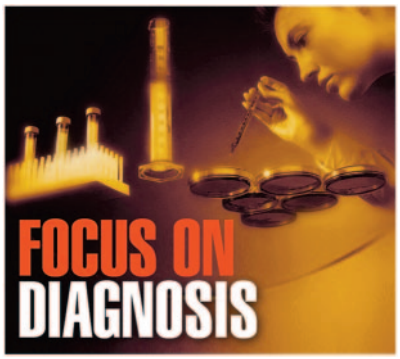

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The Alkaline Phosphatase Level: Nuances of a Familiar Test

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Introduction

Alkaline phosphatase is a commonly encountered laboratory value that is included in the panel of liver function tests. Although elevated concentrations generally are attributed to either liver or bone sources, the enzyme has been identified as a biomarker for a diverse range of diseases and physiologic processes. Elevated alkaline phosphatase may have implications ranging from indicating periodontal disease to predicting preterm labor.

Functionally, alkaline phosphatase removes a phosphate group from nucleotides and proteins. As the name suggests, the enzyme works optimally at basic pH levels. It is found throughout the body in a variety of isoenzymes unique to the tissue of origin. Highest concentrations are in liver and bone, but the enzyme is present in lesser amounts in placenta, kidney, intestines, and leukocytes.

Increased concentrations of alkaline phosphatase are derived from tissues that are either functionally disturbed (obstructed liver) or greatly stimulated (growing bone). Abnormally low concentrations are far less common and more likely are related to a genetic condition or nutritional deficiency. Normal levels can vary with age, sex, hormonal status, and blood type. In children, serum alkaline phosphatase concentrations are considerably higher than in adults and correlate with the rate of bone growth. In adults, values are slightly higher in men than in women, but after age 60 years, the enzyme value is equal or higher in women. Concentrations are increased during puberty and pregnancy and after menopause.

Measurement

Measurement of alkaline phosphatase activity in the laboratory involves the release of 1 mmol/min of phosphate from a standard compound (p-nitrophenylphosphate). The total amount of enzyme from all tissue sources is measured in the blood. Several methods are used to isolate specific tissue isoenzymes, including electrophoresis and heat inactivation. However, because neither method is widely available, adjunctive laboratory tests often are used to identify the tissue of origin. If clinical features and adjunctive test results are not sufficient to identify the tissue of origin, specimens can be submitted to a reference laboratory, with the understanding that such testing might be time-consuming and expensive.

The normal range for alkaline phosphatase is 20 to 140 IU/L, but ranges of normal must be adjusted for factors such as age, sex, and the laboratory's own normal values. Multiple factors can influence the serum value.

Liver as a Source

When the alkaline phosphatase level is elevated because of a liver condition, the pattern of abnormalities of several liver function tests and the magnitude of the elevation provide a

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better reflection of the condition of the organ than any single value. Disproportionate elevation of alkaline phosphatase and bilirubin relative to transaminases suggests a cholestatic process rather than a hepatocyte injury. However, the concentration of alkaline phosphatase can be normal, even in the face of advanced liver cirrhosis. Mild elevations of the enzyme may be consistent with a hepatocellular cause, but marked elevations (three to four times the upper limit of normal) usually are associated with biliary tract involvement.

Because identification of specific isoenzymes is not widely available, measurement of 5-nucleotidase and gamma-glutamyl transferase (GGT), both of which increase in liver but not bone diseases, may identify the liver as the source of an elevated alkaline phosphatase level. 5-nucleotidase is bound to bile canalicular and sinusoidal membranes and is elevated in biliary obstruction or hepatic infiltrative diseases. Elevated levels of GGT also are found in most cholestatic diseases of the liver. An elevated GGT concentration in isolation is not specific and may be associated with a number of conditions unrelated to cholestasis, including alcohol ingestion. Some cholestatic liver disorders in children present with elevated alkaline phosphatase levels but normal GGT concentrations.

Cholestatic processes fall into the following categories: blockage due to stones, tumor, or stricture; autoimmune liver diseases, such as sclerosing cholangitis or primary biliary cirrhosis; infiltrative disorders, such as amyloidosis, tuberculosis, sarcoidosis, hepatic abscesses, or malignancy; and the effects of drugs or toxins. Ultrasonography can help differentiate intrahepatic obstruction (no biliary duct dilatation) from extrahepatic obstruction (biliary dilatation). Additional diagnostic studies, such as serology, endoscopic retrograde cholangiopancreatography (ERCP), and liver biopsy may be indicated by the clinical scenario.

Bone as a Source

Bone formation is initiated by osteoblasts, which contain alkaline phosphatase in their cell membranes. Calcium crystallizes in an alkaline environment, and alkaline phosphatase in osteoblasts exists in an environment favorable to the mineralization of bone and growth plate cartilage. The serum concentration of bone-specific alkaline phosphatase reflects the cellular activity of osteoblasts. Conversely, bone resorption is initiated by osteoclasts, which have tartrate-resistant acid phosphatase (TRAP) anchored to their cell membranes. Acidic environments facilitate bone resorption.

Alkaline phosphatase may be elevated in conditions involved in bone formation or increased bone turnover. Growing children or individuals who have fractures would be expected to have a physiologic elevation of bone-specific alkaline phosphatase. Pathologic conditions that may result in high levels of the enzyme include rickets, osteomalacia, Paget disease, osteoblastic bone lesions or osseous metastases, hyperthyroidism, and hyperparathyroidism.

An elevated alkaline phosphatase value that is attributed to bone should prompt additional evaluation, including measurement of calcium, phosphate, parathyroid hormone, and thyroid-stimulating hormone levels as well as renal function tests, radiographs directed by symptoms, and thorough evaluation for underlying malignancy.

Other Sources of Alkaline Phosphatase

Leukocytes

The leukocyte alkaline phosphatase (LAP) score may help differentiate hematologic conditions. The score is obtained after 100 neutrophilic leukocytes are stained and given values of 0 to 4+ based on the intensity of dye in the cytoplasm. For example, a high LAP score can help distinguish a leukemoid reaction from an elevated white blood cell count due to chronic granulocytic leukemia, which characteristically has a low LAP score. Other conditions that usually have an elevated LAP score include polycythemia vera and myelofibrosis. A low LAP score is consistent with pernicious or aplastic anemia.

Intestines

Intestinal alkaline phosphatase increases in response to a fatty meal by individuals who have blood types O and B. Therefore, fasting is preferred but not required prior to obtaining blood to maximize appropriate interpretation of the result. There have been reports of benign familial elevated intestinal alkaline phosphatase.

Placenta

As a normal part of pregnancy, syncitiotrophoblasts produce alkaline phosphatase that is detectable in the maternal circulation after the first trimester. Placentalike alkaline phosphatase, the heat-stable isoform of the enzyme, has been found in men who have germ cell tumors, particularly testicular seminomas, and in women afflicted with ovarian cancer. Unfortunately, the enzyme's lack of specificity limits its use as a biomarker of disease activity.

Sepsis

In multiple retrospective studies of hospitalized adults, sepsis was among

the most common conditions associated with significantly elevated concentrations of alkaline phosphatase. Of note, patients who have sepsis can develop elevated alkaline phosphatase but have normal bilirubin levels.

Drugs

Many drugs can affect serum concentrations of alkaline phosphatase. Most often cited in the literature are phenytoin, erythromycin, chlorpromazine, estrogens, progestins, and androgenic steroids.

Causes of Lower-than-expected Alkaline Phosphatase Values

Clinically, a lower-than-expected alkaline phosphatase concentration typically does not prompt additional evaluation, but this finding is compatible with several conditions, including hypophosphatasia, a genetic condition that results in bone deformities. Another cause may be poor nutrition with deficiencies of protein, magnesium, zinc, or vitamin C. Individuals who have paroxysmal nocturnal hemoglobinuria and chronic granulocytic leukemia have been noted to lack leukocyte alkaline phosphatase.

Conclusions

Alkaline phosphatase is an enzyme found in many tissues throughout the body. Elevated concentrations may be caused by physiologic or pathologic conditions. No evidence-based guidelines exist for evaluation of asymptomatic outpatients who have abnormal alkaline phosphatase concentrations, but practice guidelines suggest investigation of values that are greater than 1.5 times the upper limit of normal on two occasions at least 6 months apart. Elevated 5-nucleotidase or GGT concentrations support the liver as the cause; normal concentrations of these enzymes suggest nonhepatic causes. For an asymptomatic patient who has a mildly elevated alkaline phosphatase value and no other abnormal test results, observation is recommended.

Suggested Reading

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