Non alcoholic fatty liver disease and NASH

Incidence prevalence and natural history

- most common cause of CLD
- associated with
  - insulin resistance,
  - overweight/obesity,
  - metabolic syndrome.
  - can also occur in lean individuals and is particularly common in those with a ***paucity of adipose depots (i.e., lipodystrophy).***
- NAFLD is a spectrum
  - accumulation of triglyceride in hepatocytes (steatosis) is most benign
  - Cirrhosis and cancer most extreme
- risk of developing cirrhosis is extremely low with isolated steatosis (nonalcoholic fatty liver NAFL)
  - increases as steatosis complicated by liver-cell injury and death and the accumulation of inflammatory cells (i.e., nonalcoholic steatohepatitis NASH).
- 1/4 with NAFLD have NASH
- NASH
  - heterogeneous
  - improves to steatosis or normal in some
  - may remain stable for years
  - may cause progressive fibrous scar leading to cirrhosis
- Liver related mortality and morbidity in NAFLD
  - predicted by advanced hepatic fibrosis (higher in)
    - age >45-50
    - overweight or obese
    - T2-DM
  - in cirrhosis primary liver cancer risk is 1-2% per year
- Imaging cannot differentiate NAFLD vs NASH (cell death and inflammation)
  - no specific blood test available
  - "cryptogenic" ALT elevations maybe predictive
    - serum ALT elevations that cannot be explained by excessive alcohol consumption, other known causes of fatty liver disease, viral hepatitis, or drug-induced or congenital liver diseases

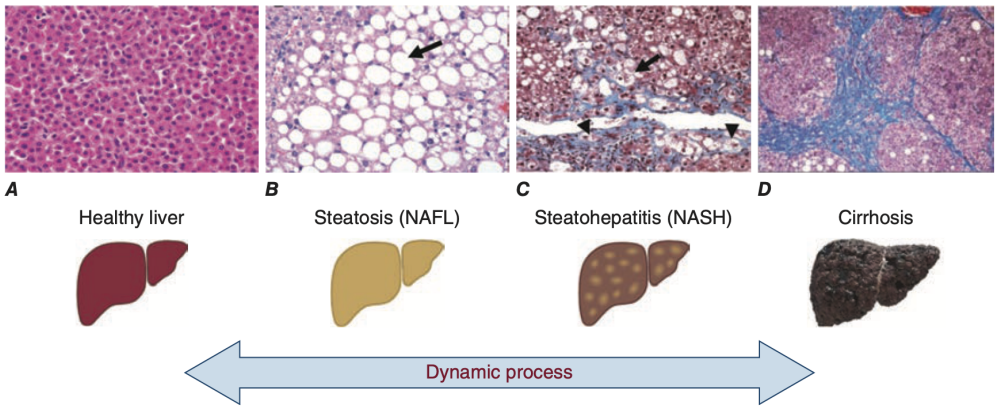

FIGURE 343-1 Histopathologic spectrum of nonalcoholic fatty liver disease (NAFLD). NAFLD encompasses a dynamic spectrum of liver pathology. ***A.*** Healthy liver. ***B.*** Simple steatosis (nonalcoholic fatty liver [NAFL]); *arrow* shows fatty hepatocyte. ***C.*** Nonalcoholic steatohepatitis (NASH); ballooned hepatocyte (*arrow*) near central vein with adjacent blue-stained pericellular fibrosis (*arrowheads*). ***D.*** Cirrhosis with blue-stained bridging fibrosis surrounding micronodules of liver parenchyma.

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- heritable factors
  - TM6SF2 or MBOAT7 (involved in lipid homeostasis)
  - palatin-like phospholipase domain-containing 3 gene (PNPLA3)
    - encodes an enzyme involved in intracellular trafficking of lipids
    - severity of NASH and liver fibrosis
  - heritance accounts for 50% risk of cirrhosis
  - Epigenetics also affects
    - intrauterine exposures influence susceptibility to obesity and the metabolic syndrome in adolescence
- increases risk of both ***HCC and intrahepatic cholangiocarcinoma***

Pathogenesis

- steatosis
  - when triglyceride ***synthesis***(lipid uptake + denovo synthesis) >> triglyceride ***disposal*** (degradative metabolism + lipoprotein export)
  - Obesity stimulates triglyceride accumulation by altering the intestinal microbiota to enhance both energy harvest and intestinal permeability.
  - Reduced barrier function increases hepatic exposure to gut-derived products, which stimulate liver cells to generate inflammatory mediators ***that inhibit insulin actions.***
  - ***adipokines*** in obesity that reduce insulin sensitivity causing hyperinsulinemia
  - hyperinsulinemia promote lipid uptake, fat synthesis and fat storage
  - triglyceride on its own not cytotoxic
    - precursors (e.g., fatty acids and diacylglycerols)
    - metabolic by-products (e.g., reactive oxygen species)
  - lipotoxicity causes cell death and compensatory cell repair
    - transient expansion of myofibroblasts and progenitor cells, that make and degrade matrix, remodel the vasculature, and generate replacement hepatocytes, as well as the recruitment of immune cells
- Cirrhosis results from futile repair, i.e., progressive accumulation of wound healing cells, fibrous matrix, and abnormal vasculature (scarring), rather than efficient reconstruction/regeneration of healthy hepatic parenchyma
- cancers develop when malignantly transformed liver cells escape mechanisms that normally control regenerative growth.

Diagnosis

- demonstration of increased liver fat in the absence of hazardous levels of alcohol consumption
  - > 1(women) >2(men) drinks per day
- exclude other causes like drugs and causes of liver injury

TABLE 343-1 Alternative Causes of Hepatic Steatosis

- Alcoholic liver disease
- Hepatitis C (particularly genotype 3)
- Inborn errors of metabolism
  - Abetalipoproteinemia
  - Cholesterol ester storage disease
  - Galactosemia
  - Glycogen storage disease
  - Hereditary fructose intolerance
  - Homocystinuria
  - Systemic carnitine deficiency
  - Tyrosinemia
  - Weber-Christian syndrome
  - Wilson's disease
  - Wolman's disease
- Medications (see Table 343-2)
- Miscellaneous
  - Industrial exposure to petrochemical
  - Inflammatory bowel disease
  - Lipodystrophy
  - Bacterial overgrowth
  - Starvation
  - Parenteral nutrition
- Surgical procedures
  - Bilopancreatic diversion
  - Extensive small-bowel resection
  - Gastric bypass
  - Jejunoileal bypass
- Reye's syndrome
- Acute fatty liver of pregnancy
- HELLP syndrome (*h*emolytic anemia, *e*levated *l*iver enzymes, *l*ow *p*latelet count)

TABLE 343-2 Medications Associated with Hepatic Steatosis

- Cytotoxic and cytostatic drugs
  - 5-Fluorouraci
  - l-Asparaginase
  - Azacitidine
  - Azaserine
  - Bleomycin
  - Methotrexate
  - Puromycin
  - Tetracycline
  - Doxycycline
- Metals
  - Antimony
  - Barium salts
  - Chromates
  - Phosphorus
  - Rare earths of low atomic number
  - Thallium compounds
  - Uranium compounds
- Other drugs and toxins
  - Amiodarone
  - 4,4′-Diethylaminoethoxyhexesterol
  - Ethionine
  - Ethyl bromide
  - Estrogens
  - Glucocorticoids
- Highly active antiretroviral therapy
  - Hydralazine
  - Hypoglycin
  - Orotate
  - Perhexiline maleate
  - Safrole
  - Tamoxifen
  - Valproic acid
  - Acetylsalicylic acid intoxication
  - Apo-B inhibitors: Mipomersen and lomitapide

- can be done by history , physical , imaging (USG, CT, MRI), blood test
  - invasive testing not needed

- liver may not be enlarged and LFTs maybe normal
- diagnosis confidence increased by risk factors presence
  - increased body mass index
  - insulin resistance/type 2 diabetes mellitus,
  - metabolic syndrome (e.g., systemic hypertension, dyslipidemia, hyperuricemia/gout, cardiovascular disease) in the ***patient or family*** members.
  - pituitary or hypothalamic neoplasms
  - women with polycystic ovary syndrome
  - Hypothyroidism and obstructive sleep apnea
- Staging NAFLD more difficult than diagnosis
- staging defines prognosis
  - steatosis vs NASH vs advanced fibrosis
- staging by
  - non-invasive (blood, physical, imaging)
  - invasive (biopsy)
- advanced NAFLD
  - Blood tests
    - hepatic dysfunction
      - hyperbilirubinemia
      - hypoalbuminemia
      - PT elongation
    - Portal hypertension (thrombocytopenia)
  - stigmata of portal hypertension
    - spider angiomata
    - palmar erythema
    - splenomegaly
    - ascites
    - clubbing encephalopathy
- biopsy
  - gold standard
  - sampling error unless tissue core >2cm acquired
  - complication less
    - significant bleeding,
    - pain, or
    - inadvertent puncture of other organs
- AST ALT not accurate markers
- algorithm with multiple tests devised
  - Enhanced Liver Fibrosis (ELF)score,
  - BARD score,
  - AST to Platelet Ratio Index (APRI)score,
  - NAFLD fibrosis score (commonly used)
  - Fibrosis-4 (FIB-4) score (common)
- NAFLD fibrosis score & FIB-4
  - age,
  - body mass index,
  - glucose,
  - platelet count,
  - albumin,
  - AST, ALT
- scores + non-invasive quantification of liver fat (better predictive power)
  - MRI using proton density fat fraction (MRI-PDFF)
  - liver stiffness, a surrogate marker of liver fibrosis
    - magnetic resonance elastography (MRE)
    - transient elastography (FibroScan)
  - factors reducing specificity of stiffness tests
    - obesity,
    - nonfasting state,
    - hepatic inflammation,
    - iron overload

- hepatic congestion

Clinical manifestations

- asymptomatic
- diagnosis by abnormal LFTs or fatty liver on other testing
- maybe diagnosed at vague RUQ pain, hepatomegaly , abnormal liver appearance at abdominal surgery
- 50-90% subjects obese (+/- metabolic syndrome)
- stigmata maybe present
- minority have complication at presentation (jaundice, portal hypertension , variceal hemorrhage)
- uncommon association
  - chronic fatigue
  - mood alterations
  - OSA
  - thyroid dysfunction
  - PCOS
  - chronic pain syndrome
- 2-3x risk of developing metabolic syndrome
- risk for endothelial dysfunction , more plaques in vessels

Treatment

- 3 component
  - specific therapy
  - comorbidities management
  - treating complication
- no FDA approved therapy

Diet and exercise

- lifestlye changes and dietary modifications
- weight loss and increase insulin sensitivity
- 3-5% weight loss improves steatosis
- > 7-10% improves steatohepatitis and fibrosis
- dietary macro changes less important than energy intake reduction
- Mediterranean-type diet has been reported to improve NASH and liver fibrosis independently of weight loss.
- reduce fructose and ***increase coffee***
- exercise
  - complements dietary caloric restriction
  - improves insulin sensitivity
  - 30 mins moderate intensity aerobic or resistance training 5x/week

PHARMACOLOGICAL

- no approved drugs
- NAFLD without NASH or fibrosis only diet and physical therapy
- NASH or fibrosis get pharma
- Metformin
  - hepatic insulin sensitivity
  - TONIC study
  - not recommended
- Thiazolidinediones
  - insulin sensitivity
  - improved histology
  - PIVENS study
  - may gain weight and liver fibrosis does not improves
- liraglutide / semaglutide may be useful
- SGLT2 inhibitors \

- antioxidants
  - Vitamin E
    - inexpensive
    - potent
    - 800 IU/day
    - improves blood, radiological , histology
    - may increase risk of cardiovascular mortality , hemorrhage stroke, prostate cancer
- USDA and betaine have no benefit
- statins should be used to treat dysplipidemia and decrease cardiovascular risk

Bariatric surgery

- ack of randomized clinical trials or adequate clinical studies prevents definitive assessment of benefits and harms of bariat- ric surgery as a treatment for NASH.
- safe in individuals with well-compensated chronic liver disease and improves hepatic steatosis and necroinflammation (i.e., features of NAFLD/NASH)
- effect on fibrosis +/-
- patients with NAFLD-related cirrhosis and, particularly, those with portal hypertension should be excluded as candidates for bariatric surgery.

transplant

- in all with end stage liver disease
- comorbidities often limit transplant candidacy.
- NAFLD may recur
  - hypertriglyceridemia
  - obesity
  - T2-DM
  - immunosuppresants