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# Phosphate, the Missing Piece in Cardiovascular Disease Control

**Hsin-Bang Leu**

No.201, Sec. 2, Shipai Rd., Beitou District, Taiwan

***Correspondence:** Hsin-Bang Leu, No.201, Sec. 2, Shipai Rd., Beitou District, Taiwan, E-mail: hsinbangleu@gmail.com; Tel: +886952769785



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## ABSTRACT

Phosphate has fundamental roles in multiple physiologic functions. It is regulated by the interplay of parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol (1,25 VitD), and fibroblast growth factor 23 (FGF23). Dysregulation of phosphate is related to the mechanisms of atherosclerotic diseases. Both phosphate dysregulation and its regulatory hormones are involved in the atherosclerotic disease process. Clinical studies have found that phosphate level has a U-shaped association with cardiovascular outcomes. However, effective treatment trials are currently lacking. In this article, we reviewed the evidence of phosphate as a marker of atherosclerosis. Its roles in all aspects of cardiovascular disease, from pathogenesis to manifestation, should prompt us to explore treating hyperphosphatemia as a mean of CVD prevention.

## 1. Introduction

Phosphorous is a fundamental element of life. Its oxidized product, phosphate, has essential roles in cellular function, genetic signaling, energy metabolism, neurotransmission and is the building block of bony structures in our body [1]. Like other crucial elements in the body, phosphate is tightly regulated by the kidney.[1]However, it is also one of the first mechanisms to fail in the disease process of chronic kidney disease (CKD) [2]. Although abnormal phosphate metabolism is considered the hallmark feature of chronic kidney disease (CKD), studies have shown that abnormal phosphate levels are associated with vascular calcification, atherosclerosis, all-cause, and cardiovascular disease(CVD) mortality, regardless of renal function [3-5]. In this brief review, we shall discuss the mechanism of phosphate control, how phosphate imbalance affects cardiovascular function, what are the known treatment options for phosphate imbalance and what remained to be investigated.

### 1.1 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]. Phosphate primarily deposit 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 via passive transport and vitamin D-dependent sodium-phosphate cotransporter (NPT2b) [7]. The kidney is responsible for excreting around 34mmol of phosphate every day [8]. About 90% of phosphate filtered through the renal glomeruli is reabsorbed by NPT2a and NPT2c sodium-phosphate cotransporters at the proximal tubules while the remaining 10% of phosphate is excreted [9]. The bone serves as the storage in which phosphate is stored or extracted constantly. PTH can reduce renal phosphate resorption by decreasing the abundance of NPT2a and NPT2c [10]. PTH also stimulates the production of 1,25 VitD and FGF23 [11]. 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]. 1,25 VitD also suppresses synthesis of PTH and enhances FGF23 production [13]. FGF23 is produced by osteocytes and osteoblasts [1]. FGF23 binds to FGF receptor-Klotho complex to exhibit its function [14]. It suppresses NPT2a and NPT2c expression at the proximal renal tubules, thereby inhibiting renal phosphate reabsorption [15]. FGF23 also reduces 1,25 VitD production and PTH synthesis [14].

### 1.2 Phosphate and cardiovascular disease

As renal function declines, the primary ability to eliminate phosphate is gradually lost [16]. Initially, phosphate homeostasis is maintained with increased PTH and FGF23 production [17,18]. These mechanisms are overwhelmed when the glomerular filtration rate falls to <30 mL/min/1.73 $m^2$ [16]. The final condition of renal failure patients is hyperphosphatemia, elevated PTH, FGF23, and low 1,25VitD production. Hyperphosphatemia may directly affect vascular health by 1. increasing oxidative damage, 2, affecting endothelial cell function, 3. initiating calcification by promoting vascular smooth muscle cell transition into the osteochondrogenic phenotype [19,20]. Indirectly, hyperphosphatemia is associated with hypocalcemia which is not only arrhythmogenic but also a trigger for PTH production [21]. Increased FGF23 is directly associated with atherosclerosis, left ventricular hypertrophy, and heart failure [22]. PTH has a myriad of on the cardiovascular system, including 1. Pro-inflammation, 2. Pro-fibrosis and 3. Sympathetic activation [23-25]. Low 1,25VitD 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 [26-27] (Figure 1).

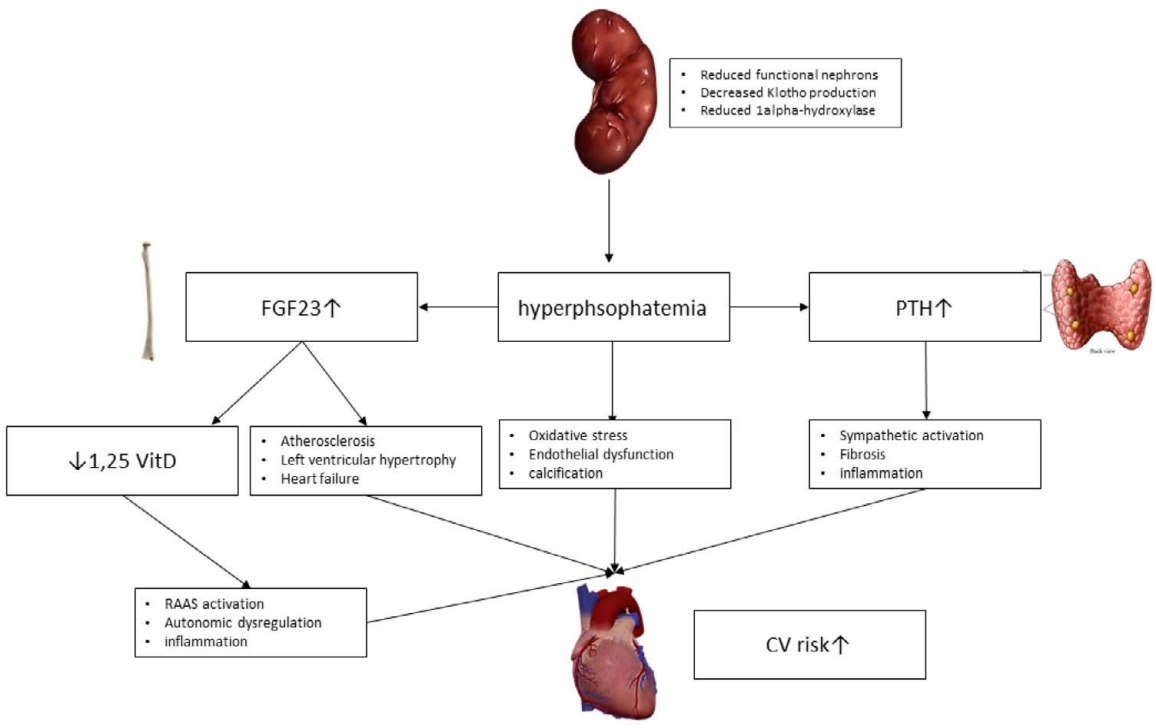


**Figure 1:** Mechanism of phosphate related CV risk

### 1.3 Phosphate control and cardiovascular outcomes

There is ample evidence that phosphate is involved in the atherosclerotic process from the initiation to manifestation. Notably, the involvement of phosphate in CVD extends beyond the CKD population [28]. Serum phosphate level is independently associated with the presence of atherosclerotic plaques [29-31]. Phosphate is also an independent marker for vascular plaque progression and calcification [32]. It is independently associated with the development of clinical coronary artery disease (CAD), heart failure, and atrial fibrillation [5,33,34]. For patients with established CAD or heart failure, phosphate is also associated with a higher event rate [35-37]. Interestingly, the association between phosphate and CV risk is U-shaped. This is repeatedly demonstrated in a large primary prevention cohort by Hayward et al. [38] and a secondary prevention study by Tsai et al. [36]. Indeed, lack of phosphate control is the most significant remaining modifiable contributor to CKD mortality in a population attributable risk analysis [39].

### 1.4 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 [39]. Traditional calcium-based phosphate binders seem to precipitate vascular calcification and CV risk [40]. Lanthanum or sevelamer phosphate binders were considered a promising tool to lower phosphate, given their initial record of reduced coronary calcium progression [41,42]. However, the multicenter, double-blind 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 [43]. The trial did not demonstrate significant improvements in the pulse wave velocity, PTH level, FGF23 level, or phosphate level. These results corroborate with previous smaller trials [44]. On the other hand, the latest randomized control trial showed that strict phosphate control is independently associated with slower CAC progression for patients who can achieve lower phosphate levels [45]. Thus, adequate phosphate control remained an unmet need. Several novel agents were developed to fill the gap. EOS789, a sodium-phosphate transporter blocker, significantly lowered phosphate in an animal study [46]. 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 outcomes data were reported [47]. 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.

## 2. Conclusion

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

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