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Alkaline Phosphatase: Biochemical and Clinical Aspects

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ABSTRACT

Alkaline phosphatase (ALP) is a family of isoenzymes, settled on the exterior of the cellular membrane; these enzymes stimulate the hydrolysis of phosphate esters found in the extracellular space. Zinc and magnesium are important co-factors for the biochemical function of alkaline phosphatases. It is estimated that over 80% of the ALPs in sera are supplied by hepatic tissue and bone and in a lower amount from the gut. Although alkaline phosphatases are present in various tissues throughout the body, their specific physiological role is still not well understood. This large family of dimeric enzymes is classified into four isozymes based on the tissue in which they are expressed, these include: tissue nonspecific alkaline phosphatase or liver/bone/kidney ALP, Germ cell ALP, Placental ALP, and Intestinal ALP. The liver is the major supplier of ALP, which is account for most elevation of this enzyme.

The next likely factor is heightened osteoblast activity, commonly seen in bone disorders or during growth phases. Additionally, in the late third trimester of pregnancy, the increase in placental ALP significantly raises levels in expectant mothers.

1. INTRODUCTION

Alkaline phosphatase is a glycoprotein typically located on the cell surface, where it catalyzes the hydrolysis of phosphate monoesters at alkaline pH levels, releasing inorganic phosphate. This enzyme also facilitates the hydrolysis of organic phosphate esters in the extracellular space. Essential cofactors for alkaline phosphatase are zinc and magnesium. It was the first known zinc enzyme, featuring three closely positioned metal ions (two zinc ions and one magnesium ion) at its active center. Zinc ions at all three sites are crucial for achieving maximum enzymatic activity (Lowe et al., 2023).

Alkaline phosphatase is huge family of isoenzymes, it is classified into four types based on the position of organ at which it is expressed, these include: tissue nonspecific alkaline phosphatase or liver/bone/kidney ALP (L/B/K ALP), Germ cell ALP (GCALP or NAGAO isozyme), Placental ALP (PLALP or Regan isozyme), and (IALP) which stands for Intestinal ALP (Stigbrand, 1984; Sharma & Prasad 2014).

Placental ALP (PLALP) is a heat-stable enzyme found in high concentrations in the placenta, with trace amounts detectable in normal blood serum. Intestinal ALP (IAP) is a partially heat-stable isozyme present at high levels in intestinal tissue and at low levels in germ cells. The heat-labile isozyme corresponds to the liver/bone/kidney or tissue nonspecific (TNSALP) form. This form is expressed in various tissues throughout the body, with significant abundance in hepatic, skeletal, and renal tissues (Sharma et al., 2014).

Alkaline phosphatases (ALPs) are divided into two types: tissue-specific and tissue-nonspecific. Tissue-specific ALPs are found exclusively in the intestine, placenta, and germinal tissues, expressed only in their respective tissues under normal conditions. However, under certain circumstances, these tissue-specific ALPs can contribute to the circulating serum ALP when their production is increased. Tissue-nonspecific ALPs are clinically significant because they make up the majority of the circulating fraction in serum. They are encoded by a single gene and are expressed in the liver, bone, and kidneys (Lowe et al., 2023).

PATHOPHYSIOLOGY

The liver is the main source of elevated enzyme levels in most patients. The next most likely contributor is increased osteoblast activity, which occurs in bone disorders or typically during growth periods. Additionally, in the late third trimester of pregnancy, the influx of placental ALP significantly raises levels. During pregnancy, ALP levels can rise to twice the normal limit due to placental release and fetal bone growth (Connolly et al., 2022).

The mechanism behind the rise in ALP levels in hepatobiliary disorders has been a topic of debate. However, research has convincingly shown that this increase is due to enhanced enzyme synthesis rather than a decrease in hepatobiliary excretion. The rise in hepatic enzyme activity is directly linked to the increase in serum ALP activity. This is mainly due to an upsurge in the translation of ALP mRNA, a process driven by rising bile acid concentrations, and the increased secretion of ALP into the serum through canalicular leakage into the hepatic sinusoid. The exact mechanism triggering its release into circulation remains unclear (Masrour Roudsari & Mahjoub, 2012).

Serum alkaline phosphatase (ALP) and its isoenzymes are indicative of bone metabolism: ALP raises the ratio of inorganic phosphate to pyrophosphate throughout the body, promoting mineralization and reducing extracellular pyrophosphate concentration, which inhibits mineral formation. Conversely, low ALP activity is linked to decreased bone turnover. The bone isoenzyme (B-ALP) plays a role in bone calcification and serves as a marker of bone turnover due to osteoblastic activity. ALP and its isoenzymes are essential in diagnosing all forms of rickets (Cannalire et al., 2023).

ETIOLOGY OF ALP ABNORMAL LEVELS

In healthy individuals, the primary source of the circulating enzyme is predominantly the liver and bone. In some cases, a minor fraction of this enzyme originates from the intestinal tract. Hepatic disease is the main cause of elevated ALP levels. Serum ALP levels display age-related variations in healthy individuals. They peak during childhood and puberty due to bone growth and development, and subsequently decrease with advancing age. The decline in serum ALP levels more than fifteen and less fifty is slightly more pronounced in males than females. These levels increase again in old age, with a notable difference between genders. The underlying reasons for these typical fluctuations remain unidentified. Research indicates a positive correlation between ALP levels and both body weight and smoking, while a negative correlation exists with height (Lowe et al., 2023).

Measuring serum ALP levels is primarily clinically significant for diagnosing cholestatic liver disease, as substantial elevations are frequently observed in patients with cholestasis. Elevations typically exceeding four times the upper limit of normal can be found in up to 75% of patients with cholestasis, whether it is intrahepatic or extrahepatic. The extent of elevation does not aid in distinguishing between these two types of cholestasis. Similar increases in ALP levels are seen in conditions such as biliary obstruction due to cancers like cholangiocarcinoma, pancreatic head adenocarcinoma, or ampullary adenocarcinoma, as well as in biliary stricture, sclerosing cholangitis, choledocholithiasis and causes of intrahepatic cholestasis such as
Severe alcoholic hepatitis, infiltrative liver diseases (such as sarcoidosis, amyloidosis, tuberculosis, and liver metastases), chronic rejection of liver transplants, drug-induced liver injury, and primary biliary cholangitis (PBC). leading to steatonecrosis (Shamban et al., 2014).

Patients diagnosed with acquired immune deficiency syndrome (AIDS) may also display significantly elevated ALP levels, often due to cholangiopathy associated with opportunistic infections such as cytomegalovirus, cryptosporidiosis, or liver granulomas from tuberculosis (Gao et al., 2011). According to Sterling et al. (2008), mild to moderate increases in liver enzymes are common in HIV patients without hepatitis C virus (HCV) or hepatitis B virus (HBV), and the absence of protease inhibitor (PI) use independently correlates with elevated levels of both AST and ALT. Factors indicative of hepatic steatosis, such as diabetes mellitus (DM) and high body mass index (BMI), are specifically associated with increased ALP levels.

Extensive testing is often unnecessary for patients with a slight increase in serum ALP, which is less than a 50% rise. Elevated bone ALP levels can be seen in conditions such as osteomalacia, hyperthyroidism, hyperparathyroidism, healing fractures, osteogenic sarcoma, Paget disease, and bone metastasis. Increased intestinal ALP activity may occur post a fatty meal and can have a hereditary component; however, it generally does not require additional evaluation (Verma et al., 2012).

Maldonado et al. (1998) studied thirty-seven hospitalized patients with elevated alkaline phosphatase levels, identifying various underlying conditions: seven had sepsis, eight had biliary obstruction, seven had malignant obstruction, one had a common bile duct stone, nine had acquired immunodeficiency syndrome (AIDS), and four had benign intrahepatic diseases, including liver hemangiomas, sarcoid hepatitis, lead toxicity, and drug-induced cholestasis. In a separate investigation, Jeyasree et al. (2018) observed significantly elevated levels of saliva and serum ALP in patients with chronic generalized periodontitis. They noted that these levels decreased notably after Phase I periodontal treatment, alongside improvements in clinical parameters. Persistent elevation of ALP often prompts further medical evaluation.

On the hand, Shamban et al. (2014) noted mild to moderate elevation of ALP in patients with congestive heart failure, with very high levels of ALP rarely observed. They highlighted that elevated ALP levels, along with increased bilirubin, have been linked to cholestatic liver injury due to heightened central venous pressure. Meanwhile, Wu et al. (2022) reported a rare case of significantly elevated alkaline phosphatase (ALP) caused by congestive hepatopathy in the context of heart failure with preserved ejection fraction. Their study concluded that intricate interactions between the heart and liver often lead to concurrent heart failure and liver disease. In cases of unexplained chronic cholestasis associated with congestive heart failure, suspicion should be raised for congestive hepatopathy.

Regarding hyperparathyroidism, total alkaline phosphatase is a more reliable predictor of adverse outcomes than hyperparathyroidism in patients undergoing hemodialysis. According to Yang et al. (2017), elevated preoperative levels of alkaline

phosphatase (ALP) in patients with refractory secondary hyperparathyroidism correlate with postoperative hypocalcemia and increased mortality rates. Factors associated with elevated preoperative ALP in secondary hyperparathyroidism patients include preoperative PTH levels. Huang et al. (1994) previously suggested that elevated serum alkaline phosphatase levels could serve as a valuable indicator, alongside high serum PTH levels, in predicting parathyroid gland hyperplasia in chronic hemodialysis patients. Ge et al. (2018) highlighted that preoperative PTH and alkaline phosphatase levels can predict the postoperative calcium requirements, enabling effective management of hypocalcemia with calcium supplementation equations after parathyroidectomy with autotransplantation in dialysis patients.

On the other hand, decreased serum levels of alkaline phosphatase (ALP) are a characteristic feature of hypophosphatasia (HPP), a group of inherited disorders characterized by impaired bone and/or tooth mineralization. HPP results from mutations in the ALPL gene, which lead to reduced activity of tissue-non-specific alkaline phosphatase isozyme (TNAP). This deficiency causes extracellular accumulation of inorganic pyrophosphate (PPi), a natural substrate of TNAP and a potent inhibitor of mineralization. The disease exhibits considerable variability in clinical presentation, ranging from severe forms with stillbirth due to lack of mineralized bone, to mild forms appearing in late adulthood with symptoms such as musculoskeletal pain, joint problems, fractures of the lower extremities, premature tooth loss, or incidental discovery of reduced serum ALP activity (Millán & Whyte, 2016; Fenn et al., 2021).

In the same line, during cardiopulmonary bypass (CPB), inflammatory reactions are triggered, potentially causing a depletion of alkaline phosphatase (AP) as it is utilized to dephosphorylate harmful extracellular nucleotides in this inflammatory state. Studies indicate that decreased AP levels following surgery correlate with higher postoperative support needs and organ dysfunction in pediatric cardiac surgery cases (Schaefer et al., 2020).

CONCLUSIONS

The majority of ALPs in serum (over 80%) originate from the liver and bone, with smaller amounts coming from the intestines. Despite being present in various tissues throughout the body, the precise physiological role of alkaline phosphatases remains largely unclear. Elevated enzyme levels in most patients typically originate from the liver. The next likely source is increased osteoblast activity, commonly seen in bone disorders or during periods of growth. Serum ALP levels vary with age in healthy individuals, peaking during childhood and puberty due to bone growth and development, and then declining as individuals mature.

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