NON ALCOHOLIC FATTY LIVER DISEASE AND NON ALCOHOLIC STEATOHEPATITIS

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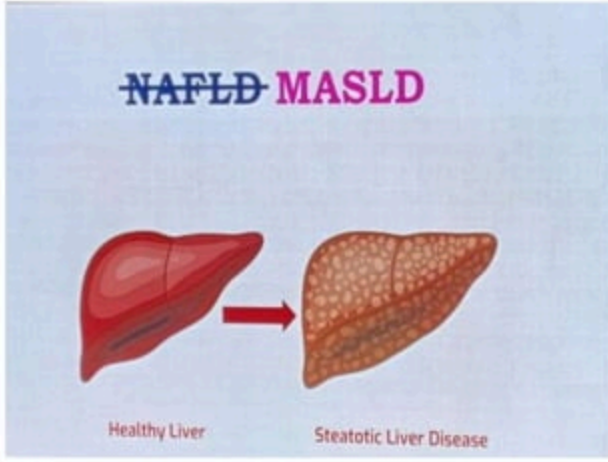
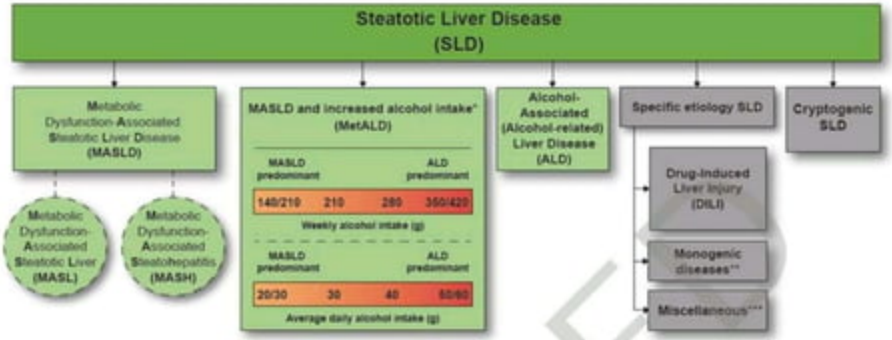
Metabolic dysfunction Associated Steatotic Liver Disease(MASLD).



INTRODUCTION.

- A global delphi consensus process co-led by American Association for the study of Liver Diseases (AASLD) and the European Association for the study of Liver (EASL) in collaboration with the Latin American Association for the study of Liver (ALEH) recommended renaming of NAFLD to MASLD on June 24, 2023.
- Steatotic Liver Disease (SLD) was chosen as an overarching term to classify individuals with hepatic steatosis(>5% fat in liver) due to various etiologies.
- The term SLD includes MASLD, MetALD, ALD, Specific etiology SLD, Cryptogenic SLD.

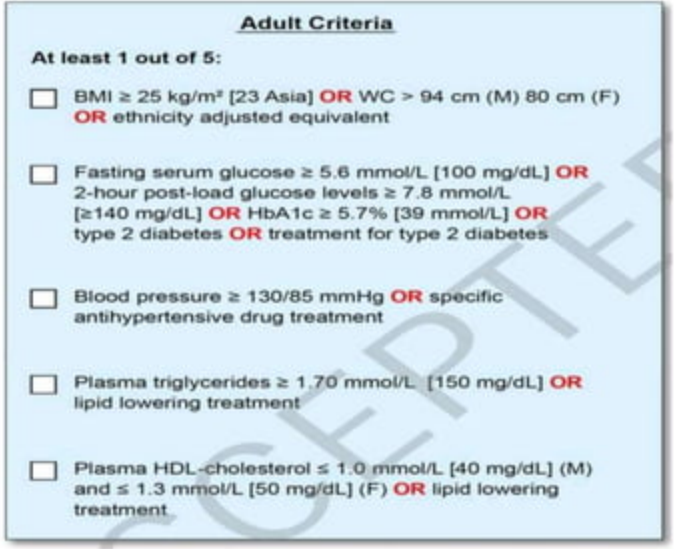
SPECTRUM OF STEATOTIC LIVER DISEASES



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

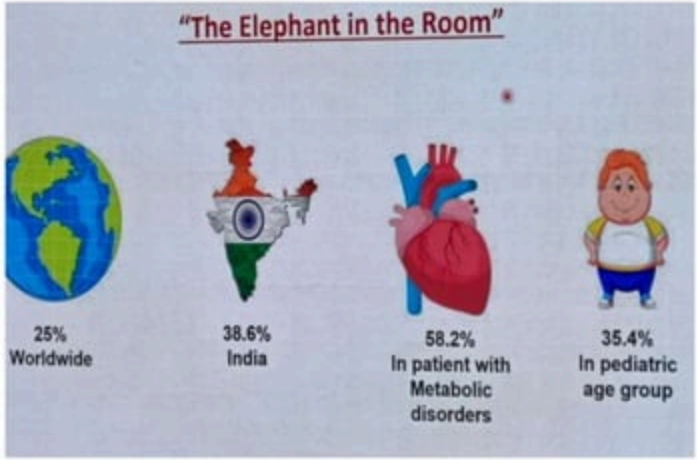
- MASLD defined as presence of hepatic steatosis with one or more cardiometabolic risk factors (CMRF), and no other identifiable cause of steatosis.
- Similarly NASH was replaced by MASH (Metabolic dysfunction Associated Steatohepatitis) and NAFL was replaced by MAFL (Metabolic dysfunction associated steatotic liver).
- Patients with hepatic steatosis, CMRFs and alcohol use are classified as having MetALD.
- Patients with steatosis consuming alcohol in excess of 50g/day in females or 60g/day in males or weekly equivalent are classified as Alcohol associated liver disease(ALD).

CRITERIA FOR MASLD



- Studies suggest a near complete overlap (99%) between MASLD defined populations and the historical NAFLD populations.
- All recommendations in the AASLD Practice guidance on clinical assessment and management of NAFLD can be applied to patients with MASLD and MASH.

PREVALENCE OF NAFLD



- NAFLD is the most common cause of Chronic liver disease in US and worldwide.
- NAFLD risk is 4-10 times higher in patients with metabolic syndrome.
- NAFLD is further classified as NAFL (isolated steatosis) and NASH (steatosis complicated by liver cell injury and accumulation of inflammatory cells).
- Around 20-25% of NAFLD patients develop NASH.
- Around 6% of NASH patients develop cirrhosis and 1-2% individuals will progress to hepatocellular carcinoma.
- NAFLD is more common in males than females in premenopausal age group, followed by later peak in postmenopausal women.

ETIOPATHOGENESIS

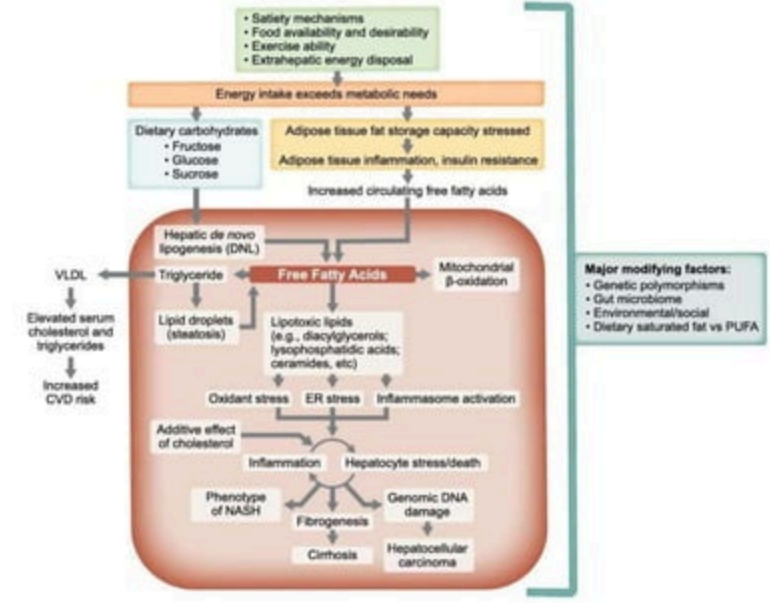
- RISK FACTORS

COMMON RISK FACTORS	OTHER RISK FACTORS	GENETIC POLYMORPHISM
Obesity	Hypothyroidism	PNPLA3 gene variants
Diabetes mellitus	Obstructive sleep apnea	
Dyslipidemia	Hypopituitary, hypogonadism	
Metabolic syndrome	Alterations in gut microbiome.	
	PCOD	

ALTERNATIVE CAUSES OF HEPATIC STEATOSIS

MICROVESICULAR STEATOSIS	MACROVESICULAR STEATOSIS	DRUGS CAUSING STEATOSIS
Pregnancy - AFLP	Chronic viral hepatitis – HCV	Tetracyclines
Reyes syndrome	Wilsons disease	Valproate
Eclampsia, HELLP syndrome	NASH	Zidovudine
Tetracyclines		Amiodarone, bleomycin
Valproate toxicity.		Estrogens, steroids
Alcohol		Metals like chromium barium antimony
Acid lipase deficiency.		

- TWO HIT HYPOTHESIS
- First hit in the form of sedentary lifestyle, obesity, high fat diet, diabetes mellitus, insulin resistance lead to accumulation of fats within hepatocytes.
- Obesity lead to altered gut microbiota and increased hepatic exposure to gut derived products as well adipokines together are responsible for insulin resistance.
- Second hit in the form of hepatocyte lipotoxicity (due to diacylglycerols, fatty acids), oxidative stress (reactive oxygen species) lead to activation of inflammatory cytokines and hepatocyte cell death.
- This lead to activation of myofibroblasts, progenitor cells that lead to progressive accumulation of wound healing cells, fibrous matrix, abnormal vasculature resulting in irreversible fibrosis.
- Cirrhosis and hepatocellular carcinoma are the potential outcomes of NASH.


• Satiety mechanisms
• Food availability and desirability
• Exercise ability
• Extrahepatic energy disposal
Energy intake exceeds metabolic needs
Dietary carbohydrates
• Fructose
• Glucose
• Sucrose
Adipose tissue fat storage capacity stressed
Adipose tissue inflammation, insulin resistance
Increased circulating free fatty acids
Hepatic de novo lipogenesis (DNL)
VLDL
Triglyceride
Free Fatty Acids
Mitochondrial β-oxidation
Elevated serum cholesterol and triglycerides
Increased CVD risk
Lipid droplets (steatosis)
Lipotoxic lipids (e.g., diacylglycerols; lysophosphatidic acids; ceramides, etc)
Oxidant stress
ER stress
Inflammasome activation
Additive effect of cholesterol
Inflammation
Hepatocyte stress/death
Phenotype of NASH
Fibrogenesis
Genomic DNA damage
Cirrhosis
Hepatocellular carcinoma
Major modifying factors:
• Genetic polymorphisms
• Gut microbiome
• Environmental/social
• Dietary saturated fat vs PUFA

CLINICAL FEATURES

- Most patients with NAFLD are asymptomatic
- Some present with vague RUQ abdominal pain fatigue malaise.
- Hepatomegaly can be found on abdominal examination.
- Signs of chronic liver disease like splenomegaly palmar erythema spider angiomata ascites can be seen in some patients.
- Most of the patients will be associated with obesity diabetes hypertension dyslipidemia cardiovascular disease.

DIAGNOSIS

- BIOCHEMICAL PARAMETERS
- LFT shows ALT and AST elevations 2 to 5 times upper limit of normal (30-150IU/L).
- AST/ALT ratio is less than 1 unlike that of alcoholic liver disease.
- Serum ferritin can be elevated
- S Bilirubin albumin prothrombin time are usually normal in NAFLD except in patients with cirrhosis.
- In Isolated fatty liver (NAFL) liver may not be enlarged and aminotransferases and LFT may be completely normal.
- Risk factors for NAFLD should be evaluated – body mass index, diabetes, lipid profile, PCOD, thyroid function tests etc.

- Other causes of fatty liver like viral hepatitis autoimmune hepatitis Wilson's disease hemochromatosis etc should be excluded.
- NAFLD can coexist in patients with HCV infection
- Serum and hepatic iron levels to be checked to rule out hemochromatosis
- Serum levels of copper ceruloplasmin to rule out Wilson's disease
- About one fourth of patients with NAFLD have antinuclear antibodies positivity in low titres (<1:320).

- IMAGING STUDIES
- Ultrasound abdomen is the first line imaging test
- USG shows fatty liver (macrovesicular steatosis)
- USG cant differentiate between NAFLD and NASH and cant detect fibrosis.
- CT and MRI enhances sensitivity for liver fat detection but adds expense.

- FIBROSCAN – TRANSIENT ELASTOGRAPHY
- It is done to detect fibrosis
- A low amplitude wave is used that propagates through the liver parenchyma.
- A low liver stiffness score excludes cirrhosis.
- MRE- MAGNETIC RESONSNCE ELASTOGRAPHY
- It combines MRI with elastography and is more accurate in staging NAFLD fibrosis.
- It has sensitivity of 86% and specificity of 85% and is better than FIBROSCAN.

BIOPSY

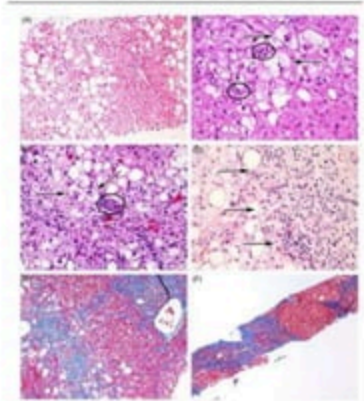
- It is the gold standard for diagnosing NAFLD and establishing severity of liver injury and fibrosis.
- It is an invasive procedure with some serious but rare complications.
- INDICATIONS
- In patients with unclear diagnosis
- Persistently elevated ALT and AST levels.
- When non invasive tests suggest significant fibrosis(>F2),
- When additional/alternate diagnosis is suspected.

- COMPLICATIONS include hemorrhage, pain, puncture of adjacent abdominal organs biliary leak, bile stasis etc..

- LIMITATIONS
- Tissue sampling errors can be seen unless tissue cores of 2cm or more are taken.
- Examining at single point does not determine whether disease is progressing or regressing.

HISTOLOGY OF NAFLD

- A) hepatic steatosis
- B) multiple ballooned hepatocytes with Mallory hyaline bodies with mild lobular inflammation
- C) ballooned hepatocytes with moderate lobular inflammation.
- D)interface hepatitis
- E) periportal and perisinusoidal fibrosis.
- F)cirrhosis



NAFLD ACTIVITY SCORE

TABLE 87-1 NAFLD Activity Score on a Liver Biopsy Specimen

Steatosis	
5%	1
5%–33%	2
33%–66%	3
Ballooning	
None	0
Few	1
Many	2
Lobular Inflammation	
Mild	1
Moderate	2
Severe	3
Total Score	
0-2	Likely not NASH
3-4	Intermediate
5-8	Likely NASH

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

NASH FIBROSIS STAGING

NASH fibrosis stage

Stage 0
No fibrosis

Stage 1
Zone 3 perisinusoidal fibrosis

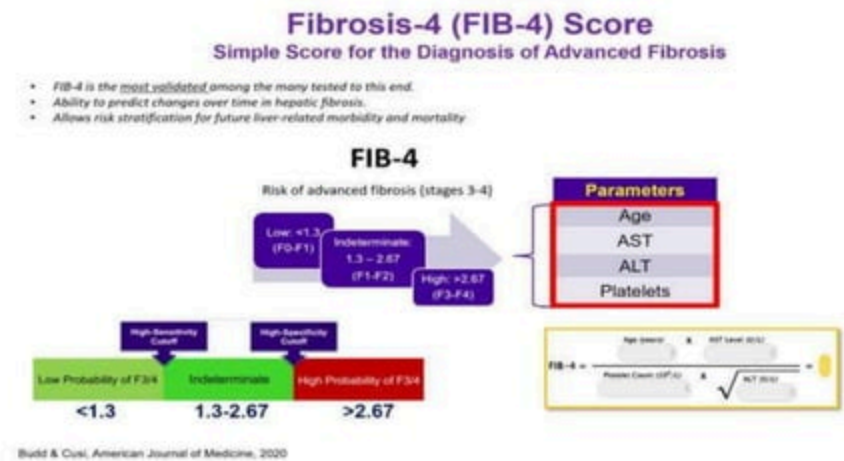
- Mild – 1a
- Moderate – 1b
- Portal/periportal – 1c

Stage 2
Perisinusoidal and portal/ periportal fibrosis

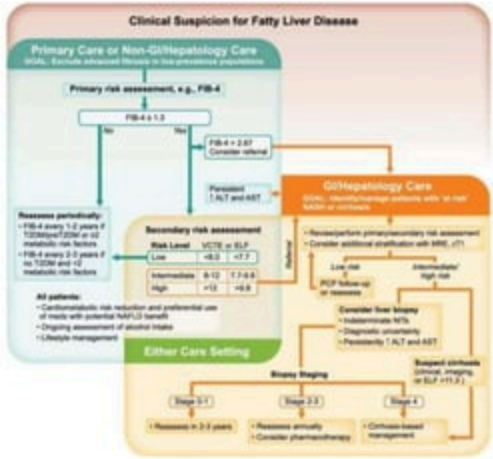
Stage 3
Bridging fibrosis

Stage 4
Cirrhosis

FIBROSIS-4 SCORE



APPROACH TO NAFLD AND NASH



MANAGEMENT

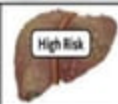
- DIET AND EXERCISE
- PHARMACOTHERAPY
- DIABETES MANAGEMENT
- HYPERTENSION MANAGEMENT
- DYSLIPIDEMIA MANAGEMENT
- BERIATRIC SURGERY
- LIVER TRANSPLANTATION.

DIET AND EXERCISE

- Reduce sedentary lifestyle and increase physical activity
- Promote weight loss – 3-5% weight loss improves steatosis
- >7-10% weight loss over 6 months promotes steatohepatitis and fibrosis.
- Increase pufa, omega 3 fatty acids intake and reduce saturated fatty acids.
- Mediterranean diet has role in NASH and liver fibrosis independent of weight loss.
- Coffee intake has shown to be beneficial in reducing risk of fibrosis.
- Avoid alcohol intake.

Weight Management in NAFLD

Fibrosis Risk Stratification

	Low Risk	Indeterminate Risk	High Risk
	 FIB-4: <1.3 LSM: 8 kPa ELF: <7.7	 FIB-4: 1.3 - 2.67 LSM: 8 - 12 kPa ELF: 7.7 - 9.8	 FIB-4: >2.67 LSM: >12 kPa ELF: >9.8
General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week)		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis if F4[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[1]	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liraglutide 3 mg/d, semaglutide 2.4 mg/wk.	GLP-1 RA preferred for NASH[1,2]	GLP-1 RA preferred for NASH[1,2]
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.

- Exercise improves steatosis as well as insulin sensitivity
- Aerobic exercise – moderate activity for 30-60 mins for 3-5 days/ week
- Intense activity for 20-30 minutes for 2-3 days/week.
- OBESITY treatment by phentermine, orlistat, topiramate GLP -1 receptor agonists can be considered for weight control although there use is not yet approved for NAFLD management.

Diabetes Management in NAFLD

Fibrosis Risk Stratification

	Low Risk	Indeterminate Risk	High Risk[1]
	 FIB-4: <1.3 LSM: <8 kPa ELF: <7.7	 FIB-4: 1.3 - 2.67 LSM: 8 - 12 kPa ELF: 7.7 - 9.8	 FIB-4: >2.67 LSM: >12 kPa ELF: >9.8
General goal	Optimize glycemic control using preferred agents that reverse steatohepatitis, whenever possible. Prefer GLP-1RA and SGLT2i in CVD. Prefer SGLT2i in CKD and HF.		
Dietary recommendations	Glycemic load reduction via emphasis on whole food carbohydrates (vegetables, legumes, fruit) versus sugar/processed carbohydrates.		
Individualize A1c target	<6.5% for persons without concurrent serious illness and at low hypoglycemic risk (<6.5% otherwise).		In advanced cirrhosis[2], caution with risk of hypoglycemia and avoid oral agents[3]
Preferred diabetes pharmacotherapy	Consider agents that reduce liver fat (pioglitazone, GLP-1RA, SGLT2i).	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1RA[3] No evidence that SGLT2i improve steatohepatitis.	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1RA[3] No efficacy data in cirrhosis.
Metformin, sulfonylurea, DPP-4i, acarbose and insulin	May continue but limited benefit on liver histology in NAFLD.	May continue but limited benefit on liver histology in NAFLD.	May continue (F2-F3) but avoid oral agents if advanced cirrhosis present. Cannot avoid insulin in patients with advanced liver cirrhosis – often only option

- Thiazolidinediones(PPAR gamma agonists)– pioglitazone, rosiglitazone
- These drugs improve systemic insulin resistance.
- Drug of choice in patients with diabetes with NASH.
- They improve aminotransferases, liver histology, but no effect on fibrosis.
- PIVENS study done showed patients treated with pioglitazone (30mg/day) showed histologic regression of NASH compared to those treated with placebo for 18 months.
- Adverse effects – Weight gain, bone fractures in females, bladder carcinoma risk, salt and water restriction.
- GLP -1 Receptor agonists – liraglutide, semaglutide
- Incretin mimetics increase insulin secretion from pancreas and improve lft.

- SGLT2 INHIBITORS – dapaglifozin, emphaglifozin
- These improve hyperglycemia by blocking renal absorption of glucose
- These are approved for use in patients with diabetes and NASH.
- They improve serum liver enzymes but have no effect on histology or fibrosis.

- Metformin – improves hepatic insulin sensitivity and has a role in improving liver enzymes.
- It has no role in improving liver histology or fibrosis.

- ANTIOXIDANTS
- VITAMIN E at a dose of 800mg/day has been accepted for use in NASH patients.
- DOC in patients without diabetes.
- PIVENS Study done showed improvement in liver enzymes, hepatic steatosis, and histology of NASH in 43% of patients treated with VITAMIN E compared to 34% in pioglitazone group and 19% in placebo group.
- TONIC trial – vit E also improved liver histology in pediatric patients with NASH.
- ADVERSE effects – hemorrhagic stroke, cardiovascular mortality, prostate cancer in patients treated for long duration.

Hypertension Management in NAFLD

Fibrosis Risk Stratification

	 Low Risk FIB-4: <1.3 LSM: <8 kPa ELF: <7.7	 Indeterminate Risk FIB-4: 1.3 - 2.67 LSM: 8 - 12 kPa ELF: 7.7 - 9.8	 High Risk[1] FIB-4: >2.67 LSM: >12 kPa ELF: >9.8
General goal	Optimize BP control and improve cardiovascular health using preferred agents, whenever possible. Assess every 3 months and intensify therapy until goal achieved.		
Goal (individualize)[2,3,4]	Systolic < 130 mm Hg / Diastolic < 80 mm Hg	Systolic < 130 mm Hg / Diastolic < 80 mm Hg	Systolic < 130 mm Hg / Diastolic < 80 mm Hg; individualize if decompensated cirrhosis
Dietary recommendations	In addition to general dietary recommendations, reduce sodium & increase high potassium foods (e.g., DASH diet)		
Pharmacotherapy for hypertension[2]	First-line therapy: ACEIs and ARBs.	First-line therapy: ACEIs and ARBs.	Same but avoid ACEI or ARB if decompensated cirrhosis.
Intensification of therapy	Second agent: CCB, BBF or thiazide diuretic (as additional agents as needed).		Same but individualize if decompensated cirrhosis. Use diuretics with caution (risk of excessive diuresis).
Additional options	Additional BP medication choices: alpha blockers, central agents, vasodilators, aldosterone antagonist.		Same but individualize if decompensated cirrhosis.

Atherogenic Dyslipidemia Management in NAFLD

Lipid risk levels are similar in the presence of NAFLD or NASH

General goal	Early intensive management of dyslipidemia needed to reduce cardiovascular risk. Intensify therapy until lipid goal is reached.		
Dietary recommendations	Increase fiber intake (25 g/d), prioritize vegetables, fruits whole grains, nuts, reduce saturated fat & added sugars (e.g., Mediterranean diet).		
Lipid risk levels	**High CV Risk[1]** ≥2 risk factors and 10-year risk 10-20% Diabetes or CKD 3/4 with no other risk factors	**Very high CV Risk[1]** Established CVD or 10-year risk >20% Diabetes with ≥1 risk factor CKD 3/4, HeFH	**Extreme CV Risk[1]** Progressive CVD CVD + diabetes or CKD 3/4 or HeFH Very premature CVD (<55 yrs male; <65 yrs female)
LDL-C goal (mg/dL)	<100	<70	<55
Non-HDL-C goal (mg/dL)	<130	<100	<80
Triglycerides goal (mg/dL)	<150	<150	<150
Apo-B goal (mg/dL)	<90	<80	<70
First line pharmacotherapy: Statins	Use a moderate-to-high intensity statin[2], unless contraindicated. Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C).		
If LDL-C not at goal[3]: intensify statin therapy	Use higher dose or higher potency statin.		
If LDL-C not at goal (or statin intolerant)[3], add 2nd agent, then add 3rd agent	Ezetemibe, PCSK9 inhibitor, bempedoic acid, colesevelam, inclisiran.		
If triglycerides >500 mg/dL	Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone)[4]		
If TG 135-499 mg/dL on max statin dose	Emphasize diet (as above)	Add icosapent ethyl.[4]	Add icosapent ethyl.[4]

Adapted from Handelsman Y et al. Endocr Pract. 2020;26:196-224.

DYSLIPIDEMIA MANAGEMENT

- Statins are first line drugs to treat dyslipidemias and to reduce cardiovascular risk.
- Use moderate to high grade statins as initial therapy.
- Statins should be avoided in decompensated cirrhosis.
- If LDL levels are not under desired range add 2nd line agents like PCSK9 Inhibitors like alirocumab, evolocumab.
- Fibrates to be used in case of increased triglyceride levels.

BERIATRIC SURGERY

- INDICATIONS
- In NASH patients with BMI> 35.
- In patients with well compensated chronic liver disease.

- CONTRAINDICATIONS
- In patients with NAFLD – CIRRHOSIS.
- CLD with portal hypertension.

LIVER TRANSPLANTATION

- NAFLD patients with end stage liver disease can be considered for liver transplantation
- It is 3rd most common cause for liver transplantation after cirrhosis caused by HCV and alcoholic liver disease.
- Outcomes are good in patients with no comorbid conditions.
- Hepatic steatosis in donor grafts is common and are associated with primary graft non function and poor overall outcomes.
- Grafts with less than 30% steatosis are acceptable for use and grafts with more than 60% steatosis are not acceptable.
- NAFLD may recur after transplantation.
- The risk factors for recurrent or de novo NAFLD after liver transplantation are multifactorial and include cardiometabolic risk factors and immunosuppressive therapies particularly steroids.

REFERENCES

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- AASLD Practice guidance on clinical assessment and management of NAFLD
- Metabolic associated steatotic liver disease (MASLD): update and impact of new nomenclature on NAFLD.
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THANK YOU