Lab 3:
Alkaline phosphatase (ALP)

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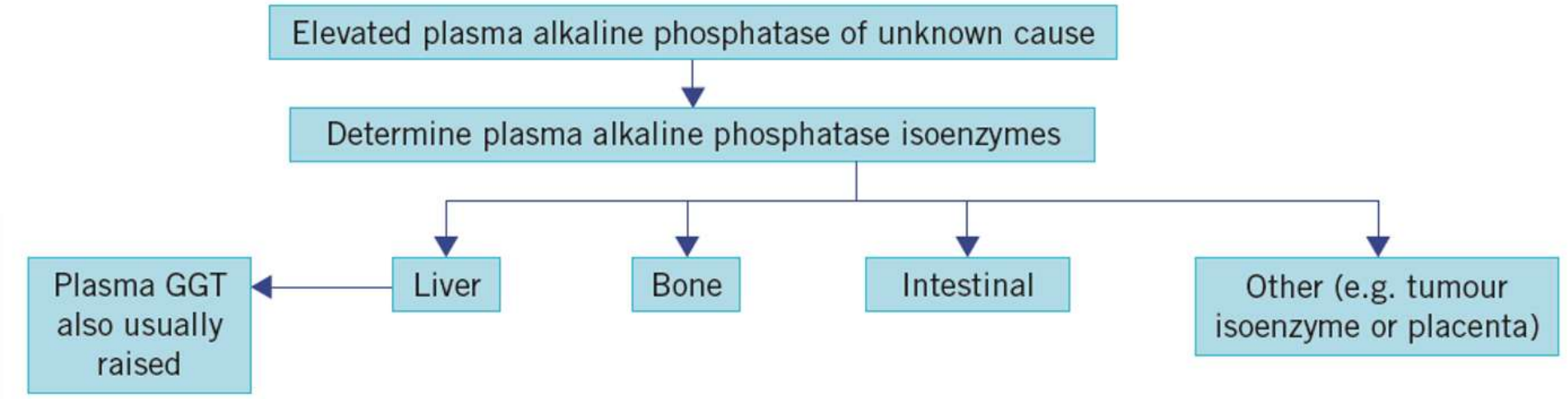
- The ALPs are a group of enzymes that hydrolyse organic phosphates at alkaline pH (around 9–10).
- They are present in most tissues but are in particularly high concentration in the osteoblasts of **bone** and the cells of **the hepatobiliary tract, intestinal wall, renal tubules, and placenta.**
- In **adults,** plasma ALP is derived mainly from **bone** and **l**



Causes of raised plasma alkaline phosphatase (ALP) activity.

- **Physiological:**
- **-During the last trimester of pregnancy**, the plasma total ALP activity rises due to the contribution of the placental isoenzyme. Plasma ALP concentration may increase by up to five times and usually returns to normal levels by 1 month postpartum.
- **-In preterm infants**, plasma total ALP activity is up to five times the upper reference limit (URL) in adults and consists predominantly of the bone isoenzyme.
- **-In children**, the total activity increases by about two to five times during the pubertal bone growth spurt
- **-In the elderly**, the plasma bone isoenzyme activity may increase slightly.

- ***Bone disease:***
- – rickets and osteomalacia,
- – Paget's disease of bone (may be very high),
- – secondary malignant deposits in bone,
- – osteogenic sarcoma (only if very extensive),
- – primary hyperparathyroidism with extensive bone disease (usually normal but may be slightly elevated), and secondary hyperparathyroidism.

- ***Liver disease*:**
- – intrahepatic or extrahepatic cholestasis
- – space-occupying lesions, tumours, granulomas and other causes of hepatic infiltration.
- ***Inflammatory bowel disease*:**
- the gut ALP isoenzyme
- can be increased in ulcerative colitis.
- ***Malignancy:***
- bone or liver involvement or direct tumour production.
- A placental-like, so-called **'Regan'** isoenzyme may occasionally be identified in plasma in patients with malignant disease, especially carcinoma of the bronchus. There is also a **Nago** isoenzyme released by certain tumours.

Causes of low plasma alkaline phosphatase activity (ALP)

- A low plasma ALP concentration is less usual, but may be caused by the following:
- ***Arrested bone growth***:
- – achondroplasia,
- – hypothyroidism,
- – severe vitamin C and vitamin B12 deficiency.
- ***Magnesium and zinc deficiency***.
- ***Hypophosphatasia***, an autosomal recessive disorder,
- associated with rickets or osteomalacia.
- ***Treatment of hyperlipidaemia*** *with a fibrate drug*, for
- example bezafibrate.

Isoenzymes of alkaline phosphatase

- **Bone disease** with increased osteoblastic activity and liver disease with **involvement of the biliary tracts** are the most common causes of an increased total ALP activity.
- Rarely, the cause is not apparent and further tests may be helpful. The isoenzymes originating from the cells of bone, liver, intestine and placenta may be separated by **electrophoresis**.
- The placental and 'Regan' isoenzymes are more stable at 65°C than the bone, liver and intestinal isoenzymes, and **heat inactivation**

Cholestasis:

alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT)

- Some enzymes, such as **alkaline phosphatase (ALP)** and **γ-glutamyltransferase (GGT)**, are normally attached, or 'anchored', to the biliary canalicular and sinusoidal membranes of the hepatocyte. For this reason, 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**.
- 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.
- However, alcohol and many drugs such as anti-convulsants may induce the expression of GGT without causing cholestasis. An isolated increase

Case scenario 1

- A 40-year-old housewife complained to her GP of generalized severe itching during the previous 9 months. She had no other symptoms.
- On clinical examination, she was slightly **jaundiced**, with positive serum **anti-mitochondrial antibodies** and **bilirubin** was detected in the urine. The results of liver function tests were as follows:
- **Serum Result with Reference range**
- Albumin 38 (35–50 g/L)
- ALP activity 450 (40–125 U/L)
- ALT activity 60 (10–50 U/L)
- Bilirubin, total 60 (3–16 µmol/L)
- GGT activity 150 (10–55 U/L)

Discussion

- This patient has cholestatic jaundice.
- Her pruritus is caused by the retention of bile salts. The presence of serum **anti-mitochondrial antibodies** in high titre indicated that the diagnosis was primary biliary cirrhosis, one of the causes of intrahepatic cholestasis. Retention of bile salts within the liver is liable to cause hepatocellular damage, which could account for the increased serum ALT activity in this patient.

Case scenario 2

- A 64-year-old man with lung carcinoma attended the oncology clinic. Some of his blood results were as follows:
- ***Plasma***
- Bilirubin 10 µmol/L (< 20)
- Alanine aminotransferase 23 U/L (< 42)
- Alkaline phosphatase (ALP) 426 U/L (< 250)
- g-Glutamyl transferase (GGT) 50 U/L (< 55)
- Albumin 36 g/L (35–45)
- Albumin-adjusted calcium 2.22 mmol/L (2.15–2.55)
- Phosphate 1.11 mmol/L (0.80–1.35)
- A liver ultrasound and bone scan were normal.

DISCUSSION

- The question here is what is the source of the raised
- ALP activity? The normal GGT activity makes a hepatic source unlikely. Similarly, the normal plasma calcium concentration and bone scan do not make a bone source likely either. However,
- ALP isoenzymes showed the presence of a Regan isoenzyme, thought to be ectopically released from his lung carcinoma.

Good luck