

ALCOHOL - RELATED LIVER DISEASE (ALD)

Chronic or excessive Alcohol consumption is one of the major cause of liver diseases.

- It mainly constitute a spectrum of disorders of 3 major
 - Hepatic steatosis
 - Steato hepatitis
 - Fibrosis

When exposed to Alcohol
 → Fatty change, Perivenular fibrosis

Severe exposure

- Necrosis of hepatocytes, Inflammation, Mallory bodies
- Fatty changes

↓ Repeated attacks

→ Diffuse loss of Architecture

→ Fibrosis

→ Regenerating nodules.

METABOLISM OF ETHANOL:

by these enzyme → Alcohol dehydrogenase -

Cytochrome P450 → generate Reactive Oxygen species
 catalase.

Acetic Acid is ~~leave~~ is obtained by conversion of Acetaldehyde by (ALDH)

ETIOLOGY:

Risk factors: directly Related to Amount of Alcohol consumed
 (80g Alcohol is injurious)

↓
 cause Reversible hepatitis
 Steatosis

Gender - > women

→ estrogen ↑ gut permeability. ↑ production of proinflammatory cytokines & chemokines
 Resulting of injury in liver cells.

→ Genetic factor → polymorphism in detoxifying enzymes

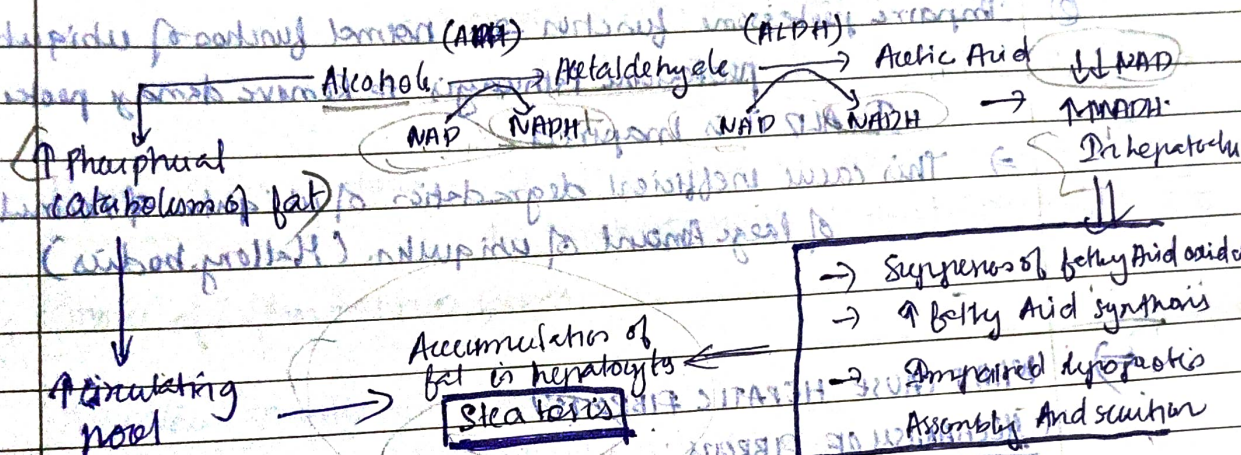
→ Associated condition → Iron overload

(iron overload) Defects → HCV & HBV

PATHOGENESIS:

→ what cause Hepatocyte Fat Accumulation?

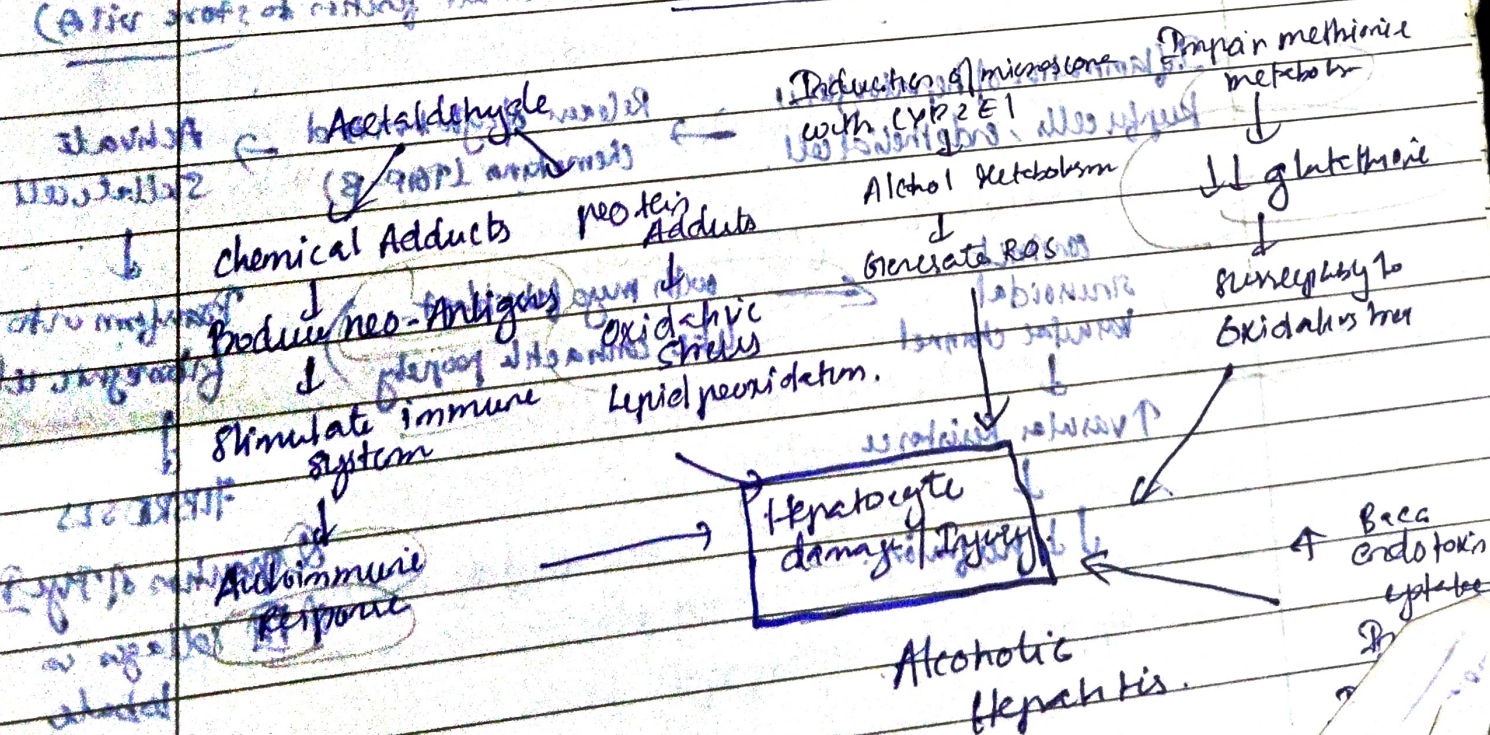
• MECHANISM OF HEPATOCELLULAR STEATOSIS



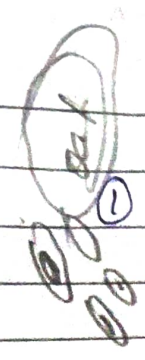
→ what cause Hepatocyte damage?

MECHANISM OF STEATOHEPATITIS AND CIRRHOSIS

Excess Alcohol



↑ production of proinflammatory cytokines occurs in two ways



- ① → Lipopolysaccharide from gram -ve bacteria (endotoxin)
 - ↑ gut permeability
 - LPS enter portal circulation
 - stimulate TNF- α & cytokines
 - from macrophages & Kupffer cells
 - (Dysregulate liver cells)

- ② Impaired proteasome function → normal function of ubiquitin proteasome pathways to remove damaged protein.
 - In ALD this is impaired
 - This cause inefficient degradation of ubiquitin of accumulation of large amount of ubiquitin. (Mallory bodies)

WHAT CAUSE HEPATIC FIBROSIS?

MECHANISM OF FIBROSIS

→ occurs due to Activation of stellate cells (cell present in space of Disse and hepatocytes normal function to store vit A)

Inflammation of hepatocytes, Kupfer cells, endothelial cell

Release of cytokines and chemokines (TNF- α , IL-1, IL-6)

→ Activate Stellate cell

with myofibroblast-like contractile property

Transform into fibrogenic cells

↑ Vascular Resistance

↓ perfusion

FIBROSIS

Deposition of type I collagen in lobule

[Handwritten notes in the left margin:]
Hepatic fibrosis
Hepatic stellate cells
Space of Disse
Hepatocytes
Kupfer cells
Endothelial cells
Cytokines
Chemokines
TNF- α
IL-1
IL-6
Myofibroblasts
Contractile property
Fibrogenic cells
Fibrosis
Deposition of type I collagen
Lobule
Vascular resistance
Perfusion

MORPHOLOGY:

GROSS

Fatty change

enlarged, soft, yellow and greasy.

MICROSCOPY:

Accumulation of fat usually begins in centrilobular hepatocytes

Microvacuolar steatoris: Accumulation of small, clear, vacuoles of lipid within cytoplasm of hepatocytes.

Affect Area zone 3 (centrilobular Region of lobule)

The nuclei of affected hepatocytes are centrally located and the cytoplasm looks foamy.

Macrovesicular steatoris: Cells large, lipid vacuole, compresses the hepatocyte nucleus to the periphery of the cell.

Absence of inflammation or fibrosis

Alcoholic Hepatitis

GROSS → yellow, enlarged, firm due to fibrosis.

MICROSCOPY:

1) Hepatocyte ballooning: scattered foci of swollen liver cells having clumped cytoplasm due to accumulation of fat, water protein.

may lead to hepatocyte necrosis

2) Hallory hyaline bodies → (Hallory - Dark bodies / Mallory hyaline)

They consist of tangled - strands (Mass / coils) of cytokeratin intermediate filament. (such as cytokeratins 1 and 18)

They appear as dense, eosinophilic, ropey cytoplasmic inclusions / clumps.

3) Neutrophilic infiltration: seen around ballooned hepatocytes. The portal tract or parenchyma infiltrated by lymphocyte & macrophages.

4) Variable degree of steatosis
5) Steato fibrosis

Stain $\rightarrow$ Hasson trichrome

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- Initially start in the centrilobular Region as a centrilobular sclerosis.

- Fibrosis in the space of Disse of centrilobular Region enclosing small group of hepatocytes is a

delimited in space pattern called as chicken wire fence pattern.

a narrow, well defined space between hepatocytes : centrilobular space.

CIRRHOSIS : a late stage of liver disease

It is a diffuse process characterized by the transformation of