Biochemistry Team 435

جامعة الملك سعود
King Saud University

LIVER FUNCTION TESTS.

* Please check out this link to know if there are any changes or additions.

Revised by

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Color index: Important | Doctors notes | Further explanation.

(Extra/ circulation system of the liver)

Unlike most organs, which have a single blood supply, the liver is an extremely vascular organ that receives its blood supply from <u>two sources</u>:

1. **The hepatic artery**

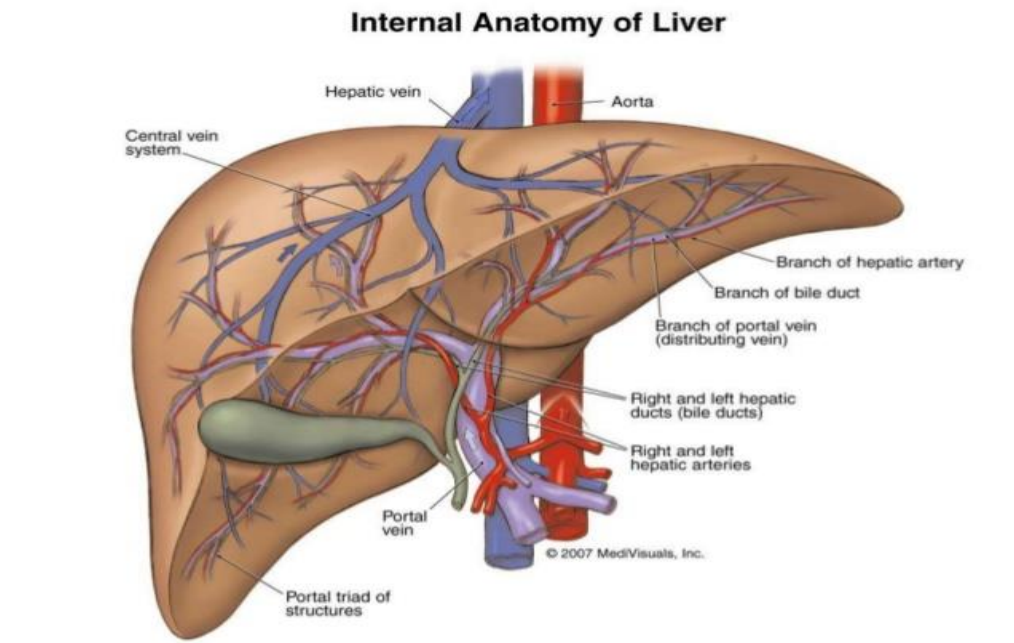
A branch of the aorta, supplies oxygen-rich blood from the heart to the liver and is responsible for providing approximately 25% of the total blood supply to the liver

2. **The portal vein**

Supplies nutrient-rich blood (collected as food is digested) from the digestive tract, and it is responsible for providing approximately 75% of the total blood supply to the liver.

The two blood supplies eventually merge and flow into the **sinusoids**, which course b tween individual hepatocytes.

The liver is drained by a collecting system of veins that empties into the hepatic veins and ultimately into the inferior vena cava



❖ **<u>The excretory system of the liver:</u>**

Bile canaliculi → intrahepatic ducts → the right and left hepatic ducts → the common hepatic duct the common hepatic duct is eventually joined with the cystic duct of the gallbladder to form the common bile duct. Combined digestive secretions are then expelled into the duodenum

OBJECTIVES:

- ✓Understand the major metabolic functions of the liver and causes of liver dysfunction.
- ✓Discuss markers of liver function tests such as liver enzymes, bilirubin, albumin and prothrombin time that can diagnose hepatic injury.

Extra (for better understanding)

❖ **Liver function tests:**

It is a group of blood tests for liver functions

❖ What is the liver functions?

The liver performs 4 major functions:

1. Excretion/secretion
2. Synthesis
3. Detoxification
4. Storage.

- The liver is so important that if the liver becomes nonfunctional, death will occur with 24 hours due to hypoglycemia. Although the liver is responsible for too many functions here we are focusing on the 4 major functions mentioned previously.

- We can say that "liver function tests" is a misnomer because we are not really measuring liver functions, instead we are measuring its dysfunctions

- There is no one test which can tell you about all the liver functions. Because the liver is a large organ and it has too many functions

- So in order to see the whole picture we take a series of tests "battery of tests" to see if there is any dysfunction. LFTs can detect how much damage is their + what is being damaged

❖ Indications of liver function tests

- Alcoholics
- The use of some medications that can cause a liver damage
- General symptoms → Anorexia / abdominal pain / nausea / vomiting

Major Metabolic Functions of the Liver

Synthesis

- Plasma proteins (albumin/globulins)
- cholesterol, triglycerides and lipoproteins

Detoxification and excretion

- Ammonia to urea (urea cycle) , bilirubin , cholesterol , drug metabolite

storage

Vitamins A, D, E, K and B_{12}

Production of bile salts

Helps in digestion

Some example of liver dysfunction

Hepatocellular disease

Cholestasis (obstruction of bile flow)

Liver cirrhosis

Jaundice (increased bilirubin)

Genetic Disorders → **Hemochromatosis** (iron storage)

Steatosis (fatty liver)

Hepatitis

Liver cancer

Liver function tests

- **What's "Liver function tests"?**
  - **Noninvasive methods** for screening of liver dysfunction.
- **When they're performed?**
  - They're performed **after** a simple blood test.
- **Benefits:**
  - Help in **identifying** general type of disorder
  - **Assess severity** and allow **prediction** of outcome
  - Disease and treatment **follow up**

"screening" is not a diagnosis (because it's not fully accurate), so we need to do an another test for confirmation or search for other markers.

- For dose adjustment
- To know if the patient is responding to the treatment or not

They're broadly classified as

Tests to detect hepatic injury

- Mild or severe; acute or chronic
- Nature of liver injury (hepatocellular or cholestasis)

Tests to assess hepatic function

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liver function tests

LFTs

Common serum liver chemistry tests

Liver chemistry test:	Clinical implication of abnormality:
Alanine aminotransferase	**Hepatocellular damage.**
Aspartate aminotransferase	
Bilirubin	Cholestasis, impaired conjugation, or biliary obstruction.
Alkaline phosphate	Cholestasis, infiltrative diseases, or biliary obstruction.
Prothrombin time	Synthetic function.
Albumin	
γ-glutamyltransferase	Cholestasis or biliary obstruction.
Bile acids	

Limitations of liver function tests

- Normal LFT values do not always indicate absence of liver disease → because the liver has very large reserve capacity
- Asymptomatic people may have abnormal LFT results. → So the diagnosis should be based on clinical examination

Liver functions tests

- Group I: Markers of liver dysfunction
  - **Serum bilirubin:** total and conjugated.
  - **Urine:** bile salts and urobilinogen
  - **Prothrombin Time** (clotting time)
  - **Total protein**, **serum albumin** and **albumin/globulin ratio**
- Group II: Markers of hepatocellular injury
- Group III: Markers of cholestasis

What is "Bilirubin"?

- A byproduct of red blood cell breakdown.
- It is the yellowish pigment observed in jaundice.

High bilirubin levels are observed in:

- **gallstones**
- **acute and chronic hepatitis**

Normal serum bilirubin levels	
Total bilirubin	0.2 to 0.8 mg/dL
Unconjugated/free/indirect (bilirubin-albumin complex)	0.2 to 0.7 mg/dL
Conjugated/direct	0.1 to 0.4 mg/dL
Abnormal serum bilirubin levels	
Latent jaundice	Above 1 mg/dL
Jaundice	Above 2 mg/dL

Liver functions tests

- Group I: Markers of liver dysfunction
  - **Serum bilirubin:** total and conjugated.
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Bilirubin levels and jaundice

Class of Jaundice	Raised Bilirubin	Causes
Pre-hepatic → "Hemolytic jaundice".	Unconjugated ONLY!	• Abnormal red cells • Antibodies; drugs and toxins; Thalessemia.Hemoglobinopathies . Gilbert's, Crigler-Naajjar syndrome
Hepatic or Hepatocellular → "Hepatocellular jaundice".	Unconjugated & conjugated	• Viral hepatitis, toxic hepatitis • Intrahepatic cholestasis
Post-hepatic → "Obstructive jaundice".	Conjugated ONLY!	• Extrahepatic cholestasis; gallstones; tumors of the bile duct • carcinoma of pancreas

Preheated and post hepatic jaundice, as the names imply, are caused by abnormalities outside of the liver, either before, as in "pre hepatic," or after, as in "post hepatic." In these conditions, liver function is normal or it may be functioning at a maximum to compensate for abnormalities occurring elsewhere.
This is not the case with hepatic jaundice, where the jaundice is due to a problem with the liver itself—an intrinsic liver defect or disease.

Bilirubin

السلايدات فيها صور بس بدون شرح، الشرح اللي بسلايدز ١٠، ١١ عبارة عن الكلام اللي قالوه الدكاتره بأسلوب لبنكوت – الشرح بعد معاد بالفزيولوجي بمحاضرة البليروبين.

❖ Degradation of heme:

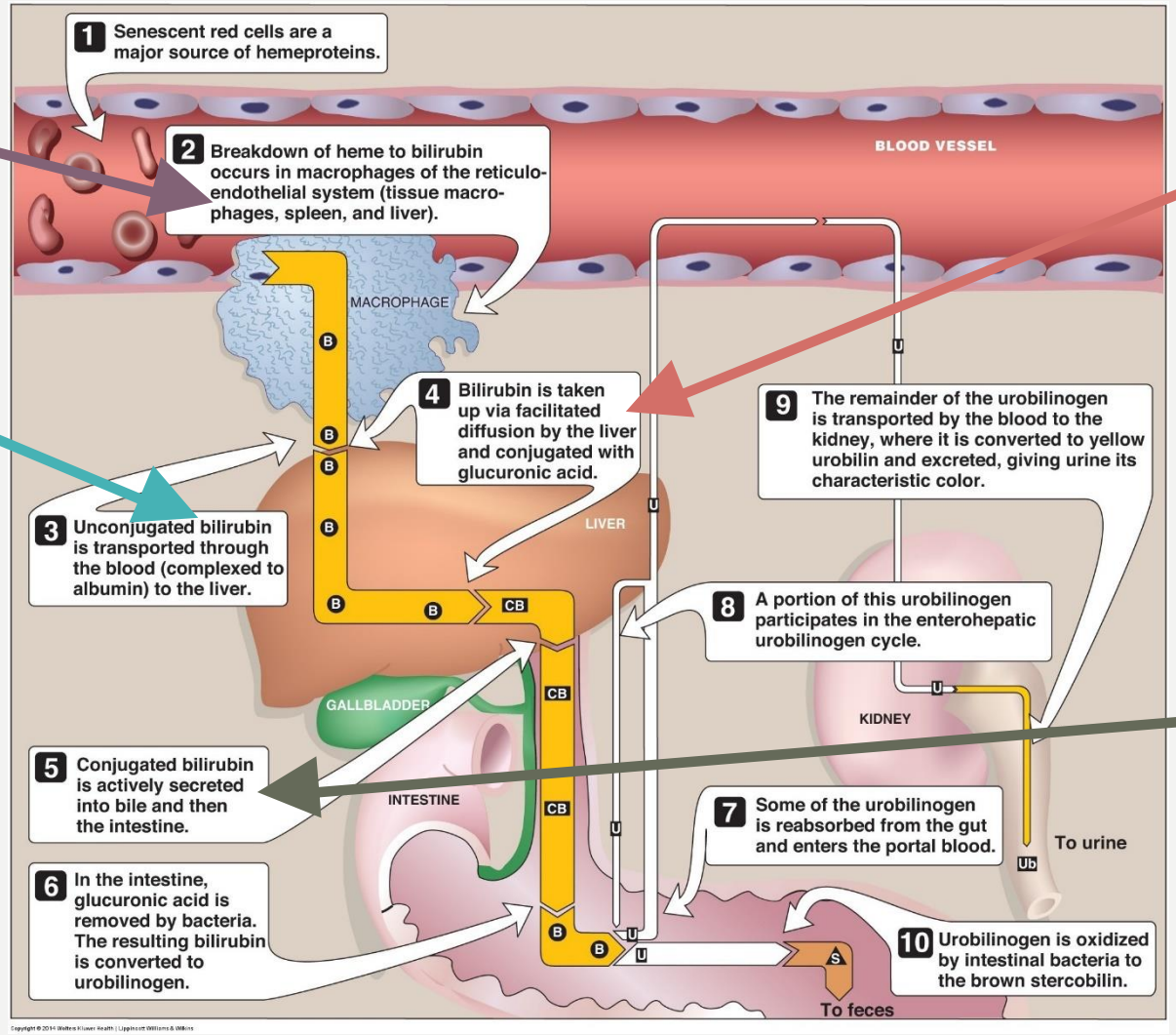
After approximately 120 days in the circulation, red blood cells are taken up and degraded by the reticuloendothelial system, particularly in the liver and spleen (RBCS → heme + globin + iron).

1. Formation of bilirubin

In the **macrophages** of the reticuloendothelial system, the heme → bilirubin.

2.Uptake of unconjugated bilirubin by the liver:

- Bilirubin is only **slightly soluble** in plasma so it is transported to the liver by binding non-covalently to **albumin**.
- Bilirubin **dissociates** from the carrier albumin molecule, enters a hepatocyte **via facilitated diffusion**, and binds the protein **ligandin**.



3.Conjugation of the bilirubin

- In the hepatocyte, the solubility of bilirubin is **increased** by the addition of 2 molecules of glucuronic acid.
- by microsomal bilirubin glucuronyl- transferase using uridine diphosphate-glucuronic acid (2-UDP-GA) as the glucuronate donor.

4. Secretion of bilirubin into bile

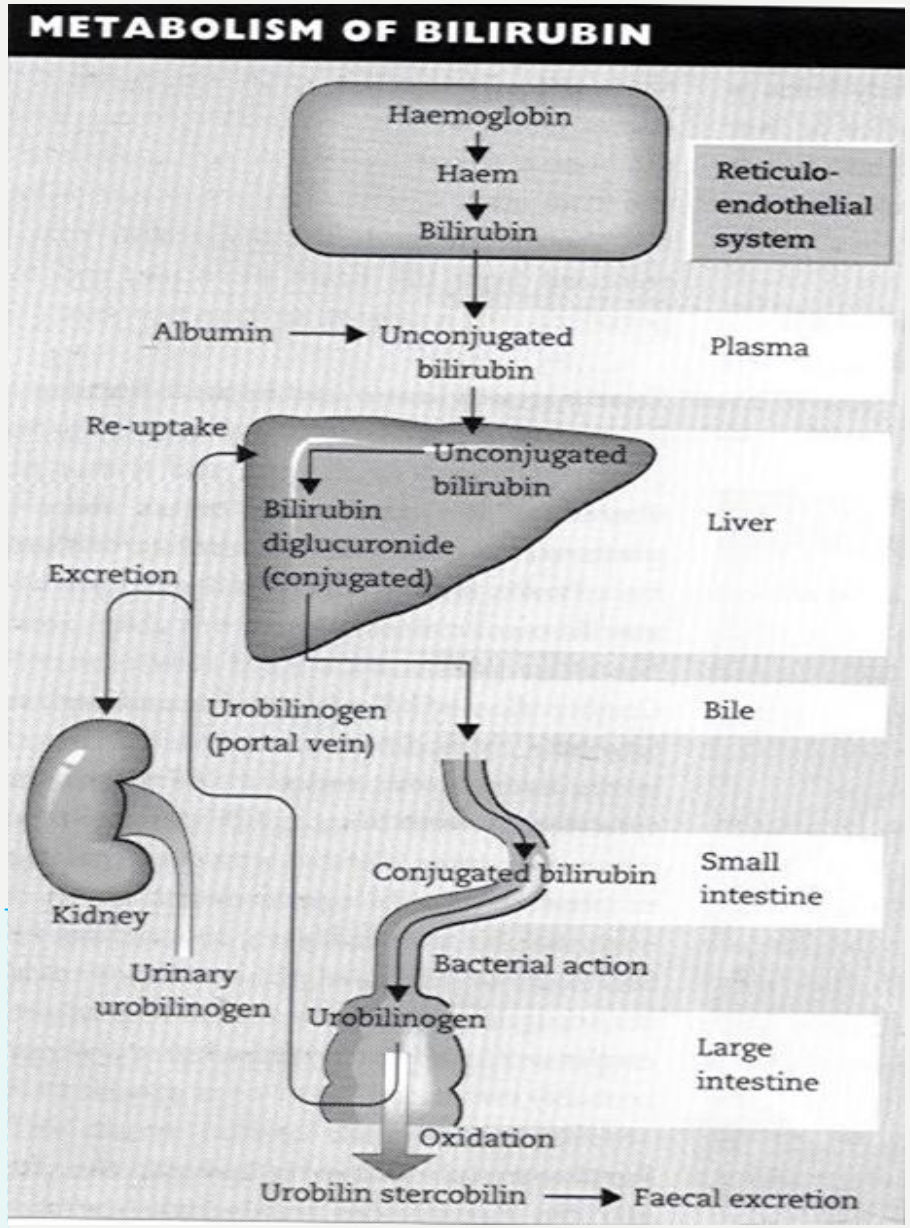
conjugated bilirubin is actively transported against a concentration gradient into the bile canaliculi and then the **bile and then the intestine**.

Bilirubin

5. Formation urobilins in the intestine

Conjugated bilirubin is hydrolyzed and reduced by bacteria in the gut to yield **urobilinogen** "colorless".

- **Feces:** **Most of the urobilinogen is** oxidized by intestinal bacteria to **stercobilin**, which gives feces the characteristic **brown color**.
- **Portal blood:** However, **some of the urobilinogen is** reabsorbed from the gut and enters the portal blood.
- **Liver:** A portion of this urobilinogen participates in the **enterohepatic** urobilinogen cycle in which it is taken up by the **liver**, and then **resecreted into the bile**.
- **Kidneys:** The remainder of the urobilinogen is transported by the blood to the **kidney**, where it is converted to **yellow urobilin** and excreted, giving urine its characteristic color.



Note: Fate of urobilinogen (3):

1. Gets metabolized in the large intestine and then excreted in feces. (stercobilin).
2. Reabsorbed through intestinal mucosa into → Portal vein → Liver "enterohepatic circulation"
3. Excreted in urine "as urobilin".

What is the purpose of conjugation?

Makes bilirubin soluble.

Where it happens?

Liver's ER.

What's the form of bilirubin which comes to the bile?

Conjugated.

Bilirubin has the ability to **function** as an **antioxidant.**

Liver functions tests

- Group I: Markers of liver dysfunction
- Group II: Markers of hepatocellular injury
- Group III: Markers of cholestasis

Serum bilirubin: total and conjugated.

Urine: bile salts and urobilinogen

Prothrombin Time (clotting time)

Total protein, serum albumin and **albumin/globulin ratio**

Urobilinogen (UBG) and bile salts

- Most UBG is metabolized in the large intestine, a fraction is excreted in urine (less than 4 mg/day). (احفظوه)
- Normally bile salts are NOT present in urine.
- **Obstruction in the biliary passages causes:**
  - leakage of bile salts into circulation.
  - leading to its excretion in urine.

Prothrombin time

- **Prothrombin:** synthesized by the liver, a marker of liver function.
- **Half-life:** 6 hrs. (indicates **the present function** of the liver).
- **Prolonged PT:**
  - PT is prolonged **ONLY** when liver loses more than 80% of its reserve capacity.
  - **Vitamin K deficiency** also causes prolonged PT.
  - Intake of vitamin K does not affect PT **in liver disease** (because the liver can't produce PT to be activated by vit K).

كيف نعرف ان سبب هالزيادة هو فايتمن كاي او مشكلة بالكبد؟
نعطي الشخص فايتمن كاي اذا تحسن خلال ٢٤ ساعة فالسبب هو فايتمن كاي واذا ماتحسن فالمشكلة بالكبد.

Liver functions tests

Group I: Markers of liver dysfunction

Group II: Markers of hepatocellular injury

Group III: Markers of cholestasis

Serum bilirubin: total and conjugated.

Urine: bile salts and urobilinogen

Prothrombin Time (clotting time)

Total protein, **serum albumin** and **albumin/globulin ratio**

Serum albumin

- The most abundant protein synthesized by the liver
- **Normal serum levels:** 3.5 – 5 g/dL
- **Synthesis depends on:** the extent of functioning liver cell mass
- **Longer half-life:** 20 days. البروثرومبين كان ٦ ساعات فتقريبا يعلمنا عن حالة الكبد الحالية، هنا ٢٠ يوم فيعطينا كفاءة الكبد على اللونق ترم
- **Its levels decrease in** all **chronic** liver diseases.

Serum globulin

- **Normal serum levels:** 2.5 – 3.5g/dL
- α and β-**globulins** mainly synthesized by the **liver**.
  - ✓ They constitute **immunoglobulins** (antibodies).
- **High** serum γ-globulins are observed in **chronic hepatitis** and **cirrhosis**:
  - **IgG** in autoimmune hepatitis.
  - **IgA in alcoholic liver disease.**

Note: α and β-globulins are for transport while γ-globulins are for immunity

Albumin to globulin (A/G) ratio

- **Normal A/G ratio: 1.2/1 – 1.5/1** For every 1 globulin molecule there are 1.2-1.5 albumin molecules
- Globulin levels **increase** in **hypoalbuminemia** as a compensation.

Hypoalbuminemia indicates a chronic diseases, whenever albumin levels are low globulins increase to maintain oncotic pressure

Liver functions tests

Group I: Markers of liver dysfunction

Group II: Markers of hepatocellular injury

Group III: Markers of cholestasis

Alanine aminotransferase (ALT).

- **More liver-specific than AST.**
- Appears in plasma many days **before** clinical signs appear.
- A normal value **DOES NOT** always indicate absence of liver damage (reserve)
- **Obese** but otherwise normal individuals may have elevated ALT levels.

NORMAL	Male: 13-35 Female: 10-30
HIGH SERUM LEVELS	acute hepatitis (300-1000U/L)
Moderate elevation	**alcoholic hepatitis** (100-300U/L)
Minor elevation	cirrhosis, hepatitis C and non-alcoholic steatohepatitis (NASH) (Fatty liver) (50-100U/L)

Aspartate aminotransferase (AST).

- **Normal range:** 8 – 20 U/L
- **A marker of: hepatocellular damage.**
- **High serum levels are observed in:**
- Chronic hepatitis.
- Cirrhosis.
- Liver cancer.

Liver functions tests

Group I: Markers of liver dysfunction

Group II: Markers of hepatocellular injury

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Alkaline phosphatase (ALP):

- **A non-specific marker of liver disease.**
- ❖ **Produced by bone osteoblasts** (for bone calcification)
- ❖ **Present on:** hepatocyte membrane.

Normal range	40 – 125 U/L.
Moderate elevation	Infective hepatitis, **alcoholic hepatitis** and hepatocellular carcinoma.
High levels	Extrahepatic obstruction (obstructive jaundice) and intrahepatic cholestasis.
Very high levels	Bone diseases.

Note: ALP is elevated in pregnancy because it is produced in placenta.
(not specific or liver, but it's specific for bones فما نعتمد عليه لحاله .)

Alkaline phosphatase (ALP).

γ- glutamyl transferase (GGT).

AST & ALT

Liver functions tests

Group I: Markers of liver dysfunction

Group II: Markers of hepatocellular injury

Group III: Markers of cholestasis

γ- glutamyl transferase (GGT).

- **Used for:** glutathione synthesis
- **Normal range:** 10 – 30U/L
- **Moderate elevation observed in:**
  - ✓ Infective hepatitis and prostate cancers
- **GGT is increased in alcoholics** despite normal liver function tests
  - ✓ **Highly sensitive to detecting alcohol abuse.**

- Is a polypeptide of 3 amino acids. Active side chain of serine has an SH group (thiol) to obtain oxygen.
- It's related to Biliary ducts obstruction.
- Don't get confused between GGT and GTT (Glucose tolerance test) !!

Alkaline phosphatase (ALP).

γ- glutamyl transferase (GGT).

AST & ALT

SUMMARY "الملخص الشامل موجود بالداونلود سنتر"

Group I: Markers of liver dysfunction	Serum bilirubin: total and conjugated.	○ **gallstones** ○ **acute and chronic hepatitis**
	Urine: bile salts and urobilinogen	Obstruction in biliary passage → Bile salts in urine.
	Total protein, serum albumin and albumin/globulin ratio	○ Albumin is the **most abundant protein** synthesized by the liver. ○ Serum albumin is **decrease in all chronic liver diseases**. ○ IgA is elevated in alcoholic liver disease.
	Prothrombin Time (clotting time)	• Prolonged in: 1. **Liver disease:** when liver loses 80% of its reserve capacity - Vit. K intake doen't affect it. 2. **Vitamin K deficiency:** Vit. K intake affects it. • indicates **the present function** of the liver (Shorter half life than serum albumin).
Group II: Markers of **hepatocellular injury**	Alanine aminotransferase (ALT).	○ More liver specific than AST. ○ Elevated in : **- Obese individuals**. - Moderately elevated in **alcoholic hepatitis.**
	Aspartate aminotransferase (AST).	○ **A marker of: hepatocellular damage.** ○ **Less specific than ALT.**
Group III: Markers of cholestasis	Alkaline phosphatase (ALP).	○ Produced by **bone osteoblasts .** ○ Moderately elevated in **alcoholic hepatitis**
	γ- glutamyl transferase (GGT).	○ **Increased in alcoholics** despite normal liver function tests

Biochemical markers used in diagnosis of alcoholic liver disease (ALD) . IMPORTANT!!!

- **γ- glutamyl transferase (GGT).**
- **Alkaline phosphatase (ALP).**
- **Alanine aminotransferase (ALT).**
- **Serum globulin (IgA).**

Check your understanding!

Q1: which one of the following compounds can be Detoxified and excreted by liver :

A. cholesterol.
B. Vitamins A.
C. Ammonia.
D. A+C.

Q2: Which of the following LFTs is more liver-specific?

A. Alanine aminotransferase
B. Alkaline phosphatase.
C. Serum bilirubin.
D. Alpha fetoprotein .

Q3: one of the reason behind LFTs limitation is:

A. Liver a has very large reserve capacity.
B. It's not useful because it's noninvasive test.
C. Doesn't asses the hepatic function.
D. All of the above.

Q4: Unconjugated is :

A. Result of breaking down RBCs.
B. Cause of yellowish pigment in jaundice.
C. Its level goes up in chronic hepatitis.
D. All of the above.

Q5: where we could find the Unconjugated Bilirubin:

A. bile.
B. Blood " plasma".
C. Small intestine.
D. Kidney.

Q6: in which form dose the Bilirubin excreted in the feces:

A. Unconjugated Bilirubin.
B. conjugated Bilirubin.
C. Urobilin stercobilin.

Q7: which form of the Bilirubin that can be found normally in the kidney in small amount:

A. Urobilinogen.
B. bile salts.
C. Indirect Bilirubin.

Q8.Increased conjugated bilirubin only is due to?

Hemolytic.
Hepatic.
Pre hepatic.
D) Post hepatic

1.D, 2.A , 3.A, 4.D, 5.B, 6.C. 7,A, 8.D

Check your understanding!

Q9: in which of the following condition the Globulin levels increase as a compensation:

A. hypoalbuminemia.
B. autoimmune hepatitis.
C. alcoholic liver disease.

Q10: which of the following indicates the present function of the liver:

A. Albumin.
B. Globulin.
C. (A/G) ratio.
D. Prothrombin.

Q11: deficiency in which of the following vitamins will cause prolonged PT :

A. vitamin A.
B. vitamin B12.
C. vitamin K.
D. vitamin E.

Q12: which of the following is Produced by bone osteoblasts?

A. Alanine aminotransferase
B. Alkaline phosphatase.
C. Serum bilirubin.
D. Alpha fetoprotein .

SAQ:

Biochemical markers used in diagnosis of alcoholic liver disease (ALD) .

- **γ- glutamyl transferase (GGT).**
- **Alkaline phosphatase (ALP).**
- **Alanine aminotransferase (ALT).**
- **Serum globulin (IgA).**

9.A, 10.D, 11.C, 12.B.

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Resources:

- 435's slides and notes.
- Lippincott's illustrated reviews: Biochemistry – sixth edition
- Clinical Chemistry - Techniques, Principals and Correlations: 6th edition.
- Liver fibrosis markers in alcoholic liver disease - National Center for Biotechnology Information (NCBI) Search database.

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