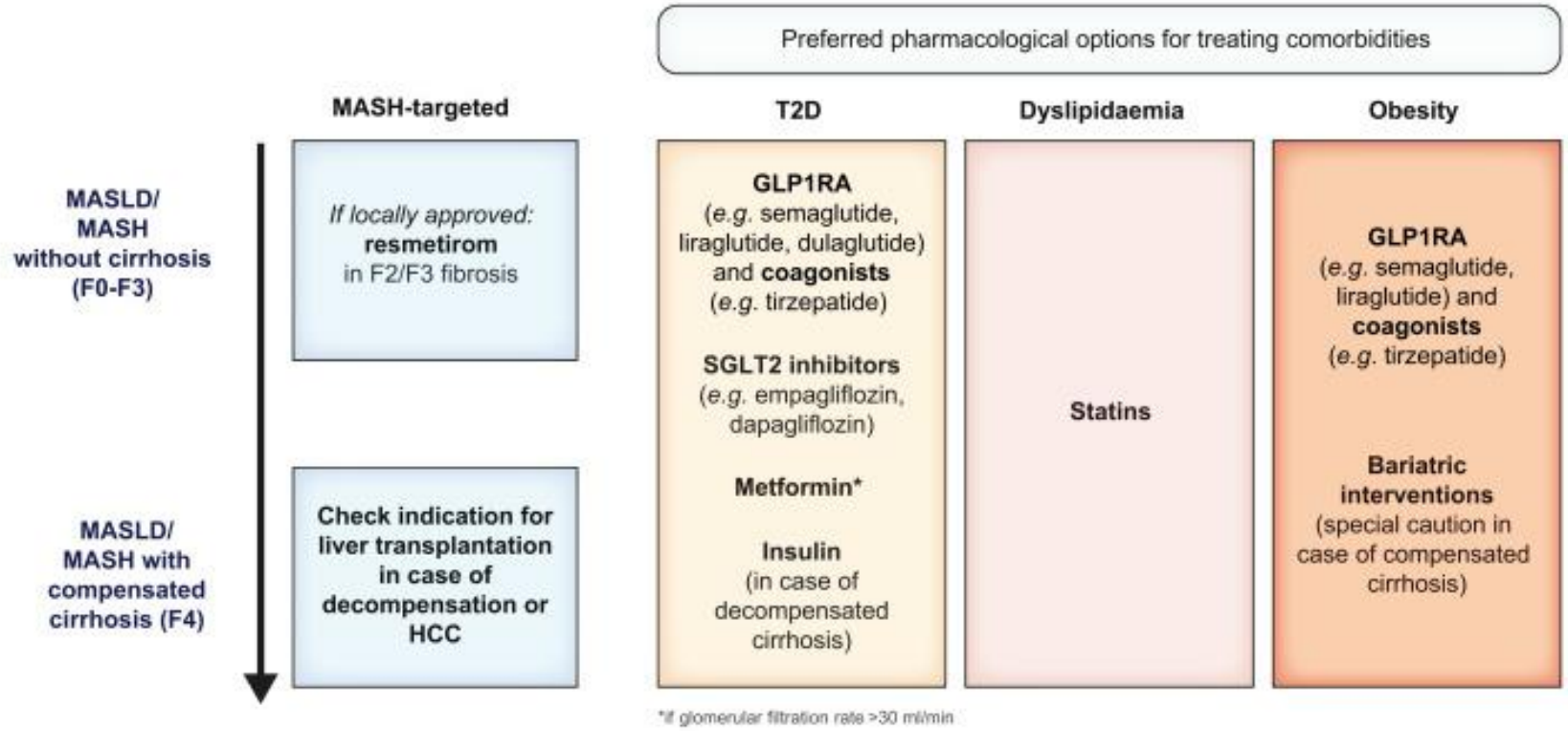
Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology 2015; 149:367.
Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia 2012; 55:885

Weight Loss

- Primary therapy for most MASLD
- Leads to improvement in liver biochemical tests, liver histology, serum insulin levels and quality of life
- For those that do not meet weight loss goals after 6 months-bariatric surgery

- Target weight loss:
  - Studies suggest 5-7% loss of body weight at a rate of 0.5 to 1 kg per week
  - For patients with suspected or biopsy proven MASH-weight loss is higher (7-10% of body weight)
  - Several studies suggest at least 5% weight loss to improve

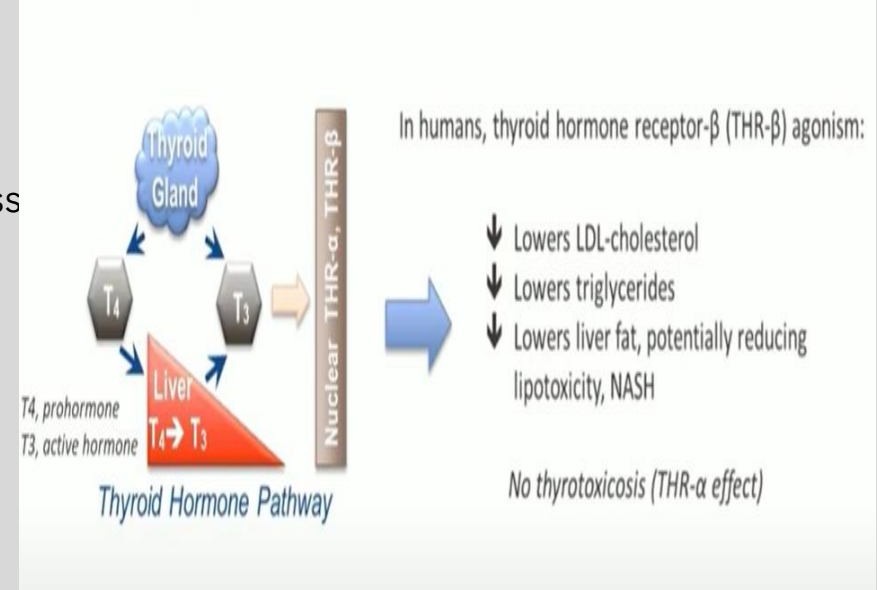
Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology 2015; 149:367.
Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia 2012; 55:885.



TREATMENT APPROACH

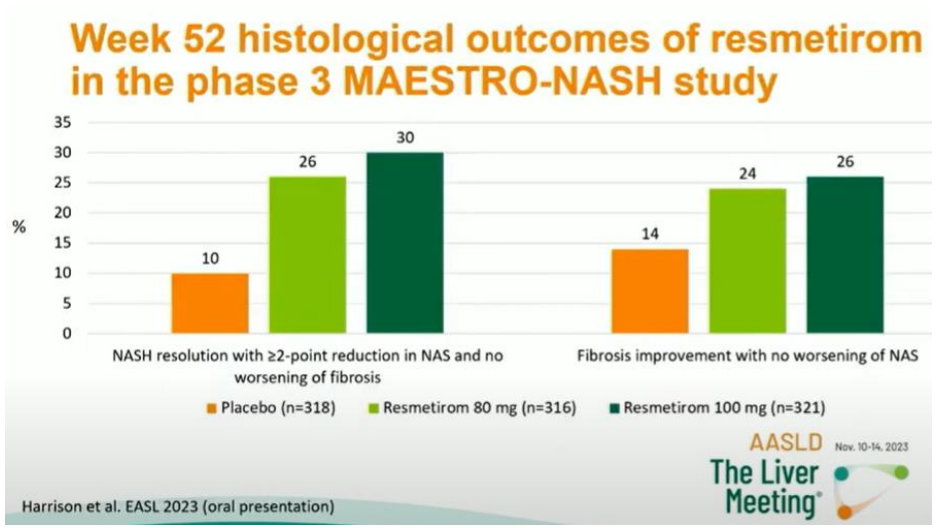
Liver Thyroid Hormone Receptor Beta Agonist

- Resmetirom
- Limited availability and cost
- MASH and fibrosis stage F2/F3 who do not achieve sustained weight loss
- Studies have excluded the use in cirrhotic patients (ongoing trials)
- Mechanism of reduction in hepatic steatosis:
  - thyroid hormones stimulate hepatic lipophagy and mitochondrial biogenesis
  - Inhibit lipogenesis
  - Interferes with fibrinogenesis by inhibiting TGF Beta signalling
- Dosing:
  - <100 kg: 80 mg PO daily
  - .100 kg: 100 mg PO daily



- Precaution-check all potential drug interactions before use
- Side effects: Diarrhoea, pruritis and nausea

1.Resmetirom. United States Prescribing Information. Revised March 2024. US Food & Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217785s000lbl.pdf (Accessed on March 17, 2024).



Liver Thyroid Hormone Receptor Beta Agonist

- Improved MASH and stage of liver fibrosis
  - Trials showed compared to placebo-MASH resolution at 52 weeks; improving fibrosis by at least one stage

Vitamin E

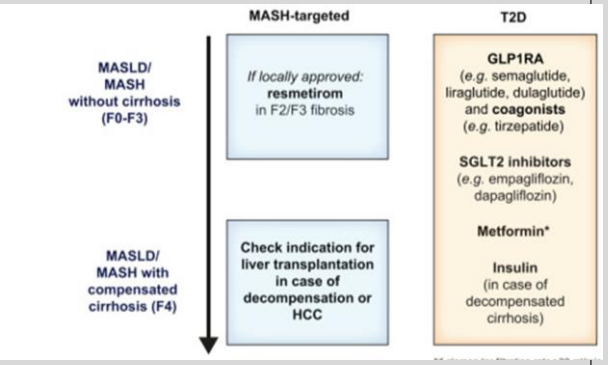
- Mechanism:
  - Lipid soluble vitamin acting as scavenger with antioxidant, anti-inflammatory and anti-apoptotic properties
  - Reduces de novo lipogenesis therefore decreases liver lipid content
- Biopsy proven MASH and fibrosis stage >/= 2 with no diabetes→ Vitamin E
- Vitamin E 800 IU daily
- Improves steatosis and inflammation in such patients
- Potential safety concerns with high dose vitamin E
- Trials compared to placebo-showed improvement in global histology and ALT compared to placebo
- However-avoid vitamin E in men with personal or strong family history of prostate cancer
- Largest RCT to date, non diabetic MASH with Vitamin E for 2 years at 800 IU showed improvements in disease activity and steatosis-reduction in liver enzymes

Sanyal, A.J. · Chalasani, N. · Kowdley, K.V. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010; 362:1675-1685

Diabetes Mellitus

- **<u>Metformin</u>** is what most patients are using as first line. However it has no benefit in improving liver histology

- **<u>Pioglitazone (Thiazolidinediones)</u>**
  - Improves fibrosis as well as inflammation and steatosis
  - When compared to placebo in trials, were more likely to improve hepatic histologic parameters such as ballooning degeneration, lobular inflammation and steatosis
  - Improvement in fibrosis noted
  - Needed to be a long term treatment; benefits may reverse once drug is stopped
  - Side effects: increased weight gain, heart failure and fractures



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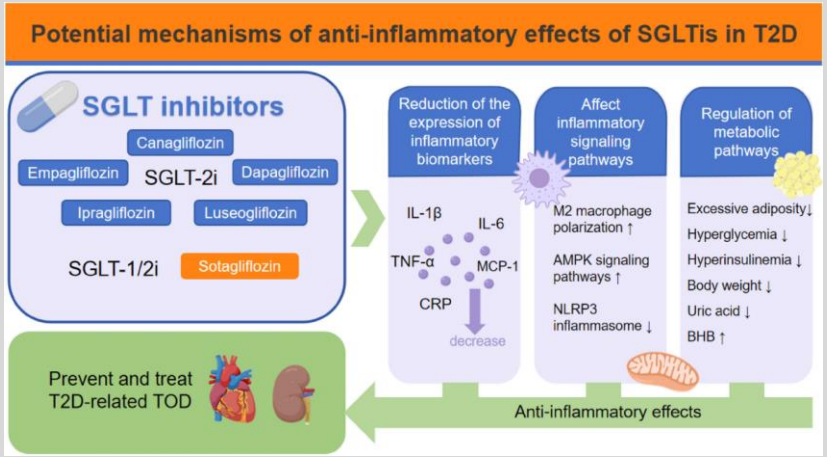
Sodium-glucose co-transporter-2 inhibitor (SGLT2 inhibitor)

- Induces renal glucosuria, weight loss, BP reduction
- Reduction in ALT with empaglifozin and licoglifozin
- The EFFECT II Study showed that the use of SGLT2i (dapagliflozin) in diabetic patients, resulted in a decrease in steatosis



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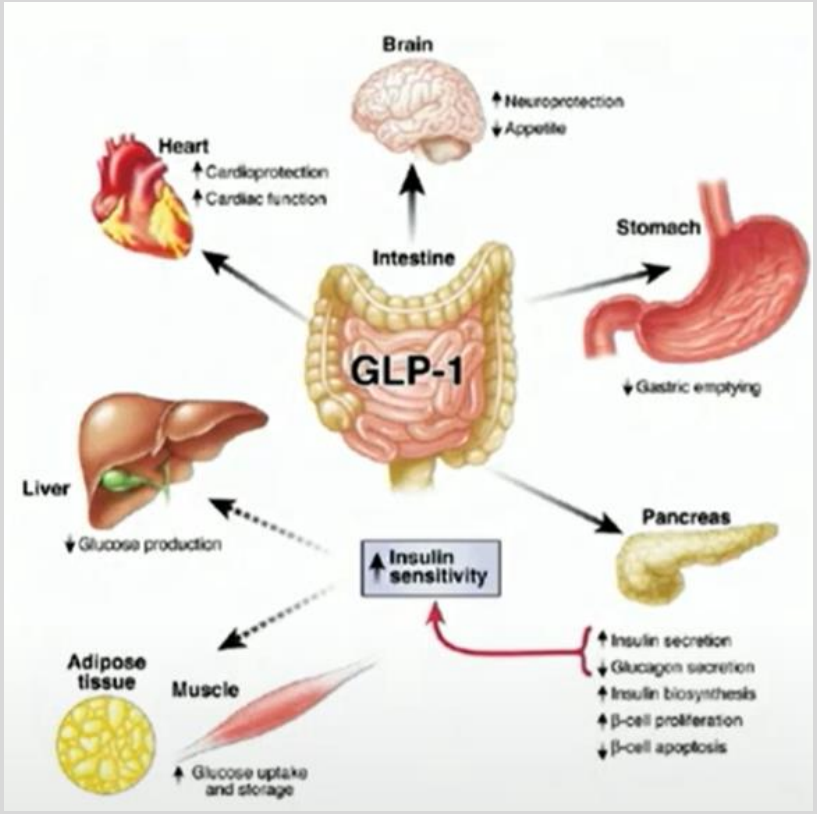
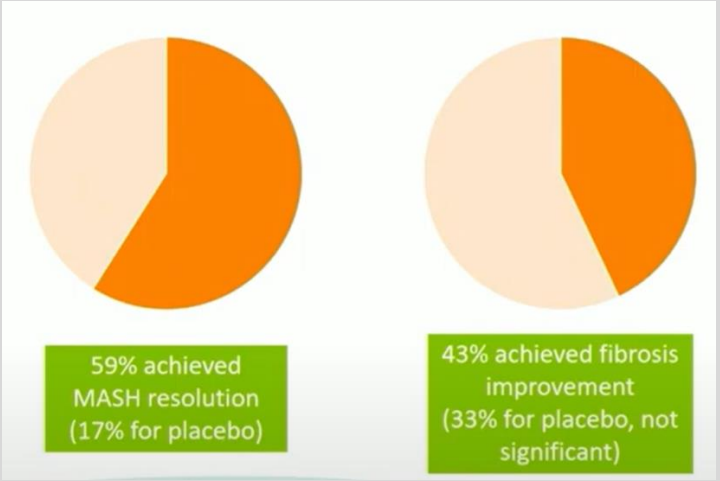
Glucagon-like Peptide 1 Receptor Agonists (GLP-1RA)



GLP1 is a hormone

- Controls urge and need to eat

Glucagon-like Peptide 1 Receptor Agonists (GLP-1RA)



GLP-1 Receptor Agonists

- Liraglutide:
  - Trial of 52 patients for 52 weeks with end of treatment biopsy
  - MASH resolved on 39% of liraglutide and 9% in placebo
  - Patients who were on liraglutide were less likely to have fibrosis progression
- Semaglutide:
  - Phase 2 trial with 320 biopsy proven MASH and liver fibrosis of stage F1, F2 or F3
  - Semaglutide 0.4 mg once daily resulted in higher rates of histologic resolution of MASH compared to placebo after 72 weeks (59% vs 17%)
  - ESSENCE MASH Phase 3 Trial
    - Participants with clinically significant fibrosis stages 2 and 3; MASLD
    - Semaglutide 2.4 mg once weekly SC
    - 240 week double blinded trial in 1200 adults with MASH
    - Trial achieved primary endpoints by improvement of steatohepattis and no worsening liver fibrosis

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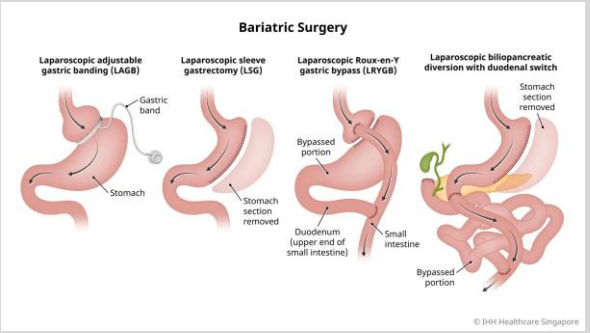
Dyslipidaemia and Statins

- MASLD induces atherogenic dyslipidaemia therefore statins prevent cardiovascular events
- Statin intake is associated with reduced risk of MASLD, MASH and liver fibrosis

Ayada, Ibrahim et al Dissecting the multifaceted impact of statin use on fatty liver disease: a multidimensional study, eBioMedicine, Volume 87, 104392

SURGICAL AND ENDOSCOPIC THERAPY

Weight Loss-Bariatric Surgery



Bariatric Surgery

- Non-cirrhotic MASLD with an approved indication; strongly recommended in consensus
- Patients with MASH or advanced fibrosis (without decompensated cirrhosis) if they do not meet their weight goals after 6 months of lifestyle changes (Including two nutritional visit counselling)-can be considered but with careful evaluation
- Promising approach with histologic improvement has been observed postoperatively.
- HOWEVER, some patients do develop worsening fibrosis
- Therefore close monitoring of liver function tests are recommended; as well as monitor for signs of decompensation

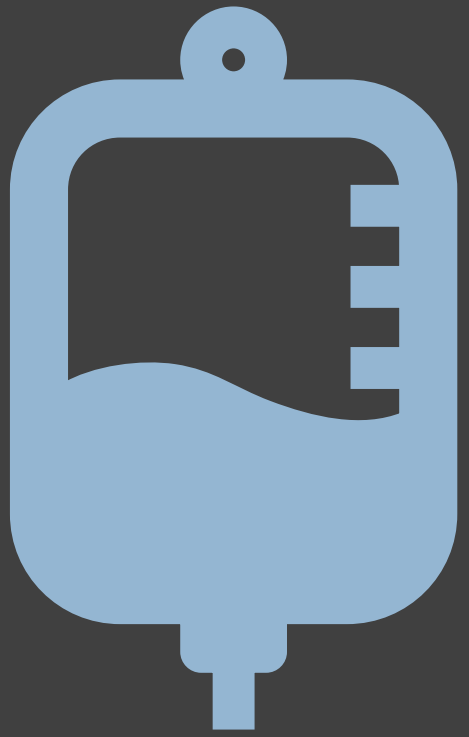
Mattar SG, Velcu LM, Rabinovitz M, et al. Surgically-induced weight loss significantly improves nonalcoholic fatty liver disease and the metabolic syndrome. Ann Surg 2005; 242:610.
Lee Y, Doumouras AG, Yu J, et al. Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2019; 17:1040.

Bariatric Endoscopic Therapy

Intragastric balloon, endoscopic sleeve gastroplasty, aspiration device, Botox injection, etc.

Needs further validation and is not currently recommeneded

Ren, M. · Zhou, X. · Zhang, Y. ...Effects of bariatric endoscopy on non-alcoholic fatty liver disease: a comprehensive systematic review and meta-analysis Front Endocrinol (Lausanne). 2022; 13, 931519



END STAGE LIVER AND TRANSPLANTATION

Table 11 Screening and management for comorbidities in individuals with MASLD before liver transplantation. Modified from.[488,526]

Condition	Recommendation
Type 2 diabetes	•Screen for impaired fasting glucose (IFG) or glucose tolerance (IGT) and/or T2D (OGTT, HbA1c)•Achieve good glycaemic control before LT•Preferentially use weight-lowering (*e.g.* SGLT2 inhibitors, GLP1RA) or weight-neutral (*e.g.* metformin) glucose-lowering medication, considering risk of other diabetes complications, if liver and/or renal function allow this
Nutrition	•Assess nutritional status before LT•Assess alcohol consumption•Healthy diet, physical exercise and lifestyle modification (including weight reduction in individuals with obesity) represent pillars in pre-LT management
Cardiovascular	•Pre-LT cardiovascular risk stratification is mandatory•Risk-adapted algorithm of cardiac work-up should be followed (see Fig. 5)•LT candidates with cardiovascular risk should be managed with goal-directed medical management (*e.g.* statins, anti-platelet agents, beta blockers, RAAS blockers), based on the stage of cirrhosis and renal function
Kidney	•Kidney function should be adequately monitored before LT•Comedications need to be adjusted (or replaced) dependent on kidney function
Malignancies	•Screening for pre-LT malignancies should follow the same protocols applied to individuals with non-MASLD related cirrhosis (including gastrointestinal and genital cancers)

End Stage Liver and Transplantation

- Recommend a multidisciplinary team for cardiovascular and metabolic comorbidities to mitigate risk if major cardiovascular events in pre-, peri- and post-transplant phase

Tacke, Frank et al. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD), Journal of Hepatology, Volume 81, Issue 3, 492 - 542

Mechanism of action	Drug
Cyclophilin inhibitor	Rencofilstat
Deuterium-modified thiazolidinedione	PXL065
DGAT2 inhibitors	ION224, PF-06865571
Fatty acid synthase inhibitor	Denifanstat
FGF21 agonists	Efruxifermin, pegozafermin
GLP-1/GIP/glucagon agonists	Tirzepatide, BI456906, pemvidutide
PPAR agonist	Saroglitazar
Structurally engineered fatty acids	Icosabutate
THRβ agonist	VK2809
MASH genes	GSK4532990 (*HSD17B13*), AZD2693 (*PNPLA3*)

THE FUTURE

Comparison of pharmacological therapies in metabolic dysfunction–associated steatohepatitis for fibrosis regression and MASH resolution: Systematic review and network meta-analysis

Study design Systematic review and network meta-analysis

Data sources 29 randomized controlled trials

9324 patients with MASH

Key findings

Fibrosis improvement ≥1 stage without worsening MASH

- 8 interventions significantly better than placebo:

3.46	2.67	1.94	1.86	1.85	1.77	1.64	1.51
Pegozafermin (SUCRA: 79.92)	Cilofexor + firsocostat	Denifanstat	Survodutide	Obeticholic acid	Tirzepatide	Resmetirom	Semaglutide

MASH resolution without worsening fibrosis

- 11 interventions significantly better than placebo:

8.65	6.62	4.65	3.51	3.23	3.03	2.54	2.29	2.03	1.93	1.87
Pegozafermin (SUCRA: 91.75)	Survodutide	Tirzepatide	Efruxifermin	Liraglutide	Vitamin E + pioglitazone	Resmetirom	Pioglitazone	Denifanstat	Lanifibranor	Semaglutide

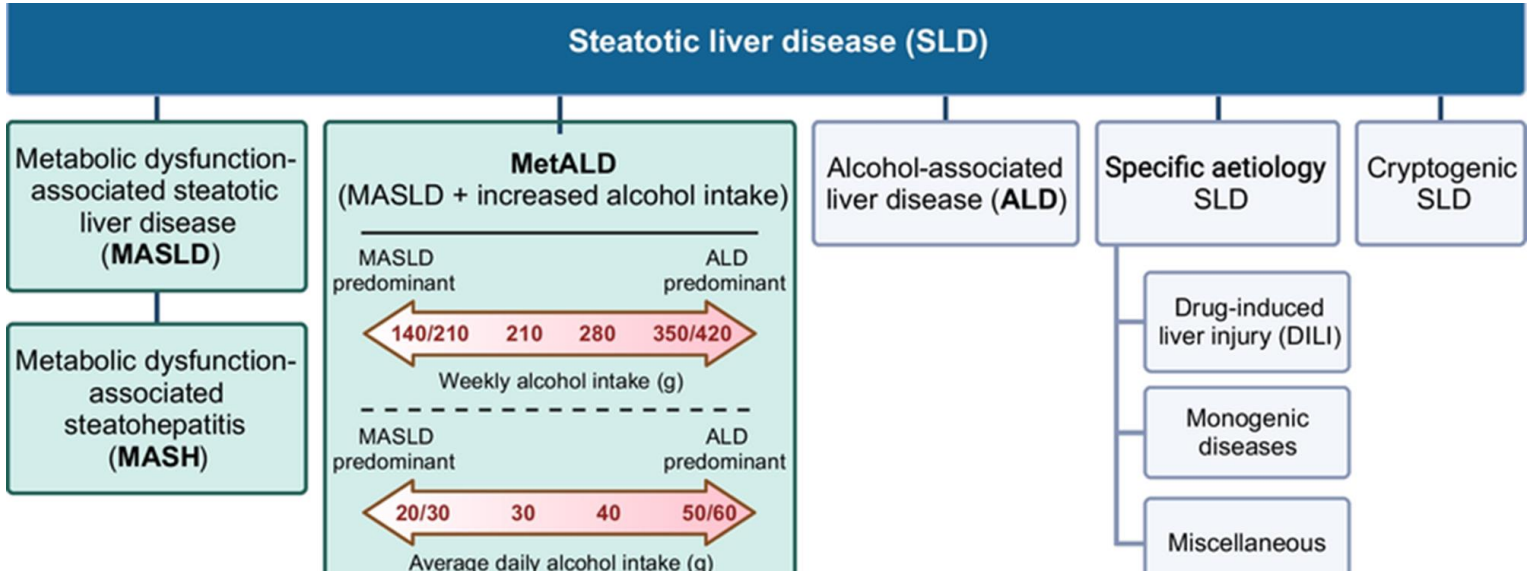
Risk ratio relative to Placebo

AASLD Souza, et al | HEPATOLOGY. 2025. HEPATOLOGY

Souza, Matheus1; Al-Sharif, Lubna2; Antunes, Vanio L.J.3; Huang, Daniel Q.4,5; Loomba, Rohit6,7. Comparison of pharmacological therapies in metabolic dysfunction–associated steatohepatitis for fibrosis regression and MASH resolution: Systematic review and network meta-analysis. Hepatology ():10.1097/HEP.0000000000001254, February 4, 2025. | DOI: 10.1097/HEP.0000000000001254

Take Home Message

- The spectrum of steatotic liver disease has been revised
- Importance of screening and identifying patients with MASLD early
- The pharmacological and non-pharmacological treatment strategies available
- Multiple trials are ongoing



Acknowledgements

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