-Liver function tests -

Biochimestry teamwork

Osamah Al-Jarallah	Al-Anood Asiri
Abdulaziz Al-Shamlan	Lama Mokhlis
Abdullah Al-Mazyad	Noha Khalil
Turki Al-Otaibi	Reem Al-Mansour
Khalid Al-Khamis	HadeelHelmi
Saud Al-awad	Nuha Al-Furayh
KhaledAlmohaimede	Jumana Al-Shammari
Meshal Al-Otaibi	DeemaJomar

By : Hadeel Helmi & MeshaL AlOtaibi

Biochemistry
Liver Function Tests

Red color = very important
Green color = Additional explanation

IF YOUR LIVER IS HEALTHY, YOU ARE HEALTHY

- N.B. → the doctor focused more on BILRUBIN & the function and damage of ALT + AST

Introduction:

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

Body is producing a lot of toxins which have to be neutralized.. AMMONIA can lead to death so it's converted in the liver to a non-toxic substance called "urea"

- Storage Function
  Vitamins K, A, D, E, B_{12}, and glycogen (source of energy)

- Production of bile salts
  Helps in digestion

SOME EXAMPLES OF LIVER DYSFUNCTION:

- Hepatocellular disease
- Cholestasis (obstruction of bile flow)
- Cirrhosis (chronic scarring)
- Hepatitis (causing inflammation)
- Jaundice (yellow discoloration of sclera and skin)
- Liver cancer
- Steatosis (fatty liver)

- G*enetic Disorders*
  Primary type Hemochromatosis (high iron storage due to increased absorption)

→ Secondary hemochromatosis is acquired, result of blood-related disorders such as certain anemias and thalassemia that increase RBC hemolysis

Blood enters the liver via the portal vein then leaves via:
→ hepatic veins *the blood used for LFTs* → systemic circulation
or → bile ducts → gall bladder → common bile duct

*click here for dr Sumbul's LFTs papers

LIVER FUNCTION TESTS

Non-invasive methods for screening of liver dysfunction.

You don't need to take a biopsy or cut out of liver just to do serum markers via blood sample

NEVER a diagnostic test;
Used as a screening method

Help in identifying general type or pattern of the disorder.

Assess severity and allow prediction of outcome.

How severe is the damage and what might be the prognosis of the patient.

By giving information about the **state of the liver** and you'll need to do other types of tests to exclude differentials.

Useful in disease and treatment follow up.

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

CLASSIFICATION:

Group I: Markers of liver dysfunction

If it is high, it will indicate something about the nature of the disease

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

The time it takes to clot the blood

Group II: Markers of hepatocellular injury

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

ALT is more specific for liver than AST

To remember:- ALT = LIVER

Group III: Markers of cholestasis

- Alkaline phosphatase (AKP)
- γ- glutamyl transferase (GGT)

LIMITATIONS:

1. Lack sensitivity as;

- Normal LFT values DO NOT always indicate absence of liver disease

Liver has very large reserve capacity, as it is a large organ

Only a large amount of damage will alter results of LFTs

- Asymptomatic people may have mild abnormal LFT results

Diagnosis should be based on clinical examination & good history taking skills

Alterations in tests may be physiological as in pregnancy (elevated AF; alpha fetoprotein) or drugs

2. Lack specificity as: some elevations or depressions in values may indicate diseases other than that of the liver.

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	Cholestasis or biliary obstruction
Bile acids	Cholestasis or biliary obstruction

Note: with obstruction of bile duct, bile content will accumulate in the ducts, backflow into the liver then exit via the hepatic vein → bilrubin and GGT enzymes will be found in the blood.

1.

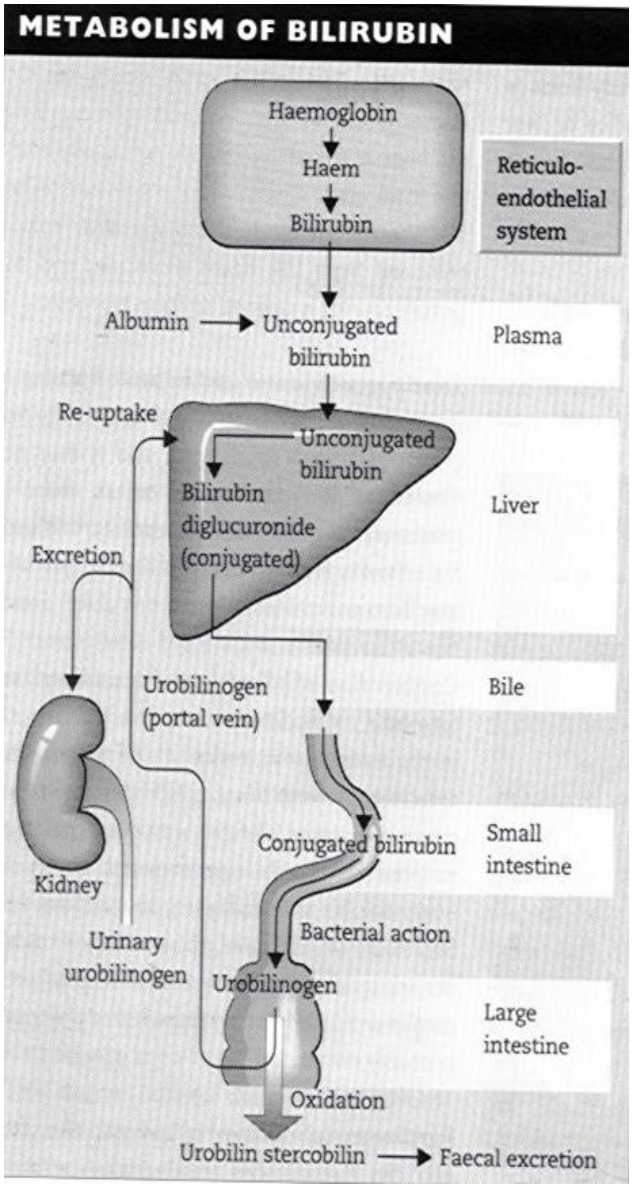
SERUM BILRUBIN: (IMPORTANT)

It is the yellowish pigment observed in jaundice

Is the end product of RBC breakdown (RBCs lifespan: 120 days)

1. Hemoglobin from the RBCs break down into a heme and a globulin
2. The heme group is taken up by macrophages of the reticuloendothelial system (including tissue macrophages and that of the liver and spleen) into bilrubin
3. Birubin is insoluble in the blood so it attaches and is carried to the liver by albumin
4. Bilrubin is derived from the albumin, enters the hepatocytes and conjugates with glucoronic acid by the enzyme UDP-glucourinile transferase
5. This soluble conjugated form is excreted via the bile duct into the intestine where the bacteria removes the glucoronic acid and converts bilrubin into urobilinogen
6. ➔ some of the urobilinogen is reabsorbed from the gut and enters the portal circulation
   → some is recycled in the enterohepatic cells
   → the remainder is transported along with the blood to the kidneys where it is converted into UROBILIN that is excreted in the urine, giving it it's characteristic YELLOW color

➔ mainly urobilinogen in the gut is **oxidized** by the bacteria **into strecobilin** which is excreted in the feces giving it its BROWN appearance



click here to see a graph of bilirubin metabolism

SERUM BILIRUBIN LEVELS:

Normal: 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

Latent jaundice: Above 1 mg/dL

→ patient does NOT presents with jaundice (subclinical jaundice)

Jaundice: Above 2 mg/dL

→High bilirubin levels are observed in gallstones, acute and chronic hepatitis

Class of Jaundice	Type of Bilirubin raised	Causes
Pre-hepatic or hemolytic	Unconjugated (always)	Increased bile production or decreased uptake, conjugation of excretion ex: Abnormal red cells; antibodies; drugs and toxins; thalessemia, Hemoglobinopathies
Hepatic or Hepatocellular	Unconjugated and conjugated	Viral hepatitis, toxic hepatitis, intrahepatic cholestasis, Gilbert's, Crigler-Naajjar syndromes → deficiency in UDP- glucourinile transferase enzyme → inability of liver to conjugate bile → we find only UNconjugated form (exception)
Post-hepatic or obstructive	Conjugated (always)	Decreased excretion Extrahepatic cholestasis; gallstones; tumors of the bile duct, carcinoma of pancreas

2. Urinary urobilinogen(UBG) and urine bile salts:

- Most UBG is metabolized in the large intestine (into strecobilin and excreted via feces)
- A small fraction is excreted in urine (less than 4 mg/day)
- 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.

3.

Serum Albumin: Major plasma protein	Serum Globulin:
The most abundant protein synthesized by the liver Normal serum levels: 3.5 to 5g/dL Its synthesis depends on the extent of functioning liver cell mass → the extent of decrease in its serum level is directly proportionate to the extent of liver damage Longer half-life of 20 days → does NOT indicate current liver functioning Its levels decrease in all chronic liver diseases →however at least 80% of the liver must be lost to show significant changes	Normal serum levels: 2.5 to 3.5g/dL α *and* β-globulins are 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

Albumin to globulin (A/G) ratio:
Normal A/G ratio: 1.2/1 – 1.5/1
Globulin levels INCREASE IN HYPOALBUMINEMIA AS A COMPENSATORY MECHANISM to maintain serum protein → results in decreased ratio

4.

Prothrombin Time (PT):

Prothrombin: synthesized by the liver, a marker of liver function

> The liver is in charge of synthesis of 11 of the 13 clotting factors!

Its half-life is 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
→ To confirm that the prolongation is a result of liver disease we do the test twice, once before and once after a supplementation of Vit K with a dose of 15-25mg/kg of body weight

Dosage of vitamin K does not affect PT in liver disease → both results there is prolonged time
If the prothrombin time decreases to by around 30% the second time → prolongation was due to Vit K deficiency

5.

Aspartate aminotransferase (AST):

Normal range: 8 – 20 U/L

AST → non-Specific
ALT → Liver only

A marker of hepatocellular damage
High serum levels are observed in chronic hepatitis, cirrhosis and liver cancer

→However, is not specific, as it is elevated in: auto immune diseases, hepatitis B & C, muscle and kidney problems

Alanine aminotransferase (ALT)

MORE LIVER-SPECIFIC THAN AST
Normal range (U/L):
- Male: 13-35
- Female: 10-30

High serum levels are observed in acute hepatitis (300-1000U/L)
Moderate elevation is observed in alcoholic hepatitis (100-300U/L)
Minor elevation is observed in cirrhosis, hepatitis C and non-alcoholic steatohepatitis (NASH) (50-100U/L)

→Appears in plasma many days before clinical signs appear (in asymptomatic patients)
A normal value does not always indicate absence of liver damage
Obese but otherwise normal individuals may have elevated ALT levels due to fatty liver

ALT-AST ratio: ALT>AST at all times **except** with chronic alcoholics → AST is double the ALT (2:1)

6.

Alkaline phosphatase (ALP):

Produced by bone osteoblasts (for bone calcification)

Normal range: 40 – 125 U/L

A non-specific marker of liver disease → also elevated in case of bone disease (pagot's disease) & in pregnancy (in placenta)

Modearte 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): (Not very specific)

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 in detecting alcohol abuse

* GGT is used to confirm liver disease in case of elevated ALP
→ both are increased in liver disease
→ only ALP will be increased in non-hepatic causes

Questions :-

1. A 26 year old male comes to the clinic with a yellowish tinge to the eyes and skin and complains of abdominal pain, fatigue and weakness, liver function tests only shows mildly elevated bilirubin (mostly unconjugated) and the rest of the parameters were all normal. Which ONE of the following is the most likely diagnosis?
A. Blau syndrome
B. Gilbert's syndrome
C. Rotor syndrome
D. Dubin-Johnson syndrome

2. **Increased conjugated biliribun is due to?**
A. Post-hepatic
B. Pre-hepatic
C. Hepatic
D. (A&C)
E. (B&C)

3. **Which one of the following has a (very high absorbed) level in bone diseases** ?
A. Aspartate aminotransferase (AST)
B. Gamma-glutamyltransferase (GGT)
C. Urinary urobilinogen(UBG)
D. Alkaline phosphatase (ALP)

4. Serum Albumin is decreased in which one of the following?
A. Chronic liver diseases
B. Liver cancer
C. Acute hepatitis
D. Bone diseases

Answers :-
1- B
2- D
3- D
4- A