

CAUSES OF HIGH BONE ALKALINE PHOSPHATASE

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ABSTRACT

Serum alkaline phosphatase (ALP) is a member of a family of zinc metalloprotein enzymes that function to split off a terminal phosphate group from an organic phosphate ester. Many things may cause increases of ALP activity in serum, the most common being obstructive liver disease and metabolic bone disease. An increase of the liver or particularly the bone isoform (bone specific ALP) in serum can provide valuable diagnostic information. Bone specific alkaline phosphatase isoenzyme is elevated as a result of increased osteoblastic activity. The highest total ALP values have been attributed to an increased bone isoenzyme level due to Paget disease or rickets/osteomalasia. The enzyme activity, which is localized in the plasma membrane of osteoblasts before extracellular release, correlates with the extent of the disease on skeletal surveys and with parameters of bone resorption. This isoenzyme is normally elevated in growing children and adults over the age of fifty. Causes of high bone ALP include bone growth, healing fracture, acromegaly, osteogenic sarcoma, or bone metastases, leukemia, myelofibrosis, and rarely myeloma; so ALP is used as a tumor marker. Hyperthyroidism, by its effects upon bone, may also elevate ALP. We presented two patients have raised alkaline phosphatase. Isoenzyme studies confirmed its bony origin.

Keywords: Bone specific alkaline phosphatase, alkaline phosphatase, osteomalacia, paget's disease

Introduction

Serum alkaline phosphatase (ALP) is a member of a family of zinc metalloprotein enzymes that function to split off a terminal phosphate group from an organic phosphate ester. This enzyme functions in an alkaline environment (optimum pH of 10). Active center of ALP enzymes includes a serine residue. Mg and Zn ions are required for minimal activity. Enzyme activity is localized in the brush border of the proximal convoluted tubule of the kidney, intestinal mucosal epithelial cells, hepatic sinusoidal membranes, vascular endothelial cells and osteoblasts of bone. The normal value of ALP is 20 to 140 IU/L (international units per liter). Adults have lower levels of ALP than children because children's bones are still growing. During some growth spurts, levels can be as high as 500 IU/L (5). Usually children are not measured because of the potential for such high amounts, so the abnormal results refer to adults. Many things may cause increases of ALP activity in serum, the most common being obstructive liver disease and metabolic bone disease. An increase of the liver or particularly the bone isoform (bone specific ALP) in serum can provide valuable diagnostic information. It is rare that the kidney-derived isoform appears in the circulation, and whereas an increase of the intestinal, placental, or germ cell isoenzymes is more common, this is of limited diagnostic value except in some patients with malignant disease. Bone isoenzyme is elevated as a result of increased osteoblastic activity (13- 18, 20, 24, 26). The highest total ALP values have been attributed to an increased bone isoenzyme level due to Paget disease or rickets/osteomalasia. The enzyme activity, which is localized in the plasma membrane of osteoblasts before extracellular release,

correlates with the extent of the disease on skeletal surveys and with parameters of bone resorption. This isoenzyme is normally elevated in growing children and adults over the age of fifty. Causes of high bone ALP include bone growth, healing fracture, acromegaly, osteogenic sarcoma, or bone metastases, leukemia, myelofibrosis, and rarely myeloma, so ALP is used as a tumor marker. Hyperthyroidism, by its effects upon bone, may elevate ALP. There is evidence that thyroid hormone (T_3) acts to stimulate bone ALP activity through an osteoblast nuclear receptor-mediated process (18, 23). Bone ALP comprises approximately 50% of total circulating ALP in normal subjects. This has been attempted with several techniques, including heat inactivation (18), wheat germ lectin precipitation (10), electrophoresis (12), isoelectric focusing (20), HPLC (11, 24), and immunoassay (19, 9). Measurement of bone ALP by IRMA reflects bone turnover more specifically and sensitively than total ALP (9, 14, 21). A decrease bone ALP in children may be attributed to cretinism or to hypophosphatasia. Lower-than-normal levels of ALP may indicate: protein deficiency, magnesium deficiency, too much vitamin D or too little vitamin C, poor nutrition (9, 20).

We presented two patients have raised alkaline phosphatase. Isoenzyme studies confirmed its bony origin.

Case report I

A 56 year old Turkish man, born and brought up in Turkey. Physical examination revealed a reduced range of movement of the right hip with pain on abduction. X-Ray showed sclerotic change in right hemipelvis suggestive of Paget disease of bone (PDB). Serum ALP was elevated to 1400 IU/l (normal range 70- 270 IU/l). Serum prostate specific antigen level was within the normal range. An isotope bone scan confirmed the



Fig. 1. Bone scan of the patient with Paget's disease involving the skull, L4 vertebra,-right and left hemipelvis is shown

increased osteoblastic activity at the skull, L4 vertebra, right and left hemipelvis (Fig.1).

Case report II

A 34 year old Turkish woman, born and brought up in Turkey. Examination revealed a reduced range of movement of the legs with pain while walking straight. She could not sit down and stand up without help. Her mother was on treatment for postmenopausal osteoporosis, for three years. Her complete blood analysis, erythrocyte sedimentation rate (ESR), general biochemistry (including calcium) and protein electrophoresis were normal. Biochemical results revealed hypophosphataemia (2.01 mg/dl; normal range: 2.5–4.5) and

hyperhydroxyprolinuria (31.09 mg/ 24 h/m²; normal range: 6–20). Serum ALP was elevated at 540 IU/l (normal range 70–270 IU/l). Serum Ca level was 8.1 mg/dl. Urinary Ca was 41 mg/dl/24 h and parathyroid hormone 2 pmol/l (normal 1.1–4.6). 25-hidroksi vitamin D was found 12.5nmol/L (n >50) and 1,25 dihidroksi vitamin D 29 pmol/L (n = 40–150). X-Ray showed a pseudofracture at right femoral neck suggesting osteomalacia (Fig. 2). DEXA disclosed mean bone mineral density of L1-4 as 545.90 g/cm². T score was -2.9. Femoral neck bone mineral density was 529.2 g/cm². Femoral neck T score was found -2.41 .



Fig. 2. Pseudofracture of the right femoral neck is shown

Results and Discussion

Paget's disease of bone has been defined in Case I. The distribution of Paget's disease throughout the world is one of the most striking features. While commonly found in the population of England, the United States, Australia, New Zealand, Canada, South Africa, and France, it appears to be rare throughout Asia and Scandinavia. There are data suggesting that the severity and prevalence of Paget's disease is decreasing, but this could be artifactual in that earlier testing for Paget's disease by ALP evaluation in the 1970's may have reduced the pool of undiagnosed patients in the population (1, 15, 3, 13, 29). It is particularly difficult to obtain a true estimate of prevalence in a population as serum ALP may be elevated in as few as 14% of individuals with x-ray evidence of Paget's disease (1). Paget's disease is a localized disorder of the skeleton with a wide range of skeletal involvement. A common feature of Paget's disease is skeletal deformity. The deformity is most visible in the skull and lower extremities. Symmetrical enlargement of the cranium may first come to attention in those individuals (4, 28). The spine is a common source of morbidity from Paget's disease. The lumbar vertebrae and sacrum are most frequently affected. A single vertebra or multiple vertebrae may be involved or, less often, two clavicles may become enlarged. An enlarged scapula is uncommonly preferred perhaps because of its location. Although Paget's disease is commonly found to affect the pelvis, only in its most severe form is it apparent on physical examination that the bone is thicker than normal (4).

Measurement of total ALP activity has been a mean of evaluating Paget's disease for more than 70 years. The circulating enzyme activity usually increases gradually or does not change during long-term follow up of patients who are untreated (2). The diagnosis of Paget's disease is suggested by X-ray findings. The rate of bone turnover may be markedly increased in the early phases of the disease. The initial lesion, because of osteolysis, appears as a radiolucency. This

lesion is often evident in the skull and is called osteoporosis circumscripta cranii. In long bone, the lucency may change to increased density or coarsened trabeculi as the bone attempts to repair itself. Later, vacular fibrous connective tissue has replaced by dense trabecular bone. This change gives the bone its characteristic 'mosaic' pattern. Involvement of the iliopectinal line with thickening of the pelvic brim (Brim sign) may help separate Paget's disease from metastatic bone carcinoma. Technetium 99 m diphosphate bone scans are useful in documenting the extent of the disease or to confirm the diagnosis. Computerized tomography and magnetic resonance imaging may help where neoplastic involvement is being considered. The use of bone biopsy may be appropriate to confirm the diagnosis (16, 7, 25, 27).

In case II, osteomalacia has been diagnosed. "Osteomalacia means "soft bones". Osteoid is the bone protein matrix, composed primarily of type 1 collagen. When there is insufficient mineral or osteoblast dysfunction, the osteoid does not mineralize properly and it accumulates. It is a disorder of diverse etiology which can be subdivided into two main categories: disorders associated with a reduction in circulating vitamin D metabolites and those associated with hypophosphatemia (8).

In children, the term rickets is used to indicate a disorder characterized by epiphyseal dysplasia, retardation of longitudinal growth, and a variety of skeletal deformities. Osteomalacia is the predominant histologic lesion. Rickets arises from etiologic factors similar to those that produce osteomalacia in adults.

Bone pain (especially in the spine, pelvis and legs) and muscle weakness appear first. If blood calcium becomes very low there may be muscle spasm in the hands, feet and throat. As bone softens, weight-bearing may lead to bowing of the legs, compression of the vertebrae and flattening of the pelvis. Weakened bones may break on slight injury.

If osteomalacia is suspected from the history, symptoms and signs, the diagnosis can be confirmed by X-rays, plus blood and urine tests. Biochemical abnormalities in patients with rickets and osteomalacia can be classified into two categories. In patients whose disorder develops as a consequence of vitamin D deficiency, abnormal vitamin D metabolism, or vitamin D resistance. The concentrations of serum calcium and phosphorus are usually reduced and the serum ALP activity is elevated. Patients who develop bone disease on the basis of chronic hypophosphatemia also have elevated serum ALP activity but have a normal serum Ca concentration. Serum total or bone specific ALP measurements appear to be more sensitive to the osteomalacic state than other indices of bone formation. Urinary calcium excretion is markedly reduced in hypocalcemic patients but may be less so in hypophosphatemic

patients. Urinary collagen crosslink excretion is elevated in osteomalacic patients (8, 23, 24).

Diagnosis of vitamin D-deficiency necessitates measurement of serum 25 hydroxy vitamin D concentration. Very low serum 25 hydroxy vitamin D levels are not simply a biochemical abnormality. It is associated with physiological, pathological, and clinical evidence of vitamin D deficiency. Serum 25 hydroxy vitamin D provides evidence of vitamin D status, and levels below 20–25 nmol/L indicate vitamin D deficiency (17).

The pathognomonic radiologic feature of osteomalacia is the presence of pseudofractures. Common sites at which they may be found include the femoral neck and shaft, ulna and radius, pubic and ischial rami, clavicles, ribs, scapulae, metacarpals and phalanges. The origin of these lesions is not known with certainty. There is an underlying excess of unmineralized osteoid, which may reflect healing of microfracture (22).

To conclude, we described two patients with raised bone specific alkaline phosphatase. These two diseases are considered in patients with high levels of bone specific alkaline phosphatase

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