Alkaline phosphatase

when to measure it and what to do next

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Alkaline phosphatase (ALP) is a family of enzymes that hydrolyse organic phosphates under alkaline conditions. Its activity is highest in the liver hepatocytes, bone osteoblasts, intestine, kidney and placenta, but its precise physiological function remains unknown. It is one of the most widely used and simple biochemical tests, and an extremely useful marker of bone and liver disease. However, the meaning of an elevated ALP is often misinterpreted.

Measurements of ALP are often performed as part of the liver function test panel or when bone turnover is being monitored. It should be measured when there are symptoms of cholestatic liver disease, bone pain, low bone mineral density (with or without fractures), and general debility. An incidental finding of ALP elevation in an otherwise well patient requires a stepwise process of exclusion, in order to minimise patient anxiety as well as unnecessary investigations. An approach is outlined in the flowchart on page 44, and ALP electrophoresis is discussed in the box on page 45.

Isolated ALP elevation

ALP is a marker of bone formation, and isolated elevation is usually due to increased osteoblast activity. Bone ALP is elevated two- to three-fold in periods of normal bone growth, and this is particularly important at puberty. Serum ALP also increases gradually with age after 40 years, more so in women than men. There can be a difference of 50% between a healthy elderly woman and a younger woman, with about 40% of the elevation being of bone origin.[1] Whether the elevation of ALP in aging bones is related to development of osteoporosis is a source of continuing discussion.

Isolated elevation of ALP can occur in various benign conditions, and levels are doubled in normal third trimester pregnancy. Intestinal ALP is released in patients with blood group O or B after a fatty meal. Benign familial hyperphosphatasaemia is a rare hereditary condition of isolated ALP elevation. Benign transient hyperphosphatasaemia of infancy and childhood is characterised by ALP elevations up to 9000 U/L in the absence of disease – this occurs in patients under 5 years of age and follows a benign course with normalisation within three months.[2]

Bone disease

ALP is elevated in healing fractures, bony metastases and primary bone tumours where bone

IN SUMMARY

- **Total serum ALP should be measured in a patient who has symptoms of cholestatic liver disease, bone pain, low bone mineral density (with or without fractures), or general debility.**
- **An isolated raised serum ALP level is usually due to increased osteoblast activity.**
- **ALP is elevated in several bone conditions. Paget's disease can result in an increase to more than 10 times normal.**
- **If an elevated total ALP is accompanied by an elevated gamma glutamyl transpeptidase (γGT) level then the cause is most likely of liver origin.**

continued

formation is occurring. In osteolytic neoplasms such as multiple myeloma and sometimes breast cancer metastases, bone resorption occurs in the absence of bone formation and the ALP level may be normal.

Paget's disease can result in an ALP elevation to more than 10 times normal and may be accompanied by fractures and localised pain. It can be diagnosed on x-ray and bone uptake scan. ALP is used to monitor the adequacy of bisphosphonate treatment. Hyperparathyroidism, be it primary or secondary to renal failure, causes increased bone resorption and an inadequate but increased rate of bone formation, resulting in release of calcium and ALP into the circulation. Hypercalcaemia is accompanied by normal or high serum parathyroid hormone and low serum phosphate in primary hyperparathyroidism.

In rickets and osteomalacia caused by vitamin D deficiency, ALP is increased because of secondary hyperparathyroidism. Serum levels of 25-hydroxyvitamin D, calcium and phosphate are low. ALP normalises when vitamin D deficiency is corrected.

Other endocrine causes of elevated ALP include thyrotoxicosis and acromegaly. Thyrotoxicosis causes increased bone resorption accompanied by a lesser rate of bone formation and can result in osteoporosis. In acromegaly, increased bone formation in the hands, feet and skull contributes to the osteoblast ALP activity.

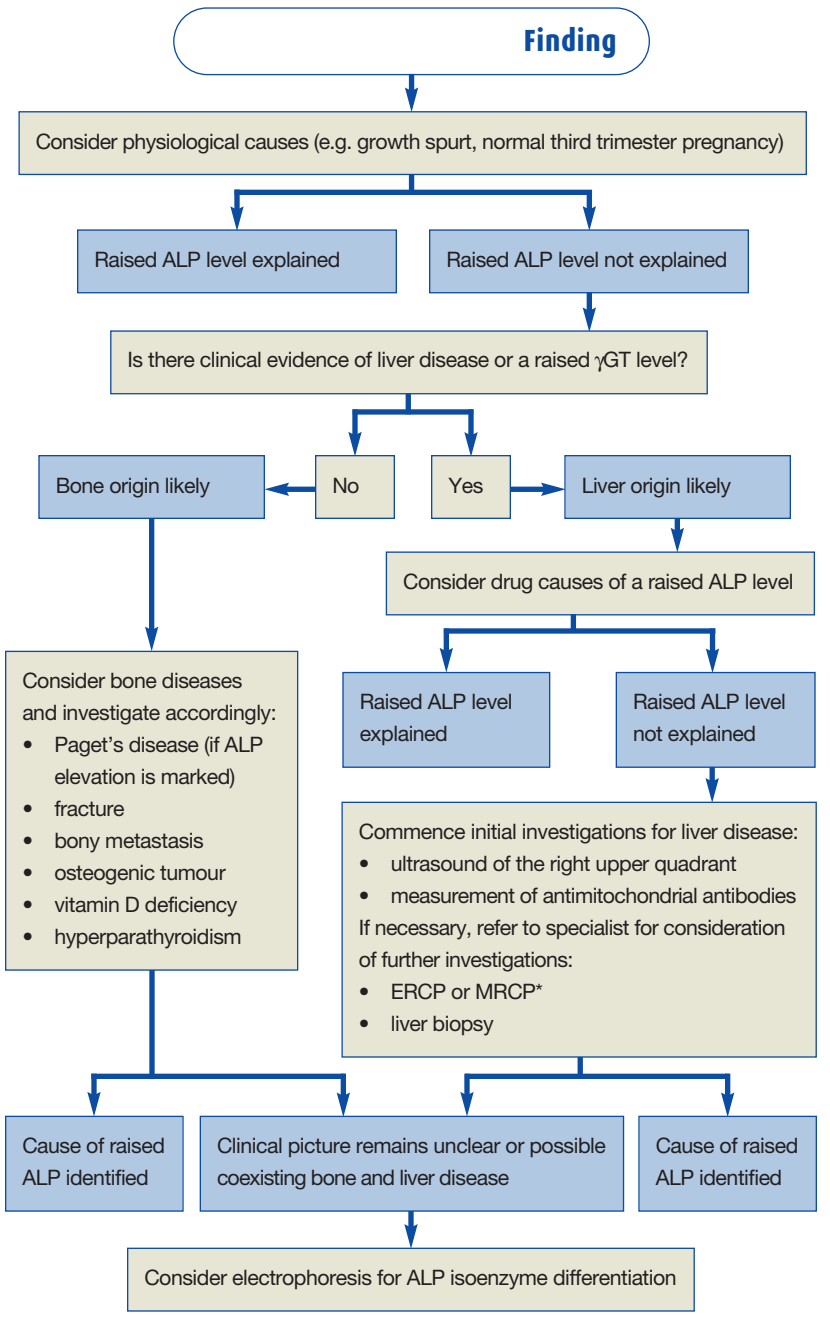
Fanconi's syndrome is a generalised dysfunction of the proximal renal tubule with glucosuria, uricosuria, phosphaturia, aminoaciduria and proteinuria. It is characterised by a normal anion gap metabolic acidosis due to reduced reabsorption of bicarbonate. ALP is mildly elevated due to osteomalacia from renal phosphate wasting.

ALP is generally normal in osteoporosis, unless a recent fracture or osteomalacia is also present. Long term corticosteroid therapy can depress osteoblastic activity after a fracture and suppress the usual elevation of ALP.

Hepatobiliary disease

Biliary tree stasis induces ALP production in hepatocytes located immediately adjacent to the canaliculi, but the degree of elevation does not accurately differentiate

Investigating the patient with a raised serum ALP level



* ERCP = endoscopic retrograde cholangiopancreatography, MRCP = magnetic resonance cholangiopancreatography.

extrahepatic from intrahepatic obstruction. Since gamma glutamyl transpeptidase (γGT) is more sensitive than ALP in cholestatic diseases, a rise in γGT always accompanies the rise in ALP.

Marked elevation (>4 times the upper limit of normal) can be due to biliary obstruction, such as from cancer, common duct stones, bile duct stricture, primary biliary cirrhosis or sclerosing cholangitis. Drugs such as androgens, oestrogens and progestogens, penicillin-based antibiotics and captopril can cause intrahepatic cholestasis.[3] Other medications such as phenytoin and valproic acid can cause a mixed hepatocellular–cholestatic picture. The effect is reversible after cessation of the offending drug. Intrahepatic cholestasis can be caused by total parenteral nutrition, nonhepatobiliary sepsis and malignancies.

Lesser increases in ALP can occur in congestive cardiac failure and all types of liver diseases. These include hepatitis, cirrhosis and infiltrative diseases (e.g. amyloidosis, sarcoidosis).

When a cholestatic picture is apparent in an otherwise asymptomatic patient, initial tests should include an abdominal ultrasound to look for biliary tree dilatation or obstruction and a serum antimitochondrial antibody measurement (a positive result is highly suggestive of primary biliary cirrhosis). If initial tests are unrevealing and the ALP elevation is more than 50% above normal and persists for longer than six months then a liver biopsy and ERCP or MRCP might be warranted.

ALP as a tumour marker

The Regan isoenzyme is a placental ALP associated with osteosarcoma, Hodgkin's disease and other malignancies (such as lung, gastric, renal, ovarian and uterine cancer).[4] Other ALP isoenzymes associated with malignancies include Nagao ALP (in testicular cancers) and Kasahara ALP (a type of fetal intestinal ALP). Malignancies can also cause hepatic leakage of ALP by an unknown mechanism.

The role of ALP as a screening tumour marker is very limited because its predictive value is low. However, isoenzyme electrophoresis might be helpful if a dense band corresponding to placental ALP (in a nonpregnant female) or bone ALP is found and can guide the radiological search for the primary cancer. It is also useful in the monitoring of known bony metastases (such as from breast or prostate cancers) and liver metastases (such as from lung or colorectal cancers).

Final comments

Alkaline phosphatase measurement is commonly performed in general practice. Isolated elevation usually suggests bone disease. Persistent elevation in an adult requires investigation. MT

ALP electrophoresis

Specific ALP isoenzymes can be quantified by immunoselective enzyme assays, which are used in the research setting. For most clinical purposes, a total serum ALP measurement will suffice to monitor known metabolic diseases of the bone. However, differentiation of ALP isoenzymes by electrophoresis can be helpful if liver and bone diseases coexist (e.g. Paget's disease in an alcohol-dependent patient) and it is pertinent to identify the source of the ALP rise. Isoenzyme differentiation can also be helpful in determining the ALP origin in a patient who has isolated ALP elevation that does not fit the clinical picture and has no evidence of bony disease on bone scan.

Electrophoretic separation cannot be performed if the total ALP level is less than 150 U/L (i.e. less than 50% above the normal cutoff).

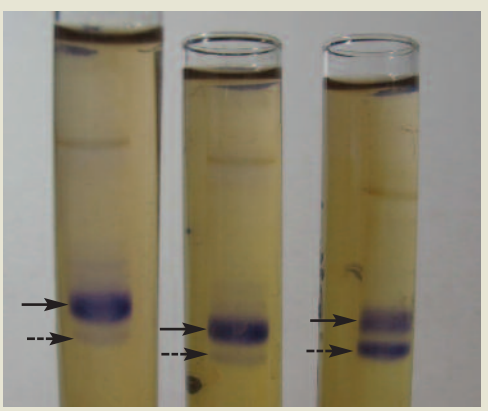


Figure. ALP electrophoresis in polyacrylamide gel. A serum sample is shown alone (left), and in combination with a bone ALP control (centre) or liver ALP control (right). A dense band is visible corresponding to bone ALP (solid arrows) above a faint band corresponding to liver ALP (dashed arrows) in a ratio of about 10 to 1. This patient's raised total serum ALP is therefore mostly of bone origin.

Acknowledgements

The authors thank S. Ratnaike, M. Jenkins and L. Martin for their assistance in gel preparation.

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DECLARATION OF INTEREST: None.