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SCHOOL OF MEDICINE AND HEALTH SCIENCES
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DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

MBBS SEMINAR & BMLS CLINICAL CHEMISTRY

LIVER FUNCTION TESTS – An Overview

What are some of the functions of the Liver?

- Plays major role in metabolism of Proteins, Carbohydrates and Lipids
- Involves in biosynthesis and of breakdown of blood cells
- Detoxify and excrete both endogenous and exogenous compounds
- Formation of Bile, Storage of Glycogen, Formation of Urea and Ketone Bodies
- Reduction and Conjugation of Adrenal and Gonadal steroid hormones,
- Detoxification of Drugs and Toxins,
- Biosynthesis of Plasma Proteins,
- Inactivation of Polypeptide hormones
- **Significance of a Healthy Liver to the various biochemical processes occurring in the living organism cannot be over emphasized**

What do you understand as Liver Function Tests (LFT)?

- LFT are crude Indices of Hepatic Structure, Cellular Integrity, and Function
- LFT are based on measurements of substances released from damaged hepatic cells into the blood
- LFT are measurements of blood components that gives an idea of the Existence, Extent and Type of Liver damage
    - They provide useful information regarding the Presence and Severity of Hepatobiliary Injury or Impairment of Liver Function

What biochemical parameters are in LFT?

- Biochemical parameters in LFT are:
    - Bilirubin (Conjugated and Unconjugated)
    - Aminotransferases (ALT, AST)
    - Alkaline Phosphatase,
    - Serum Albumin and Total Protein

What do the biochemical parameters indicate?

- The biochemical parameters assist in differentiating:
- Obstruction to the biliary tract
    - Indices of Cholestasis, blockage of bile flow are indicated by
        i. Serum Total Bilirubin concentration and
        ii. Serum Alkaline Phosphatase activity

- Acute Hepatocellular damage
    - Serum Aminotransferase (ALT & AST) activities are measure of the Integrity of Hepatocytes

- ALT & AST levels in plasma/serum are sensitive index of hepatocellular damage
- ALT & AST are located mainly in the Peri-portal Hepatocytes, thus do not give reliable indication of Centri-lobular Liver damage

- Chronic liver disease:
  - Serum Albumin concentration is a Crude measure of the Synthetic Capacity of the Liver, although it is affected by many other factors

Can a single biochemical test be used to assess liver function?

- Liver is highly Compartmentalized, therefore No Single Biochemical Test can be used to fully access functional state of Liver
- LFT is needed to ascertain hepatic dysfunction if any
  - Objectives of LFT and diagnostic models for the tests:
    - Sensitive detection of suspected dysfunction
    - Document an abnormality
    - Determine the type (e.g., Cholestasis versus Hepatocellular disease) and Site (i.e., Intra-hepatic versus Extra-hepatic) of Injury
    - Follow-up of patients with Hepatic diseases

- No single biochemical test can satisfy all these objectives,
- Tests are therefore used in combination: Liver Function Test
- Each selected test must satisfy the following:
  - Diagnostic sensitivity in screening for dysfunction;
  - Specificity for liver disease;
  - Selectivity in differentiating these disorders

What are the criteria used to select parameters in LFT?

- Some of these criteria include the following:
- Tests based on substances produced or synthesized by Liver
  - Example: Albumin, Cholinesterase, Coagulation factors

- Tests based on substances released from damaged Hepatocytes
  - Tests separated into two groups:
    - Endogenous compounds released by damaged hepatocytes
      - Examples: Enzymes such as AST and ALT
    - Endogenous compounds synthesized at Increased rate or Released by Canalicular membrane, Bile duct epithelium and Endothelium of central and periportal veins Examples: ALP, GGTP, 5'Nucleotidase

- Test based on substances cleared from plasma by Liver:
  - Can be separated into two groups:
    - Endogenous metabolites: Examples: Bilirubin, Bile acids, Ammonia;
    - Exogenous compounds: Examples: Aminopyrine, Lidocaine, Indocyanine green, Caffeine

Give three reasons for increase levels of Bilirubin in blood?

- Three main reasons why bilirubin levels in blood may rise:
- Hemolysis:
    - Damage to RBC causes increased breakdown of Hb to produce Unconjugated Bilirubin, which overloads Conjugating mechanism in Liver causing Hyperbilirubinemia
- Failure of Conjugating mechanism within Hepatocytes,
- Obstruction in the Biliary System

TAKE NOTE:

- Conjugated and Unconjugated Bilirubin may be present in plasma
- Conjugated Bilirubin is soluble in aqueous medium
- Conjugated Bilirubin can appear in urine
- Unconjugated Bilirubin is not soluble in aqueous medium, it binds to Albumin and transported to the liver
- Unconjugated Bilirubin cannot appear in the urine
- Unconjugated Bilirubin is neurotoxic, and if levels rise too high in Neonates, permanent brain damage can occur
- Conjugated Bilirubin is excreted into the bile
- Bacteria in gut metabolize Bilirubin, producing a group of colorless compounds known collectively as Urobilinogen or Starcobilinogen
- Urobilinogen is partly reabsorbed via Enterohepatic circulation of Urobilinogen in adults
- Urobilinogen is responsible for coloration of urine
- Urobilin is responsible for the brown coloration of feces
- If Bilirubin does not reach the gut the stool color becomes pale

What is the diagnostic significance of AST?

- Aspartate Aminotransferase (AST) was formerly called Serum Glutamate Oxaloacetate Transaminase (SGOT)
- AST is high in Heart muscle, Liver, Skeletal muscle, but found in lesser degree in Kidneys, Pancreas, RBC
- Damage tissues releases AST in blood: serum/plasma level rises
- AST elevation is directly related to extent of cellular damage or injury
- Elevation of AST in plasma depends on length of time that the blood is drawn after damage or injury (**Why?)**
    - Because AST is cleared from the blood in a few days

- AST level in plasma is elevated 8 hours after cellular injury, peak at 24 to 36 hours, and return to normal in 3 to 7 days
- AST level is persistently elevated in chronic Hepatocellular disease
- In Acute Hepatitis, AST can be elevated as much as 20 times the normal value
- In Acute Extra-hepatic Obstruction (e.g., Gallstone), AST levels quickly rise to 10 times the normal and swiftly fall
- In Cirrhotic patients level of AST depends on the amount of active inflammation

What factors can interfere with serum AST levels?

- Factors that interfere with serum AST include:
  - Pregnancy – can cause decreased levels of AST
  - Exercise – can cause increased levels of AST
  - Drugs such as Anti-hypertensives, Cholinergic agents, Coumarin-type Anticoagulants, Oral Contraceptives, Opiates, Salicylates, Hepatotoxic medications,

What is the diagnostic significance of ALT?

- **Alanine Aminotransferase (ALT)** was formerly called Serum Glutamate-Pyruvate Transaminase (SGPT)
- **ALT** is mainly in Liver, lesser quantities are in Kidneys, Heart and Skeletal muscle
- Liver dysfunction or injury causes elevation of ALT level in blood
- ALT is a sensitive and specific indicator of Hepatocellular disease
- Plasma ALT level is more Liver-specific than AST
- ALT elevation is directly related to extent of cellular damage or injury
- Elevation of ALT in plasma depends on length of time that the blood is drawn after damage or injury (**Why?)**
  - Because ALT is cleared from the blood in a few days

- ALT level in plasma is elevated 8 hours after cellular injury, peak at 24 to 36 hours, and return to normal in 3 to 7 days
- AST is released more than ALT in Chronic Hepatocellular disease (Cirrhosis)
- In most Hepatocellular disease other than Viral Hepatitis ALT/AST ratio (DeRitis ratio) is usually less than 1
- In viral hepatitis the ratio is usually greater than 1
- Large number of drugs can increase serum level of ALT

What is the diagnostic significance of Alkaline Phosphatase (ALP)?

- ALP activity is increased in an Alkaline (pH of 9 to 10) medium
- ALP is highest in Liver, Biliary Tract Epithelium, Bone, Placenta
  - ALP is in Kupffer's cells lining Biliary collecting system

- Plasma/Serum ALP level use to detect disorders in Liver and Bond
- In Liver disease, increase plasma ALP is due to increased synthesis by cells lining the Bile Canaliculi, usually in response to Cholestasis, which may be either Intra-hepatic or Extra-hepatic
- Levels of ALP in plasma/serum are greatly increased in both Extra-hepatic and Intra-hepatic Obstructive Biliary Disease and Cirrhosis
- Hepatic tumors, Hepatotoxic drugs and Hepatitis, cause smaller elevations in serum ALP levels

What are some of the Extra-hepatic sources of ALP?

- Bone is the most frequent Extra-hepatic source of ALP
- New bone growth is associated with elevated levels of ALP
- Healing fractures, Rheumatoid Arthritis, Hyperparathyroidism
- Placenta, (Placental ALP appears in the maternal blood usually in the third trimester of pregnancy), Small intestine, Kidney

How are the Isoenzymes of ALP used in diagnosis?

- **Isoenzymes of ALP are used to distinguish between liver and bone diseases**
- Isoenzymes are most easily differentiated by Heat Stability Test and by Electrophoresis
- ALP Isoenzyme produced in **Liver** (**ALP 1**) is **Heat Stable**
- ALP Isoenzyme produced in **Bone (ALP 2) is Inactivated by heat**
- Detection of Isoenzymes help differentiate the source of the Pathologic condition associated with Elevated Total ALP
- ALP 1 is expected to be higher in Liver disease

How is the source of ALP elevation in blood be determined by 5` Nucleotidase?

- Sources of elevated ALP can be determined by analyzing 5` Nucleotidase in the same serum sample
- 5` Nucleotidase is produced predominantly in the Liver
- If both total ALP and 5` Nucleotidase are elevated, then it is Liver disease
- If 5` Nucleotidase is normal and ALP is elevated then Bone is the most probable source of the elevated ALP
- In certain individuals with type B and type O blood, the serum ALP is elevated

What is the diagnostic significance of GGTP?

- **Gamma Glutamyl Transpeptidase (GGTP or γGT)** participates in the transfer of Amino Acids and Peptides across Cellular membrane and possibly participates in Glutathione metabolism
- GGTP level is very high in Liver and Biliary Tract
- Lesser concentrations are in Kidney, Spleen, Heart, Intestine, Brain, and Prostate gland
- Men may have higher GGTP levels than women because of the additional levels in the prostate
- Test for GGTP is used to detect Liver cell dysfunction,
- GGTP test is highly accurate in indicting Cholestasis
- GGTP is the most sensitive Liver enzyme for detecting Biliary Obstruction, Cholangitis, or Cholecystitis
- Elevation of GGTP parallels that of ALP in Liver disease
- GGTP is not increased in Bone disease

TAKE NOTE:

- Normal GGTP level with an elevated ALP would imply Skeletal disease
- Elevated GGTP and elevated ALP would imply Hepato-biliary disease
- Unlike ALP, GGTP is not elevated in childhood or pregnancy
- GGTP can be used to detect Chronic Alcohol Ingestion
- GGTP is very useful in the screening and evaluation of alcoholic patients
- GGTP is elevated in about 75% of patients who chronically drink alcohol
- GGTP level is usually elevated about 1 to 2 weeks after infarction

TATAL PROTEINS (Albumin and Globulins):

- Albumin and Globulin constitute most of the proteins in blood and are measured as Total Protein
- Albumin is synthesize in the Liver
- Albumin transports important blood constituents, such as drugs, hormones, and enzymes
- Globulins are the key building block of Antibodies, Glycoproteins, Lipoproteins, Clotting Factors, Complement Proteins, Acute-Phase Reactant
- Some Globulins are synthesize in the Liver, but most are made in the Reticuloendothelial System
- Both Albumin and Globulins can be measured separately

What is the diagnostic significance of Albumin in blood?

- Albumin is the major protein synthesized within the liver, thus can be use to assess hepatic function
- Estimation of Pre-albumin is a better assessment of liver func**tion**
- When disease affects the liver, the Hepatocytes lose ability to synthesize albumin, and the serum albumin level is diminished
- Because the half-life of albumin is 12 to 18 days, severe impairment of hepatic albumin synthesis may not be recognized for several weeks or even months
- Hypo-albuminaemia is a feature of advanced chronic liver disease and severe acute liver damage
- In some cases of Chronic liver disease, Albumin level is low, but tGlobulin level is high given a normal Total Protein level
- Reason for this might be that the liver cannot produce Albumin, thus accounting for the low albumin level, whereas the Globulins are mostly made in the Reticuloendothelial system and therefore their levels tend to increase
- These changes can however be detected by measuring the Albumin/Globulin (A/G) ratio or performs Protein Electrophoresis
- A/G ratio is not a diagnostic parameter
- Malnutrition can cause decrease in Albumin level in blood

What is the significant of Prothrombin Time in LFT?

- **Prothrombin Time** is a measure of the activities of certain Coagulation Factors made by the Liver,
- It is used as an indicator of Hepatic Synthetic Function
- Prothrombin has a very short half-life, and **an increased Prothrombin time may be the earliest indicator of hepatocellular damage**