Lecture 4[2hrs]

3 –Hemochromatosis

*Hemochromatosis is a condition in which the amount of total body iron is increased. Hemochromatosis may be primary or secondary to other diseases.
*Hereditary Hemochromatosis (HHC). Primary hemochromatosis is an autosomal recessive disorder characterized by the absorption of too much iron, which then accumulates (as hemosiderin) in the liver, pancreas, heart, pituitary, skin, and joints
*The gene associated with this disorder is the HFE gene, on the short arm of chromosome 6.
*50% of homozygous for the C282Y mutations will develop HH.
*About 90% of patients with HHC are Males.
*Iron loss in menstruation and pregnancy compensate for the excess iron absorption that can delay the onset of HHC in females.

Pathophysiology

*The total daily iron absorbed by the small intestine about1-2mg.
*in homozygote C282Y mutation absorption increase to 2-4 mg/day or more.
*The HFE gene is involved in regulating dietary iron absorption by interaction with the transferrin receptor on intestinal epithelial cells. Mutant HFE leading to increase iron absorption by enterocytes results in a loss of regulation of iron absorption from the small intestine even when the iron-binding protein, transferrin, is fully saturated.
*In HH the total body iron accumulation may reach 40-60 g leading to target organ damage.
Excess of iron in hepatocytes induced lipid peroxidation. kupffer cells become activated after the phagocytosis of iron-loaded hepatocytes, activated kupffer cells producing cytokines which stimulate hepatic stellate cells to produce collagen leading to fibrosis and cirrhosis.

Clinical Features:

*Excess iron is deposited in organs, such as the liver, pancreas, pituitary, skin, and joints, which over many years leads to organ damage and dysfunction
*Liver disease in HH is characterized by slowly progressive fibrosis but without significant inflammation.
*Skin pigmentation due to excess in melanin and not due to iron excess.
*Cardiac manifestations-include congestive heart failure and arrhythmia due to restrictive cardiomyopathy
*Diabetes mellitus due to iron deposition in the pancreas
*Impotence*loss of libido* testicular atrophy *Fatigue
*Arthritis with chondrocalcinosis secondary to calcium pyrophosphate deposition.
*Impaired of phagocytosis in patients with HH leads to increased risk of bacterial and viral infection.

Investigations

*Transferrin saturation > 45% .
*High ferritin concenration> 1000 µg/L suggest liver damage
*MRI has high specificity for iron overload.
*Liver biopsy allows assessment of fibrosis and distribution of iron and calculation of Hepatic Iron Index (HII) = liver iron (µmol of iron per g dry weight of liver/age in years).
*HII of more than 1.9 suggests genetic hemochromatosis.
*HEF mutation analysis.

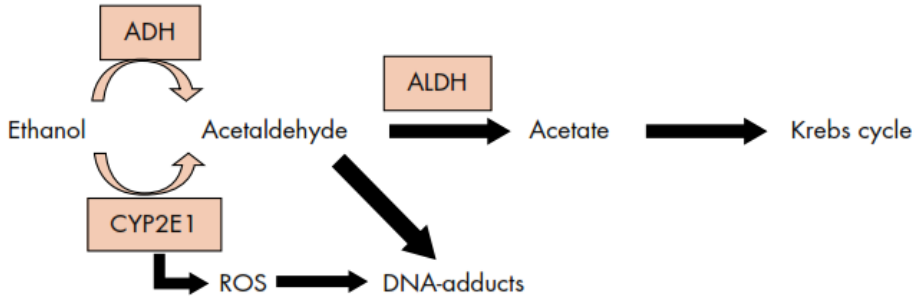
Treatment:

Treatment should begin before the development of fibrosis or cirrhosis.
*If treatment is initiated before cirrhosis the patient will have a normal life span.
1-Phlebotomy –phlebotomy or venesection of 500 mL of blood [contain 250 mg iron] once or twice a week. for a year or more until the serum ferritin is in the low normal range (50 µg/L) and then three or four times a year.
*Skin pigmentation is reversible on iron removal.
*Liver and cardiac problems improve after iron removal.
*Diabetes mellitus does not resolve after venesection.
*Phlebotomy does` not improve [Arthritis and Hypogonadisim].
*Liver cirrhosis cannot be reversed by the removal of iron.
2-Chelation therapy-
*Desferrioxamine can be used in patients who do not tolerate phlebotomy (anemia, congestive heart failure, iron overload secondary to an iron loading).
Desferrioxamine can be given continuously subcutaneously.
*Avoid vitamin C supplements, which increase iron absorption.
3-Liver Transplantation- For end-stage liver disease. But does not heal the original genetic defect.
Screening of first-degree family members by
*Genetic screening
*Ferritin, transferrin saturation.
*Liver biopsy should be done in asymptomatic relatives with abnormal LFT and or serum ferritin is greater than 1000micrograms/L
*Asymptomatic disease should be treated.
Prognosis
HH has a good prognosis compared with other forms of cirrhosis.
The risk of death from hepatocellular carcinoma in patients with HH is increased.
Causes of Secondary HaemoChromatosis are.
*Rrepeated blood transfusion(> 50 L) . *Thalassaemia * Sideroblastic anemia *Pyruvate kinase deficiency)*Liver disease*Porphyria cutanea tarda *Dietary iron overload *Alcoholic cirrhosis, *Juvenile hemochromatosis, and Neonatal hemochromatosis.

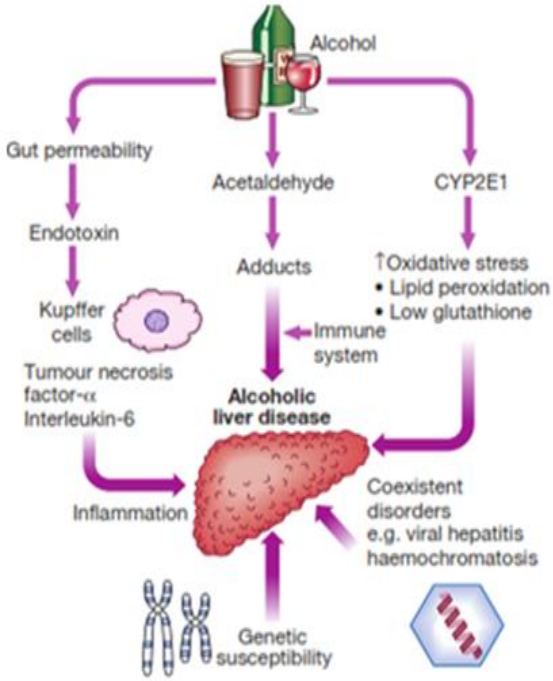
Alcoholic Liver Disease [ALD].

*The threshold for developing ALD is variable and depends on the amount, duration of alcohol intake and sex.
*Males drinking > 30 gr (3 unit) and females 20 gr (2 unit) of alcohol per day for 10 years are at a high risk of developing cirrhosis.
*The incidence of cirrhosis amongst alcoholics is approximately10 – 20%.
Factors involved in the development of Alcoholic liver disease are
1-Genetic pleomorphism of alcohol dehydrogenase systems.
2-Female are more susceptible to alcoholic liver injury because they have lower levels of gastric ADH.
3-Coexistent viral hepatitis HBV and HCV.
Pathophysiology
*Alcohol reaches peak blood concentrations after about 20 minutes.
*Alcohol is metabolized by the liver by the following pathways.
1-Approximately 80% of alcohol is metabolized to acetaldehyde by alcohol dehydrogenase.

*Acetaldehyde is then metabolized to acetyl-CoA and acetate by aldehyde dehydrogenase. This generates NADH from NAD (nicotinamide adenine dinucleotide), which changes the redox potential of the cell.
2-The remaining 20% of alcohol is metabolized by the microsomal ethanol-oxidizing system (MEOS) pathway. Cytochrome CYP2E1 is an enzyme that oxidizes ethanol to acetate.



The Following Events leads to hepatocytes damage in alcoholic liver disease
1-Acetaldehyde forms adduct with cellular proteins in hepatocytes that activate the immune system causing hepatocytes injury.
2-During metabolism of ethanol it releases oxygen free radicals, leading to lipid peroxidation causing increase oxidative stress and low glutathione.
3-increasing gut permeability and translocation of bacterial products such as LPS into the portal circulation by Alcohol. leading to release of tumor necrosis factor-alpha (TNF-α) and interleukin 1 (IL-1), IL-2 and IL-8 from immune cells
4-Alcohol causing Exaggerated gradient of hypoxia from the portal vein to the central vein
5-Genetic susceptibility play a role in susceptibility to alcoholic liver injury
6-Coexistence liver disease
All the above-mentioned events are implicated in the pathogenesis of liver fibrosis by stimulating stellate cells.
Stimulated stellate cells lead to liver fibrosis by
*Chemotaxis and cytokine production
*The production of the collagen matrix.
*Production of inhibitors of collagen breakdown.
* Production of endothelin 1 (ET1) causing vasoconstriction.
Fibrosis and vasoconstriction contribute to the development of portal hypertension.



Factors involved in the pathogenesis of the alcoholic liver disease
The Spectrum of ALD include.
1-Fatty liver - is the first response of the liver to alcohol abuse. usually presents with elevated transaminases. It has a good prognosis and steatosis usually disappears after 3 months of abstinence.
2-Alcoholic Steato-Hepatitis- is characterized by steatosis and inflammatory infiltrate of predominantly PMN cells with hepatocellular damage usually reversible.
3-Cirrhosis - irreversible
Clinical Features
Fatty Liver
*Usually presents with elevated transaminases in the absence of hepatomegaly.
*It has a good prognosis
*Disappears after 3 months of abstinence
Alcoholic Hepatitis
*This presents with jaundice and hepatomegaly; anorexia, nausea, vomiting, and abdominal pain, weight loss, weakness, fever, and jaundice
*Complications of portal hypertension may also be present.
*It has a significantly worse prognosis than AFLD.
Alcoholic Cirrhosis
*Evidence of compensated or decompensated cirrhosis.
*Symptoms of liver failure in the end stages of cirrhosis
*Only half of such patients will survive for 5 years from presentation
*Signs of systemic alcohol toxicity such as peripheral neuropathy, dementia, Dupuytrens contracture, and diarrhea.
Investigations
***Aim to establish alcohol misuse
*Exclude alternative or additional coexistent causes of liver disease
*Assess the severity of liver damage.

*High aminotransferases, bilirubin, alkaline phosphatase, GGT, with the AST/ALT ratio > 2. *Macrocytosis in the absence of anemia may suggest and support a history of alcohol abuse, *Leukocytosis and prolongation of the prothrombin time which does not respond to vitamin K.
*Low serum albumin. *High Serum lgA.*hypersplenism [thrombocytopenia, anemia ,leukopenia].

Assessing ALD severity by

1-Discriminant function = 4.6 X (prothrombin time PT (sec) -control PT) + serum bilirubin in mg.**):** A value > 32 indicate severe liver disease with a poor prognosis and is used to guide treatment decision.

2- Mayo End-Stage Liver Disease (MELD), that takes into account bilirubin, International Normalized Ratio (INR), and creatinine levels: When the MELD index is >25, the short-term survival rate is about 50%

Prognosis

*Fatty liver: the prognosis is excellent. Complete abstinence from alcohol and a balanced diet will lead to the disappearance of the fat over four to six weeks.
*About one-third of patients with alcoholic hepatitis die in the acute episode, particularly those with hepatic encephalopathy or a prolonged PT.
*About ½ of patients with Alcoholic cirrhosis survive 5 yr.

Treatment

1-Alcohol abstinence*Stop smoking*Balanced diet [high protein, low fat]
*Multivitamin supplements (with extra thiamine).
2-Short-acting benzodiazepine for Withdrawal symptoms.

Specific Treatment for alcoholic hepatitis includes the use of

1-Corticosteroids.
A discriminant function of > 32 is a predictor of poor prognosis and favorable response to corticosteroid therapy in the absence of active infection.
Corticosteroid (40 mg/day or methylprednisolone 32mg/day for four weeks and then taper). to reduce short term mortality.
2-Antioxidant - Vit E and *N*-acetylcysteine.
**N*-acetylcysteine- restore the glutathione store and consequently limits oxidative stress
3-Pentoxifylline which has a weak anti-TNF action may be beneficial in severe alcoholic hepatitis
4-Treatment of Complication– [Encephalopathy, Ascites, and Variceal bleeding].
5-Periodic screening for hepatoma.
6-Liver Transplantation.

Non-Alcoholic Fatty Liver Disease [NAFLD].

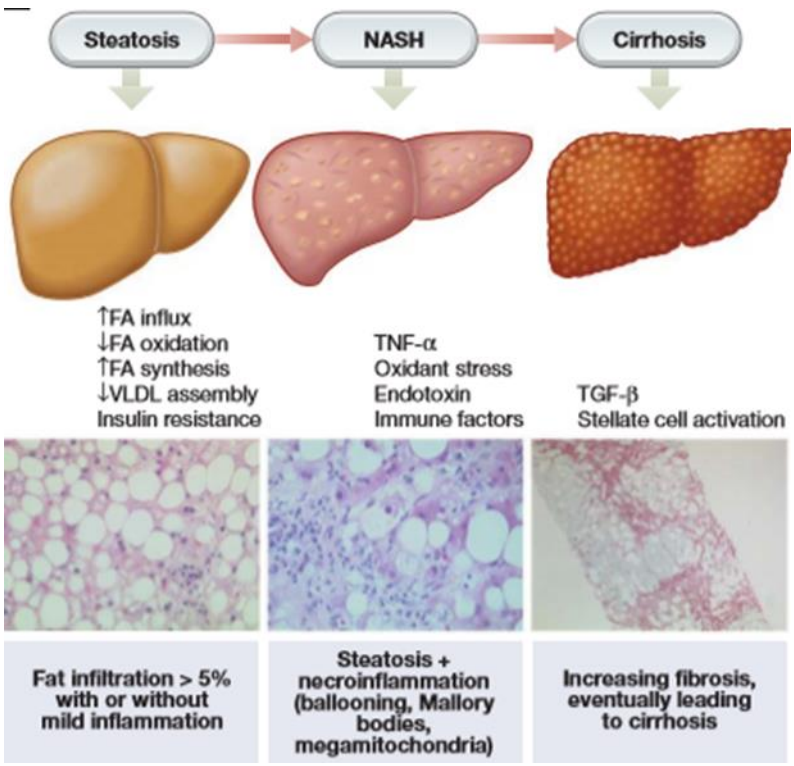
*NAFLD is the hepatic manifestation of the 'metabolic syndrome.
Metabolic syndrome is strongly associated with obesity, dyslipidemia, type 2 diabetes, and hypertension.
*NAFLD includes a spectrum of progressive liver disease ranging from fatty infiltration alone (steatosis) to fatty infiltration with inflammation (non-alcoholic steatohepatitis, NASH) and may progress to cirrhosis and hepatocellular cancer.

Pathogenesis of NAFLD.

Pathophysiology (two hit hypothesis)

- First hit: insulin resistance results in increased liver gluconeogenesis, increased adipose tissue lipolysis and decreased fatty acid oxidation. The released fatty acids are taken up

by the liver leading to increased lipogenesis. This results in increased fat storage and macrovesicular steatosis.
Steatosis cannot itself produce necroinflammatory activity [NASH] unless there is a combination of several different 2nd hit including:
1- fatty acid oxidation. Oxidative stress due to free radicals produced during react with DNA, lipids, protein, and carbohydrates leading to tissue injury
[Oxidative stress is defined as an imbalance between the production of free radicals and antioxidant defense.]
2-Direct lipotoxicity from fatty acids.
3-Gut-derived endotoxin causing hepatotoxic oxidative injury.
4-Cytokine release (TNF-α and interleukins (IL)-6) and immune-mediated hepatocellular injury.
5-Genetic predisposition.
The cellular damage and inflammation lead to stellate cell activation and development of hepatic Fibrosis eventually leading to cirrhosis.



Causes of NAFLD include
* 94% of obese patients (body mass index (BMI) > 30 kg/m2).
*67% of overweight patients (BMI > 25 kg/m2).
*25% of normal-weight patients found to be NAFLD.
*40% to 70% of patients with type 2 diabetes.
*Polycystic ovary syndrome *obstructive sleep apnea *small-bowel bacterial overgrowth, *Tamoxifen *amiodarone toxicity.

Clinical Features

NAFLD is a diagnosis of exclusion.it should be suspected as a cause of CLD inpatient with a negative history of alcohol consumption and have a negative serologic test for viral, Congenital and acquired causes of liver disease.

* Patients may be asymptomatic or presented with fatigue and right upper quadrant discomfort.

*NASH may present with complications of cirrhosis and portal hypertension.

Risk factors for disease progression are *age over 45 years* presence of diabetes * obesity (BMI > 30 kg/m2) * hypertension.

Investigations

*LFT may be normal in steatosis

*Elevations serum ALT and AST in NASH.

*Elevations of GGT.

*Ultrasound - liver appears 'bright' due to increased echogenicity.

*Fibroscan, CT, and MRI.

*Liver biopsy is the 'gold standard' investigation for diagnosis and assessment.

NASH characterized by [macro vesicular fat deposition, Mallory bodies, neutrophil infiltration, and pericellular fibrosis].

Management.

*Weight Reduction *Strict control of hypertension, diabetes, and lipid levels.

*Caffeine 2 cups of coffee daily may reduce fibrosis progression in patients with NASH.

*Metformin the first-line treatment in type 2 diabetes with NAFLD improve LFTs.

*Thiazolidinediones such as pioglitazone improve LFTs, inflammation and fibrosis.

*HMG-CoA reductase inhibitors (statins) do not ameliorate NAFLD but can be used to treat coexistent dyslipidemia.

*Liver Transplantation is reserved for end-stage cirrhosis.

Drug-induced liver injury

Liver injury induced by drugs that causing abnormalities in liver function after excluding other causes of liver injury.

the liver is the primary site of drug metabolism. Drug toxicity should be considered in the differential diagnosis of patients presenting with jaundice, abnormal liver function test, or acute liver failure. The presence of jaundice indicates severe liver damage. Most drug reactions are self-limiting. Patients with compensated cirrhosis have a lesser extent of impaired drug metabolism as compared to patients with decompensated cirrhosis.

Classification and examples of drug-induced hepatic injury.

1-Hepatocyte Necrosis

This involves direct hepatocyte membrane damage by the drug or a toxic metabolite.

It is dose-related

Causes include-paracetamol, Diclofenac, (COX)-2 inhibitors), and isoniazid. Granulomas may be seen in liver injury following the use of allopurinol, herbal remedies, and cocaine.

investigations –

*High serum transaminase concentrations, alkaline phosphatase < 3 times the upper limit of normal, the serum bilirubin may be elevated or within the normal range.

2-Cholestasis

Pure Cholestasis- selective interference with bile flow in the absence of liver injury.
Causes include high concentrations of estrogens (50 µg/day) were used as contraceptives.
Cholestatic hepatitis, which is characterized by inflammation and canalicular injury.
Causes include - Anabolic steroids, chlorpromazine, flucloxacillin, Co-amoxiclav is the most common antibiotic to cause abnormal LFTs but unlike other antibiotics, it may not produce symptoms until 10–42 days after it is stopped.

3-Steatosis

Microvesicular hepatocyte fat deposition due to direct effects on mitochondrial beta-oxidation **causes include** *Tetracycline's *Sodium valproate.
Macrovesicular hepatocyte fat deposition **causes include**- *Tamoxifen *Amiodarone toxicity produces a similar histological picture to NASH.

4-Vascular/Sinusoidal lesions.

*Alkylating agents used in oncology can damage the vascular endothelium and lead to hepatic venous outflow obstruction.

5-Hepatic Fibrosis. causes include*Methotrexate *Chronic overdose of vitamin A.
Risk factors for drug-induced hepatic fibrosis include pre-existing liver disease and high alcohol intake.

6-Tumors.

*Benign hepatic adenomas. caused by Prolonged intake of oral contraceptives.
*Angiosarcoma –caused by chronic exposure to vinyl chloride.

The diagnosis of acute drug-induced liver disease includes

•Tabulate the drugs taken-Prescribed, Self-administered.
• Establish whether hepatotoxicity is reported in the literature.
• Relate the time at which the drugs were taken to the onset of illness [4 days to 8 weeks] usual.
• Establish the effect of stopping the drugs on the normalization of liver biochemistry.
• Exclude other causes like Viral hepatitis and Biliary disease.
• Consider liver biopsy- if there is suspicion of pre-existing liver disease or if blood tests fail to improve when the suspect drug is withdrawn.

Treatment

*Withdrawal of the drug and general support.
*N-acetylcysteine for-acetaminophen toxicity
*L-carnitine may be helpful for valproate induced Microvesicular steatosis
*Ursodiol –for drug-induced cholestasis
*Glucocorticoids –for hypersensitivity reactions or patients with drug-induced autoimmune hepatitis

VASCULAR DISORDERS OF THE LIVER

Because the liver is a highly active organ and needs large oxygen requirements. This makes the liver at risk of ischaemic injury in settings of hypoperfusion.
*The risk of ischemia is lowered by the dual perfusion of the liver by the portal vein and hepatic artery. *Portal V with a low-pressure perfusion system that offers protection against the potential effects of arterial hypotension.
*The single outflow through the hepatic vein and the low-pressure perfusion system of the portal vein makes the liver vulnerable to venous thrombotic ischemia in the context of Budd–Chiari syndrome and portal vein thrombosis.