BMJ

BMJ 2013;346:f976 doi: 10.1136/bmj.f976 (Published 3 April 2013)

PRACTICE

RATIONAL TESTING

Interpreting an isolated raised serum alkaline phosphatase level in an asymptomatic patient

This article discusses the most common causes of raised alkaline phosphatase levels in an asymptomatic patient and provides advice on the relevant investigations.

Kate Elizabeth Shipman *specialist trainee year 4, metabolic medicine*, Ashley David Holt *foundation year 2 doctor*, Rousseau Gama *consultant chemical pathologist*

New Cross Hospital, Clinical Chemistry, Wolverhampton WV10 0QP, UK

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

A 51 year old asymptomatic woman presented to her general practitioner for cascade screening for familial hypercholesterolaemia. Blood tests revealed a normal full blood count, renal function, thyroid function, lipid profile, glucose levels, bone profile, and liver profile except for an isolated increased alkaline phosphatase (ALP) concentration at 171 U/L (reference interval 30-130).

What is the next investigation?

ALP is found in high concentrations in liver, bone, kidney, intestine, and placenta. In adults, circulating ALP is predominantly of hepatic and bony origin. Serum ALP levels increase in pregnancy and by the third trimester can be twofold to fourfold higher as a result of a physiological increase in placental ALP. Reference intervals are age and sex related, gradually increasing from age 40 to 65 years, especially in women, and can be up to threefold to sevenfold higher in rapidly growing adolescents.[1] Reference intervals contain 95% of the population, therefore 2.5% of the normal population have values above the upper reference limit. The combined analytical and biological variation for serum ALP is around 8%,[1 2] and levels increase by up to 6% if analysis is delayed for 96 hours in samples stored at room temperature.[3] For example, an ALP result of 125 U/L could be between 108 U/L and 143 U/L, spanning the upper reference limit. Minor increases in serum ALP levels are therefore more likely to be analytical, physiological, or statistical anomalies rather than indicating disease.

An evidence base is lacking on the differential diagnosis and outcome of an isolated increased serum ALP level—that is, a raised serum ALP level in the presence of normal serum levels of bilirubin, transaminases (alanine aminotransferase or aspartate aminotransferase, or both), and calcium. It is reassuring that over 95% of ambulatory patients with an unexplained raised serum ALP level during a multiphasic screening examination developed no overt disease during a two year follow-up.[4] Furthermore, all important disease in the remaining 5% would have been detected by simple history, examination, and routine laboratory investigations.[4]

In a case series of patients admitted to hospital, an isolated raised serum ALP level was associated with a variety of medical illnesses, including congestive cardiac failure (16%), benign bone disease (8%; fractures and osteomyelitis), hyperthyroidism (2%), and end stage renal disease (5%).[5] In over 50% of patients, serum ALP levels returned to the normal range within one year and mostly within three months. Usually there was a known clinically obvious cause, such as metastatic malignancy, for a persistently isolated raised serum ALP level, which was more likely if the initial level was more than 1.5 times the upper reference limit.[5]

The next step

A reasonable approach in adults with an isolated raised serum ALP level is therefore a careful medical and drug history (table⇓) and physical examination.[4 6 7] Key features include abdominal pain or swelling, unintentional weight loss, back pain, bone pain, clinical indicators of liver disease, congestive cardiac failure, and end stage chronic kidney disease.[4 5] If patients are asymptomatic but have raised ALP levels of unknown cause, then the test for ALP should be repeated with γ-glutamyltransferase to confirm and define the abnormality and adjusted calcium levels, thyroid function tests, renal profile, and haemoglobin levels[4] checked within four weeks if not part

Correspondence to: K E Shipman kate.shipman@doctors.net.uk

Learning points

If alkaline phosphatase is raised in an asymptomatic patient and serum bilirubin, liver transaminases, creatinine, adjusted calcium, thyroid function, and blood count are normal:

- Consider growth spurts in adolescents, pregnancy in women, drugs, and age related increases
- As most likely sources are either bone or liver, differentiate by measuring γ-glutamyltransferase (raised in liver) and investigate accordingly
- For liver cases investigate with abdominal ultrasound scan (cholestasis and hepatic space occupying lesion) and antimitochondrial antibodies (primary biliary cirrhosis)
- For bone cases investigate vitamin D

of the original profile. These tests should identify the major pathological causes, with anaemia indicating potential systemic illness. Haematological, renal, thyroid, and calcium abnormalities should be further investigated and managed appropriately; however, if the results are normal then the raised ALP level is isolated (further investigations are discussed below).

Raised hepatic ALP level: raised serum ALP with raised serum γ-glutamyltransferase level

Raised γ-glutamyltransferase levels indicate a hepatic rather than bony origin for raised ALP levels.[6] In some patients a raised level may originate from both liver and bone (for example, in metastatic cancer), but they are likely to have symptoms or a history of cancer.

If the serum ALP level is raised but less than 1.5 times the upper reference limit then the test should be repeated in three months. If the level is more than 1.5 times the upper reference limit or persistently raised, then appropriate investigations would be a liver ultrasound examination to detect cholestasis or an infiltrative liver lesion[8] and measurement of antimitochondrial antibodies to detect primary biliary cirrhosis, and any abnormalities should be investigated accordingly.[8 9] Although primary biliary cirrhosis is uncommon, if diagnosed early treatment improves outcome. If these tests produce normal results and the serum ALP level is less than 1.5 times the upper reference limit, then patients should be evaluated clinically for symptoms in six months as further investigation is not cost effective.[4 10] If, however, the serum ALP level is persistently more than 1.5 times the upper reference limit and ultrasound examination and serology give normal results, the patient should be referred to a hepatologist for consideration of a liver biopsy and further specialist imaging.[8 9]

Raised non-hepatic ALP level: raised serum ALP but normal serum γ-glutamyltransferase level

A normal serum γ-glutamyltransferase level indicates that the raised serum ALP level is non-hepatic and most likely bony in origin and due to vitamin D deficiency,[11] Paget's disease of bone (increasing in incidence from age 55 years onwards and becoming particularly significant in those over 75 years of age),[12 13] or growth spurts in adolescents. Other uncommon causes of increased serum bony ALP levels, such as bone tumours and healing fractures, will be clinically evident. The hypercalcaemia of primary hyperparathyroidism may be masked by vitamin D deficiency and only become apparent after vitamin D replacement.[14]

In patients with raised or persistently isolated increases in non-hepatic serum ALP levels and no symptoms, serum vitamin D levels should be measured and any hypovitaminosis D managed. If vitamin D levels are in the normal range and the serum ALP level is less than 1.5 times the upper reference limit, then observation of the patient should be continued, with further investigations if patients develop symptoms.[4] It is questionable whether the absence of symptoms in the presence of non-hepatic serum ALP levels more than 1.5 times the upper reference limit should be investigated further,[15] but bone scintigraphy may be considered in patients who are vitamin D replete to identify asymptomatic Paget's disease, as some[12] but not all[13] suggest that this is an indication for active treatment.

Studies to clarify the ALP isoform may be considered in the presence of diagnostic uncertainty and noticeable increases in serum ALP levels. Outside pregnancy, increased levels of serum placental ALP may be due to tumour secretion but rarely increases the total serum level. Increased serum intestinal ALP levels may occur with intestinal disease or as a familial benign entity. Increased serum renal ALP levels may be encountered in renal diseases. Rarely, ALP binds to an immunoglobulin to form macroALP, which may be detected by precipitation studies. MacroALP is of no significance but has been associated with inflammatory bowel disease.[16]

Outcome

As the patient was asymptomatic, took no drugs, and had no abnormal physical findings, her general practitioner repeated the test for serum ALP level. Her serum γ-glutamyltransferase level was also checked. This was normal, as was her serum ALP, now at 121 U/L. The patient was reassured and needed no further follow-up.

Contributors: All authors performed the literature search. KES wrote the first draft of the manuscript, with RG and ADH involved in revisions. All authors approved the final article. RG is the guarantor.

Competing interests: All authors have completed the ICMJE form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

1 Schiele F, Henny J, Hitz J, Petitclerc C, Gueguen R, Siest G. Total bone and liver alkaline phosphatases in plasma: biological variations and reference limits. *Clin Chem* 1983;29:634-41.
2 Ricós C, Iglesias N, García-Lario JV, Simón M, Cava F, Hernández A, et al. Within-subject biological variation in disease: collated data and clinical consequences. *Ann Clin Biochem* 2007;44:343-52.
3 Lott JL, Wolf PL. *Clinical enzymology: a case-orientated approach* . Field, Rich and Associates, 1986.
4 Rubenstein LV, Ward NC, Greenfield S. In pursuit of the abnormal serum alkaline phosphatase: a clinical dilemma. *J Gen Intern Med* 1986;1:38-43.
5 Lieberman D, Phillips D. "Isolated" elevation of alkaline phosphatase: significance in hospitalized patients. *J Clin Gastroenterol* 1990;12:415-9.
6 Aragon G, Younossi Z. When and how to evaluate mildly elevated liver enzymes in apparently healthy patients. *Cleve Clin J Med* 2010;77:195-204.
7 Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology* 2002;123:1367-84.
8 American Gastroenterological Association. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology* 2002;123:1367-84.

9 Collier J, Bassendine M. How to respond to abnormal liver function tests. *Clin Med* 2002;2:406.
10 Sorbi D, McGill DB, Thistle JL, Therneau TM, Henry J, Lindor KD. An assessment of the role of liver biopsies in asymptomatic patients with chronic liver test abnormalities. *Am J Gastroenterol* 2000;95:3206-10.
11 Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010;340:b5664.
12 Josse RG, Hanley DA, Kendler D, Ste Marie LG, Adachi JD, Brown J. Diagnosis and treatment of Paget's disease of bone. *Clin Invest Med* 2007;30:E210-23.
13 Kotowicz KK. Paget disease of bone. Diagnosis and investigation for treatment. *Aust Fam Physician* 2004;33:127-31.
14 Mikhail N. Clinical significance of vitamin D deficiency in primary hyperparathyroidism, and safety of vitamin D therapy. *South Med J* 2011;104:29-33.
15 Smellie WSA, Forth J, Ryder S, Galloway MJ, Wood AC, Watson ID. Best practice in primary care pathology: review 5. *J Clin Pathol* 2006;59:1229-37.
16 McTaggart MP, Rawson C, Lawrence D, Raney BS, Jaundrill L, Miller LA, et al. Identification of a macro-alkaline phosphatise complex in a patient with inflammatory bowel disease. *Ann Clin Biochem* 2012;49:405-7.
17 Young DS. *Effects of drugs on clinical laboratory tests,* vol 1: listing by test (5th ed). American Association for Clinical Chemistry Press, 2000.

Cite this as: *BMJ* 2013;346:f976

Table

Table 1| Common drug causes of raised alkaline phosphatase levels[6 17]

Drugs	Mechanism
Antibiotics:	
Penicillin derivatives	Intrahepatic cholestasis
Erythromycin	Intrahepatic cholestasis
Aminoglycosides	Enzyme induction
Antiepileptic drugs:	
Carbamazepine	Intrahepatic cholestasis
Phenobarbital	Enzyme induction
Phenytoin	Enzyme induction
Antihistamines:	
Cetirizine	Intrahepatic cholestasis
Cardiovascular drugs:	
Captopril	Intrahepatic cholestasis
Diltiazem	Enzyme induction
Felodipine	Enzyme induction
Disease modifying agents:	
Penicillamine	Intrahepatic cholestasis
Sulfa drugs	Intrahepatic cholestasis
Polycyclic aromatic hydrocarbons:	
Oral contraceptive pill (oestrogen)	Enzyme induction
Steroids	Enzyme induction
Psychotropic drugs:	
Monoamine oxidase inhibitors	Intrahepatic cholestasis
Chlorpromazine	Intrahepatic cholestasis