

Liver

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- The liver is the largest, most versatile organ in the body
 - It consists of two main lobes that, together, weigh from 1400-1600 g in the normal adult
 - It has an abundant blood supply receiving about 15 ml/minute from two major vessels: the hepatic artery and the portal vein ②
 - The hepatic artery a branch of the aorta, contributes 20% of the blood supply and provides most of the oxygen requirement
 - The portal vein, which drains the gastrointestinal tract, transports the most recently absorbed material from the intestine to the liver

Liver function

- **The excretion of bile:** Total bile production averages about 3 L per day, although only 1 L is excreted.
- The primary bile acids, cholic acid and chenodeoxycholic acid, are formed in the liver from cholesterol. The bile acids are conjugated with the amino acids glycine or taurine, forming bile salts.
- During fasting and between meals, bile acid pool is concentrated up to 10-fold in the gallbladder.
- When the conjugated bile acids (salts) come into contact with bacteria in the terminal ileum and colon, dehydration to secondary bile acids occurs, and these secondary bile acids are subsequently absorbed.
- The absorbed bile acids enter the portal circulation and return to the liver, where they are reconstituted and reexcreted. The enterohepatic circulation of bile occurs 2-5 times daily.

Bilirubin

- The principal pigment in bile is derived from the breakdown of hemoglobin when aged red blood cells are phagocytized by the reticuloendothelial system, primarily in the spleen, liver, and bone marrow
- When hemoglobin is destroyed, the protein portion- globin-is reused by the body, The iron enters the body's iron stores and is also reused. The porphyrin is broken down as a waste product and excreted
- Bilirubin is transported to the liver in the bloodstream bound to albumin where it is conjugated with diglucuronide on its two carboxylic acids and excreted to the intestine.
- The normal flora in the colon oxidize it further where it is reabsorbed, excreted to the stool (urobilin, reddish brown) or excreted in kidney (urobilinogen, colourless)

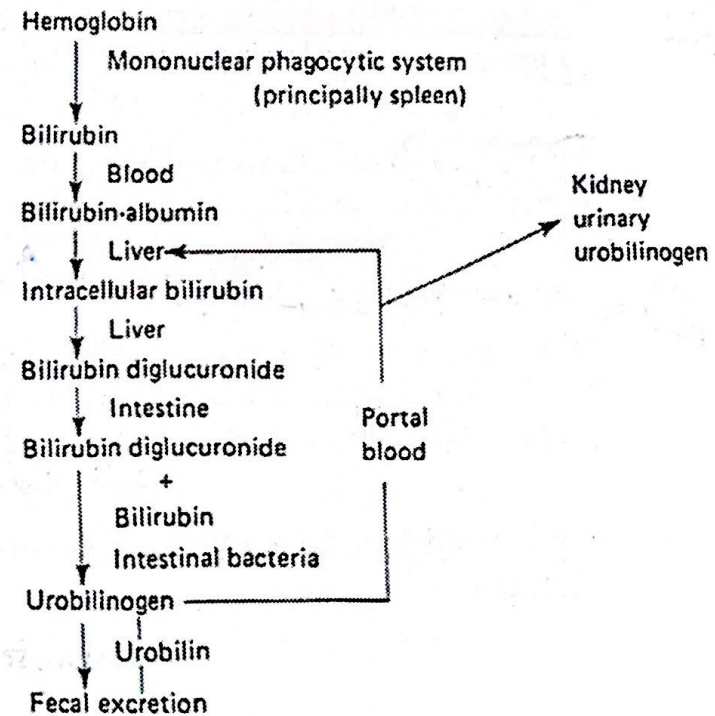
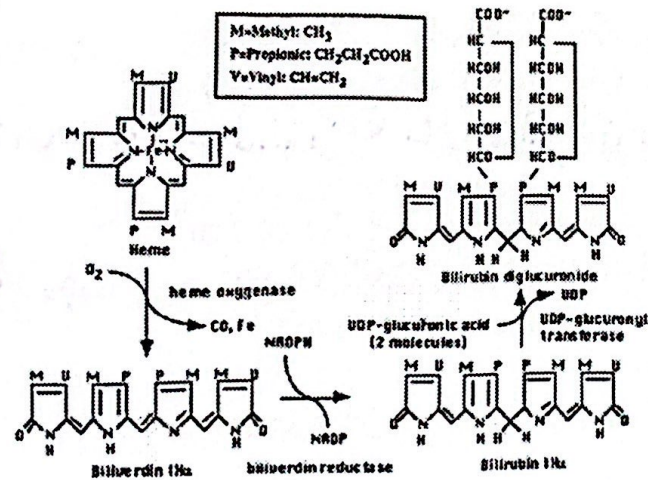
bilirubin bound to albumin \Rightarrow conjugated

bilirubin is free in bloodstream \Rightarrow unconjugated

Bilirubin $\xrightarrow[\text{(oxidation)}]{\text{intestine normal flora}}$ urobilin (reddish brown)

bilirubin $\xrightarrow{\text{kidney}}$ urobilinogen (no color)

Bilirubin



Bilirubin → المادة التي تسبب صفير الجفون والجلد

- When the bilirubin concentration in the blood rises, the pigment begins to be deposited in the sclera of the eyes and in the skin. This yellowish pigmentation in the skin or sclera is known as jaundice, or icterus
- The cause can be:

① hemolytic anemia: انحلال الدم

② الذي يرتفع في الدم:

↳ unconjugated bilirubin

③ ما بين بال urin

④ ما يرتفع كثير بالدم لذلك

قدرة liver على التخلص من

كميات كبيرة من unconjugated bilirubin

طبيعية واما عن مشكلة بال liver

• hyperbilirubinemia

➤ Prehepatic: results when an excessive amount of bilirubin is presented to the liver for metabolism, such as in hemolytic anemia. This type of jaundice is characterized by unconjugated (direct) hyperbilirubinemia

- The serum bilirubin levels rarely exceed 5 mg/dL because the normal liver is capable of handling most of the overload. bilirubin will not appear in the urine in this type of jaundice.

↑ urobilin

↑ urobilinogen

= عند الأطفال حديثي الولادة تكون Liver Function غير كاملة عنم فبسر مع hyperbilirubinemia

Bilirubin

بكون في مشكلة بال liver
نتيجة hepatitis أو تشمع الكبد.

Hepatic: Impaired cellular uptake, defective conjugation, or abnormal secretion of bilirubin by the liver cell are the main causes of this kind of jaundice
↳ secretory problem.

→ ↑ unconjugated
↑ conjugated-
secretory problem

➤ **Posthepatic:** results from the impaired excretion of bilirubin caused by mechanical obstruction of the flow of bile into the intestine. This may be due to gallstones or a tumor

↑ conjugated (Liver function is normal)

بيلجل قارر بيلجل امراض لا
gall bladder
bilirubin

➤ When bile ceases to flow into the intestine, there is a rise in the serum level of conjugated bilirubin and the stool loses its source of normal pigmentation and becomes clay-colored
له لون بليت

→ ↓ urobilinogen
↓ urobilin

➤ Conjugated bilirubin appears in the urine, and urine urobilinogen levels decrease

له لون مشرقا عدي يوصل لا intestine

ارتفاع bilirubin حتى كثير مشكلة بالنسبة للكبار، هو مشكلة خطيرة بالنسبة لك أطفال لانه
ما يكون ممكن عندهم BBB ويمكن يدخل bilirubin للدماغ ويسبب مشاكل كبيرة عند الطفل.

Major Synthetic Activity

- ①
- > The liver plays an important role in **plasma protein production**, synthesizing albumin and the majority of the α and β -globulins. All the **blood-clotting factors** (except VIII) are synthesized in the liver

• صافي بروتينات

في حالة Chronic Liver dysfunction

- ②
- > The deamination of glutamate in the liver is the primary source of ammonia, which is then converted to urea → hyperammonemia.

← ما ينتج في الكبد

- ③ ④ ⑤ ⑥
- > Glycogenesis and gluconeogenesis, lipogenesis, metabolism of cholesterol into bile acids, Very-low-density lipoproteins (transport TG into the tissues), High-density lipoproteins, phospholipids are all made in the liver

• دور كائن المشكلة بالكبد acute عادي

يمكن خلال يومين ثلاثة تنحل ويصح liver طبي

- ⑦
- > The formation of **ketone bodies** (in malnutrition)

← يستخدم Brain كمصدر للطاقة في حالة نقص glucose

- ⑧
- > The liver is the storage site for all fat-soluble vitamins (A, D, E, and K) and several water-soluble vitamins, such as B12 and is responsible for the conversion of carotene into vitamin A

Liver dysfunction → ↓ Clotting factors → ↑ prothrombin time → ↑ Bleeding.

• clotting factor activated by vitamin K (as CoFactor)

= ال bile يساعد على امتصاص الدهون والفيتامينات الذائبة فيها (Vitamin K).

له اذا ما في تصنيع bile ← ما في امتصاص Vit K ← ما في activation لل clotting factors
• يعني لا تصنيع ولد activation.

Synthesis of liver enzymes

(10)

- > Many enzymes are synthesized by liver cells, but not all of them have been found useful in the diagnosis of hepatobiliary disorders, this includes:

(not specific) Kidney و liver ← موجود بال

- > Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which escape into the plasma from damaged liver cells

very specific for liver

differential test.

- > Alkaline phosphatase (ALP) and 5'-nucleotidase (5NT): induced or released when the canalicular membrane is damaged and biliary obstruction occurs

← موجود بالعظم و بال Gall bladder

- > γ -glutamyltransferase (GGT): increased in both hepatocellular and obstructive disorders

له يكون مرتفع في حالة liver damage بسبب alcohol .

= انزيم (ALT) موجود بكثرة في خلايا Liver ← Liver specific ← من يمكن تكميته مرتفع لو المشكلة Gall bladder
= بقيس (ALT) و AST اذا الئين مرتفعين معناها المشكلة بال Liver .

= انزيم ALP يكون موجود بتركيز مرتفع ب ٣ حالات ← ١. Gall bladder disease ٢. pregnant woman ٣. Children .
* بين اذا كانت المشكلة Gall bladder عند طريق (5NT) يكون مرتفع بسبب اذا كانت المشكلة Gall bladder .

Detoxification and Drug Metabolism

... from potentially injurious substances

Detoxification and Drug Metabolism

- The liver protects the body from potentially injurious substances absorbed from the intestinal tract and toxic by-products of metabolism.
- The most important mechanism in this detoxification activity is the microsomal drug-metabolizing system of the liver. It is responsible for many detoxification mechanisms, including oxidation, reduction, hydrolysis, hydroxylation, carboxylation, and demethylation that convert many insoluble compounds into other forms that are less toxic or more water-soluble and, so excretable by the kidney.

phase 1

phase 2

Conjugation with moieties, such as glycine, glucuronic acid, sulfuric acid, glutamine, acetate, cysteine, and glutathione, occurs mainly in the cytosol or smooth ER. This mechanism is the mode of bilirubin and bile acid excretion.

Disorders of the liver jaundice

> Jaundice, or icterus: is the yellowish discoloration of the skin and sclerae resulting from hyperbilirubinemia

> Although the upper limit of normal for total serum bilirubin is 1 mg/dL, jaundice is not clinically apparent until the bilirubin level exceeds 2-3 mg/dL

↔ ما بين الصفر من لون الشرج فيمنهم من لون العين
> In African American or Asian patients, yellowing of the sclerae may be the only clinical evidence of jaundice

> Except in infants, hyperbilirubinemia is generally well tolerated. in adults

BBB ما يكون دكتور
> In infants, hyperbilirubinemia (>15-20 mg/dL) may be associated with kernicterus (serious disorder of the CNS resulting from increased bilirubin levels) it only occurs in infants because the immature CNS does not have a well-developed blood-brain barrier

حتى الشخص المريض Jaundice لزم يكون bilirubin level بين (2-3 mg/dL)

Jaundice

Jaundice

- Although all cases of jaundice result from hyperbilirubinemia, not all are caused by hepatic dysfunction.
- hyperbilirubinemia may also result from erythrocyte destruction, or hemolysis in patients with normal liver function
- Hypercarotenemia (excessive ingestion of vitamin A) may produce skin discoloration indistinguishable from that of hyperbilirubinemia. In hypercarotenemia, the sclerae are usually not discolored.

لے الجلد بكون اُصفربس العيون لک

Cirrhosis

تشمع الكبد

- Cirrhosis refers to the irreversible scarring process by which normal liver architecture is transformed into abnormal nodular architecture.
↳ nodules may be macro or micro
- One way to classify cirrhosis is by the appearance of the liver (by the size of the nodules). These conditions are referred to as **macronodular** and **micronodular** cirrhosis, although **mixed** forms occur
- In the USA, Canada, and Western Europe, the leading cause of cirrhosis is alcohol abuse, which leads to a micronodular type of cirrhosis.
↳ accumulation of iron in liver (رسم الكبد الذي يتجمع فيه الحديد)
- Other causes of cirrhosis include hemochromatosis, postnecrotic cirrhosis (occurs as a late consequence of hepatitis), and primary biliary cirrhosis (an autoimmune disorder).
↳ after hepatitis.

Cirrhosis

يمكن الرصد يعيش فترة طويلة وهو مع تشع كبد
ليس مشكلته بال complications

- > Cirrhosis is a serious disorder and one of the ten leading causes of death in the United States. It causes many complications:

⑤ > Portal hypertension results when blood flow through the portal vein is obstructed by the cirrhotic liver. This may result in splenomegaly and esophageal varices (may rupture and lead to fatal hemorrhage) → تضخم الكبد
ما في مسار يدخل فيه الدم جوا
السراريين بالمريء يتلفش تتعبر دما

- > The synthetic ability of the liver is reduced, causing hypoalbuminemia and deficiency of the clotting factors, which may lead to hemorrhage

> Ascitic fluid may accumulate in the abdomen → hypoelectrolytes / hypervolemia
سبب و osmolality قلت عن ر
قل albumin في الدم .

- > Although some patients with cirrhosis are capable of prolonged survival, generally this diagnosis is an ominous one

Tumors

- On a worldwide basis, primary malignant tumors of the liver, known as hepatocellular carcinoma are an important cause of cancer mortality
- سببه غالباً التهاب كبدى - hepatitis
- In the United States, these tumors are relatively uncommon. Most cases of hepatocellular carcinoma can be related to previous infection with a hepatitis virus.
- أعتب ال Liver Cancer هو مش benign
- Liver is frequently involved secondarily by tumors arising in other organs. Metastatic tumors to the liver from primary sites, such as the lung, pancreas, gastrointestinal tract, or ovary, are common. Benign tumors of the liver are relatively uncommon
- = صعب كشفه بسريره ولذا علاجه يكون صعب
- Whether primary or secondary any malignant tumor in the liver is a serious finding with a poor prognosis
- The only hope For cure relies on surgical resection, which is usually impossible. Patients with malignancies of the liver usually have a survival measured in months

Reye's Syndrome *(viral infection in children and give aspirin)*

- Reye's syndrome is a disorder of unknown cause, involving the liver and arising primarily in children,
- It is a form of hepatic destruction that usually occurs following recovery from a viral infection, such as varicella (chickenpox) or influenza.
- It has been related to aspirin therapy. Shortly after the infection, the patient develops neurologic abnormalities, which may include seizures or coma
- Liver functions are always abnormal, but the bilirubin level is not usually elevated
- Without treatment, rapid clinical deterioration, leading to death, may occur

Drug- and Alcohol-Related Disorders

- Many drugs and chemicals are toxic to the liver. This toxicity may take the form of overwhelming hepatic necrosis, leading to coma and death, or it may be subclinical and pass entirely unnoticed
- In small amounts, alcohol may cause mild, inapparent injury. Heavier consumption leads to more serious damage, and prolonged, heavy use may lead to cirrhosis (exact amount is unknown)
- Certain drugs, including tranquilizers (phenothiazines), certain antibiotics, antineoplastic agents, and anti-inflammatory drugs, may cause liver injury
- Usually this is mild and manifested only by elevation of liver function tests, which return to normal when the drug is discontinued. This may lead to massive hepatic failure or cirrhosis
- The most common drug associated with serious hepatic injury is acetaminophen. When taken in massive overdose, it produces fatal hepatic necrosis unless rapid treatment is initiated

مستوى معروف كمية ما
السكر

(atorvastatin) +

Lethal dose 15g