HYPOPHOSPHATASIA (HPP)

WHAT IS HYPOPHOSPHATASIA?

Hypophosphatasia (HPP) is a **rare, inherited and progressive metabolic disease** characterised by defective mineralisation (the process that hardens and strengthens bones and teeth), impaired calcium and phosphate regulation and non-skeletal manifestations, such as muscle weakness, generalised fatigue and pain.[1-3]

HPP is caused by deficient activity of an enzyme known as **alkaline phosphatase (ALP)**, which is important for building healthy bones as well as proper function of muscles.[1]

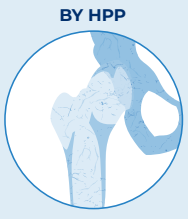
ALP deficiency can lead to poor growth and development and a variety of **skeletal and non-skeletal abnormalities**, including soft bones, deformity of bones, bone fractures, muscle weakness, fatigue, abnormal gait, early loss of primary teeth with the root intact and progressive damage to vital organs.[1,2]

As a result, the disease can have a debilitating impact, including loss of physical function and chronic pain.[1]

HEALTHY BONES AND MUSCLES

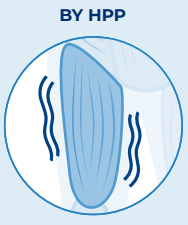
When ALP functions normally, **muscles are strong**, and calcium and phosphate bind together to **form healthy, strong bones**.[1]

BONE IMPACTED BY HPP



People living with HPP have low ALP levels, which can **impair mineral metabolism** and **prevent proper bone development.** Although more than half of people with HPP do not have apparent bone manifestations, they can still experience **considerable disability and reduced quality of life**.[1,3,4]

MUSCLE IMPACTED BY HPP



Low ALP activity can also cause **non-skeletal signs and symptoms**, including **musculoskeletal pain, muscle weakness and fatigue**.[1,4,5]

The severity of HPP can be wide-ranging and may present in many different ways.[1]

HPP can **affect males and females of all ages**, with approximately 80% of people living with HPP aged ≥18 years. Certain signs and symptoms of HPP may be more common **based on a person's age**.[1,6]

When signs and symptoms are present **before 6 months of age**, HPP is referred to as **perinatal or infantile HPP and can be fatal**.[1,5]

People of all ages living with HPP may experience **significant disease burden that impacts their daily life**, including the ability to perform daily tasks or walk.[1,5,7]

SIGNS AND SYMPTOMS MAY VARY AND CAN IMPACT MANY DIFFERENT PARTS OF THE BODY, INCLUDING:[1-3,7-10]

Bones
(abnormally shaped head, pseudofractures, bone deformities, softening of bones, rickets*, frequent fractures, persistent musculoskeletal pain, waddling gait)

Muscles and joints
(muscle weakness, neuromuscular pain, generalised body pain, joint stiffness or swelling, fatigue, arthritis, fibromyalgia)

Ribs and lungs
(underdeveloped ribs and lungs†, severe breathing difficulties*, respiratory failure*)

Central nervous system
(pain, headaches, vitamin B6-dependent seizures†, brain fog, depressed mood)

Kidneys
(kidney stones, decreased kidney function)

Teeth
(early loss of primary teeth with the root intact*, gum disease)

Symptoms can appear at **any age and accumulate or worsen over time**, causing significant **disability, impaired mobility or life-threatening complications**.

*Signs and symptoms in infants and/or young children
†Signs and symptoms in infants

HOW IS HPP DIAGNOSED?

Since HPP shares symptoms with other, more common musculoskeletal diseases, it **is frequently misdiagnosed and diagnosis is often delayed**. Diagnostic criteria help to **enable earlier diagnosis** and **continue to evolve** as the scientific understanding of the diverse signs and symptoms of the disease advances.[1,10]

Perinatal or infantile HPP **may be diagnosed earlier** due to more apparent signs and symptoms, while children and adults **may remain underdiagnosed for decades** due to non-specific and more variable symptoms. Once a person shows signs and symptoms of HPP, **a full clinical assessment and blood test** for low ALP can help lead to a correct diagnosis.[10,11]

Imaging tests may help to evaluate bone injuries and abnormalities (including X-rays, magnetic resonance imaging (MRI) and computed tomography). **Genetic testing** may also be helpful in confirming HPP, **but a negative result does not rule out a diagnosis**.[10]

HPP is a lifelong disease that can **result in progressive complications**, so an **early and accurate diagnosis is critical** to ensure appropriate disease management.[11]

Content created by Alexion, AstraZeneca Rare Disease.

References:

1. Rockman-Greenberg C. Hypophosphatasia. *Pediatric Endocrinology Reviews*. 2013;10(2):380-388.
2. Dahir KM, et al. Clinical profiles of treated and untreated adults with hypophosphatasia in the Global HPP Registry. *Orphanet J Rare Dis.* 2022;17(1):277.
3. Seefried L, et al. Burden of illness in adults with hypophosphatasia: data from the Global Hypophosphatasia Patient Registry. *J Bone Miner* Res. 2020;35(11):2171-2178.
4. Uday S, et al. Tissue non-specific alkaline phosphatase activity and mineralization capacity of bi-allelic mutations from severe perinatal and asymptomatic hypophosphatasia phenotypes: results from an in vitro mutagenesis model. *Bone.* 2019;127:9-16.
5. Whyte MP. Physiological role of alkaline phosphatase explored in hypophosphatasia. *Ann N Y Acad Sci.* 2010;1192:190-200.
6. Fang S, et al. Diagnosed prevalence of hypophosphatasia in the United States: a real-world analysis of electronic health records [poster]. Poster presented at: Annual International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 23-27 August 2023, Halifax, Nova Scotia, Canada.
7. Weber TJ, et al. Burden of disease in adult patients with hypophosphatasia: results from two patient-reported surveys. *Metabolism.* 2016;65(10):1522-1530.
8. Whyte MP, et al. Natural history of perinatal and infantile hypophosphatasia: a retrospective study. *J Pediatr.* 2019;209(4):116-124.
9. Beck C, et al. Whole-body MRI in the childhood form of hypophosphatasia. *Rheumatol Int.* 2011; 31(10):1315-1320.
10. Khan AA, et al. Hypophosphatasia diagnosis: current state of the art and proposed diagnostic criteria for children and adults. *Osteoporos Int.* 2024; 35(3):431-438.
11. Brandi ML, et al. The challenge of hypophosphatasia diagnosis in adults: results from the HPP international working group literature surveillance. *Osteoporos Int.* 2024;35(3):439-449.

GL/UNB-H/0040 V1 10/2024
US/UNB-H/0663 V1 11/2024