جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Liver Function Test

Biochemistry Team 437

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GNT block

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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 and assess hepatic function.

Introduction:

- In this lecture, we will discuss the biochemical markers we test in the blood to tell if the patient has a liver disease, and also to be able to differentiate the type of liver disease.
- Biochemical markers along with history, radiology, clinical examination and other diagnostic methods help us get a full picture of the diagnosis, but we can't diagnose a disease just from laboratory tests.
- We have two types of markers we test to assess the liver function:
    - **Liver enzymes:**
      Present inside the hepatocytes, whenever the hepatocytes are injured, they release them into the blood. E.g. ALT, AST, GGT (direct markers)
    - **Other markers:**
      Bilirubin, albumin...etc, Not present inside the hepatocytes, but are affected by the liver function in one way or another. (indirect markers)

Major Metabolic Functions of the Liver

Synthetic Function	Detoxification[2] and Excretion	Storage Function	Production of Bile Salts
Plasma proteins (albumin, globulins)[1], cholesterol, triglycerides and lipoproteins	Ammonia to urea (urea cycle), bilirubin, cholesterol, drug metabolites	Vitamins A, D, E, K and B12	Helps in digestion

Some Examples of Liver dysfunction

- Hepatocellular disease
- Cholestasis[3] (obstruction of bile flow)
- Cirrhosis
- Hepatitis
- Jaundice
- Liver cancer
- Steatosis (fatty liver)
- *Genetic Disorders*
  - Hemochromatosis (increased iron storage causing iron overload)

[1]Albumin: acts as carrier, globulins like antibodies
[2]Scavenge or removal of toxins
[3]Cholestasis is due to extra/intra hepatic cause
ALT+AST+GGT will be released into blood due to rupture of hepatocytes

Liver Function Tests (LFTs)

- Noninvasive methods for screening of liver dysfunction
- **Just like any marker,it is used for:**
  - Help in identifying general types of disorder (diagnosis)
  - Assess severity and allow prediction of outcome
  - Disease and treatment follow up
- **Broadly classified as:**
  1. **Tests to detect hepatic injury:**
     a. Mild or severe; acute or chronic
     b. Nature of liver injury (hepatocellular or cholestasis)
  2. **Tests to assess hepatic function**

Actually, Any Blood extraction is mildly invasive not totally noninvasive, but it is considered routine and easy to do.

- Non invasive tests: urine collection
- Mildly invasive: venous blood extraction
- More invasive: arterial blood extractions
- Very invasive: liver biopsy

Classification of LFTs

- Group I: **Markers of liver dysfunction**
  - Serum bilirubin: total and conjugated
  - Total protein, serum albumin and albumin/globulin ratio
  - Prothrombin Time
  - Urine: bile salts, urobilinogen

Blood

- We need 2 samples : blood+urine
- Albumin is the major protein that synthesized in liver

- Group II: **Markers of hepatocellular injury** "e.g. hepatitis"
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)

- **ALT is the most specific**
- AST not specific for the liver, it is also present in the smooth muscle cells and the RBCs

- Group III: **Markers of cholestasis** "e.g. gallstones, malignancies"
  - Alkaline phosphatase (ALP)
  - γ-glutamyltransferase (GGT)

- ALP is also seen in bone+placenta, and is usually high in growing teens or in case of bone disease (osteomalacia)
- GGT has an important function as glutathione systems "antioxidant" inside blood cells and its **related to alcohol consumption**

Limitations of LFTs

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Normal LFT values do not always indicate absence of liver disease

- Liver a has very large reserve capacity

Asymptomatic people may have abnormal LFT results

- Diagnosis should be based on clinical examination

Important!

Common Serum Liver Chemistry Tests

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tip

احفظوه صم!

Summary for all the markers, we will discuss each one alone later in the lecture

Liver chemistry test	Clinical implication of abnormality
Alanine aminotransferase	Hepatocellular damage
Aspartate aminotransferase	Hepatocellular damage
Bilirubin	Cholestasis, impaired conjugation, or biliary obstruction
Alkaline phosphatase	Cholestasis, infiltrative disease, or biliary obstruction
Prothrombin time	Synthetic function
Albumin	Synthetic function
γ-glutamyltransferase[1]	Cholestasis or biliary obstruction
Bile acids[2]	Cholestasis or biliary obstruction

[1]GGT in alcoholic

[2]Bile salts normally not found in the urine, if they were found, it indicates biliary obstruction

Important!

Bilirubin

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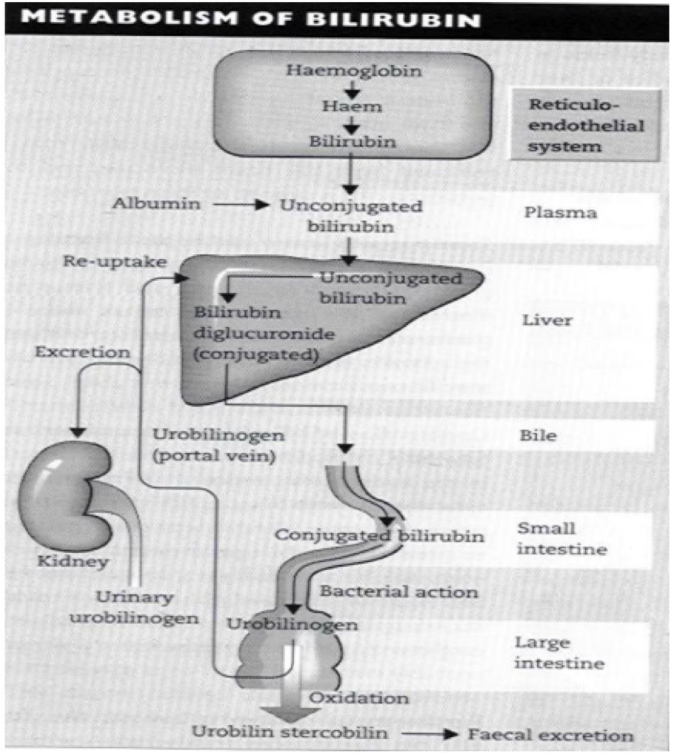
- A byproduct of red blood cell breakdown
- It is the yellowish pigment observed in jaundice
- High bilirubin levels are observed in:
  - Gallstones, acute and chronic hepatitis

Do not memorise numbers, only know the red numbers for your information

Serum bilirubin levels:

- Normal: 0.2 – 0.8 mg/dL
- Unconjugated (indirect): 0.2 – 0.7 mg/dL
- Conjugated (direct): 0.1 – 0.4 mg/dL
- Latent jaundice: Above 1 mg/dL
- Jaundice: Above 2 mg/dL

Indirect and direct refers to the way of calculation.
Direct: measured directly from the blood
Indirect: you mesure the total bilirubin minus the conjugated to get the unconjugated "indirect"



هذي قصة البيليروبين الدكتور قال اخذتوها بالنظري وبتاخذونها بالعملي واحتمال كبير تاخذونها بالاختبار

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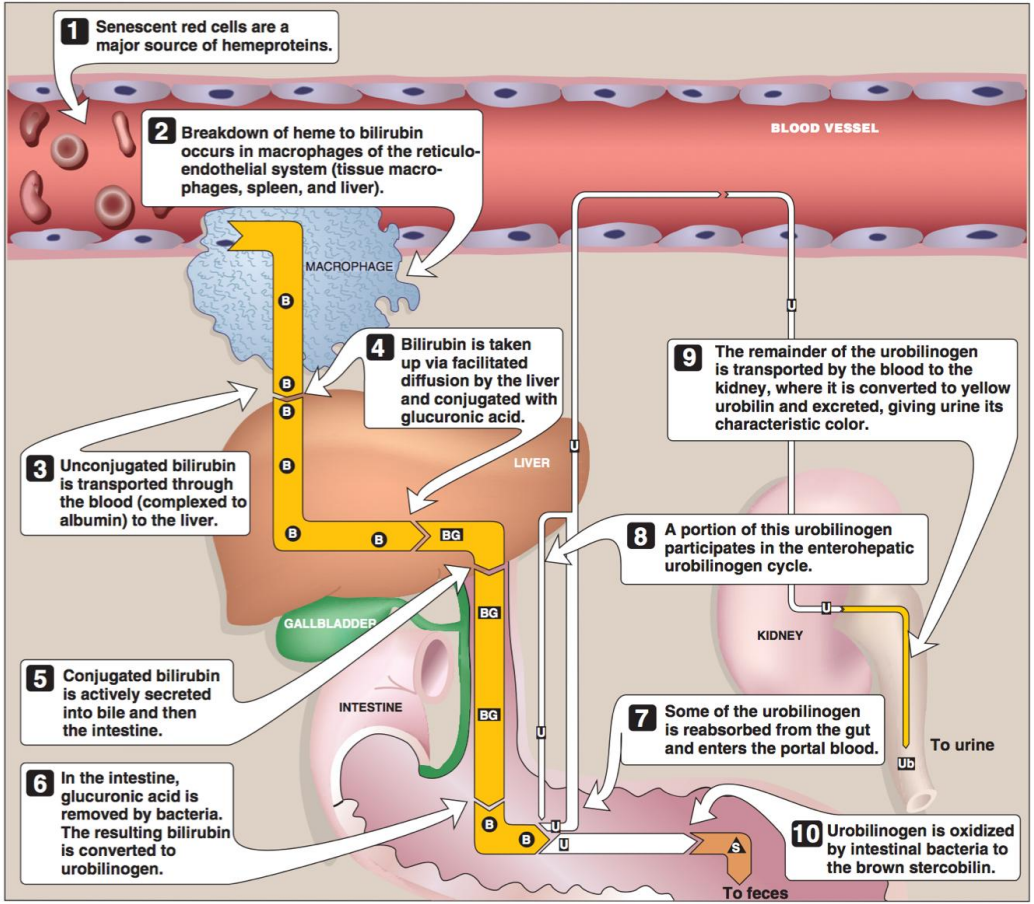


- After RBCs breakdown hemoglobin is broken down into Globin, and heme
- The globin is a protein and is therefor catabolized in the protein catabolism pathway.

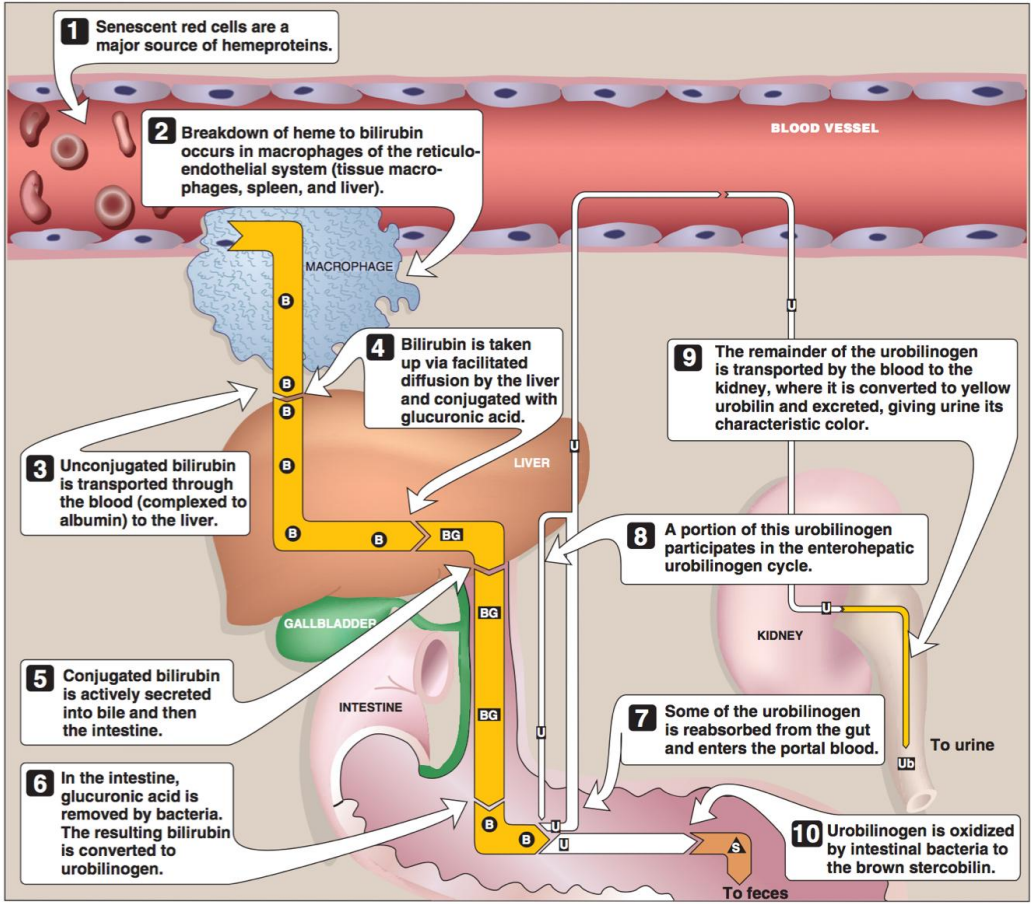
Inside the tissue macrophages/spleen:

- Heme contains iron and other components, mainly biliverdin. They are separated by the enzyme heme oxygenase
- Then biliverdin will be reduced into bilirubin by the enzyme biliverdin reductase. This bilirubin is unconjugated

In the plasma:

- Unconjugated bilirubin now must be transported into the blood, but since it is hydrophobic, it has to bind to a carrier.
- Albumin will be the carrier, together they form a more soluble complex “still unconjugated”
- Before the bilirubin enters the liver, albumen dissociates and the unconjugated bilirubin enters the liver.

Cont.



In the liver:

- Bilirubin conjugates with 2 glucuronic acid, becoming a water soluble compound called bilirubin diglucuronide, by the enzyme **UDP Glucuronyl Transferase**.
- Through the bile duct, it goes to the intestine

In the intestine:

- By the intestinal bacteria, glucuronic acid is removed, and the bilirubin becomes urobilinogen
- Urobilinogen will have three fates:

  1- Some is oxidized to stercobilinogen which is excreted in the feces

  - Some is reabsorbed into the blood and taken to

    2- the liver by the portal vein (hepatobiliary reuptake)

    3- or to the kidney to be secreted as urinary urobilin

Important!

Bilirubin Levels and Jaundice

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Any obstruction in the previous cycle leads to high bilirubin levels in the blood and therefore jaundice

Class of Jaundice	Causes
Pre-hepatic or hemolytic Before conjugation happens “Liver is fine, but there is increase in hemolysis”	Abnormal red cells; antibodies; drugs and toxins; thalassemia Hemoglobinopathies, Gilbert’s, Crigler-Najjar syndrome*
Hepatic or Hepatocellular	Viral hepatitis, toxic hepatitis, intrahepatic cholestasis (inside the liver) *E.g. cancer Inside the liver biliary tracts, NOT gallstones*
Post-hepatic	Extrahepatic cholestasis; gallstones; tumors of the bile duct, carcinoma of pancreas

*UDP glocroiod transferase deficiency, Occurs in infants and G6PD deficiency, both are benign

Urobilinogen (UBG) and Bile Salts

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Urobilinogen (UBG)

- Most UBG is metabolized in the large intestine,
  but a fraction is excreted in urine (less than 4 mg/day)

Bile salts :

- Normally bile salts are NOT present in urine
- Obstruction in the biliary passages causes:
  - Leakage of bile salts into circulation
  - Excretion in urine

- Normally the bile salt are not found in urine, if so that indicates obstruction of bile passage.
- Important : Urobilinogen usually present in the urine but bile salts is not !

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 (hepatocytes)
- Longer half-life: 20 days "not helpful in diagnosing acute injury"
- Its levels decrease in all chronic liver diseases

Albumin levels are decreased in case of:

- Less albumin synthesis: chronic liver disease leading to cirrhosis/ fibrosis
- Or increase albumin excretion: nephrotic syndrome

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 **(+GGT)**
- They're transporter mainly for copper

Important!

Albumin to Globulin (A/G) Ratio

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- Normal A/G ratio: 1.2/1 – 1.5/1
- Globulin levels increase in hypoalbuminemia as a compensation

- Usually, the body tries to maintain a constant protein level, so if either the albumin or the globulins are decreased, the body will try to compensate by increasing the other.
- In case of Liver disease: Albumin is low so Globulin becomes high
- **Why is it important to know the ratio?**
- In chronic liver disease, if you test the total protein level it will be normal, only when you see the ratio you will realize that the albumin is very low and the globulin is high indicating liver disease.

Prothrombin Time (PT)

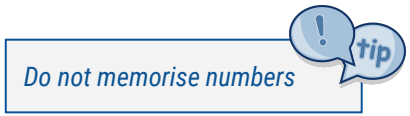
Biochemical and haematological test

- Prothrombin: synthesized by the liver, a marker of liver function
- Half-life: 6 hrs. (indicates the present function of the liver) “acute state”
- 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

- Notice that prothrombin level is not measured, we measure prothrombin time
- PT is measured in pre operation
- PT is prolong in the late phase of the liver disease
- Vitamin K is stored in the liver

Aspartate Aminotransferase (AST)

- Normal range: 8 – 20 U/L
- A marker of hepatocellular damage
- High serum levels are observed in:
  - Chronic hepatitis, cirrhosis and liver cancer



- It is **non specific**
- The most important to detect high serum of AST in **chronic** hepatitis

تكون جوا عشان كذا بس تطلع بال chronic

Alanine Aminotransferase (ALT)

- More liver-specific than AST
- Normal range (U/L):
  - Male: 13-35
  - Female: 10-30

High serum hepatitis is most important
يكون أقرب الـ cell membrane عشان كذا تطلع في ال Acute

- High serum levels in acute hepatitis (300-1000U/L)
- Moderate elevation in alcoholic hepatitis (100-300U/L)
- Minor elevation in cirrhosis, hepatitis C and non-alcoholic steatohepatitis (NASH) (50-100U/L)
- Appears in plasma many days before clinical signs appear (first thing to appear)
- A normal value does not always indicate absence of liver damage
- Obese but otherwise normal individuals may have elevated ALT levels

Alkaline Phosphatase (ALP)

- A nonspecific marker of liver disease
- Produced by bone osteoblasts (for bone calcification)
- Present on hepatocyte membrane
- Normal range: 40 – 125 U/L
- Moderate elevation observed in:
  - Infective hepatitis, alcoholic hepatitis and hepatocellular carcinoma
- High levels are observed in:
  - Extrahepatic obstruction (obstructive jaundice) and intrahepatic cholestasis
- Very high levels are observed in:
  - Bone diseases

γ-glutamyltransferase (GGT)

- Used for glutathione synthesis which assist removal of free radical
- 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

Take Home Messages

- LFTs help detect liver injury and function
- LFTs do have some limitations

Dr.mujamamy recap:

- 4 alcoholic detecting markers:
  1- IgA
  2- ALT
  3- alkaline phosphatase
  4- GGT : it's the most sensitive
- ALT is the most sensitive for hepatocellular damage
- Prothrombin time is the most sensitive for liver synthesis the albumin is the second most sensitive.

لازم تحفظ قصة البيليروبين

Important!

Quick Review:

- **Bilirubin:** A byproduct of red blood cell breakdown
- **Serum Bilirubin level: Latent jaundice**: Above 1 mg/dL | **Jaundice**: Above 2 mg/dL

Class of Jaundice	Causes
Pre-hepatic or hemolytic	Abnormal red cells; antibodies; drugs and toxins; thalassemia Hemoglobinopathies, Gilbert's, Crigler-Najjar syndrome
Hepatic or Hepatocellular	Viral hepatitis, toxic hepatitis & **intrahepatic** cholestasis
Post-hepatic	**Extrahepatic** cholestasis; gallstones; tumors of the bile duct, carcinoma of pancreas

- **Urobilinogen (UBG):** 1- Metabolized in the large intestine (into stercobilinogen by oxidation → excreted in feces) 2- Reuptake by the liver (hepatocellular circulation) 3- Fraction is excreted in urine
- **Bile salts:** Normally NOT present in urine,finding it in urine indicates obstruction
- **Prothrombin Time (PT):** prolonged ONLY when liver loses more than 80% of its reserve capacity
- **Prothrombin:** synthesized by the liver, a marker of **present liver function**
- **Aspartate aminotransferase (AST):** A marker of **hepatocellular damage**
- **Alanine aminotransferase (ALT):** More specific than AST, appears in plasma many days before clinical signs appear

Important!

Quick Review:

Marker	Indication
↑ **Bilirubin**	**Gallstones**, **acute** & **chronic hepatitis**
↓ **Serum Albumin**	**All chronic liver diseases**
↑ **Serum γ-globulins**	**Chronic hepatitis** & **cirrhosis**: - IgG in autoimmune hepatitis - IgA in alcoholic liver disease **Hypoalbuminemia**
↑ **Aspartate aminotransferase (AST)**	**Chronic hepatitis**, cirrhosis & liver cancer
↑ **Alanine aminotransferase (ALT)**	**Acute hepatitis**
↑ **γ-Glutamyl transferase (GGT)**	Highly sensitive to detecting **alcohol abuse**
Moderate ↑ **Alkaline phosphatase (ALP)**	**Infective hepatitis**, **alcoholic hepatitis** & **hepatocellular carcinoma**
↑ **Alkaline phosphatase (ALP)**	**Extrahepatic obstruction (obstructive jaundice)**

Summary :

Liver Function Tests

Noninvasive methods for screening of liver dysfunction
Help in identifying general types of disorder
Assess severity and allow prediction of outcome
Disease and treatment follow up

- Normal LFT values do not always indicate absence of liver disease
- Asymptomatic people may have abnormal LFT results

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 Total protein, serum albumin and albumin/globulin ratio Prothrombin Time	Alanine aminotransferase (ALT) Aspartate aminotransferase (AST)	Alkaline phosphatase (ALP) g-glutamyl transferase (GGT)

Marker	Normal level	Abnormal levels	Causes
Bilirubin: A byproduct of red blood cell breakdown It is the yellowish pigment observed in jaundice	**Normal** 0.2 – 0.8 mg/dL **Unconjugated (indirect):** 0.2 – 0.7 mg/dL **Conjugated (direct):** 0.1 – 0.4 mg/dL	**Latent jaundice:** Above 1 mg/dL **Jaundice:** Above 2 mg/dL	Gallstones, acute and chronic hepatitis
Urobilinogen (UBG) and bile salts: Most UBG is metabolized in the large intestine but a fraction is excreted in urine. Normally bile salts are NOT present in urine	- Less than 4 mg/day) of urobilinogen is excreted in urine - Bile salt are NOT present in urine	- More than 4 mg/day in urobilinogen - If bile salt is found	Obstruction in the biliary passages which will cause: Leakage of bile salts into circulation and Excretion in urine
Serum Albumin: The most abundant protein synthesized by the liver Synthesis depends on the extent of functioning liver cell mass Longer half-life: 20 days	Normal serum levels: 3.5 – 5 g/dL	Its levels decrease	In all chronic liver diseases
Serum Globulin: a and b-globulins mainly synthesized by the liver They constitute immunoglobulins (antibodies)	Normal serum levels: 2.5 – 3.5g/dL	High serum gamma-globulins are observed	Chronic hepatitis and cirrhosis: IgG in autoimmune hepatitis IgA in alcoholic liver disease
Prothrombin Time (PT): synthesized by the liver, a marker of liver function	Half-life: 6 hrs. (indicates the present function of the liver)	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

Marker	Normal level	Abnormal levels	Causes
Group II			
Aspartate aminotransferase (AST): A marker of hepatocellular damage	Normal range: 8 – 20 U/L	High serum levels are observed	Chronic hepatitis, cirrhosis and liver cancer
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 Obese but otherwise normal individuals may have elevated ALT levels	Normal range (U/L): Male: 13-35 Female: 10-30	- Acute hepatitis (300-1000U/L) - Alcohol hepatitis (100-300U/L) - In cirrhosis, hepatitis C and non-alcoholic steatohepatitis (NASH) (50-100U/L)	- High serum levels in acute hepatitis. - Moderate elevation in alcoholic hepatitis. - Minor elevation in cirrhosis, hepatitis C and non-alcoholic steatohepatitis

Marker	Normal level	Abnormal levels	Causes
Group III			
Alkaline phosphatase (ALP): - A nonspecific marker of liver disease - Produced by bone osteoblasts (for bone calcification) - Present on hepatocyte membrane	Normal range: 40 – 125 U/L	Moderate elevation observed in	Infective hepatitis, alcoholic hepatitis and hepatocellular carcinoma
		High levels are observed	Extrahepatic obstruction (obstructive jaundice) and intrahepatic cholestasis
		Very high levels	Bone diseases
Gamma- glutamyl transferase (GGT) Used for glutathione synthesis	Normal range: 10 – 30 U/L	Moderate elevation observed	Infective hepatitis and prostate cancers
		GGT is increased in alcoholics despite normal liver function tests	Highly sensitive to detecting alcohol abuse

MCQs:

Q1: Which ONE of the following enzymes is more liver specific?

A. ALT
B. AST
C. LD
D. None of them

Q2: Which of these enzymes are highly sensitive in detecting alcohol abuse?

A. Alkaline phosphatase (ALP)
B. gamma–glutamyl-transferase (GGT)
C. Alanine aminotransferase (ALT)
D. Aspartate aminotransferase (AST)

Q3: Increased conjugated bilirubin is due to?

A. Pre hepatic
B. Post hepatic
C. Hepatic
D. Both (B&C)

Q4: in which of the following condition the Globulin levels increase as a compensation?

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

Q5: which of the following indicates the present function of the liver?

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

Q6: deficiency in which of the following vitamins will cause prolonged PT ?

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

SAQs:

Q7: What does Prothrombin Time (PT) means? And how is that relevant to liver dysfunction?

Q8: Explain why albumin is not a good indicator of an acute hepatic dysfunction?

Answers:

1. A
2. B
3. D
4. A
5. D
6. C
7. PT means how much time it takes for the blood to clot, PT is synthesized by the liver
8. It has a long half-life of 20 days. It's good in detecting chronic liver diseases

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