LIVER FUNCTION TESTS

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What are some of the functions of the Liver?

Live is involved in:

- Metabolism of Proteins, Carbohydrates and Lipids,
- Biosynthesis and breakdown of blood cells,
- Detoxification of endogenous and exogenous compounds,
- Formation of Bile,
- Storage of Glycogen,
- Formation of Urea and Ketone Bodies,
- Conjugation of steroid hormones,
- Detoxification of Drugs and Toxins,
- Biosynthesis of Plasma Proteins,
- Inactivation of Polypeptide hormones,
- **Significance of Healthy Liver to biochemical processes occurring in living organism cannot be over emphasized;**

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

- Liver Function Tests (LFT) are:
  - Crude Indices of Hepatic Structure, Cellular Integrity, and Function;
  - Based on measurements of substances released from damaged hepatic cells into the blood;
  - Measurements of blood components that gives idea of the Existence, Extent and Type of Liver damage;
- LFT provide useful information about 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),
  - Alanine Aminotransferase (ALT,
  - Aspartate Aminotransferase (AST)
  - Alkaline Phosphatase (ALP),
  - Gamma Glutamyl Transpeptidase (GGTP or **γGT**)
  - 5`-Nucleotidase,
  - Serum or Plasma Albumin,
  - Total Protein,

What do the biochemical parameters indicate?

Biochemical parameters assist in differentiating:

- **Acute Hepatocellular damage:**
  - Serum Aminotransferase (ALT & AST) activities are measure of the Integrity of the Hepatocytes;
    - ALT & AST levels in plasma/serum are sensitive index of hepatocellular damage,
    - ALT & AST are located mainly in the **Peri-portal** area of the Hepatocytes, thus do not give reliable indication of **Centri-lobular** Liver damage;

- **Obstruction to the biliary tract:**
  - Indices of Cholestasis and blockage of bile flow:
    - Serum Total Bilirubin concentration, and
    - Serum Alkaline Phosphatase (ALP) activity;
    - Gamma Glutamyl Transpeptidase (GGTP),
    - 5`-Nucleotidase,
- **Chronic liver disease**:
  - Serum Albumin concentration
    - (It 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;
- No Single Biochemical Test can be used to fully access functional state of the Liver;
- LFT is used to determine hepatic dysfunction, if any,
- Objectives of LFT and diagnostic models for LFT are:
  - **Sensitive detection of suspected dysfunction,**
  - **Document an abnormality,**
  - **Determine type (Cholestasis vs Hepatocellular disease) and Site (Intra-hepatic vs Extra-hepatic) of Injury,**
  - **Follow-up of patients with Hepatic diseases;**

- No single biochemical test can satisfy all these objectives,
- Combination of Tests used: **Liver Function Tests**
- 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 that are produced or synthesized by Liver,** Examples:
  - **Albumin,**
  - **Cholinesterase,**
  - **Coagulation factors**

- **Tests based on substances released by damaged Hepatocytes:**
- These Tests are separated into two groups:
  - Endogenous compounds released by damaged hepatocytes,
    - Examples: **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 major causes for increase in blood Bilirubin level

- Major causes for increase bilirubin levels in blood:
- **Hemolysis**:
  - Damage to RBC may cause increased breakdown of Hb producing Unconjugated Bilirubin, which may overload liver Conjugating system, causing Hyperbilirubinemia;
- **Failure of Conjugating system in the liver,**
- **Obstruction in the Biliary System**,

IMPORTANT TO NOTE

- Conjugated & Unconjugated Bilirubin are in plasma,
- Conjugated Bilirubin is soluble in aqueous medium,
- Conjugated Bilirubin can appear in urine,
- Unconjugated Bilirubin is not soluble in aqueous medium, Albumin binds and transported it to liver,
- Unconjugated Bilirubin cannot appear in urine,
- Unconjugated Bilirubin is Neurotoxic; if blood levels rise too high in Neonates, permanent brain damage may occur;

- Conjugated Bilirubin is excreted into the bile,
- Bacteria in gut metabolize conjugated bilirubin, producing Urobilinogen and Stercobilinogen,
- Urobilinogen is partly reabsorbed via Entero-hepatic circulation of Urobilinogen in adults,
- Urobilinogen is excreted as Urobilin that is responsible for coloration of urine,
- Stercobilinogen is excreted as Stercobilin that is responsible for coloration of feces,
- If Stercobilinogen is not formed in the GIT the stool color is pale;

What is the diagnostic significance of AST?

- **AST:** {old name is: Serum Glutamate Oxaloacetate Transaminase (SGOT)}
- **AST** is high in Heart muscle, Liver and Skeletal muscle, but low in Kidneys, Pancreas, RBC;
- Damage tissues releases AST in blood;
- AST level in blood is directly related to extent of cellular damage or injury;
- Amount of **AST** in plasma depends on length of time that the blood was drawn after injury (**Why?)**
  - Because AST is cleared from the blood in a few days;

- **AST** level in plasma is elevated 8 hrs after cellular injury, peak at 24 to 36 hrs, and return to normal in 3 to 7 days;
- **AST** level in blood is always high in patients with chronic Hepatocellular disease,
- Acute Hepatitis: AST in plasma is about 20 times the normal value;
- Acute Extra-hepatic Obstruction (e.g., Gallstone), AST levels quickly rise to 10 times normal and swiftly falls
- Cirrhotic patients: level of AST in plasma depends on the amount of active inflammation;

What factors can interfere with levels of AST in Serum?

- Factors that interfere with serum AST include:
  - Pregnancy: causes decreased levels of AST,
  - Exercise: causes 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?

- **ALT:** {Old name Serum Glutamate Pyruvate Transaminase (SGPT)}
- **ALT** found mainly in Liver, lesser quantities are in Kidneys, Heart and Skeletal muscle;
- Liver injury causes elevation of ALT level in blood;
- **ALT:** sensitive, specific indicator of liver disease,
- ALT level is more Liver-specific than AST;
- ALT level is directly related to extent of liver injury,
- Elevation of ALT in plasma depends on length of time that the blood was drawn after damage or injury (**Why?)**
  - Because ALT is cleared from the blood in a few days

- **ALT** level in plasma is elevated 8 hrs after cellular injury, peak at 24 to 36 hrs, 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 ALP?

- ALP activity is increased in an Alkaline (pH 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 ALP level is use to detect disorders in Liver and Bone;
- Liver disease: increase plasma ALP is due to synthesis by cells lining Bile Canaliculi, in response to Intra-hepatic or Extra-hepatic Cholestasis;
- ALP level in plasma is greatly increased in both Extra-hepatic and Intra-hepatic Obstructive Biliary Disease and Cirrhosis;
- Hepatic tumors, Hepatotoxic drugs and Hepatitis may 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 causes elevated blood levels of ALP;
- Healing fractures,
- Rheumatoid Arthritis,
- Hyperparathyroidism;
- Placenta,
  - Placental ALP appears in maternal blood usually in the third trimester of pregnancy;
- Small intestine,
- Kidneys,

How are the Isoenzymes of ALP used in diagnosis?

- Two major Isoenzymes: ALP-I, ALP-II
- ALP-I: produced mainly in Liver is Heat Stable,
- ALP-II: produced in Bone (ALP 2) is Inactivated by heat,
- They are used to distinguish liver and bone diseases;
  - By Heat Stability Test and by Electrophoresis,
- Detection of Isoenzymes help determine source of pathology condition causing elevated Total ALP in blood;
- ALP-I is expected to be higher in Liver disease;

How can 5`-Nucleotidase be used to determining source of high level of ALP in blood?

- Source of elevated ALP can be determined by testing the same serum sample for 5`-Nucleotidase,
- 5`-Nucleotidase is produced predominantly in the Liver,
- If both total ALP and 5`-Nucleotidase are elevated in plasma, then Liver is the source of the ALP;
- If plasma level of 5`-Nucleotidase in normal, but level of 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 may be elevated;

What is the diagnostic significance of GGTP?

- **GGTP (γGT):** Catalyzes transfer of Amino Acids and Peptides across membrane and involve in Glutathione metabolism;
- GGTP level is very high in Liver and Biliary Tract, but low in Kidney, Spleen, Heart, Intestine, Brain and Prostate gland,
- GGTP levels are higher males because of levels in 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,

IMPORTANT TO NOTE

- Normal plasma level of GGTP with elevated ALP level may indicate Skeletal disease,
- Elevated plasma level of GGTP and elevated ALP may indicate Hepato-biliary disease,
- GGTP is not elevated in childhood or pregnancy;
- GGTP can be used to detect Chronic Alcohol Ingestion,
- GGTP is useful in screening and evaluation of alcoholics,
  - GGTP is elevated in about 75% of patients who chronically drink alcohol,
- GGTP level is usually elevated about 1 to 2 weeks after myocardial infarction;

TATAL PROTEIN (Albumin and Globulins)

- Albumin and Globulins 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: key components of Antibodies, Glycoproteins, Lipoproteins, Clotting Factors, Complement Proteins, Acute-Phase Reactant,
- Some Globulins are synthesize in Liver, but most are made in Reticuloendothelial System,
- Albumin and Globulins can be measured separately,

What is the diagnostic significance of Albumin in blood?

- Albumin is the major protein synthesized in liver, thus can be use to assess hepatic function,
- Estimation of Pre-albumin is a better assessment of liver function,
- In some diseases of the liver, hepatocytes are unable to synthesize albumin, thus plasma albumin level drops,
- Half-life of albumin is 12 to 18 days, thus, 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 Chronic liver diseases, Albumin level is low, but Globulin level is high given normal Total Protein level,
  - Reason might be that liver cannot produce Albumin, thus the low albumin level, but Globulins are mostly made in Reticuloendothelial system, thus their levels may increase during infection;
- These changes can 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 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 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,**

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