





An Expert Perspective on Phosphate Dysregulation With a Focus on Chronic Hypophosphatemia

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ABSTRACT

Because of their rarity, diseases characterized by chronic hypophosphatemia can be underrecognized and suboptimally managed, resulting in poor clinical outcomes. Moreover, serum phosphate may not be measured routinely in primary care practice. Authors participated in several working sessions to advance the understanding of phosphate homeostasis and the causes, consequences, and clinical implications of chronic hypophosphatemia. Phosphate levels are regulated from birth to adulthood. Dysregulation of phosphate homeostasis can result in hypophosphatemia, which becomes chronic if phosphate levels cannot be normalized. Chronic hypophosphatemia may be underrecognized as serum phosphate measurement is not always part of routine analysis in the primary care setting and results might be misinterpreted, for instance, due to age-specific differences not being accounted for and circadian variations. Clinical consequences of chronic hypophosphatemia involve disordered endocrine regulation, affect multiple organ systems, and vary depending on patient age and the underlying disorder. Signs and symptoms of chronic hypophosphatemic diseases that manifest during childhood or adolescence persist into adulthood if the disease is inadequately managed, resulting in an accumulation of clinical deficits and a progressive, debilitating impact on quality of life. Early identification and diagnosis of patients with chronic hypophosphatemia is crucial, and clinical management should be started as soon as possible to maximize the likelihood of improving health outcomes. Furthermore, in the absence of a universally accepted description for “chronic hypophosphatemia,” a definition is proposed here that aims to raise awareness of these diseases, facilitate diagnosis, and guide optimal phosphate management strategies by improving monitoring and assessment of patient response to treatment. © 2021 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: PHOSPHATE HOMEOSTASIS; HYPOPHOSPHATEMIA; OSTEOMALACIA AND RICKETS; PARATHYROID HORMONE/VITAMIN D/FIBROBLAST GROWTH FACTOR 23

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Introduction

The role of phosphate is well established, with its critical involvement in numerous biological processes and structures.⁽¹⁻⁵⁾ Phosphate requirements change throughout life and appropriate levels are required to develop and maintain optimal functioning of multiple body systems. In healthy individuals, serum phosphate levels are maintained within a fairly narrow range, influenced by circadian and dietary fluctuations. Levels are mainly controlled by fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D (1,25(OH)₂D), and inadequate control can result in hyperphosphatemia or hypophosphatemia.⁽³⁾ Hyperphosphatemia can result from kidney disease, hypophosphatasia, vitamin D intoxication, or defects in PTH and FGF23 secretion or activity. Excess FGF23 and PTH activity can lead to chronic hypophosphatemia and rickets or osteomalacia in addition to other deleterious and cumulative effects on multiple body systems.^(3,6,7) Diseases that are characterized by FGF23-related renal phosphate wasting may be inherited (eg, X-linked hypophosphatemia [XLH]), caused by somatic mutations (eg, fibrous dysplasia/McCune Albright Syndrome), acquired (eg, tumor-induced osteomalacia [TIO]), or drug-induced (eg, intravenous iron supplementation therapy).^(3,8-12) These rare diseases often remain underrecognized, underdiagnosed, and suboptimally managed.⁽³⁾ As such, there is a need for increased awareness and understanding of the causes and consequences of such conditions.

This article summarizes the opinions of the authors from several working sessions to advance the understanding of phosphate homeostasis and the causes, consequences, and clinical implications of chronic hypophosphatemia. The authors comprise experts (from both pediatric and adult medicine) in the fields of rare metabolic bone disease, phosphate metabolism, endocrinology, nephrology, and osteology. In the absence of a universally accepted definition for “chronic hypophosphatemia,” the authors propose a definition with the intention of harmonizing nomenclature and to raise awareness of diseases caused by defective phosphate metabolism leading to hypophosphatemia.^(13,14)

Phosphate: Role and Regulation

Role and requirements through life

Phosphorus (in the form of organic phosphate) is an essential component of cell membranes, proteins, nucleic acids, bones, and teeth, as well as having roles in the structure and function of smooth and skeletal muscles.⁽³⁾ Phosphorus-containing compounds are also involved in the storage and release of metabolic energy (via adenosine triphosphate[ATP]), cell signaling, and normal acid–base balance.⁽¹⁾

Phosphate requirements vary with age and sex because of changing developmental and physiologic needs (Table 1).⁽¹⁵⁻¹⁷⁾ The age-associated decline in serum phosphate levels, more predominantly shown in men after middle age, reflects changes in renal tubular phosphate reabsorption postulated by age-dependent changes in tubular phosphate handling or levels of hormonal modulators (eg, PTH, phosphatonins, and growth hormone).⁽¹⁸⁻²⁰⁾

Regulation of phosphate homeostasis

Under normal conditions, phosphate levels are maintained by a balance between dietary phosphate intake with appropriate

Table 1. Reference Ranges for Serum Phosphate

Age (years)	Males		Females	
	mmol/L	mg/dL	mmol/L	mg/dL
1–4	1.39–1.74	4.3–5.4	1.39–1.74	4.3–5.4
5–13	1.19–1.74	3.7–5.4	1.29–1.68	4.0–5.2
14–15	1.13–1.52	3.5–5.3	1.13–1.58	3.5–4.9
16–17	1.0–1.52	3.1–4.7	1.0–1.52	3.1–4.7
≥18	0.81–1.45	2.5–4.5	0.81–1.45	2.5–4.5

Iron and creatinine are modifying factors for plasma phosphate concentrations.⁽¹⁷⁾

Source: Mayo clinic (<https://www.mayocliniclabs.com/testcatalog/Clinical+and+Interpretive/8408>).

intestinal absorption, renal phosphate excretion through changes in renal tubular reabsorption, and the transcellular movement of phosphate between intracellular fluid and bones (Fig. 1). These processes are regulated via multiple endocrine negative feedback loops involving FGF23, PTH, and 1,25(OH)₂D (Fig. 2).^(1,21,22) Briefly, FGF23 is a key regulator of phosphate homeostasis and vitamin D metabolism^(23,24) that controls renal phosphate absorption and excretion.⁽²⁵⁾ Under physiologic conditions, FGF23 is produced by osteocytes and osteoblasts in response to high phosphate intake, elevated serum phosphate levels, or elevated 1,25(OH)₂D.⁽²⁶⁾ PTH is released from the parathyroid glands in response to low calcium levels and/or high phosphate in the blood, resulting in the production of 1,25(OH)₂D and, potentially, FGF23.^(1,22) In contrast, 1,25(OH)₂D increases in response to low plasma phosphate and potentiates the capacity of the gut to absorb dietary phosphate.⁽¹⁾ Maintenance of phosphate homeostasis is important throughout life as phosphate dysregulation can lead to hyperphosphatemia or hypophosphatemia, with potentially fatal complications if untreated.⁽¹⁾

Hyperphosphatemia

Hyperphosphatemia (defined in adults as serum phosphate >1.45 mmol/L [4.5 mg/dL]) often occurs in patients with acute or chronic kidney disease (CKD), hypophosphatasia, or vitamin D intoxication.^(3,7,15,27) Rare genetic disorders of

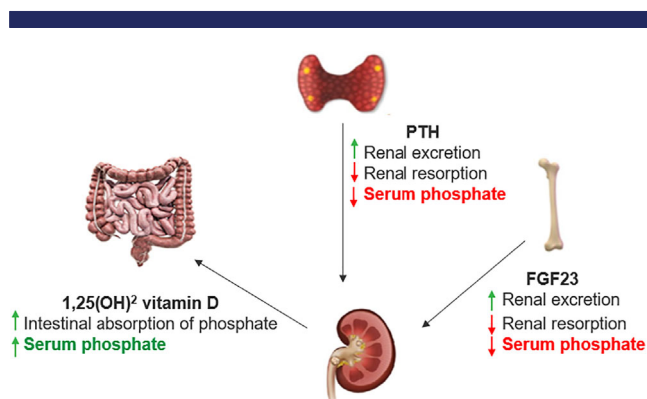


Fig 1. Direct action of FGF23, PTH, and 1,25(OH)₂D in regulating phosphate homeostasis. 1,25(OH)₂D = 1,25 dihydroxyvitamin D; FGF23 = fibroblast growth factor 23; PTH = parathyroid hormone.

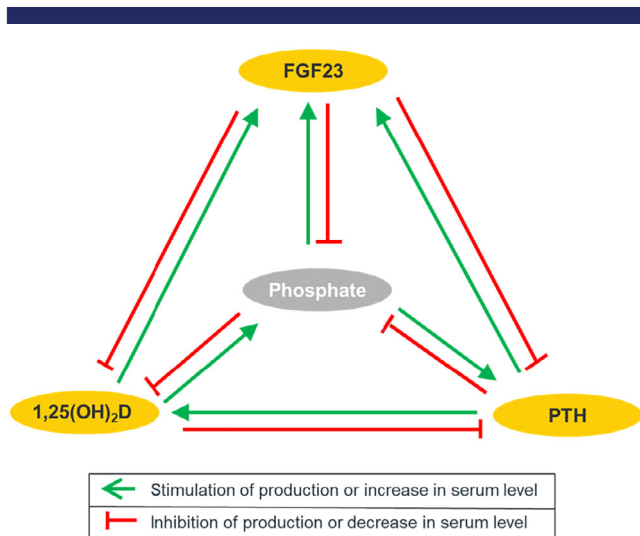


Fig 2. Overview of physiologic interactions between phosphate and its key regulators. 1,25(OH)₂D = 1,25 dihydroxyvitamin D; FGF23 = fibroblast growth factor 23; PTH = parathyroid hormone.

hyperphosphatemia include familial tumoral calcinosis (associated with reduced intact FGF23 levels) and hypoparathyroidism (associated with reduced PTH production).^(28,29) Higher phosphate levels, even if within the normal range, are associated with an increased risk of cardiovascular disease in the normal population and can result in overt hyperphosphatemia, particularly in patients with CKD.^(1,30,31) Serious complications associated with prolonged hyperphosphatemia include vascular calcification and heart failure.^(27,32)

Hypophosphatemia

In general, diseases characterized by hypophosphatemia can be divided into those mediated by or independent of FGF23—these may be genetic (hereditary or somatic mosaicism), acquired, or drug-induced (Table 2).^(3,11,12,21,33-36)

In adults, hypophosphatemia can be defined as mild (serum phosphate of 0.6 to 0.8 mmol/L; 1.8 to 2.5 mg/dL), moderate (0.4 to 0.5 mmol/L; 1.0 to 1.7 mg/dL), or severe (serum phosphate <0.3 mmol/L; 0.9 mg/dL); in children, hypophosphatemia is defined based on the age-related normal range (Table 1).^(3,37)

Hypophosphatemia can also be categorized based on its onset, ie, acute or chronic. Acute hypophosphatemia often results from redistribution of phosphate into the intracellular compartment without total body phosphate depletion, as found in refeeding states, severe burns, or with treatment of diabetic ketoacidosis.^(3,38) By contrast, chronic hypophosphatemia, which is not universally defined, is usually accompanied by total body phosphate depletion.⁽³⁾

Although an acute milder hypophosphatemic excursion is often clinically insignificant, severe forms can be associated with cardiac impairment, hematological complications, respiratory failure, and neurologic manifestations.⁽³⁾ Chronic hypophosphatemia impacts multiple body systems, including the skeletal, muscular, joint, and dental systems, and if unresolved will have lifelong deleterious and cumulative effects, resulting in impaired mobility and physical function, as well as reduced health-related

quality of life.^(8,39-41) It should be considered that some deficits observed in chronic hypophosphatemic disorders may be due to other causes and not as a direct consequence of hypophosphatemia, eg, hearing loss and craniosynostosis in XLH.

Direct Consequences of Chronic Hypophosphatemia

The clinical effects of chronic hypophosphatemia have predominantly been reported in FGF23-related disorders such as XLH and TIO.⁽³⁾ Evidence indicates that chronic hypophosphatemia impairs the development and quality of mineralized tissue, directly impacting the skeletal system, with association of skeletal muscle, dental, and hearing deficits. Moreover, childhood-onset chronic hypophosphatemia, if suboptimally managed or left untreated, is associated with long-term sequelae that extend into adulthood, including bony deformation, early onset hip and knee osteoarthritis, fractures/pseudofractures, and delayed fracture healing.^(8,26) However, it is important to consider that some deficits may be due to disease-specific effects not directly associated with hypophosphatemia.

Skeletal deficits

Rickets

In healthy children, phosphate-regulated apoptosis of hypertrophic chondrocytes at the growth plate is required for bone mineralization and lengthening.^(8,42,43) In chronic hypophosphatemia, this apoptosis is arrested, leading to deficient mineralization and accumulation of osteoid at the metaphysis, commonly described as rickets.^(42,43)

Because of the high phosphate requirements needed to maintain normal longitudinal growth velocity, growth impairment is often a presenting feature of some forms of genetic hypophosphatemia, such that despite normal measurements at birth, growth declines within the first few months of life.^(8,44,45)

Other related observations are deformities of the weight-bearing long bones of the lower limbs, including genu varum (outward bowing of the lower leg)/valgus (inward bowing) with associated gait abnormalities, reduced efficiency of walking, and fatigue.^(4,46,47) Lower extremity torsion and rotation may also be found in patients with XLH.^(47,48)

Osteomalacia

Osteomalacia is a condition of impaired mineralization due to insufficient phosphate, calcium, and vitamin D, leading to hypomineralized soft bones in both children and adults.⁽⁴³⁾ In infancy and childhood, the soft bones can bend when mechanical load is applied (eg, when a child starts to stand or toddle), resulting in lower limb deformities.^(9,43,49) Osteomalacia can arise due to chronic hypophosphatemia, where it is associated with impaired bone turnover, diffuse bone pain, and an increased risk of fractures and pseudofractures (Looser zones).^(4,50) Pseudofractures are observed radiologically as transverse zones of rarefaction⁽⁵¹⁾ and most often occur in the weight-bearing bones of the lower extremities, especially the shaft of the femur or tibia.⁽⁵²⁾ Chronic hypophosphatemia may also delay healing of pseudofractures and fractures.⁽⁵³⁾

Table 2. Causes of Diseases/Conditions Characterized by Hypophosphatemia

Human disease	Cause/mechanism of disease
FGF23-associated hypophosphatemic conditions/diseases (high plasma FGF23)	
Genetic (hereditary)	
X-linked hypophosphatemia	<i>PHEX</i> mutation
Autosomal dominant hypophosphatemic rickets	<i>FGF23</i> mutation
Autosomal recessive hypophosphatemic rickets 1/osteomalacia	<i>DMP1</i> mutation
Autosomal recessive hypophosphatemic rickets 2	<i>ENPP1</i> mutation
Raine syndrome-associated hypophosphatemic rickets	<i>FAM20C</i> mutation
Osteoglophonic dysplasia	<i>FGFR1</i> mutation
Genetic (mosaicism)	
Fibrous dysplasia/McCune-Albright syndrome	<i>GNAS1</i> gain of function
Epidermal nevus syndrome	<i>FGFR3</i> mutation
Sporadic/acquired	
Tumor-induced osteomalacia	<i>FGF23</i> -producing tumor
Drug-induced	
Chronic intravenous iron supplementation therapy-induced hypophosphatemia	Intravenous iron-induced increase in FGF23 levels (dependent on the type of intravenous iron; detailed mechanism not fully elucidated)
Non-FGF23-associated hypophosphatemic conditions/diseases (low-to-normal plasma FGF23)	
Genetic (hereditary)	
Hypophosphatemic rickets with hypercalciuria	<i>SLC34A3</i> (encoding the proximal tubule phosphate cotransporter NaPi-IIc) loss of function
Infantile idiopathic hypercalcemia	<i>SLC34A1</i> (encoding the proximal tubule phosphate cotransporter NaPi-IIa) mutation
Genetic Fanconi syndrome (including Wilson's disease, Lowe syndrome, Dent's disease)	
Inherited Vitamin D-dependent rickets	<i>CYP2R1</i> , <i>CYP27B1</i> , or <i>VDR</i> mutation
Sporadic/acquired	
Primary hyperparathyroidism	PTH effect on sodium-phosphate cotransporters
Secondary hyperparathyroidism due to nutritional, phosphate, calcium, and/or vitamin D deficiencies	Lack of adequate sun exposure, dietary insufficiency, or malabsorptive disorders
Intracellular phosphate shift	Insulin administration or refeeding after starvation, respiratory or metabolic alkalosis, drug-induced redistribution of phosphate, alcohol intake and withdrawal
Acquired Fanconi syndrome	Direct renal tubular damage by a drug or toxin, which results in a generalized proximal tubulopathy

FGF23 = fibroblast growth factor 23; PTH = parathyroid hormone.

Joint complications

Osteoarthritis is a degenerative disease of the synovial joints characterized by progressive deterioration and loss of articular cartilage with concomitant structural and functional changes in the entire joint and pain,⁽⁴⁹⁾ both impacting on mobility. These have been observed in adults with diseases characterized by chronic hypophosphatemia, eg, XLH, and may be caused by long-term abnormal mechanical loading of joints resulting from skeletal deformities that occurred during childhood.⁽⁵⁴⁻⁵⁶⁾ Work in animal models of XLH have linked osteoarthropathy with FGF23 signaling that was not mediated by hypophosphatemia, and investigation is ongoing.⁽⁵⁷⁾

Skeletal muscle system

Chronic hypophosphatemia manifests as weakness and fatigue in skeletal muscle, which may be partially explained by decreased ATP synthesis and consequent reduced oxidative phosphorylation due to low serum phosphate levels.^(58,59)

Muscle pain and stiffness is common in both children and adults with XLH.⁽⁴⁰⁾

It is unclear whether poor muscle quality and quantity observed in chronic renal phosphate wasting diseases are a direct result of hypophosphatemia or instead mediated by indirect disease effect (eg, decreased physical activity).⁽⁵⁾ A reduction in muscle volume is known to be related to decreased muscle strength,⁽⁵⁾ and deficits in muscle (jump) power and grip strength have been observed in adults with XLH (personnel communication G Orlando, S Clark, M Javaid). Furthermore, impaired mobility in these adults is strongly associated with deficits in aerobic fitness and muscle function.

Dental deficits

Insufficient mineralization of dental tissue is characteristic of chronic hypophosphatemia,⁽³⁹⁾ resulting in thin enamel and microscopic cracks, irregular surface structures,^(8,60) and spontaneous abscesses in XLH.⁽⁶¹⁾ The resultant deep fissures are a major predisposing factor for bacterial penetration and the occurrence of periapical abscesses despite the absence of caries.⁽⁶¹⁾

The molecular mechanisms responsible for the dental manifestations in XLH remain poorly understood.⁽⁸⁾ Further studies are warranted to determine whether phosphate insufficiency contributes to the impaired tooth mineralization in XLH and other hypophosphatemic disorders.

Potential hypophosphatemia-related sequelae

Hearing deficits have been observed in some genetic forms of hypophosphatemia,⁽⁸⁾ with audiologic impairment reported in patients with XLH.^(62,63) Hearing loss develops progressively, even before the structural degeneration, and is most common in adulthood.⁽³⁾ However, it is unclear whether hearing loss is the consequence of hypophosphatemia or other effects of *PHEX* (the gene mutated in XLH) in the inner ear, as hearing loss is not associated with other causes of hypophosphatemia.

Craniosynostosis, the premature fusion of cranial sutures, during the growth period causes head-shape deformity and may lead to increased intracranial pressure, ophthalmologic problems, and developmental delay.⁽⁶⁴⁾ In a study of children with XLH, 59% presented with craniosynostosis and 18% with Chiari I malformation (defined by a caudal descent of the cerebellar tonsils >5 mm through the foramen magnum).⁽⁶⁵⁾ It is unclear whether these manifestations are directly caused by hypophosphatemia.

Chronic hypophosphatemia may also be associated with abnormal calcification at the fibrocartilage of tendons and ligaments (enthesopathies), resulting in pain, stiffness, and limited joint mobility, which impact quality of life in adults with XLH.^(62,66) In some instances, calcification of the ligamentum flavum in the spinal canal can lead to spinal stenosis that requires urgent spinal decompression.⁽⁴⁾

Impact of Restoring Phosphate Homeostasis in Chronic Hypophosphatemia

Evidence suggests that restoring phosphate homeostasis improves or prevents progression of many of the clinical manifestations associated with chronic hypophosphatemia,^(8,13,50,52) as described in the previous sections.

Until recently, pharmacologic management of chronic hypophosphatemia was limited to supplementation with phosphate salts, together with active vitamin D analogs to avoid decreased serum calcium and elevated PTH. This treatment is beneficial in some forms of chronic hypophosphatemia, particularly in children with XLH, where its use improves growth, clinical and radiographic signs of rickets, leg deformities, bone pain, and dental health.^(8,13,52,67,68) However, important unmet needs remain with phosphate supplementation, including: (i) it does not restore phosphate homeostasis due to persistent renal losses; (ii) it is not always effective in ameliorating the effects of chronic hypophosphatemia;⁽⁶⁹⁾ and (iii) it is associated with risks of hypercalciuria, nephrocalcinosis, kidney failure, and secondary/tertiary hyperparathyroidism, as well as palatability issues and gastrointestinal symptoms.^(3,52,67,70) More recently, burosumab, an anti-FGF23 monoclonal antibody, has been approved as an alternative option in XLH.⁽³³⁾

Whether specific musculoskeletal deficits resulting from chronic hypophosphatemia are reversible depends on the age at which phosphate homeostasis is restored. Bone pain, proximal myopathy, or impaired mineralization may be reversible regardless of duration of hypophosphatemia. However, other

consequences (eg, limb deformity, short stature, hearing loss, dental abnormalities, and osteoarthritis) may be irreversible, or only partially correctable, when development is complete.

Expert Opinion: Practical Considerations for the Diagnosis and Management of Chronic Hypophosphatemia

A standardized definition for chronic hypophosphatemia

To help harmonize nomenclature, raise awareness, and guide clinical decision making for diseases characterized by chronic hypophosphatemia, it is important to establish a standard definition. Definitions of hypophosphatemia exist for children and adults,^(37,71,72) yet there is currently no universally accepted definition of chronic hypophosphatemia. This definition should consider age- and sex-specific normal phosphate reference ranges, as well as the duration of low phosphate levels.

While we acknowledge the difficulties in defining chronic hypophosphatemia, we propose the following definition may be used in children and adults:

“At least three consecutive, morning fasting serum phosphate readings below the lower limit of normal (LLN) for healthy age- and sex-matched reference ranges, taken at least 3 months apart (eg, 0, 3, and 6 months).”

However, we emphasize the importance of using clinical judgment when managing patients with hypophosphatemia. Further investigations and management should be considered without delay when there is suspicion of an underlying condition that may require earlier intervention, if severe hypophosphatemia is identified (eg, serum phosphate in adults <0.3 mmol/L),⁽⁷³⁾ if hypophosphatemia is associated with severe symptoms or in patients with a known genetic risk (eg, a mother with XLH) and causes of acute hypophosphatemia have been excluded. In children beyond perinatal age, the first measurement of low phosphate should prompt additional investigations. In such situations, serum phosphate measurement should be repeated as soon as possible, and treatment should be initiated promptly, without the need to formally define hypophosphatemia as a chronic condition. In all cases of chronic hypophosphatemia, it is crucial to determine the underlying cause because some disorders (eg, TIO) may require extensive diagnostic investigations and surgical treatment, whereas others may need lifelong therapy and follow-up (eg, XLH).

Renal phosphate wasting assessment

Assessment of renal phosphate wasting for diagnostic and treatment monitoring purposes can be measured by the fractional tubular reabsorption of phosphate (TRP) or the ratio of maximum tubular phosphate reabsorption to glomerular filtration rate (TmP/GFR).^(33,52,74) TmP/GFR is preferred as TRP depends on nutritional phosphate intake and if measured using 24-hour urine collection, it may overlook the circadian variability of serum phosphate concentrations, hence becoming unreliable. European clinical practice recommendations also outline TmP/GFR for XLH diagnosis and management.⁽³³⁾ When using TmP/GFR to evaluate renal phosphate wasting, reference ranges,^(18,33,75,76) online calculators,^(77,78) and normal reference ranges according to age and sex are available (Table 3).⁽⁷⁵⁾

However, challenges associated with TmP/GFR assessment include the lack of universally accepted guidelines regarding

Table 3. Normal Ranges for TmP/GFR (Adapted from Chong et al.⁷⁵⁾)

Age	Female mg/dL (mmol/L)	Male mg/dL (mmol/L)
Newborn	5.7–8.1 (1.27–2.59)	
1 month–2 years	3.6–5.4 (1.15–1.73)	
2–12 years	3.8–5.0 (1.22–1.60)	
12–16 years	3.4–4.6 (1.09–1.47)	
16–25 years	3.18–6.41 (1.01–2.05)	3.33–5.90 (1.07–1.89)
25–45 years	2.97–4.45 (0.95–1.42)	3.09–4.18 (0.99–1.34)
45–65 years	2.72–4.39 (0.87–1.40)	2.78–4.18 (0.89–1.34)
65–75 years	2.47–4.18 (0.79–1.34)	2.47–4.18 (0.79–1.34)

fasting requirements and timing of urine and blood sampling, as well as reference values obtained before the isotope-dilution mass spectrometry (IDMS) international standardization of creatinine assays. We recommend the simultaneous collection of fasting second morning urine void and blood for TmP/GFR determination. Timing of urine and blood sampling should stay the same for individual patients to optimize validity of longitudinal determinations. For example, adults should fast for at least 12 hours from oral phosphate supplementation and 48 hours from active vitamin D, where feasible; fasting serum and urine samples can then be taken 2 hours after the first morning urine void. Alternatively, a 24-hour urine collection sample can be used.

Monitoring and assessment of response to treatment

Parameters and clinical features commonly used in assessing adequacy of response to phosphate management strategies are shown in Table 4.

Serum phosphate monitoring

There is a lack of standardization of phosphate monitoring across the clinical literature.⁽³⁵⁾ We highlight the need to consider age- and sex-specific reference values when monitoring serum phosphate response to treatment, including consideration of menopause⁽¹⁸⁾ and puberty influencing target serum levels. Impact of circadian rhythm variation should be minimized by measuring morning fasting serum phosphate,^(28,79) and blood samples should be drawn with care, to avoid hemolysis, which could mask hypophosphatemia.⁽⁷⁶⁾ The phosphate-monitoring schedule should be based on the causative disease and individual patient needs.

Additional considerations

The appropriateness of a target in terms of serum phosphate levels should be questioned or clarified. In our experience, treatment with oral phosphate supplementation and active vitamin D analogs should not aim to normalize serum phosphate levels in patients with XLH. Although hypophosphatemia frequently persists (with serum phosphate below or toward the lower normal ranges for age and sex), the treatment still provides clinical benefits, especially in children and when initiated early.^(8,33,50,80)

Table 4. Assessment of Adequacy of Response to Management Strategies for Chronic Hypophosphatemia

Clinical features	
Pediatric patients	Adult patients
Musculoskeletal <ul style="list-style-type: none"> • Appropriate linear growth (height/stature) • Absence of long bone deformities • Absence of active rickets 	Musculoskeletal <ul style="list-style-type: none"> • Reduced muscle weakness • Absence of (pseudo) fractures at specific sites
Patient-reported <ul style="list-style-type: none"> • Absence of pain • Optimized quality of life (eg, regular participation in daily activities and schooling) 	Patient-reported <ul style="list-style-type: none"> • Absence of pain • Improved quality of life (eg, regular participation in daily activities and work life) • Improved physical mobility • Reduced fatigue
Assessment parameters <ul style="list-style-type: none"> • Long bone deformity • Absence of active rickets (RSS, radiographic) • ALP (versus age- and sex-specific reference values) • Normalized serum phosphate (versus age- and sex-specific reference values)^a • Serum/blood/plasma calcium • Serum/blood/plasma calcitriol • Absence of iatrogenic outcomes (nephrolithiasis, nephrocalcinosis, hyperparathyroidism, hypercalciuria)^b • 50% increase in TmP/GFR (only applicable with burosumab treatment) 	<ul style="list-style-type: none"> • Absence of (pseudo) fractures at specific sites • (Pseudo)fracture healing (radiographic) • b-ALP (versus age- and sex-specific reference values)

ALP = alkaline phosphatase; b-ALP = bone-specific alkaline phosphatase; TmP/GFR = maximum tubular phosphate reabsorption to glomerular filtration rate.

^aNot applicable to XLH patients receiving oral phosphate supplementation and active vitamin D analogs (only applicable if receiving burosumab therapy).

^bUrinary calcium/creatinine ratio, 24-hour calcium measurement preferred, otherwise on spot urine test.

However, oral phosphate dosing should always be monitored and adjusted as necessary to avoid treatment-related complications (eg, hyperparathyroidism or hypercalciuria).

In contrast, when using burosumab, dosing is adjusted to normalize serum phosphate levels. Although some patients with XLH treated with burosumab may not achieve a consistent serum phosphate level above the age-adjusted lower limit of normal (LLN), clinical improvements are still observed.⁽⁸¹⁾ In general, we consider the following to be useful indications of a good response to burosumab therapy in patients with XLH, as has been shown in clinical trials when analyzed at the midpoint between doses:^(50,82) a 50% increase from baseline in serum phosphate concentration (even if LLN is not achieved); a 50% decline from baseline in fractional excretion of phosphate; and/or a 50% increase in TmP/GFR. Assessment of total alkaline phosphatase (ALP) in children, or bone-specific ALP in adults, can also be used to monitor response.^(50,82)

Several endocrine factors, especially PTH, 1,25(OH)₂D, and kidney function, influence serum phosphate homeostasis, and these should be monitored in parallel with serum and urinary phosphate concentrations.

Summary

Given the physiologic importance of phosphate for optimal health, phosphate homeostasis control is necessary throughout life.^(3,8,9) Chronic hypophosphatemic diseases are rare, often underrecognized, and may be suboptimally managed.⁽³⁾ Moreover, serum phosphate is not always routinely measured in primary care practice and may be misinterpreted if not compared against age- and sex-specific normal phosphate reference ranges. These diseases have a multisystem impact that impair quality of life.^(8,39,40,62) In some genetic forms of these diseases, inadequate management during childhood or adolescence leads to further complications in adulthood.

Given the considerable clinical impact of chronic hypophosphatemic diseases, we emphasize the need to identify these as early as possible. A universally well-accepted definition of chronic hypophosphatemia will help raise awareness of these diseases, aid in the identification and management of affected individuals, and facilitate further clinical studies. We propose a definition for chronic hypophosphatemia in this article, although we note that further investigations should be performed in patients without delay if necessary. Finally, we provide our recommendations for assessing renal phosphate wasting and highlight the urgency to restore phosphate homeostasis with the aim to improve patient outcomes.

Disclosures

This article was based on a series of meetings organized and sponsored by Kyowa Kirin International. Medical writing support was provided by ApotheCom and funded by Kyowa Kirin International. FA consults for and has received lecture fees from KKI. JB consults for Kyowa Kirin International, Amgen, and Bayer and has received lecture fees and grants from Kyowa Kirin International. MLB was previously employed at the University of Florence, Italy, in the last 2 years. She has consulted for Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, and UCB and has received honoraria, grants, or speaker fees from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, Abiogen, Alexion, Echolight, Eli Lilly, SPA, Theramex, and UCB. PF consults for Kyowa Kirin/Ultragenyx and has received lecture fees and a research grant from Ultragenyx. MKJ consults for UCB, Amgen, and Kyowa Kirin Hakin and previously consulted for Consilient Healthcare. He has received lecture fees from all four of these companies and received an Amgen industry grant. OM consults for Kyowa Kirin and BridgeBio. She previously consulted for Alexion, Sandoz, and Ultragenyx and received lecture fees from Kyowa Kirin. AR consults for Kyowa Kirin and has received lecture fees from Kyowa Kirin and Ipsen Pharma. He has also received support for attending meetings from Ferring and Merck. MR consults for and has received lecture fees from Viphor, Amgen, and Kyowa Kirin. He has received grant support from Amgen. HS has served as an advisory board member for Shire/Takeda, UCB, and Kyowa Kirin, and is currently one for Takeda, Kyowa Kirin. She has received speaker's fees from Shire/Takeda, UCB, Alexion, Kyowa Kirin, Merck/Serono, Biomarin, and Amgen, and has grant support from Takeda. She is spokesperson for the German network of rare bone diseases, member of the ECTS Action group of Rare Bone Diseases, member of the ESE Education committee and representative in the PARAT programme of ESE, and treasurer of the German Society of Osteology. MV consults for Astra Zeneca, Vifor Pharma, Otsuka, and Kyowa Kirin. He

previously consulted for Medice and Amgen, and has received lecture fees and grant support from Amgen, Vifor, and Fresenius Medical Care. He has participated on a Data Safety Monitoring Board or Advisory Board in the OASIS and DIPAK trials. He is on the KDIGO committee on CKD-MBD and the chair of the ERA-EDTA working group on CKD-MBD. CW consults for Kyowa Kirin, Ardelyx, and Medice, and previously consulted for Chugai. He has received lecture fees in the last 2 years from Kyowa Kirin, Medice, Advicenne, and Salmon Pharma and grant support from Chugai.

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Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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