Liver Function Test

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Objectives

To understand:

✓ the biochemical functions of the liver;
✓ the different reasons for jaundice and how the pattern of liver function tests can aid the differential diagnosis of liver disease;
✓ the more specialist biochemical tests that are available in the investigation of liver disease;
✓ that minor abnormalities in liver enzyme tests are common in relation to the problem of obesity.
Structure of the liver

• Only about 80% of the cells in the liver are hepatocytes.
• the remainder consists of endothelial (Kupffer) cells lining the hepatic sinusoids and vascular and supporting tissue cells.
• Hepatocytes in the periportal area.

✓ zone 1, receive relatively well-oxygenated blood.
✓ whereas the hepatocytes surrounding the central vein, zone 3, receive blood that has lost much of its oxygen and exchanged other substances with the cells of zones 1 and 2.
✓ Cells in zone 3 are the most susceptible to anoxia and injury by a wide range of toxic substances.
Cells in zone 1 have relatively high concentrations of the enzymes usually measured in blood for diagnostic purposes (e.g. ALP and the aminotransferases ALT and AST).

while cells in zone 3 are relatively deficient in these enzymes.

This may help to explain why some patients with centrilobular liver damage may have normal serum enzyme activities.
Liver disease is relatively common, and the measurements of serum levels of bilirubin, Hepatic enzymes and albumin, as well as the Prothrombin time (PT), provide simple tests to determine whether disease is present and give some guidance as to its nature.
Liver function tests:

Most laboratories perform a standard group of tests which do not assess genuine liver function but are useful for:

1. Detecting the presence of liver disease.

2. Placing the liver disease in the appropriate broad diagnostic category. This then allows the selection of further, more expensive and time-consuming investigations such as ultrasound, CT scanning, magnetic resonance spectroscopy, endoscopy and liver biopsy.

3. Following the progress of liver disease.
Functions of liver

1- Metabolic function:
   - Liver actively participates in carbohydrate, lipid, protein, mineral & vitamin metabolisms.

2- Excretory function:
   - Bile pigments, bile salts & cholesterol are excreted in bile into intestine.

3- Hematological function:
   - Liver participates in formation of blood (particularly in embryo)
   - Liver is also produces clotting factors like factor V, VII.
   - Fibrinogen involved in blood coagulation is also synthesized in liver.
   - It synthesize plasma proteins & destruction of erythrocytes.
4-Storage function:

• Glycogen, vitamins A, D & B12 & trace element iron are stored in liver.

5-Protective function & detoxification:

• Ammonia is detoxified to urea.
• kupffer cells of liver perform phagocytosis to eliminate foreign compounds.
• Liver is responsible for the metabolism of xenobiotics.
Major liver function tests may be classified as follows:

1-Tests based on excretory function:
   Measurement of bile pigments, bile salts, bromosulphthalein.

2-Tests based on serum enzymes derived from liver:
   Determination of transaminases, alkaline phosphatase, 5'-nucleotidase, γ-glutamyltranspeptidase.

3-Tests based on metabolic capacity:
   Galactose tolerance, antipyrine clearance.

4-Tests based on synthetic functions: – Prothrombin time, serum albumin.

5-Tests based on detoxification: - Hippuric acid synthesis.
Bilirubin production and metabolism

Production:

- The body usually produces about 300 mg of bilirubin per day as a breakdown product of haem. About 80% arises from red cells, with the remainder coming from red cell precursors destroyed in the bone marrow (ineffective erythropoiesis)
- and from other haem proteins such as myoglobin and the cytochromes.
- Iron is removed from the haem molecule, and the porphyrin ring is opened to form bilirubin.
- Bilirubin is insoluble in water and is carried in plasma bound to albumin, and is thus not filtered at the glomerulus unless there is glomerular proteinuria.
Conjugation of bilirubin and secretion into bile

✓ In the endoplasmic reticulum of the hepatocyte, the enzyme bilirubin UDP-glucuronyltransferase conjugates bilirubin with glucuronic acid to produce bilirubin glucuronides which are water soluble and readily transported into bile.

✓ Secretion of bilirubin glucuronides into bile occurs against a high concentration gradient and is the rate-limiting step in removing bilirubin from the body.

✓ Bilirubin glucuronides cannot be reabsorbed from the gut and are degraded by bacterial action, mainly in the colon, to a mixture of colourless, water-soluble compounds collectively termed urobilinogen.

✓ These compounds oxidise to brown compounds known as urobilins and stercobilins and are excreted in the faeces.
Measurements of serum bilirubin

• Normally, more than 95% of bilirubin in serum is unconjugated,
  o but in liver disease the conjugated form may predominate.
  o For most purposes, the measurement of serum [total bilirubin] is sufficient,
    especially when results are interpreted in relation to the patient’s history, findings
    on clinical examination and the results of urine urobilinogen and bilirubin
    measurements.
  ➢ it may be helpful to measure serum [conjugated bilirubin] and serum
    [unconjugated bilirubin] separately especially in neonates.
Hepatocellular damage: aminotransferase measurements

✓ Soluble cytoplasmic enzymes and, to a lesser extent, mitochondrial enzymes are released into plasma in hepatocellular damage.

• The measurement of the activity of ALT or AST in serum provides a sensitive index of hepatocellular damage. Serum ALT measurements are more liver specific than those of AST.

• Cytoplasmic and mitochondrial isoenzymes of AST exist and, in chronic hepatocellular disease (e.g. cirrhosis).

• Serum AST tends to be increased to a greater extent than ALT.

• The aminotransferases are mainly located in the peripheral hepatocytes, and they do not give a reliable indication of centrolobular liver damage.

• As with all tests based on the release of enzymes from damaged tissue, there is a lag period of some 24 h from the initiation of tissue damage to the first appearance of increased enzyme levels in the plasma.
Cholestasis: alkaline phosphatase and $\gamma$-glutamyltransferase

✓ ALP and GGT tend to be released into plasma in only small amounts following hepatocellular damage.

✓ However, they are released in much greater amounts when there is cholestasis, since their synthesis is induced and they are rendered soluble due, to the presence of high hepatic concentrations of bile acids.

✓ Changes in the activities of GGT and ALP often parallel each other in cholestatic liver disease.

✓ Serum GGT has the advantage of being more liver specific, as serum ALP may also be increased due to release from bone in bone disease.
Hepatic protein synthesis: Albumin

• In chronic hepatocellular damage, there is impaired albumin synthesis with an accompanying fall in serum [albumin].

• In acute liver disease, however, there may be little or no reduction in serum [albumin], as the biological half-life of albumin is about 20 days and the fractional clearance rate is therefore low.

• Ascites:

• Increased portal venous pressure, a low plasma colloid oncotic pressure and Na+ retention due to secondary hyperaldosteronism combine to cause ascites in cirrhotic patients. This often develops when serum [albumin] falls below 30 g/L.
Coagulation factors

- In liver disease, the synthesis of prothrombin and other clotting factors is diminished, leading to an increased PT. This may be one of the earliest abnormalities seen in patients with hepatocellular damage, since prothrombin has a short half-life (<6 h).
Immunoglobulins

• Serum Ig measurements are of little value in liver disease because the changes are of low specificity.

• In most types of cirrhosis, serum [IgA] is often increased,

• while in primary biliary cirrhosis, serum [IgM] increases greatly.

• In chronic active hepatitis, serum [IgG] tends to be most increased.
Serological tests

- Anti-mitochondrial antibodies are present in over 95% of patients with primary biliary cirrhosis, and anti-smooth muscle and anti-nuclear factor antibodies are found in about 50% of patients with chronic active hepatitis.

- Viral antigens and antibody measurements are also important in detecting infective causes of liver disease.
Marker of fibrosis

- A variety of markers have been described that may be of help in the assessment of hepatic fibrosis.
- Procollagen type III terminal peptide and hyaluronic acid (hyluronin) are the most commonly used tests.
Disordered metabolism

Patients with severe liver disease may have:

1- significant decreases in serum [urea], due to failure of the liver to convert amino acids and NH3 to urea; these changes occur late in the disease.

2- hypoglycaemia due to impaired gluconeogenesis or glycogen breakdown, or both.

3- raised concentrations of all the serum lipid fractions, if cholestasis is present.

4- An abnormal lipoprotein that contains high concentrations of phospholipid, lipoprotein X, is present in serum in nearly all the cases of cholestasis.
Pre-hepatic hyperbilirubinaemia

This is due to overproduction of bilirubin causing increased serum [unconjugated bilirubin]. It occurs in:

• haemolytic anaemia.

• haemolytic disease of the new born, due to rhesus incompatibility.

• ineffective erythropoiesis (e.g. pernicious anaemia).

• rhabdomyolysis.
Hepatocellular hyperbilirubinaemia

This can arise from:

1- hepatocellular damage caused by infective agents, drugs and toxins.

2- cirrhosis – usually as a relatively late complication.

3- low activity of bilirubin UDP-glucuronyltransferase in congenital deficiency (Gilbert’s syndrome and Crigler–Najjar syndrome), premature infants (the enzyme normally develops at about full term), or competitive inhibition of the enzyme by drugs (e.g. due to novobiocin). This leads to increased serum [unconjugated bilirubin].
Cholestatic hyperbilirubinaemia

- Cholestasis may be intrahepatic or extrahepatic. In both, there is conjugated hyperbilirubinaemia and bilirubinuria.
- Cholestasis commonly occurs in acute hepatocellular damage (e.g. due to infectious hepatitis).
- Cirrhosis.
- Intrahepatic carcinoma (most commonly secondary).
- Primary biliary cirrhosis.
- Drugs (e.g. methyltestosterone, phenothiazines).
Extrahepatic cholestasis is most often due to:

- gallstones.
- carcinoma of the head of the pancreas.
- carcinoma of the biliary tree.
- bile duct compression from other causes.
Gilbert’s syndrome

- Gilbert’s syndrome is caused by decreased expression of bilirubin UDP-glucuronyltransferase 1A1, due to a mutation in the promoter portion of the gene.

- Gilbert’s syndrome can most easily be differentiated from the mild degree of hyperbilirubinemia in haemolytic anaemia by haematological investigations.

- Confirmatory tests for Gilbert’s syndrome include monitoring the effects on serum [bilirubin] of a reduced energy intake (1.67 MJ/day; 400 kcal/day), particularly a reduction in the intake of lipids, for 72 h.
Crigler–Najjar syndrome

- This rare condition, due to low activity of bilirubin UDP-glucuronyltransferase, gives rise to severe hyperbilirubinemia in neonates.

Dubin–Johnson syndrome and Rotor syndrome:

- These rare disorders are characterised by a benign conjugated hyperbilirubinemia, accompanied by bilirubinuria.
- In both, there is a defect in the transfer of conjugated bilirubin into the biliary canaliculus.
- Urinary coproporphyrins are normal in patients with Dubin–Johnson syndrome, but increased in Rotor syndrome.
Acute hepatitis

✓ This is usually caused by viruses (hepatitis A, B, C, D and E, cytomegalovirus or Epstein–Barr).
✓ Toxins such as ethanol and paracetamol can also damage the liver.
✓ There is often a pre-icteric phase when increases in ALT and AST activities and in urobilinogen in urine occur.
✓ By the time clinical jaundice appears, serum ALT and AST activities are usually more than six times, and occasionally more than 100 times, the upper reference value.
✓ The stools may be very pale, due to impaired biliary excretion of bilirubin, and urobilinogen.
✓ ALP activity is usually only slightly increased, up to about twice the upper reference value.
Poisoning and drugs

- Findings similar to those in acute viral hepatitis are observed in patients with hepatocellular toxicity due to drugs (e.g. paracetamol overdose, halothane jaundice, carbon tetrachloride poisoning).

- Drugs such as chlorpromazine and other anti-psychotics may produce cholestasis, with increased serum ALP and GGT.

- While phenytoin, barbiturates and ethanol induce GGT synthesis without necessarily causing liver damage.

- Certain herbal remedies and recreational drugs such as ecstasy may also induce liver damage.
Acute liver failure

- This condition is usually caused by paracetamol poisoning or viral infection causing severe hepatitis.
- It is accompanied by major metabolic disturbances including hyponatraemia, hypocalcaemia, hypoglycaemia and lactic acidosis often masked by respiratory alkalosis.
- The levels of the aminotransferases do not correlate well with the severity of the disease.
- The prognosis is often poor unless treated by transplantation. Survival rates of 60% at 1 year following transplantation for acute liver failure are reported.
Other liver diseases:

✓ Cholestatic liver disease: Both extrahepatic (e.g. gallstones) and intrahepatic (e.g. tumours, certain drugs) causes of obstruction cause cholestasis.

✓ Cirrhosis of the liver: Alcoholism, viral hepatitis, autoimmune disease and prolonged cholestasis are the most frequent known causes of cirrhosis in Britain, although in half the cases no obvious cause is found.

✓ Copper in liver disease: The liver is the principal organ involved in copper metabolism. The amount it contains is maintained at normal levels by excretion of copper in bile and by incorporation into ceruloplasmin. The liver’s copper content is increased in Wilson’s disease, primary biliary cirrhosis, prolonged extrahepatic cholestasis and intrahepatic bile duct atresia in the neonate.