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# Identification of hypophosphatasia in a clinical setting: Clinical manifestations and diagnostic recommendations in adult patients☆

## Identificación de hipofosfatasia en la práctica clínica: Manifestaciones clínicas y recomendaciones diagnósticas en pacientes adultos

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## Introduction

Hypophosphatasia (HPP) is a rare disease caused by a genetic metabolic defect biochemically characterized by low serum activity values of alkaline phosphatase. It is caused by mutations in the gene encoding the *tissue-nonspecific alkaline phosphatase* (TNSALP) isoenzyme, with a loss of function.[1]

It should be noted that there are 4 genes encoding alkaline phosphatase: *TNSALP*, and 3 genes encoding specific tissue isoenzymes (intestinal, placental and germ cells). TNSALP is expressed in the bone, liver, kidney and developing teeth. Thus, a concentration of natural TNSALP substrates occurs in HPP, among which inorganic pyrophosphate stands out, an inhibitor of mineralization, which, when accumulated extracellularly, can cause osteomalacia by blocking the propagation of hydroxyapatite crystals,[2] loss of teeth and arthropathy or periarticular involvement caused by calcium crystal deposition.[1] In this sense, the accumulation of inorganic pyrophosphate promotes the formation of calcium pyrophosphate crystals and subsequent deposition in articular cartilage.[3]

The dominant or recessive inheritance of this disease, with more than 300 mutations described to date in the gene *TNSALP*,[4] explains the great variability of its clinical expression. Sporadic cases are rare. The clinical manifestations of HPP range from very severe forms, usually neonatal with absence of bone mineralization at birth, to only dental forms during childhood or adulthood.

The accumulation of other TNSALP natural substrates such as pyridoxal 5′-phosphate can have important clinical consequences in the neonate, causing seizures, since this circulating form of vitamin B6 is necessary for the synthesis of neurotransmitters. In the adult, determining their plasma concentration is very useful in the diagnostic suspicion of HPP.[5]

Finding low serum alkaline phosphatase (hypophosphatasaemia) levels is not synonymous with HPP. Thus, a study that evaluated the genetic abnormalities of a group of patients between 20 and 77 years of age who had inexplicably low alkaline phosphatase levels, detected that only half of them had a mutation in the gene encoding TNSALP, with the majority being asymptomatic or with mild symptoms.[6]

It is important to note that the most severe forms of HPP occur during childhood, and that the clinical expression of this disease in adults varies greatly, from less symptomatic to more severe forms. The typical symptom is recurrent stress fractures predominantly in metatarsals and, occasionally, HPP can be manifested by proximal femur pseudofractures. In severe, sporadic adult forms, HPP may manifest by fractures anywhere in the skeleton. In general, the most severe manifestations of HPP occur in patients with the lowest values of alkaline phosphatase.[1,5,7]

The diagnosis of HPP in clinical practice is a challenge. Its low prevalence makes identification difficult, especially when there is overlapping of symptoms with other more prevalent diseases. In

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**Table 1**
Clinical characteristics of hypophosphatasia in adult patients.

| Subtypes | Symptomatology's onset age | Main clinical manifestations | Diagnostic tests | Natural course |
|---|---|---|---|---|
| Adult form (AR/AD inheritance) | Median age | *Skeletal abnormalities*[1,2,5,14]<br>Stress fractures in metatarsals<br>Femoral pseudo-fractures<br>Recurrent fractures<br>History of fractures with delayed consolidation<br>History of mild rickets in childhood<br>*Articular and periarticular disorders*[16]<br>Chondrocalcinosis<br>Multiple calcific tendinitis<br>*Muscle abnormalities*<br>Muscle pain<br>*Renal abnormalities*[7]<br>Low glomerular filtration[a]<br>Nephrocalcinosis[a]<br>Nephrolithiasis[a]<br>*Psychiatric disorders*[7]<br>Anxiety[a]<br>Depression[a]<br>*Dental abnormalities*[7,11,16]<br>History of premature loss of primary teething<br>Premature loss of permanent teeth<br>*Other abnormalities*[7]<br>Hyperphosphatemia<br>Hypercalcemia[a] | *Complete history*<br>*Imaging tests*<br>X-rays: associated typical skeletal abnormalities<br>Bone densitometry: low bone density<br>*Lab tests*<br>Total AP activity: low<br>High AP substrates: plasma PLP, urinary PEA<br>*Genetic analysis*<br>Mutations in the *TNSALP* gene | Very variable clinical manifestations<br>Better prognosis than the paediatric forms of the disease |

AD: autosomal dominant; AR: autosomal recessive; AP: alkaline phosphatase; PEA: phosphoethanolamine; PLP: pyridoxal 5′-phosphate; *TNSALP*: gene encoding the *tissue-nonspecific alkaline phosphatase* isoenzyme.
[a] Low prevalence.

addition, the little importance given in clinical practice to decreased serum alkaline phosphatase activity, in contrast with the high regard given to an increase in alkaline phosphatase, is another limiting factor for diagnosis. In fact, it has been estimated that in patients admitted to a tertiary hospital the prevalence of persistently low alkaline phosphatase is 0.13% and that, in addition, it is only recognized in 3% of cases.[8] Likewise, a study that analyzed the clinical and radiological characteristics of 269 patients with persistently low alkaline phosphatase from a series of 885,165 patients visited between 2002 and 2012 in a multidisciplinary clinic were published in 2014. Patients with low alkaline phosphatase values had more frequent bone and joint manifestations (chondrocalcinosis, calcific tendinitis, hyperostosis and orthopaedic surgery) than the population with normal alkaline phosphatase. Therefore, the authors suggested that clinicians should consider the diagnosis of HPP when faced with persistent hypophosphatasemia.[9]

The diagnosis is of particular relevance due to the potential severity of the disease, the significant impact on the quality of life that many of the patients may experience, or the possible iatrogenesis that can determine a wrong diagnosis. Along with this, the recent availability of an enzyme replacement treatment specific to HPP,[10] especially indicated in severe forms, determines the need for a correct diagnosis for the sake of an early and adequate treatment.

The objective of this article is to provide an eminently practical document with general recommendations to facilitate the identification and diagnosis of adult patients with HPP.

## Diagnosis of hypophosphatasia in adult patients

The clinical manifestations of the adult form of HPP are very variable, requiring a high index of suspicion for its diagnosis. Consequently, this is probably the most underdiagnosed form of HPP. The delay in diagnosis is common and most of the patients diagnosed report having experienced symptoms of rickets or premature loss of primary teething in childhood.[11] In a study that analyzed the spectrum of presentation of HPP in adults, it was observed that the average age of onset of the first symptoms was 44 years and the mean age at diagnosis, 49 years.[12] Almost one-third of the patients were asymptomatic at the time of diagnosis,[12] which is made based on physical examination, family history and laboratory results (Table 1). Despite this, some authors consider that the diagnosis of HPP requires evidence of at least one complication of the disease, even in those patients with characteristic biochemical findings and genetic abnormalities in *TNSALP*.[13] In general, in adult patients who recurrently present with stress or complete fractures and dental abnormalities, serum determination of total alkaline phosphatase activity should be considered (Fig. 1).

A deficiency in mineralization is the cause of the development of the most common bone manifestations in adult patients, such as stress fractures that are difficult to consolidate (non-traumatic recurrent fractures are the key element of HPP in apparently healthy adults).[14] In addition, patients with HPP may have articular, periarticular and muscle pain. Early loss of adult teeth is also a characteristic sign of HPP. The said loss may be secondary to the presence of hypoplasia of the tooth cement, to defects in the mineralization and formation of dental enamel, or to the poor quality of the underlying alveolar bone.[1] Additionally, a higher frequency of anxiety and depression has been described in adult patients with HPP. The cause of these psychological disorders has not been defined, but TNSALP has been associated with the synthesis of neurotransmitters such as serotonin and dopamine, through its effect on the metabolism of vitamin B6.[5,7]

The most commonly described radiological manifestations in the adult form of HPP are metatarsal stress fractures, femoral