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Review

Etiology of hypophosphatemia in adults

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ABSTRACT

Long-term hypophosphatemia, defined by serum phosphorus (P) levels <2.5 mg/dl, impairs the development and quality of mineralized tissue of the skeletal, dental, and auditory systems. P homeostasis depends mainly on intestinal absorption and renal excretion. Hypophosphatemia may be due to the redistribution of P to the intracellular space, increased renal losses, or decreased intestinal absorption. Hypophosphatemia can be categorized as acute or chronic, depending on the time course. Most cases, either acute or chronic, are due to acquired causes. However, some chronic cases may have a genetic origin. Accurate and early diagnosis, followed by adequate treatment, is essential to limit its negative effects on the body.

Etiología de la hipofosfatemia en el adulto

Palabras clave:
Fosfato
Hipofosfatemia aguda
Hipofosfatemia crónica
Vitamina D
Hipofosfatemia genética

RESUMEN

La hipofosfatemia, definida por cifras de fósforo (P) sérico <2,5 mg/dl, a largo plazo perjudica el desarrollo y la calidad del tejido mineralizado del sistema esquelético, dental y auditivo. Su homeostasis depende principalmente de la absorción intestinal y de la excreción renal. La hipofosfatemia puede deberse a algunos de estos mecanismos: redistribución del P al espacio intracelular, aumento de las pérdidas renales o disminución de la absorción intestinal. Según el curso temporal, las hipofosfatemias se pueden clasificar en agudas o crónicas, con diferentes manifestaciones clínicas y mecanismos etiopatogénicos. Las agudas suelen ser de causa adquirida; las crónicas, en su mayoría, también, aunque pueden ser de origen genético. El diagnóstico preciso y precoz, seguido de un tratamiento optimizado, resulta fundamental para limitar sus efectos negativos sobre el organismo.

Introduction

Phosphorus (P) is a chemical element that forms tetrahedral phosphate complexes (HPO_4^{2}).[1] Phosphate is the most abundant anion in the human body, accounting for 1% of total body weight. Up to 85% is found in bones and teeth in the form of calcium hydroxyapatite and 14% in cells, forming part of ATP, phospholipid membranes and nucleic acids. Only 1% of total body P is found in the extracellular fluid. Up to one third of extracellular P is found in inorganic form (Pi), in free form as hydrogen phosphate (HPO_4^{2-}) or dihydrogen phosphate (H_2PO_4-) or bound to proteins forming complexes with other cations.

Serum phosphate concentration varies with age. Concentrations are highest in the neonatal period (5.8–7.4 mg/dl) and decrease progressively until adolescence, when values fall to adult levels (2.5–4.5 mg/dl), with no differences with respect to sex.[2,3]

P homeostasis is determined by the balance between intestinal absorption and renal reabsorption. P absorption takes place mainly in the jejunum, by a paracellular mechanism (in situations of normal or high phosphate intake) or by a transcellular mechanism, thanks to the presence in the luminal membrane of enterocytes

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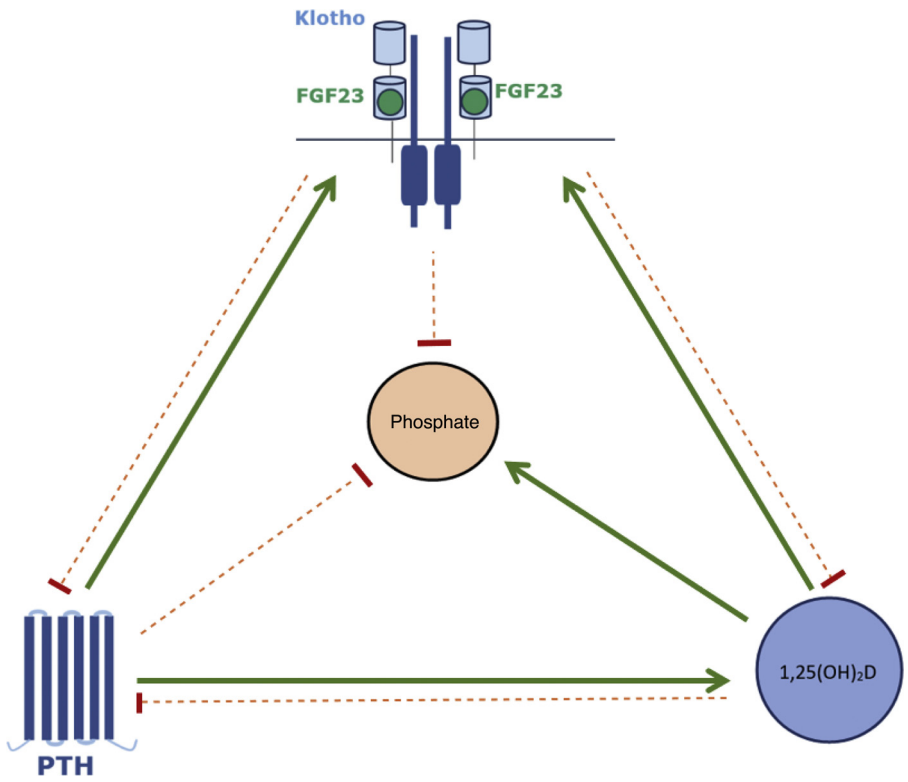

Figure 1. Regulatory mechanisms of P homeostasis. $1,25(OH)_2D$ tends to increase phosphataemia, PTH and FGF23 to decrease it. It seems that the effect of PTH is immediate, whereas that of FGF23 requires more time. In addition, serum phosphate can regulate the production of PTH, $1,25(OH)_2D$ and FGF23.[9] Green arrows represent increased serum level, red dashed lines represent decreased serum level.
FGF23: fibroblast growth factor 23; PTH: parathyroid hormone; 1,25(OH)2D: 1,25-dihydroxyvitamin D.

of a sodium/P type IIb cotransporter (NPT2b) encoded by the SCLC34A2 gene and type III cotransporters (Pit1 and Pit2) encoded by the SLC20A1 and SLC20A2 genes.[4,5] P excretion occurs essentially via the renal route. However, 80% of filtered P is reabsorbed in the proximal tubule, thanks to two sodium-phosphate-dependent cotransporters, NPT2a and NPT2c, encoded by the SLC34A1 and SLC34A3 genes, respectively.

Several systemic factors regulate P homeostasis, such as parathyroid hormone (PTH), calcitriol ($1,25(OH)_2D$) and phosphatonins, mainly fibroblast growth factor (FGF23), which tends to reduce P concentration. The role of other phosphatonins (such as FGF7, sFRP-4 and MEPE) in P homeostasis appears to be much less relevant. The interactions between FGF23, calcitriol and PTH are complex. FGF23 is a phosphaturic hormone, secreted under physiological conditions mainly by osteocytes, but sometimes also by osteoblasts, and regulates phosphate and vitamin D metabolism by binding to the Klotho-fibroblast growth factor receptor (FGFR) complex.[6] FGF23 suppresses calcitriol production through inhibition of renal 1α-hydroxylase and also PTH secretion. On the other hand, calcitriol stimulates FGF23 secretion by osteocytes and suppresses PTH secretion. In addition, PTH stimulates calcitriol production through activation of 1α-hydroxylase, and it is not entirely clear whether it stimulates FGF23 production directly or, more likely, indirectly by increasing calcitriol production[7–9] (Fig. 1).

The prevalence of hypophosphatemia is highly variable depending on the population studied. It has been identified as 0.2%–2.2% in hospitalised patients but may be as high as 50% in intensive care unit (ICU) patients.[10,11]

The causes of hypophosphatemia can be attributed to three main pathophysiological mechanisms: redistribution of P into the intracellular space, increased renal losses of P and decreased intestinal absorption of P. Depending on the speed of onset, they can be classified as acute or chronic hypophosphatemia, with different aetiopathogenic mechanisms involved. Acute hypophosphatemia is usually of acquired origin. Most cases of chronic hypophosphatemia are also due to acquired or secondary causes, but can sometimes be of genetic origin, although the first manifestations appear in adults[12–14] (Table 1).

In terms of manifestations, long-term phosphate deficiency affects the development and quality of mineralised tissues of the skeletal, dental or auditory system, with bone deformities, early osteoarthritis of the hips and knees, osteomalacia, fractures/pseudofractures and delayed healing. Severe chronic hypophosphatemia (<1 mg/dl) may cause proximal myopathy, stiffness and haematological disorders (leukocyte dysfunction, platelet disorders and haemolysis). Severe neurological manifestations, including encephalopathy, seizures and even coma, as well as impaired myocardial contractility, ventricular arrhythmias and impaired diaphragmatic contractility may occur in acute-onset severe hypophosphatemia.

Acute hypophosphatemia

The most common aetiological mechanism of acute hypophosphatemia is redistribution of P to the intracellular space, particularly common in critically ill patients, with prevalence in ICUs reaching 30–50%[15] (Table 2). Acute hypophosphatemia may be due to multiple causes. These include alcoholic ketoacidosis, which causes a multifactorial decrease in P, including the correction of acidosis, together with compensatory respiratory alkalosis or renal and digestive losses. In addition, the insulin surge generated by concomitant administration of glucose-containing fluids may contribute to hypophosphatemia.[16] Another cause of acute P depletion is acute respiratory alkalosis. Increased intracellular pH, with diffusion of carbon dioxide across cell membranes, stimulates

Table 1
Diagnostic approach to the causes of hypophosphatemia, both acute and chronic, based on FGF23 levels and phosphaturia (assessed by urine P and tubular phosphate reabsorption rate [TRP]).

Acquired	FGF23 not increased	Alcohol Malnutrition, malabsorption Total parenteral nutrition, refeeding Acute respiratory alkalosis Nephropathies: dialysis, transplantation Drugs: antiretrovirals, antibiotics, proximally-acting diuretics, valproate, antacids Acquired Fanconi syndrome PTHrP-producing tumours Sepsis Severe burns Lymphoproliferative syndromes	
	Increased FGF23	Tumor-induced osteomalacia Drugs: iron carboxymaltose Post renal transplantation	
Genetic	FGF23 not increased	Increased phosphaturia[a]	Transporter abnormalities: NPT2a/2c Dent's disease Renal tubular Fanconi syndrome
		Phosphaturia not increased	Vitamin D-dependent rickets
	Increased FGF23	Increased phosphaturia[a]	X-linked hypophosphatemic rickets Hypophosphatemic rickets AD and AR Fibrous bone dysplasia

NPT2a/2c: sodium-phosphate dependent cotransporters type 2a and 2c.
[a] In the presence of hypophosphatemia, TRP should be >95% if renal function is preserved. With hypophosphatemia, ñormalTRP values (80–95 %) are actually ïnappropriately normaländ indicate renal phosphate loss.

Table 2
Prevalence in different series of patients with acute hypophosphatemia according to the population studied.[10]

Study population	Prevalence
Admitted for various reasons	2% (P < 2.0 mg/dl) 3% (P < 2.2 mg/dl) 0.2% (P < 1.0 mg/dl)
Patients with alcohol abuse	
Admitted for detoxification	3% (P < 2.5 mg/dl)
Alcoholics treated in the emergency department	30% (P < 2.5 mg/dl)
Polytrauma patients	75% (P < 2.5 mg/dl)
Chronic obstructive pulmonary disease	22% (P < 2.5 mg/dl)
Surgical patients in ICU	29% (P < 2.5 mg/dl)
ICU patients	34% (P < 2.0 mg/dl)
Infections	
Infection	65% (P < 2.5 mg/dl)
Sepsis	80% (P < 2.5 mg/dl)
Hepatic lobectomy	100% (P < 1.5 mg/dl)
Iron therapy with carboxymaltose	
Gynaecological pathology	30% (P < 2.0 mg/dl)
Gastrointestinal pathology	51% (P < 2.0 mg/dl)
Neurological pathology	56% (P < 2.0 mg/dl)
Cardiac surgery	34% (P < 1.5 mg/dl)
Stage 3-5 chronic kidney disease	3% (P < 2.5 mg/dl)
Continuous haemofiltration	30%(P < 2.5 mg/dl)
Diuretic treatment (furosemide) in patients with CHF (NYHA III-IV)	13%(P < 2.5 mg/dl)

CHF: congestive heart failure; ICU: intensive care unit; NYHA: *New York Heart Association* classification.

phosphofructokinase activity, which in turn promotes glycolysis, requiring phosphorylation of glucose and its derivatives. Thus, in situations of accelerated glycolysis, P enters the cells, especially those of the liver and muscle, with a consequent decrease in serum P levels. Correction of diabetic ketoacidosis also causes a decrease in P, as insulin administration stimulates glycolysis.[17] Total parenteral nutrition or refeeding after prolonged malnutrition, with an excess of carbohydrates and amino acids, leads to an anabolic state with P consumption.[18] Dialysis patients may also develop hypophosphatemia.[19] Other causes of low P include severe burns, lymphoproliferative syndromes, sepsis and mannitol administration.[9,20]

Chronic hypophosphatemia

Alterations in the mechanisms that regulate intestinal absorption or renal excretion of P lead to chronic hypophosphatemia.

Hypophosphatemia due to an increase in PTH

Hypersecretion of PTH, either primary or secondary (e.g., due to vitamin D deficiency), can lead to hypophosphatemia. Primary hyperparathyroidism is due to dysfunction of a single gland in up to 80% of cases.[21] 15–20% of cases of chronic hypophosphatemia in our setting are due to hyperparathyroidism.[22] Familial hypocalciuric hypercalcaemia and severe neonatal primary hyperparathyroidism, due to mutations in the calcium-sensing receptor (CaSR), are extremely rare genetic causes of hypercalcaemia which present with elevated PTH and secondary hypophosphataemia. Other genetically based causes of primary hyperparathyroidism include multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A) and hyperparathyroidism-jaw tumour syndrome.[11,23] Causes of secondary hyperparathyroidism include *vitamin D deficiency or resistance*, as decreased levels or activity of $1,25(OH)_2D$ leads to decreased intestinal absorption of phosphate and also calcium, causing secondary hypocalcaemia with increased PTH production.[10] Other causes of hypophosphatemia are the *intake of calcium salts* that are *phosphate chelators* (calcium acetate, carbonate or citrate) or the use of *antiresorptive drugs*, such as pamidronate or zoledronate, due to the increase in PTH levels following the decrease in serum calcium levels. Hypophosphataemia may be observed in 12–32% of patients treated with the antiresorptive drug denosumab (anti-RANKL).[24–26] *Idiopathic renal hypercalciuria* also presents with increased PTH due to a primary decrease in renal tubular calcium reabsorption.[11] *Hungry bone syndrome* can cause hypophosphatemia due to massive deposition of calcium and P in the bone matrix following parathyroidectomy in patients with pre-existing skeletal involvement.[21] Similar features may be seen in patients with extensive osteoblastic metastases, or in the early healing stages of rickets or osteomalacia.

On the other hand, *paraneoplastic hormone syndromes* with increased parathyroid hormone-related protein (PTHrP) also

Table 3
Main biochemical characteristics of the most common genetic disorders causing chronic hypophosphatemia, grouped by pathophysiological mechanism.[48]

Mechanisms/Disorders	Gene	Inheritance pattern	uP	uCA	1,25(OH) D_2	PTH	FGF23
Increase in FGF23							
X-linked hypophosphataemic rickets	PHEX	X-linked	↑	↓	N / ↓	N	↑ / N
Autosomal dominant hypophosphatemic rickets	FGF23	AR	↑	↓	N / ↓	N	↑ / N
Autosomal recessive hypophosphatemic rickets type I	DMP1	AR	↑	↓	N / ↓	N	↑ / N
Autosomal recessive hypophosphatemic rickets type II	ENPP1	AR	↑	↓	N / ↓	N	↑ / N
Impaired renal P transporters							
Hypophosphataemic rickets associated with hypercalciuria	SLC34A3	AR	↑	↑	↑	N / ↓	N
Hypophosphataemic rickets with nephrolithiasis and osteoporosis type I	SLC34A1	AR	↑	↑	↑	N / ↓	N
Hypophosphataemic rickets with nephrolithiasis and osteoporosis type II	SLC9A3R1	AR	↑	↑	↑	N	↑
Recessive hypophosphatemic rickets type I or Dent's disease	CLCN5	X-linked	↑	↑	↑	N / ↓	N
Primary renal-tubular Fanconi syndrome	SLC34A1, GATM, EHHHADH, HNF4, NDUFAF6	AD/AR	↑	↑	N / ↓	N / ↑	N
Decreased intestinal absorption							
Vitamin D-dependent rickets type IA	CYP27B1	AR	Varies	↓	↓	↑	N / ↓
Vitamin D-dependent rickets type IB	CYP2R1	AR	Varies	↓	Varies	↑	N
Vitamin D-dependent rickets type IIA	VDR	AR	Varies	↓	↑	↑	N / ↓

1,25$(OH)_2$D: 1,25-dihydroxyvitamin D; AD: autosomal dominant; AR: autosomal recessive; FGF23: fibroblast growth factor 23; N: normal; PTH: parathormone; uCA: urinary calcium; uP: urinary phosphorus.

present with hypophosphatemia. PTHrP is a protein structurally similar to PTH, but encoded by a different gene, which is ubiquitously expressed and acts as a paracrine and autocrine factor in a pathological manner in some patients with tumours, mainly squamous cell carcinomas (lung, oesophagus, skin, cervix), breast and renal carcinomas.[9,27,28] Like PTH, PTHrP has a phosphaturic effect, but unlike hyperparathyroidism, these conditions usually present with low calcitriol levels.

Hypophosphatemia due to an increase in FGF23

FGF23 increases phosphate excretion by reducing the expression of NPT2a and NPT2c cotransporters in the proximal tubule. In addition, it reduces intestinal P absorption by decreasing circulating levels of 1,25$(OH)_2$D, exerting an inhibitory effect on 1α -hydroxylase and increasing the expression of 24-hydroxylase.[29,30] FGF23-mediated disorders can be of acquired or genetic cause.

Acquired causes include tumour-induced osteomalacia, a very rare paraneoplastic syndrome caused by increased secretion of phosphatonins, mainly by a mesenchymal or bone tumour.[11,31] Cases associated with neurofibromatosis, B-cell non-Hodgkin's lymphoma, colorectal and prostate cancer have also been reported.[32] Administration of certain *drugs,* such as intravenous ferric carboxymaltose, causes an increase in circulating levels of intact FGF23, possibly by affecting the intracellular metabolism of this molecule.[33] Hypophosphatemia occurs in 40–90% of patients after kidney transplantation, and the causal mechanisms are incompletely understood, but are thought to include increased PTH secretion (secondary and tertiary hyperparathyroidism), persistence of inappropriately high levels of FGF23, and possibly tubular dysfunction mediated by other mechanisms.[34]

Increased FGF23 may be due to genetic disorders (Table 3). *X-linked hypophosphatemic rickets* (XLH) is the most common cause of inherited phosphate loss and the most prevalent form of genetic hypophosphatemic rickets related to FGF23, with an estimated prevalence in some regions of 1/25,000 live births.[35] However, in the study conducted by our group we found a considerably lower prevalence (approximately 1/200,000), similar to some other series.[36] The mode of inheritance is X-linked dominant and is caused by mutations in PHEX (gene located on Xp22.1), which encodes an endopeptidase mainly expressed in osteoblasts, osteocytes and teeth. Approximately 20–30 % of cases are due to sporadic or *de novo* mutations of the *PHEX* gene, in the absence of a family history. To date, 574 mutations have been described in HGMD®. The phenotypic spectrum is very broad.

The second most common genetic cause is *autosomal dominant hypophosphatemic rickets* (ADHR). It is caused by mutations in the FGF23 gene, located on chromosome 12p13. These mutations result in a gain of function in a proteolytic cleavage domain of FGF23. As a result of the amino acid sequence change, an FGF23 molecule is formed that is resistant to the degradative action of peptidase. FGF23 binds to the FGF receptor (FGFR), whose cofactor is the Klotho protein and inhibits the NPT2a and NPT2c cotransporters in the renal tubules. This in turn leads to decreased renal phosphate reabsorption and increased phosphaturia. As mentioned above, activation of this receptor also decreases renal production of 1,25(OH) D_2.[35,37] It is less common than X-linked rickets. Only 22 mutations have been described in HGMD®. Although the mode of inheritance is autosomal dominant, penetrance is incomplete, with variable expressivity. Unlike XLH patients, ADHR patients do not have enthesopathy and may have early or late onset, making differential diagnosis with FGF-23-dependent acquired hypophosphatemic rickets difficult.[38]

Other rare forms of rickets include *autosomal recessive hypophosphatemic rickets.* Autosomal recessive hypophosphatemic rickets type 1 is caused by a mutation of the dentin matrix protein 1 (DMP1) gene, located on chromosome 4q22.1, resulting in the loss of function of a protein that inhibits FGF23 secretion. DMP1 is expressed in osteoblasts/osteocytes in bone tissue and in odontocytes in teeth. Patients with this mutation manifest rickets and osteomalacia, with isolated renal phosphate wasting associated with elevated FGF23 concentrations and normocalciuria. Autosomal recessive hypophosphatemic rickets type 2 is caused by loss-of-function mutations in the ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) gene, located on chromosome 6q23. The ENPP1 protein is involved in the production of extracellular pyrophosphates that inhibit the deposition of hydroxyapatite crystals and therefore vascular calcifications are observed in affected patients. Autosomal recessive hypophosphatemic rickets type 3 (Raine's disease) is due to mutations in FAM20C or DMP4; it presents with dental abnormalities, intracranial calcifications, osteosclerosis and dysmorphic patterns.[39]

Bone fibrous dysplasia is another cause of increased FGF23. It is caused by postzygotic mutations in the GNAS gene that activate the alpha subunit of guanine stimulator protein (Gsα), with an inappropriate increase in cyclic adenosine monophosphate (cAMP), a molecule involved in the intracellular signalling of various hormones. Mutations in GNAS alter the differentiation of osteoblasts, adipocytes and haematopoietic cells. The variant affects the Arg201 position in 95% of cases and the Gln227 position in <5% of cases.[40] Fibrous dysplasia can occur in association with skin and endocrine disorders and is then called McCune-Albright syndrome. Mazabraud syndrome is characterised by fibrous dysplasia and myxomas; Jaffe-Lichtenstein syndrome presents with monostotic or polyostotic disease, with skin involvement, but no endocrine abnormalities. These patients may present with hypophosphatemia due to increased FGF23. Most patients with fibrous dysplasia will have urinary phosphate leakage, but only a minority develop severe hypophosphatemia. Increased FGF23 concentrations appear to be related to the degree of bone involvement. Patients with more extensive bone disease have very low phosphate levels on a chronic basis. These patients tend to have more bone deformities and pain than those who maintain phosphate levels in the normal range.

Another less common genetic disorder with high levels of FGF23 is *cutaneous-skeletal hypophosphatemia syndrome.* It is caused by the activation of somatic mutations in the RAS gene, which encodes proteins involved in several cellular signalling pathways. It presents with epidermal nevi and bone dysplasia. Elevated FGF23 levels are thought to be caused by bone rather than skin lesions, but this is not fully understood.[41]

Osteoglophonic dysplasia is a disorder caused by activating mutations in the FGFR1 gene, resulting in increased FGF23 receptor activity. Clinical features include short stature, brachydactyly, facial dimorphism, craniosynostosis and abnormal eruption of teeth. To date, very few cases have been described in the literature.[42]

Treatment of hypophosphatemia in FGF23-dependent disorders is generally based on the administration of phosphate and calcitriol.[43] Some new treatments have shown efficacy in X-linked hypophosphatemic rickets. This is the case of burosumab, a human monoclonal antibody targeting FGF23. Other treatments under study, such as infigratinib, are aimed at blocking FGFR (FGF23 receptor).[44] New therapies under study for the treatment of *cutaneous-skeletal hypophosphatemia syndrome* are MEK inhibitors, such as trametinib, which targets the RAS/MAPK pathway.[45]

Impaired renal P transporters

Altered phosphate transporters in the proximal tubule interfere with normal reabsorption, resulting in abnormal phosphaturia and hypophosphatemia. They may be acquired or primary (genetic).

Acquired causes of hypophosphatemia include drugs and toxins. *Drugs,* particularly proximally acting diuretics such as acetazolamide, are a common cause of abnormal phosphaturia through mechanisms related to carbonic anhydrase inhibition. Some loop of Henle diuretics, such as furosemide and thiazides, may also increase phosphaturia11. *Chronic alcohol consumption* leads to renal tubular dysfunction, reversible with 4 weeks of abstinence.[46] In fact, excessive alcohol consumption is a common cause of hypophosphatemia and accounts for about 15% of cases of acquired hypophosphatemia in our setting.[22] Another cause of hypophosphatemia is *Fanconi syndrome.* Acquired forms in adults are mainly due to drugs, multiple myeloma, heavy metal poisoning or Sjögren's syndrome. The most commonly associated drugs are anti-tumour agents (tyrosine kinase inhibitors such as imatinib mesylate, mTOR inhibitors -temsirolimus- or vascular endothelial growth factor inhibitors such as sorafenib), antiviral drugs (adenofovir, cidofovir and tenofovir), sodium valproate or antibiotics such as tetracyclines or aminoglycosides.[47]

As for genetic disorders related to changes in renal transporters (Table 3), *hypophosphataemic rickets associated with hypercalciuria* is the most common. It is caused by mutations in SLC34A3, which increase renal phosphate excretion secondary to reduced tubular reabsorption, either by directly preventing the transport activity of the protein, or by altering the trafficking of newly synthesised transporter proteins to the cell membrane. The disorder has a recessive inheritance pattern, although cases with a semi-dominant pattern have been described. These patients have a normal physiological response of FGF23 to hypophosphatemia. Consequently, decreased phosphataemia leads to a decrease in FGF23, which stimulates 1α-hydroxylase, and, on the other hand, suppresses PTH. Increased $1,25(OH)_2D$ leads to increased intestinal absorption and renal excretion of calcium. Half of the patients with this disease develop kidney stones and nephrocalcinosis. There is great clinical heterogeneity, as patients may develop bone disease, kidney disease, or both.

Other less common disorders of genetic origin affecting tubular transport include *hypophosphatemic rickets with nephrolithiasis and osteoporosis type I and hypophosphatemic rickets with nephrolithiasis and osteoporosis type II. Type I is* due to a mutation of the sodium/phosphate transporter gene (SLC34A1, located at 5q35) and is characterised by the coexistence of nephrolithiasis, osteoporosis and hypophosphatemic rickets. The abnormalities tend to improve in adulthood. Type II is due to a mutation in the SLC9A3R1 gene (located at 17q25.1), which encodes the cytoplasmic sodium/hydrogen exchange protein (NHEFR1). It presents with impaired renal phosphate reabsorption and hypophosphatemia.[37,48]

Recessive X-linked recessive hypophosphatemic rickets type I or Dent's disease is due to mutations in CLCN5 (Xp11.22), a chloride channel located in the proximal tubule and associated with renal phosphate wasting. Dent's disease is associated with hypercalciuric nephrolithiasis, low molecular weight proteinuria, haematuria and progressive deterioration of glomerular filtration rate.[49] *Recessive X-linked recessive hypophosphatemic rickets type II or Lowe syndrome* is due to mutations in the OCRL gene. It presents with ocular, neurological and renal manifestations.[50]

Primary Fanconi syndrome is another possible cause of hypophosphatemia. It is caused by mutations in different genes related to tubular phosphate transporters, such as SLC34A1, GATM, EHHHADH, HNF4 and NDUFAF6. Fanconi syndrome may also be part of the spectrum of manifestations of several genetic disorders, such as cystinosis, galactosemia, hereditary fructose intolerance, tyrosinemia, lysinuric protein intolerance, Wilson's disease, Lowe's syndrome, Dent's disease, glycogenosis, arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome and mitochondrial cytopathies.[51]

Cystinosis is an inherited lysosomal storage disease characterised by defective transport of cystine out of lysosomes. The causative gene, CTNS, encodes a seven-transmembrane domain lysosomal protein, cystinosin. The condition can be diagnosed from infancy to adulthood, with variable clinical manifestations. Classically, cystinosis presents with renal impairment secondary to Fanconi syndrome, but the adult patient manifests other extra-renal symptoms, such as eye damage, central nervous system damage, myopathy or endocrine disorders, such as hypothyroidism or diabetes.[49]

Treatment of hypophosphatemia caused by alteration of renal P transporters is aimed at eliminating the aetiological agent, correcting rickets if present, in addition to phosphate supplementation. In *hypophosphatemic rickets associated with hypercalciuria*, thiazides are used to decrease urinary calcium excretion, although the

efficacy in preventing or ameliorating kidney stones and nephrocalcinosis remains uncertain.[52,53] Some animal studies have suggested a beneficial effect of citrate-rich diets in Dent's disease.[54]

Decreased intestinal absorption

Decreased phosphate bioavailability due to decreased intestinal absorption is another mechanism that can lead to hypophosphatemia.

Possible causes include *poor intake*, which alone is rarely responsible for severe phosphate depletion. However, if poor intake is combined with chronic diarrhoea or vitamin D deficiency, it can cause severe chronic hypophosphatemia. Certain *drugs*, such as antacids with an aluminium and magnesium base and some calcium salts, bind dietary phosphate and form insoluble phosphate salts. Niacin and its derivatives may also promote faecal phosphate losses by reducing intestinal expression of the NPT2b cotransporter.[55] Antiepileptic drugs (phenobarbital, carbamazepine, phenytoin) or rifampicin, which are inducers of cytochrome CYP3A4 activity, may increase the hydroxylation of various vitamin D metabolites and lead to vitamin D deficiency resulting in hypophosphatemia and osteomalacia.[56] *Short bowel syndrome* due to bowel resection following bariatric surgery or other reasons, *celiac disease*, *inflammatory bowel disease* and, in general, malabsorption of any cause can lead to hypophosphatemia, which is aggravated by the association with secondary hyperparathyroidism if there is concomitant vitamin D deficiency.[57,58]

Genetic disorders affecting vitamin D metabolism or activity (Table 3) include vitamin D-dependent rickets type IA or vitamin D pseudodeficiency, due to mutations in the CYP27B1 gene (locus 12q14.1). These mutations decrease renal 1α-hydroxylase activity, with decreased hydroxylation of 25(OH)D to $1,25(OH)_2D$. They are associated with hyperphosphatemia (increased alkaline phosphatase), hypophosphatemia and hypocalcaemia, accompanied by secondary hyperparathyroidism. The serum level of $1,25(OH)_2D$ is usually undetectable and 25(OH)D levels are above normal or within reference values. The only effective treatment is the administration of $1,25(OH)_2D$ in individually adjusted doses.[37,48] Vitamin D-dependent rickets type IB is caused by mutations in the CYP2R1 gene (locus 11p15.2), which encodes the 25-hydroxylase responsible for hydroxylation of vitamin D to 25(OH) D in the liver. It has an autosomal recessive inheritance and very few cases have been described. The treatment consists of high doses of 25(OH)D.[59]

Vitamin D-dependent rickets type IIA is caused by a mutation of the gene encoding the vitamin D receptor (VDR). The VDR defect prevents $1,25(OH)_2D$ signalling and, as a result, calcium absorption in the intestine is impaired. VDR mutations in the DNA-binding domain result in total resistance to $1,25(OH)_2D$. However, partial resistance may occur when mutations affect the ligand binding domain. Response to treatment depends on the location of the mutation and the affinity of the receptor for $1,25(OH)D_2$.[37] *Vitamin D-dependent rickets type IIB* is a form of vitamin D-dependent rickets, but with a normal functioning vitamin D receptor. It is due to overexpression of a heterogeneous nuclear ribonucleoprotein that interferes with VDR and ligand binding. 25(OH)D is normal, while $1,25\ (OH)_2D$ is increased.[37]

Another very rare form is *vitamin D-dependent rickets type III* due to a gain-of-function mutation in CYP3A4, a gene encoding a P450 group oxidase. The enzyme degrades various metabolites of vitamin D. This mutation was identified by whole exome sequencing analysis in two unrelated patients with early onset rickets, reduced serum levels of vitamin D metabolites such as $25(OH)_2D$ and $1,25(OH)_2D$, and poor response to supplementation.[60]

Conclusions

Persistent hypophosphatemia can have many causes. The most common are secondary to drugs, excessive alcohol consumption, primary hyperparathyroidism or organ transplantation, among others. However, in cases of hypophosphatemia of unknown origin, once secondary causes have been ruled out, a possible genetic aetiology must be considered.

Although serum P is not usually included in routine analyses, it is important to analyse it in patients with risk factors for developing hypophosphatemia (e.g., excessive alcohol consumption, renal transplantation, malnutrition, etc.), as well as in those with skeletal changes suggesting a mineralisation defect, pseudofractures, early osteoarthritis, bone deformities or a history of renal lithiasis. If hypophosphatemia is confirmed, analysis of renal P excretion will help guide the diagnostic approach.

CRediT authorship contribution statement

All authors have approved the manuscript and agree to its publication. All authors confirm the authenticity of the work and the absence of previous publication, nor under current consideration for publication elsewhere.

Ethical considerations

The data collected in this study were used for research purposes only and were handled in accordance with established ethical standards.

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Declaration of competing interest

All authors declare that they have no conflict of interest for this publication.

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