Revised & Approved

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BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY

Liver function tests

Editing File

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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.

Major Metabolic Functions of the Liver

Synthetic function

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

Detoxification and excretion

Ammonia to urea (urea cycle), bilirubin, cholesterol, drug metabolites

Storage function

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

Production of bile salts

Helps in digestion

We do LFTs if we have patient we suspect liver disease or when we want to prescribe drug with side effects on liver

Some examples of liver dysfunction :

- **Hepatocellular disease**
- **Cholestasis** (obstruction of bile flow)
- **Cirrhosis** Scars of the liver
- **Hepatitis**
- **Jaundice**
- **Liver cancer**
- **Steatosis** (fatty liver)
- **Genetics** Hemochromatosis (iron storage)

Liver Function Tests (LFTs)

- **Noninvasive methods for screening of liver dysfunction**
- **Help in identifying general types of disorder**

We don't depend on LFTs alone for diagnosis

- **Assess severity and allow prediction of outcome**
- **Disease and treatment follow up**
- **Broadly classified as :**

1. Tests to detect hepatic injury :
   - Mild or severe; acute or chronic
   - Nature of liver injury (hepatocellular or cholestasis)
2. Tests to assess hepatic function

Classifications of LFTs

Group I:
Markers of liver dysfunction

- **Serum bilirubin:** total and conjugated
- **Urine:** bile salts and urobilinogen
- **Total protein**, serum albumin and albumin/globulin ratio
- **Prothrombin Time**

Prothrombin time means clotting time and prothrombin is the clotting factor synthesis in liver and give u an Idea about whether the liver lost it function and how much has been lost

Group II:
Markers of hepatocellular injury

- **Alanine aminotransferase** (ALT)
- **Aspartate aminotransferase** (AST)

Group III:
Markers of cholestasis

- **Alkaline phosphatase** (ALP)
- **γ-glutamyltransferase** (GGT)

Limitations of LFTs

The liver is filled with these substances so we have to reach a certain level of destruction for LFTs to be abnormal

Normal LFT values do not always indicate absence of liver disease

- Liver has a very large reserve capacity

Because the liver is very large organ it can compensate any small damages and we don't notice anything in the test so we only noticing the change from the test in case of massive damages

Asymptomatic people may have abnormal LFT results

- Diagnosis should be based on clinical examination

We can't depend on it because sometimes the coffee or pregnancy can affect these enzymes and look abnormal while the liver is completely healthy

Common Serum Liver Chemistry Tests

Liver chemistry test	Clinical implication of abnormality
Alanine aminotransferase	Hepatocellular damage
Aspartate aminotransferase	Hepatocellular damage
Bilirubin	• Cholestasis • Impaired conjugation • Biliary obstruction
Alkaline phosphatase	• Cholestasis • Infiltrative disease • Biliary obstruction
Prothrombin time	Synthetic function
Albumin	Synthetic function
γ-glutamyltransferase	• Cholestasis • Biliary obstruction
Bile acids	• Cholestasis • Biliary obstruction

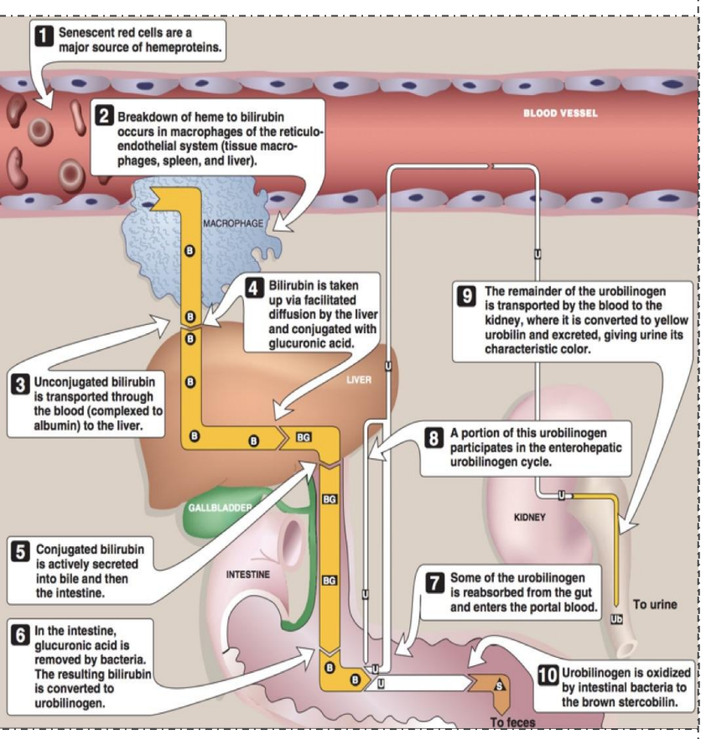
Bilirubin

- **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

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

Class of jaundice	Pre-hepatic jaundice	Hepatic or hepatocellular	Post-hepatic
Causes	• Abnormal red cells • Antibodies; drugs and toxins • Thalassemia Hemoglobinopathies Gilbert's • Crigler-Najjar syndrome	• Viral hepatitis toxic hepatitis • Intrahepatic cholestasis	• Extrahepatic cholestasis • Gallstones • Tumors of the bile duct • Carcinoma of pancreas

Metabolism of Bilirubin



Explanation:

1- Rupture of RBCs lead to release of heme

2- Heme is converted to biliverdin catalyzed by microsomal heme oxygenase which is reduced to bilirubin

3- bilirubin is complexed with albumin and released at
entrance to the liver (unconjugated bilirubin).

4- Bilirubin is conjugated with UPD-glucuronic acid.(dr.Sumbul;the only enzyme name you have to memorize here is UPD-glucuronic transferase)

5- Conjugated bilirubin is secreted into bile and then into the intestine.

6- Bacteria utilize glucuronic acid so it remove it from bilirubin converting it into urobilinogen.

★ Fate of urobilinogen:

7- Some enter the portal circulation where:

8- Returns back to the liver.

9- filtered by the kidney as urobilin

10- majority is excreted with feces as stercobilin (gives the feces its characteristic color)

special thanks to #438 Explanation

Dr.sumbul questions on the picture

1- if there is increase in RBCs breakdown for any reason what will happen ?

Increase bilirubin production

2-If there's a problem at level of liver what kind of bilirubin you will find in circulation?

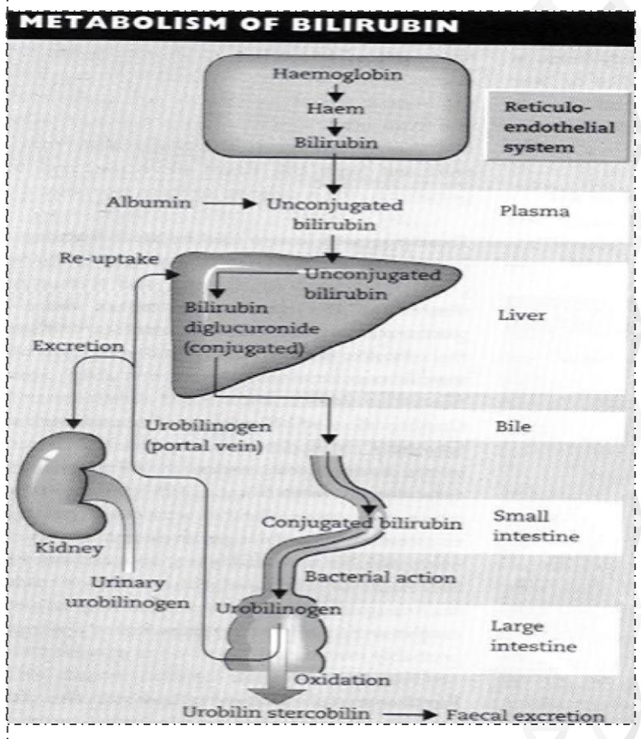
Unconjugated bilirubin, because liver is damaged and unable to conjugate it

3-if there is little damage what kind of bilirubin you will see?

Mixed conjugated and unconjugated , because the liver in this case is doing it work but not in the perfect way because of some cell damage

4-if the problem is after the liver like obstruction what will happen?

No bilirubin in intestines so pale stool + bilirubin will start leaking to blood then to kidney and we will have dark urine



Markers of liver dysfunction

Marker	Urobilinogen	Bile salts	Serum albumin Synthesized in the liver only	Serum globulin	Prothrombin time Specific to the liver ما يصنع الا بالكبد بس الفرق بينه وبين Albumin انه يعطي فكرة عن acute function because of it short half-life
Normal value	Most are metabolised in the large intestine, but a fraction is excreted in the urine: less than 4 mg/day	Normally not found in urine	3.5 - 5 g/dL (measured from the serum)	2.5-4.5 g/dL Normally less than albumin	
Features		Obstruction of biliary passages → leakage of bile salts into the circulation → excretion in urine	The most abundant protein synthesized by the liver Synthesis depends on the extent of functioning liver cell mass Longer half life: 20 days -> chronic function	- α and β globulins are mainly synthesized in the liver - They constitute immunoglobulins (antibodies)	Synthesized by the liver - Half life = 6 hours → indicates present function of the liver
Disease		Excreted in urine	Low in all chronic liver diseases	High serum γ-globulins in chronic hepatitis & cirrhosis: • IgG: autoimmune hepatitis • IgA: alcoholic liver disease	It is prolonged only when the liver loses more than 80% of its reserve capacity
Notes			Albumin to globulin (A/G) ratio: • Normally: 1.2/1 - 1.5 /1 • Hypoalbuminemia: globulin levels increase as a compensation mainly γ because α and β are synthesized by the liver which is already damaged		Vitamin K deficiency also causes prolonged PT Vitamin K intake does not affect PT in liver disease to different ate we give The patient Vit.K injection if It help the patient that's means problem is not in liver

Markers of hepatocellular injury

Marker	Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)
Normal Value	8-20 U/L	• Male: 13-35 • Female: 10 - 30
Features	Marker for hepatocellular damage	• More liver-specific than AST • Appears in plasma many days before clinical signs appear • Obese but otherwise normal individuals may have elevated ALT levels
Disease DR Sumbul :Memorize the normal voles is not IMP because they will put it in the Question **BUT** it's Important to know the level of increasing in each disease	High serum levels are observed in: • Chronic hepatitis • Cirrhosis • Liver cancer	Minor elevations (50 - 100 U/L): • Cirrhosis • hepatitis C • non-alcoholic steatohepatitis (NASH) Moderate elevations (100 - 300 U/L): • alcoholic hepatitis High serum levels (300 - 1000 U/L): • acute hepatitis
Notes	Less specific	It's more specific to the liver and moderate elevation is seen in **alcoholic hepatitis**

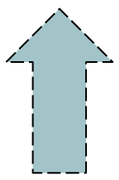
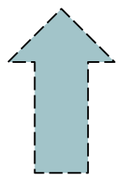
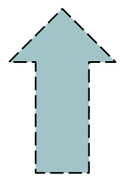
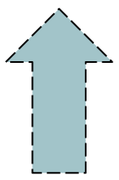
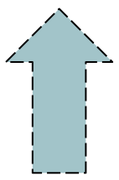
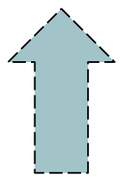
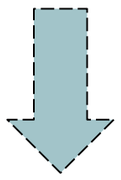
Markers of cholestasis

Marker	Alkaline phosphatase (ALP)	ɣ Glutamyltransferase (GGT) It's a scavenger for ROS
Normal Value	40 - 125 U/L	10 - 30 U/L
Features	• Non-specific marker of liver disease • Produced by bone osteoblasts (for bone calcification) • Present on hepatocyte membrane	• Used for glutathione synthesis • Highly sensitive for alcohol abuse; it is increased in alcoholics despite normal liver function tests
Disease	Minor elevations observed in: ◆infective hepatitis ◆ alcoholic hepatitis ◆ hepatitis ◆ hepatocellular carcinoma High elevations observed in: ◆ Extrahepatic obstruction (obstructive jaundice) ◆ Intrahepatic cholestasis Very high levels observed in: ◆ Bone diseases	• Moderate elevations observed in: ◆ Infective hepatitis ◆ Prostate cancers • High in alcoholics
Notes	biliary duct so elevation in case of يروح لل obstruction	The most specific for alcoholic hepatitis More to less specific: GGT > ALT > ALP

Take Home Messages

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

Summary

Marker	Bilirubin	Serum globulin	AST	ALT	ALP	GGT	Bile salts	Prothrombin time	Serum albumin
Change							Excreted in urine	Prolonged	
Disease	1- Gallstone 2- Acute &chronic hepatitis	1- Chronic hepatitis & cirrhosis: -IgG: autoimmune hepatitis - IgA: alcoholic liver disease	1- Chronic hepatitis 2- Cirrhosis 3- Liver cancer	1- Minor: cirrhosis, hepatitis C, NASH 2- Moderate: alcoholic hepatitis 3- Severe: acute hepatitis	1- Minor: infective hepatitis, alcoholic hepatitis, hepatitis, hepatocellular carcinoma 2- Moderate: extrahepatic obstruction, intrahepatic cholestasis 3- Severe: bone diseases	1-Moderate: infective hepatitis, prostate cancer 2- High in alcoholics	Biliary passage obstruction	When the liver loses more than 80% of its reserve capacity	All chronic liver diseases

MCQs

1- What type of immunoglobulin is increased in autoimmune hepatitis?			
A- IgA	B- IgM	C-IgG	D-IgD
2- Which one of the following markers is sensitive to alcoholism?			
A- ɣ Glutamyltransferase (GGT)	B- ALT	C- ALP	D- AST
3- A 47 year old male came to the ER complaining of right upper quadrant abdominal pain with nausea and vomiting, the ER doctor ordered some tests including LFTs which shows ALT levels of 275 U/L what might be the reason to this elevation?			
A- Hepatitis C infection	B- Alcoholic hepatitis	C- Cirrhosis	D- Acute hepatitis
4-Which one of the following is stored in the liver :			
A-Bile salts	B- Vitamin A	C- Vitamin C	D- Vitamin B_6
5- Which one of the following is an example of genetic disorders of the liver :			
A- Jaundice	B- Hepatitis	C- Steatosis	D-Hemochromatosis
6- One of the causes of pre-hepatic jaundice :			
A-Viral hepatitis	B- Toxic hepatitis	C- Abnormal RBCs	D-Tumors of the bile duct

Answers key

1- C 2- A 3- B 4- B 5- D 6- C

SAQs

1- Enumerate markers for cholestasis and their normal levels.

Answer

1- Alkaline phosphatase (ALP) 40 - 125 U/L
2- ɣ Glutamyltransferase (GGT) 10 - 30 U/L

2- A- Mention the causes of high AST levels
B- what is the normal range.

Answer

A- Chronic hepatitis - Cirrhosis - Liver cancer
B- 8-20 U/L

3- What are the limitations of LFTs ?

Answer

1) Normal LFT values do not always indicate absence of liver disease

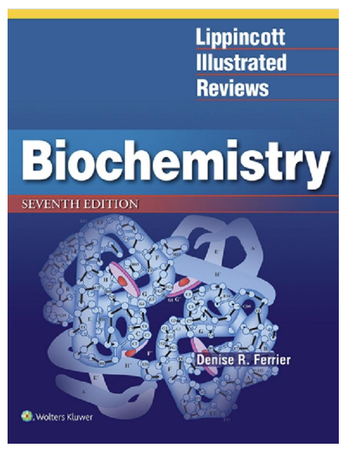
- Liver a has very large reserve capacity

2) Asymptomatic people may have abnormal LFT results

- Diagnosis should be based on clinical examination

Resources

Click on the book to download the resource



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Special thanks to Fahad AlAjmi for designing our team's logo.