Biochemical Investigations in Liver Disease

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Biochemical markers

- Albumin
- ALP
- ALT, AST
- Gamma-glutamyl transpeptidase (γGGT)
- Serum bilirubin
- Urine bilirubin
- Cirrhosis
  - Autoantibodies
  - Ceruloplasmin
  - Serum ferritin
  - Alpha 1 antitrypsin
  - Sweat test
- Alpha feto protein

Serum albumin

- Albumin is the major protein in the human body
- Albumin is synthesized in the liver, and low serum albumin may be indicative of liver failure or diseases such as cirrhosis or chronic hepatitis

Serum albumin

- Decreased serum albumin levels are not seen in acute liver failure because it has a long half life
- As the albumin level drops in liver disease, there is insufficient oncotic pressure to hold fluids within cells.
- Fluid moves into the interstitial spaces, causing generalized edema

Low Serum albumin

- Not specific for liver disease
- Low levels of albumin may be the result of
  - Inadequate production
  - Inadequate intake
    - Protein malnutrition
  - Excessive loss
    - Nephrotic syndrome
    - Protein losing enteropathies
    - Burns

Albumin/globulin ratio

- Albumin/(total protein – albumin)
- Normally, there is a little more albumin than globulins, giving a normal A/G ratio of slightly over 1

Low A/G ratio

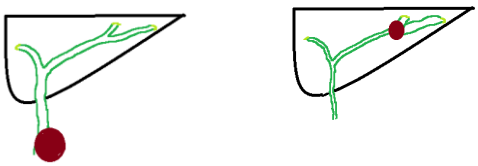
- cirrhosis
- nephrotic syndrome
- multiple myeloma
- autoimmune diseases

High A/G ratio

- hypothyroidism
- glucocorticoid excess
- hypogammaglobulinemia

Alkaline Phosphatase

- Half from liver & the other half from bone
- Increased in any form of biliary tree obstruction→induce hepatocytic syn. of ALP
- Extrahepatic > intrahepatic obstruction (x 3)



Alkaline Phosphatase Cont.

- Increase in the activity of ALP in liver disease is not due to hepatic cell disruption but due to increased synthesis of hepatic ALP
- The stimulus for this increased synthesis in patients with liver disease has been attributed to bile duct obstruction

Alkaline Phosphatase Cont.

- Billiary obstruction
- Iry/IIry hepatic cancer
- Infectious hepatitis
- Drugs
- Pregnancy (placental)
- Bone disorders- Paget disease, osteomalacia
- Transient ALP increase in children

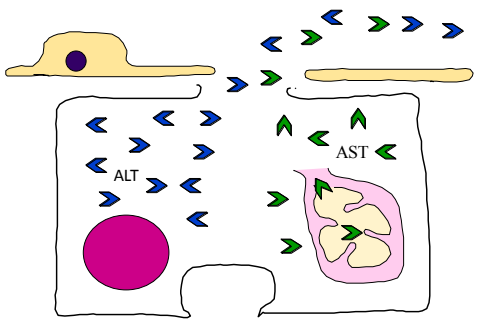
Alkaline Phosphatase Cont.

- Reference intervals
- ALP isoenzyme analysis

Aminotranferases

- Aspartate aminotransferase (AST or SGOT)
  - Liver, cardiac muscle, skeletal muscle, kidneys, brain, etc.
  - Cytosol/mitochondria
- Alanine aminotransferase (ALT or SGPT)
  - 1° in liver
  - Cytosol
- Sensitive indicators of liver cell injury
  - Even very mild liver abnormalities can cause slightly elevated AST/ALT. eg. mild fatty liver.

Release of AST/ALT from Liver Cells during Acute Hepatocellular Injury



Aminotranferases

- Convenient to measure
- Present in liver cells in large amounts
- Direct release of enzymes into blood through fenestrated endothelium allows rapid "quantitative" assessment of ongoing hepatocyte necrosis
- Blood level roughly proportional to the number of hepatocytes that died recently (hours-days)

Problems with using transaminases to assess liver injury

- Only assess injury over the past 1-2 days as enzymes are cleared efficiently from blood by RES
- May not accurately assess hepatocyte death from apoptosis
- Magnitude of elevation does not necessarily correlate with extent of liver function or dysfunction at the present time or in the future.

- AST and ALT = rate of destruction of hepatocytes
- Liver function = number of functional hepatocytes left

AST/ALT Ratio *

- AST:ALT <1
  - Viral hepatitis
  - Ischaemic necrosis
  - Toxic hepatitis
- AST:ALT >1
  - Alcoholic steatosis
  - Alcoholic hepatitis
  - Alcoholic cirrhosis
    - Low levels of cofactor pyridoxine-5-phosphate

Gamma-glutamyl transpeptidase

- Among the most sensitive tests in detecting early hepatobiliary disease
- Elevated in most subjects with liver disease regardless of the cause
- Most sensitive, but least specific of all LFTs
- Similar to ALP in detecting disease of the biliary tract
- More sensitive marker for cholestatic damage than ALP
- Helpful in identifying the cause of an isolated elevation in ALP

Gamma-glutamyl transpeptidase

- Activity increased by alcohol. (upto 1 month)
- Is not specific to alcohol intoxication
- Isolated elevation or disproportionate elevation compared to other liver enzymes (ALP or ALT) can indicate alcohol abuse or alcoholic liver disease.
- Can indicate excess alcohol consumption up to 3 or 4 weeks prior to the test.

Gamma-glutamyl transpeptidase

- Drugs can raise GGT levels
  - barbiturates
  - phenytoin

- Extrahepatic causes
  - Pancreatitis
  - Carcinoma of prostate
  - Carcinoma of breast and lung
  - Systemic lupus erythematosus

Serum bilirubin

- The byproduct of Hb breakdown
- In mammals bilirubin must be conjugated to glucuronic acid and excreted in bile
- Total bilirubin
  - indirect bilirubin (when >80% of total bilirubin is unconjugated→indirect hyperbilirubineamia)
  - direct bilirubin

Hyperbilirubinemia

•Conjugated hyperbilirubinemia
- –BR reached liver and was conjugated but not excreted in bile
  - Cholestasis/biliary obstruction
  - Hepatocellular damage (collateral damage to all liver functions) bile formation impaired >> conjugation impaired
  - Rare disorders of canalicular secretion of conjugated bilirubin
    - –DJ, Rotor

•Unconjugated hyperbilirubinemia
- –BR didn't reach liver efficiently or wasn't conjugated
  - Massive overproduction - acute hemolysis
  - Impaired conjugation
    - common: Gilbert's syndrome (mild)
    - rare: Crigler-Najjar syndrome (severe)

Sample handling

- Exposure to direct sunlight can decrease bilirubin in samples by 50% within one hour

Gilbert's syndrome

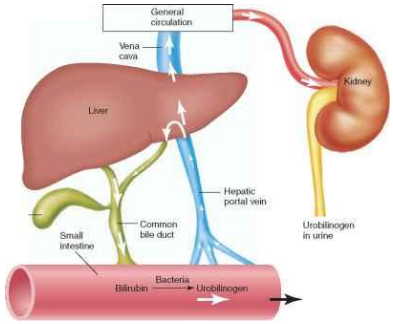
- Benign, familial disorder
- Present in 5% of the population
- Males > females
- Genetic origin-reduction in the glucuronidation activity of UGT
- Exacerbated by fasting, illness & menstruation
- Confirm unconjugated hyperbilirubinaemia
- Rule out haemolysis and underlying liver disease

Urine Bilirubin/Bile

- Not present in the urine of normal, healthy individuals
- Bilirubin leaks back into the blood stream and is excreted in urine in
  - obstructive jaundice
  - hepatitis

Urine Urobilinogen

- Conjugated bilirubin is excreted via bile salts to intestine.
- Bacteria in the intestine break down bilirubin to urobilinogen for excretion in the feces
- Normally there are mere traces of urobilinogen in fresh urine.
- Detected by the Ehrlich's test



Condition	Urine Bilirubin Result	Urine Urobilinogen Result
Hemolytic disease	Negative	Increased
Hepatitic disease	Positive or negative	Increased
Biliary obstruction	Positive	Normal*

Cirrhosis

Suspected Disorder	Confirmatory Investigations
Iry biliary cirrhosis	•Antinuclear antibodies (ANAs) •immunoglobulin levels (mainly IgM)
Haemachromatosis	•Serum ferritin •Transferrin saturation
Wilsons disease	•Caeruloplasmin •Serum copper
Alpha 1 antitrypsin deficiency	•Alpha1 antitrypsin
Cystic fibrosis	•Sweat test

AFP

- Major serum protein in fetus
- Indicates HC carcinoma
- <6.0 ng/mL
- Patients with cirrhosis or viral hepatitis may have higher AFP values, usually less than 500 ng/mL
- AFP levels are abnormal in 80 percent of patients with HC ca and exceed 1,000 ng/mL in 40 percent of patients with this cancer.

AFP

- Annual AFP and ultrasound screening in patients with cirrhosis
- In patients with a hepatic mass and an AFP level above 500 ng/mL is often used in lieu of biopsy to diagnose hepatocellular carcinoma