MAFLD

by

Dr Sandy Mpho Mosenye

Facilitator

Prof. C. Wendy Spearman

(27/03/23)

OUTLINE

- Introductory Overview
- Epidemiology of NAFLD
- Definition of terms
- Pathogenesis of NAFLD/MAFLD
- Clinical Presentation/diagnosis of NAFLD/MAFLD
- Investigations
- Management

INTRODUCTION

- In 1980, Ludwig and his colleagues described a then un-named disease characterized by presence of striking fatty changes with evidence of lobular hepatitis, focal necrosis with mixed inflammatory infiltrates, and, in most instances, Mallory bodies, in moderately obese patients, many of whom had obesity-associated diseases, such as diabetes mellitus and cholelithiasis.
- These were patients not taking alcohol.
- They named the disease **N**on **A**lcoholic **S**teato**H**epatitis (NASH)

Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholicsteatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434–438.

NAFLD

Presence of >5% hepatic steatosis without causative factors such as alcohol (<30g/day for men and <20 g/day for women)., certain drugs, or other defined liver disorders.

- Histological spectrum: Simple steatosis, non-alcoholic steatohepatitis (NASH) & advanced fibrosis
- Overall, 3–5% patients develop NASH, with 1-2% developing advanced fibrosis
- Under-recognised liver manifestation of the Metabolic syndrome

INTRODUCTION

- Despite the devastating impact and the rising prevalence of this disease, the nomenclature and diagnostic criteria for this disease had not been revised until 2020 when a panel of international experts from 22 countries proposed a new definition for the diagnosis of this disease that is both comprehensive, simple and is independent of other liver diseases.
- They called it MAFLD (**M**etabolic (dysfunction) **A**ssociated Liver **D**isease.

Mohammed Eslam et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. Journal of Hepatology 2020 vol. 73 j 202–209

Proposal to amend definition-From the known NAFLD to MAFLD

Metabolic dysfunction-associated fatty liver disease: MAFLD

Hepatic steatosis (histology, imaging, biomarkers or scores) with 1 of the following 3 criteria

- Overweight (BMI ≥25kg/m^2) or Obesity (BMI ≥30kg/m^2)
- Type 2 diabetes
- 2 metabolic risk factors: Increased waist circumference, HPT, hypertriglyceridemia, low HDL, prediabetes, insulin resistance, subclinical inflammation with increased CRP

Based on positive criteria: NOT a diagnosis of exclusion

Does not exclude alcohol, can coexist with other liver diseases

Emphasises the role of the metabolic syndrome

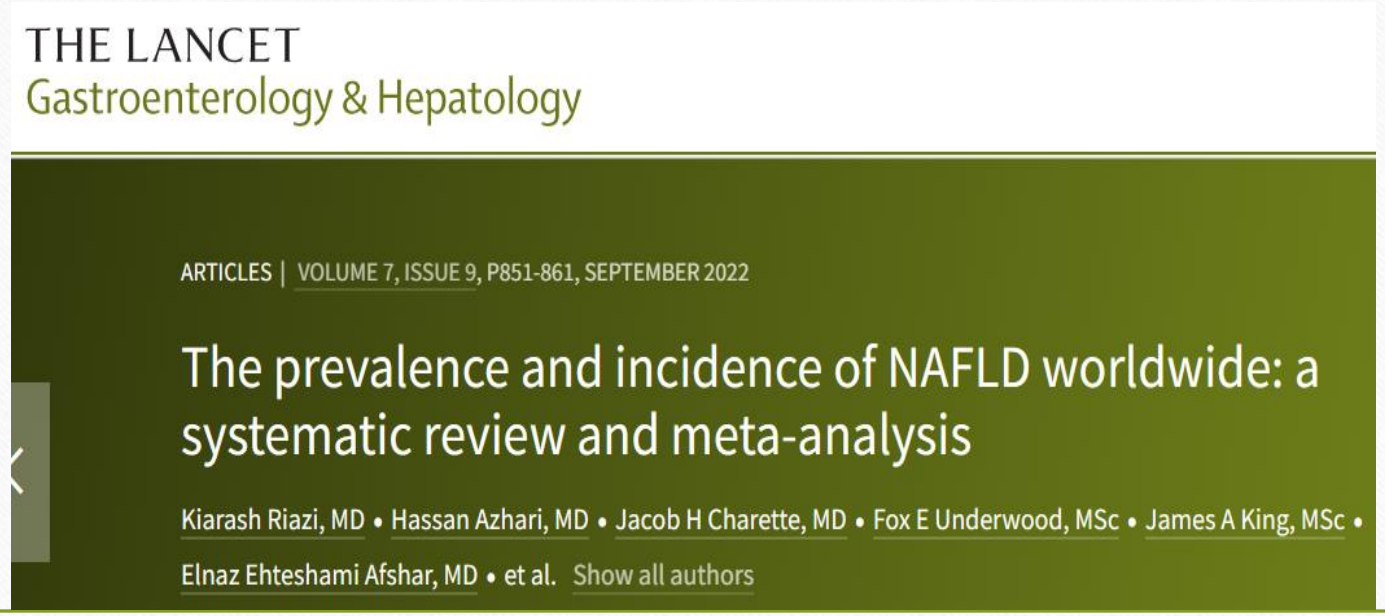
EPIDEMIOLOGY

- Reported studies on epidemiology and risk factors are based on the criteria for NAFLD.
- Prevalence estimates for this NAFLD vary widely depending on the information available in a given population and the diagnostic criteria used to establish the diagnosis (i.e., liver biochemical test levels, imaging study results, or liver biopsy findings).
- Nearly 1 billion people globally are affected by NAFLD.

Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018; 15:11–20.

EPIDEMIOLOGY

- A recent systematic review and meta-analysis by Kiarash R et al estimated the overall prevalence of NAFLD worldwide to be 32·4%.

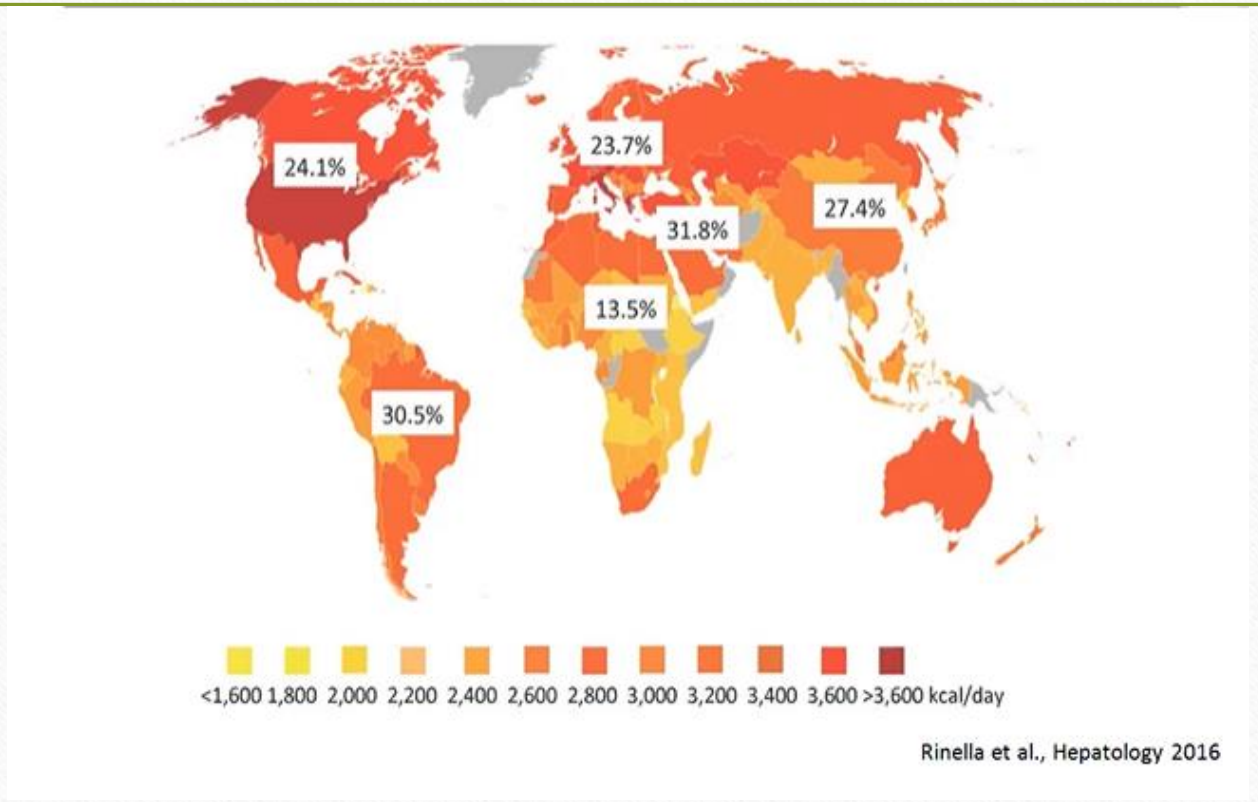


EPIDEMIOLOGY

- Data on the prevalence of NAFLD in Africa is scarce, but it is estimated to be 13.5% for the general population.

Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15(1):11–20.

EPIDEMIOLOGY



EPIDEMIOLOGY

- Most cases of NAFLD are discovered in middle age during the fourth to sixth decades of life.

- There is however an increasing frequency in children and adolescents, in whom the frequency of overweight and obese persons has been reported to be 30% of the population.

Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007-2008. JAMA 2010;303:242–9.

EPIDEMIOLOGY

- Studies have reported NAFLD to be more common in men than women.

- There is later peaking prevalence in women than men, including propensity for more advanced disease in postmenopausal women, suggesting relationship with sex hormones and menopause.

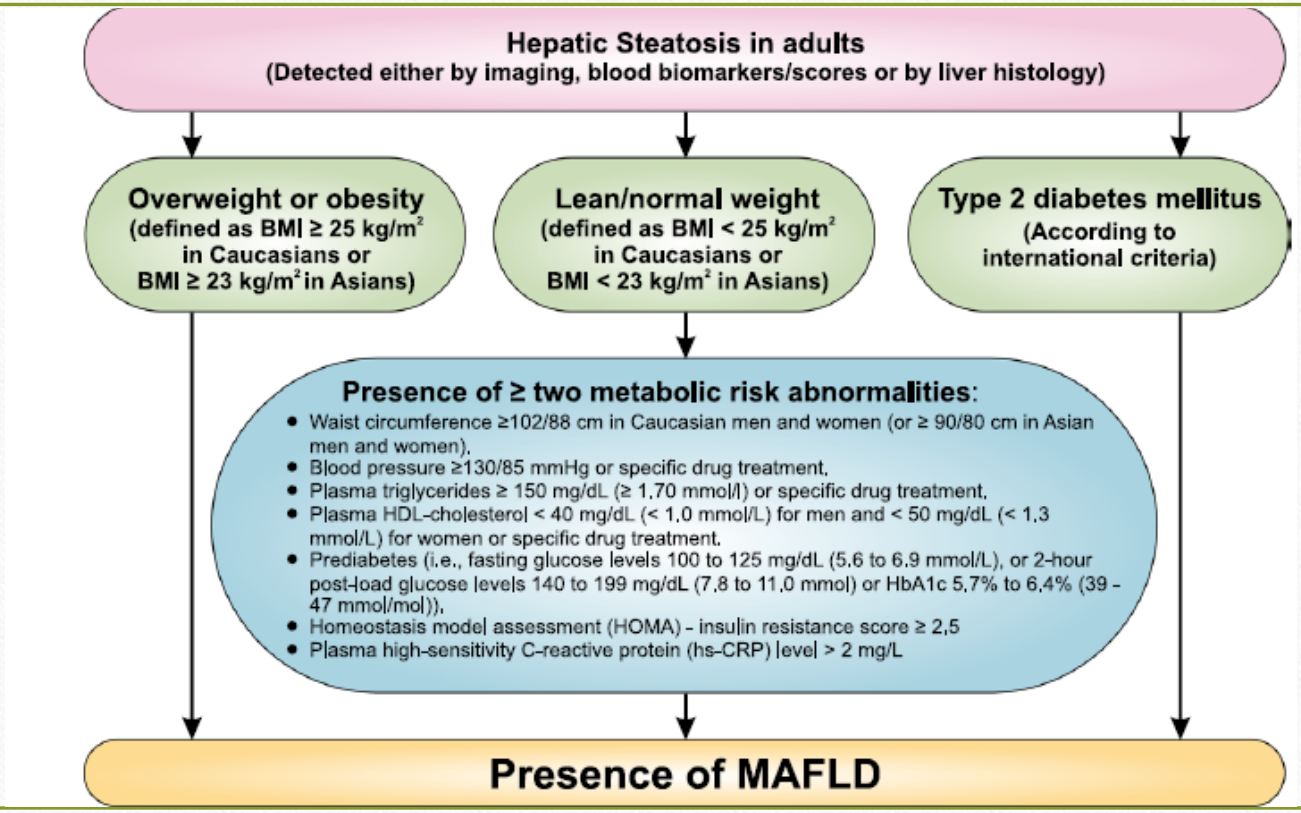
1) Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2012;10:837–58.
2) Ruhl CE, Everhart JE. Epidemiology of nonalcoholic fatty liver disease. Clin Liv Dis 2004;8:501–19.

WHAT IS THIS NAFLD/MAFLD?

- NAFLD
- **N**on-**A**lcoholic **F**atty **L**iver **D**isease
- -Fatty Liver on imaging, biopsy or serum biomarkers in the absence of;
- 1)Other liver diseases (HBV, HCV, Autoimmune Hep),
- 2)Other causes of fatty liver (Wilson's disease, Medication, Inherited Disorders)
- 3)Significant alcohol intake, <30g/day for men and <20 g/day for women.

- MAFLD
- **M**etabolic (dysfunction) **A**ssociated **F**atty **L**iver **D**isease
- -Fatty liver on imaging, biopsy or serum biomarkers plus one of the following;
- 1)Type 2 Diabetes
- 2) Overweight or obesity
- 3) Metabolic dysregulation

MAFLD


Hepatic Steatosis in adults
(Detected either by imaging, 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 international criteria)
Presence of ≥ 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
Presence of MAFLD

PROPOSED NEW NAME (MAFLD)

The Delphi process was followed to change NAFLD to MAFLD and the following are some of the reasons raised for why new name was needed.

- The Term NAFLD is diagnosis of exclusion, because you must exclude other liver diseases, significant alcohol intake and others.
- From Patient's perspective, the term "Non-Alcoholic Fatty Liver Disease" trivializes the problem.
- The " Non" and "alcoholic" part of the definition potentially places the blame on patients.
- Implies that treatment must lie entirely on the patients' hands.
- MAFLD is inclusive- meaning it takes into account that you can have concomitant fatty liver with other liver diseases e.g HBV infection in patient with fatty liver or alcohol in patient with fatty liver.
- Better reflects the pathogenetic basis of the disease and allows a more comprehensive and standardized approach to patient management.

PROPOSED NEW NAME (MAFLD)

- A number of societies endorsed the new name;

PROPOSED NEW NAME (MAFLD)

HEPATOLOGY AASLD

Special Article

From NAFLD to MAFLD: Implications of a Premature Change in Terminology

Zobair M. Younossi, Mary E. Rinella, Arun J. Sanyal, Stephen A. Harrison, Elizabeth M. Brunt, Zachary Goodman, David E. Cohen, Rohit Loomba

First published: 16 June 2020 | https://doi.org/10.1002/hep.31420 | Citations: 157

They appreciate that there has been some dissatisfaction with the terminology "non-alcoholic" which overemphasizes "alcohol" and underemphasizes the root cause of this liver disease.

BUT They said:

Although MAFLD reflects the relevant risk factors for this liver disease, this term is still suboptimal, leaving a great deal of ambiguity

Changing the terminology without new understanding of the molecular basis of the disease entity, new insights in risk stratification or other important aspect of this liver disease, can create unnecessary confusion which could negatively impact the field

They recommended:

The creation of a true international consensus group to include all the relevant scientific liver societies (AASLD, EASL, ALEH, APASL), patient advocacy organizations, bio-pharmaceutical industry, regulatory agencies and policy makers.

AASLD

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Practice Guidelines | Meetings & Events | Learning & Growth | Journals & News | About AASLD

Home > News > Reaching Consensus on NAFLD Nomenclature

Reaching Consensus on NAFLD Nomenclature

February 11, 2022

There has been much progress regarding the ongoing discussions over nomenclature for nonalcoholic fatty liver disease (NAFLD). AASLD has been leading and participating in a global multi-stakeholder process that includes extensive involvement from patient groups to examine the options and ramifications around nomenclature in this condition.

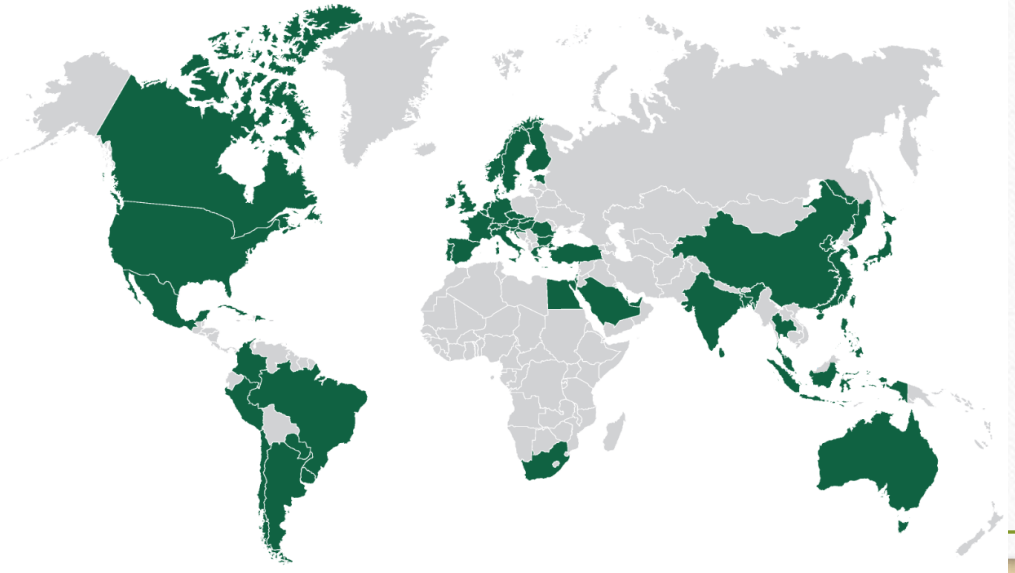
LD and EASL are encouraging our sister societies to await the
ort for any particular nomenclature. There is great value in an
l multi-stakeholder consensus position.

GLOBAL NAFLD NOMENCLATURE CONSENSUS DEVELOPMENT

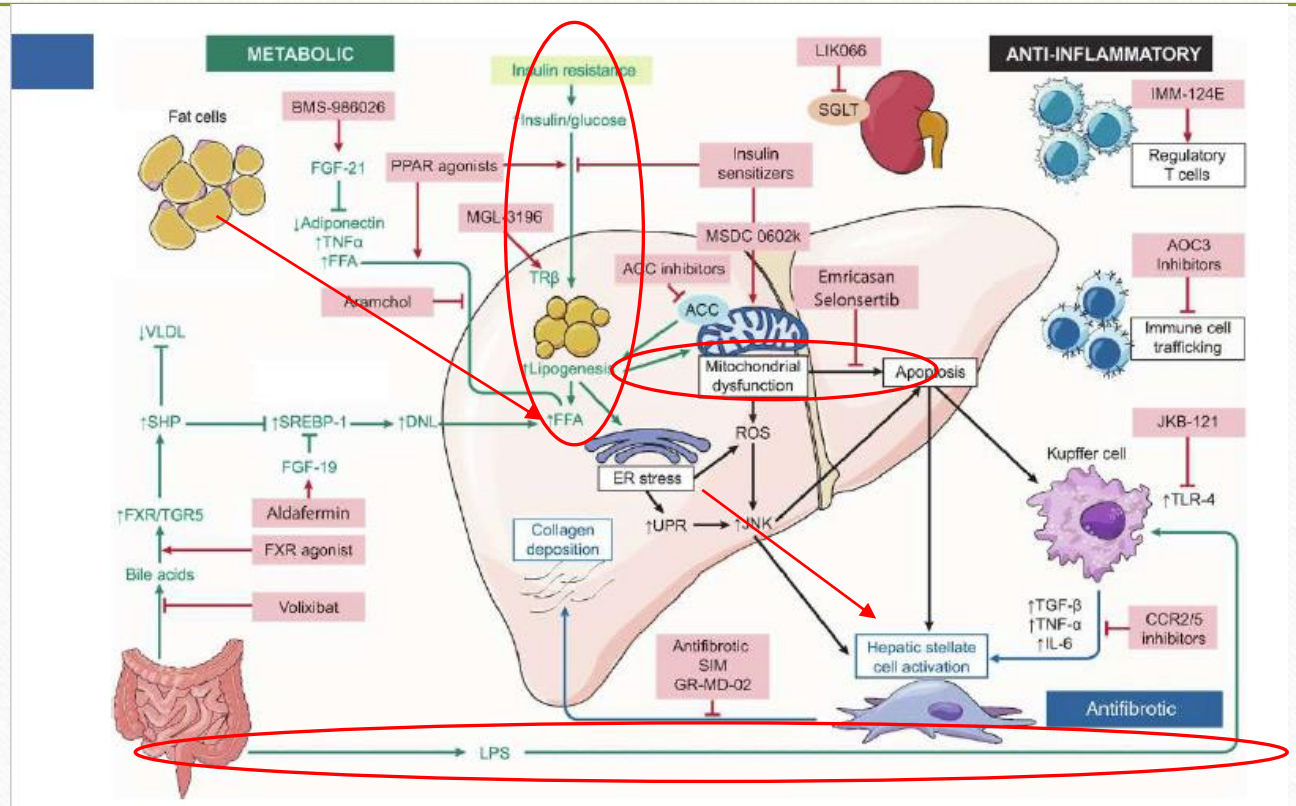
***Process* at The Liver Meeting®**

The "*Pan-Society Presentation of NAFLD Nomenclature Consensus Process*," live streamed on Sunday, November 6, 2022 at The Liver Meeting® in Washington, DC, USA, provided an update to the community, including the results of the most recent Delphi round. Watch the recorded

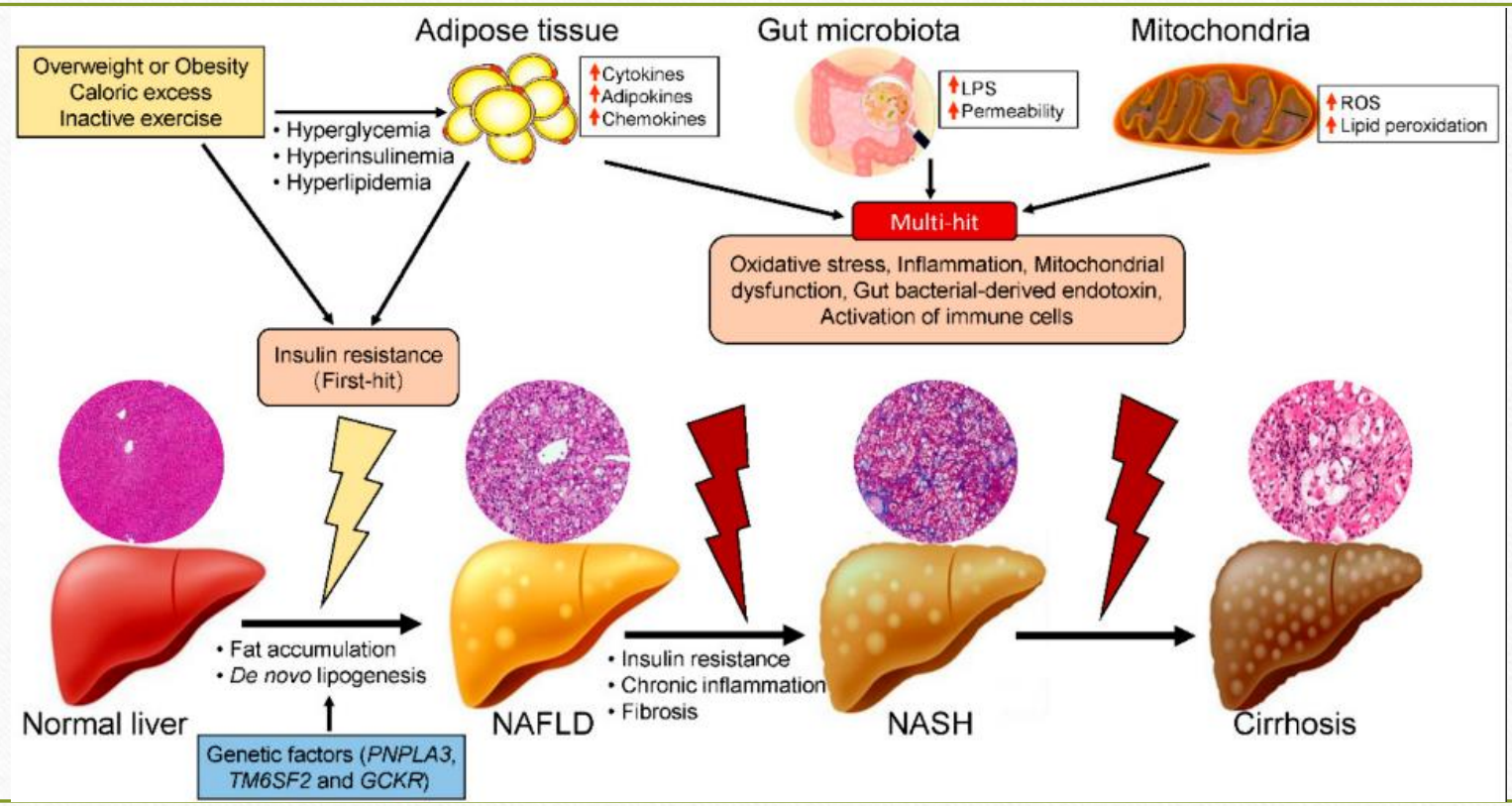
Global NAFLD Nomenclature Engagement



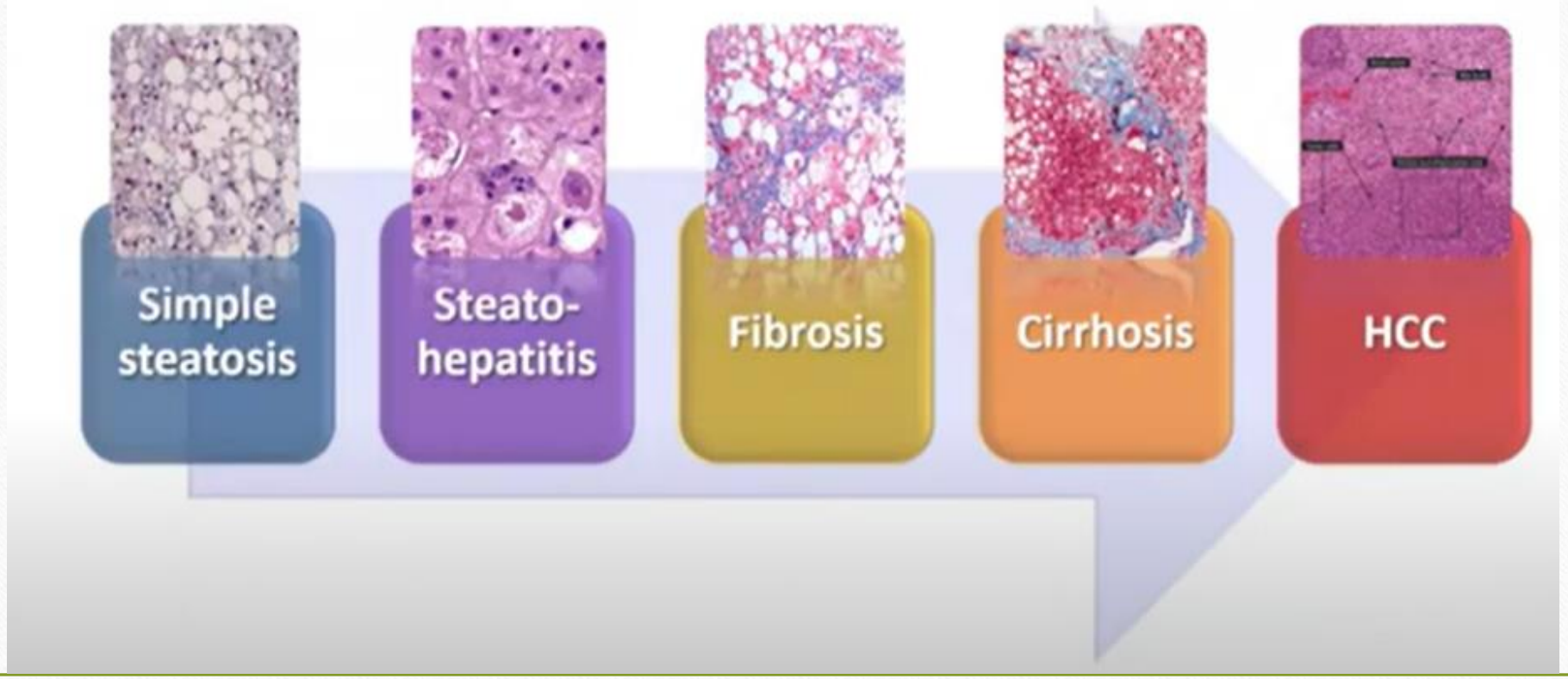
PATHOGENESIS OF NAFLD/MAFLD



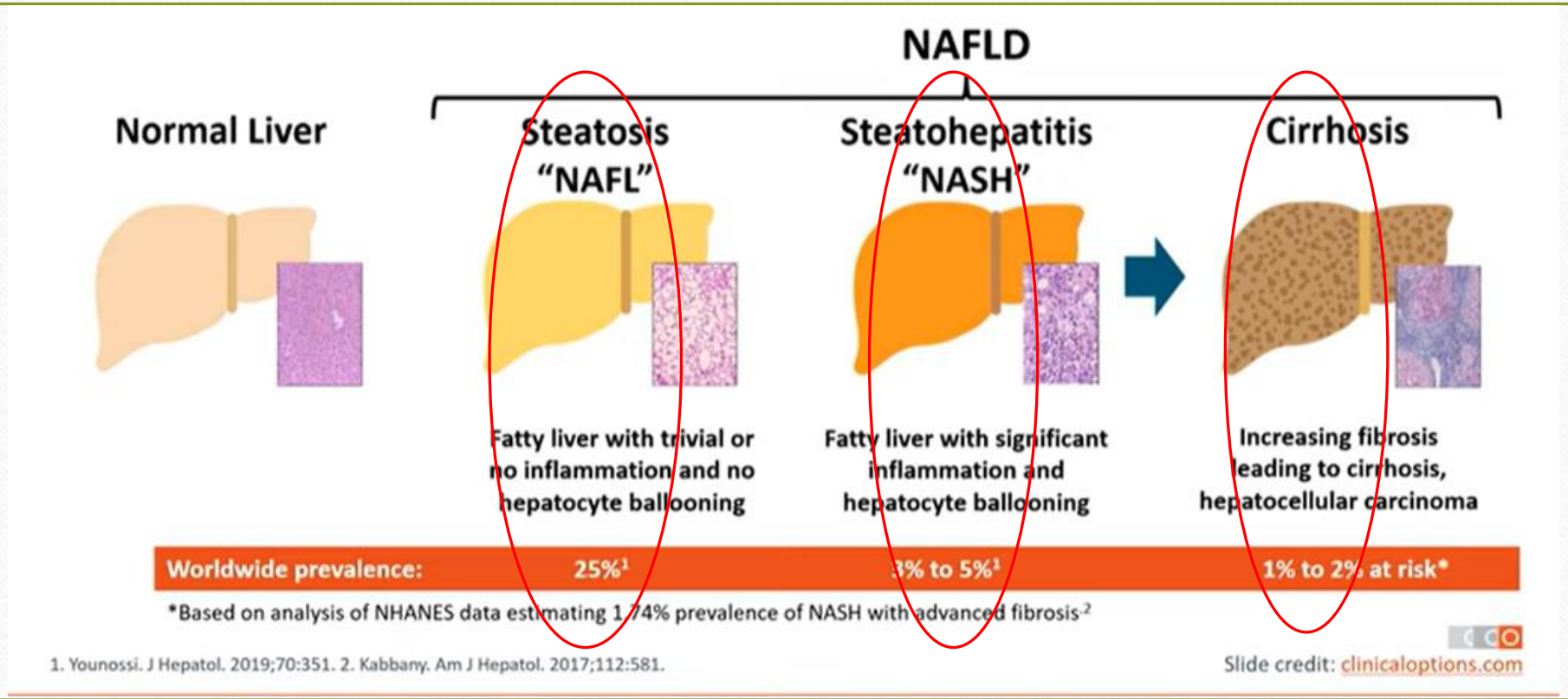
PATHOGENESIS



PATHOLOGY


Simple steatosis
Steato-hepatitis
Fibrosis
Cirrhosis
HCC

PATHOLOGY


NAFLD
Normal Liver
Steatosis
"NAFL"
Steatohepatitis
"NASH"
Cirrhosis
Fatty liver with trivial or no inflammation and no hepatocyte ballooning
Fatty liver with significant inflammation and hepatocyte ballooning
Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma
Worldwide prevalence:
25%[1]
3% to 5%[1]
1% to 2% at risk*
*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis[2]
1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.
Slide credit: clinicaloptions.com

RISK FACTORS OF NAFLD/MAFLD

Major risk factor	Common and uncommon risk factor
Overweight/obesity	
Central obesity	
Type 2 diabetes mellitus	
Dyslipidemia	
Arterial hypertension	
Metabolic syndrome	
Insulin resistance	
Dietary factors: high-calorie diets r soft drinks high in fructose, highl	*3*, *TM6SF2*, *GCKR*, *MBOAT7*, and
Sedentary lifestyle or sedentary occ ity	NAs (miR), DNA methylation, histone ination alterations
Sarcopenia	y of T2DM, premature vascular disease, and high blood pressure (metabolic syn-

Should the high-risk population be screened for MAFLD?

Recommendations

- Screening for MAFLD by ultrasonography should be considered in at-risk populations such as patients with overweight/obesity, T2DM and metabolic syndrome (A1).
- Patients with MAFLD should be assessed for other components of metabolic syndrome and be treated accordingly (A1).
- Patients with MAFLD should receive advice and support for lifestyle interventions to reduce the risk of events from metabolic and cardiovascular disease, and to resolve fatty liver disease (A1).

Notably, many of these factors could be association, it is hard to ascertain the causality

PNPLA3 patatin-like phospholipase domain-containing protein 3; *TM6SF2* transmembrane 6 superfamily member 2, *GCKR* glucokinase regulator, *MBOAT7* membrane bound O-acyltransferase domain containing 7 HSD17B13: hydroxysteroid 17-beta dehydrogenase-13

Mohammed Eslam at al.The Asian Pacific Association for the Study of the Liver clinical practiceguidelines for the diagnosis and management of metabolic associated fatty liver disease

RISK FACTORS OF NAFLD/MAFLD

- ***1) METABOLIC SYNDROME***
- Metabolic Syndrome is a major risk factor for NAFLD. In fact NAFLD is the liver manifestation of metabolic syndrome and is part of a multisystem disease.
- It is core to Non communicable diseases and its pooled prevalence is Sub-Saharan Africa ranges from 11.1%- 23.9%. Ezzati M, Pearson-Stuttard J, Bennett JE, Mathers CD. Acting on non-communicable diseases in low- and middle-income tropical countries. *Nature* 2018; **559**: 507–16.
- The pathogenesis of NAFLD involves a complex interplay between genetics, epigenetics (gut microbiome), and environmental triggers, **with obesity and type 2 diabetes** being the predominant modulators of NAFLD and NASH.

RISK FACTORS OF NAFLD/MAFD

- ***2) OBESITY***
- Obesity is associated with a 3·5-times increased risk of NAFLD.
- Visceral adiposity (and its surrogate marker, waist circumference), is a key risk factor for many complications of metabolic syndrome and has a stronger association with NAFLD than does BMI alone, predisposing to a greater risk of NASH and fibrosis.
- Increased visceral adiposity is a risk factor in the development of NAFLD in lean individuals (ie, BMI <25 kg/m²), especially in Asian populations (in whom lean BMI is <23 kg/m²), with the **PNPLA3 I148M allele** playing a contributing role.

Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. JHEP Rep 2019; 1: 329–41.
Younes R, Bugianesi E. NASH in lean individuals. Semin Liver Dis2019; 39: 86–95.

RISK FACTORS OF NAFLD/MAFLD

- ***3)TYPE 2 DIABETES***
- The relationship between NAFLD and type 2 diabetes is bidirectional. The global prevalence of NAFLD in patients with type 2 diabetes, based on ultrasound or proton magnetic resonance spectroscopy, is 55·48% (95% CI47·26–63·67).
- NAFLD is associated with a roughly 2·2-fold increased risk of incident diabetes, with risk paralleling the underlying NAFLD severity.
- Type 2 diabetes accelerates the progression of liver disease in NAFLD and is a predictor of advanced fibrosis and mortality.
- The global prevalence of NASH among individuals with type 2 diabetes is 37·3% (95% CI 24·7–50·0), with advanced fibrosis occurring in 17·0% (7·2–34·8) of patients with NAFLD and type 2 diabetes.

RISK FACTORS OF NAFLD/MAFLD

- ***4) DYSLIPIDAEMIA***
- Ratios of high total cholesterol to HDL cholesterol and high triglyceride to HDL cholesterol are associated with increased risk of advanced NAFLD.

- The global pooled dyslipidaemia prevalence estimates are 69·2% (95% CI 49·9–83·5) in patients with NAFLD and 72·1% (54·6–84·8) in patients with NASH.1

- The pooled overall prevalence estimates for hypertriglyceridaemia are 40·7% (30·8–51·5) in patients with NAFLD and 83·3% (36·87–97·72) in patients with NASH.1

RISK FACTORS OF NAFLD/MAFLD

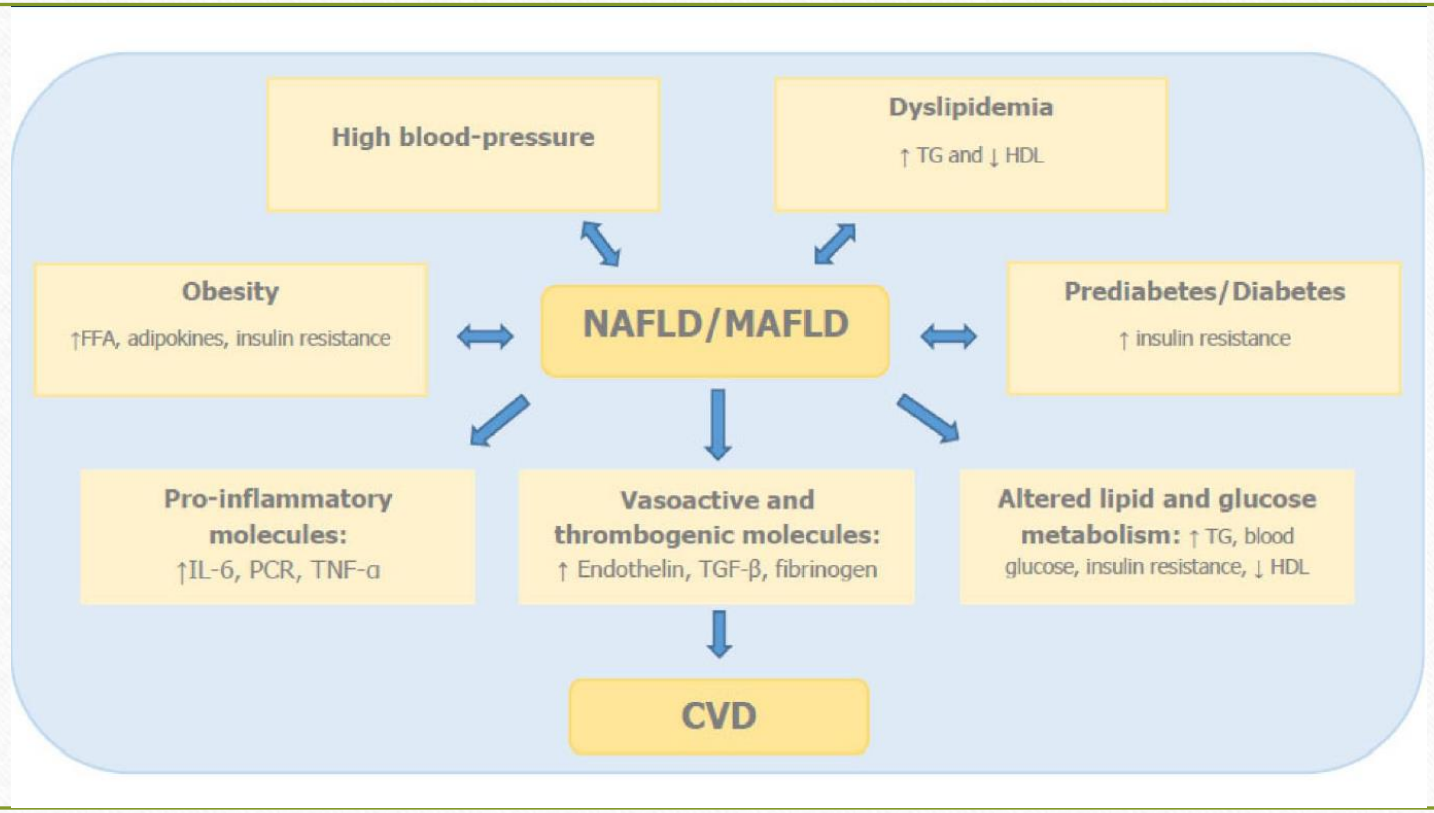
- ***5) POLYCYSTIC OVARY SYNDROME***
- Polycystic ovary syndrome is associated with insulin resistance and metabolic syndrome, and affects about 10% of the female population.

- This is a high-risk group for the development of NAFLD and NASH.

RISK FACTORS OF NAFLD/MAFLD

- ***6) GUT MICROBIOME***
- The gastrointestinal tract and the gut microbiome composition play a role in the development of NAFLD.
- Clinical studies have shown that NAFLD is associated with dysbiosis characterised by increased growth of bacteria such as Enterobacteriaceae and Escherichia coli, and a decrease in Faecalibacterium prausnitzii.
- Intestinal dysbiosis and microbiome instability influenced by the consumption of saturated fatty acids, fructose, and advanced glycated end-products contribute to development of liver disease.

CLINICAL FEATURES



CLINICAL PRESENTATION

- NAFLD can present with extrahepatic manifestations, which include; cardiovascular disease, cerebrovascular disease, chronic kidney disease, extrahepatic malignancies, polycystic ovary syndrome, and sleep apnoea.

Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. *Lancet Gastroenterol Hepatol* 2021; **6**: 578–88.

- NASH with advanced hepatic fibrosis can rapidly progress to cirrhosis and decompensate with hepatic encephalopathy, ascites, variceal bleeding, and death.

Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepatology* 2019; **70**: 1913–27.

- Although liver-related mortality is increased, cardiovascular disease remains the leading cause of death in patients with NAFLD and liver fibrosis stages F3 or F4.

DIAGNOSIS

A noninvasive method of predicting NAFLD, the " fatty liver index (FLI)" is calcu es (TGs

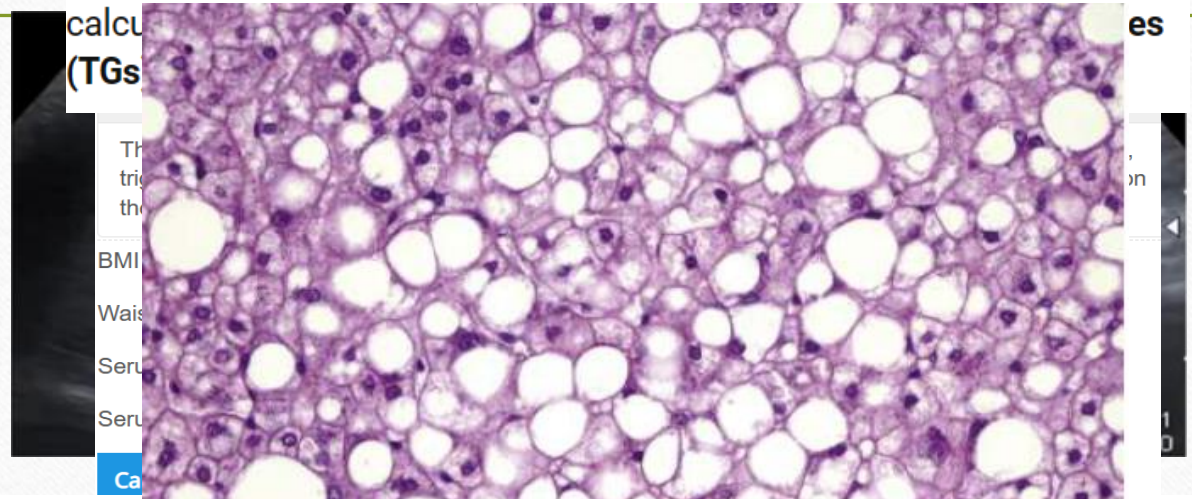


Fig. 87.1 Histologic features of isolated fatty liver. The characteristic feature is diffuse macrovesicular steatosis without significant necro-inflammation or fibrosis. Glycogenated nuclei are common (H&E). (Courtesy Dr. Gregory Y. Lauwers, Boston, MA.)

FLI interpretation

The fatty liver inde rvals within this range is the followi

- FLI below 30 me ;
- FLI between 30
- FLI of 60 and ab from 4.3).

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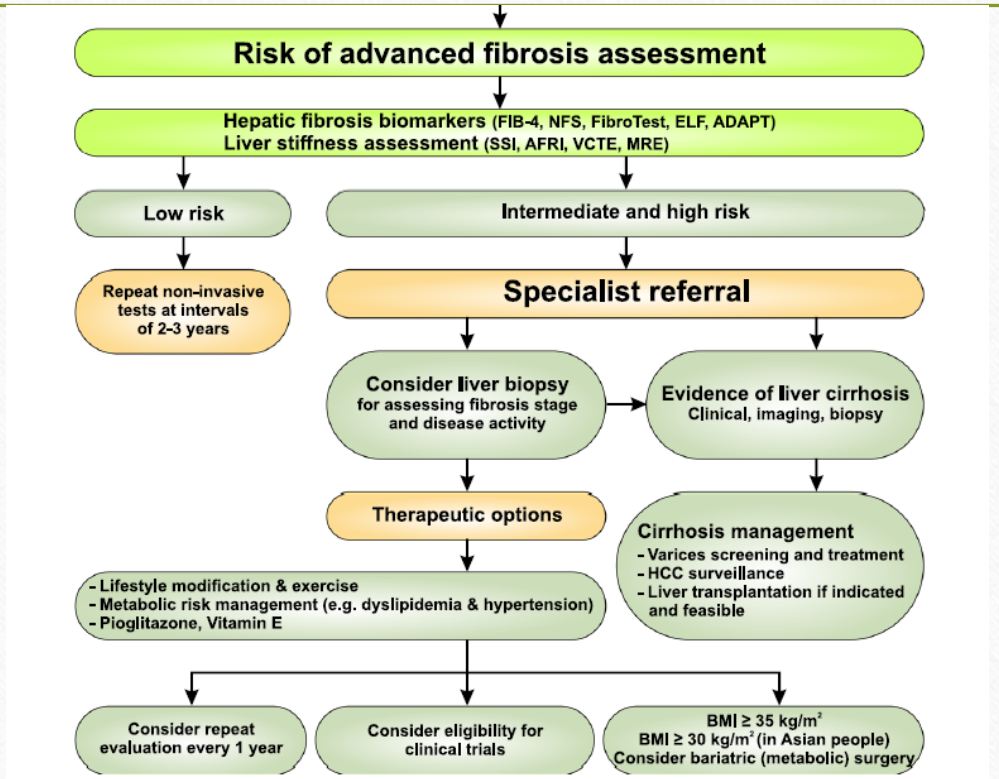
ASSESSMENT FOR FIBROSIS



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ASSESSMENT FOR FIBROSIS

HEPATIC FIBROSIS BIOMARKERS

- FIB-4 - Fibrosis-4 Index
- APRI - AST -to-Platelet Ratio Index
- NFS - NAFLD Fibrosis Score
- ELF - Enhanced Liver Fibrosis
- ADAPT
- FibroTest

LIVER STIFFNESS ASSESSMENT

- SSI - Supersonic Shear Imaging
- ARFI-Acoustic Radiation Force Impulse
- VCTE-Vibration-Controlled Transient Elastography
- MRE- Magnetic Resonance Elastography

ASSESSMENT FOR FIBROSIS

Hepatic Steatosis Biomarker Cut off's- Risk Stratifying into low Risk, Intermediate risk and High risk
APRI (0.5 and 1.5),
FIB-4 (1.30 and 2.67)
NFS (< − 1.455 and > 0.67611)

Mohammed Eslam et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatology International (2020) 14:889–919

NON INVASIVE TESTS FOR MAFLD

- These Non-invasive tests are needed in MAFLD management to;
- 1) establish the diagnosis of MAFLD,
- 2) assess disease severity,
- 3) monitor disease progression and treatment response

NON INVASIVE TESTS FOR MAFLD

- Among the various histological features of MAFLD, the degree of liver fibrosis has the strongest correlation with future liver-related morbidity and mortality.
- Therefore non invasive tests of fibrosis are very important and they have been divided into;
- 1) Simple fibrosis scores- (AST)-to-platelet ratio index (APRI), Fibrosis-4 index (FIB-4) , and NAFLD fibrosis score (NFS).
- 2) Specific fibrosis biomarkers, -enhanced liver fibrosis panel, The ADAPT
- 3)Imaging biomarkers-VCTE, shear wave elastography,

NOTE

Table 2 Etiology of fatty liver disease

Etiology classification	Specific causes
Metabolic associated fatty liver disease	Overweight/obese, type 2 diabetes mellitus, metabolically unhealthy normal weight subjects
Alcohol associated fatty liver disease	Significant alcohol consumption (> 21 standard drinks per week in men and > 14 standard drinks per week in women over a 2-year period), binge drinking (> 5 standard drinks in men and > 4 standard drinks in women over a 2-h period), and lifetime alcohol intake > 100 kg [31]
Alternative causes of fatty liver disease	Long-term use of steatogenic medications (corticosteroids, valproic acid, tamoxifen, methotrexate, amiodarone, etc.), exposure to some chemicals, HCV genotype 3 infection, Wilson's disease, coeliac disease, starvation, total parenteral nutrition, severe surgical weight loss, disorders of lipid metabolism (abetalipoproteinemia, hypobeta lipoproteinemia, lysosomal acid lipase deficiency, familial combined hyperlipidaemia, lipodystrophy and Mauriac syndrome), Weber–Christian syndrome, glycogen storage disease, Cushing's syndrome, etc

DIAGNOSIS OF MAFLD IN THE SETTING OF OTHER LIVER DISEASES

- Since MAFLD is no longer a diagnosis of exclusion and is based on the presence of metabolic dysfunction, it is now possible to diagnose its coexistence with other liver diseases; such as
- 1)alcoholic liver disease (ALD),
- 2)chronic hepatitis B virus infection (CHB), and
- 3)chronic hepatitis C virus infection (CHC),
- 4)primary biliary cholangitis, and
- 5)genetic hemochromatosis

IMPACT OF MAFLD ON OTHER LIVER DISEASES

- Individuals with concomitant MAFLD and other liver diseases are likely to have a different natural history and response to therapy than those with liver disease of a "single" etiology. Eslam M, Newsome PN, Anstee QM, Targher G, Gomez MR, Zelber-Sagi S, Wong VW, et al. A new definition for metabolic associated fatty liver disease: an international expert consensus statement. J Hepatol 2020. https://doi.org/10.1016/j.
- MAFLD may accelerate the progression of liver disease in patients with ALD and CHB, and synergistically induce liver cirrhosis or even HCC development.
- MAFLD independently increased the risk of HCC development by 7.3-fold(OR: 7.3, 95%CI 1.52–34.76) in patients with CHB Chan AW, Wong GL, Chan HY, Tong JH, Yu YH, Choi PC, Chan HL, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol 2017;32:667–676.
- MAFLD significantly impacts the entire natural course of CHC including progression of the liver disease, therapeutic responses, and the development of some extrahepatic complications.

MANAGEMENT OF NAFLD/MAFLD

- The optimal therapy for NAFLD has not been established.
- There is however a general consensus that treatment efforts should be targeted to patients with Steatohepatitis, particularly with fibrosis.
- Histologic improvement in steatosis, inflammation, and fibrosis is the ultimate goal of treatment.

MANAGEMENT OF NAFLD/MAFLD

- Treatment strategies are grouped into lifestyle modification, surgical interventions for weight loss, and pharmacotherapy.

TABLE 87.3 Current and Future Treatment Options for NAFLD

Modality	Effect	Comment(s)
DIETARY ADVICE		
Weight loss 5%-10% Moderate caloric restriction with goal 500-750 kcal fewer per day	Improves most features of NASH	Difficult to sustain
Eliminate or reduce SFAs, high fructose corn syrup	High consumption risk factor for NASH and ↑ fibrosis	Prospective trials lacking
Consider omega-3 fatty acid replacement	Decreases hepatic steatosis improves serum triglycerides	Lack of histologic improvement in NAFLD/NASH Useful for hypertriglyceridemia
Consider regular coffee consumption, 2-3 cups per day	Decreased risk of fibrosis	Optimal amount unclear
EXERCISE ADVICE		
Aerobic and/or resistance training 3-4 times per wk with the goal of 400 kcal expended	Improves insulin resistance	Best results when leads to weight loss
BARIATRIC SURGERY		
Sleeve gastrectomy, RYGB, LABG	Improves or resolves NASH in 60%-80% cases as well as fibrosis	Use only when failed lifestyle modification and comorbid conditions justify risk of surgery
PHARMACOTHERAPY (CURRENT)		
Vitamin E 800 IU daily	Improves NASH but modestly; no fibrosis benefit	Useful in nondiabetic populations ? Prostate cancer risk
Pioglitazone 30-45 mg daily	Improves NASH, possible fibrosis improvement	Side effect profile is often prohibitive (e.g., weight gain, osteoporosis, edema, congestive heart failure) Not FDA approved for NASH
Incretin mimetics (exenatide and liraglutide)	Improve insulin resistance, promote weight loss, modest histologic improvement in small trials	GI side effects Ongoing trial with semaglutide
Pentoxifylline	Possible NASH and fibrosis improvement	Small pilot trials
Statins	Does not improve NASH histology	Safe in NAFLD and reduces risk of cardiovascular disease
Ezetimibe	Modest improvement in pilot trial	Safe in NAFLD and can be used for hyperlipidemia but not as NAFLD/NASH therapy
PHARMACOTHERAPY (FUTURE)		
FXR agonists: Obeticholic acid	Improves NASH histology	Side effects: pruritus, increased LDL, lowered HDL
Aldafermin	Ongoing phase 2 studies	Side effects: diarrhea, nausea, diabetes mellitus
Antifibrotics: Cenicriviroc, emricasan, selonsertib, GR-MD-02	Ongoing phase 2 and phase 3 studies	Promising but more data needed
PPAR-α/δ agonist: Elafibranor	Relatively modest efficacy	Side effects: ↑ serum creatinine

FXR, farnesoid X receptor; *LAGB,* laparoscopic adjustable gastric banding; *PPAR,* peroxisome proliferator-activated receptor; *RYGB,* Roux-en-Y gastric bypass; *SFA,* saturated fatty acid.

MANAGEMENT OF NAFLD/MAFLD

- LIFESTYLE MODIFICATIONS; Lifestyle modification is often divided into a reduction in calories with a goal of weight loss, macronutrient modification, and physical activity, including aerobic and resistance activity.
- Nutritional counseling and caloric restriction leading to weight loss have been shown to improve hepatic histology in several randomized controlled trials.

- BARIATRIC SURGERY : Bariatric surgery leads to substantial weight loss that results in improved metabolic parameters and hepatic histology in patients with NAFLD, according to numerous large retrospective and prospective cohort studies.

MANAGEMENT NAFLD/MAFLD

- PHARMACOTHERAPY
- Weight loss medications, insulin sensitizers, antioxidants, and cytoprotective or antifibrotic agents.
- LIVER TRANSPLANTATION
- The last resort for Fatty Liver induced Cirrhosis.

MANAGEMENT OF NAFLD/MAFLD

- ***Lifestyle changes, dietary intervention, weight loss, and physical activity***
- Diet, as part of lifestyle changes, is key in NAFLD treatment. It has the strongest association with improved outcomes of all interventions and improves histology in NASH.
- A decreased caloric intake and reductions of at least 5% of bodyweight achieve a significant reduction in intrahepatic lipid content with a reduction in NAFLD activity scores.102
- A meta-analysis of eight studies showed that weight loss of 7% or more was associated with improved NAFLD activity scores, while a prospective paired liver biopsy study of 261 patients found that 10% body weight reduction produced complete resolution of NASH in 26 (90%) of 29 patients.

European Association for the Study of the Liver (EASL). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64: 1388–402
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: 885–904.

MANAGEMENT OF NAFLD/MAFLD

- Exercise improves cardiovascular comorbidities, insulin-resistance, and hepatic triglyceride content.
- The general consensus is that exercise should be prescribed for 150−200 minutes per week in three to five sessions of moderate-intensity aerobic and resistance exercise.
- A systematic review showed that resistance exercise improves NAFLD with lower energy consumption.
- This is a useful intervention in patients with NAFLD who have impaired cardiorespiratory fitness or are unable to do aerobic exercise.
- Exercise at sustained levels is also beneficial in maintaining weight loss.

Hashida R, Kawaguchi T, Bekki M, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: a systematic review. J Hepatol 2017; 66: 142–52.
Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol 2017; 67: 829–46.

MANAGEMENT OF NAFLD/MAFLD

- ***Vitamin E***
- Vitamin E is an antioxidant that has been extensively studied for NAFLD.
- The landmark PIVENS study showed that vitamin E reduced inflammation and steatosis but not fibrosis in patients with NASH without cirrhosis or diabetes.

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., et al., for the NASH CRN*

MANAGEMENT OF NAFLD/MAFLD

- ***MANAGEMENT OF COMORBIDITIES/ RISK FACTORS***
- Management of Type 2 Diabetes/ Hypertension/Dyslipidaemia/ Obesity which are major risk factors and prognostic factors in NAFLD is very important.
- ***Type 2 Diabetes***
- Appropriate glycaemic control is associated with a reduction in steatosis, a decrease in serum aminotransferases, and improvement of liver inflammation and fibrosis.

MANAGEMENT OF NAFLD/MAFLD

- Specific anti-diabetic drugs might have potential effectiveness in NAFLD, beyond their glycaemic effect.
- Example:
- Metformin, while improving HbA1c, also has some modest weight loss benefits.
- The thiazolidinediones, including *rosiglitazone* and *pioglitazone*, have been extensively studied for the treatment of NASH.
- In a meta-analysis of eight randomized controlled trials, use of pioglitazone improved advanced fibrosis in NASH, including in individuals without diabetes.

Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. *JAMA Intern Med* 2017; 177: 633–40.

MANAGEMENT OF NAFLD/MAFLD

- Liraglutide, a GLP-1 agonist, has shown significant improvement in glycaemic control and a reduction in cardiovascular events and deaths in people with diabetes.
- Liraglutide was associated with a significant improvement in NASH histology (reduced progression of fibrosis), ALT improvement, and weight loss in a study by Armstrong MJ et al

Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016; **387**: 679–90.

- Semaglutide: Weight loss, improvement in NASH histology, no improvement in fibrosis *N Engl J Med 2021; 384:1113-1124*
- Sodium-glucose co-transporter-2 (SGLT2) inhibitors: Reduces steatosis, improves CVS profile *Diabetes Metab 2019; 45: 213–23.*

MANAGEMENT OF NAFLD/MAFLD

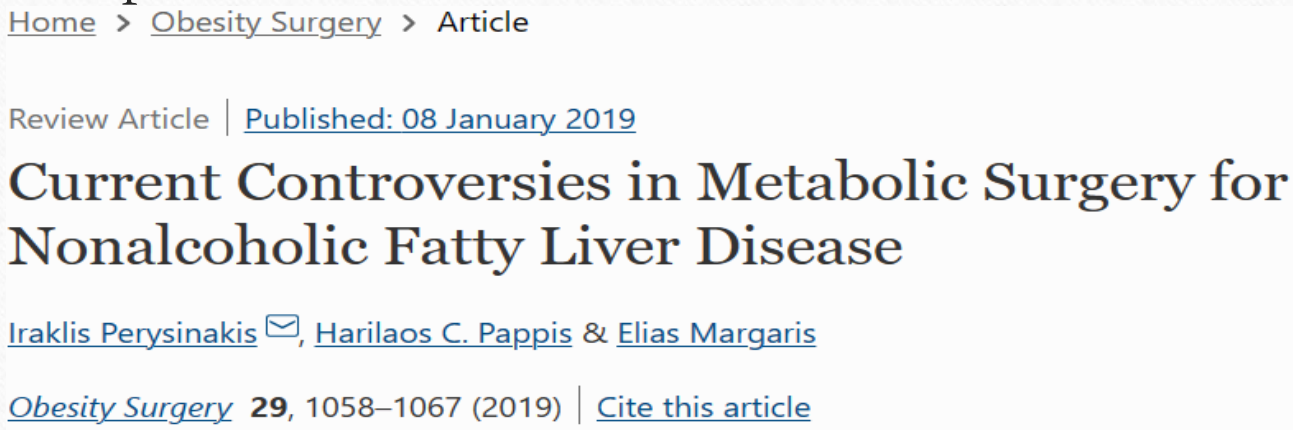
- ***Hypertension***
- Hypertension is a major risk factor promoting the development of NAFLD, occasionally independent of other risk factors.
- Good blood pressure control protects against NAFLD and the absence of hypertension mitigates against liver fibrosis in NAFLD.
- Additionally, blood pressure control is crucial to offsetting the cardiovascular risks associated with NAFLD.

MANAGEMENT OF NAFLD/MAFLD

- ***Dyslipidaemia***
- Multiple studies have shown the efficacy of lipid-lowering drugs in patients with NAFLD and NASH.
- These drugs include statins, fibrates, and ezetimibe.
- Statins are the most widely used and have known efficacy in reducing cardiovascular mortality in patients with coronary artery disease and type 2 diabetes.
- Statins are safe and effective in patients with NAFLD or NASH and have no excess hepatotoxicity.

MANAGEMENT OF NAFLD/MAFLD

- ***Obesity***
- Bariatric surgery is an effective treatment for obesity; with regard to NAFLD and NASH, it achieves histological resolution of NASH through both weight loss-dependent and weight loss-independent mechanisms.



COMPLICATIONS

- 1) MAFLD related cirrhosis- with complications- Portal Hypertension
- 2) Hepatocellular Carcinoma

TAKE HOME MESSAGE

- Metabolic (dysfunction) Associated Fatty Liver Disease (MAFLD) is fatty liver on imaging, serum biomarkers and/or histology plus either Type 2 diabetes/ overweight or obesity or metabolic dysregulation.
- Its worldwide prevalence is 32.4%. The prevalence estimate in Africa is 13.5%.
- It is commoner in Males than females.
- The pathogenesis involves- Metabolic dysregulation, GUT microbiota dysbiosis, Inflammation and some genetic involvement.
- The Risk factors are: Overweight/obesity, Central adiposity, Type 2 Diabetes, Metabolic syndrome, Arterial Hypertension etc.
- The major indicator for morbidity and mortality in MALFD is Fibrosis.
- There are Non Invasive measures of Fibrosis, that have been validated in measuring Fibrosis. Examples: FIB-4, NSF, APRI, SSI, VCTE, MRE etc.
- MAFLD can lead to cirrhosis and even Hepatocellular Carcinoma

References

- 1) Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholicsteatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434–438.
- 2) Mohammed Eslam et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. Journal of Hepatology 2020 vol. 73 j 202–209.
- 3) Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007-2008. JAMA 2010;303:242–9.
- 4) Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2012;10:837–58.
- 5) Ruhl CE, Everhart JE. Epidemiology of nonalcoholic fatty liver disease. Clin Liv Dis 2004;8:501–19.
- 6) Mohammed Eslam at al.The Asian Pacific Association for the Study of the Liver clinical practiceguidelines for the diagnosis and management of metabolic associated fatty liver disease
- 7) Sleisenger and Fordtran's Gatrointestinal and Liver Disease, 11th Edition
- 8) C.Wendy Spearman at al. Non-alcoholic fatty liver disease in sub-Saharan Africa 1 ,Epidemiology, risk factors, social determinants of health, and current management for non-alcoholic fatty liver disease in sub-Saharan Africa. . Lancet Gastroenterol Hepatol. 2021 Dec; 6(12):1047-1056
- 9) C.Wendy Spearman at al. Non-alcoholic fatty liver disease in sub-Saharan Africa 2, Health-care provision and policy for non-alcoholic fatty liver disease in sub-Saharan Africa. Lancet Gastroenterol Hepatol. 2021 Dec; 6(12):1047-1056