Liver Diseases

ALCOHOLIC LIVER DISEASE

- Alcohol is most widely abused agent, it is the 5th leading cause of death in USA due to: 1) Accidents, 2) Cirrhosis

- 80 – 100 mg/dl is the legal definition for driving under the influence of alcohol >> 44 ml of ethanol is required to produce this level in 70kg person
- 50 – 60gm/day → borderline effect
- Ethanol toxicity is dose dependant
  - — Short term ingestion of 80 gms/d of ethanol (8 bears) >> fatty change in liver (mild reversible hepatic changes)
  - — Long term ingestion (10-20yrs) of 160gm of ethanol per day >> severe hepatic injury
  - — In occasional drinkers, blood level of 200 mg/dl >> produces coma & death. At 300-400 mg/dl >> Resp. failure
  - — Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect due to metabolic tolerance explained by 5-10X induction of cytochrome P-450 and system that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetominophen
- Women are more susceptible to hepatic injury due to ↓ gastric metabolism of ethanol

■ Ethanol Metabolism:

- — Primarily in liver by enzymes.
- — Ethanol is Absorbed → Acetaldehyde → Acetic Acid

- — After absorption, ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level
- — less than 10% of absorbed ethanol is excreted unchanged in urine, sweat & breathe
- — Women have ↓ gastric alcohol dehydrogenase enzyme activity than men → They develop ↑ blood alcohol levels after drinking the same quantity
- — There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism
  e.g 50% of chinese , vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme → accumulation of acetaldehyde → facial flushing, tachycardia & hyperventilation

■ Mechanism of ethanol toxicity:

1. Fatty change
   - Shunting of lipid catabolism toward lipid bio-synthesis due to excess production of NADH over NAD in cytosol & mitochondria
   - Acetaldehyde forms adducts with tubulin & ↓ function of microtubules → ↓ in lipoprotein transport from liver
   - ↑ peripheral catabolism of fat → ↑ FFA (Free fatty acids) delivery to the liver
   - ↓ secretion of lipoproteins from hepatocytes
   - ↓ oxidation of FFA by mitochondria
2. Induction of cytochrome P-450 enhances the metabolism of drugs to toxic metabolites (e.g acetominophen) → ↑ the injury of the liver
3. Increase free radicals production due to (+) of cytochrome P-450 leads to membrane & protein damage within hypatocytes
4. Alcohol directly affect microtubular & mitochondrial function & membrane fluidity
5. Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack
6. Superimposed HCV infection causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)
7. Alcohol causes release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver
8. Alcohol causes regional hypoxia in the liver due to release of endothelins which are potent vasoconstrictors → ↓ hepatic sinusoidal perfusion
9. Alteration of cytokine regulation: ▼TNF is a major effector of injury ▼IL6 ▼IL8 ▼IL18

Liver Diseases

■ Forms of alcoholic liver disease:

1. Hepatic steatosis (90-100% of drinkers):

- Ethanol causes ↑↑ FA release, or its synthesis → ↑↑ free fatty acids in the blood → accumulate in liver

- Can occur following even moderate intake of alcohol → microvesicular steatosis
- Chronic intake → diffuse steatosis (liver is ◆large (hepatomegaly, 4 - 6 kg), ◆soft yellow & greasy)
- Continued intake → fibrosis
- Fatty change is reversible with complete absention from further intake of alcohol

- Clinical features: ◆Enlargement of liver, ◆Increased liver enz. ◆Severe hepatic dysfunction is unusual
- Reversible

2. Alcoholic hepatitis (1-35% of drinkers):

- Characteristic Findings:

1) Hepatocyte swelling (hepatomegaly) & necrosis:
   - Accumulation of fat, water & proteins
   - Cholestasis (reduced flow of bile from liver >> accumulation of bile within the liver in the cytoplasm of hypatocytes & small bile ducts)
   - Hemosiderin deposition in hepatocytes & Kupffer cells

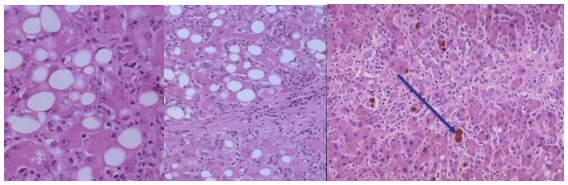
2) Mallory-hyaline bodies:
   - Eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments & other proteins
   - Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease

3) Neutrophilic reaction: infiltration of inflammatory cells→ further damage (necrosis) to hepatocytes

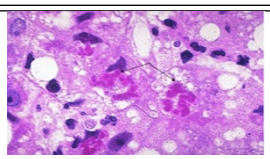
4) Fibrosis: (depends on the duration of alcohol intake)
   - Sinusoidal & perivenular fibrosis
   - Periportal fibrosis

5) Cholestasis: ↓↓ flow of bile from liver

6) Mild deposition of hemosiderin in hepatocytes & Kupffer cells



Alcoholic hepatitis
Fig. 1+2) Inflammatory infiltration.
Fig. 3) Cholestasis



Mallory-hyaline bodies
The arrows >> cytoplasmic granules

Mallory-hyaline bodies are also seen in:
- ▲Primary biliary cirrhosis
- ▲Wilson disease
- ▲Chronic cholestatic syndromes
- ▲Hepatocellular carcinoma

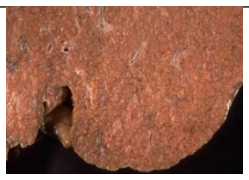
- Clinical features: ◆15-20 years of excessive drinking & and presence of injury, ◆Non-specific symptoms, malaise, anorexia, weight loss, ◆Enlargement of the liver & spleen, ◆increased LFT (liver function test)
- Each bout of hepatitis: ◆carries a 10-20% risk of death ◆With repeated bouts, cirrhosis appears in 1/3 of patients in few years.

Steatosis & hepatitis may develop independently

3. Cirrhosis (14% of drinkers/Only 8 - 20% of alcoholics):

- After chronic ingestion of alcohol → Liver toxicity
- Usually it develops slowly, but can develop rapidly in the pressure of alcoholic hepatitis (within 1-2 yrs)

- Clinical features: ◆Portal hypertension
- Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ s.t < 1 kg in weight, There's bile stasis
- Mallory bodies are only rarely evident at this stage
- Laennec cirrhosis = liver appears as scar tissue
- Irreversible



Liver with Alcoholic Cirrhosis with macronodules appearnce

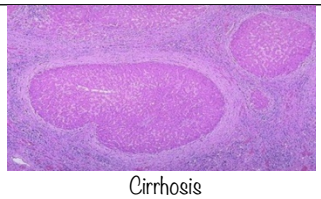
■ Causes of death in alcoholic liver disease: ◆Hepatic failure ◆Massive GI bleeding ◆Infections ◆Hepatorenal syndrome (Multiorgan failure) ◆HCC (hypatocellular carcinoma) in 3-6% of cases

Liver Diseases

CIRRHOSIS

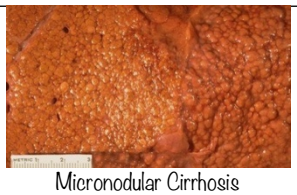
- It is a diffuse process characterized by fibrosis & the conversion of liver parenchyma into nodules.
- Main characteristics: ▲Bridging fibrous septae ▲Parenchymal nodules encircled by fibrotic bands ▲Diffuse architecture disruption

- Types (Depending on the diameter of the nodule):
  1. Micronodules < 3mm in diameter
  2. Macronodules > 3 mm in diameter
     - In alcoholic cirrhosis, micronodular → or mixed micro & macronodular



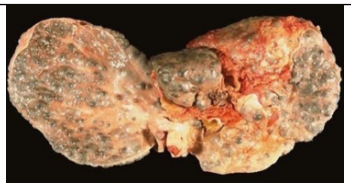
Cirrhosis

The normal liver parenchyma is replaced by parenchyma encircled with fibrous tissue that could be infiltrated by lymphocytes



Micronodular Cirrhosis

The liver surface is normally smooth, after cirrhosis it is changed into nodular one by a diffused process



Macronodular Cirrhosis

- Causes:
  - Common: ◆Chronic alcoholism (the most common cause in Western world) ◆Chronic viral infection HBV& HCV ◆Biliary disease ◆Hemochromatosis (Excessive deposition of iron in liver tissue) ◆Autoimmune hepatitis ◆Wilson disease ◆α-1-antitrypsin deficiency
  - Rare: ◆Galactosemia ◆Tyrosinosis ◆Glycogen storage disease III &IV ◆Lipid storage disease ◆Hereditary fructose intolerance ◆Drug induced e.g methyldopa
  - Cryptogenic cirrhosis: The underlying cause is unknown (10% of cases)

- Pathogenesis of cirrhosis:

- The mechanism of cirrhosis involves:
  1. Hepatocellular death (#Occurs over a long period of time #Accompanied with fibrosis #Regardless of the initial cause)
  2. Regeneration of hepatocytes
  3. Progressive fibrosis
  4. Vascular changes
- Cell death should occur over a long period of time & accompanied by fibrosis

Effect of Cirrhosis on ECM components and stellate cells		
	Normal	Cirrhosis
ECM Collagen (types I, III, V& XI)	Present only in: 1. Liver capsule 2. Portal tracts 3. Around the central vein	Deposited in the space of Disse → This interferes with the exchange function of hepatocytes
Delicate framework of type IV collagen & other proteins	Lie in the space of Disse.	
Perisinusoidal cells / stellate cells / Ito cells (Lie in the space of Disse)	Act as storage cells for: 1. Vitamin A 2. Fat	- The major source of collagen in cirrhosis. (How?↓) - Transforming growth factor β (TGF-β) stimulates these stellate cells (they're myofibroblast-like cells) to produce collagen - The stimuli for the activation of stellate cells & production of collagen: ▲Reactive oxygen species (Produced during inflammatory process) ▲Growth factors ▲Cytokines: TNF, IL-1, lymphotoxins

Liver Diseases

■ The vascular changes include:

- Loss of sinusoidal endothelial cell fenestration (normally responsible for the exchange between hepatocytes and the blood) → Associated with the loss of function of hepatocytes
- Development of vascular shunts as ▲Portal vein - hepatic vein ▲Hepatic artery – portal vein
  → That will result with defect in liver function in exchanging substances between blood and hepatocytes
- Loss of microvilli from hepatocytes → decreased transport capacity of the cells
  - Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange.
  - The movement of proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes and the plasma is markedly impaired.
  - These functional changes are aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity of the cell.

■ Clinical features of Cirrhosis: ◆Silent, asymptomatic (due to the functional capacity of the parenchymal hepatocytes), ◆Minimal non-specific symptoms: Anorexia, Weight loss, Weakness

■ Complications: ▼Progressive hepatic failure ▼Hepatocellular carcinoma ▼Portal hypertension

Portal Hypertension

■ Develops because of:

1. Increased resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules (which is characteristic for cirrhotic lesion)
2. Arterial-portal anastomosis in the fibrous bands → increase in the blood pressure in portal venous system (imposing arterial pressure on the normally low-pressure portal venous system)

■ Causes:

1. Prehepatic: ◆Portal vein thrombosis ◆Massive splenomegaly
2. Post hepatic: ◆Severe Rt. sided heart failure ◆Constrictive pericarditis ◆Hepatic vein out flow obstruction
3. Hepatic: ◆Cirrhosis ◆Schistosomiasis ◆Massive fatty change ◆Diffuse granulomatosis as sarcoidosis, TB ◆Disease of portal microcirculation as nodular regenerative hyperplasia

■ Clinical consequence of portal hypertension: ◆Ascitis ◆Portosystemic shunts ◆Splenomegaly ◆Hepatic encephalopathy

Ascitis

- Collection of excess fluid in peritoneal cavity
- Dx: It becomes clinically detectable when at least 500 ml have accumulated

■ Features: ◆Serous fluid ◆Contains as much as 3g/ml of protein (albumin) ◆It has the same concentration as blood of glucose, Na+, & K+ ◆Contains mesothelial cells & lymphocytes ◆Presence of Neutrophils = indicates that there is infection ◆Presence of RBCs = DISSEMINATED CANCER

■ Pathogenesis: Causes:

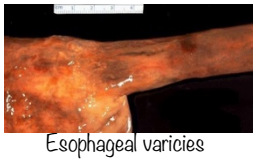
- Sinusoidal increase of blood pressure
- Hypoalbuminemia: decrease in synthesis of albumin in the liver → decrease the osmotic pressure → ascites
- Leakage of hepatic lymph into the peritoneal cavity (due to increase in duct flow)
- Renal retention of Na+ & water due to secondary hyperaldosteronism (↑ blood volume & the hydrostatic pressure → leakage of fluid to extra vascular space)

Normal thoracic duct lymph flow is 800-1000 ml/d in cirrhosis is 20L /d

Liver Diseases

Portosystemic Shunt

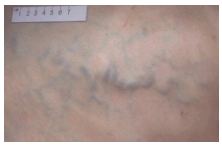
- Because of ↑ portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds (Where blood chooses to flow in less resistant circulation)



Esophageal varicies
(The dark linear areas)

■ Sites:

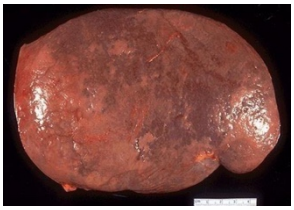
1. Around and within the rectum → Hemorrhoids
2. Gastroesophageal Junction → Varices (Gastroesophageal varicies = appears in 65% of patients with advanced cirrhosis and causes death in 50% of them due to upper GI bleeding)
3. Retroperitoneum
4. Falciform ligament of the Liver (Between the paraumbilical and abdominal wall collaterals) → Caput medusae



Caput medusae
The anterior abdominal wall for a patient with portosystemic shunt showing the dilated tortious veins

Splenomegaly

- Weight of the spleen: ♦Normal: <300grams, ♦Cirrhosis: 500-1000 grams
-Not necessarily correlated with other features of portal hypertension
-May result in hypersplenism (Excessive removal & destruction of RBCs or other blood elements in the spleen (which is enlarged and filled with blood) → resulting in thrombocytopenia)



Hepatic Encephalopathy

- It is a complication of acute & chronic hepatic failure
- Disturbance in brain function ranging from behavioural changes to marked confusion & stupor to deep coma & death
- The changes may progress over hours, days, or weeks.

■ Neurological signs: ♦Rigidity ♦Hyper-reflexia ♦Non-specific EEG ♦Seizures ♦Asterixis (Non-rhythmic, rapid extension-flexion movements of the head & extremities) ♦Brain shows edema & astrocytic reaction ♦no brain inflammation

■ Pathogenesis:

- Physiologic factors important in development of hepatic encephalopathy:

1. Severe loss of hepatocellular function
2. Shunting of blood around damaged liver

} Exposure of Brain to toxic metabolic products that accumulated in the blood especially ↑ NH3 level in blood → generalized brain edema impaired neuronal function, alteration in central nervous system amino acid metabolism

- In this condition, the liver is unable adequately remove toxins from the blood → This causes a buildup of toxins in your bloodstream, which can lead to brain damage.
- It's a terminal stage of portal hypertension and may lead to the death of the patient.

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اذكروا الله فيها وادعولنا

Liver Diseases

DRUG – INDUCED LIVER DISEASE

- Most of the drugs are metabolized in the liver, that's why chronic drug usage will be associated with chronic liver injury and disease process

■ Drug reactions are divided into:

1. Predictable (intrinsic)
   - depends on the dose (dose-dependent)
2. Unpredictable (idiosyncratic)
   - depends on:
   a-The immune response of the host to the antigenic stimulus (the drug)
   b-The rate at which the host metabolizes the agent

Predictable drugs	Unpredictable drugs
Acetaminophen	Chlorpromazine
Tetracycline	Halothane
Antineoplastic agents	Sulfonamides
CCL4	Methyldopa
Alcohol	Allopurinol

- Injury could be immediate or could take weeks to months after the drug uptake.
- Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic viral or autoimmune hepatitis.

■ Mechanism of drug injury:

1. Direct toxic damage of hepatocyte
   - Examples: ▲Acetaminophen ▲CCl4 ▲Mushroom toxins
2. Immune-mediated damage
   - Initiated by a drug that acts as an antigen → The antigen stimulates the immune reaction that targets the hepatocytes causing their damage

■ Patterns of injury within the liver: ⭐Hepatocellular necrosis, ⭐Cholestasis ⭐Steatosis, ⭐Steatohepatiti, ⭐Fibrosis, ⭐Vascular lesions, ⭐Granuloma, ⭐Neoplasms benign & malignant

■ Drugs that may cause acute liver failure: (important to recognize because they can be associated with severe liver damage and failure)

1. Acetaminophen: most common
   - it's the precursor of Paracetamol
   - Used in suicidal attempts
2. Halothane:
   - Anesthetic drug that can be associated with severe injury (even on first exposure) and it can progress into acute liver failure.
3. Antituberculosis drugs (Rifampin, Isoniazid)
4. Antidepressant monoamine oxidase inhibitors
5. Toxins such as CCL4 & mushroom poisoning

■ Morphology: ▲Massive necrosis → 500 – 700 gm liver ▲Submassive necrosis ▲Patchy necrosis

NOTE: The doctor deleted Fulminant hepatitis & Chronic Hepatitis from our slides & our recorded lectures

AUTOIMMUNE HEPATITIS

- It's one important form of hepatitis
- Chronic hepatitis with immunologic abnormalities
- Histologic features are similar to chronic viral hepatitis → that's why chronic viral and autoimmune hepatitis should be considered as cases of chronic hepatitis. Also, both of them should be differentiated from each other because their treatment differs.
- It can have either an Indolent or a severe course

Liver Diseases

- Dramatic response to immunosuppressive therapy (A very important characteristic of autoimmune hepatitis, Therefore, we need to differentiate between different causes chronic hepatitis as the treatments vary)

- Characteristic features of autoimmune hepatitis: (when they are present, we should consider disease process):
  - Female predominance (70%)
  - Negative serology for viral Antigens. 3-↑serum Immunoglobulins (>2.5 g/dl)
  - High titers of autoantibodies (80% of cases)
  - The presence of other autoimmune diseases as RA, thyroiditis, Sjogren syndrome, Ulcerative Colitis in 60% of the cases.

- Types of autoantibodies that can be found in these patients are:
  1. Anti-smooth muscle antibodies: ▼Anti actin ▼Anti-troponin ▼Anti-tropomyosin
  2. Liver/kidney microsomal antibodies: ▼Anti-cytochrome P-450 components ▼Anti UDP-glucuronosyl ▼Transferases
  3. Anti-soluble liver/pancreas antigen (the least common)

- Outcome: ◆Mild to severe chronic hepatitis ◆Full remission is unusual ◆Risk of cirrhosis is 5% (which is the main cause of death)

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

- Types:
  1. Steatosis (fatty liver)
  2. Steatohepatitis: ◆Hepatocyte destruction ◆Parenchymal inflammation ◆Progressive pericellular fibrosis

- Predisposing factors for nonalcoholic liver disease:
  1. Type 2 DM
  2. Obesity : body mass index (BMI)
     > 30 kg /m2 in Caucasians
     > 25 kg /m2 in Asians
  3. Dyslipidemia: ↑TG (triglycerides), ↑LDL, ↓HD

- Pathogenesis

- Fat accumulation in the liver can be due to a metabolic syndrome such as: ▲Insulin resistance, ▲Obesity, ▲Dyslipidemia
- Mechanism of fatty accumulation:

1.Impaired oxidation of fatty acids 2.Increased synthesis & uptake of FFA 3.Decreased hepatic sec. of VLDL → All these are associated with increasing free FA in the circulation and their deposition in the liver

- In addition, presence of any chronic anti-inflammatory process is associated with increase in inflammatory mediators such as: ↑TNF, IL6, chemokine → liver inflammation & damage to liver parenchyma.

- Clinical features:
  - NAFLD is the most common cause of incidental increase in transaminases that are produced by the liver.
  - Most patients are asymptomatic
  - Non-specific symptoms: Fatigue, malaise, RUQ (right upper quadrant) and discomfort
  - Severe symptoms may present.
  - Dx: Liver biopsy is required for diagnosis.
  - NAFLD may be a significant contributor to cryptogenic cirrhosis that is associated with undefined reason for cirrhosis.

Liver Diseases

HEMOCHROMATOSIS

- Excessive accumulation of body iron (liver & pancreas).
- Primary or secondary (genetic or acquired)

■ Causes of acquired hemosiderosis: 🔷Multiple transfusions, 🔷Blood condition that is characterized by the presence of ineffective erythropoiesis (thalassemia), 🔷Increased iron intake (Bantu sidrosis), 🔷Chronic liver disease

■ Features of hemochromatosis: 🔶Micronodular cirrhosis (all patients) 🔶D.M (75 – 80%) 🔶Skin pigmentation (75-80%) 🔶Cardiomegaly, joints disease, testicular atrophy

- skin pigmentation in patients with liver disease along with DM >> we should think of hemochromatosis as a possible disease

🔶Symptoms appear 5th – 6th decades and not before age of 40.

🔶Male:Female ratio is 5-7: 1 (more common in males)

■ Genetic hemochromatosis (4 variants)

- The most common form is autosomal recessive disease of adult onset caused by mutation in the HFE gene on chromosome number 6.

■ Pathogenesis:

- Primary defect in hemochromatosis is in intestinal absorption of dietary iron.
- Normally, the total body iron 2-6gm in adults , 0.5gm in liver mostly in hepatocytes .
- In disease >50gm Fe accumulated → 1/3 in liver
- In herediatary hemochromatosis, there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5-1 gm/yr (that's why the disease is usually after the age of 40)

- The gene responsible is HFE gene located on chromosme 6 close to HLA gene complex.
    - HFE gene regulates the level of hepcidin hormone synthesized in liver
    - Hepcidin → inhibition of Fe absorption from intestinal enterocytes.
    - HFE gene deletion → decreasing the hepcidin in the blood and causing iron overload due to the increased absorption of iron.

■ Two mutation can occur in HFE gene:

1. Mutation at 845 nucleotide → tyrosine substitution for cystine at AA 282 site (C282 Y)
2. Aspartate substitution for histidine at AA 63 (H63D) (less common) [AA refers to Amino Acid]

- 10% of the patients have other gene mutations

- Carrier rate for C282Y is 1/70 cases
- Homozygosity is 1/200 cases
- 80% of patients are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation
- 10% of patients are either homozygous for H63D mutation or compound heterozygous for both types of gene mutations (C282Y/H63D mutation)

- Excessive Fe deposition in the tissues particularly in the liver→ toxicity of the tissues and damage to hepatocytes due to:

1. Lipid peroxidation
2. Stimulation of collagen formation
3. DNA damage

Liver Diseases

- Morphological changes:
  1. Deposition of iron in the form of hemosiderin in different organs like: Liver, Pancreas, Myocardium, Pituitary, Adrenal, Thyroid & parathyroid, Joints, Skin
  2. Cirrhosis
  3. Pancreatic fibrosis associated with damage to the islets of Langerhans and development of DM

- Examination of these tissues will show: ▼No inflammation, ▼Fibrosis, ▼Cirrhosis in liver, ▼Joint involvement (Synovitis), ▼Polyarthritis (pseudogout), ▼Pigmentation of liver and skin, ▼Fibrosis of pancreas & myocardium, ▼Atrophy of testes because of excessive deposition of iron and tissue damage.

- Clinical presentation: ◆Hepatomegaly ◆Abdominal pain ◆Skin pigmentation ◆D.M ◆Cardiac dysfunction ◆Atypical arthritis ◆Hypogonadism ◆↑ Serum Fe ferritin
- ◆These patients can have HCC (hepatocellular carcinoma) 200x higher in the risk compared to normal individuals
- ◆M:F 5-7:1
- ◆5th-6th decades

Reload/Refresh the same link after 2 days for lecture 5 & 6

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