Skeletal

Ostase (Bone alkaline phosphatase)

Analyte Information

Ostase (Bone alkaline phosphatase - BAP)

Introduction

Ostase® is a trademark of an immunoassay for the quantitative measurement of bone alkaline phosphatase – BAP.

Bone alkaline phosphatase is one of isoenzymes of alkaline phosphatase.

Alkaline phosphatase (ALP) is a membrane-bound enzyme which catalyzes the hydrolytic cleavage of phosphoric acid esters at an alkaline pH. It is found in many tissues, including bone, liver, kidney, intestine and placenta.

There are three main isoenzymes of ALP: placental, intestinal and tissue nonspecific ALP. Bone alkaline phosphatase (BAP, or BALP), together with slightly different liver and kidney isoforms, belongs to tissue nonspecific ALP. The others known isoforms are germ-cell (placental-like) and so-called oncogenic isoenzymes, produced by tumor cells. Determination of ALP activity in blood is mainly used to assess bone and hepatobiliary diseases.

BAP is a tetrameric glycoprotein, consisting of 507 amino acids. BAP is found on surface of osteoblasts and reflects the biosynthetic activity of these bone-forming cells. Osteoblasts are responsible for lying down the protein matrix of bone, in which calcium salts (particularly phosphates) are deposited. Therefore, BAP can serve as indicator of osteoblastic activity. It is mainly used as an aid in the management of Paget's disease and postmenopausal osteoporosis.

Bone alkaline phosphatase is also called skeletal alkaline phosphatase (SAP or B-ALP), or tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP).

Metabolism

The intestinal ALP is a galactosyl-terminal glycoprotein that reacts with a galactosyl-specific receptor on the hepatocyte membrane and undergoes subsequent endocytosis.

On the other hand, BAP is sialoglycoprotein[3] that don´t react with the galactosyl receptor and is therefore protected from rapid uptake from blood.

BAP is cleared by the liver. The half-life of intestinal ALP is less than 1 hour, while BAP half-life is significantly longer 1-3 days. BAP is also relatively unaffected by diurnal variation.

Physiological function

ALP is a hydrolase enzyme responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins, and alkaloids. The process of removing the phosphate group is called dephosphorylation. As the name suggests, ALP is the most effective in an alkaline environment[8].The precise metabolic function of ALP is not yet well understood.

The majority of bone is made of the bone matrix, which is the ground substance and in which the cells of bone exist. Bone matrix has inorganic and organic parts. The inorganic part of bone is mainly formed by crystalline of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). The matrix is manufactured by osteoblasts and initially laid down as un-mineralized osteoid. Osteoblasts are also responsible for osteoid mineralization. They secrete vesicles containing BAP[7], which cleaves the phosphate groups. The vesicles then rupture and act as a centre for crystals to grow on. The regulation of mineralization relies largely on a substance called inorganic pyrophosphate, which inhibits abnormal calcification. BAP seems to be antagonistic regulator of mineralization toward inorganic pyrophosphate formation and degradation under physiological conditions[9].

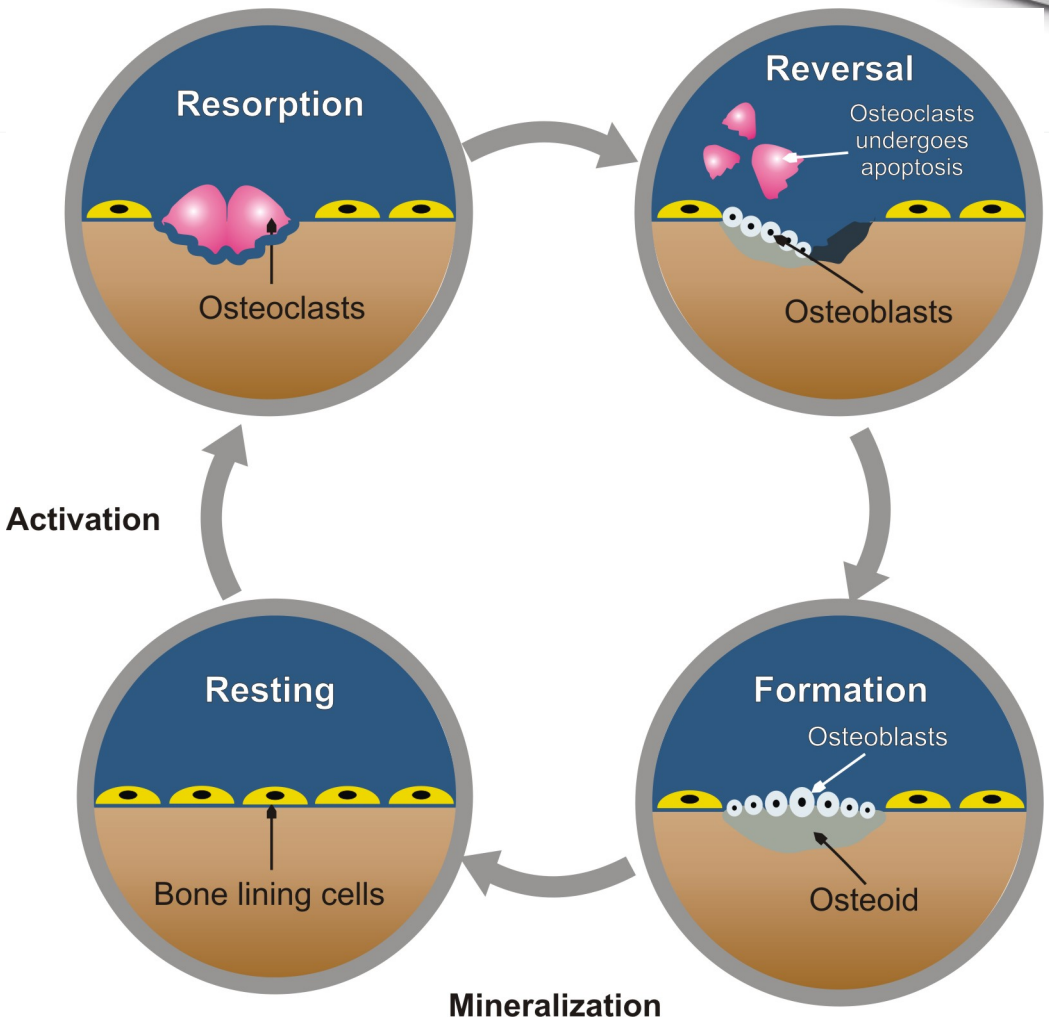
The bone tissue is metabolically active tissue, which is continuously remodeling. Bone remodeling enables bone to repair damages and adjust strength. This process is characterized by two opposite activities, the formation of new bone and the degradation (resorption) of old bone. Bone formation and resorption are interdependent processes that are, under normal circumstances, tightly coupled in time and space.

There are two main types of bone cells, located on bone surface, which acts in bone remodeling. Osteoclasts resorb bone, whereas osteoblasts participate in the synthesis of new bone. They make the protein mixture known as osteoid, which is mineralized. BAP plays an essential role in this process of minarelization.

The bone remodeling cycle consists of several consecutive phases, Fig.1.:

ACTIVATION: micro-cracks of bone and consequent osteocytes signalization, seem to be the main activators of bone remodeling cycle.
RESORPTION: during this phase osteoclasts digest old bone. Circulating osteoclast precursors are recruited, proliferate, and fuse to form osteoclasts. These giant multinucleated cells resorb bone and digest organic matrix. Osteoclasts seal off an area on the surface, and develop a region of intense activity in which the cell surface is highly irregular, called a ruffled border. This ruffled border contains transport molecules that transfer hydrogen ions from the cells to the bone surface where they can dissolve the mineral. In addition, several enzymes (e.g. acid phosphatase) are secreted from the ruffled border that can break down the matrix.
REVERSAL: starts when the resorbed surface is prepared for the subsequent formation phase. The mononuclear cells appear on the surface of resorption cavity and form a cement line. This thin layer of protein, rich in sugars, helps form a strong bond between the old bone and the newly formed bone.
FORMATION: stromal lining cells differentiate to osteoblasts, the mononucleate cells, which form bone by synthesizing the organic matrix, including type I collagen, and participate in the mineralization of newly produced matrix. The organic matrix of bone, i.e. young bone that has not undergone calcification, is called osteoid. The resorbed bone is completely replaced by new bone.

Fig.1: The bone remodeling cycle



Levels

The predominant ALP forms present in normal serum can be characterized as the bone and liver varieties[7]. BAP comprises approximately 50% of total circulating ALP in normal subjects.

Some preparation for the treatment of osteoporosis (e.g. Forsteo) may cause increased levels of BAP.

Typical BAP levels[17] in children and in adults are given in Tab.1. For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Tab.1: Typical Ostase levels in serum or plasma[17]

Specimen (serum or plasma)	Reference interval (ng/mL)
Children	
2-24 months	25.4-124
2-9 years	24.2-89.5
Tanner I-II	19.5-87.5
Tanner III-IV	19.5-156
Adult	
Male	8.8-30.0
Female	5.7-22.0

Diagnostic utility — prospects and possibilities

The rate of formation or degradation of the bone matrix can be assessed by measuring markers of bone turnover. These markers are classified into two categories: bone formation markers and bone resorption markers. BAP belongs to the group of bone formation markers.

BAP, one of isoenzymes of ALP, is produced by osteoblasts[5], therefore it is obvious that BAP measurement reflects bone turnover more specifically and sensitively than total ALP measurement.

An accurate assessment of bone metabolism is critical for determining the severity of metabolic bone diseases and responses to their therapy. Measurement of BAP levels has been shown to be useful mainly in evaluating patients with Paget's disease, osteoporosis, osteomalacia, primary hyperparathyroidism, renal osteodystrophy, and metastases to bone.

BAP exhibits little diurnal variation due to its relatively long half-life. Therefore, when compared with other markers of bone formation e.g. osteocalcin, BAP shows the least variability and its measurement is more reliable and robusts.

Transient BAP elevations may be found during healing of bone fractures. Increased levels of BAP sometimes occur in childhood and adolescence due to increased osteoblastic activity in connection with the growth of bones[1,2].

Elevated BAP levels are associated with:

- Paget´s disease
- high turnover osteoporosis
- primary or secondary hyperparathyroidism
- renal osteodystorphy
- hyperthyroidism
- osteomalacia
- metastatic bone disease
- recent bone fractures
- acromegaly
- menopause
- children during bone growth
- pregnancy
- adults >50 years

Decreased BAP levels are associated with:

- growth hormone deficiency
- hypothyroidism
- hypoparathyroidism
- hypophosphatasia

Diagnosis and severity assessment of metabolic bone diseases and monitoring antiresorptive therapies efficacy

Paget's disease

Paget‘s disease[10] of the bone (osteitis deformans) is the second most common metabolic illness that typically results in enlarged and deformed bones. It is prevalent in Northern Europe, affecting up to 4% of people over the age of 40 and up to 10% over the age of 60.

Paget's disease is a disorder of bone remodeling. The precise cause of Paget’s disease is not known, but it appears to be the consequence of both genetic factors and environmental factors, possibly a viral infection. In the initial stages of the disease, osteoclastic activity predominates so that bones become soft and deformed and may fracture. Later increased osteoblastic activity results in thickened deformed, so called “woven” bone. This can trap nerves or leave abnormal bone in the joint areas. Thus, neurological and rheumatological symptoms are associated with Paget's disease. The worst complication is the progression to bone sarcoma, but this occurs rarely (<1%).

This disorder is very often asymptomatic and diagnosed coincidentally from radiological investigation performed for another purpose. The most common complaints in symptomatic patients are pain and deformity. Because early diagnosis and treatment is important, after age 40, siblings and children of someone with Paget's disease may wish to have BAP blood test every two or three years.

Biochemical investigations of this disease show that serum calcium is usually in the normal range whilst serum BAP is raised. **This is a useful marker of disease activity and for assessing the response to bisphosphonate therapy used to inhibit bone resorption**. **BAP levels decreases following antiresorptive therapy in Paget´s disease[9].**

Osteomalacia and rickets[12]

It is the term used to describe the pathological condition in bone in which the osteoid matrix (the proteinaceous scaffolding in bone) remains uncalcified.
Osteomalacia is a condition affecting adults, where the bones become weak and softer than normal. Symptoms include bone pain and muscle weakness. The condition is usually caused by vitamin D deficiency, and can be treated by vitamin D supplements. Some people are more at risk of osteomalacia, particularly pregnant or breast-feeding women, black or Asian people and the elderly. People with an increased risk of osteomalacia can take vitamin D supplements to prevent it developing.
In children, where the bones are still growing, the same condition is called rickets.
Elevated serum BAP is a hallmark of this condition.

Osteoporosis

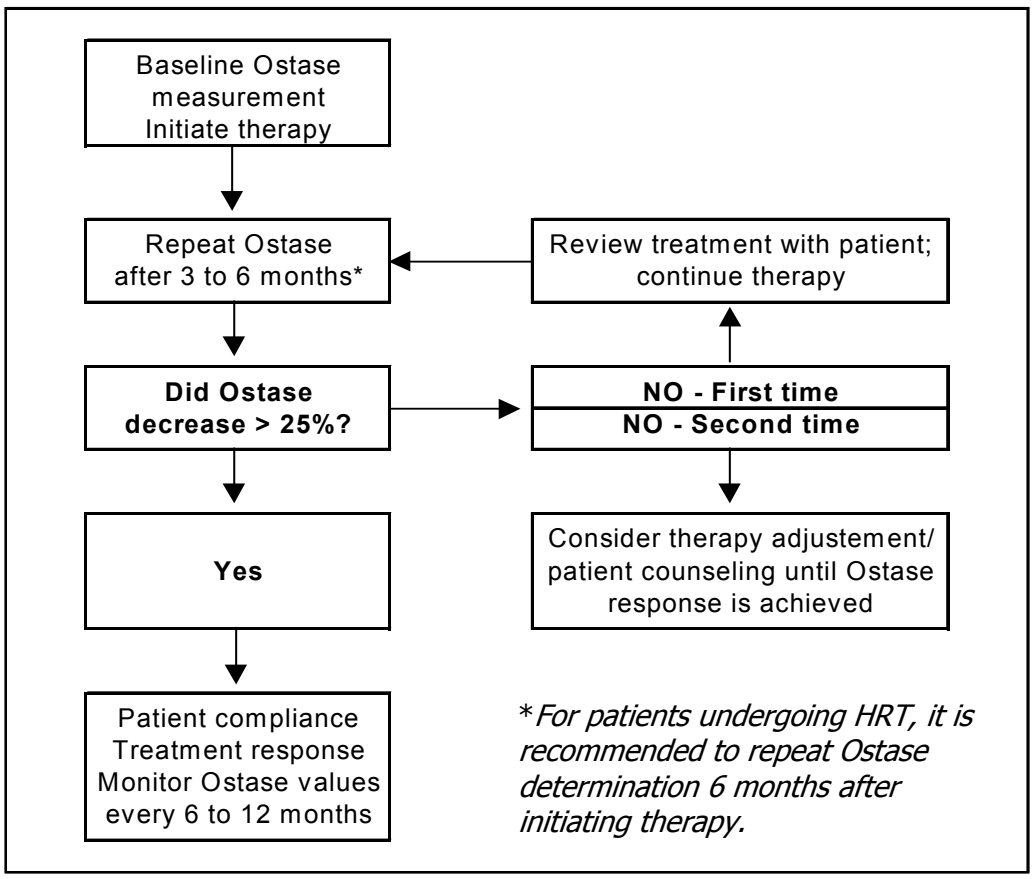
Osteoporosis is the disease of bone that leads to an increased risk of fracture. In osteoporosis the bone mineral density (BMD) is reduced, bone microarchitecture is disrupted and the amount and variety of proteins in bone are altered. Osteoporosis is the most common in women after menopause, when it is called postmenopausal osteoporosis as the result of estrogen deficiency. Rapid bone loss accompanies the decline of estrogen levels at the onset of menopause or after ovariectomy, as a result of the combined effects of an imbalance in bone remodelling and an increase in bone turnover. The serum level of BAP is the specific and sensitive marker of this menopausal alteration[14,15]. Hormone replacement therapy (HRT) is often used for the prevention of osteoporotic fractures in postmenopausal women. However many women cannot avail themselves of HRT, because of the increased risk of cancer and the resumption of menstrual bleeding. Therefore, other compounds such as bisphosphonates, a standard treatment for Paget's disease of bone, have been used to treat osteoporosis. The antiresorptive properties of bisphosphonates decrease bone remodeling and, consequently, decrease the overall loss of bone. Osteoporosis may also develop in men. Particularly, it may occur in the presence of certain hormonal disorders and other chronic diseases or as a result of medications, specifically glucocorticoids (so called steroid- or glucocorticoid-induced

osteoporosis - SIOP or GIOP). BAP values reflect the increased turnover associated with bone destruction in aging, menopause and various conditions affecting bone metabolism. BAP levels decrease rapidly as the reflection of the therapeutic effect of antiresorptive agents. Measurements of bone turnover markers are not useful for the diagnosis of osteoporosis; diagnosis of osteoporosis should be made on the basis of bone density.

Several studies have shown that successful antiresorptive therapies for management of osteoporosis patients should result in at least a 25% decrease in BAP within 3 to 6 months of initiating therapy[4,6]

When used as a marker for monitoring purposes, it is important to determine the critical difference (or at least significant change). The critical difference is defined as the difference between two determinations that may be considered to have clinical significance. The critical difference for this method was calculated to be 25% with a 95% confidence level[16], see Tab.2

Tab.2: Ostase and anti-resorptive therapy proposed algorithm:



Primary hyperparathyroidism[12]

Primary hyperparathyroidism causes hypercalcemia (elevated blood calcium levels) through the excessive secretion of parathyroid hormone (PTH), usually by an adenoma of the parathyroid glands. Blood tests are in this case performed to reveal increased levels of PTH, calcium, and BAP and decreased levels of phosphorus.

Renal osteodystrophy or chronic kidney disease-mineral and bone disorder[11]

It is bone pathology, characterized by bone mineralization deficiency, that is a direct result of the electrolyte and endocrine derangements which accompany chronic kidney disease. Renal osteodystrophy can be further divided into metabolic states associated with either high or low bone turnover. Renal osteodystrophy may exhibit no symptoms. If it does show symptoms, they include bone pain, joint pain, bone deformation or bone fracture.

Bone cancer (osteogenic sarcoma or osteosarcoma)[7]

Very high BAP levels are present in patients with osteogenic bone cancer. It is one of the most common primary bone cancers. This cancer starts in the bone cells. It most often occurs in young people between the age of 10 and 30, but about 10% of osteosarcoma cases develop in people in their 60s and 70s. It is rare during middle age and is more common in males than females. These tumors develop most often in bones of the arms, legs or pelvis.

Prostate cancer

Prostate cancer metastasizes primarily to the skeleton and only occasionally to the lungs and the liver. The total PSA and BAP assessments in the patients with the risk of developing bone metastases are used to monitor the disease and may help to avoid unnecessary bone scintigraphies.

Hypophosphatasia[13]

Hypophosphatasia is a rare inherited disorder[8] characterized by defective bone and teeth mineralization, and deficiency of serum BAP activity. The prevalence of severe forms of the disease has been estimated at 1/100 000.

The symptoms are highly variable in their clinical expression, which ranges from stillbirth without mineralized bone to early loss of teeth without bone symptoms. Clinical symptoms are respiratory complications, premature craniosynostosis, widespread demineralization and rachitic changes in the metaphyses. The childhood form is characterized by skeletal deformities, short stature, and waddling gait. The adult form is characterized by stress fractures, thigh pain, chondrocalcinosis and marked osteoarthropathy. The disease is due to mutations in the liver/bone/kidney ALP gene encoding the tissue-nonspecific ALP.
The BAP levels are decreased in this disease.

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