Significance of Low Serum Alkaline Phosphatase Activity in a Predominantly Adult Male Population

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The causes for low serum alkaline phosphatase (ALP) activity (reference range 30–115 U/L) in a large Veterans Medical Center were reviewed. Of 69 864 ALP determinations made over a 4-year period, 130 were low (<30 U/L, 0.19%), representing 88 individual patients. Of these, 83 (primarily men, 96%) patients' charts were reviewed and classified into two groups, those with and those without conditions previously reported to be associated with decreased serum ALP activity: 47% had conditions associated with low ALP activity, the most frequent being cardiac surgery and cardiopulmonary bypass (26.5%), malnutrition (12.0%), magnesium deficiency (4.8%), hypothyroidism (2.4%), and severe anemia (1.2%); 53% of patients did not have clinical conditions previously associated with low ALP activity. No case of clinically apparent hypophosphatasia, for which low ALP activity is the defining characteristic, was found in this population of veterans. A low serum ALP may be of significance in other patient populations such as children, where it is associated with achondroplasia and cretinism, or in postmenopausal women with osteoporosis taking estrogen replacement therapy. In the predominantly adult male population in this study, low ALP activity was rare; it was seen most frequently in cardiac surgery patients postoperatively, a clinical condition heretofore not commonly associated with low serum ALP activity.

Indexing Terms: *cardiac surgery/cardiopulmonary bypass/ malnutrition/magnesium deficiency/hypothyroidism/hypophosphatasia*

Serum alkaline phosphatase (EC 3.1.3.1; ALP) activity is usually measured to detect increases in its activity. Little attention has been focused on clinical conditions associated with low or decreased ALP activity in patients. Accordingly, I undertook this study to determine the clinical correlates of low ALP activity in a patient population of predominantly adult males at a large metropolitan Veterans Hospital.

Table 1 summarizes the clinical conditions associated with low ALP activity. Using these clinical causes for low ALP activity as a paradigm for conditions associated with low ALP activity, I attempted to determine whether these conditions could be verified as reasons for a low ALP activity in the patient population reported here.

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Materials and Methods

Patients' samples and analytical methods. Samples of serum collected from patients over a 4-year period were assayed for ALP activity within 24–72 h after receipt of the specimen. Specimens not assayed on the same day were stored at 4°C until the assay was completed. ALP assays were performed in automated chemistry analyzers (Astra 8E, Astra Ideal, and Synchron CX-7; all from Beckman Instruments, Clinical Instrument Div., Brea, CA) with *p*-nitrophenyl phosphate as substrate (*19*). The calibration curve for ALP is linear from 0 to 1000 U/L. ALP activities were comparable for all Beckman instruments, correlation studies documenting comparability of enzymatic activities having been done before these automated instruments were placed in service.

Reference range and definition of low ALP activity. The reference interval for ALP activity, 30–115 U/L, is based on previous studies (*20, 21*) and on the determination of serum ALP activity in 200 apparently healthy men, ages 20–70, at this medical center. After logarithmic transformation of serum ALP activities in these 200 subjects, the reference interval containing 95% of the ALP results was calculated with a nonparametric method for comparison (central 95 percentiles). An ALP activity <30 U/L was defined as decreased or low.

Selection of patient study groups. This study fell into the category of exempt research in accordance with federal policy for the protection of human subjects (38 CFR, part 16). A list of all patients with ALP activities <30 U/L during the 4-year study was generated by the hospital computer, from which their medical records could be reviewed.

Medical chart review and disease classification. I reviewed each medical chart and abstracted the following clinical information: age, sex, clinical diagnosis, cardiac surgery history, serum magnesium, drugs, and transfusions. No attempt was made to look for subtle clinical conditions such as mild vitamin or magnesium deficiencies if these were not noted in the medical record. For simplicity, patients were divided into two groups, those with and those without clinical conditions previously associated with low ALP activity.

Results

During the 4-year period, 69 864 ALP measurements were made for hospitalized and ambulatory patients. The frequency distribution (Fig. 1) is not gaussian but is skewed to higher values, with >10% of the values being >120 U/L. The frequency of low ALP (<30 U/L) was 0.19%, representing 130 determinations for 88

Table 1. Clinical conditions associated with low ALP activity.

Clinical condition (and references)	No. cases (%) in this study
Zinc deficiency (*1,2*)	0
Magnesium deficiency (*1,2*)	4 (4.8)
Hypophosphatasia (*3–5*)	0
Cardiac surgery and cardiopulmonary bypass (*6,7*)	22 (26.5)
Artifacts associated with collection of blood in EDTA or oxalate anticoagulant (*8*)	0
Hypothyroidism (*9–11*)	2 (2.4)
Severe anemia (*1*)	1 (1.2)
Pernicious anemia (*12,13*)	0
Protein/calorie deficiency (*1,14*)	10 (12.0)
Estrogen replacement therapy in postmenopausal women (*15,16*)	0
End-stage osteopenia of chronic renal osteodystrophy (*5*)	0
Achondroplasia and cretinism in children (*17*)	0
Vitamin C deficiency (*18*)	0
Milk–alkali syndrome, excess ingestion of vitamin D, inanition, celiac disease, hypoparathyroidism, intake of radioactive heavy metal, drugs such as clofibrate, recent massive blood transfusions, or posthepatic resection and transplantation (*1*)	0

individual patients; medical records for 83 of these were available for review. Eighty were men (96.4%), mean age 64.4 (range 23–90) years, and three (3.6%) were women (mean age 45.3, range 32–56). Patients with low ALP activity were comparable in age and sex with the population at this medical center.

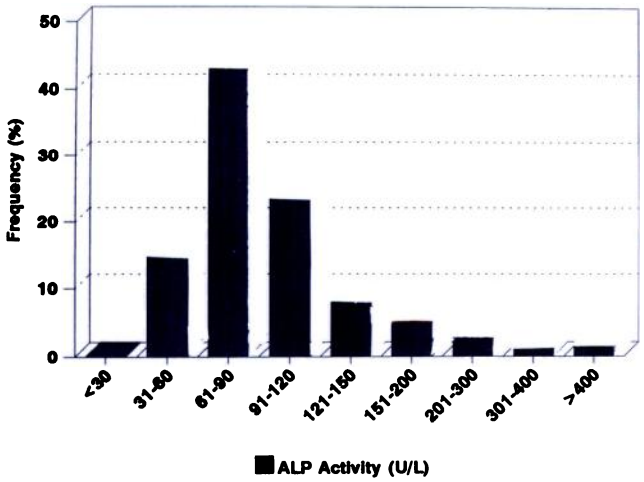

Fig. 1. Frequency distribution of results of 69 864 serum ALP activity determinations.

Table 1 summarizes the patients with conditions associated with low ALP activity: 22 (56%) were cardiac surgery cases (coronary artery bypass and cardiac valve replacement with cardiopulmonary bypass); their mean presurgical ALP activity was 71 U/L (range 38–100 U/L), which fell to 20 U/L (range 8–29 U/L) on the first postoperative day (mean decrease 71.8%). The mean magnesium concentration was 24 mg/L (range 19–27) preoperatively, which fell to 13 mg/L (range 9–17) on the first postoperative day (45.8% decrease); magnesium returned to normal ranges (18–24 mg/L) by the 6th postoperative day.

Ten patients (12.0%) with protein malnutrition had a mean ALP activity of 18 U/L; four of these were diagnosed with chronic malnutrition, two with malignancy, three with alcoholic liver disease, and one with alcoholic cirrhosis.

Four patients (4.8%) had severe magnesium deficiency (mean concentration 12 mg/L) and a mean ALP activity of 21 U/L. In contrast, only one of the patients with low ALP had severe anemia attributed to iron deficiency (2.6%).

Table 2 summarizes the data for patients at this medical center with a clinical condition associated with low ALP activity (n = 39): the percentage of patients with the diagnosis of the total; all cases with each diagnosis as a percentage of the total admissions/discharges at this medical center; and finally, all cases with each diagnosis as a percentage of the total in the five diagnostic groups. For example, malnutrition patients represented 26% (10 of 39) of patients with a condition associated with low ALP activity; all patients with this diagnosis were 1.3% of the total admissions/discharges at this medical center; and all patients with malnutrition represented 15% of the total in the five diagnostic categories. As Table 2 shows, the percentage of cases with low ALP activity for cardiac surgery, malnutrition, and hypothyroidism roughly corresponds to the frequency of the diagnoses. Patients with magnesium deficiency, however, represent a disproportionate number of patients with low ALP (10%), although they account for only 0.03% of the total admissions/discharges and represent only 0.3% of the total in the five diagnostic groups. Conversely, patients with severe anemia represent a very small fraction of patients

Table 2. Summary of patients with conditions previously associated with low ALP activity.

Diagnosis category	% of total with low ALP activity	Diagnosis as % of total admissions/discharges	Diagnosis as % of five diagnostic categories
Cardiac surgery	56	3.9	43.6[a]
Malnutrition	26	1.3	14.5
Magnesium deficiency	10	0.03	0.3
Hypothyroidism	5	0.82	9.2
Severe anemia	3	2.9	32.4
Total	100	8.95	100

[a] Sample calculation: 3.9/8.95 × 100 = 43.6.
χ^2 = 180, P <0.0001.

with low ALP (2.9%), although they are 32.4% of the total diagnoses in the five categories.

The remaining 44 patients (53%) did not have any clinical condition reportedly associated with a low ALP activity. These clinical conditions included: alcoholic liver disease and diabetes, six cases each (7.2%); cardiovascular disease, malignant neoplasm, and urinary tract infection, five cases each (6.0%); acute/chronic renal failure and surgery other than cardiac, four cases each (4.8%); psychiatric disorders and acute myocardial infarction, three cases each (3.6%); aortofemoral bypass surgery, two cases (2.4%); and acute pancreatitis, one case (1.2%). None of the five patients with malignant neoplasms in this group was diagnosed with malnutrition. In addition, none of these 44 patients had end-stage osteopenia of chronic renal osteodystrophy, and none had bone biopsy or bone densitometric evaluations to exclude other forms of bone disease. Also, there were no cases diagnosed with the many commonly cited causes for low ALP activity, including scurvy, clofibrate therapy, excess vitamin D ingestion, and recent massive blood transfusions. No case of clinically apparent hypophosphatasia was found.

Discussion

The frequency of low ALP activity in this patient population was 0.19% (130 of 69 864 determinations), a finding comparable with that of other investigators, e.g., 0.26% (261 of 101 710 determinations) (*6*). The rare occurrence of low serum ALP activity in this population of veterans probably reflects an abnormal patient population of sick individuals with a high prevalence of diseases associated with increased rather than normal ALP activity. As Fig. 1 illustrates, >10% of patients exceed the upper limit of the ALP reference interval.

The major reason for low ALP activity in this population was cardiac surgery and use of a cardiopulmonary bypass pump. Mean reported decreases of 48.4% (*7*) and 62% (*6*) in ALP activity and of 38.3% in magnesium (*7*) are comparable with my observations of decreases of 71.8% for ALP and 45.8% for magnesium. The decreases in both ALP and magnesium observed in the postcardiac surgery patients appear to be a consequence of the cardiac surgery and cardiopulmonary bypass (*7*), and could not be attributed to hemodilution alone (*7*). Magnesium ion is an activator of ALP activity (*19*), but the addition of magnesium to serum samples from postoperative cardiac surgery patients with low ALP activity failed to restore ALP activity (*7*); this suggests that factors other than magnesium necessary for ALP activity were removed by the cardiopulmonary pump (*7*).

Malnutrition (protein/calorie deficiency) was the next largest group of conditions associated with low ALP activity. The decline in ALP activity is thought to be secondary to decreased activity of the bone and hepatic fractions of ALP in patients with malnutrition (*14*).

Four patients had magnesium deficiency and low ALP activity. Low dietary magnesium has been associated with low ALP activity, and rats fed a magnesium-deficient diet for 34 days demonstrated depressed ALP activity that was reversed by adding magnesium to their diet (*2*).

Others have shown that hypothyroidism is associated with low serum ALP activity, which returns to normal after therapy with thyroid hormones (*9*). In the two patients in this study, the ALP activity also returned to normal after such treatment. The decrease in ALP activity in hypothyroidism may be related to the low serum concentrations of magnesium and zinc in this condition, since restoring serum zinc and magnesium to normal concentrations also restored the serum ALP activity to normal (*9, 10*), or it may be related to decreased production of ALP by osteoblasts, which require thyroid hormone and vitamin B_{12} for activity (*11*).

No obvious reason for the association of low ALP activity and severe anemia has been cited (*1*). The single such patient in this study had severe iron-deficiency anemia and not pernicious anemia, a condition reported to be associated with low ALP activity in about one-third of affected patients (*12*). In pernicious anemia, osteoblast activity is dependent on cobalamin, and bone metabolism is affected by deficiency of cobalamin (*12*). Cobalamin-deficient patients have significantly lower concentrations of serum ALP (skeletal ALP) and osteocalcin than do unaffected control patients (*13*).

This study did not include a large population of children or women, in whom decreased serum ALP may have other diagnostic value. In children, decreased or low ALP activity may signal disturbed skeletal growth (*17*), the cessation of bone growth, or clinical conditions such as cretinism and achondroplasia (*9, 17*). Estrogen replacement therapy in postmenopausal women with osteoporosis is associated with low ALP concentrations, an effect attributed to inhibition of bone resorption by estrogen (*15, 16*).

No case of clinically apparent hypophosphatasia was evident in this patient population. This particular disease, an inborn error of metabolism, is characterized clinically by defective bone mineralization, resulting in excessive unmineralized bone matrix, and biochemically by deficient activity of the tissue-nonspecific isoenzyme of ALP in tissues and in serum, increased urinary excretion of phosphoethanolamine and inorganic pyrophosphate, increased plasma pyridoxal 5′-phosphate, decreased total serum ALP activity, and radiological, histological, and clinical features of rickets (*3–5*). It is not surprising that this condition, which is usually seen in pediatric populations, was absent among these male veterans.

In contrast to the reasons cited in the older medical literature, we found that the majority of our patients (53%) did not fit into disease categories traditionally associated with low ALP activity. Although some such conditions (e.g., mild malnutrition) may have been present but undiagnosed, many conditions associated

with low serum ALP activity such as vitamin C deficiency (scurvy), vitamin D intoxication, and milk–alkali syndrome were not found, perhaps because these conditions are becoming rare with the advent of newer medications. In a more recent study (*6*), the commonly cited causes for low ALP activity shown in Table 1 were not seen in 126 patients with low ALP activity except for 7 neonates who had received plasma transfusions; however, ~10% of the patients in that study (15 of 126, all adults) had undergone cardiopulmonary bypass and had associated low ALP activity (*6*). That report and the present study show that low ALP activity is frequent in cardiac surgery patients postoperatively, a clinical condition previously not universally recognized as a cause for low serum ALP activity.

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