Liver Function Tests / Lec.2

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PRE-HEPATIC

In pre-hepatic jaundice, there is excess production of bilirubin that overtakes the ability of liver to conjugate the bilirubin and excrete into the gut. This is predominantly unconjugated hyperbilirubinemia. The most common cause of pre-hepatic jaundice is hemolytic anemia which causes excess heme breakdown.

INTRA-HEPATIC

Intra-hepatic causes are due to parenchymal liver disease with inability to either conjugate or excrete bilirubin. In this case, the fraction of bilirubin that is elevated varies. Viral hepatitis often has a predominantly unconjugated bilirubinemia. A conjugated hyperbilirubinemia is seen with cholestasis from drugs or primary biliary cholangitis.

POST-HEPATIC

In post-hepatic jaundice or obstructive jaundice, there is an impediment to the flow of bile due to a partial or complete obstruction of the extrahepatic biliary passage between the liver and duodenum. Obstruction can occur within the biliary ducts themselves or more distal within the pancreas. This is predominantly a conjugated hyperbilirubinemia.

	PRE-HEPATIC	INTRA-HEPATIC	POST-HEPATIC
PHYSIOLOGY	Excessive hemolysis leading to increased bilirubin delivered to the liver	Defective conjugation Impaired cellular uptake Abnormal secretion	Mechanical obstruction of bile flow causing impaired excretion
ELEVATED BILIRUBIN	Unconjugated	Conjugated and unconjugated is possible	Conjugated
URINE COLOR	Normal	Dark	Dark
STOOL COLOR	Normal	Normal	Acholic

Urobilinogen is a yellow by-product of bilirubin reduction.

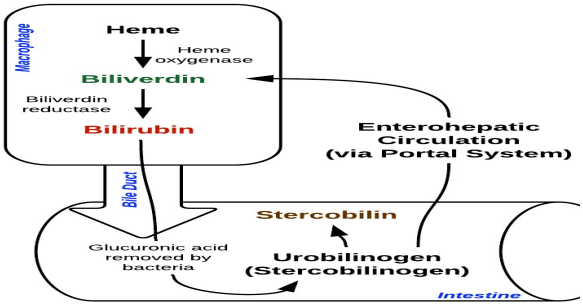
It is formed in the intestines by the bacterial enzyme bilirubin reductase.

About half of the urobilinogen formed is reabsorbed and taken up via the portal vein to the liver, enters circulation and is excreted by the kidney.

Increased amounts of bilirubin are formed in hemolysis , which generates increased urobilinogen in the gut.

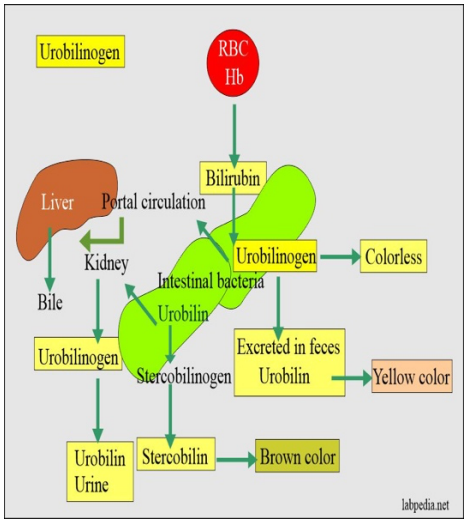
Urobilinogen is converted to the yellow pigmented urobilin apparent in urine

The urobilinogen in the intestine is directly reduced to brownish color stercobilin , which gives the feces their characteristic color.



It can also be reduced to stercobilinogen , which can then be further oxidized to stercobilin.
Urobilinogen has several fates:
1-partial oxidation to urobilin
2-partial reabsorption in the small intestine and
3- recirculation back to the liver - enterohepatic circulation reabsorption into blood and passage to kidney for excretion.

Urobilinogen excretion in the urine



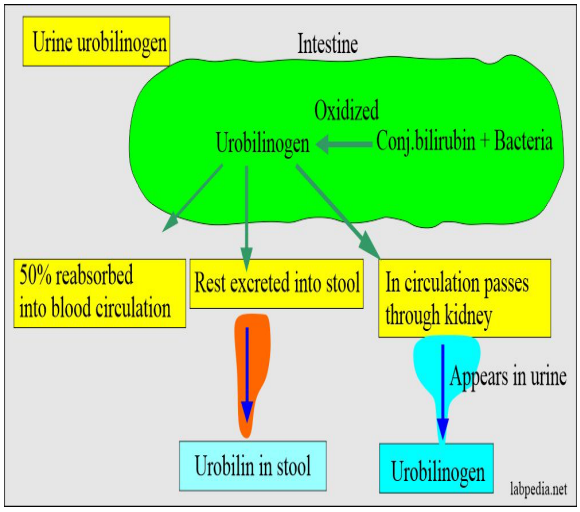


Table showing the presence of urine bilirubin and urobilinogen in various conditions

Test	Normal Person	Hemolytic Anemia	Liver Disease	Biliary Obstruction
Urine Bilirubin	negative	negative	Positive/ negative	Positive(+++)
Urine Urobilinogen	negative	Positive(+++)	Positive(++)	Absent(low)

Lab tests in jaundice:

1. Serum Bilirubin direct and indirect:
    1. Direct bilirubin is increased in obstructive jaundice.
    2. Indirect bilirubin increased hemolytic jaundice and infections, and toxic hepatitis.
2. Urobilinogen quantitative:
    1. Increased urobilinogen is seen in a liver infection, and toxic hepatitis is reabsorbed from the intestine.
    2. There is also an increase in the various types of hemolytic diseases.
    3. The absence of urobilinogen is strongly suggestive of post-hepatic biliary obstruction.
3. Urine bilirubin:
    1. There is an increase in the urine bilirubin due to the excessive production of bilirubin which is usually because of the post-hepatic type.
4. Fecal urobilin:

This will lead to a clay-colored stool.

5.Alkaline phosphatase:

1. It is increased in post-hepatic jaundice, cholangitis, and primary or metastatic cancer.
2. There may be a mild increase in hepatic jaundice.

6.Cholesterol esters: It is a decrease in liver disease.

7.Response to vitamin K: A poor response to vitamin K is seen in liver disease.

8.Flocculation test: Positive cephalin flocculation or thymol flocculation tests indicate liver diseases like infections or toxic hepatitis.

9.Galactose tolerance test: There is decreased tolerance to galactose is found in liver disease.

10.Liver needle biopsy:

This will diagnose liver disease.

- **How to differentiate the types of jaundice?**
- A- Hemolytic:
- 1- Increased unconjugated more than (conjugated) bilirubin.
- 2- Hemoglobin level low.
- B- Hepatic:
- 1- Increased amount of both conjugated and unconjugated.
- 2- Increased in AST and ALT more than increase in ALP.
- C- Obstructive:
- 1- Increased amount of direct (conjugated).
- 2- Significant increase in ALP more than AST and ALT.

Table of diagnostic tests

Function test	Pre-hepatic Jaundice	Hepatic Jaundice	Post-hepatic Jaundice
Total bilirubin	Normal / Increased	Increased	
Conjugated bilirubin	Normal	Increased	Increased
Unconjugated bilirubin	Normal / Increased	Increased	Normal
Urobilinogen	Normal / Increased	Increased	Decreased / Negative
Urine Color	Normal	Dark (urobilinogen + conjugated bilirubin)	Dark (conjugated bilirubin)
Stool Color	Normal	Normal/Pale	Pale
Alkaline phosphatase levels	Normal	Increased	
Alanine transferase and Aspartate transferase levels		Increased	
Conjugated Bilirubin in Urine	Not Present	Present	
Splenomegaly	Present	Present	Absent

- Liver Enzymes
- There are three types of enzymes:
- 1. Enzymes which are normally present inside the hepatocytes released into the blood when there is a hepatocellular damage (markers of hepatocellular damage).
- 2. Enzymes which are primary membrane bound (plasma membrane or side of hepatocytes) (markers of cholestasis).
- 3. Enzymes which are synthesized in the hepatocyte (indicates disturbances in the hepatocellular synthesis).

Hepatitis

It is an inflammation of the liver. Hepatitis viruses are the most common cause of hepatitis in the world but other infections, toxic substances (e.g. alcohol, certain drugs), and autoimmune diseases can also cause hepatitis.
There are 5 main hepatitis viruses, referred to as types A, B, C, D and E. In particular, types B and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis and cancer.

Hepatitis A and E are typically caused by ingestion of contaminated food or water. Common modes of transmission for these viruses include receipt of contaminated blood or blood products, invasive medical procedures using contaminated equipment and for hepatitis B transmission from mother to baby at birth, from family member to child, and also by sexual contact.

Acute infection may occur with limited or no symptoms, or may include symptoms such as jaundice (yellowing of the skin and eyes), dark urine, extreme fatigue, nausea, vomiting and abdominal pain.

Alkaline phosphatase

Alkaline phosphatase (ALP, ALKP, ALPase, Alk Phos) is a hydrolase enzyme responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins, and alkaloids.

The process of removing the phosphate group is called dephosphorylation.

- As the name ,alkaline phosphatases are most effective in an alkaline environment. It is an enzyme originating mainly in the bone, liver and placenta with minor contributions from kidney and intestine. It is called alkaline because it functions best at pH of 9.
- Serum ALP levels are age and gender dependent

The alkaline phosphatase (ALP) functions:
1.The exact metabolic function of ALP is still not known.
2.The main function is to remove the phosphate group from the proteins and other molecules.
3.These are necessary for the hydrolysis of organic phosphate and are important for digestion and mucosal absorption.
4.ALP is associated with lipid transport in the intestine.
5.The second role is in the osteoblastic tissues. The metabolic activity of the osteoblasts is associated with ALP activity.
6.ALP is also associated with the calcification process of the bone.
7.ALP is beneficial in distinguishing various bone diseases and hyperparathyroidism when combined with serum calcium and X-rays.
8.Alkaline phosphatase is called Alkaline because its function is seen between a pH of 9 to 10 and best at a pH of 9.0.

- Serum ALP is of interest in the diagnosis of 2 main groups of conditions-hepatobiliary disease and bone disease associated with increased osteoblastic activity.
- The response of the liver to any form of biliary tree obstruction is to synthesize more ALP.
- ALP also is elevated in disorders of the skeletal system that involve osteoblast hyperactivity and bone remodeling.
- A considerable rise in alkaline phosphatase activity caused by increased osteoblast activity following accelerated bone growth is sometimes seen in children and juveniles.
- Elevated alkaline phosphatase
- The elevated level can occur in :
- 1)Biliary obstruction. 2)Bone conditions 3)Osteoblastic bone tumors
- 4)Osteomalacia. 5)Liver disease or hepatitis 6)Leukemia
- 7)Lymphoma 8) Paget's disease 9)Hyperparathyroidism
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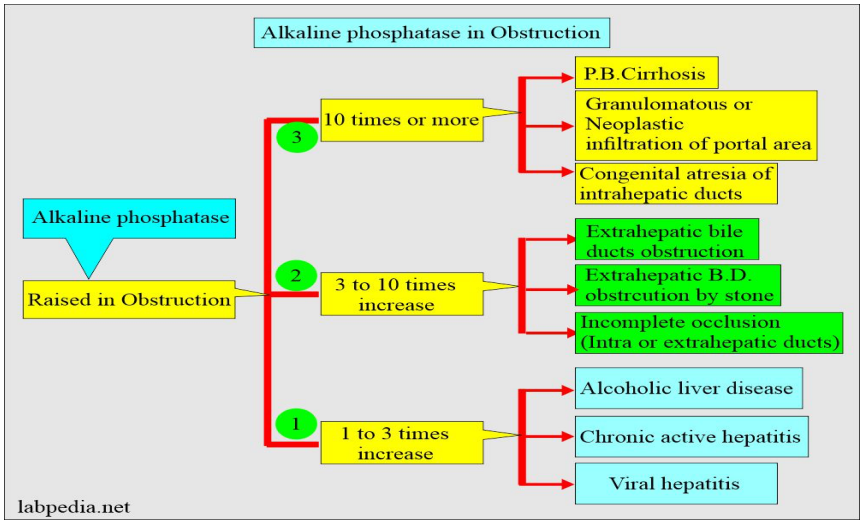
Effects of Obstruction on ALP:

1. The liver ALP is increased in biliary obstruction when its excretion is impaired. While in intrahepatic obstruction, there is less increase in ALP level than in biliary obstruction, which may go up to 2.5 times.

2. In extrahepatic obstruction, it may reach 10 to 12 times the upper limit and normal when surgically obstruction is removed.
3. In the case of infectious hepatitis, there may be moderate elevation or even normal.

Interpretation of your test results can involve consideration of multiple factors

- The degree of elevation: Very high levels are often seen with blockages of the bile ducts, but these levels alone cannot distinguish between liver problems and other conditions.
- Other test measurements: ALP is often measured along with other enzymes, such as aspartate aminotransferase(AST) , alanine aminotransferase(ALT, gamma-glutamyl transpeptidase(GGT) and/or 5′-nucleotidase (5'-NT), and the levels of ALP relative to these enzymes can help determine the significance of the test result.



Alkaline phosphatase level (ALP) may be mildly raised in:

1. Metastatic diseases of the liver.
2. Hepatocellular carcinoma.
3. Biliary Cirrhosis.
4. Intrahepatic and extrahepatic cholestasis.
5. Gilbert's syndrome.
6. Chronic alcohol ingestion.
7. Diabetes mellitus and diabetic hepatic lipidosis.

Alkaline phosphatase raised level in various conditions:

Level of raised Alkaline phosphatase (ALP)	Causes of raised Alkaline phosphatase (ALP)
• >5 times the normal (marked elevation)	1. Biliary cirrhosis 2. Intrahepatic biliary duct obstruction 3. Extrahepatic biliary duct obstruction 4. Paget's disease 5. Hyperparathyroidism 6. Osteogenic sarcoma
• 3 to 5 times the normal (Moderate elevation)	1. Infectious mononucleosis 2. Granulomatous infiltration of the liver 3. Metastatic tumors in bone 4. Rickets 5. Osteomalacia
• Up to 3 times the normal (Mild elevation)	1. Cirrhosis 2. Viral hepatitis 3. Pregnancy (placental ALP) 4. Physiologic in children