NON ALCOHOLIC FATTY LIVER DISEASE

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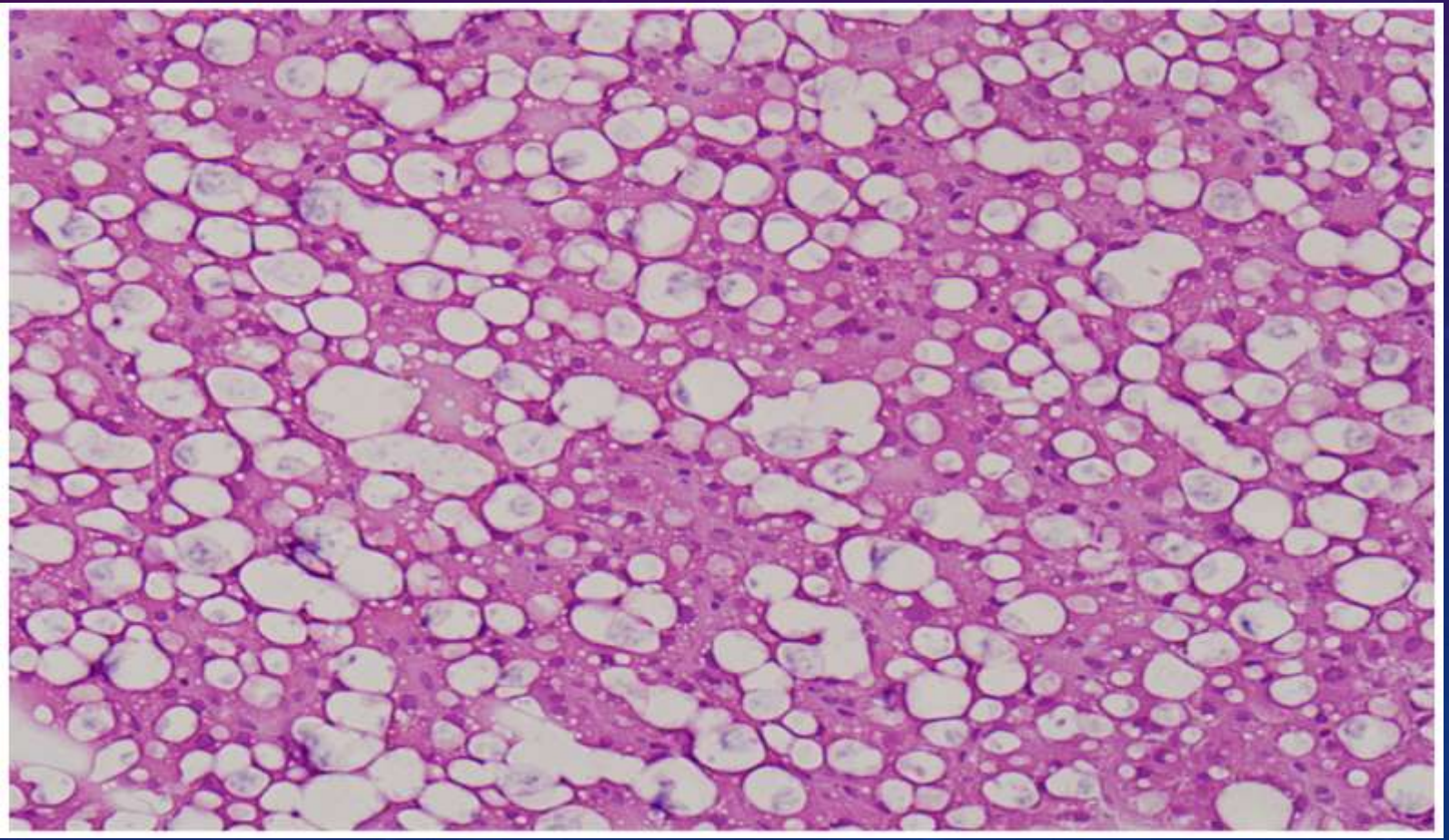
HISTORICAL PERSPECTIVE

- Observations, Biopsies
- Clinical scenarios
- Progression
- NIH slide reviews
- Clinical follow up
- Dr Anna Mae Diehl
- AASLD Practice Guidelines 2012
- AASLD Practice Guidance 2018/ Data up to 2016
- More Recently

DEFINITION OF NAFLD

- (1) Evidence of hepatic steatosis (HS), either by imaging or histology
- (2) Lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, longterm use of a steatogenic medication, or monogenic hereditary disorders

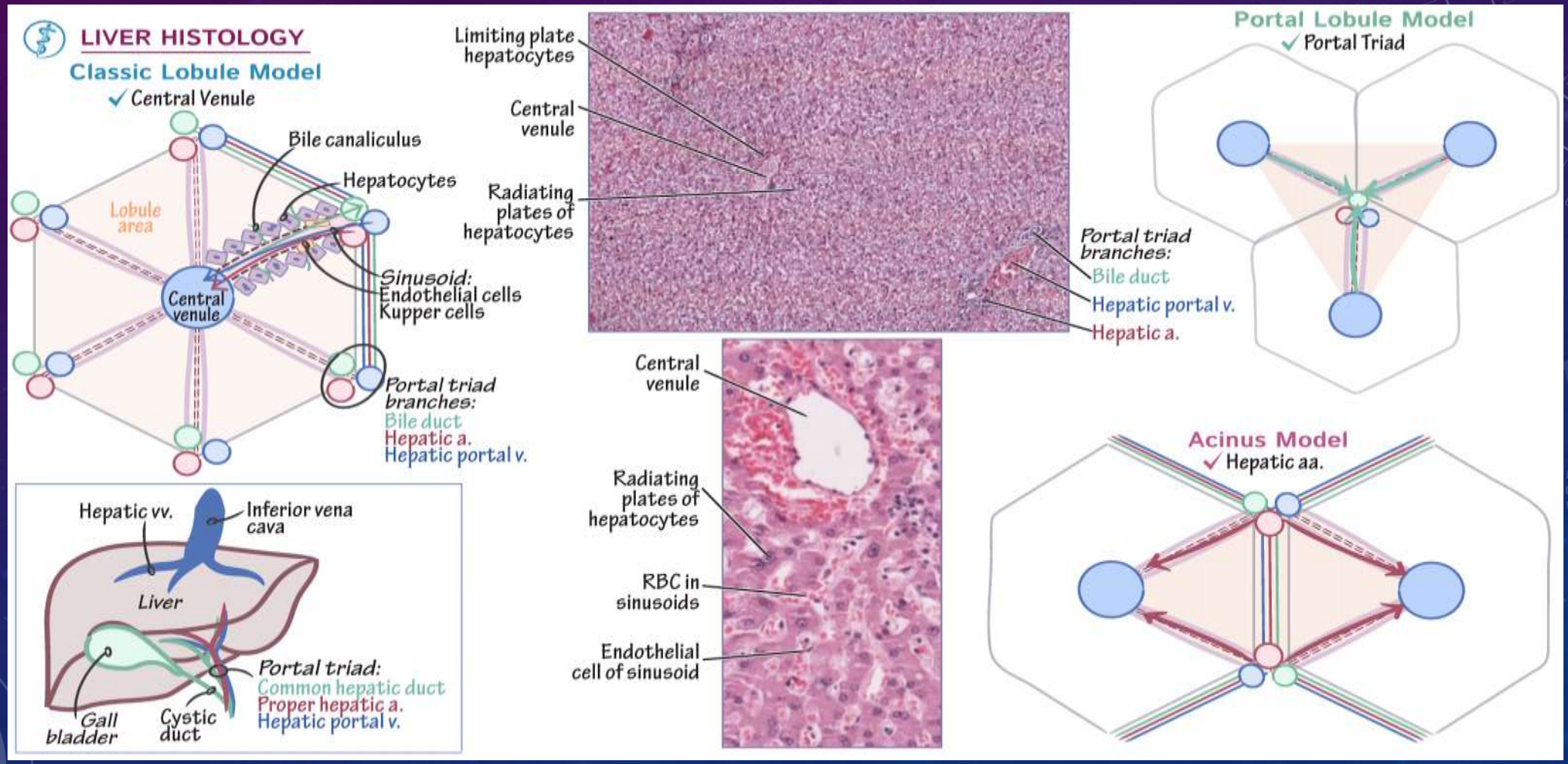
STEATOSIS



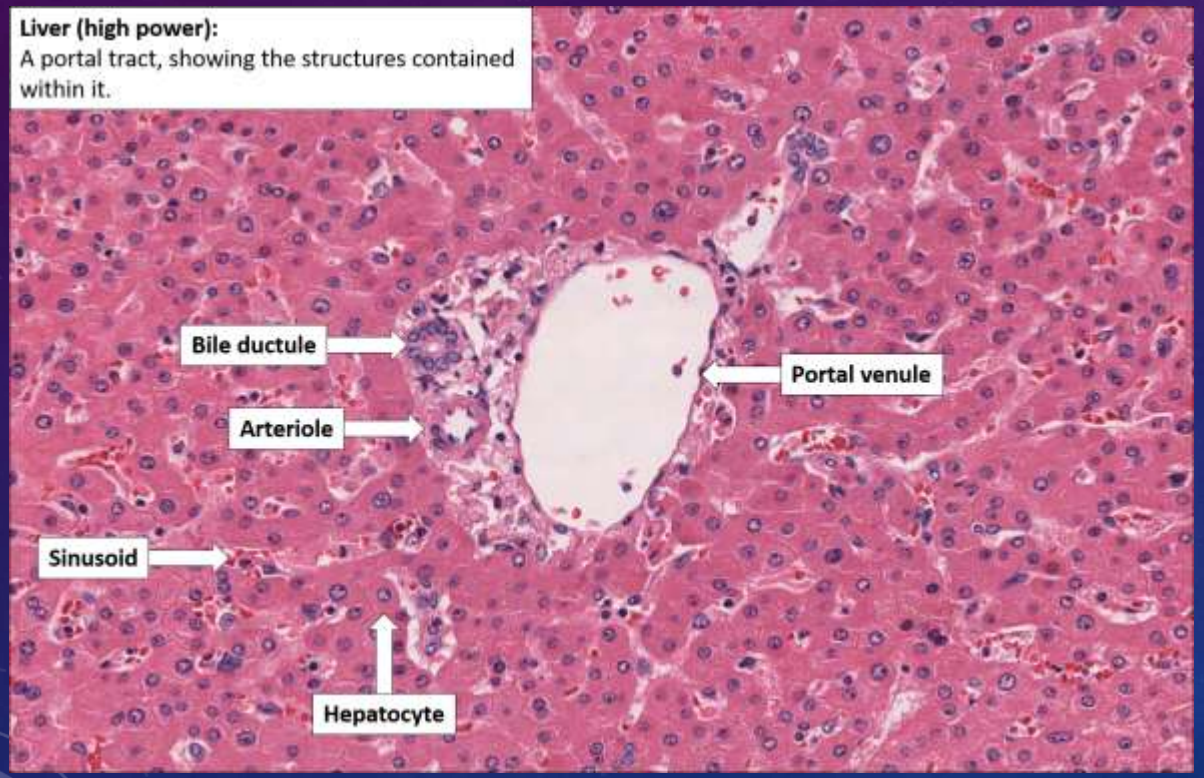
COMMON CAUSES OF SECONDARY HEPATOSTEATOSIS

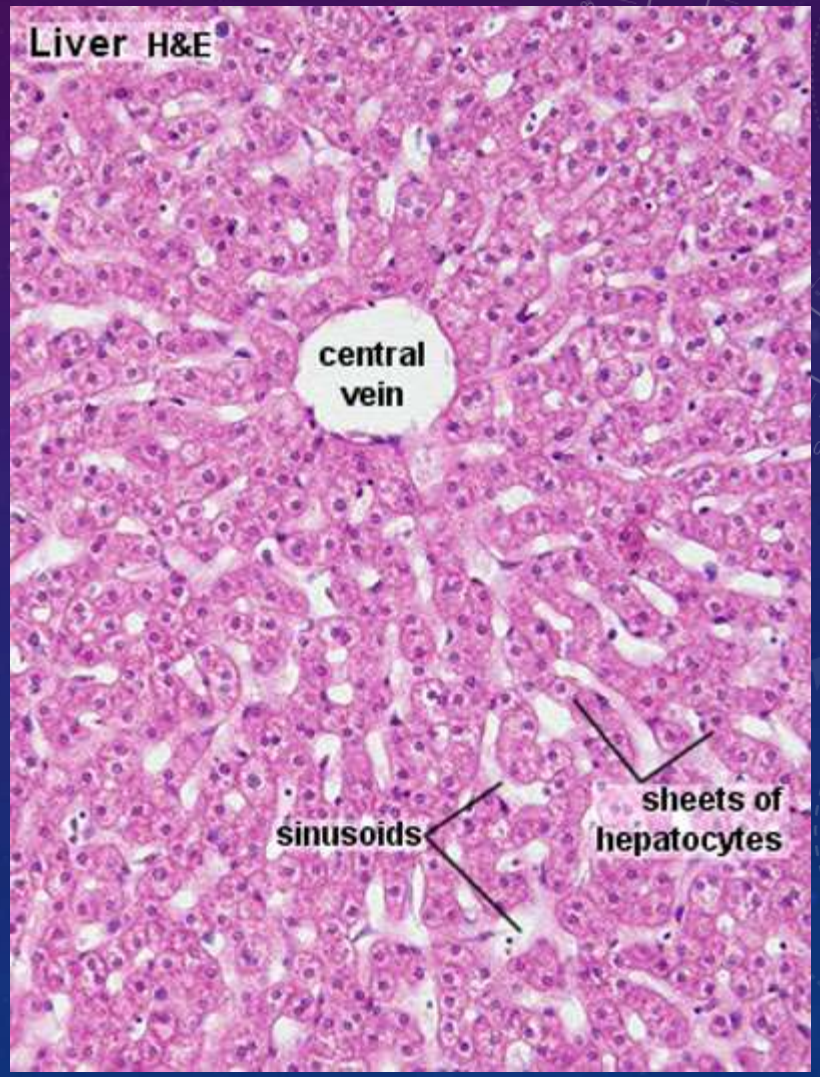
- Macrovesicular steatosis
- - Excessive alcohol consumption
- - Hepatitis C (genotype 3)
- - WD
- - Lipodystrophy
- - Starvation
- - Parenteral nutrition
- - Abetalipoproteinemia
- - Medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)
- Microvesicular steatosis
- - Reye's syndrome
- - Medications (valproate, antiretroviral medicines)
- - Acute fatty liver of pregnancy
- - HELLP syndrome
- - Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase
- deficiency, cholesterol ester storage disease, Wolman's disease)

THE NORMAL LIVER STRUCTURE

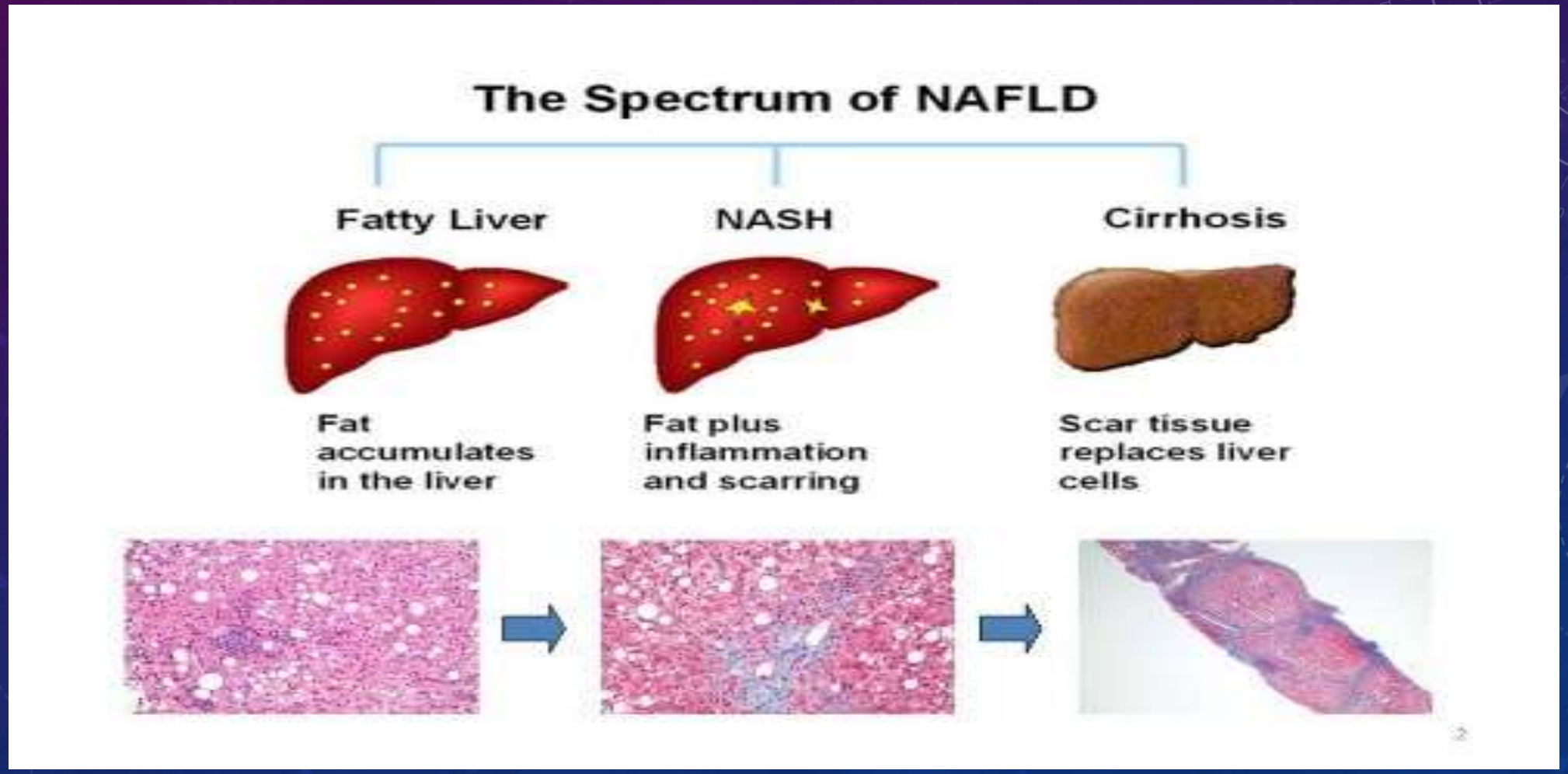


NORMAL HISTOLOGY

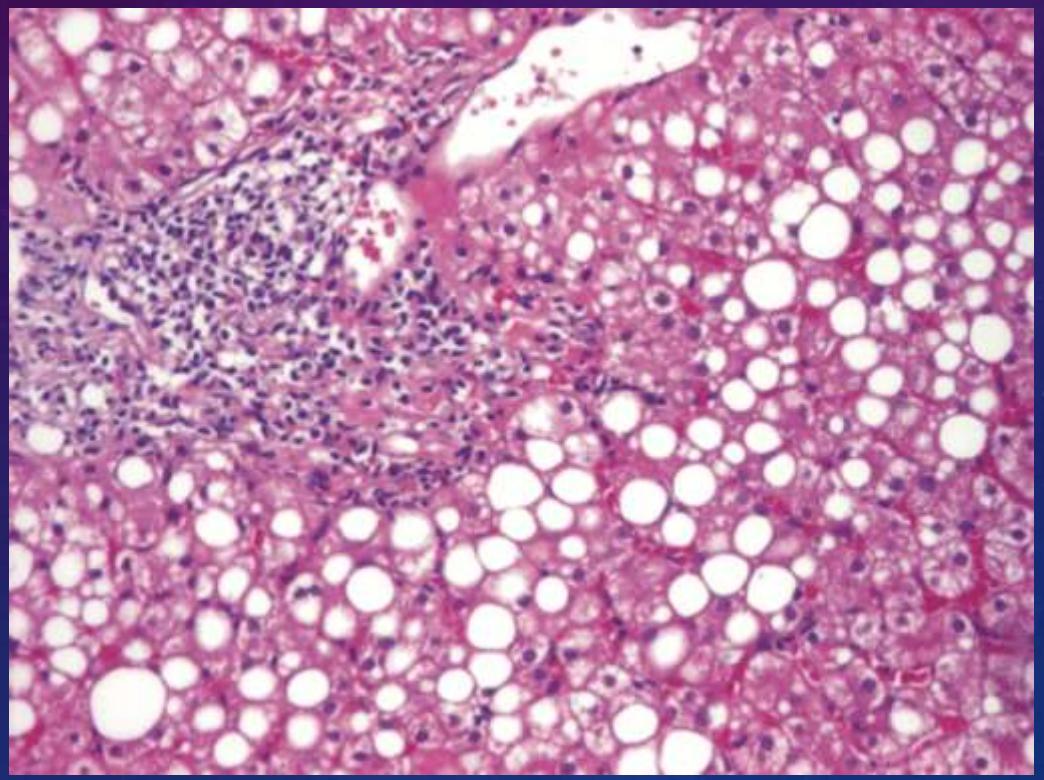




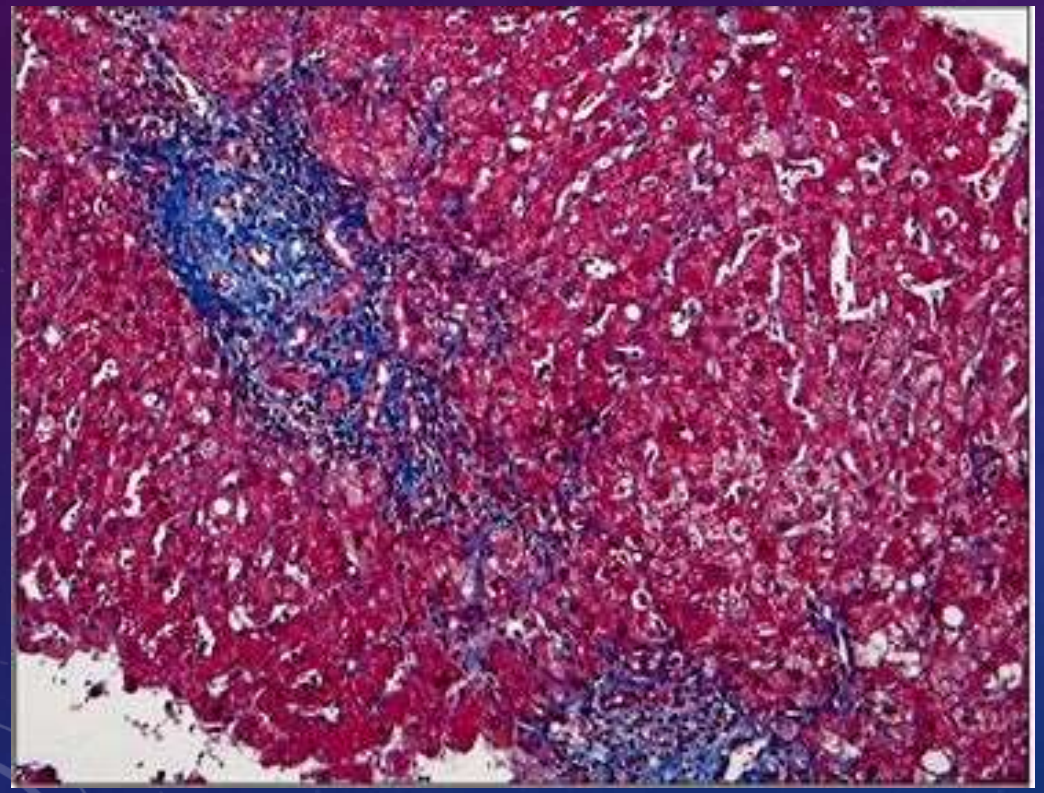
FROM NORMAL TO CIRRHOSIS

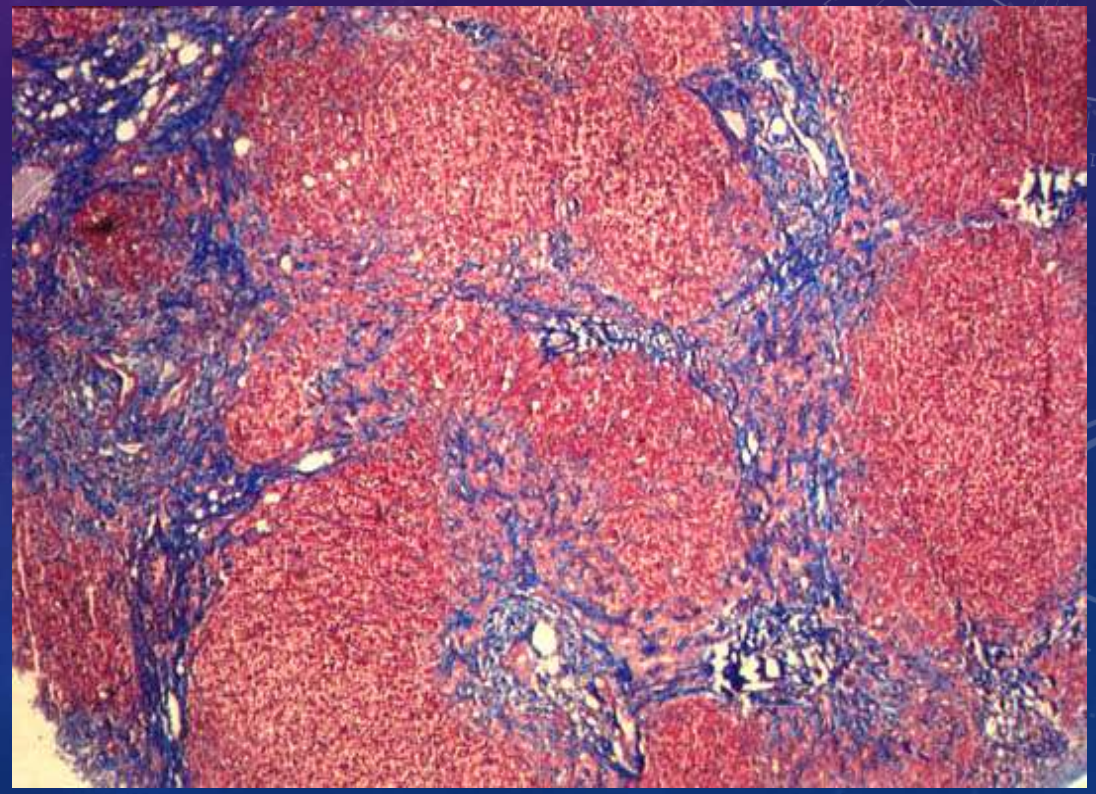


STEATOHEPATITIS

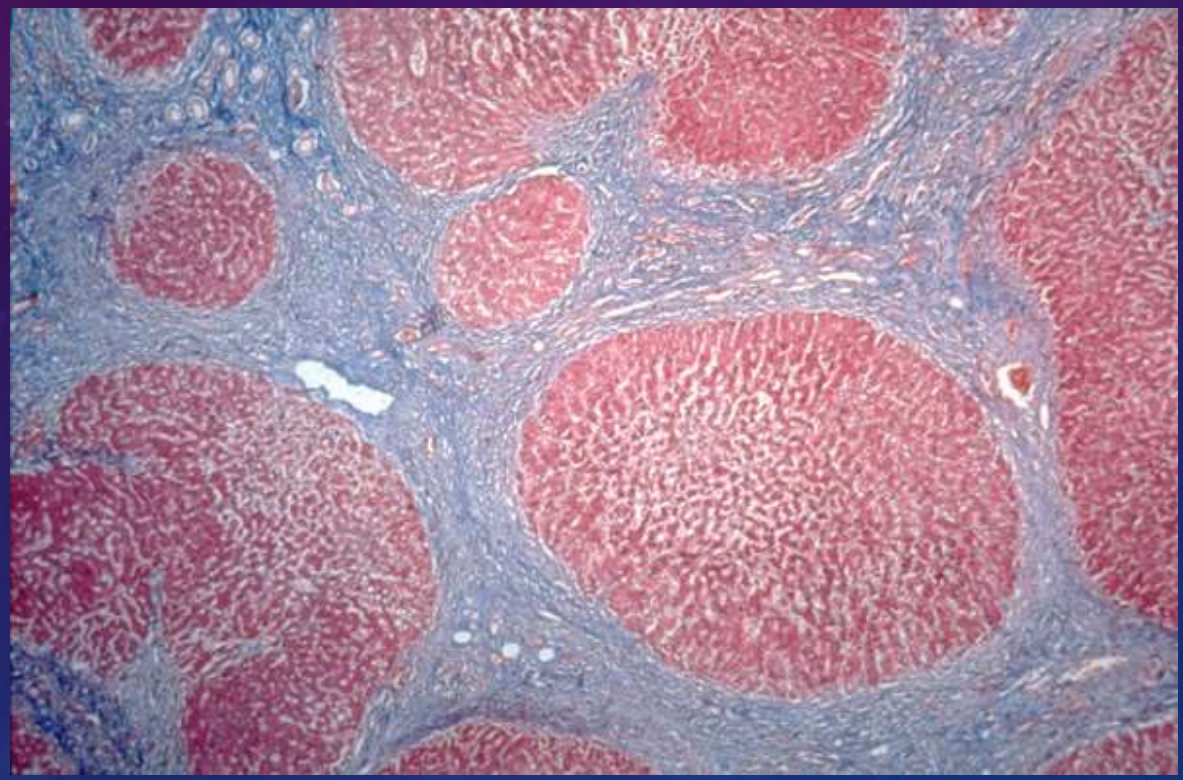


FIBROSIS-BRIDGING
F1-F4





CIRRHOSIS



NAFLD AND RELATED DEFINITIONS

- NAFLD — Encompasses the entire spectrum of FLD in individuals without significant alcohol consumption, ranging from fatty liver to SH to cirrhosis
- NAFL — Presence of 5% HS without evidence of hepatocellular injury in the form of ballooning of the hepatocytes or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is considered minimal.
- NASH — Presence of 5% HS with inflammation and hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure, and rarely liver cancer.
- NASH cirrhosis — Presence of cirrhosis with current or previous histological evidence of steatosis or SH
- Cryptogenic cirrhosis — Presence of cirrhosis with no obvious etiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and MetS.
- NAS — An unweighted composite of steatosis, lobular inflammation, and ballooning scores. NAS is a useful tool to measure changes in liver histology in patients with NAFLD in clinical trials. Fibrosis is scored separately
- SAF score — A semiquantitative score consisting of steatosis amount, activity (lobular inflammation plus ballooning), and fibrosis

INCIDENCE AND PREVALENCE

- NAFLD Incidence: Paucity of studies

A recent meta-analysis estimated that the pooled regional incidence of NAFLD from Asia to be 52.34 per 1,000 person-years (95% confidence interval [CI], 28.31-96.77) whereas the incidence rate from the West is estimated to be around 28 per 1,000 person-years (95% CI, 19.34- 40.57).

- NAFLD Prevalence: More data

The meta-analysis estimated that the overall global prevalence of NAFLD diagnosed by imaging is around 25.24% (95% CI, 22.10-28.65).(16) The highest prevalence of NAFLD is reported from the Middle East (31.79% [95% CI, 13.48- 58.23]) and South America (30.45% [95% CI, 22.74-39.440]) whereas the lowest prevalence rate is reported from Africa (13.48% [5.69- 28.69]).

NASH: BIOPSY GOLD STANDARD NOT FEASIBLE IN LARGE POPULTION STUDIES

Estimate of prevalence of NASH:

6.45%

RISK FACTORS ASSOCIATED WITH NAFLD: BIDIRECTIONAL RELATIONSHIP

- Common Conditions With Established Association

Obesity (most common), T2DM (highest risk), Dyslipidemia, Metabolic Syndrom (MetS*), Polycystic ovary syndrome

- Other Conditions Associated With NAFLD

Hypothyroidism, Obstructive Sleep Apnea, Hypopituitarism, Hypogonadism, Pancreatoduodenal resection, Psoriasis

- Age (increase), Sex (M), Ethnicity

Ethnic differences reported for NAFLD may be explained by the genetic variation related to the patatin-like phospholipase domain-containing protein 3 (PNPLA-3) gene.

- *The Adult Treatment Panel III clinical definition of MetS requires the presence of three or more of the following features: (1) waist circumference greater than 102 cm in men or greater than 88 cm in women; (2) TG level 150 mg/dL or greater; (3) HDL cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women; (4) systolic blood pressure 130 mm Hg or greater or diastolic pressure 85 mm Hg or greater; and (5) fasting plasma glucose level 110 mg/dL or greater.(

NATURAL HISTORY AND OUTCOMES OF NAFLD

- Growing evidence that patients with histological NASH, especially those with some degree of fibrosis higher risk for adverse outcomes such as cirrhosis and liver-related mortality.
- NAFLD: increased overall mortality compared to matched control populations. Most common cause of death is cardiovascular disease (CVD), independent of other metabolic comorbidities.
- Liver-related mortality is the 12th leading cause of death in the general population, but the second or third cause of death among patients with NAFLD.
- Cancer-related mortality is among the top three causes of death in subjects with NAFLD.
- NASH has an increased liver-related mortality rate. In a recent meta-analysis, liver-specific and overall mortality rates among NAFLD and NASH were determined to be 0.77 per 1,000 and 11.77 per 1,000 person-years, and 15.44 per 1,000 and 25.56 per 1,000 person-years, respectively.

NEJM 0CT.21, 2021

- “Prospective Study of Outcomes in Adults with Non Alcoholic Fatty Liver Disease”. Sanyal et Al.

- Over Median of 4 years follow up: NAFLD,F3,F4 associated with increased risk of liver-related complications and death

NATURAL HISTORY AND OUTCOMES OF NAFLD FIBROSIS-HCC

- The most important histological feature of NAFLD associated with long-term mortality is fibrosis; specifically, zone 3 sinusoidal fibrosis plus periportal fibrosis (stage 2) to advanced (bridging fibrosis [stage 3] or cirrhosis [stage 4]). These are independently predictive of liver related mortality.

- NAFLD is now considered the third-most common cause of hepatocellular carcinoma (HCC) in the United States, likely attributed to the enormous number of patients with the condition.

- Given the growing epidemic of obesity, the incidence of NAFLD-related HCC has been shown to increase at a 9% annual rate.

- Patients with NAFLD-related HCC are older, have a shorter survival time, more often have heart disease, and are more likely to die from their primary liver cancer than other HCC patients.

- Around 13% of HCC reported from a study of patients from the Veteran Administration did not have cirrhosis. Among other factors, having NAFLD was independently associated with HCC in the absence of cirrhosis. This study confirms past small reports of HCC in NAFLD patients without cirrhosis.

NATURAL HISTORY AND OUTCOMES OF NAFLD "BURNED OUT"/CRYPTOGENIC

- It is important to recognize that most patients with cryptogenic cirrhosis may have what is considered "burned out" NAFLD. This particular group of patients with cryptogenic cirrhosis have a disproportionately high prevalence of metabolic risk factors (T2DM, obesity, and MetS) that resemble patients with NAFLD, but the pathological assessment seldom reports histological features consistent with NASH or even steatosis in the presence of cirrhosis.

NATURAL HISTORY AND OUTCOMES OF NAFLD RATE OF FIBROSIS/CIRRHOSIS

- One of the important surrogates for advanced liver disease is documentation of progressive hepatic fibrosis (HF).
- HF progression in patients with histological NASH at baseline showed a mean annual fibrosis progression rate of 0.09
- One large, prospective, U.S.-based study observed a lower rate of decompensation and mortality in patients with NASH cirrhosis as compared to patients with hepatitis C cirrhosis.
- However, a more recent international study of 247 NAFLD patients with advanced fibrosis (bridging fibrosis and cirrhosis) followed over a mean duration of 85.6 and 54.5 months showed an overall 10- year survival of 81.5%—a survival rate not different from matched patients with hepatitis C cirrhosis.
- This is confirmed with increasing numbers of patients with NAFLD presenting with HCC or requiring liver transplantation (LT).
- NASH was ranked as the second-most common cause of LT and has overtaken hepatitis as the number one cause of LT in the future, as more hepatitis C virus (HCV) patients are treated with highly curative antiviral regimens.

NATURAL HISTORY AND OUTCOMES OF NAFLD HCC PERSPECTIVE

- The current HCC incidence rate among NAFLD patients was determined to be 0.44 per 1,000 person-years.
- 54.9% of the HCC cases were related to HCV, 16.4% to alcoholic liver disease, 14.1% were related to NAFLD, and 9.5% to hepatitis B virus.
- It is estimated that the risk for developing HCC in NAFLD patients without cirrhosis is very small given the extremely large number of patients with NAFLD without cirrhosis within the general population.

EVALUATION OF INCIDENTALLY DISCOVERED HEPATIC STEATOSIS (HS)

- A recent study showed that 11% of patients with incidentally discovered HS may be at high risk for advanced hepatic fibrosis based on the calculated NAFLD fibrosis score (NFS). However, the natural history and optimal diagnostic and management strategies for this patient population have not been investigated.

Guidance Statements:

- Patients with unsuspected HS detected on imaging who have symptoms or signs attributable to liver disease or have abnormal liver chemistries should be evaluated as though they have suspected NAFLD and worked up accordingly.
- Patients with incidental HS detected on imaging who lack any liver-related symptoms or signs and have normal liver biochemistries should be assessed for metabolic risk factors (e.g., obesity, diabetes mellitus, or dyslipidemia) and alternate causes for HS such as significant alcohol consumption or medications.

SCREENING FOR NAFLD IN PRIMARY CARE, DIABETES, AND OBESITY CLINICS

- Routine Screening for NAFLD in high-risk groups attending primary care, diabetes, or obesity clinics is not advised at this time because of uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to long-term benefits and cost-effectiveness of screening.

- There should be a high index of suspicion for NAFLD and NASH in patients with type 2 diabetes. Clinical decision aids such as NFS or fibrosis-4 index (FIB-4) or vibration controlled transient elastography (VCTE) can be used to identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis)

* Systematic screening of family members for NAFLD is not recommended currently.

INITIAL EVALUATION OF THE PATIENT WITH SUSPECTED NAFLD

- When evaluating a patient with suspected NAFLD, it is essential to exclude competing etiologies for steatosis and coexisting common CLD.
- In patients with suspected NAFLD, persistently high serum ferritin, and increased iron saturation, especially in the context of homozygote or heterozygote C282Y HFE mutation, a liver biopsy should be considered.
- High serum titers of autoantibodies in association with other features suggestive of autoimmune liver disease (>5 ULN aminotransferases, high globulins, or high total protein to albumin ratio) should prompt a work-up for autoimmune liver disease.
- Initial evaluation of patients with suspected NAFLD should carefully consider the presence of commonly associated comorbidities such as obesity, dyslipidemia, IR or diabetes, hypothyroidism, polycystic ovary syndrome, and sleep apnea.

NONINVASIVE ASSESSMENT OF HEPATO STEATOSIS (HS)

- Basic: Sonography, CT. Compare to spleen
- Necessity: Liver Biopsy not practical for all
- MR imaging, either by spectroscopy or by proton density fat fraction,is an excellent noninvasive modality for quantifying HS
- The use of Transient Elastography (TE) to obtain continuous attenuation parameters is a promising tool for quantifying hepatic fat in an ambulatory setting.
- However, the utility of noninvasively quantifying HS in patients with NAFLD in routine clinical care is limited.

NONINVASIVE PREDICTION OF STEATOHEPATITIS (SH)

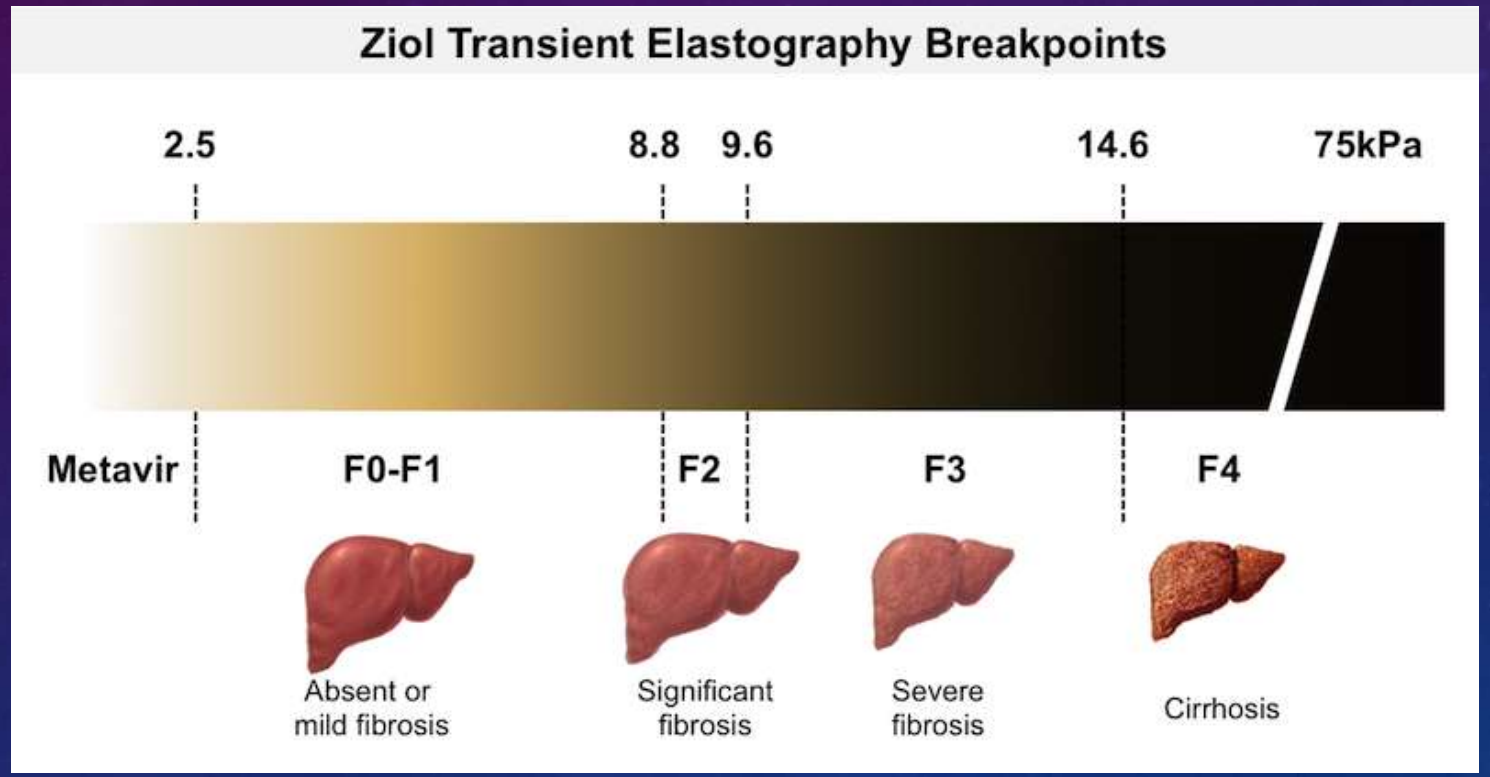
- Risk factors: MetS, DM, Obesity, IR, Dyslipidemia, HTN
- NASH Fibrosure: clinical and laboratory values composite score
- Cytokeratin-18 Fragments: not yet available in the clinical setting

NONINVASIVE ASSESSMENT OF ADVANCED FIBROSIS

Many Indices: NAFLD fibrosis score (NFS), FIB-4 index, aspartate aminotransferase [AST] to platelet ratio index [APRI]), serum biomarkers (Enhanced Liver Fibrosis [ELF] panel, Fibrometer, FibroTest, and Hepascore. Beyond our scope

- In patients with NAFLD, MetS predicts the presence of SH, and its presence can be used to target patients for a liver biopsy.
- NFS or FIB-4 (Fibrosure) index are clinically useful tools for identifying NAFLD patients with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4).
- Vibration Controlled Transient Elastography (VCTE or Fibroscan) or MRE are clinically useful tools for identifying advanced fibrosis in patients with NAFLD.

ELASTOGRAPHY EXAMPLE



WHEN TO OBTAIN A (HELPFUL) LIVER BIOPSY

- To be considered in patients with NAFLD who are at increased risk of having SH and/or advanced fibrosis.
- To be considered in the presence of MetS, NFS or FIB-4, or liver stiffness measured by VCTE or MRE may be used for identifying patients who are at risk for SH and/or advanced fibrosis.
- To be considered in patients with suspected NAFLD in whom competing etiologies for HS and the presence and/or severity of coexisting CLDs cannot be excluded without a liver biopsy.

- Clinically useful pathology reporting should include a distinction between NAFL (steatosis), NAFL with inflammation, and NASH (steatosis with lobular and portal inflammation and hepatocellular ballooning). A comment on severity (mild, moderate, or severe) may be useful. Specific scoring systems such as NAS(128) and/or SAF(128,129) may be used as deemed appropriate. The presence or absence of fibrosis should be described. If present, a further statement related to location, amount, and parenchymal remodeling is warranted

WHOM AND HOW TO TREAT

- The management of NAFLD should consist of treating liver disease as well as the associated metabolic comorbidities.
- Patients with NAFLD without SH or any fibrosis have excellent prognosis therefore pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis.
- Weight loss generally reduces HS, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. A combination of a hypocaloric diet (daily reduction by 500-1,000 kcal) and moderate-intensity exercise is likely to provide the best likelihood of sustaining weight loss over time.
- Weight loss of at least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH, including fibrosis.
- Exercise alone in adults with NAFLD may prevent or reduce HS, but its ability to improve other aspects of liver histology remains unknown.

INSULIN SENSITIZERS

- Metformin is helpful in improving aminotransferase levels and Insulin Resistance but NOT liver histology, thus not recommended for treating NASH in adult patients.

- Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH. Therefore, it may be used to treat these patients. Risks and benefits should be discussed with each patient before starting therapy.

- Until further data support its safety and efficacy, pioglitazone should not be used to treat NAFLD without biopsy-proven NASH.

GLUCAGON-LIKE PEPTIDE-1 ANALOGUES

- In a recently published randomized, placebo-controlled trial consisting of 52 patients with biopsy-proven NASH, liraglutide administered subcutaneously once-daily for 48 weeks was associated with greater resolution of SH and less progression of fibrosis.
- As expected, liraglutide was associated with greater weight loss, but also gastrointestinal side effects.
- It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH

VITAMIN E

- Vitamin E (rrr alpha-tocopherol) administered at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population. Risks and benefits should be discussed with each patient before starting therapy.

- Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

BARIATRIC SURGERY

- Foregut bariatric surgery can be considered in otherwise eligible obese individuals or NASH.
- It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH.
- The type, safety, and efficacy of foregut bariatric surgery in otherwise eligible obese individuals with established cirrhosis attributed to NAFLD are not established.
- In otherwise eligible patients with compensated NASH or cryptogenic cirrhosis, foregut bariatric surgery may be considered on a case-by-case basis by an experienced bariatric surgery program

URSODEOXYCHOLIC ACID, OMEGA-3 FATTY ACIDS, AND MISCELLANEOUS AGENTS

- UDCA is not recommended for the treatment of NAFLD or NASH.
- Omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, but they may be considered to treat hypertriglyceridemia in patients with NAFLD.
- Near a dozen miscellaneous agents under small trial investigations

ALCOHOL CONSUMPTION

- Related to the Definition of NAFLD

Ongoing or recent alcohol consumption >21 standard drinks on average per week in men and >14 standard drinks on average per week in women is a reasonable threshold for significant alcohol consumption when evaluating patients with suspected NAFLD.

According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), a standard alcoholic drink is any drink that contains about 14 g of pure alcohol

ALCOHOL USE

- National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines heavy or at-risk drinking as more than four standard drinks on any day or more than 14 drinks per week in men or more than three drinks on any day or seven drinks per week in women.
- There are no longitudinal studies reporting the effect of ongoing alcohol consumption on disease severity or natural history of NAFLD or NASH. Unclear light alcohol consumption is helpful.
- Patients with NAFLD should not consume heavy amounts of alcohol.
- There are insufficient data to make recommendations with regard to nonheavy consumption of alcohol by individuals with NAFLD.

MANAGEMENT OF CVD AND DYSLIPIDEMIA STATINS

- Patients with NAFLD are at high risk for cardiovascular morbidity and mortality. Thus, aggressive modification of CVD risk factors should be considered in all patients with NAFLD.

- Patients with NAFLD or NASH are not at higher risk for serious liver injury from statins. Thus, statins can be used to treat dyslipidemia in patients with NAFLD and NASH. While statins may be used in patients with NASH cirrhosis, they should be avoided in patients with decompensated cirrhosis.

PROMISING NEW AGENTS

- Obeticholic acid (OCA; NCT02548351) Elafibranor (NCT02704403) Lanifibranor
- OCA, a potent farnesoid X receptor agonist, administered at a 25-mg/day dose improved steatohepatitis and fibrosis over a 72-week period in a large, multicenter trial. In this study, OCA was associated with dyslipidemia and itching. This compound was recently approved by the FDA for treating patients with primary biliary cirrhosis who are unresponsive to UDCA therapy in a dose up to 10 mg/day.
- Elafibranor 120 mg/day. In a recently reported study, exhibited an efficacy signal for improving NASH without fibrosis worsening over a 12-month study period.
- Lanifibranor a pan-PPAR (peroxisome proliferator-activated receptor) agonist at 1200mg/day, in a phase 2b randomized placebo controlled prospective trial (NEJM Oct.21, 2021 Francque et Al.) showed regression of SAF score without worsening of fibrosis.
- Current off label use is not encouraged.

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