Phosphate: The Missing Piece in Cardiovascular Disease Control

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Introduction

Phosphorus is a fundamental element of life. Its oxidized product, phosphate, plays an essential role in maintaining basic cellular functions including membrane structural integrity via glycerophospholipids, genetic signaling via DNA and RNA, energy transfer via adenosine triphosphate (ATP) and neurotransmission via cyclic adenosine monophosphate (cAMP), and it is the building block of all bony structures in our body.[1] Like other crucial ions in the body, serum levels of phosphate are tightly regulated by the kidney through intricate feedback loops.[1] However, this is also one of the first mechanisms to malfunction in the disease process of chronic kidney disease (CKD).[2] While abnormal phosphate metabolism is considered the hallmark of chronic kidney disease (CKD), studies have shown that abnormal phosphate levels are also associated with vascular calcification, atherosclerosis and all-cause- and cardiovascular disease(CVD) mortality, regardless of renal function.[3-5] In this brief review, we discuss the mechanism of phosphate control in the cardiovascular system, how phosphate imbalance affects cardiovascular function, known treatment options for phosphate imbalance and important issues remaining to be investigated, that are related to phosphate control and cardiovascular disease protection.

Mechanism of phosphate control

Phosphate homeostasis is achieved through the interplay of parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol (1,25 VitD), and phosphatonins such as fibroblast growth factor 23 (FGF23).[1] However, many aspects of phosphate metabolism remain unclear and in need of further investigation. Phosphate is deposited primarily in bony and muscular tissues, with less than 1% in the extracellular fluid.[6] The body regulates phosphate at the bowels, the kidneys and the bones. The small bowel absorbs phosphate passively via paracellular transport and actively via the vitamin D-dependent sodium-phosphate cotransporter (NPT2b).[7] An average adult ingests 1400 mg of phosphate per day (typical Western diet); of this, 1120 mg (80%) is absorbed in the upper intestine to the extracellular fluid, and 210 mg (15%) is returned to the intestine by secretion, resulting in 910 mg (65%) net phosphate absorption and 490 mg (35%) fecal excretion. At the kidney, 5040 mg of phosphate is filtered through the glomerulus every day and 4130 mg return to the ECF by tubular reabsorption, with

Received: Sep. 24, 2022; Accepted: Oct. 28, 2022
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910 mg excreted in the urine.[8] This means that about 90% of phosphate filtered through the renal glomeruli is reabsorbed by NPT2a and NPT2c sodium-phosphate cotransporters at the proximal tubules, while only the remaining 10% of phosphate is excreted.[9] The bone serves as the reservoir where phosphate is constantly stored or extracted. Healthy adults maintain a net skeletal phosphorus balance close to zero by adjusting the amounts of phosphate absorption and urinary excretion (typically 180 mg per/day). Thus, the daily net phosphate change in the body is nearly zero. This intricate balance of phosphate level is maintained through the interaction of PTH, 1,25 VitD, FGF23 and perhaps other less-understood phosphatonins. PTH can reduce renal phosphate resorption by decreasing the abundance of NPT2a and NPT2c.[10] PTH can also stimulate the production of 1,25 VitD and FGF23.[11] Although 1,25 VitD is called a vitamin, it is in fact not a co-enzyme but a powerful hormone with multifaced effects over multiple systems. 1,25 VitD originates from Vitamin D3 (cholecalciferol), a fat-soluble steroid synthesized in the skin through exposure to ultraviolet radiation or directly absorbed from the diet. It is activated by a hepatic enzyme, 25-hydroxylase, into 25-hydroxycholecalciferol (calcidiol) and then further converted to its most active form, 1,25 VitD by enzymes in the proximal tubules of the kidney. During hypophosphatemia, 1,25 VitD increases intestinal absorption by enhancing the expression of NPT2b and increases renal resorption by improving the expression of NPT2a and NPT2c.[12] This includes the suppression of PTH synthesis and enhancement of FGF23 production.[7] FGF23 is a critical hormone produced by osteocytes and osteoblasts.[1] FGF23 binds to the FGF receptor-Klotho complex to activate its function.[13] When phosphate level is increased, FGF23 suppresses NPT2a and NPT2c expression at the proximal renal tubules, thereby inhibiting renal phosphate reabsorption.[14] FGF23 also reduces 1,25 VitD production and PTH synthesis.[13]

Phosphate and cardiovascular disease

As renal function declines, the primary ability to eliminate phosphate is gradually lost.[15] Initially, phosphate homeostasis is maintained through increased PTH and FGF23 production.[16,17] These mechanisms are eventually overwhelmed when the glomerular filtration rate falls below 30 mL/min/1.73 m.[2,15] However, gradual accumulation of phosphate can already be observed since early stage 3 CKD.[2] The final common presentation of renal failure patients, regardless of the cause, is that of hyperphosphatemia, elevated PTH, FGF23 and low 1,25 VitD production. Hyperphosphatemia may directly affect vascular health by the following mechanisms: 1. Increasing oxidative damage; 2. Affecting endothelial cell function; 3. Initiating calcification by promoting vascular smooth muscle cell transition into the osteochondrogenic phenotype and by remodeling of extracellular matrix and degradation of elastin.[18,19] Indirectly, hyperphosphatemia is associated with hypocalcemia, which is not only arrhythmogenic but also a trigger for PTH production.[20] In addition, hyperphosphatemia also indirectly leads to cardiovascular complications by promoting hypertension,[21] causing poorer blood pressure control and blunted nocturnal dipping of blood pressure in patients with or without CKD.[22,23] Furthermore, increased FGF23 is directly associated with atherosclerosis, left ventricular hypertrophy and heart failure.[24] FGF23 also takes part in vascular calcification by promoting the expression of osteogenic-related proteins.[25] PTH has myriad effects on the cardiovascular system, including 1. Promotion of inflammation, 2. Promotion of fibrosis and 3. Sympathetic activation.[26-28] Low 1,25 VitD production and subsequent unopposed renin-angiotensin-aldosterone system activation is associated with decreased cardiac contractility, autonomic dysregulation, coronary artery calcification, myocardial fibrosis, and systemic inflammation.[29,30]

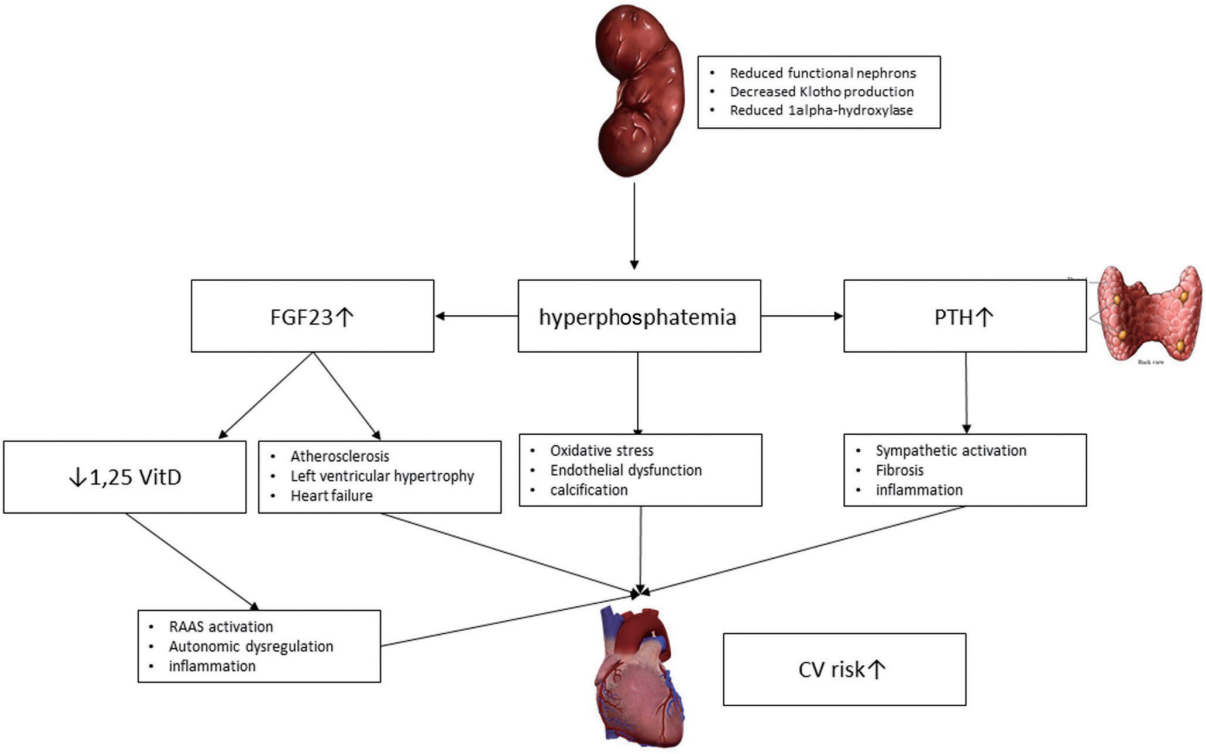

Figure. Mechanism of phosphate related CV risk.

Phosphate control and cardiovascular outcomes

There is ample evidence that phosphate is involved in the atherosclerotic process from initiation to manifestation. Notably, the involvement of phosphate in CVD extends beyond the CKD population.[31] Serum phosphate level is independently associated with the presence of atherosclerotic plaques.[3,17,32] Importantly, even mildly elevated phosphate level is independently associated with higher cardiovascular risk.[33,34] Phosphate is also an independent marker for vascular plaque progression and calcification.[35] It is independently associated with the development of clinical coronary artery disease (CAD), heart failure, and atrial fibrillation.[33,34,36] With regard to more generalized atherosclerotic and non-atherosclerotic cardiovascular events and mortality, phosphate has also been shown in multiple studies to have a significant association.[37] Additionally, in patients with established CAD or heart failure, phosphate is associated with a higher event rate.[38-40] Interestingly, the association between phosphate and CV risk is U-shaped. This was repeatedly demonstrated in a large primary prevention cohort by Hayward et al.[41] and a secondary prevention study by Tsai et al., which showed that high serum phosphate levels are significantly associated with poor outcomes in CAD patients receiving PCI. The association between phosphate level and clinical outcome is J-shaped, with the lowest future CV risk observed for levels around 3.0-3.4 mg/dL after adjustment for comorbidities and renal function.[39] Indeed, in a population attributable risk analysis, lack of phosphate control was the most significant remaining modifiable contributor to CKD mortality.[42]

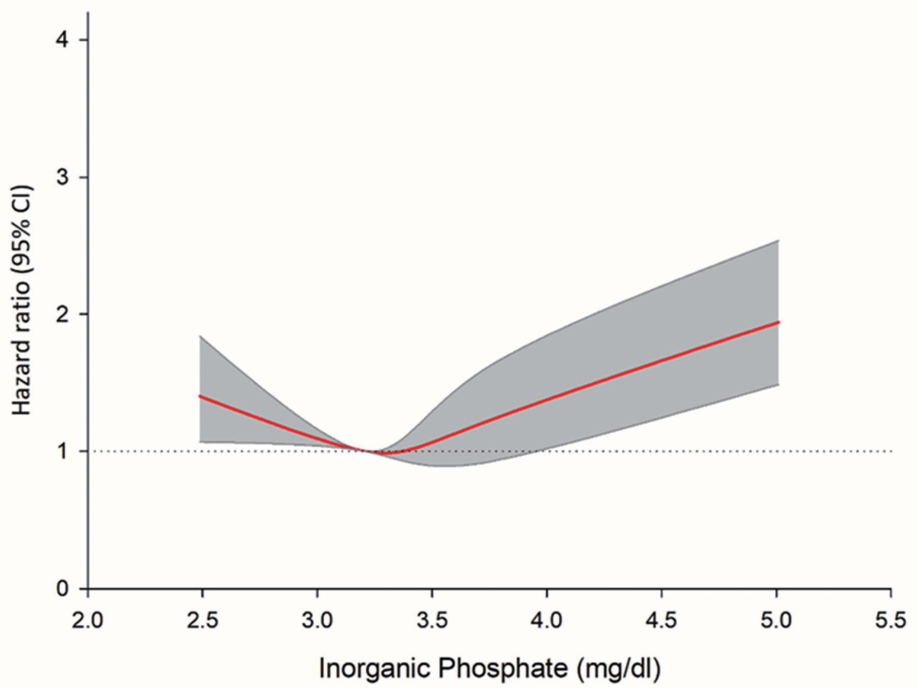

Figure 2. The relationship between serum phosphate as a continuous variable and the probability of MACE through cubic spline analysis. MACE = major adverse cardiovascular events. From Tsai et al.[39]

Challenges and future perspectives

While the connection between phosphate and CVD is well accepted, there is a lack of treatment trials. Those that exist are almost exclusively for CKD patients. Current methods of phosphate management, including diet restriction and phosphate binders, are insufficient to achieve adequate phosphate control.[42] Traditional calcium-based phosphate binders seem to precipitate vascular calcification and CV risk.[43] Lanthanum or sevelamer phosphate binders were considered a promising tool to lower phosphate, given their initial record of reduced coronary calcium progression.[44,45] However, the multicenter, double-blinded IMPROVE-CKD trial, which randomized 278 CKD patients to either lanthanum or placebo, showed disappointing results at the price of high pill burden and cost.[46] The trial did not demonstrate significant improvements in the pulse wave velocity, PTH level, FGF23 level, or phosphate level. These results corroborate those of previous smaller trials.[47] In another larger cohort study of 2639 patients of the United States Renal Data System, a similar risk of cardiovascular events and death was noted for sevelamer and calcium acetate initiators after adjusting for 78 potential confounders, including serum calcium and phosphorus levels.[48] This result suggests that changing to sevelamer from calcium-based phosphate binders has no clinical benefit as regards cardiovascular risk.

By contrast, a recent randomized controlled trial showed that strict phosphate control is independently associated with slower CAC progression for patients who can achieve lower phosphate levels.[49] Thus, adequate phosphate control remains an unmet need. Several novel agents have been developed to fill the gap. EOS789, a sodium-phosphate transporter blocker, significantly lowered phosphate in an animal study.[50] Clinical trials of EOS789 are ongoing (NCT02965053). Tenapanor is a paracellular absorption blocker that inhibits phosphate

absorption in the GI tract. In a phase 3 trial, tenapanor significantly reduced the phosphate level in patients receiving hemodialysis though no CVD outcome data were reported.[51] Given the current understanding of phosphate homeostasis and its CVD hazard, clinicians should consider adopting novel therapy early, on top of traditional diet control and binders, to achieve a normal phosphate level for all patients.

Conclusion

In summary, the evidence thus far should convince us that phosphate is not merely a marker of CKD, but a marker of atherosclerosis as well. Its roles in all aspects of cardiovascular disease, from pathogenesis to manifestation, should prompt us to explore treating hyperphosphatemia as a means of CVD prevention. As long as practical methods to control hyperphosphatemia remain elusive, a piece to the puzzle of atherosclerosis management remains missing.

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