Alcoholic liver disease and Non-alcoholic fatty liver disease

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Alcoholic liver disease

- Alcohol is one of the most common causes of chronic liver disease worldwide, with rising consumption in many countries.
- The risk threshold for developing ALD is variable but begins at 30 g/day of ethanol for several years, but no clear linear relationship between dose and liver damage is recognized.
- Since only 10–20% of people who drink heavily will develop cirrhosis, a genetic predisposition is certainly present.

23.51 Amount of alcohol in an average drink

Alcohol type	% alcohol by volume	Amount	Units*
Beer	3.5	440 mL (1 pint)	2
	9	440 mL	4
Wine	10	mL	1
		750 mL	9
'Alcopop'		330 mL	2
Sherry	17.5	750 mL	13
Vodka/rum/gin	37.5	25 mL	1
Whisky/brandy	40	700 mL	28

*1 unit = 8 g.

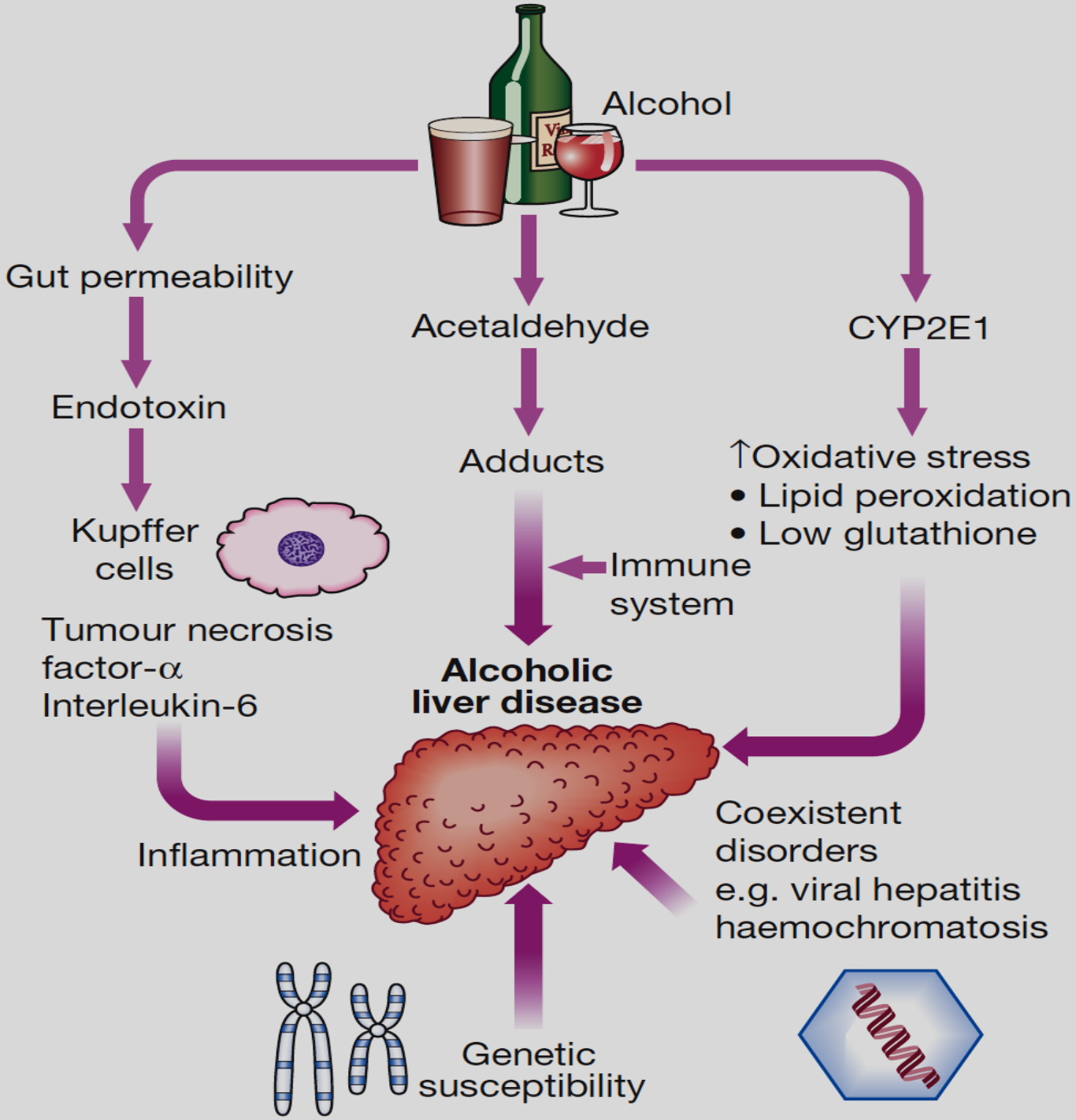
½ bottle/day = ½ x 28 x 8 = 112 g/day

So, what are the risk factors for ALD?

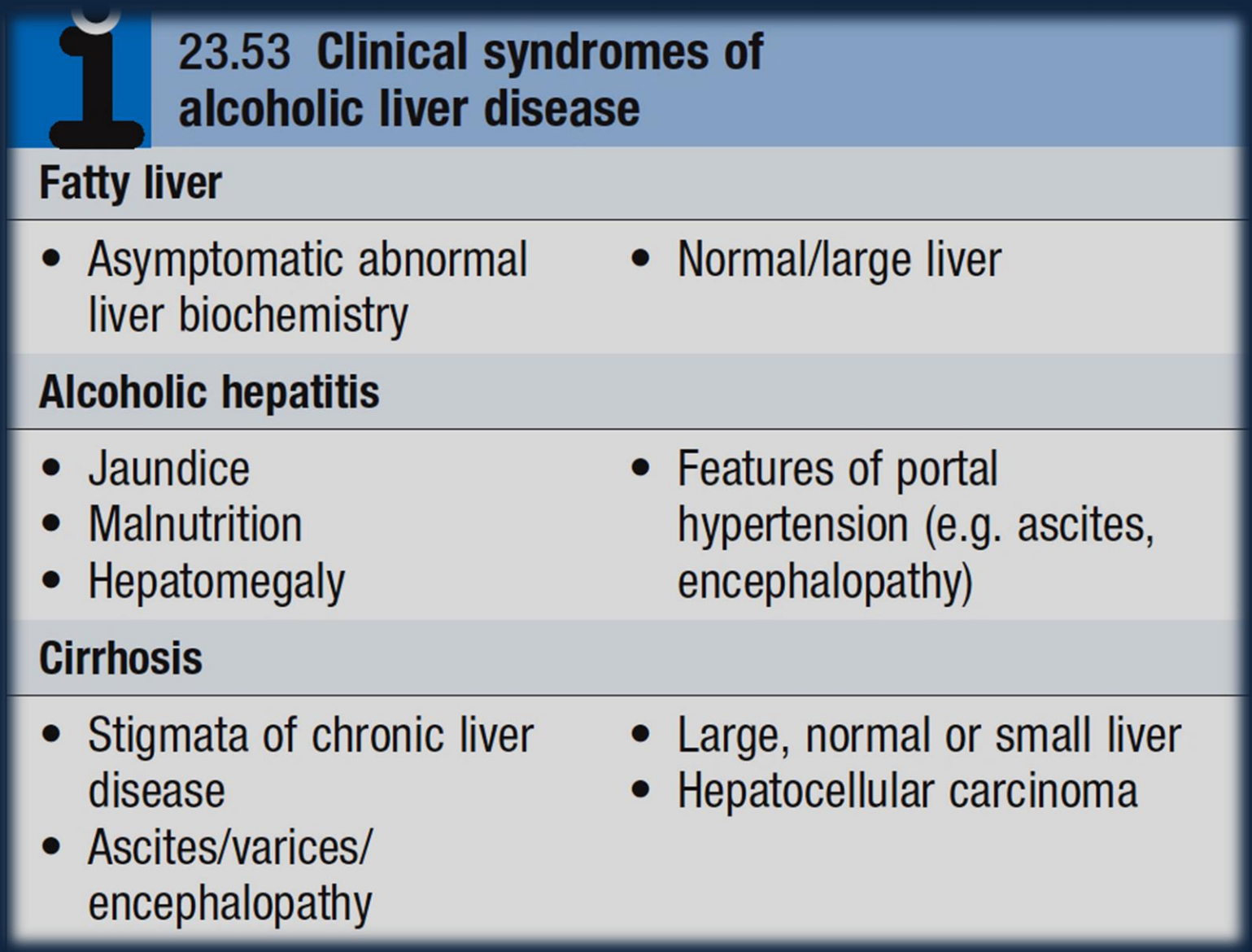
- Amount and duration of alcohol intake.
- Drinking pattern: continuous > ‘binge’ drinkers.
- Gender: women > men (gastric enzyme)
- Genetics: susceptibility genes (e.g. PNPLA3 or adiponutrin), mild phenotypes of other chronic liver diseases (e.g. HFE gene heterozygote).
- Co-existent chronic viral hepatitis particularly HCV.
- Nutrition: obesity and malnutrition.

What is the pathophysiology of ALD?

- about 80% of alcohol is metabolised by mitochondrial alcohol dehydrogenase to acetaldehyde.
- remaining 20% of alcohol is metabolised by inducible microsomal cytochrome CYP2E1 releasing oxygen free radicals.
- acetaldehyde forms protein adducts, while oxygen free radicals cause lipid peroxidation, both contributing to liver injury.


Alcohol
Gut permeability
Endotoxin
Kupffer cells
Acetaldehyde
Adducts
CYP2E1
↑Oxidative stress
• Lipid peroxidation
• Low glutathione
Immune system
Tumour necrosis factor-α
Interleukin-6
Alcoholic liver disease
Inflammation
Coexistent disorders
e.g. viral hepatitis
haemochromatosis
Genetic susceptibility

What are the clinical features of ALD?



23.53 Clinical syndromes of alcoholic liver disease

Fatty liver

- Asymptomatic abnormal liver biochemistry
- Normal/large liver

Alcoholic hepatitis

- Jaundice
- Malnutrition
- Hepatomegaly
- Features of portal hypertension (e.g. ascites, encephalopathy)

Cirrhosis

- Stigmata of chronic liver disease
- Ascites/varices/ encephalopathy
- Large, normal or small liver
- Hepatocellular carcinoma

What are the lab findings in ALD?

- Alcoholic fatty liver:
  - CBC: ↑MCV
  - LFTs: normal or ↑AST&ALT, ↑GGT
  - US: bright echogenic liver
  - Liver biopsy: simple macrovesicular steatosis
- Alcoholic hepatitis (steatohepatitis):
  - CBC: ↑WBC (neutrophils)
  - LFTs: ↑bilirubin, ↑AST>ALT, ↑ALP, ↑PT,↓albumin
  - Liver biopsy: same as non-alcoholic steatohepatitis
- Alcoholic cirrhosis:
  - lab tests are as for cirrhosis in general

How to manage a patient with ALD?

- For all ALD patients:

  Life-long abstinence is most important.

  Benzodiazepines can be used for withdrawal symptoms.

  Nutritional support is important.
- Alcoholic fatty liver: just as above.
- Alcoholic cirrhosis: as for cirrhosis in general but abstinence improves prognosis and slows disease progression.

How to manage a patient with ALD?

- Alcoholic hepatitis:
  - Severe cases require hospital admission
  - Nutrition with enteral feeding may be needed
  - Thiamine iv given to prevent Wernicke encephalopathy
  - Corticosteroids improve severe cases defined by a discriminant function (DF) > 32;
    DF = [4.6 × ΔPT (sec)] + bilirubin (mg/dL)
  - Pentoxifylline may be used in severe cases if steroids are contraindicated (sepsis, GI bleeding, uncontrolled diabetes).

Which patients with ALD are candidates for liver transplantation?

- In many hepatology centers, ALD is a common indication for liver transplantation.
- Patients with a high likelihood of returning to alcohol use should not be offered a transplant.
- Many centers require a 6-month period of abstinence before a patient is considered for transplantation.
- The outcome of transplantation for ALD is good if the patient remains abstinent as there will be no risk of disease recurrence.

Non-alcoholic fatty liver disease

- NAFLD refers to the accumulation of fat within hepatocytes that results from insulin resistance.
- NAFLD is now recognized as the most common chronic liver disease in the Western world.
- NAFLD encompasses a spectrum of severity starting from simple steatosis, which is generally benign, to nonalcoholic steatohepatitis (NASH), which can progress to liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC).

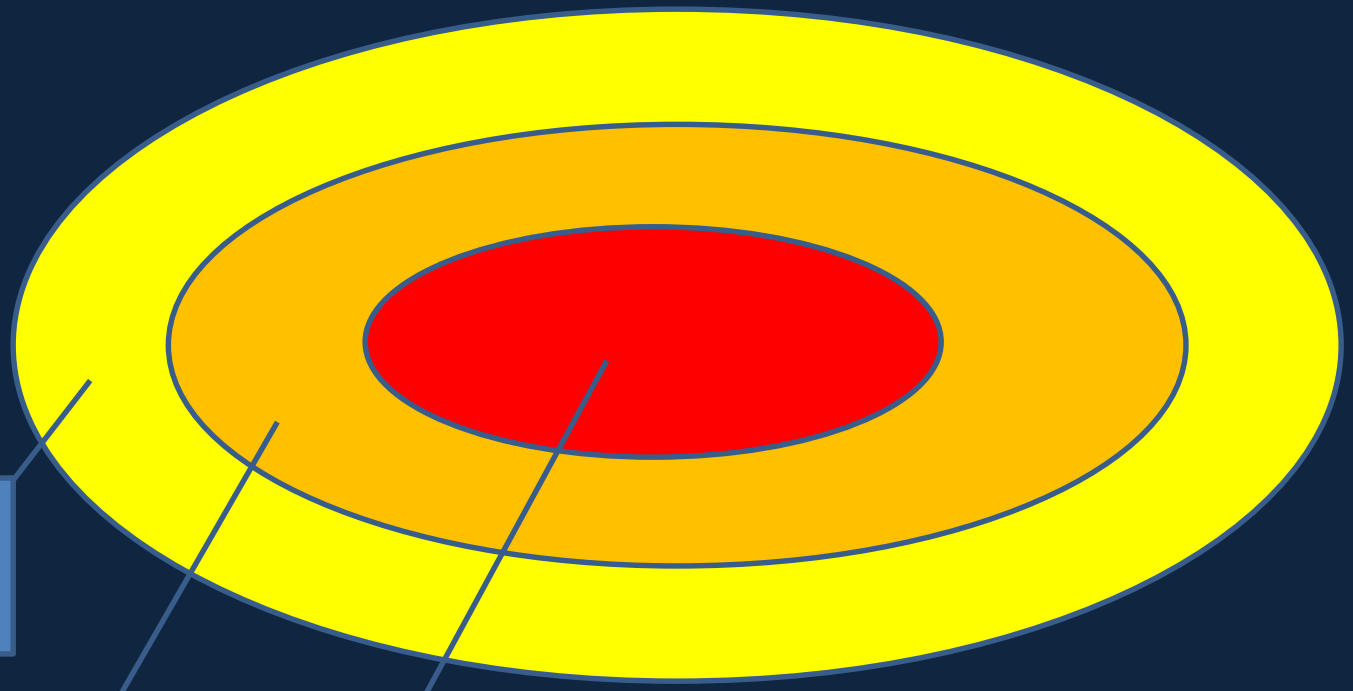
Who is at risk of NAFLD?

- NAFLD is strongly associated with obesity, dyslipidemia, hypertension, insulin resistance and type 2 diabetes mellitus, and is considered to be the hepatic manifestation of the metabolic syndrome.
- NAFLD is also associated with polycystic ovary syndrome, obstructive sleep apnea and small-bowel bacterial overgrowth.

How common is NAFLD?

- A large European study found NAFLD in:
  - 94% of obese persons (BMI >30).
  - 67% of overweight persons (BMI >25).
  - 25% of normal-weight persons.
- In type 2 diabetes, 40-70% of patients has NAFLD.
- NASH was found in up to 16% of apparently healthy potential living liver donors.

The spectrum of NAFLD



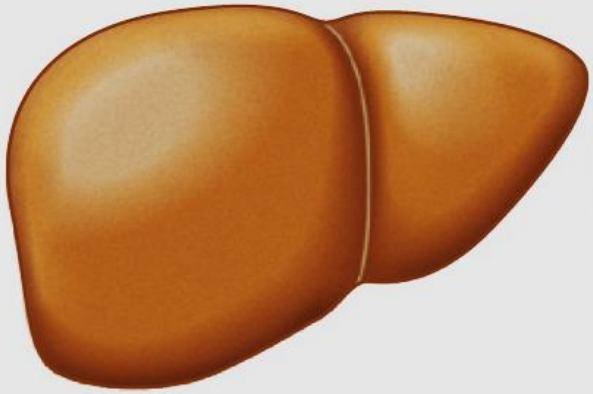
metabolic syndrome

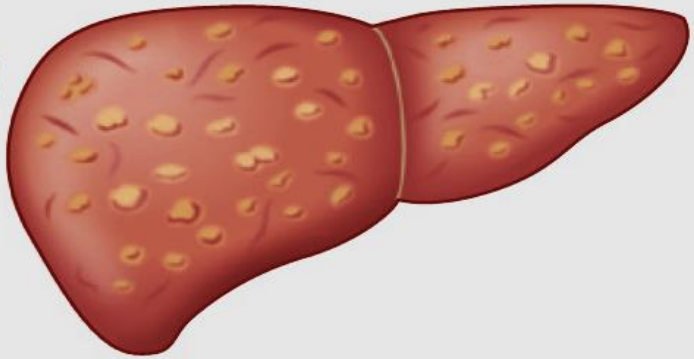
steatosis

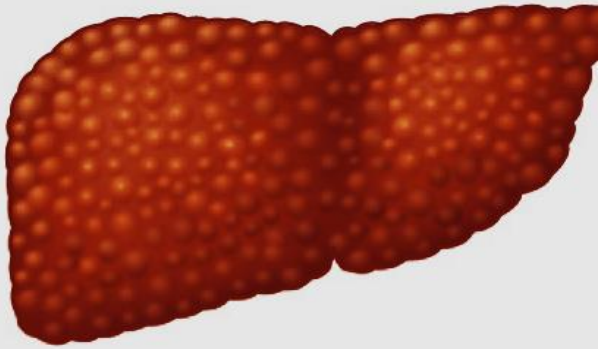
NASH

What is the pathophysiology of NAFLD?

Steatosis → NASH → Cirrhosis



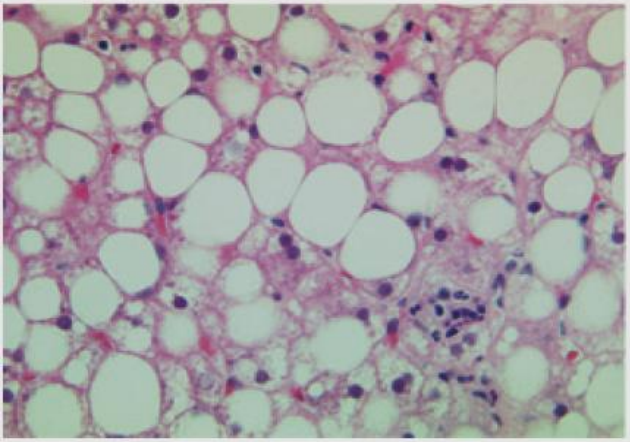


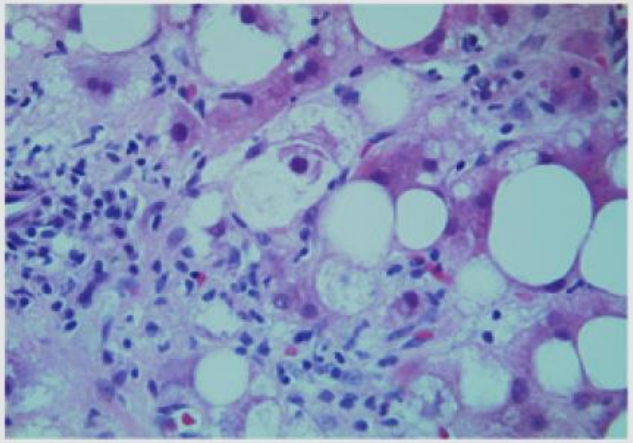


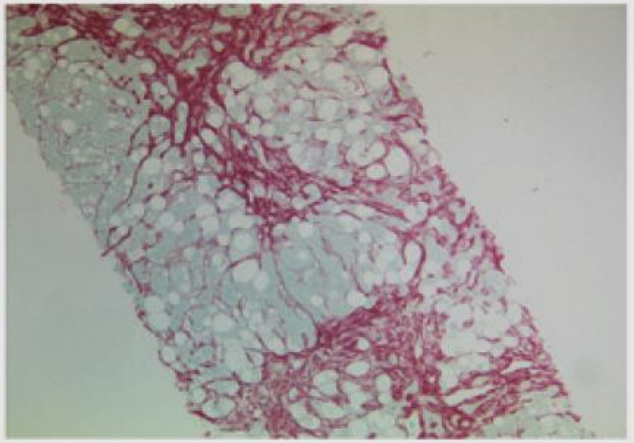
↑FA influx
↓FA oxidation
↑FA synthesis
↓VLDL assembly
Insulin resistance

TNF-α
Oxidant stress
Endotoxin
Immune factors

TGF-β
Stellate cell activation







Why do some patients develop progressive NASH while other patients with NAFLD do not?

- As with many other liver diseases, subtle inter-patient genetic variations and environmental factors interact to determine disease progression.
- As in alcoholic liver disease, PNPLA3 and its product, adiponutrin, may influence NAFLD severity.

What are the clinical features of NAFLD?

- Most patients are asymptomatic and identified by incidental abnormal LFTs.
- Some patients may complain of fatigue and mild right upper quadrant discomfort.
- Hepatomegaly is commonly found on physical examination.

How to diagnose NAFLD?

- Exclude excess alcohol intake and other chronic liver diseases (including viral, autoimmune and other metabolic causes)
- Confirm the presence of NAFLD, differentiate simple steatosis from NASH and determine the extent of hepatic fibrosis.
- Liver biopsy is the standard for the diagnosis of NASH and assessing hepatic fibrosis but it is invasive and has low patient acceptability.

What are the lab findings in NAFLD?

- LFTs:

  mild ↑ALT&AST and AST:ALT ratio <1.
  ALT↓ as fibrosis↑ and AST:ALT ratio
  reverses (become >1) as cirrhosis develops.

- Other lab abnormalities:

  non-specific ↑GGT

  low-titer ANA in 20-30% of patients

  ↑ferritin levels

What are the radiological findings in NAFLD?

- Ultrasound:

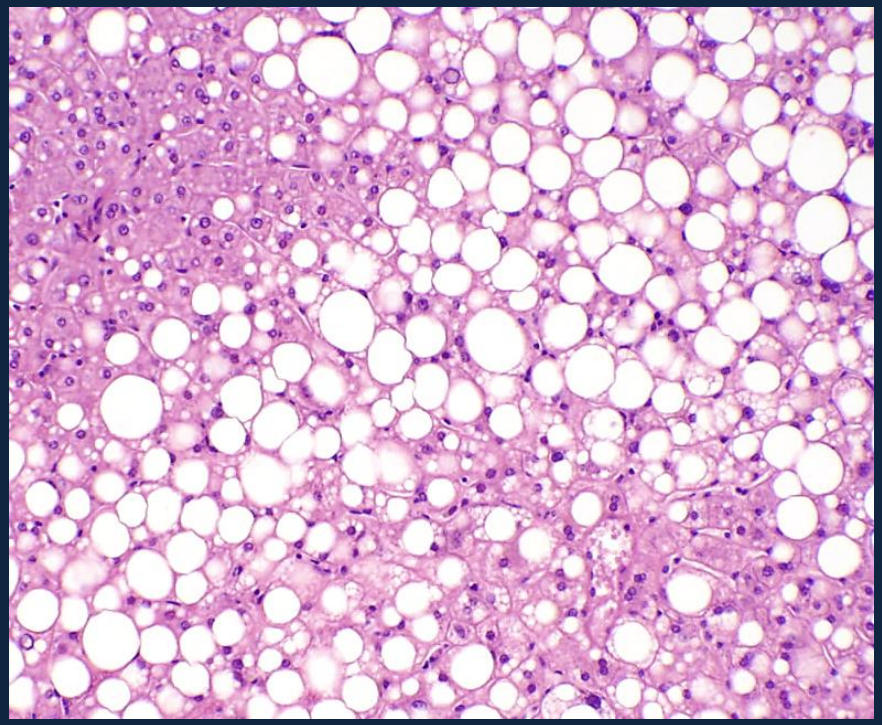
  a bright liver usually indicates steatosis but this is not a sensitive finding.

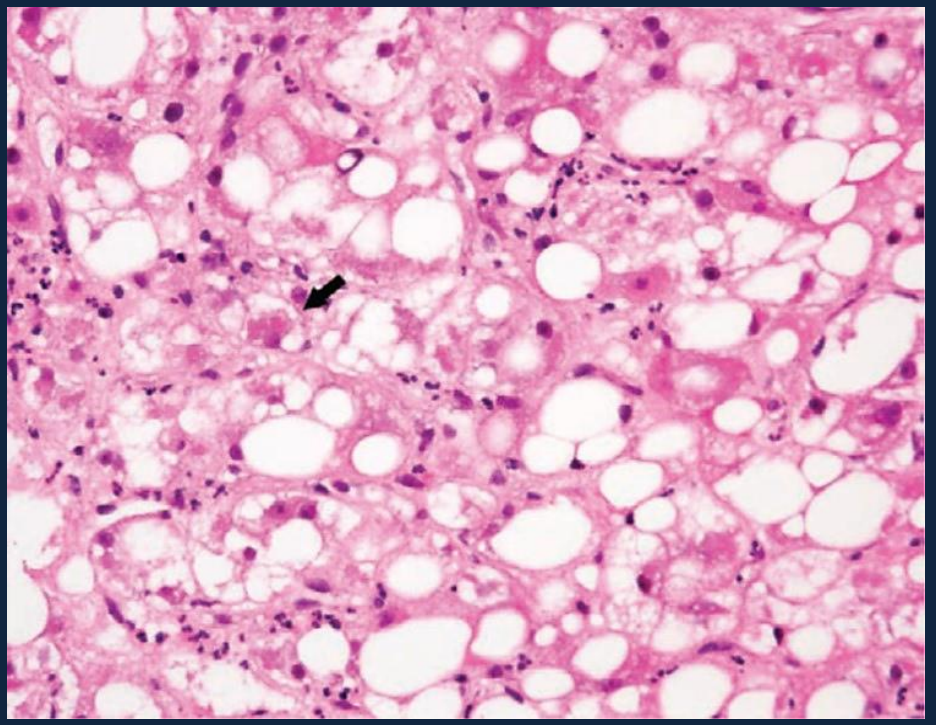
- CT, MRI, MR spectroscopy:

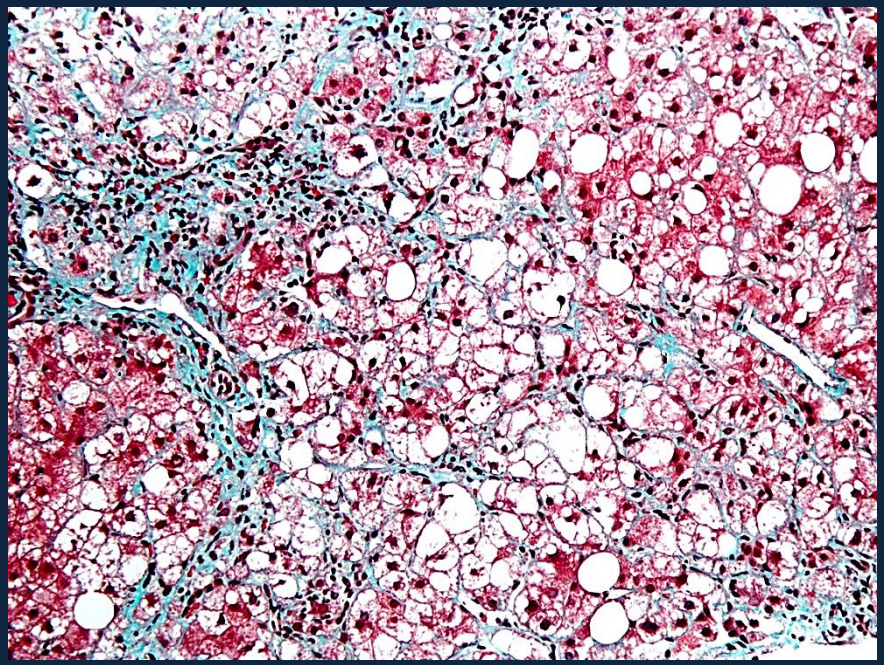
  more sensitive than US but are expensive and not widely available.

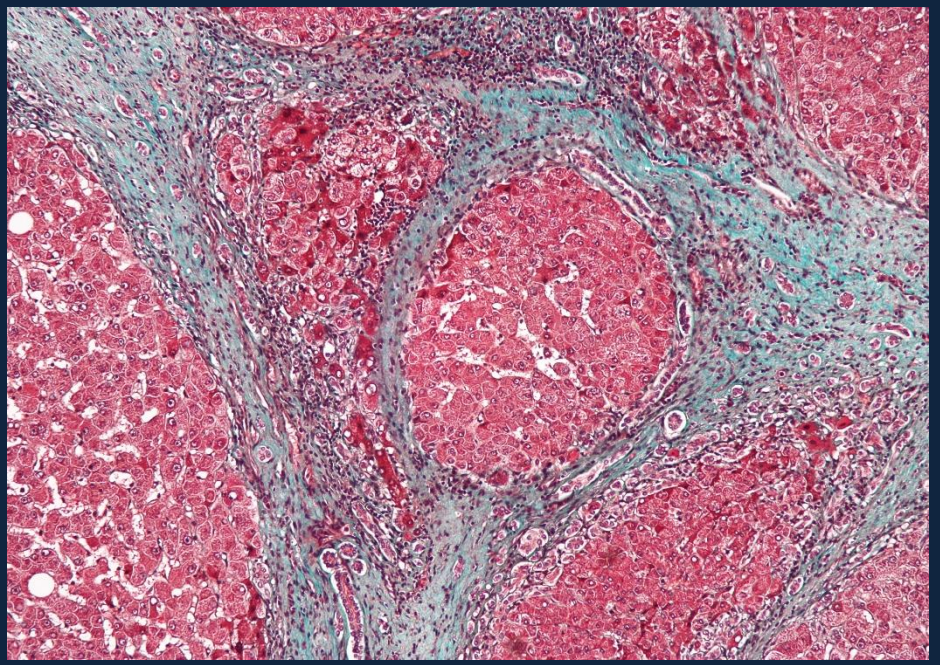
- No imaging modality can yet distinguish simple steatosis from steatohepatitis or reliably quantify pre-cirrhotic liver fibrosis.

What are the liver biopsy findings in NAFLD and are there any "specific" changes?









How to manage a patient with NAFLD?

- Focus on patients with NASH, not simple steatosis.
- Weight loss (7–10% of BW), exercise, strict control of hypertension, diabetes and lipid levels are the only treatments currently available.
- Vitamin E, metformin, glitazones, and other drugs were used with little or no benefit.
- Liver transplant is reserved for decompensated cirrhosis but NAFLD can recur in the allograft.

Thank you