CONTINUING EDUCATION SERIES

CONTACT HOUR: 2.0 HRS

Hyperphosphatemia and vascular calcification in chronic kidney disease

By Oluwakonyinsolami Ogunrinde, Joy A. Gatmaitan, Simerdeep Chouhan, Hitesh Mehta, and Rosa M. Marticorena

LEARNING OBJECTIVES

By the end of this article, readers should be able to:

1. Describe the pathophysiology of hyperphosphatemia in renal disease.
2. Describe the vascular calcification in renal disease.
3. Describe current approaches to managing hyperphosphatemia and opportunities to improve the management of hyperphosphatemia in hemodialysis.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD) and is present in more than 50% of patients receiving dialysis (Doshi & Wish, 2022). The risk of death from CVD is 20 times higher in these patients compared to the general population. (Jankowski et al., 2021). Risk factors for cardiovascular mortality in CKD and end-stage renal disease (ESRD) can be broadly categorized as traditional (diabetes, hypertension, and dyslipidemia) and non-traditional risk factors (vascular calcification and inflammation) (Jankowski et al., 2021). The ability of the kidneys to maintain mineral homeostasis progressively declines with the loss of renal function. Mineral metabolism imbalance is characterized by an increase in serum concentration of phosphate, calcium, and parathyroid hormone (PTH) levels, and decrease in serum levels of vitamin D, parathyroid vitamin D receptors, and parathyroid calcium receptors, often seen with glomerular filtration rates (GFR) of 30mL/min or lower (Zhou et al., 2021; Jankowski et al., 2021).

Hyperphosphatemia (HP) has been identified as an independent risk factor for the development of bone mineral disease and vascular disease including vascular calcification, and metastatic calcification of the heart valves and soft tissues prevalent in the dialysis population (Doshi & Wish, 2022; KDIGO Working Group [KDIGO], 2017; Jankowski et al., 2021). Epidemiological data from the Dialysis Outcomes Practice Patterns Study (DOPPS) showed that HP is a strong predictor of cardiovascular (CV) mortality in dialysis patients, with the lower death rates in patients with phosphate levels closer to normal ranges sustained over a period of six months (Lopes et al., 2020). Strict control of HP has been shown to delay the progression for coronary artery calcification in HD patients (Isaka et al., 2021). This paper focuses on the development of vascular calcification related to HP in patients receiving HD and current therapy options to control HP.

AUTHOR NOTE

Oluwakonyinsolami Ogunrinde, BScN, Toronto Metropolitan University, Toronto, ON

Joy A. Gatmaitan, BScN, CRC, William Osler Health System, Brampton, ON

Simerdeep Chouhan, BScN, CRC, William Osler Health System, Brampton, ON

Hitesh Mehta, MD, FRCPC, Nephrologist, William Osler Health System, Brampton, ON

Rosa M. Marticorena, CNS, PhD, CNeph(C), Research Manager, William Osler Health System, Brampton, ON

Correspondence should be addressed to: Rosa M. Marticorena, William Osler Health System, 2100 Bovaird Drive East, Brampton, ON L6R 3J7

Email: **rosamyrna.marticorena@williamoslerhs.ca**

PHOSPHATE REGULATION AND HYPERPHOSPHATEMIA

Phosphate is an abundant mineral in the human body and an important component of genetic material, lipids on cell membranes, and adenosine triphosphate (ATP); it is tightly regulated through dietary absorption, bone flux, and renal excretion. (Zhou et al., 2021). Normal serum phosphate levels range from 0.81 to 1.58 mmol/L with HP defined as a serum phosphate level greater than 1.58 mmol/L (Zhou et al., 2021). HP due to decreased GFR can induce hypertension, vascular calcification, cardiac vascular calcification, atherosclerosis, left ventricular hypertrophy (LVH), and myocardial fibrosis (Zhou et al., 2021). It can also cause hypocalcemia, hyperparathyroidism, metabolic bone disease, and adverse cardiovascular events. The kidneys excrete about 90% of the phosphate intake in the body and the gastrointestinal tract excretes the rest; however, phosphate does not bind to albumin, and it is

usually filtered through the glomerulus with 75% of filtered phosphate being reabsorbed in the proximal tubule, approximately 10% in the distal tubule, and 15% lost in the urine. Phosphate homeostasis is under the direct hormonal influence of calcitriol, PTH, Vitamin D receptors, calcium-sensing receptors (CaSR), and phosphatonins including fibroblast growth factor (FGF) 23 (Goyal & Jialal, 2021). Serum phosphate level is maintained through a complex interaction between intestinal phosphate absorption, renal phosphate handling, and phosphate transcellular movement between intracellular fluid and bone storage pool (Goyal & Jialal, 2021).

Effects of hyperphosphatemia on the vascular and cardiac systems

HP is an important factor in the development of adverse cardiac events that result from hypertension, vascular calcification, cardiovascular calcification, atherosclerosis, LVH, and myocardial fibrosis (Cozzolino et al., 2018). Vascular calcifications can increase the incidence of arrhythmia, sudden cardiac death, stroke, and mortality. This is because it can lead to ischaemic CVD and increases in pulse pressure and pulse wave velocity, resulting in the reduction of diastolic coronary perfusion and LVH. Vascular calcification also results in aortic stenosis, which causes an increase in cardiac afterload (Jankowski et al.2021). In HD patients, calcification of the lower part of the abdominal aorta appeared to be most predictive of CV events and mortality (NasrAllah, 2016). Abdominal radiographs are recommended as part of screening for vascular calcification in patients with HP and GFR categories G3a to G5 (i.e., GFR less than 60 mL/min/1.73 m^2) (KDIGO, 2017).

Mechanism of vascular calcification

Blood vessels (aside from the capillaries) are made of three layers. The inner layer or *tunica intima* consists of an endothelial lining that provides a frictionless pathway for the movement of blood. The middle layer or *tunica media* is composed of elastic and muscular tissue that regulates the internal diameter of the vessel. Finally, the outer layer or *tunica adventitia* provides structural support and shape to the vessel (Tucker et. al., 2022).

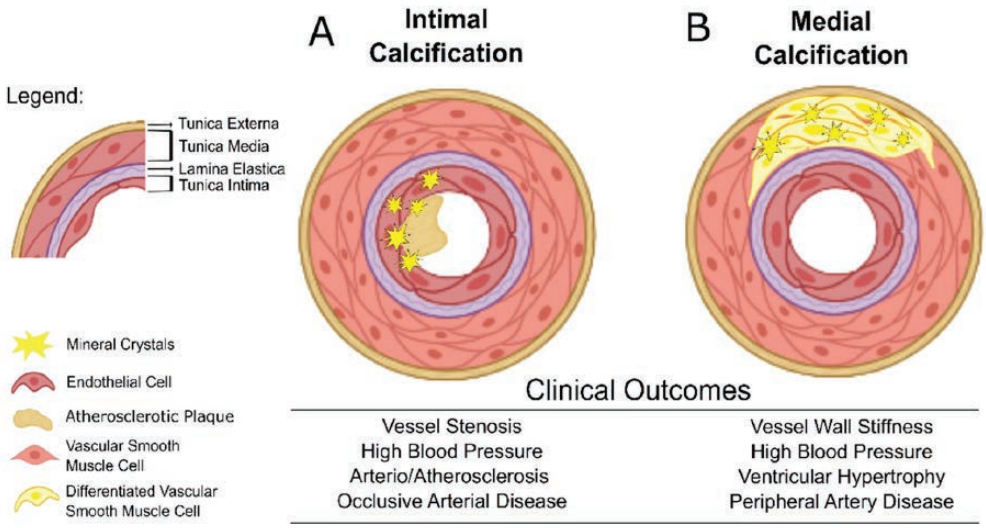
Vascular calcification is an active process driven partly by smooth muscle cells in the media of the vascular wall (Vahed et al., 2020). Vascular smooth muscle cells (VSMC) are cellular components of the medial layer that can switch from a contractile phenotype to a synthetic phenotype in response to injury (Jankowski et al., 2021). VSMC can undergo trans-differentiation to osteoblast-like cells and extrude matrix vesicles containing proteins that resemble osteoblastic vesicles (Durham et al., 2018). The excretion of these proteins creates an osteogenic environment that results in vascular calcification (Lee et al., 2020). In essence, the vascular wall converts into bone. Smooth muscle cells are highly sensitive to the increased levels of phosphate, calcium, and PTH, which trigger cell transformation from a contractile cell type to an osteoblastic/chondrogenic cell type (Vahed et al., 2020).

Vascular calcification occurs in both the intimal and medial layers of the arteries (Figure 1). Intimal calcification has been linked to arterial obstruction and atherosclerotic plaque rupture, whereas medial calcification has been linked to vessel stiffness, systolic hypertension, and increased pulse wave velocity resulting in increased diastolic dysfunction

Figure 1

Intimal and Medial Calcification

(A) Intimal calcification is confined to the lumen of the endothelium of the vessel mainly associated with atherosclerosis, contributing to vessel stenosis, lumen narrowing and increased BP. (B) Medial calcification affects the medial layer of the vessel wall mainly composed of vascular smooth muscle cells, leading to increased vessel wall stiffness with compromised blood pumping and compliance, reflecting in high BP, peripheral artery disease or even ventricular hypertrophy.



Note. From "Targeting a Silent Disease: Vascular Calcification in Chronic Kidney Disease," by C. Marreiros, C. Viegas, & D. Simes, 2022, *International Journal of Molecular Sciences*, *23*(24), p. 3. Copyright 2022 by the authors. Reprinted with permission. *al Journal of Molecular Sciences*, *23*(24), 16114. Retrieved from http://dx.doi.org/10.3390/ijms232416114

and heart failure (Vahed et al., 2020; Lee et al., 2020). Coronary artery calcification, prevalent in HD patients, is associated with hyperphosphatemia and increased mortality rate in this population. In patients receiving dialysis, reduction of phosphate level to closer to normal level is associated with a slower progression of coronary artery calcification (Isaka et al., 2021).

Management of hyperphosphatemia

There are three main therapies to combat hyperphosphatemia: phosphate binders, diet regulation, and dialysis (Fishbane & Nigwekar, 2021). However, studies have shown that 77% of dialysis patients struggle with maintaining a phosphate level of less than or equal to 1.58 mmol/L. Fishbane and Nigwekar (2021) found that dialysis patients, on average, are prescribed 10.8 phosphate binders daily, accounting for approximately 50% of their daily medication pill burden. Some phosphate binders cause unpleasant gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and constipation. The calcium-based phosphate binders have been found to increase calcium levels and contribute to vascular calcification, further worsening the situation (Fishbane & Nigwekar, 2021).

Dietary changes are the first line of treatment when caring for patients with hyperphosphatemia (Goyal & Jialal, 2021). Patients are encouraged to reduce their consumption of foods with high phosphate content, but it is very difficult to do so when there is a large amount of food products that contain phosphate hidden in chemicals used to preserve packaged food. Still, this line of intervention does not show a marked reduction in phosphate levels for patients receiving dialysis (Floege, 2019). In addition, concerns about the dietary phosphate restriction include the potential to reduce protein intake and risk protein malnutrition (Floege, 2019). A recent meta-analysis of randomized trials comparing various dietary interventions in addition to phosphate binder therapy showed a 0.02 mmol/L decline in serum phosphate levels in dialysis patients over six months of therapy, and the effect seemed to disappear with discontinuation of the dietary intervention (St. Jules et al., 2021).

The main aim of standard therapies is to help reduce the phosphate level to an acceptable range close to the norm (Goyal & Jialal, 2021). Medication options for phosphate binders largely fall into the following categories of binders: aluminum-based, calcium-based, non-calcium-based, and iron-based (Chan et al., 2017). Aluminium-based binders (aluminum hydroxide or Amphojel) are very effective, but their use is no longer popular due to concerns about aluminum toxicity. Their use is restricted to controlled short-term therapy when the levels of phosphate are extremely high, and control needs to be achieved with urgency (Liu & Pemas, 2021; KDIGO, 2017).

Calcium-based binders such as calcium carbonate (TUMS) replaced aluminum binders and are currently the first choice of therapy due to their low cost. However, large doses are required to be taken with meals above the recommended daily amount (Frazão & Adragão, 2012). Doses over two grams per day increase the risk of calcium overload and hypercalcemia, which have been linked to vascular calcification (Hutchison, 2009; KDIGO, 2017). Non-calcium-based binders such as lanthanum carbonate (Fosrenol) and sevelamer hydrochloride (Renagel) are currently being used due to their ability to reduce phosphate levels at a rate similar to the calcium-based binders while eliminating the risk of calcium overload (Frazão & Adragão, 2012; Ogata et al., 2021). Lanthanum carbonate is a chewable tablet that is also available in powder form. Sevelamer hydrochloride is a polymeric amine non-absorbed, binder approved for use in reducing phosphate levels.

Iron-based phosphate binders such as sucroferric oxyhydroxide (Velphoro) are formulated as chewable berry-flavoured tablets approved for use in patients undergoing dialysis, that have the added advantage of requiring a lower number of tablets, thus decreasing pill burden in these patients (Ketteler et al., 2019; Frazão & Adragão, 2012). Tenapanor hydrochoride is a treatment used for irritable bowel syndrome and has been studied as a new non-binding therapy to control hyperphosphatemia. It inhibits phosphate absorption in the GI tract. It has been shown to lead to good results in controlling serum levels of phosphate; however, the long-term effects of this drug are currently under evaluation (Pergola, et al., 2021). It is not approved in Canada to be used to treat HP in CKD.

IMPLICATIONS FOR NURSING PRACTICE

Hyperphosphatemia has far-reaching effects extending to vascular calcification. Treatment of hyperphosphatemia is complex, it requires diet control, use of phosphate lowering medications and HD. Management of HP requires a multipronged approach requiring intervention and counselling from multiple disciplines, particularly from nurses at the bedside. Knowledge of the pathophysiology of vascular calcification as a sequela of hyperphosphatemia is an important component of hemodialysis nursing practice. Nephrology nurses play a pivotal role in providing continuous education and reinforcement to patients regarding the importance of adherence to therapy to prevent complications. Nephrology nurses are best positioned to provide consistent guidance and support to these patients during their HD sessions. Important consideration needs to be given to the side-effects of phosphate binders such as gastrointestinal upset, nausea, and other symptoms that could contribute to suboptimal adherence to HP management. Having an honest discussion with patients and providing continuous education to inform them of available options for treatment are just as crucial as being able to engage patients in their own medical care. Advocating for patients in this regard is not the sole domain of nurses. Nephrologists and the renal allied health team comprising dietitians, pharmacists, and social workers can all similarly engage in advocacy by working together to expedite the sometimes-complex process of procuring access to medications that are not covered by provincial drug plans. Such a collaborative interdisciplinary approach to care that puts patients front and centre is pivotal in the management of hyperphosphatemia that would mitigate serious complications such as vascular calcification.

REFERENCES

Chan, S., Au, K., Francis, R. S., Mudge, D. W., Johnson, D. W., & Pillans, P. I. (2017). Phosphate binders in patients with chronic kidney disease. *Australian Prescriber, 40*(1), 10. https://doi.org/10.18773/AUSTPRESCR.2017.002

Cozzolino, M., Mangano, M., Stucchi, A., Ciceri, P., Conte, F., & Galassi, A. (2018). Cardiovascular disease in dialysis patients. *Nephrology Dialysis Transplantation, 33*(Suppl. 3), Iii28–Iii34. https://doi.org/10.1093/ndt/gfy174

Doshi, S. M., & Wish, J. B. (2022). Past, present, and future of phosphate management. *Kidney Interanational Reports, 7*(4), 688-698. https://www.sciencedirect.com/science/article/pii/S2468024922010737

Durham, A. L., Speer, M. Y., Scatena, M., Giachelli, C. M., & Shanahan, C. M. (2018). Role of smooth muscle cells in vascular calcification: Implications in atherosclerosis and arterial stiffness. *Cardiovascular Research, 114*(4), 590–600. https://doi.org/10.1093/cvr/cvy010

Fishbane, S. N., & Nigwekar, S. (2021). Phosphate absorption and hyperphosphatemia management in kidney disease: A physiology-based review. *Kidney Medicine, 3*(6), 1057–1064. https://doi.org/10.1016/j.xkme.2021.07.003

Floege, J. (2019). Phosphate binders in chronic kidney disease: An updated narrative review of recent data. *Journal of Nephrology 2019, 33*(3), 497–508. https://doi.org/10.1007/S40620-019-00689-W

Frazão, J. M., & Adragão, T. (2012). Non-calcium-containing phosphate binders: Comparingefficacy, safety, and other clinical effects. *Nephron Clinical Practice*, *120*(2), c108–c119. https://doi.org/10.1159/000337087

Goyal, R., & Jialal, I. (2022). Hyperphosphatemia. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK551586/https://www.ncbi.nlm.nih.gov/books/NBK551586/

Hutchison, A. J. (2009). Oral phosphate binders. *Kidney International, 75*(9), 906–914. https://doi.org/10.1038/ki.2009.60

Isaka, Y., Hamano, T., Fujii, H., Tsujimoto, Y., Koiwa, F., Sakaguchi, Y., Tanaka, R., Tomiyama, N., Tatsugami, & F., Teramukai, S. (2021). Optimal phosphate control related to coronary artery calcification in dialysis patients. *Journal of the American Society of Nephrology*, *32*(3), 723–735. https://doi.org/10.1681/ASN.2020050598

Jankowski, J., Floege, J., Fliser, D., Böhm, M., & Marx, N. (2021). Cardiovascular disease in chronic kidney disease: Pathophysiological insights and therapeutic options. *Circulation*, *143*(11), 1157. https://doi.org/10.1161/CIRCULATIONAHA.120.050686

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. (2017). KDIGO 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney International Supplements*, *7*(3), e1. https://doi.org/10.1016/j.kisu.2017.10.001

Ketteler, M., Sprague, S. M., Covic, A. C., Rastogi, A., Spinowitz, B., Rakov, V., Walpen, S., &Floege, J. (2019). Effects of sucroferric oxyhydroxide and sevelamer carbonate on chronic kidney disease–mineral bone disorder parameters in dialysis patients. *Nephrology Dialysis Transplantation*, *34*(7), 1163–1170. https://doi.org/10.1093/ndt/gfy127

Lee, S. J., Lee, I. K., & Jeon, J. H. (2020). Vascular calcification—New insights into its mechanism. *International Journal of Molecular Sciences*, *21*(8). https://doi.org/10.3390/IJMS21082685

Liu, F. & Pemas, M. (2021). 'Phos'ing over phosphorus: A primer on updates in phosphate binders. *CANNT Journal, 31*(1), 20–25.

Lopes, M.B., Karaboyas, A., Bieber, B., Pisoni, R.L., Walpen, S., Fukagawa, M., Christensson, A., Evenepoel, P., Pegoraro, M., Robinson, B.M., Pecoits-Filho, R. (2020). Impact of longer-term phosphorus control on cardiovascular mortality in hemodialysis patients using an area under the curve approach: Results from the DOPPS. *Nephrol Dial Transplant., 35*(10), 1794–1801. doi: 10.1093/ndt/gfaa054. PMID: 32594171; PMCID: PMC7538234.

Marreiros, C., Viegas, C., & Simes, D. (2022). Targeting a silent disease: Vascular calcification in chronic kidney disease. *International Journal of Molecular Sciences*, *23*(24), 16114. http://dx.doi.org/10.3390/ijms232416114

NasrAllah, M. M., Nassef, A., Elshaboni, T. H., Morise, F., Osman, N. A., & Sharaf El Din, U. A. (2016). Comparing different calcification scores to detect outcomes in chronic kidney disease patients with vascular calcification. *International Journal of Cardiology*, *220*, 884–889. https://doi.org/10.1016/j.ijcard.2016.06.064

Ogata, H., Fukagawa, M., Hirakata, H., Kagimura, T., Fukushima, M., Akizawa, T., & LANDMARK Investigators and Committees (2021). Effect of treating hyperphosphatemia with lanthanum carbonate vs calcium carbonate on cardiovascular events in patients with chronic kidney disease undergoing hemodialysis: The LANDMARK randomized clinical trial. *JAMA*, *325*(19), 1946–1954. https://doi.org/10.1001/jama.2021.4807

Pergola, P. E., Rosenbaum, D. P., Yang, Y., & Chertow, G. M. (2021). A randomized trial of tenapanor and phosphate binders as a dual-mechanism treatment for hyperphosphatemia in patients on maintenance dialysis (AMPLIFY). *Journal of the American Society of Nephrology*, *32*(6), 1465–1473. https://doi.org/10.1681/ASN.2020101398

St-Jules, D. E., Rozga, M. R., Handu, D., & Carrero, J. J. (2020). Effect of phosphate-specific diet therapy on phosphate levels in adults undergoing maintenance Hemodialysis: A systematic review and meta-analysis. *Clinical Journal of the American Society of Nephrology*, *16*(1), 107–120. https://doi.org/10.2215/CJN.09360620

Tucker, W. D., Arora, Y., & Mahajan, K. Anatomy, blood vessels. (2022, August 8). Anatomy, blood vessels. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470401/

Vahed, S. Z., Mostafavi, S., Khatibi, S. M. H., Shoja, M. M., & Ardalan, M. (2020). Vascular calcification: An important understanding in nephrology. *Vascular Health and Risk Management*, *16*, 167. https://doi.org/10.2147/VHRM.S242685

Zhou, C., Shi, Z., Ouyang, N., & Ruan, X. (2021). Hyperphosphatemia and cardiovascular disease. *Frontiers in Cell and Developmental Biology*, *9*, 644363. https://doi.org/10.3389/fcell.2021.644363