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Review

Phosphate Metabolism in Cardiorenal Metabolic Disease

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Abstract
Hyperphosphatemia is a major risk factor for cardiovascular disease, abnormalities of mineral metabolism and bone disease, and the progression of renal insufficiency in patients with chronic renal disease. In early renal disease, serum phosphate levels are maintained within the 'normal laboratory range' by compensatory increases in phosphaturic hormones such as fibroblast growth factor-23 (FGF-23). An important co-factor for FGF-23 is Klotho; a deficiency in Klotho plays an important role in the pathogenesis of hyperphosphatemia, renal tubulointerstitial disease, and parathyroid and bone abnormalities. Clinical hyperphosphatemia occurs when these phosphaturic mechanisms cannot counterbalance nephron loss. Hyperphosphatemia is associated with calcific uremic arteriolopathy and uremic cardiomyopathy, which may explain, in part, the epidemiologic connections between phosphate excess and cardiovascular disease. However, no clinical trials have been conducted to establish a causal relationship, and large, randomized trials with hard endpoints are urgently needed to prove or disprove the benefits and risks of therapy. In summary, hyperphosphatemia accelerates renal tubulointerstitial disease, renal osteodystrophy, as well as cardiovascular disease, and it is an important mortality risk factor in patients with chronic kidney disease.

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Introduction

Chronic kidney disease (CKD) is a condition characterized by a progressive decrease in kidney function over months or years, caused by various disease processes or natural aging. The prevalence of CKD is approaching epidemic proportions worldwide [1, 2]. More than 26 million Americans, or 13% of the total population, have CKD [3]. Most patients with CKD die prematurely, not from kidney failure, but from early onset of common diseases, such as cardiovascular disease (CVD), cancer, and infection [3–10]. There is increasing evidence suggesting that abnormalities in mineral metabolism in CKD play a major role in accelerating CVD and metabolic abnormalities associated with CKD [4–19]. Hyperphosphatemia plays a major role in promoting the comorbid conditions that are associated with CKD.

Normal Phosphate Homeostasis and Alterations in CKD

In the absence of CKD, normal serum levels of phosphorus and calcium are maintained through integrative actions of two hormones: parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 (calcitriol), the principal metabolite that activates the vitamin D receptor [20–29]. There is also increasing evidence to support the existence of various factors (historically known as phosphatonins) that directly control the renal excretion of phosphorus, and elucidation of their precise role in the regulation of phosphorus metabolism is an area of active research [20, 29, 30]. These hormones and novel factors act on the primary target organs, bone, kidney, parathyroid glands and intestine to regulate systemic mineral metabolism (table 1).

One of the important phosphatonins, fibroblast growth factor-23 (FGF-23), is produced primarily by osteocytes and acts on renal proximal tubule cells to decrease the expression and/or the apical surface content of type 2a sodium-dependent phosphate co-transporters (NaPi-2a) and by decreasing the expression of the 1α-hydroxylase enzyme that converts 25-hydroxyvitamin D_3 to calcitriol [12, 23–39]. FGF-23 exerts downstream signal transduction via the FGF receptors and requires another phophatonin, the co-receptor Klotho, for optimal signaling [40]. Klotho forms a constitutive binary complex with FGF receptors and functions as an obligate coreceptor for FGF-23 [40–50]. Klotho is primarily expressed in the distal convoluted tubules where it exerts some signaling effects [44], but its major action is on proximal tubule cells [45–58]. Parathyroid tissue also expresses Klotho [59–62], where it may also act as a co-activator of FGF-23 [59]. PTH and Klotho increase FGF-23 production by osteocytes, while FGF-23 inhibits PTH secretion, thus forming an important activation pathway with negative feedback control [61, 62]. Important hormonal regulation of Klotho is also evident: increases in insulin signaling and PPAR-γ activation up-regulate and angiotensin II down-regulates Klotho expression and secretion [51, 55]. Actions of Klotho include activation of transient receptor potential calcium channels (TRPVs), especially TRVP5 and TRVP6 [53, 54]. TRVP5 is expressed in distal nephrons and mediates calcium reabsorption at that site. TRVP6 is expressed in small intestinal epithelial cells where it mediates calcium absorption. Additionally, Klotho influences potassium channel activity in the kidney by activating ROMK1, a renal outer medullary potassium channel, in distal nephrons [52]. This action of Klotho to increase ROMK1 activity promotes potassium ion secretion into the urine.

Because normal kidney function has a critical role in calcium and phosphorus homeostasis, loss of renal function has important consequences. Clinically evident derangements in serum calcium and phosphorus and the hormones that govern plasma levels are initially seen at glomerular filtration rates (GFRs) <60 ml/min and are almost always present at a

Table 1. Hormonal influences on phosphate homeostasis and their derangements in CKD

Hormone/ growth factor	Effects on normal phosphate homeostasis	Derangement in CKD	Net effect in CKD
PTH	↑ renal phosphate excretion ↑ FGF-23 expression ↑ 1α-hydroxylation of 25-OH-vitamin D (↑ calcitriol synthesis)	increased	↑ bone resorption
FGF-23	↓ proximal renal tubular NaPi-2a cotransport ↓ PTH ↓ 1α-hydroxylase activity	increased production/ decreased effect	↓ phosphaturia (due to ↓ functional nephron mass)
Klotho	↑ FGF-23 activity	decreased	↑ vascular calcification ↓ FGF-23 effects ↓ renal phosphate excretion ↑ hyperphosphatemia faster progression of renal disease
Calcitriol (1,25-OH-vitamin D)	↑ intestinal phosphate absorption	decreased	↓ intestinal phosphate absorption ↓ intestinal calcium absorption

GFR <30 ml/min [21–23]. As CKD progresses, hyperphosphatemia ensues, and CKD severity increases with progressive diminution of renal function. Far from an innocent bystander, hyperphosphatemia is known to be an important mortality risk factor in patients with CKD [9–12]. Studies have shown that increased serum FGF-23 and PTH, and decreased calcitriol levels precede the onset of clinical hyperphosphatemia during CKD progression (fig. 1) [29, 30]. In this regard, phosphaturic hormones are able to maintain normal levels of serum phosphate during the early stages of kidney disease [31–33]. As CKD progresses towards end-stage renal disease, high levels of FGF-23 and PTH are offset by deficiency in Klotho and the intrinsic capacity for phosphate excretion due to functional loss of a critical mass of nephrons.

The FGF-23 coreceptor Klotho has considerable potential as a biomarker and as a potential therapeutic target in the detection and treatment of patients with CKD. Klotho protein levels in the urine are decreased in relatively early stages (stages 1 and 2) of CKD [46, 63]. In CKD, relative deficiency in Klotho expression is associated with renal tubulointerstitial disease [45–58], hyperphosphatemia, hyperkalemia, secondary hyperparathyroidism [59–61], renal osteodystrophy [62], vascular calcification and uremic cardiomyopathy (fig. 1, 2) [63]. Accordingly, hyperphosphatemia and diminution of Klotho is associated with and possibly contributory to several of the key cardiovascular abnormalities that constitute the cardiorenal metabolic syndrome (fig. 2). In mouse models of CKD, transgenic overexpression or gene delivery of Klotho results in improvements in kidney function and reduces renal glomerular damage and tubulointerstititial fibrosis [45, 46]. Increased Klotho is associated with improved FGF-23-mediated phosphaturia. Increased Klotho expression in parathyroid glands likely amplifies the effect of FGF-23 on PTH suppression, thereby attenuating the severity of CKD-related hyperparathyroidism. In this regard, the development of strategies to increase the production or delivery of Klotho to kidneys, bone and parathyroid glands may decrease the rate of development of progressive kidney disease, renal osteodystrophy, and hyperparathyroidism in patients with CKD.

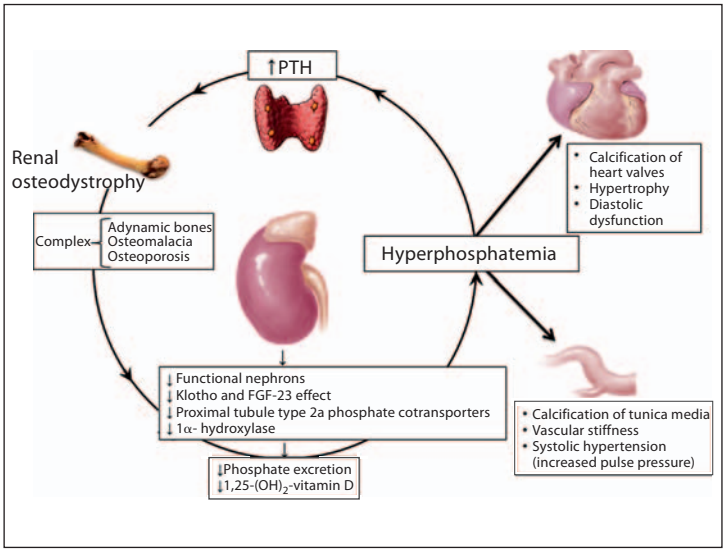

Fig. 1. Pathways involved in the pathogenesis of hyperphosphatemia in CKD. As nephron mass is lost in progressive CKD, renal capacity for phosphate excretion diminishes and renal production of Klotho decreases. Klotho normally enhances the effects of FGF-23 and PTH on phosphate excretion, and in the setting of CKD, bone production of FGF-23 and PTH secretion both increase. However, the effects of increased FGF-23 and PTH are inadequate to return phosphate excretion to normal.

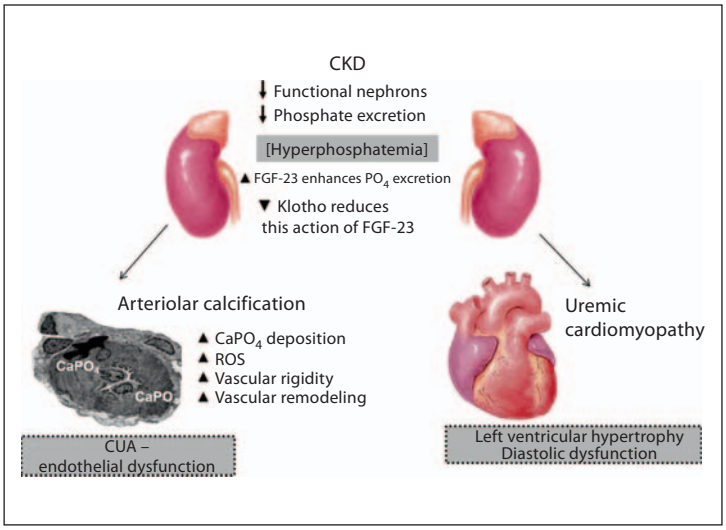

Fig. 2. Role of hyperphosphatemia and decreased Klotho in the cardiorenal metabolic syndrome. This illustration demonstrates that in CKD associated with the cardiorenal metabolic syndrome there is a decrease in the functional nephron number with subsequent hyperphosphatemia. $CaPO_4$ = Calcium phosphate.

Low Klotho levels in bone may contribute to the decreased osteoblast function and bone formation seen in CKD [62]. Thus, correcting the deficiency in Klotho might correct this impaired skeletal anabolism via direct actions and indirectly by increasing active vitamin D levels. In early renal disease, the increasing requirements for phosphate excretion per remaining nephron results in a compensatory increase in FGF-23, decreased calcitriol, increased PTH, and decreased Klotho. Thus, dietary restriction of phosphate intake and/or administration of a phosphate binder should be initiated relatively early in CKD, perhaps as soon as elevated serum or urine levels of FGF-23 or suppressed levels of Klotho are detected. There is also emerging evidence that angiotensin receptor blocker or angiotensin-converting enzyme inhibitor therapy may upregulate Klotho and help interrupt the detrimental cycle associated with hyperphosphatemia.

Renal Osteodystrophy

Since bone represents the largest reservoir of calcium and phosphate in the body, understanding the regulation of calcium-phosphate deposition and reclamation from bone is integral to appreciating the derangements in mineral homeostasis in CKD (fig. 1) [64]. The bone disease linked to CKD is termed renal osteodystrophy, and this entity comprises a complex spectrum of adynamic bone disease, osteomalacia and osteoporosis, any of which may be predominant in a given patient. Growth retardation and skeletal deformities predominate in children, whereas bone pain and muscle weakness may occur at any age and often predominate in adults. The heterogeneous skeletal and mineral disorders of CKD are now classified in aggregate as CKD mineral bone disorder [64]. The earliest recognized manifestation of this disorder occurs in early CKD (stage 2), a stage characterized by elevated FGF-23 and normal serum phosphorus, calcium, PTH and calcitriol levels [65, 66]. As CKD progresses beyond stage 2, depletion of the functional nephron mass gradually results in hyperphosphatemia and the progression of renal osteodystrophy (fig. 1).

Hyperphosphatemia is a potent stimulus for both FGF-23 production by osteocytes and PTH secretion by parathyroid glands. The synergistic phosphaturic effects of FGF-23 and PTH limits, but typically does not overcome, the decreased capacity for phosphate excretion in evolving CKD. In stage 4 and 5 CKD, when GFR falls to <30% of normal, hyperphosphatemia persists despite marked elevation in FGF-23 and PTH [67]. The combination of diminished nephron mass (limiting functional 1α-hydroxylase availability) [68], hyperphosphatemia, and elevated FGF-23 result in decreased synthesis of calcitriol by the kidney. In turn, low serum calcitriol causes decreased intestinal calcium (and phosphate) absorption. Hyperphosphatemia further decreases serum calcium through physicochemical binding and precipitation of calcium phosphate salts in soft tissue. Hypocalcemia, hyperphosphatemia, and low calcitriol levels all stimulate synthesis and secretion of PTH and gradually lead to diffuse nodular hyperplasia of the parathyroid gland [69]. This state of secondary hyperparathyroidism accelerates skeletal remodeling and osteoclastic bone resorption, and leads to net bone resorption. Hyperphosphatemia causes abnormal osteoblast-mediated bone matrix mineralization, osteoblastic transcription factor gene expression [70], and osteoclastic bone resorption [71]. In aggregate, all mineral and hormonal derangements associated with advancing CKD contribute to a mixed bone disease characterized by excessive bone resorption and defective organic bone formation and mineralization. Defective bone mineralization, high serum calcium-phosphorus double products exceeding solubility, and increased FGF-23 activity result in increased heterotopic mineralization or calcific uremic arteriolopathy (CUA), formerly known as metastatic calcification, or calciphylaxis of blood vessels and heart tissue (fig. 3) [72, 73].

Calcific Uremic Arteriolopathy

CUA is associated with multiple vascular abnormalities that include medial calcific, fibrotic, proinflammatory and prothrombogenic arterioles compatible with a calcific obliterative arteriolopathy-vasculopathy (fig. 2, 3) [74]. While vascular calcification was initially described as a passive degenerative process, it is currently understood as an active coordinated process similar to osteogenetic bone modeling and physicochemical deposition of mineral in bone [74–76]. The existing model for vascular calcification begins with differentiation of vascular smooth muscle cell(s) [VSMC(s)] into chrondrocytes, which have an osteoblast-like cellular phenotype. This mechanism is initiated with the interaction of factors (hyperphosphatemia, uremic toxins, and reactive oxygen species) and the decrease in local

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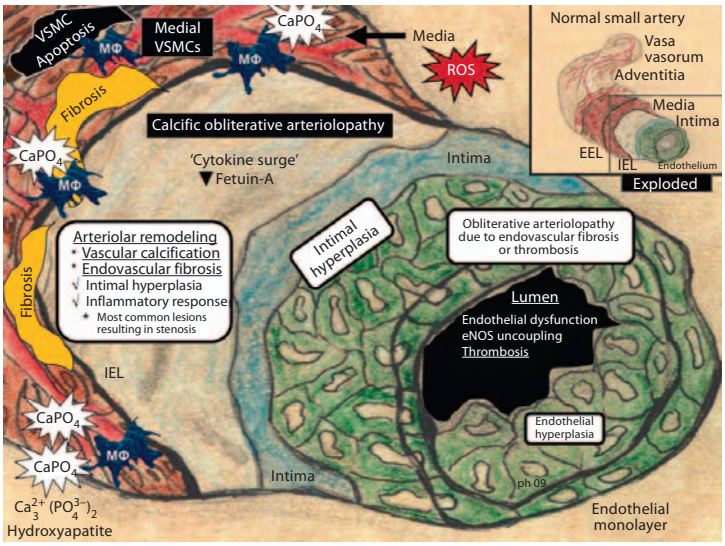

Fig. 3. Role of hyperphosphatemia in promoting calcemic arteriolopathy. Phosphate deposition is associated with the development of CUA/calciphylaxis due to arteriolar calcification, which is known to be associated with hyperphosphatemia and excessive reactive oxygen species (ROS). EEL = External elastic lamina; eNOS = endothelial nitric oxide synthase; IEL = internal elastic lamina; MΦ = macrophage (figure used with permission [74]).

vascular calcification-inhibitory proteins such as MGP (matrix Gla protein) and the systemic globulin: fetuin-A (fig. 3) [74]. Elevation in serum phosphate and the calcium-phosphate product have been closely associated with the degree of CUA [74]. Indeed, the treatment of human VSMCs with a solution containing elevated phosphate induces these cells to differentiate into osteoblast-like cells, as shown by the expression of osteoblast differentiation markers such as osteocalcin [74]. There is also evidence that FGF-23 is protective against the development of CUA, and decreased vascular action of this factor contributes to the development of this devastating disease [74, 77]. Thus decreased FGF-23 signaling, in part related to reduced Klotho activation as well as decreased MGP and fetuin-A, are important contributing factors in the pathogenesis of CUA.

Uremic Cardiomyopathy

Uremic cardiomyopathy is another pathological condition that develops in patients with hyperphosphatemia and CKD (fig. 2) [78]. In this disorder, cardiomyocytes enlarge and there is excessive myocardial fibrosis. Uremic cardiomyopathy is characterized by diastolic dysfunction similar to that seen in cardiomyopathy associated with obesity and diabetes [79, 80]. It has been estimated that almost 75% of patients have left ventricular hypertrophy at the time of initiation of dialysis, and that the presence of this abnormality is a strong independent risk factor for reduced survival in this population [78]. There is emerging evidence that the molecular pathways responsible for uremic cardiac hypertrophy involve various growth factors, including angiotensin II, which activate the mammalian target of rapamycin (mTOR) and downstream ribosomal kinase (S6-K) signaling pathways [78]. Activation of this pathway promotes mRNA translation for cardiomyocytes and collagen/fibrin protein synthesis [68–70]. Indeed, uremic cardiac hypertrophy in experimental animals is reversed with rapamycin treatment [78], thus documenting the importance of this signaling pathway in cardiomyopathy. The importance of the mTOR/S6-K signaling pathways in the pathogenesis of kidney [3, 79] and heart diseases [79, 80] associated with overnutrition and impaired insulin metabolic signaling has previously been reviewed.

Conclusion

An important evolving concept links deranged phosphate metabolism in CKD with the increased CVD morbidity and mortality as well as progression of renal insufficiency [81]. Serum PTH and FGF-23 increase in response to rising serum phosphate as renal capacity for phosphate excretion is lost and their increased levels are accompanied by increased renal osteodystrophy, hyperparathyroidism, calcemic uremic arteriopathy and uremic cardiomyopathy. Furthermore, as renal function is lost, renal production of Klotho diminishes, resulting in diminished FGF-23 ability to promote phosphaturia [82, 83]. The vascular disease and cardiomyopathy associated with hyperphosphatemia and reduced Klotho levels contribute to the development of the cardiorenal metabolic syndrome and increased CVD morbidity and mortality in association with CKD.

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Disclosure Statement

The authors have nothing to disclose.

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