Liver Function Test and Bilirubin Metabolism

Tests of liver injury

Transaminases (ALT & AST)

- Tests of hepatocellular damage (not functional capacity) – enter circulation following hepatocellular lysis
- Function to transfer amino group from an amino acid to a ketoacid
- ↑ acutely in : acute viral hepatitis, drug reactions, cholestasis, shock, cardiac failure
- ↑ persistently in : chronic liver disease (chronic viral hepatitis, autoimmune hepatitis), metastases
- **Alanine aminotransferase (ALT)** [<35U/L] : Liver-specific enzyme, highly suggestive of liver disease
- **Aspartate aminotransferase (AST)** [<40U/L] : Enzyme found in liver, skeletal muscle, myocardium, kidney, pancreas & RBCs ∴ damage to any of these may cause ↑.
- With liver disease, ALT elevation is approximately double the AST elevation – if AST > ALT must consider other tissues as source of enzymes ∴ do CK (for muscle or cardiac injury)

Lactate dehydrogenase (LDH)

- Glycolytic enzyme presents in all cells ∴ many causes of elevation (hepatocytes!)

Alkaline phosphatase (ALP, AlkPhos) [35-100U/L]

- Enzyme localised to biliary & sinusoidal membranes of hepatocytes (also found in bone, intestine & placenta) → isoenzymes give specificity
- ↑ ALP in : Biliary disease (esp cholestatic disorders), hepatic infiltrative diseases, pregnancy, growth spurts
- If solitary ↑ ALP, think Paget's, bone tumours, acromegaly, or infarcts

Gamma glutamyl transferase (GGT) [♂ < 50U/L, ♀ < 30U/L]

- Microsomal enzyme found in hepatocytes & epithelium of small bile ducts; also pancreas, kidney & intestine
- ↑ with any liver disease, esp in cholestatic disorders (if ALP ↑), pancreatitis, obesity, hyperlipidaemia, anorexia nervosa, DM, hyperthyroidism, porphyria (a genetic disease in which the production of haem is disrupted), MI, various GGT-enzyme inducing drugs (eg TCAs, alcohol, phenytoin, barbiturates)

Interpretation

- Need to consider all results together
- **Hepatocellular damage** : ↑↑ aminotransferase + ↑ AlkPhos
- **Biliary obstruction (cholestasis)** : ↑↑ GGT & ↑↑ AlkPhos + ↑ aminotransferase
- Microsomal enzyme-inducing drugs : Isolated ↑ GGT

Plasma tests of liver function

Bilirubin

- Total bilirubin < 17μmol/L; Conjugated (direct) bilirubin < 7μmol/L
- Reflects production, hepatic uptake, processing (conjugation) & secretion
- ↑ *bilirubin may occur in all forms of liver disease* (although a jaundiced patient does not necessarily have significant hepatic disease), especially in *cholestasis*
- Requires several days of insult to become abnormal

Serum albumin (35-45g/L)

- Major synthetic protein product of liver → maintains plasma oncotic pressure & acts as carrier for low MW substances in blood
- Depends on nutrition, hepatic synthesis & loses (eg protein-losing enteropathy)
- ↓ albumin may be due to **chronic liver disease**; also ↓ in malnutrition, alcoholism, oedema/ascites

Prothrombin time (PT) or INR

- Vitamin K dependent clotting factors synthesised by liver (II, VII, IX, X) → PR/INR assesses the activity of these coagulation factors ($t_{1/2} \approx$ 5-72hrs)
- Severe liver damage & prolonged biliary obstruction associated with ↓ fibrinogen concentration & prolongation of PT
- The reference range for prothrombin time is usually around 8-13 seconds
- Abnormal due to liver disease, vitamin K deficiency or warfarin Rx

TEST	Acute Hepatitis	Chronic Active Hepatitis	Chronic Persistent Hepatitis	Cirrhosis	Cholestasis	Malignancy & infiltrations
Bilirubin	N to ↑↑	N to ↑	N	N to ↑	↑ or ↑↑↑	N
Transaminases	↑↑↑	↑↑	↑	N to ↑	N to ↑	N to ↑
Alkaline phosphatase	N to ↑	N (corrected by parenteral vit K)	N	N to ↑↑	↑↑↑	↑↑
Albumin	N	N to ↓	N	N to ↓	N	N to ↓
γ-Globulins	N	↑	↑	↑	N	N
Prothrombin time	N to ↑ (not corrected by parenteral vit K)	N to ↑	N	N to ↑ (not corrected by parenteral vit K)	N to ↑	N

Our patient's result is match up with liver cirrhosis due to alcohol consumption

Biochemical Profiles:
Specimen type: Plasma
Alb = 36 g/l (Ref range 35-45 g/l)
Bilirubin(Total) = 38 umol/l (Ref range 0-17 umol/l)
AlkP = 142 Units/l (Ref range 35-100 Units/l)
GGT = 240 Units/l (Ref range 0-50 Units/l)
ALT = 85 Units/l (Ref range 0-35 Units/l)
AST = 160 Units/l (Ref range 0-42 Units/l)

FBC and ESR:
Hb = 100 g/L (Ref range 130-180 g/L)
WCC = 12.0 x 10^9/L (70% neutrophils) (Ref range 4.0-11.0 x 10^9/L)
Platelet = 88 x10^9/L (Ref range 150-400 x10^9/L)

Coagulation profile:
Prothrombin time = 14 sec (Ref range 8-13s)
APTT = 40 sec (Ref range 25-38s)
Plasma Fibrinogen = 3.3 g/l (Ref range 1.5-4.0 g/L)

Bilirubin Metabolism

Heme catabolism occurs when red blood cells membranes rupture and release their haemoglobin. The haemoglobin is phagocytosed almost immediately by macrophages in many parts of the body, particularly:

- The Kupffer cells of the liver and,
- Macrophages of the spleen and bone marrow.

This sort of macrophage process occurring in the tissues is knows as the reticuloendothelial system.

The **haemoglobin** is split into **heme** and **globin**. The heme ring is then split into two substances:

(1) Iron that is carried by transferrin into the bloodstream to the bone marrow for the production of new red blood cells, or to the liver and other tissues for storage in the form of ferritin (Iron recycle)

(2) The polyphyrin portion of the haemoglobin molecule is opened up and carbon monoxide and biliverdin (enzyme: heme oxidase) are produced. **Biliverdin** (green) is then reduced to **bilirubin** (yellow) by enzyme biliverdin reductase. It then leaves the spleen and enters the blood and binds to albumin in its unconjugated form.

Unconjugated bilirubin is transported to the liver where it is uptake by a specific membrane transporter. Once inside the liver it is bound by an enzyme called **glutathione-S-transferase**, which carries it to the endoplasmic reticulum. Here it is glucuronidated twice in succession to form the **diglucuronide** or **conjugated-bilirubin** by the enzyme **UDP-glucuronyl transferase.** The conjugated bilirubin is excreted from the hepatocytes into the bile canaliculi and then into the intestines.

Upon reaching the colon the **conjugated bilirubin** is deconjugated by the metabolic actions of resident bacteria to **urobilinogen** and **stercobilinogen**. **Stercobilinogen** and 80% of the **urobilinogen** is further metabolised to **urobilin** (yellow) and **stercobilin** (dark red-brown in colour, major pigment of the stool). The remaining 20% of the **urobilinogen** is reabsorbed into the portal circulation. 95% of this re-enters the liver and the other 5% is excreted in the urine (colourless, but oxidised to urobilin on standing in air, turning yellow)