Liver function and clinical chemistry of liver

INTRODUCTION

The liver plays a major role in carbohydrate, lipid and protein metabolism with the processes of glycolysis, the Krebs cycle, homeostasis synthesis and glycogenolysis, gluconeogenesis, glycogen synthesis and degradation, and protein lipogenesis, ketogenesis, amino acid synthesis synthesis; all taking place in the hepatocytes

Hepatocytes also metabolize and detoxify endogenous (haem) and products (drugs), which are then excreted via the biliary tree

<table>
<thead>
<tr>
<th>Test</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma albumin</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Plasma total and direct bilirubin</td>
<td>Hepatic anion transport</td>
</tr>
<tr>
<td>Plasma enzyme activities ALT/AST</td>
<td>Hepatocellular integrity</td>
</tr>
<tr>
<td>Alkaline phosphatase and GGT</td>
<td>Presence of Cholestasis</td>
</tr>
</tbody>
</table>

Some of routine liver function test group

1-Bilirubin

The Sources of Bilirubin is haemoglobin which is produced from RBC breakdown; 90% of RBC breakdown occurs within reticuloendothelial system (RES) cells mainly in spleen or ineffective erythropoiesis in bone marrow and other haem containing proteins e.g. myoglobin and cytochrome P450 (mainly in liver to 80% of daily bilirubin production is derived from the breakdown of senescent red blood cells, while the remainder is derived from ineffective erythropoiesis and the breakdown of other haem-containing proteins
Total daily bilirubin production is 450 up to 550 µmol/day.

Formation of Bilirubin:
Hemoglobin is broken down to globin and haem. Globin (a protein) is broken down to its constituent amino acids. Haem (a 4 ring structure containing Fe2+ at its center) is broken down (via biliverdin) to carbon monoxide, iron and bilirubin Biliverdin gives the green colour sometimes seen in a resolving bruise The bilirubin at this stage is termed un-
Conjugated bilirubin because it has not yet been processed by conjugation in the liver

**Un-Conjugated Bilirubin (Hemo-Bilirubin, Indirect Bilirubin)**
A hydrophobic molecule Strongly bound (high affinity) to hydrophobic sites on albumin Does not appear in urine Free un-conjugated bilirubin normally <3 µmol/l Can be displaced from binding sites on albumin by drugs (salicylates sulphonamides) Free un-conjugated bilirubin is neurotoxic At high concentrations it deposits in cell membranes (esp. basal ganglia causing kernicterus

**Uptake by the Liver**
The un-conjugated bilirubin - albumin complex is carried in the plasma to the hepatic sinusoids, enters and dissociates at the hepatocyte membrane

**Conjugation by the Liver**
The bilirubin is then conjugated with glucuronic acid by UDP-glucuronyl transferase (UDPGT-I) to bilirubin mono-glucuronide (BMG) and by UDPGTII to bilirubin diglucuronide (BDG)

Conjugated bilirubin is more water soluble and can be excreted in bile or urine

Under normal circumstances there is no conjugated bilirubin present in plasma

**Excretion into Bile:**
Conjugated bilirubin is transported out of the liver cells into the bile canaliculi

**Urobilinogen:**
In the GIT, bacterial flora converts conjugated bilirubin to urobilinogen, Most of the urobilinogen (colourless) is further converted by colon
bacteria to urobilin and stercobilin (brown In the absence of bowel flora (newborns, broad spectrum antibiotic therapy faeces are Yellow due to bilirubin, 20% of urobilinogen in the small intestine is reabsorbed into the portal circulation, taken up by the liver again and re-excreted (enterohepatic circulation) Some urobilinogen appears in normal urine Easy to test with dipstick

LIVER DISORDERS AND JAUNDICE

Jaundice is the yellow appearance of skin and sclerae due to the presence of an excessive amount of bilirubin (jaundice becomes clinically visible when serum bilirubin is > 40 μmol/l).

The liver has a large reserve capacity- jaundice only appears with severe impairment of liver function

CLASSIFICATION OF JAUNDICE ACCORDING TO ITS CAUSE

A. Prehepatic: Excess bilirubin production

B. Intrahepatic:

Decreased uptake of bilirubin into liver cells, Decreased conjugation of bilirubin by liver cells Decreased excretion of bilirubin into bile canaliculi

C. Posthepatic: Biliary obstruction

BILE ACID (= BILE SALT) METABOLISM

Bile acids are soluble metabolites of cholesterol The products of cholesterol metabolism are chenodeoxycholic acid and cholic acid, known as primary bile acids because of their hepatic origin The rate limiting and regulated step in their formation is 7-hydroxylation of cholesterol

Prior to secretion into the bile canaliculi, the primary bile acids are conjugated to glycine or taurine
In the GIT, bacterial enzymes deconjugate and dehydroxylate the primary bile acids and convert them to the secondary bile acids lithocholic acid and deoxycholic acid.

Most of the bile acids in the GIT are reabsorbed into the portal circulation taken up by the liver again and reexcreted (enterohepatic circulation)

Re-uptake of bile acids by the liver is highly efficient, but sensitive to liver damage

**Structure of Bile Acids:**

Bile acids are amphipathic molecules. Thus one side is hydrophilic (due to -OH groups), the other hydrophobic, which gives detergent properties. This facilitates the formation of micelles when mixed with triglyceride or other lipids, and allows lipid absorption

**LIVER ENZYMES**

The usefulness of serum enzymes as markers of liver disease is limited by the fact that they are also found in and released from other tissues

A- Enzymes Reflecting Liver Cell Damage

These enzymes are released from damaged cells, due to increased cell membrane permeability or cell necrosis

1- Transaminases

Aspartate transaminase (AST) has widespread tissue distribution including liver, red blood cells, skeletal and cardiac muscle. No tissue-specific isoenzymes. Cytosolic and mitochondrial

2-Alanine transaminase (ALT) is more liver-specific. Cytosolic only

They are important for formation of non-essential amino acids (through reactions of -ketoacids with glutamate) They are important for
formation of sugar amines and They convert amino acids into ketone bodies or glucose for energy production during starvation

ALT / AST Ratio Normal value: 1

ALT / AST > 1: ALT is a liver specific enzyme increased under infectious hepatitis or liver cirrhosis

ALT / AST < 1: AST is a heart specific enzyme increased under heart disease as myocardial infraction & ischemic heart disease

ALT / AST = 1: AST & AST both increased mainly in viral hepatitis

Lactate Dehydrogenase (LD or LDH)

has widespread tissue distribution including liver, red blood cells, skeletal and cardiac muscle. Tissue-specific isoenzymes can be separated by electrophoresis. The LD5 isoenzyme is found in liver and skeletal muscle only

B- Enzymes Reflecting Cholestasis

Alkaline phosphatase (ALP) has widespread tissue distribution including liver, bone, placenta and GIT. The natural function of this enzyme is unknown It is an ecto-enzyme, located on the outside of the cell membrane, canalicular side of liver cell. It is released into plasma in cholestasis.

Gamma-glutamyl transpeptidase (GGT) is more liver-specific. It is involved in the transport of amino acids across the liver cell plasma membrane

Serum level increased by cholestasis or chronic ingestion of alcohol barbiturates, phenytoin and other drugs which induce the enzyme

PLASMA PROTEINS

The liver synthesises all plasma proteins except immunoglobulins Albumin is decreased in chronic liver disease, but is insensitive as an index of liver function Not useful in acute liver disease because of its long half-life (18 days)
Clotting factors have short half-lives, e.g. factor VII $t_{1/2} = 4h$ The prothrombin time (PT) and partial thromboplastin time (PTT) may be prolonged in liver disease due to decreased synthesis of clotting factors or secondary vitamin K deficiency resulting from fat malabsorption.

Immunoglobulins show a generalized increase (polyclonal) in chronic liver disease, especially cirrhosis. This results from increased antigenic stimulation due to shunting of blood from GIT directly into systemic circulation.

Alpha-foetoprotein (AFP) is the embryonic form of albumin, normally absent from plasma. It is increased markedly in primary liver cell carcinoma (hepatoma).

Moderate elevations may occur when liver tissue is regenerating, such as in the recovery stage after hepatitis or in cirrhosis.

Ferritin is the form in which iron is stored in the liver. Increased levels reflect increased iron stores or liver cell necrosis.

**PLASMA AMMONIA**

Normal level $< 40 \mu\text{mol/ l}$ Hyperammonaemia occurs in Generalised liver disease with hepatic failure, Urea cycle enzyme deficiencies. These mostly present in childhood, with neurological symptoms.

**TOXIC HEPATITIS**

The liver is the site of metabolism of most drugs. Many drugs are hepatotoxic. Drugs may cause either Toxic hepatitis (e.g. alcohol, paracetamol). Biochemical changes similar to acute viral hepatitis or Intrahepatic cholestasis.

Drugs (usually salicylates) in combination with viral infection have been implicated, Characterised by enlarged liver with fatty change, encephalopathy, hyperammonaemia and elevated transaminases with high mortality (Rey's syndrome).
FATTY LIVER

It is a disease condition in which liver content of neutral lipids exceeds normal range due to imbalance between fat efflux out and influx into the liver. Mostly, due to deficient apolipoproteins and lipotropic factors.

Lipotropic factors:

They are nutritional factors and factors that facilitate mobilization of fat from the liver and prevent fatty liver. They include:

1. Essential polyunsaturated fatty acids
2. Vitamin B complex: lack of pantothenic acids leads to deficiency of CoASH required for fatty acid activation. B6 interfere with polyunsaturated fatty acids and CoASH metabolism. Also, biotin increase fatty acid synthesis.
3. Choline, inositol and methionine are required for synthesis of phospholipids. Other essential amino acids are required for synthesis of apolipoproteins. Casein is lipotropic due to its high biological value and high content of methionine.
4. Growth hormone, estrogen and certain androgens.
5. Proteins of high biological value including all essential amino acids required for apoproteins, choline and carnitine synthesis.