Fatty Liver Disease and Updated Nomenclature:

by

Sarah Oberste DO,FACOI

April 20,2024

Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

Objectives:

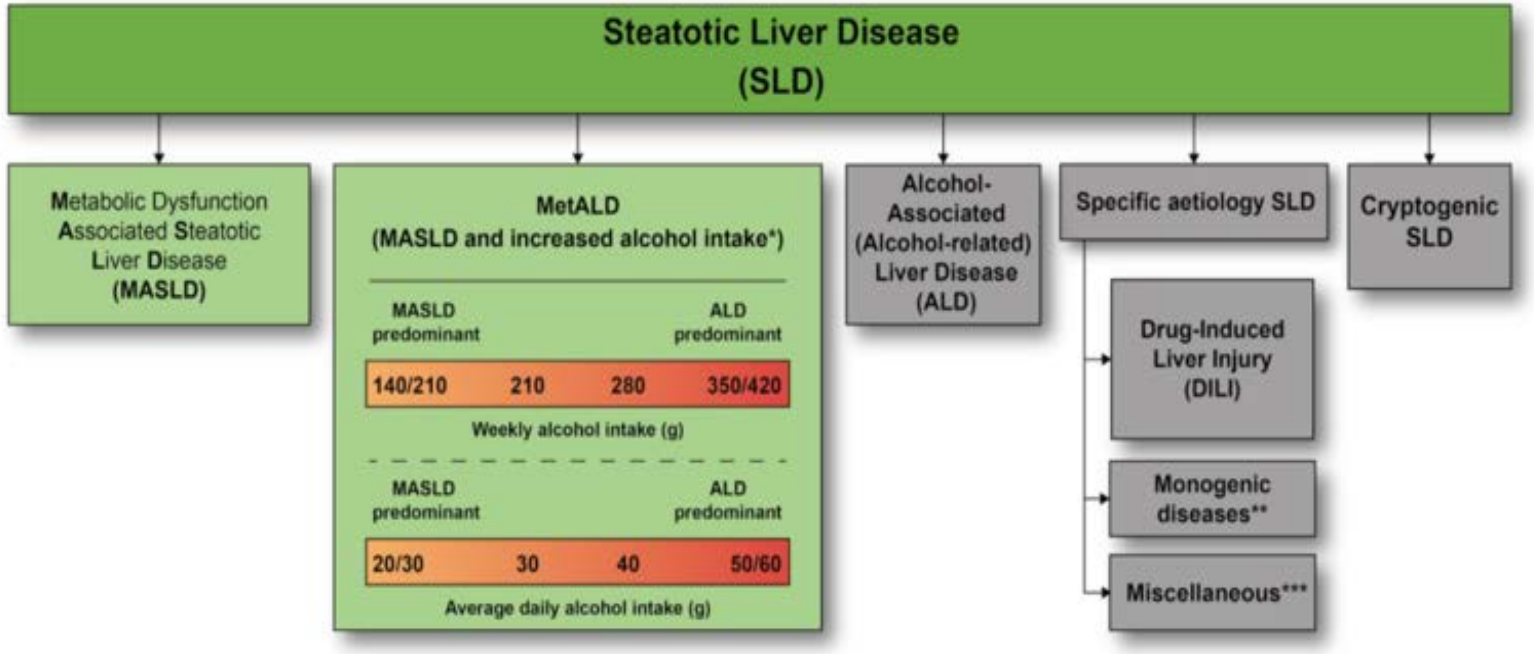
- Updated nomenclature on Fatty Liver disease
- Update on epidemiology and natural history
- Pathology
- Comorbid conditions associated with NAFLD
- Initial evaluation
- How should NAFLD be managed in Primary care

New MASLD Nomenclature:

- NAFLD will be replaced with metabolic dysfunction-associated steatotic liver disease (MASLD).
- MASLD-encompasses patients with hepatic steatosis and at least one of five cardiometabolic risk factors.
- MetALD- those with MASLD who consume greater amount of alcohol per week (140 g/week and 210 g/week for females and males.
- Metabolic dysfunction-associated steatohepatitis is the replacement for NASH

Steatotic Liver Disease Classifications

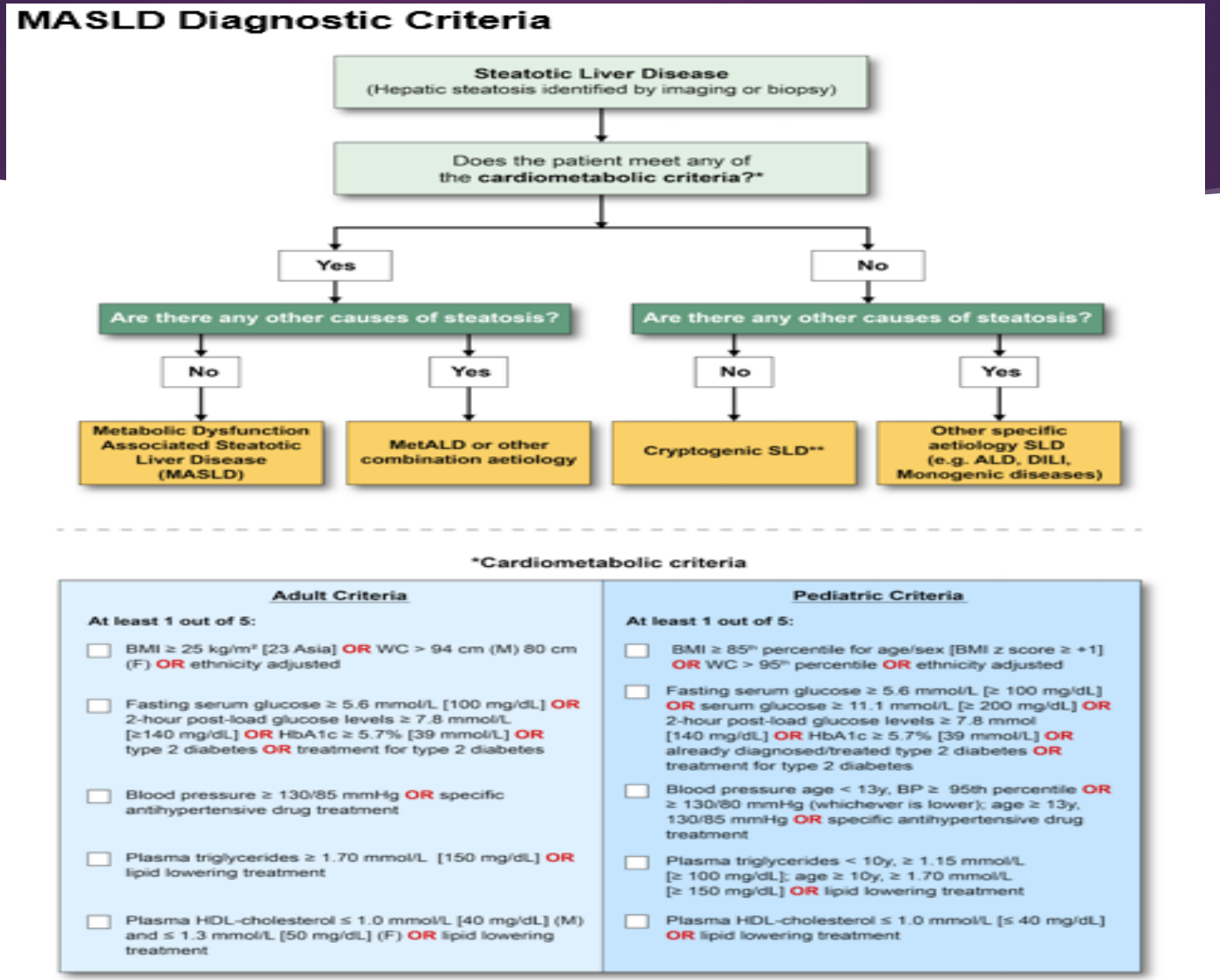
Steatotic Liver Disease Sub-classification



*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

This depicts the schema for Steatotic Liver Disease (SLD) and its sub-categories. SLD, diagnosed histologically or by imaging, has many potential etiologies. MASLD, defined as the presence of hepatic steatosis in conjunction with one CMRF and no other discernible cause, ALD, and an overlap of the 2 (MetALD), comprise the most common causes of SLD. Within the MetALD group there exists a continuum across which the contribution of MASLD and ALD will vary. To align with current literature, limits have been set accordingly for weekly and daily consumption, understanding that the impact of varying levels of alcohol intake are evolving. Other causes of SLD need be considered separately, as is already done in clinical practice, given their distinct pathophysiology. Multiple etiologies of steatosis can coexist. If there is uncertainty

MASLD Diagnostic Criteria



In the presence of hepatic steatosis, the finding of any of a cardiometabolic risk factor, would confer a diagnosis of MASLD if there are no other causes of hepatic steatosis. If additional drivers of steatosis are identified, then this is consistent with a combination etiology. In the

Guidelines Review of non-Alcoholic Fatty liver disease

BACK TO THE BASICS….

Definitions:

- 1. NAFLD-overarching term includes all disease grades and stages and refers to greater than or equal to 5% of hepatocytes macrovesicular steatosis in the absence of alternative causes.
  - Individuals drink little to no alcohol.
  - Fe <20 grams and <30 grams M
- 2. NASH- NAFLD plus inflammation and cellular damage (ballooning), fibrosis with or without
- Cirrhosis- bands of fibrous septa leading to formation of cirrhotic nodules.

Epidemiology and Natural History

- NAFLD and NASH- rising worldwide and parallel with metabolic comorbid disease (insulin resitance, dyslipdidemia, central obesity and Htn).
- Prevalence- 25%-30% general population varies with race/ethnicity and geographic region often remains undiagnosed.
- Significant fibrosis stage 2 or higher has increased > 2 fold.
- Nash cirrhosis is the leading indication for liver transplant for woman and those over 65.

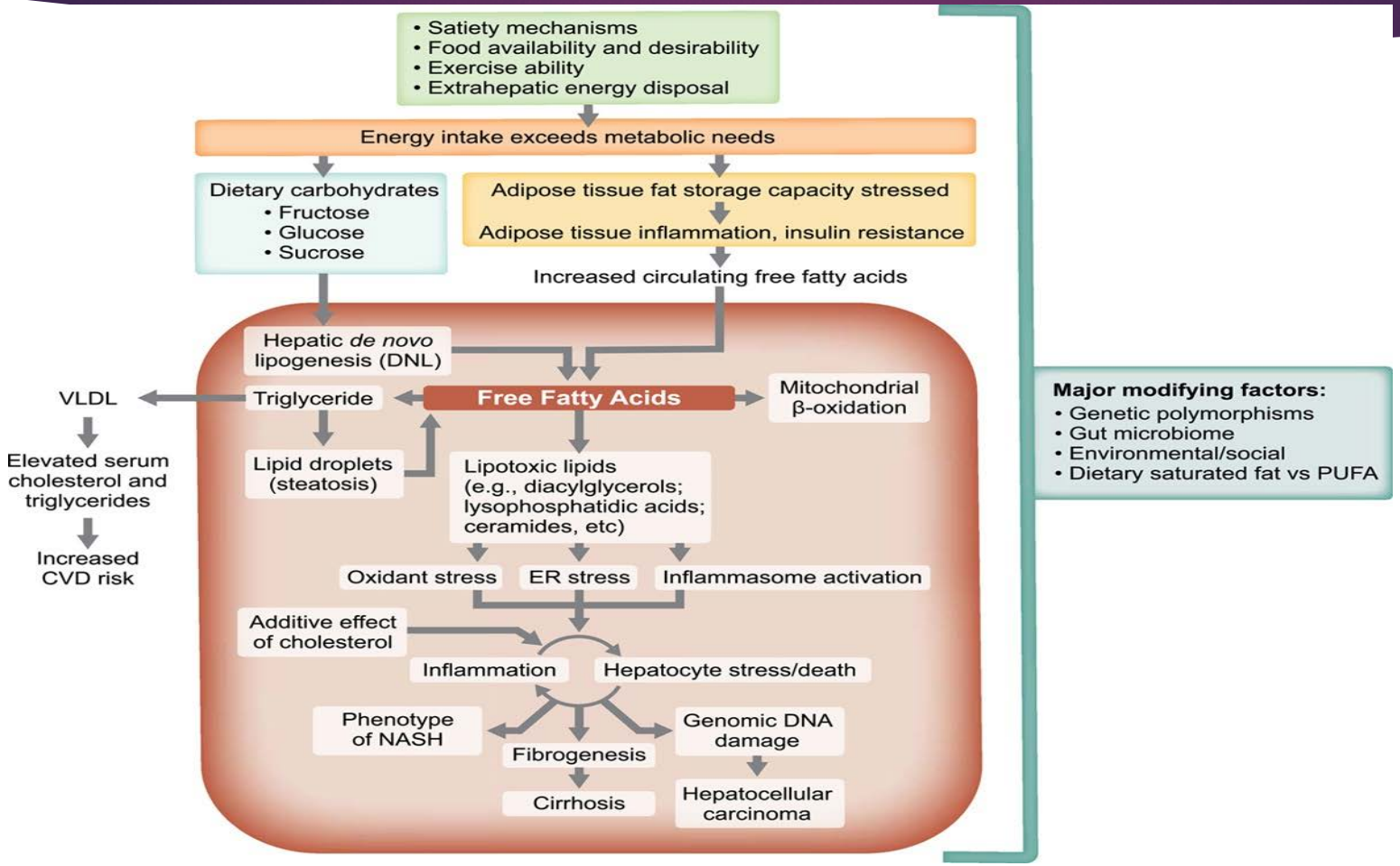
Disease progression

- Primary predictors- Fibrosis and steatohepatitis.
- NASH with stage 2 fibrosis, “at risk” NASH, higher risk of liver related morbidity and mortality.
- Progression associated with other medical factors: severity and presence of comorbid disease, genomic profile and environment.
- Minimal progression with frequent clinical visits and lifestyle changes.
- NAFLD fibrosis stage 1:14 years and 1:7 years for NASH

Association between disease stage and adverse outcomes.

- NASH and F2-F4 fibrosis – higher risk for liver related events and mortality, “at risk”
- Fibrosis progression and hepatic decomp vary depending on baseline disease severity, genetic, environmental and comorbid disease.
- CVD and non-hepatic malignancies are the most common cause of mortality in NAFLD with no fibrosis.
- Death from liver disease predominates in patients with advanced fibrosis.

Molecular and Cellular Pathogenesis



Key Points of pathogenesis:

- *Fundamental elements of NASH pathogenesis include an imbalance between nutrient delivery to the liver and their utilization and disposal coupled with adipose tissue dysfunction. Interindividual differences in genetic, dietary, behavioral, and environmental factors influence disease course.*
- *Systemic inflammation, particularly stemming from dysfunctional adipose tissue, contributes to disease progression.*
- *Insulin resistance contributes to the development of NAFLD and promotes disease progression.*

Comorbid Conditions Associated with NAFLD

- NAFLD is closely linked to and often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, central obesity, and hypertension)

Comorbid Conditions

- 1. Obesity- The severity is associated with NAFLD and disease progression.
  - Distribution is an important determinant of the contributory role in NAFLD
  - Android body fat distributions, increased truncal subc fat and visceral fat increase risk of insulin resistance, CVD, and hepatic fibrosis.
  - Fat distribution in the hips and buttocks is protective against NAFLD.

CC

- T2DM
  - Is the most impactful risk factor for the development of NAFLD, fibrosis progression and HCC.
  - Prevalence of 30-75% NAFLD and higher risk of developing NASH with Fibrosis.
  - Patient with NAFLD should be screened for T2DM/insulin resistance

CC

- HTN- Higher incidence in NAFLD, associated with fibrosis progression.
- Dyslipidemia: twice as likely to exhibit plasma lipid abnormalities.
  - Use moderate-intesity to high-intensity statins in NAFLD statins are safe across the disease spectrum.
  - Demonstrate reduction in CV morbidity and mortality in NAFLD.
- OSA- associated with more advanced NAFLD/NASH histology.
- CVD- Important cause of death in NAFLD.
  - Aggressively treating comorbid conditions such as above and promoting tob cessation is recommended to decrease CVD risk.

Guideline Statements

- 1. Statins are safe and recommended for CVD risk reduction in patients with NAFLD across the disease spectrum, including compensated cirrhosis.
- 2. Limited data exist on the safety and efficacy of statins in patients with decompensated cirrhosis, although statin use with careful monitoring could be considered in patients with high CVD risk.
- 3. Hypertriglyceridemia can be managed through lifestyle changes and supplementation with omega-3 fatty acids, or fibrates.
- 4. Patients with diabetes are at higher risk for NASH and advanced fibrosis and should be screened for advanced fibrosis.
- 5. Patients with NAFLD should be screened for the presence of T2DM.

Initial Evaluation of a Patient with NAFLD:

History	Weight history; medical comorbidities; recent and current medications; family history of T2DM, NAFLD, or cirrhosis; screening for OSA; alcohol use, including amount, pattern of use, and duration
Physical examination	Body fat distribution (eg, android vs. gynoid, lipodystrophic), features of insulin resistance (eg, dorsal-cervical fat pad, acanthosis nigricans), features of advanced liver disease (eg, firm liver, splenomegaly, prominent abdominal veins, ascites, gynecomastia, spider angiomata, palmar erythema)
Laboratory tests	Hepatic panel, CBC with platelets, fasting plasma glucose and glycated hemoglobin (A1c), fasting lipid profile, creatinine and urine microalbumin or protein to creatinine ratio, hepatitis C if not previously screened. Consider as appropriate other causes of steatosis/steatohepatitis (). Additional evaluation if elevated liver chemistries present: autoimmune serologies, transferrin saturation, ceruloplasmin, alpha-1 antitrypsin genotype, or phenotype

Initial evaluation

- 1. ALT ranges 29-33 in men and 19-25 in women
- 2. Assessment of alcohol intake and exclusion of other causes of liver disease
- 3 . Medication evaluation

Drugs linked to macrovesicular steatosis or steatohepatitis.

Drug	Mechanism	Histological pattern	References
Amiodarone	Promotion of DNL, impairment of β-oxidation	Hepatic steatosis and steatohepatitis, phospholipidosis, cirrhosis	179–184
5-FU	Accumulation of 5-FU catabolites reduce hepatic capacity to metabolize lipids	Hepatic steatosis	185–188
Irinotecan	Induces mitochondrial dysfunction, impaired autophagy	Steatohepatitis	189–194
Tamoxifen	Estrogen receptor modulator, promotion of DNL, impairment of β-oxidation. *May or may not be independent of concomitant metabolic risk factors	Steatosis and steatohepatitis	195–203
Methotrexate	Mitochondrial injury (inhibits mitochondrial electron transport chain), injury to canals of Hering	Steatosis, steatohepatitis, cirrhosis	204–206
Corticosteroids	Exacerbation of metabolic comorbidities, impairment of β-oxidation, impairment of hepatic triglyceride secretion, lipid peroxidation	Steatosis	207,208

Alcohol Consumption

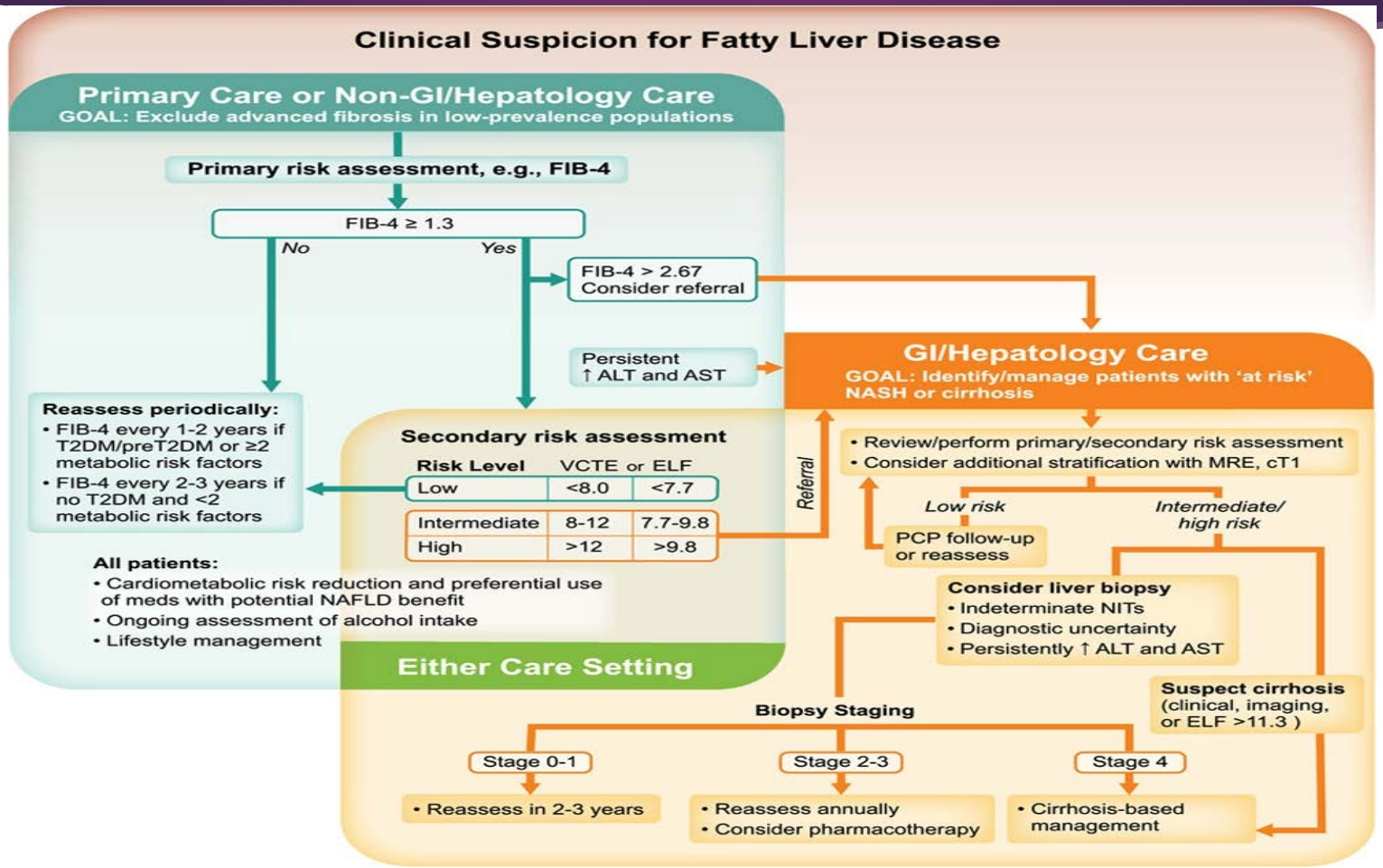
- Broadly classified :
  - Mild 20 g, moderate21-39g and heavy > 40g in women
  - Mild 30 g , moderate 31-59 g and heavy > 60 g in men
- Moderate alcohol use increases the probability of advanced fibrosis, in obese or T2DM patients working synergistically increases liver disease, cirrhosis, HCC and death from liver disease.
- Patients with clinically significant fibrosis greater than or equal to F2 should abstain from alcohol use.

Which patients should be screened for the presence of clinically significant Fibrosis??

F2 screening:

Screening recommended[a]	Prevalence of advanced fibrosis, %	References
T2DM	6–19	10,112,113,115,118,280–284
Medically complicated obesity	4–33	256–262,473–480
NAFLD in context of moderate alcohol use	17	285–291,300–307
First-degree relative of a patient with cirrhosis due to NAFLD/NASH	18	

How should NAFLD be Managed by PCP



General Guidance

- General population-based screening for NAFLD is not advised.
- 1. All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4.
- 2. High-risk individuals, T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption.
- 3. In patients with pre-DM, T2DM, or 2 or more metabolic risk factors (or imaging evidence of hepatic steatosis), assessment with FIB-4 should be repeated every 1–2 years.
- 4. Patients with NASH cirrhosis should be followed by GI/Hepatology.
- 5. Patients with suspected advanced NASH or discordant NITs should be referred to a specialist for evaluation,
- 6. Aminotransferase levels are frequently normal in patients with advanced liver disease due to NASH and should not be used in isolation to exclude the presence of NASH with clinically significant fibrosis.

Biomarkers/NITS for Dx and Assessment of NAFLD

- Hepatic steatosis:
  - US, low sensitivity
  - VCTE
  - MRI-Proton density fat fraction (PDFF)- accurate, reproducible and precise

Liver fibrosis estimation in NAFLD

- FIB-4 – based on age, AST, ALT and platelet count
  - < 1.3 low risk
  - >2.67 high risk
- ELF panel, Fibrospect and imaging-based elastography to detect fibrosis
  - ELF- 3 elements hyaluronic acid, tissue inhibitor metalloproteinase and N-terminal procollagen III peptide. Involved in matrix turnover.
  - ELF- greater than or equal to 9.8, identified NAFLD patients with increased progression to cirrhosis.

Elastography

- Liver stiffness associated with fibrosis severity, passive congestion, marked inflammation and infiltrative diseases.
- VCTE (fibroscan): LSM <8 rule out advanced fibrosis, 8-12 kPa fibrotic NASH, and LSM > 12 high likelihood for advanced fibrosis.
- Cirrhosis identification: FIB-4 >3.48 and LSM by VCTE > 20 kPA
- MRE- more sensitive than VCTE in detection fibrosis stage > 2.
  - Most accurate noninvasive imaging test. LSM >5 suggestive of cirrhosis.
    - Assesses risk of decompensation: <5 1.6% decomp over 3 years, 5-8 17%, >8 19%

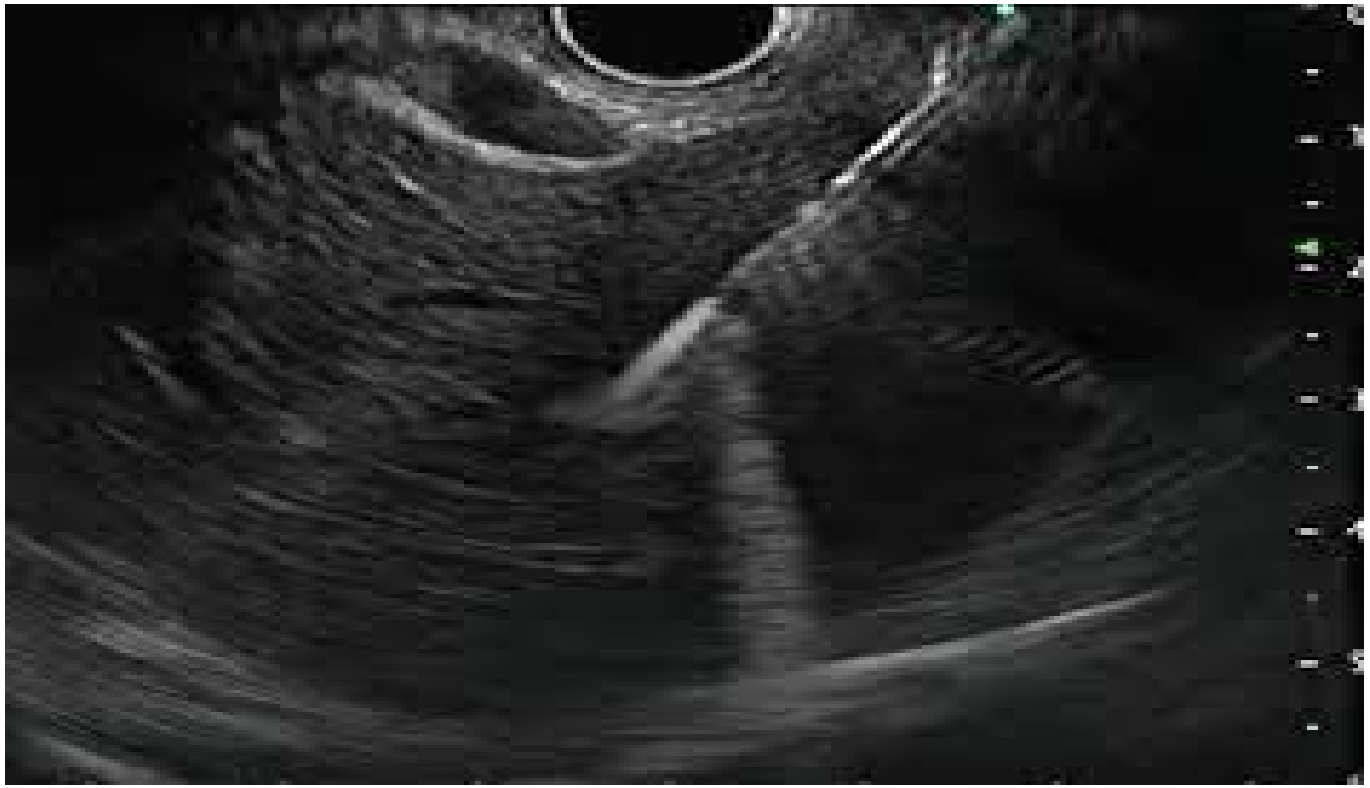
Parameters for Noninvasive Assessment of NAFLD

Modality type	Likely	Unlikely	Strengths/limitations, references/caveats
Identification of hepatic steatosis			
Imaging			
Ultrasound	"Detected"	NA	Semiquantitative assessment: mild/moderate/severe; low sensitivity with less severe steatosis[322]; steatosis can have similar echo characteristics as advanced fibrosis
FibroScan: CAP	≥288 dB/min		Limited accuracy for quantification[323]
MRI-PDFF	≥5%	<5%	Most sensitive across spectrum of steatosis; accurate to assess dynamic change[324]
Identification of "at-risk" NASH			
FAST	≥0.67	<0.35	≤0.35 (sensitivity 90%), ≥0.67 (specificity 90%); in validation cohorts, the PPV of FAST ranged between 0.33 and 0.81[28,325]
MAST	≥0.242	≤0.165	0.242 (specificity 90%),[326] 0.165 (sensitivity 90%)[326]
MEFIB	FIB-4 ≥1.6 plus MRE ≥3.3 kPa	FIB-4 <1.6 plus MRE <3.3 kPa	Sequential approach identifies patients with at least stage 2 fibrosis with >90% PPV[327]
cT1	≥875 ms	<825 ms	Requires further validation[328]

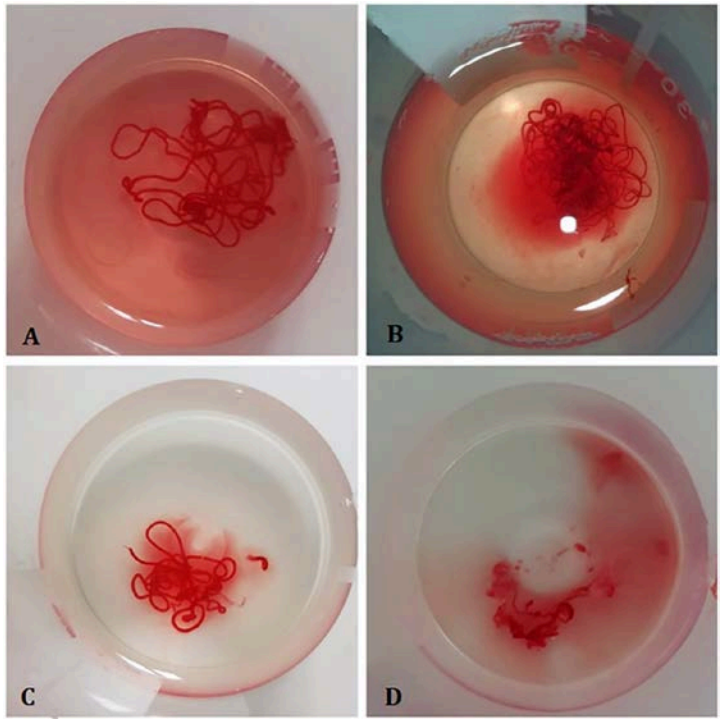
Parameter cont'd

Detection of advanced fibrosis			
Serum			
FIB-4	≥2.67	<1.3	No added cost[117,329,330]; not accurate in age <35 y and lower rule-out threshold among high-risk individuals who have high pretest probability
NFS	≥0.672	<−1.44	No added cost; not accurate in age <35 y, people with obesity and/or type 2 diabetes[117,329,330]
ELF	≥9.8	<7.7	Blood test sent to a reference laboratory[331]; cost
FIBROSpect II	≥17	<17	Blood test sent to a reference laboratory[332]; cost
Imaging			
VCTE	≥12 kPa	<8 kPa	Point of care[4]

Liver Biopsy EUS



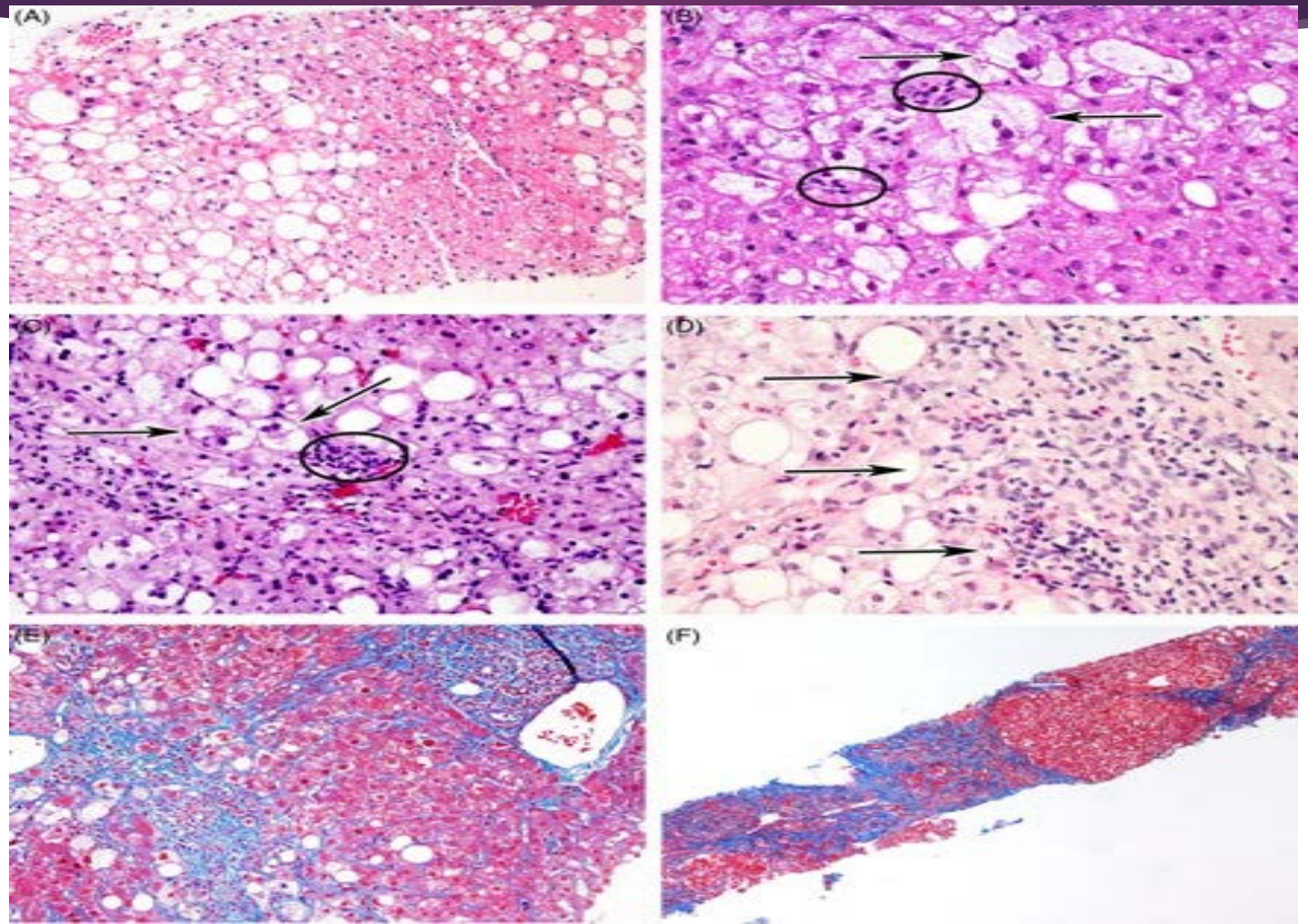
EUS FNB



Interpretation Liver Biopsy:

- Histological evaluation provides 3 basic pieces of information: diagnosis, grading of necroinflammatory activity and staging of fibrosis severity.
- Distinct patterns of injury: zone 3 steatohepatitis, zone 1 steatosis-fibrosis pattern, and steatosis with or withouit inflammation.
- Ballooning injury and portal inflammation predictors of fibrosis progression.
- NAS score: Histological score, steatosis, activity and fibrosis score
- Biopsy remains the best method for providing information on injury, inflammation and fibrosis.

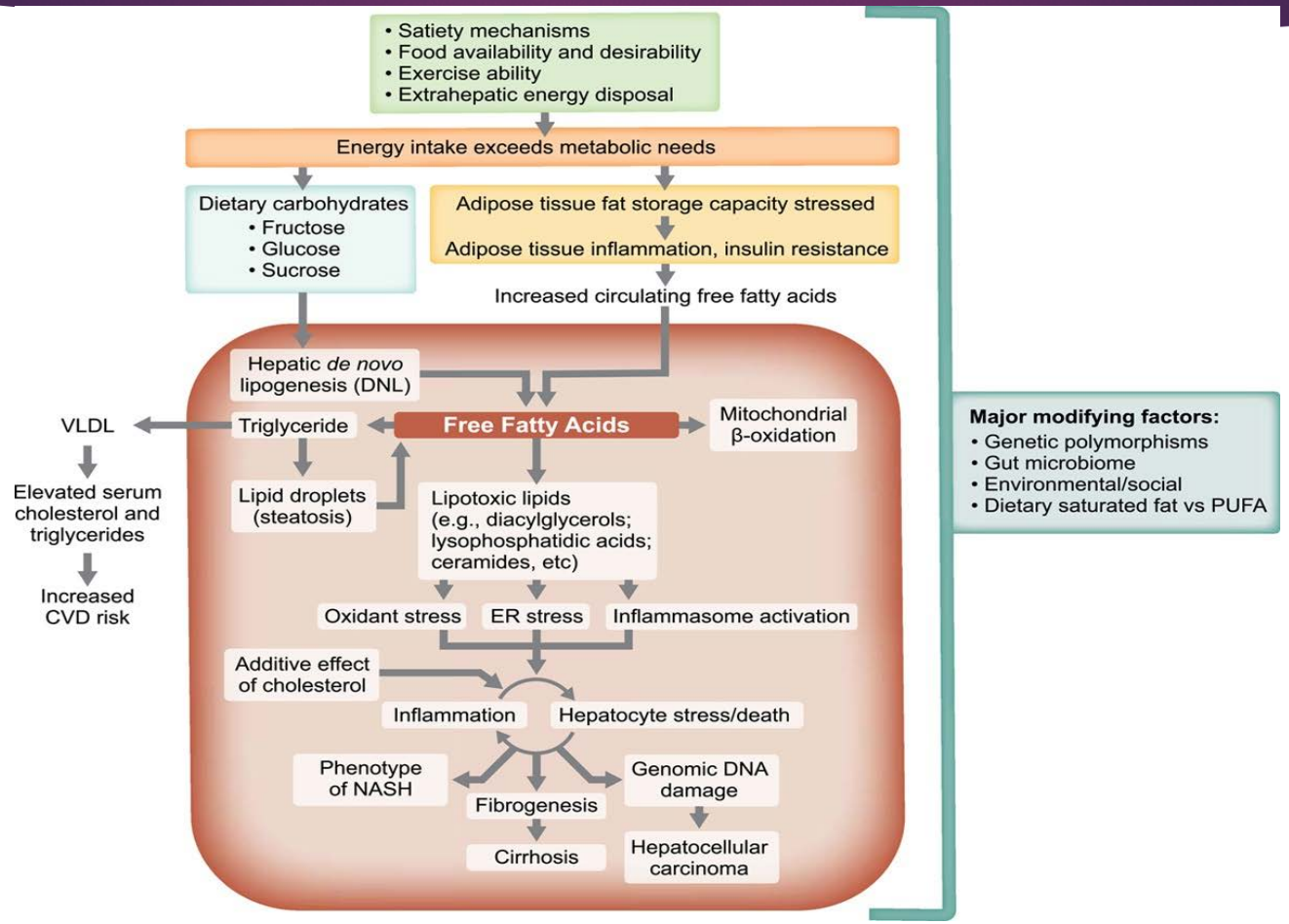
Histology



Treatment!!

- Healthy diet and regular exercise form the foundation of treatment for NAFLD.

Treatment


• 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

treatment

- Wt loss: >10 % improve NASH and fibrosis, 3-5% improved steatosis
  - *Weight loss improves hepatic steatosis, NASH, and hepatic fibrosis in a dose-dependent manner.*
- Caloric deficit : low-carbohydrate vs. low-fat diets, saturated vs. unsaturated fat diets, intermittent fasting, **Mediterranean diet**
  - Coffee consumpotion at least 3 cup associated with less advanced fibrosis
- Exercise, independent of weight loss, has hepatic and cardiometabolic benefit and should be routinely recommended and tailored to the patient's preferences and physical abilities.

Bariatric surgery

- Criteria: BMI over 40kg/m_2 or BMI greater than 35 with comorbidities(T2DM pre- DM, uncontrolled htn, OA, urinary incontinence), NAFLD/NASH accepted.
- Bariatric surgery can resolve NASH, improve hepatic fibrosis without cirrhosis and reduces mortality from CVD and malignancy.

Medications??

- There are currently no FDA-approved medications for the treatment of NAFLD (something new), but drugs approved to treat associated comorbidities with potential benefit in NAFLD may be considered in the appropriate clinical setting.

Medications:

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
Vitamin E (rrr-alpha) 800 IU daily[427,428]	NA	NASH without T2DM or cirrhosis	Liver related: improves steatosis, NASH resolution? No proven benefit on fibrosis	Hemorrhagic stroke, risk of prostate cancer?	No
Pioglitazone 30–45 mg po daily[429–431]	T2DM	NASH with and without T2DM	Liver related: improves steatosis, activity and NASH resolution, fibrosis improvement? Nonliver related: improves insulin sensitivity, prevention of diabetes, CV risk reduction and stroke prevention	Weight gain, risk of heart failure exacerbation, bone loss	Yes
Liraglutide[a] 1.8 mg s.c. daily (T2DM) 0.6–3 mg s.c. daily (obesity)[432]	T2DM, obesity	NASH without cirrhosis	Liver: improves steatosis, no proven impact on fibrosis. Nonliver related: improvement in insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Semaglutide[b] 0.4 mg s.c. daily, 0.25–2.4 mg SQ weekly[433]	T2DM, obesity	NASH without cirrhosis	Liver related: improves steatosis, activity, and NASH resolution, no proven benefit on fibrosis, but may slow fibrosis progression. Nonliver related: improvement in insulin sensitivity, weight loss, improves CV and renal outcomes, stroke prevention	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes

Treatment guidance

- 1. Semaglutide can be considered for (T2DM/obesity) in patients with NASH, as it confers a cardiovascular benefit and improves NASH.
- 2. Pioglitazone improves NASH considered in the context of patients with T2DM .
- 3. Vitamin E improves NASH in some patients without diabetes.
- 4. Available data on semaglutide, pioglitazone, and vitamin E do not demonstrate an antifibrotic benefit.

New Fatty liver disease Medication!!

- Rezdiffra
- Treatment of adults with non-cirhotic non-alcoholic steatohepatitis with moderate to advanced liver firbrosis,to be used along with diet and exercise.

Marker for Histological treatment response

- *ALT reduction of ≥17 U/L is associated with histological improvement;* or reduction in liver fat content by imaging in response to an intervention can be used as a surrogate for histological improvement in disease activity.

Call to Action:

- Most patient with NAFLD and NASH are seen in primary care or endocrine clinics… not knowing which patients might benefit from secondary care and when to refer them to Gatroenterology and Hepatology.
- Screening at the primary care level is critical!

Questions:

- 1. The Majority of patients with simple steatosis will develop moderate fibrosis within 5 years.
- A. true
- B. False

Question 2

- According to recent estimates, what is the current prevalence of NAFLD in people with obesity or type 2 diabetes?
- A. < 15%
- B. 25%
- C. 35%
- D. 50%

Question 3

- Individuals with which of the following conditions are at the highest risk for NASH?
- A. Overweight with no comorbidities
- B. Autoimmune liver disease
- C. Type 2 diabetes plus obesity
- D Obesity without type 2 diabetes

Question 4

- What is the leading cause of death in NAFLD?
- A. Cardiovascular disease
- B. extrahepatic cancer
- C. hepatic cirrhosis
- D. Hepatocellular carcinoma

Question 5

- What is the most important determinant of liver and non liver outcomes in NAFLD?
- A. Cardiovascular disease
- B. Atherogenic dyslipidemia
- C. Fibrosis
- D. steatosis burden

References:

- AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease: Rinella, Mary E.[1]; Neuschwander-Tetri, Brent A.[2]; Siddiqui, Mohammad Shadab[3]; Abdelmalek, Manal F.[4]; Caldwell, Stephen[5]; Barb, Diana[6]; Kleiner, David E.[7]; Loomba, Rohit[8],
- Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328–57.
- Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med. 2021;385:1559–69.
- Mózes FE, Lee JA, Selvaraj EA, Jayaswal ANA, Trauner M, Boursier J, et al. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. Gut. 2022;71:1006–19.