Revista de Osteoporosis y Metabolismo Mineral

Special Article

Dialogues between basic and clinical researchers: hyperphosphatemia

Minerva Rodríguez García[1], Manuel Naves Díaz[2]

[1]Clinical Management Area of Nephrology. [2]Clinical Management Unit of Bone Metabolism. Hospital Universitario Central de Asturias. Universidad de Oviedo. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA). Oviedo, Spain

Abstract

Physiological regulation of mineral metabolism is determined by serum levels of phosphorus, FGF23, Klotho, PTH, calcidiol, and calcium. When renal function is normal, the kidney, bone, parathyroid tissue, and intestine collaborate effectively in maintaining this regulation, even in cases of phosphorus excess.

The issue arises when renal function is compromised, as the regulators of mineral metabolism become altered, including decreased soluble Klotho, increased PTH and FGF23, and subsequent reductions in calcidiol and calcium. These changes lead to vascular and bone abnormalities, with significant impacts on the morbidity and mortality of renal patients.

From a therapeutic standpoint, dietary phosphorus restriction is the initial approach for controlling hyperphosphatemia in patients with chronic kidney disease (CKD). When dietary measures are insufficient, phosphorus binders are used to limit intestinal absorption of this ion.

In summary, it is crucial to identify and treat hyperphosphatemia adequately to achieve comprehensive clinical improvements, including a significant reduction in mortality.

Keywords:
Phosphorus. Renal disease. Morbidity and mortality.

PATHOPHYSIOLOGICAL AND MOLECULAR SIGNIFICANCE OF HYPERPHOSPHATEMIA

The physiological regulation of mineral metabolism is governed by several factors contributing to its maintenance and regulation to varying degrees. For hyperphosphatemia, the critical determinant is serum phosphorus levels, though FGF23, Klotho, PTH, calcidiol, and calcium also play vital roles. Under normal renal function, the organism effectively manages mineral metabolism through the coordinated activity of the kidney, bone, parathyroid tissue, and intestine. However, compromised renal function impairs phosphorus excretion, leading to its accumulation. As kidney disease progresses, the levels of various mineral metabolism regulators become increasingly disturbed. While some controversies remain, it appears that the initial event is a decrease in soluble Klotho levels. Additionally, excess phosphorus leads to increased PTH and

Received: 16/09/2024 • Accepted: 26/09/2024

Acknowledgments: this study was funded by Instituto de Salud Carlos III (ISCIII)-Health Research Fund (PI16/00637, PI17/00715, PI19/00532, PI20/00753, and PI22/00195), the European Regional Development Fund (FEDER), the Science, Technology, and Innovation Plan 2013-2017 and 2018-2022 of the Principality of Asturias (IDI-2018-000152, IDI-2021-000080, IDE/2024/000706), the Íñigo Álvarez de Toledo Renal Foundation (FRIAT), the ISCIII REDinREN network (RD16/0009/0017 and RD16/0009/0018), and RICORS2040 (Kidney Disease; RD21/0005/0019).

Conflict of interest: the authors declare no conflict of interest.

Artificial Intelligence: the authors declare that they did not use artificial intelligence (AI) or any AI-based tools for the drafting of this article.

Rodríguez García M, Naves Díaz M. Dialogues between basic and clinical researchers: hyperphosphatemia. Rev Osteoporos Metab Miner 2024;16(4):149-153

DOI: 10.20960/RevOsteoporosMetabMiner.00062

Correspondence:
Manuel Naves Díaz. Clinical Management Area of Nephrology. Hospital Universitario Central de Asturias. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA). Avenida de Roma, s/n. 33011 Oviedo, Spain
e-mail: mnaves.huca@gmail.com

FGF23 levels, followed by reductions in calcidiol and calcium (1-3). These changes culminate in vascular and bone abnormalities with profound effects on the morbidity and mortality of renal patients.

Although clinical and experimental settings make it challenging to isolate the role of each factor due to tissue interconnections, animal models have clarified the contributions and specific impacts of these elements.

One of the main regulators of phosphorus is FGF23, primarily expressed in bone tissue and synthesized by osteocytes (4). Osteocytes detect excess phosphate and stimulate FGF23 synthesis and secretion via receptor FGFR1(5) and phosphate transporter Pit2 (6). FGF23 acts on renal tubules with Klotho to internalize and degrade the NaPi2a phosphorus transporter, decreasing reabsorption and enhancing excretion.

FGF23 also acts independently on the heart, promoting cardiac damage via FGFR4 through the calcineurin pathway (7,8), although it does not have similar deleterious vascular effects (9).

The deficiency or absence of Klotho in experimental models has demonstrated an increase in cardiac hypertrophy and fibrosis, both at the molecular and histological levels (10,11). Similarly, the absence of Klotho produces an accelerated aging phenotype at the vascular and bone levels (12). Klotho deficiency has also shown vascular and bone alterations (3,13). In contrast, the addition of soluble Klotho in experimental models is capable of preventing or reversing cardiac damage (10).

Experimental models of parathyroidectomy with hyperphosphatemia, maintaining PTH levels within normal ranges through exogenous administration, have demonstrated that phosphorus alone van cause vascular and bone damage. However, this effect is much more pronounced when PTH is very elevated (14), leading to bone deterioration at the trabecular bone level, but especially at the cortical bone level (15). Additionally, there is an increase in calcium content in the arteries with an exacerbated rise in the expression of osteogenic genes, such as Runx2 or osterix, along with sharp decreases in the expression of vascular phenotype genes, such as alpha-actin (15). Increases in PTH have also been associated with cardiac alterations, where an increase in hypertrophy and particularly in cardiac fibrosis has been observed at both the histological and molecular levels (elevations in the gene expression of collagen I, TGF beta, or fibronectin) (16).

Experimental and clinical studies have shown that vitamin D or calcidiol deficiency is associated with an increased risk of cardiovascular disorders (17,18). However, to date, the bone is the only organ where vitamin D has demonstrated causality, proving to be an effective treatment for reducing the risk of hip fractures and non-vertebral fractures (19).

The role of calcium is less clear. Probably, the more refined management of the organism to maintain calcium homeostasis makes the effects at the systemic level much more subtle. In the presence of chronic kidney disease (CKD) and hyperphosphatemia, decreases in calcium could have a more potent effect than increases, mainly at the cardiovascular level (20), probably partly due to the direct effect that hypocalcemia exerts on the parathyroid gland, stimulating the synthesis and secretion of PTH (21).

In vitro studies have shed more light on the systemic effects of hyperphosphatemia and the pathophysiological mechanisms involved. At vascular level, experimental studies are confirmed: the additive effect of phosphorus increases, sufficient available calcium, but especially PTH, on vascular damage, as they promote vascular calcification through the increase in the expression of typically osteogenic genes (Runx2, osterix, alkaline phosphatase) and the drastic decrease in genes related to the vascular and contractile phenotype, such as alpha-actin (15). At this level, the role of soluble Klotho is fundamental for maintaining vascular health, as its addition to in vitro models in vascular smooth muscle cells exposed to calcifying stimuli prevents the increase in the expression of typically osteogenic genes, reduces extracellular calcium deposition, and prevents the loss of alpha-actin, the main protein for maintaining the vascular phenotype (3). There are still doubts about the mechanism through which this protective effect could be exerted, but there is some data suggesting that one of these mechanisms might be the increase in autophagic flow, which would prevent the vascular calcification process (3), although more studies are needed to demonstrate this causality.

Recently, our group has shown that this loss of vascular phenotype with a predisposition to vascular calcification is mainly due to the loss of microRNA 145, the predominant microRNA in the vascular wall responsible for maintaining its contractile phenotype (22). These results, initially revealed in nephrectomized animals with hyperphosphatemia, but also in animals with normal renal function and hyperphosphatemia, have been confirmed in vitro in vascular smooth muscle cells subjected to calcifying stimuli from excess phosphorus, calcium, and/or PTH (23). These results could have important clinical implications, as in the general population, the expression of this microRNA shows a ROC curve with an area under the curve of 0.83 (22), showing that microRNA 145 has a high predictive power for vascular calcification. These novel findings suggest that the combination of non-invasive, low-cost, and simple biomarkers would constitute an important predictor of vascular damage in not only the renal population but also the general population.

The regulation of microRNA 145 levels by vitamin D is another revealing aspect, as vitamin D increases the expression of microRNA 145 (24). Therefore, maintaining calcidiol levels could positively impact vascular health through the maintenance of microRNA 145 levels (25), as confirmed by other clinical studies in both renal and general populations.

DETECTION, SIGNIFICANCE, AND THERAPEUTIC MANAGEMENT

Hyperphosphatemia originates when the phosphorus entering the extracellular fluid exceeds the amount that can be excreted. One of the most common causes of reduced phosphorus excretion is acute and chronic kidney disease. Other causes include the mobilization of intracellular phosphorus to the extracellular fluid (lactic acidosis, diabetic ketoacidosis, or severe hyperglycemia), acute phosphorus overload (endogenous or exogenous, such as tumor lysis syndrome, muscle necrosis, or excessive laxative intake), or increased tubular phosphate reabsorption (hypoparathyroidism, acromegaly, fibroblast growth factor receptor inhibitors, vitamin D, or tumoral calcinosis).

Hyperphosphatemia has been linked to endothelial dysfunction, arteriosclerosis, and calcification of the arterial media, both generalized and coronary, as well as cardiac valve calcification, myocardial fibrosis leading to ventricular wall stiffness, diastolic dysfunction, heart failure, and arrhythmias (26).

There is extensive scientific evidence linking elevated serum phosphorus with increased cardiovascular events and mortality, both in the general population (27) and in those with chronic kidney disease (20,28), and especially among dialysis patients (a population at maximum risk for developing hyperphosphatemia) (29,30). Hyperphosphatemia is currently considered a non-traditional cardiovascular risk factor.

In hemodialysis patients, a U-shaped relationship has been described between serum phosphorus levels and mortality, where both below and above the recommended range are associated with increased mortality risk. Moreover, improved control of serum phosphorus in patients with elevated baseline levels is significantly associated with better survival during a 3-year follow-up period (30).

It should be considered that serum phosphorus levels can fluctuate throughout the day, with postprandial increases. For this reason, fasting serum phosphorus has been most closely associated with higher cardiovascular mortality risk, both in the general population and in patients with chronic kidney disease (31).

On the other hand, high-phosphorus diets have been linked to increased blood pressure, both through previously mentioned mechanisms (arteriosclerosis, arterial wall stiffness), and due to their effect on increased sodium reabsorption at the renal tubular level and activation of the sympathetic nervous system (26).

Hyperphosphatemia has also been associated with the development of CKD in healthy individuals, as well as with disease progression in patients who already have it (32).

Additionally, a recent study has linked serum phosphorus values in hemodialysis patients with an increased risk of fragility fractures, suggesting that serum phosphorus could be a new risk marker for bone fractures (33).

Therapeutic approach varies depending on whether the hyperphosphatemia is acute or chronic. In cases of acute hyperphosphatemia, resolution can occur within 6 to 12 hours if renal function remains intact. Phosphorus excretion can be increased with saline infusion, although this could lower serum calcium concentration due to dilution, requiring caution, especially in the presence of severe hypocalcemia, due to the associated life-threatening risk. In cases of severe symptomatic hypocalcemia and renal function deterioration, hemodialysis may be necessary for effective management.

For patients with CKD, the initial measure for controlling hyperphosphatemia is to restrict dietary phosphorus intake (34), which is classified into two types: organic, found mainly in protein-rich foods, and inorganic, present in additives, carbonated beverages, and processed foods. Inorganic phosphorus is less biologically relevant but has a considerably higher absorption rate.

It is very important to control both phosphorus levels and secondary hyperparathyroidism in these patients, due to all the previously mentioned implications.

Phosphate binders work by limiting intestinal absorption of this ion (34). They are classified based on their calcium content, into calcium-containing binders such as calcium carbonate or calcium acetate, and calcium-free binders like sevelamer carbonate, lanthanum carbonate, and sucroferric oxyhydroxide, which must be taken with meals to be effective.

Therefore, it is crucial to emphasize the importance of identifying and appropriately treating hyperphosphatemia to achieve an overall improvement in clinical outcomes, including a significant reduction in mortality.

REFERENCES

1. Sakan H, Nakatani K, Asai O, Imura A, Tanaka T, Yoshimoto S, et al. Reduced renal α-Klotho expression in CKD patients and its effect on renal phosphate handling and vitamin D metabolism. Plos One 2014;9(1):e86301. DOI: 10.1371/journal.pone.0086301

2. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Review Annu Rev Physiol 2013;75:503-33. DOI: 10.1146/annurev-physiol-030212-183727
3. Martín Vírgala J, Fernández-Villabrille S, Martín-Carro B, Tamargo-Gómez I, Navarro-González JF, Mora-Fernández C, et al. Serum and Urinary Soluble α-Klotho as Markers of Kidney and Vascular Impairment. Nutrients 2023;15(6):1470. DOI: 10.3390/nu15061470
4. Liu S, Quarles LD. How fibroblast growth factor 23 works. J Am Soc Nephrol 2007;18:1637-47. DOI: 10.1681/ASN.2007010068
5. Takashi Y, Kosako H, Sawatsubashi S, Kinoshita Y, Ito N, Tsoumpra MK, et al. Activation of unliganded FGF receptor by extracellular phosphate potentiates proteolytic protection of FGF23 by its O-glycosylation. Proc Natl Acad Sci U S A 2019;116(23):11418-27. DOI: 10.1073/pnas.1815166116
6. Bon N, Frangi G, Sourice S, Guicheux J, Beck-Cormier S, Beck L. Phosphate-dependent FGF23 secretion is modulated by PiT2/Slc20a2. Mol Metab 2018;11:197-204. DOI: 10.1016/j.molmet.2018.02.007
7. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy J Clin Invest 2011;121:4393-408. DOI: 10.1172/JCI46122
8. Grabner A, Amaral AP, Schramm K, Singh S, Sloan A, Yanucil C, et al. Activation of cardiac fibroblast growth factor Receptor 4 causes left ventricular hypertrophy. Cell Metabolism 2015;22:1020-32. DOI: 10.1016/j.cmet.2015.09.002
9. Lindberg K, Olauson H, Amin R, Ponnusamy A, Goetz R, Taylor RF, et al. Arterial klotho expression and FGF23 effects on vascular calcification and function. Plos One 2013;8:e60658. DOI: 10.1371/journal.pone.0060658
10. Chen K, Wang S, Sun QW, Zhang B, Ullah M, Sun Z. Klotho deficiency causes heart aging via impairing the Nrf2-GR pathway. Circ Res 2021;128(4):492-507. DOI: 10.1161/CIRCRESAHA.120.317348
11. Xie J, Yoon J, An SW, Kuro-o M, Huang CL. Soluble Klotho protects against uremic cardiomyopathy independently of fibroblast growth factor 23 and phosphate. J Am Soc Nephrol 2015;26(5):1150-60. DOI: 10.1681/ASN.2014040325
12. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature 1997;390:45-51. DOI: 10.1038/36285
13. Hu MC, Shi M, Zhang J, Quiñones H, Griffith C, Kuro-o M, et al. Klotho deficiency causes vascular calcification in chronic kidney disease. J Am Soc Nephrol 2011;22(1):124-36. DOI: 10.1681/ASN.2009121311
14. Neves KR, Graciolli FG, dos Reis LM, Graciolli RG, Neves CL, Magalhães AO, et al. Vascular calcification: contribution of parathyroid hormone in renal failure. Kidney Int 2007;71(12):1262-70. DOI: 10.1038/sj.ki.5002241
15. Carrillo-López N, Panizo S, Alonso-Montes C, Martínez-Arias L, Avello N, Sosa P, Dusso AS, et al. High-serum phosphate and parathyroid hormone distinctly regulate bone loss and vascular calcification in experimental chronic kidney disease. Nephrol Dial Transplant 2019;34(6):934-41. DOI: 10.1093/ndt/gfy287
16. Martínez-Arias L, Panizo-García S, Martín-Vírgala J, Martín-Carro B, Fernández-Villabrille S, Avello-Llano N, et al. Contribución de fósforo y PTH al desarrollo de hipertrofia y fibrosis cardiaca en un modelo experimental de insuficiencia renal crónica. Nefrología 2021;1(6):640-51. DOI: 10.1016/j.nefro.2021.02.001
17. Naves-Díaz M, Cabezas-Rodríguez I, Barrio-Vázquez S, Fernández E, Díaz-López JB, Cannata-Andía JB. Low calcidiol levels and risk of progression of aortic calcification. Osteoporos Int 2012;23(3):1177-82. DOI: 10.1007/s00198-011-1550-0
18. Schmidt N, Brandsch C, Kühne H, Thiele A, Hirche F, Stangl GI. Vitamin D receptor deficiency and low vitamin D diet stimulate aortic calcification and osteogenic key factor expression in mice. PLoS One 2012;7(4):e35316. DOI: 10.1371/journal.pone.0035316
19. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293(18):2257-64. DOI: 10.1001/jama.293.18.2257
20. Naves-Díaz M, Passlick-Deetjen J, Guinsburg A, Marelli C, Fernández-Martín JL, Rodríguez-Puyol D, et al. Calcium, phosphorus, PTH and death rates in a large sample of dialysis patients from Latin America. The CORES Study. Nephrol Dial Transplant 2011;26:1938-47.
21. Berdud I, Martin-Malo A, Almaden Y, Aljama P, Rodriguez M, Felsenfeld AJ. The PTH-calcium relationnship during a range of infused PTH doses in the parathyroidectomized rat. Calcif Tissue Int 1998;62(5):457-61. DOI: 10.1007/s002239900460
22. Fernández Villabrille S, Martín Carro B, Martín Vírgala J, Alonso Montes C, Palomo Antequera C, García Castro R, et al. MicroRNA-145 and microRNA-486 are potential serum biomarkers for vascular smooth muscle cells osteogenic differentiation. Nephrol Dial Transplant 2023;38(7):1729-40. DOI: 10.1093/ndt/gfad027
23. Fernández-Villabrille S, Martín-Carro B, Martín-Vírgala J, Alonso-Montes C, Fernández-Fernández A, Martínez-Salgado C, et al. Phosphorus May Induce Phenotypic Transdifferentiation of Vascular Smooth Muscle Cells through the Reduction of microRNA-145. Nutrients 2023;15(13):2918. DOI: 10.3390/nu15132918
24. Carrillo-López N, Panizo S, Arcidiacono MV, de la Fuente S, Martínez-Arias L, Ottaviano E, et al. Vitamin D treatment prevents uremia-induced reductions in aortic microRNA-145 attenuating osteogenic differentiation despite hyperphosphatemia. Nutrients 2022;14(13):2589. DOI: 10.3390/nu14132589
25. Caus M, Alonso-Montes C, Fernandez-Martin JL, Marti-Antonio M, Bozic M, Valdivielso JM. Vitamin D receptor from VSMCs regulates vascular calcification during CKD: A potential role for miR-145a. Arterioscler Thromb Vasc Biol 2023;43(8):1533-48. DOI: 10.1161/ATVBAHA.122.318834
26. Rroji M, Figurek A, Spasovski G. Should we consider the cardiovascular system while evaluating CKD-MBD? Toxins 2020;12:36. DOI: 10.3390/toxins12030140
27. Torrijo Belanche C, Moreno Franco B, Muñoz Cabrejas A, Calvo Galiano N, Casasnovas JA, Sayón-Orea C, et al. High serum phosphate is associated with cardiovascular mortality and subclinical coronary atherosclerosis: systematic review and meta-Analysis. Nutrients 2024;16(11):1599. DOI: 10.3390/nu16111599
28. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease a systematic review and meta-analysis. Vol. 305. JAMA 2011;305(11):1119-27. DOI: 10.1001/jama.2011.308
29. Fernández-Martín JL, Dusso A, Martínez Camblor P, Dionisi MP, Floege J, Ketteler M, et al. Serum phosphate, optimal timing, and range associated with patient survival in haemodialysis:

the COSMOS study. Nephrol Dial Transplant 2019;34:673-81. DOI: 10.1093/ndt/gfy093
30. Fernandez-Martin JL, Martinez-Camblor P, Dionisi MP, Floege J, Ketteler M, London G, et al. Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: The COSMOS study. Nephrol Dial Transplant 2015;30(9):1542–51. DOI: 10.1093/ndt/gfv099
31. Vervloet MG, Sezer S, Massy ZA, Johansson L, Cozzolino M, Fouque D. The role of phosphate in kidney disease. Nat Rev Nephrol 2017;13(1):27-38. DOI: 10.1038/nrneph.2016.164
32. Chang WX, Xu N, Kumagai T, Shiraishi T, Kikuyama T, Omizo H, et al. The impact of normal range of serum phosphorus on the incidence of end-stage renal disease by a propensity score analysis. PLoS One 2016;11(4):e0154469. DOI: 10.1371/journal.pone.0154469
33. Barrera-Baena P, Rodríguez-García M, Rodríguez-Rubio E, González-Llorente L, Ortiz A, Zoccali C, et al. Serum phosphate is associated with increased risk of bone fragility fractures in hemodialysis patients. Nephrol Dial Transplant 2023;39(4):618-26. DOI: 10.1093/ndt/gfad190
34. Torregrosa JV, Bover J, Rodríguez Portillo M, González Parra E, Arenas MD, Caravaca F, et al. Recomendaciones de la Sociedad Española de Nefrología para el manejo de las alteraciones del metabolismo óseo-mineral en los pacientes con enfermedad renal crónica: 2021 (SEN-MM). Nefrología 2022;42:1-37. DOI: 10.1016/j.nefro.2022.03.007