REGULATION OF PHOSPHATE IN HEALTH AND DISEASE*

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ABSTRACT

As is true of many physiologically critical systems, phosphate metabolism is a highly regulated process. The traditional view of hormonal control of the physicochemical relationship between minerals and tissues has given way to an expanding view of elaborate, active processes that bridge multiple organ systems. The impact of early changes in mineral metabolism that accompany loss of renal function in chronic kidney disease (CKD) may be more important to cardiovascular complications of CKD than previously thought. An understanding of these metabolic processes is critical to treating hyperphosphatemia and to preventing the serious consequences of this common complication of CKD.


Mineral metabolism is modulated by complex neuroendocrine interactions involving multiple organ systems. Calcium and phosphorus homeostasis is maintained through a combination of effects on kidney and bone orchestrated by parathyroid hormone (PTH). In the kidney, PTH modulates calcium and phosphorus reabsorption and excretion. In bone, PTH regulates turnover of these minerals. Serum mineral concentrations reflect dietary intake as well as the actions of PTH, vitamin D, and other hormones.

In patients with chronic kidney disease (CKD), the progressive loss of renal function is uniformly accompanied by altered mineral metabolism. PTH levels begin to rise as glomerular filtration rate (GFR) decreases to 60 mL/min/1.73 m². As GFR declines and the intake of dietary phosphorus does not change, the filtered load of phosphorus ultimately also decreases. Increasing secretion of PTH appears to be an adaptive response to the need for increased fractional phosphorous excretion in order to maintain phosphorus balance. Eventually, even a state of hyperparathyroidism and other adaptive mechanisms cannot compensate for loss of kidney function, and serum phosphate levels rise beyond the physiologic range.

Apart from the effects on PTH secretion and serum calcium levels, the resulting state of hyperphosphatemia is an independent risk factor for mortality in patients with stage 5 CKD. With less severe forms of renal dysfunction, incremental increases in serum phosphate levels—even within the generally accepted reference range—are associated with cardiovascular events that are, in turn, a major cause of morbidity and mortality in these patients.

This article will describe the regulation of phosphate homeostasis in individuals with normal renal function and the progressive changes in phosphate
metabolism that occur in CKD. The correlations between disordered mineral metabolism and cardiovascular risk will also be explained.

**Phosphate Metabolism**


Phosphorus is one of most abundant elements in the body, accounting for approximately 1% of total body weight. Eighty-five percent of phosphorus is found in bones and teeth, 14% is intracellular, and the remaining 1% is extracellular. Phosphate is continuously in flux between bone and extracellular fluid. Phosphate is a component of an array of biologically active molecules, such as nucleic acids, signaling proteins, phosphorylated enzymes, and cell membranes. All tissues can absorb and secrete phosphate to meet tissue demand. Therefore, it is not surprising that maintenance of phosphate homeostasis is a complex, highly regulated process (Figure 1).

**Phosphorus Intake**

Dietary phosphorus intake plays an important regulatory role in mineral homeostasis. The recommended daily allowance for phosphorus is 800 mg and is similar to that of calcium. However, the current average daily dietary intake is approaching 1500 mg, in large part because of the use of phosphates as food preservatives. Consequently, the desired balanced ratio of dietary calcium to phosphorus is difficult to achieve.

In individuals with normal dietary phosphorus intake and renal function, serum phosphate levels vary from a peak of approximately 4.6 ± 0.2 mg/dL (1.5 ± 0.1 mmol/L) to a nadir of 3.3 ± 0.3 mg/dL (1.1 ± 0.1 mmol/L), with a fairly predictable circadian rhythm. The generally accepted reference range for adult serum phosphorus levels is 2.5 to 4.6 mg/dL (0.80–1.45 mmol/L). However, the reference range should not necessarily be considered the normal range. Because individuals with CKD of varying degrees may have been included in the reference population, it is possible that the upper limit for the true normal range (i.e., for those without CKD) is below 4.5 mg/dL (<1.45 mmol/L). In addition, the time of measurement is important. In healthy subjects eating 3 meals per day, serum phosphorus levels have been found to decrease in the early morning, reaching a nadir of 3.3 ± 0.3 mg/dL at 11:00 AM, followed by an increase to a plateau at 4:00 PM, and a further increase to a peak of 4.6 ± 0.2 mg/dL between 1:00 AM and 3:00 AM.

**Phosphorus Absorption**

The percentage of dietary phosphorus that is absorbed varies with intake. At high levels of intake (>10 mg/kg/d), approximately 70% of the ingested phosphorus is absorbed, whereas at lower levels of intake, as much as 80% to 90% may be absorbed. Net intestinal phosphorus absorption may be somewhat lower in patients with end-stage renal disease (ESRD). Phosphorus is absorbed throughout the entire small intestine. In the highly acidic environment of the stomach (pH of 1–3.5), phosphorus exists as the

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**Figure 1. Phosphate Homeostasis**

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weak acid H₃PO₄ and the monobasic ion H₂PO₄⁻ (pH = 2.1). As the gut becomes progressively less acidic—duodenum (pH = 2-6.4), jejunum (pH = 6), and ileum (pH = 7)—phosphorus exists in varying proportions as the monobasic ion H₂PO₄⁻ and the dibasic ion HPO₄²⁻ (pH = 6.8).

**Phosphorus Transport**

Intestinal inorganic phosphate (Pi) absorption involves 2 separate processes. The first is a paracellular pathway that is a sodium-independent process and operates by passive diffusion down an electrochemical potential gradient. This pathway is most important when the intraluminal concentration of phosphorus is high, as occurs following a meal. The second is a trans-cellular, sodium-dependent, carrier-mediated pathway that involves the type IIb sodium-dependent phosphate cotransporter (NaPi-IIb) located on enterocytes. This pathway falls under the control of 1,25-dihydroxyvitamin D₃, dietary phosphorus, and other regulatory signals.

**NaPi Cotransporters**

In addition to enterocytes lining the intestine, NaPi cotransporters are found in many epithelial cells throughout the body. Three types of NaPi cotransporters have been described based on structural similarities deduced from their amino acid sequence. They differ by their affinity for phosphate, distribution in the body, and mechanisms that control their action. The type I NaPi cotransporters (NPT1, NPT3, NPT4) are expressed at the plasma or at the microsomal membranes of the cells in the kidney, the intestine, and the liver. Although they display phosphate uptake capacity, they may also transport other anions, and their physiologic role and contribution to renal phosphorus reabsorption remains to be established.

Members of the type III NaPi cotransporter family (PiT1, PiT2) transport phosphate into cells and have high affinity for phosphate. Both transporters are widely expressed in tissues. Functional differences exist between PiT1 and PiT2. These cotransporters appear to be important in controlling intracellular phosphate content and bone mineralization, and they may be involved in the pathologic calcification of soft tissue. Phosphate uptake through PiT1 appears to be essential for smooth muscle cell calcification, phenotypic modulation, and the induction of osteogenic markers in response to elevated phosphorus levels.

The type II NaPi cotransporters (NPT2a, NPT2b, NPT2c) are expressed on different cell types and are differentially regulated. NPT2a cotransporters are the most abundant of the renal NaPi cotransporters. They are expressed on apical domains of renal proximal tubular cells and are responsible for the major portion of renal phosphate reabsorption. The NPT2c cotransporters are similar to NPT2a and colocalize with NPT2a in the brush border membrane of renal proximal tubular cells, and may play an important role in the maintenance of phosphorus homeostasis.

**Phosphorus Excretion**

Renal excretion is dependent on the filtered load of phosphorus and the amount of phosphorus reabsorbed by the renal tubules. The majority of the phosphorus is reabsorbed in the proximal convoluted tubule, with evidence of additional phosphorus reabsorption in the proximal straight tubule and possibly the distal tubule. PTH decreases phosphorus reabsorption at all 3 sites. Ultimately, a steady state is achieved so that the daily excretion usually balances the amount absorbed.

As GFR declines, there is a tendency for serum phosphorus concentration to rise, although serum phosphorus levels are generally maintained at less than 4.6 mg/dL until GFR falls below 25 mL/min/1.73 m². The fact that a persistent increase in serum phosphorus concentration is not observable until late stage 4 or early stage 5 CKD is associated with several interrelated adjustments in PTH secretion and 1,25-dihydroxyvitamin D₃ formation, and in some cases with dietary phosphate intake. Further studies are needed to address the role of phosphatonin.

The majority of patients with ESRD will eventually develop overt hyperphosphatemia (ie, serum phosphorus concentration >4.6 mg/dL). Phosphorus homeostasis is maintained through a combination of effects on kidney and bone orchestrated by PTH. The decrease in the filtered load of phosphorus that accompanies decline in GFR is exquisitely balanced by an increase in the fractional excretion of phosphorus by the kidney. This is due to an increase in PTH secretion and its effect on decreasing proximal tubule phospho-
Parathyroid Hormone

In healthy individuals, when circulating levels of calcium are low, PTH is secreted by the parathyroid gland. It acts on the kidney to increase reabsorption of calcium and to decrease reabsorption of phosphorus. In addition, PTH stimulates renal 1α-hydroxylase, the enzyme that converts vitamin D to its active form, calcitriol. As circulating levels of calcium rise, PTH secretion is inhibited. In this way, PTH contributes to calcium and phosphorus homeostasis. However, a similar compensatory mechanism is activated by loss of renal function. Once renal excretory function declines to a GFR of 60 mL/min/1.73 m² or below, PTH levels begin to rise. The threshold GFR for compensatory PTH increases may vary from less than 70 mL/min/1.73 m² to less than 40 mL/min/1.73 m².

In dogs, increases in PTH concentrations appear to be an adaptive response, allowing increased phosphorous excretion by the remaining nephrons. However, a compensatory rise in PTH results in phosphorus and calcitriol levels returning to the reference range until GFR declines to approximately 25 to 30 mL/min/1.73 m². Eventually, hypertrophy of parathyroid gland may occur, leading to secondary parathyroidism. The altered mineral metabolism that occurs elicits profound changes in bone turnover that begin long before patients reach stage 5 disease.

As CKD progresses, abnormalities in the endocrine function of the kidney appear, including a decline in the level of 1,25-dihydroxyvitamin D₃, which is apparent as early as stage 3. In addition to renal parenchymal injury, elevation of the serum phosphorus concentration directly inhibits 1α-hydroxylase production. The net result is a decrease in intestinal calcium absorption and a further increase in PTH production. Moreover, 25-hydroxyvitamin D deficiency and insufficiency are common in patients with CKD and may influence the coexisting abnormalities in 1,25-dihydroxyvitamin D₃ and PTH (measured as intact PTH) metabolism.

Hyperphosphatemia in Chronic Kidney Disease

In patients with ESRD, elevations in serum phosphorus are associated with increased mortality, even among patients undergoing dialysis 3 times weekly. In patients with CKD but not undergoing dialysis, average serum phosphate levels increase slowly with declining renal function until GFR (estimated from deduced urinary clearance of creatinine) falls below 30 mL/min/1.73 m². At estimated GFR below 30 mL/min/1.73 m², serum phosphate levels increase progressively. Serum phosphate levels above 3.5 mg/dL were independently associated with a significantly increased risk of death.

Risk of hyperphosphatemia was also observed in patients with near-normal kidney function. In a post-hoc analysis of the Cholesterol and Recurrent Events trial, postmyocardial infarction patients with relatively preserved kidney function were studied. A significant and graded association between baseline serum phosphate concentration (ranges of 2.5–4.0 mg/dL) and risk of mortality and cardiovascular events over 5 years were examined. These findings demonstrate that even small increases in serum phosphorus concentrations that fall within or near the normal range in the early stages of kidney disease contribute to cardiovascular risk.

Elevated serum phosphate is also predictive of poor renal outcomes. In the African American Study of Hypertension and Kidney Disease, 1094 black patients with hypertensive nephrosclerosis (GFR, 20–65 mL/min/1.73 m²) were studied. At baseline, mean GFR was 46.4 ± 13.6 mL/min/1.73 m² and serum phosphorus was 3.52 ± 0.56 mg/dL. In this population, the risk of reaching the renal composite outcome of 50% reduction in GFR or a 25-mL/min/1.73 m² decline in GFR, or the occurrence of ESRD, was significantly associated with elevated levels of serum creatinine, urea nitrogen, and phosphorus. The hazard ratio was 1.09 (95% confidence interval, 1.02–1.16) for each 0.3-mg/dL increase in phosphorus.
**Phosphatoninns**

There are several factors in addition to PTH and vitamin D that are known to influence phosphorus balance. The so-called phosphatoninns include fibroblast growth factor (FGF-23), secreted frizzled-related protein-4, and matrix extracellular phosphoglycoprotein. Of these, FGF-23 is the best characterized, originally identified in a patient with tumor-induced osteomalacia and renal phosphorus wasting.35

FGF-23 is emerging as a key regulatory factor in phosphate homeostasis (Figure 2).36 This 251-amino acid circulating protein is synthesized in bone by osteoblasts, suppresses phosphate reabsorption in renal proximal tubular cells,37 and decreases 1α,25-dihydroxyvitamin D3 production in the kidney.36 Reduced serum concentrations of 25-hydroxyvitamin D 1α-hydroxylase are found in transgenic mice with overexpressing FGF-23,38 with the opposite being the case in mice with ablation of the FGF-23 gene.39 In turn, 1α,25-dihydroxyvitamin D3 stimulates FGF-23.36 When FGF-23 is overexpressed, urinary phosphate excretion increases and serum phosphate levels decrease. These effects are accompanied by a decrease in NPT2a expression.11,37

FGF-23 levels increase with dietary phosphate content.40,41 Calcitriol causes suppression of PTH as a result of increases in gastrointestinal calcium absorption and directly suppresses PTH production by the parathyroid glands. FGF-23 is hypothesized to be a counterregulatory phosphaturia factor that prevents hyperphosphatemia in response to calcitriol-mediated increases in gastrointestinal phosphate absorption consequent to the loss of PTH-mediated phosphaturia (Figure 3).42,43

FGF-23 is thought to be a substrate for a membrane-bound metallopeptidase, phosphate-regulating gene with homology to endopeptidases on the X chromosome (PHEX), found in bone and teeth but not kidney. PHEX and klotho protein are newly identified regulators of phosphate metabolism.44

**Klotho Gene**

The klotho gene was first described in 1997 and named after the mythical Greek Fate, who controlled the length of normal life. Klotho is a membrane protein that is abundantly expressed in the kidney. A unique short-lifespan mouse strain with a single gene mutation was developed that caused multiple age-related disorders, including arterial calcification.45

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**Figure 2. Phosphate Homeostasis Regulated by FGF-23**

FGF = fibroblast growth factor; PHEX = phosphate-regulating gene with homology to endopeptidases on the X chromosome; Pi = phosphate.


**Figure 3. Model Depicting the Potential Role of FGF-23 in Mineral Homeostasis**

PTH actions initiate control of phosphate and calcium balance (A). The proposed function of FGF-23 to counterbalance PTH regulation of vitamin D (B).

FGF = fibroblast growth factor; PTH = parathyroid hormone.

Klotho null mutant mice (kl-/-) display abnormal calcium and phosphorus homeostasis. As early as 3 weeks of age, elevated levels of serum calcium, phosphorus, and 1,25-dihydroxyvitamin D3 are observed with ensuing vascular and soft-tissue calcification. Notably, the vascular lesions follow a pattern that resembles Monckeberg’s medial calcification. A reduction in 1,25-dihydroxyvitamin D3 by dietary means results in the alleviation of most phenotypes, including hyperphosphatemia. The klotho gene appears to be negatively controlled by dietary phosphorus. A low-phosphorus diet promotes growth and prolongs life.

**Conclusions**

Phosphorus homeostasis is regulated by a complex combination of dietary, endocrine, and paracrine factors. New regulatory factors are now being investigated that may improve our understanding and lead to specific therapies for the disordered mineral metabolism of CKD. At the present time, the complexity of this critical physiological system makes targeted intervention difficult.

**References**


