

Chapter 2

Disorders of Phosphorous Homeostasis in CKD

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I. Introduction

Inorganic phosphorus is critical for numerous normal physiologic functions including skeletal development, mineral metabolism, cell membrane phospholipid content and function, cell signaling, platelet aggregation, and energy transfer through mitochondrial metabolism. Because of its importance, normal homeostasis maintains serum phosphate concentrations between 2.5 and 4.5 mg/dl (0.81 to 1.45 mmol/L). Levels are highest in infants and decrease throughout growth, reaching adult levels in the late teens. The total adult body store of phosphorus is approximately 700 g, of which 85% is contained in bone in the form of hydroxyapatite $[(Ca)_{10}(PO_4)_6(OH)_2]$. Of the remaining, 14% is intracellular, and only 1% is extracellular. Of the extracellular phosphorus, 70% is organic (phosphate) and contained within phospholipids and 30% is inorganic, 15% is protein bound, and the remaining 85% is either complexed with sodium, magnesium, or calcium or circulates as the free monohydrogen or dihydrogen forms. It is this latter 0.15% of total body phosphorus (15% of extracellular phosphorus) that is freely circulating and measured (Fig. 2-1). At pH 7.4, it is in a ratio of about 4:1 HPO_4^{-2} to H_2PO^{-1} . For this reason, P_i is usually expressed in millimoles rather than milliequivalents per liter. Thus, serum measurements reflect only a minor fraction of total body phosphorus, and therefore do not accurately reflect total body stores in the setting of abnormal homeostasis such as in chronic kidney disease (CKD). The terms phosphorus and phosphate are often used interchangeably, but strictly speaking, the term phosphate means the inorganic freely available form (HPO_4^{-2} to H_2PO^{-1}). However, most laboratories report this measurable, inorganic component of total body phosphorus as “phosphorus.” In the remainder of the chapter we use the abbreviation P_i to represent phosphate and/or phosphorus.

The average Western diet contains approximately 1000 to 1400 mg of P_i per day, while the recommended daily allowance (RDA) is 800 mg/day.

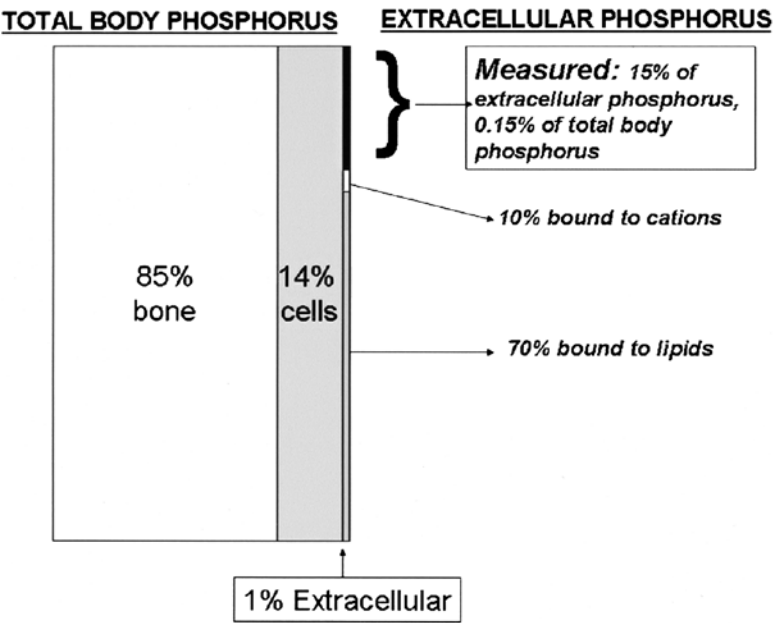


Figure 2-1. Distribution of total body phosphorus.

Table 2-1. Phosphorus Content of Food.

High (> 200 mg P per 100 g)
Milk products
Meats
Fish
Dry fruits
Chocolate
Medium (> 100 but < 200 mg P per 100 g)
Cereals
Legumes
Low (< 100 g P per 100 g)
Vegetables
Fruits

Approximately two thirds of the ingested P_i is excreted in the urine, and the remaining one third in stool. Thus, as detailed later, patients with advanced CKD will retain P_i on a typical American diet. Many prepackaged, fast food, and dark (cola) beverages contain extra P_i as a preservative and it is difficult to accurately predict P_i intake based on the food type alone. In general, foods high in protein and dairy products contain the most P_i , whereas fruits and

vegetables contain the least (Table 2-1). In addition, some protein foods have increased protein: P_i ratio and thus would be ideal for a CKD patient who has increased protein needs, whereas others have a low protein: P_i ratio and are not recommended.¹ This complexity and the abundance of P_i in foods make it difficult for patients with CKD to adhere to a phosphate-restricted diet while simultaneously increasing protein intake.

II. Normal Phosphorus Homeostasis

Three organs are involved in P_i homeostasis (regulation of extracellular and intracellular P_i levels): intestine, kidney, and bone. The major hormones controlling P_i levels are vitamin D and parathyroid hormone (PTH). More recently, there is increasing evidence for an important role of a group of circulating factors called phosphatonins in the regulation of serum P_i .

III. Intestinal Absorption

Between 60% and 70% of dietary P_i is absorbed by the gastrointestinal tract, in all intestinal segments.² P_i absorption is dependent on both passive transport related to the concentration in the intestinal lumen (i.e., increased after a meal) and active transport stimulated by 1,25-(OH)₂D (calcitriol), the active metabolite of vitamin D (see Chapter 5). Passive absorption (dependent on luminal P_i concentration) occurs via the epithelial brush border sodium phosphate cotransporter (NPT2b) utilizing energy from the basolateral sodium–potassium ATPase transporter. The NPT2b is in the terminal web, just below the brush border in “ready to use” vesicles that are then transported to the brush border in response to acute and chronic changes in P_i concentration.³ Medications or foods that bind intestinal P_i (antacids, phosphate binders, calcium) can decrease the net amount of P_i absorbed by decreasing the free phosphate for absorption. Calcitriol can upregulate the sodium–phosphate cotransporter and therefore actively increase P_i absorption.⁴ However, in contrast to calcium, the active vitamin D-mediated absorption is a minor component of total absorption, supported by data that there is near normal intestinal absorption in the absence of vitamin D. However, similar to calcium, the kidneys play a critical role in the maintenance of normal homeostasis.

IV. Renal Handling

Most inorganic P_i is freely filtered by the glomerulus. Approximately 70% to 80% of the filtered load of P_i is reabsorbed in the proximal tubule, which

serves as the primary regulated site of the kidney. The remaining approximately 20% to 30% is reabsorbed in the distal tubule. Factors that increase P_i excretion are primarily an increased plasma P_i concentration and PTH. Conversely, acute or chronic P_i depletion will decrease excretion. Renal P_i excretion is also increased, although to a lesser extent, by volume expansion, metabolic acidosis, glucocorticoids, and calcitonin. Additional factors that may decrease P_i excretion include growth hormone and thyroid hormone. The majority of this regulation occurs in the proximal tubule via the sodium–phosphate cotransporter.³ Similar to the intestine, the sodium–phosphate cotransporter rests in the terminal web, and can be acutely moved to the brush border in the presence of acute or chronic phosphate depletion. Alternatively, after a phosphate load or in the presence of PTH, the exchanger is removed from the brush border and catabolized.⁵ The ability of the kidneys to control P_i becomes impaired because of decreased renal mass at glomerular filtration rates (GFR) of approximately 50 ml/min. However, the subtle elevations in serum P_i (due to decreased kidney function) stimulate PTH, which in turn increases P_i excretion to maintain normal serum P_i levels. This compensatory mechanism is why frank hyperphosphatemia is seen only in patients with very advanced kidney disease.

V. Bone Remodeling

The majority of the total body stores of calcium and P_i are located in bone in the form of hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$]. Trabecular (cancellous) bone is located predominately in the epiphyses of the long bones, which is 15% to 25% calcified, and serves a metabolic function with a relatively short turnover rate. In contrast, cortical (compact) bone is in the shafts of long bones, and is 80% to 90% calcified. This bone serves primarily a protective and mechanical function, and has a turnover rate of months. Bone consists principally (90%) of highly organized crosslinked fibers of type I collagen; the remainder consists of proteoglycans and “noncollagen” proteins such as osteopontin, osteocalcin, osteonectin, and alkaline phosphatase. Osteoclasts are the bone-resorbing cells and derive from circulating hematopoietic cells, and osteoblasts are the bone-forming cells that derive from the marrow.

Bone is a dynamic organ and remodels or turns over in response to hormones, cytokines, and changes in mechanical forces. The control of bone remodeling is highly complex, but appears to occur in very distinct phases: (1) osteoclast resorption, (2) reversal, (3) preosteoblast migration and differentiation, (4) osteoblast matrix (osteoid or unmineralized bone) formation, (5) mineralization, and (6) quiescent stage. At any one time, less than 15% to 20% of the bone surface is undergoing remodeling, and this process in a single bone

remodeling unit can take 3 to 6 months.⁶ How a certain piece of bone is committed to undergo a remodeling cycle, and how the osteoclasts and osteoblasts signal each other, is not completely clear but is likely mediated through the interaction of osteoprotegerin (OPG) and receptor activator of nuclear-factor κ B (RANK). This important control system is regulated by nearly every cytokine and hormone thought important in bone remodeling, including PTH, 1,25-(OH)₂D, estrogen, glucocorticoids, interleukins, prostaglandins, and members of the transforming growth factor-beta (TGF- β) superfamily of cytokines.⁷⁻⁹ Thus, all of these factors, by inducing bone remodeling, can affect P_i homeostasis. However, of these, PTH is most clinically relevant, especially in CKD.

VI. Phosphatonins

This is a group of proteins that have been identified in patients with renal phosphate wasting. Fibroblast growth factor 23 (FGF-23) is produced by tumors from patients with tumor-induced osteomalacia, and corresponding genetic defects were identified in autosomal dominant hypophosphatemic rickets (ADHR). FGF-23 is made in bone cells, and directly affects the conversion of

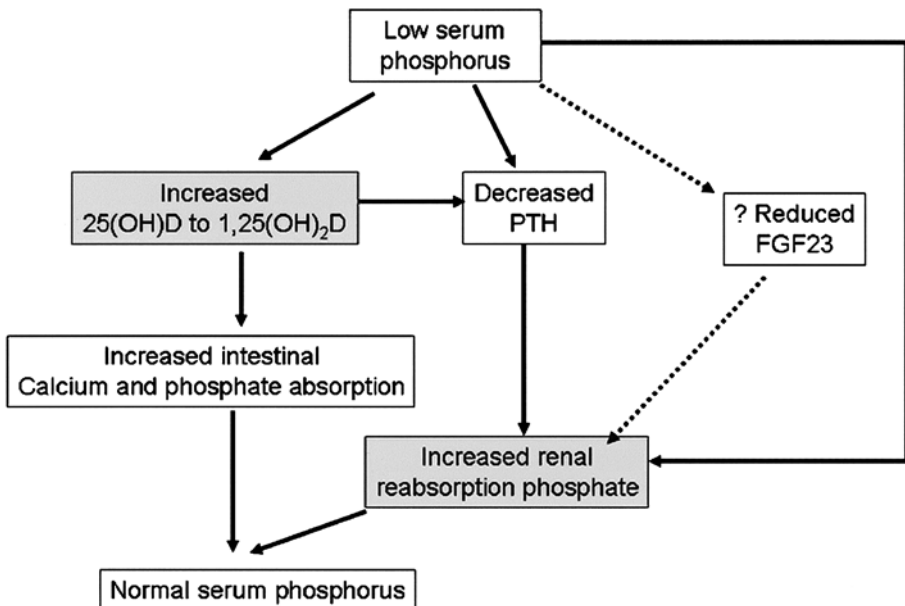


Figure 2-2. Normal homeostatic response to hypophosphatemia. The solid lines represent known pathways. The dotted line represents an important pathway in disease, but of unclear importance in normal physiology.

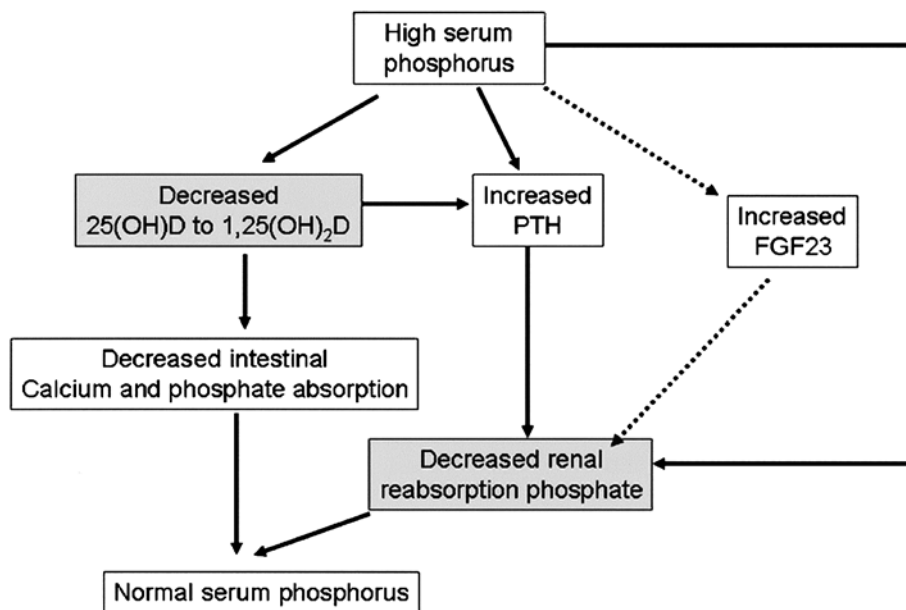


Figure 2-3. Normal homeostatic response to hyperphosphatemia. The solid lines represent known pathways. The dotted line represents an important pathway in disease, but of unclear importance in normal physiology.

25- to 1,25-(OH)₂D by inhibition of the 1 α -hydroxylase enzyme in the renal tubules. Levels of FGF-23 are very elevated in patients with CKD, presumably because of net phosphate retention.^{10,11} Another factor, secreted frizzled-related protein 4 (FRP-4), also can induce renal phosphate wasting.^{10,11} Thus, these factors are important in non-PTH-mediated urinary phosphate handling, although their precise role in normal homeostasis is not yet clear.

In summary, homeostasis, or control of serum homeostasis is controlled primarily by the serum level of P_i/dietary intake, PTH, and possibly phosphatonins. This regulation occurs primarily at the level of the kidney, although the intestine and bone are also involved (Figs. 2-2 and 2-3).

VII. Disorders of P_i in Non-CKD Patients

A. Hypophosphatemia

Hypophosphatemia can occur when there is decreased P_i intake (decreased intestinal absorption or increased gastrointestinal losses), or excess renal wasting from renal tubular defects or hyperparathyroidism. In addition, low serum P_i levels may also occur in the setting of extracellular to intracellular shifts. In the case of cellular shifts, total body P_i may not be depleted. By convention,

Table 2-2. Cause of Hypophosphatemia.

Decreased intestinal absorption: Antacid abuse, malabsorption, chronic diarrhea, vitamin D deficiency, starvation, anorexia, alcoholism

Increased urinary losses: Primary hyperparathyroidism, postrenal transplant, extracellular fluid volume expansion, glucosuria (after treating DKA), post obstructive or resolving ATN diuresis, acetazolamide, Fanconi's syndrome, X-linked and vitamin D-dependent rickets, oncogenic osteomalacia

Redistribution: Respiratory alkalosis, alcohol withdrawal, severe burns, TPN, recovery from malnutrition when inadequate phosph is provided (post-feeding syndrome), leukemic blast crisis

hypophosphatemia is often graded as mild (< 3.5 mg/dl), moderate (< 2.5 mg/dl), or severe (< 1.0 mg/dl). Moderate and severe hypophosphatemia will generally occur only when there are multiple problems. The causes of hypophosphatemia are listed in Table 2-2.

Hypophosphatemia is a common finding; it is seen in 3% of all hospitalized patients, 10% of hospitalized alcoholic patients, and more than 50% of ventilated ICU patients.¹² Symptoms of hypophosphatemia are usually seen only in patients with moderate or severe hypophosphatemia and include muscle weakness (and difficulty weaning from a ventilator), hemolysis, impaired platelet and white blood cell function, rhabdomyolysis, and in rare cases neurologic disorders. Hypophosphatemia is probably overtreated in the ICU, where the “difficult to wean” patient is given P_i , when the low levels are actually caused by cellular shifts from respiratory alkalosis due to difficulty weaning. A careful review of the trend in serum P_i with arterial blood pH can help discern which patients need to be treated.

The treatment of hypophosphatemia in the non-CKD patient is based on the underlying cause. The differential diagnosis and treatment approach will be based on the cause and site of P_i loss. Usually the cause is clinically apparent, but if not, the simplest test is to measure a 24-hour urine P_i . In the setting of hypophosphatemia, the kidney should be reabsorbing all P_i . If the urinary excretion is < 100 mg/24 hours, then the kidney has an appropriate response, and there are gastrointestinal losses or extracellular to intracellular shifts. P_i can be replaced by increased intake, but is usually necessary only in patients with moderate to severe hypophosphatemia. Oral intake is preferable, as the acute intravenous administration of phosphate can complex calcium and lead to extraskeletal calcification. Oral P_i supplementation can be given with skim milk (1000 mg/quart), whole milk (850 mg/quart), Neutraphosph K capsules[®] (250 mg/capsule; maximum dose is 3 tablets every 6 hours), or Neutraphosph[®] solution (128 mg/ml solution). Milk is much better tolerated (and less expensive!). Intravenously, P_i can be replaced as K phosphate (3

mmol/ml of phosphate, 4.4 mEq/ml of K) or Na phosphate (3 mmol/ml of phosphate, 4.0 mEq/ml of Na).

B. Hyperphosphatemia

Because elevated serum P_i levels can stimulate rapid renal P_i excretion, persistent hyperphosphatemia for more than a few hours occurs almost exclusively in the setting of acute or chronic kidney disease. It is important to emphasize that serum creatinine is not a sufficient indicator of abnormal kidney function and formulas for predicting GFR should be used. These include either the Cockcroft–Gault formula that utilizes creatinine, age, gender, and weight,¹³ or the modified diet in renal disease (MDRD)¹⁴ that utilizes creatinine, age, gender, and race (black or non-black). The latter can be downloaded from the National Kidney Disease Education Program Web Page into a PDA.

The causes of hyperphosphatemia are listed in Table 2-3. As indicated previously, hyperphosphatemia can occur from increased intestinal absorption or rapid intracellular to extracellular shifts. However, persistent hyperphosphatemia requires kidney dysfunction as any increase in serum P_i will quickly lead to increased renal excretion and a compensatory rise in serum PTH, with normalization of serum P_i . Demonstration of this rapid physiologic response is shown in Fig. 2-4. The graphs represent data from patients with normal kidney function who underwent bowel preparation with oral sodium phosphate solution for a colonoscopy. As shown in Fig. 2-4, after administration of 45 ml of oral sodium phosphate cleansing preparation (arrows), there is an acute rise in serum P_i (top panel), and an almost immediate increase in urine P_i excretion (bottom panel). PTH also increases modestly. After a second dose the serum and urinary P_i levels again increase.¹⁵ This study illustrates the importance of the kidneys in the maintenance of serum P_i levels. It also illustrates that the administration of P_i by oral or intravenous routes can increase the serum level acutely, which can lead to precipitation of calcium and P_i in some situations. Thus P_i repletion should be judiciously used in the treatment of hypophosphatemia.

Table 2-3. Causes of Hyperphosphatemia.

Increased intake: Phosphate-containing solutions (oral or enema sodium phosphate, intravenous phosphate), vitamin D overdose

Decreased renal excretion: Kidney disease (acute or chronic), thyrotoxicosis, acromegaly

Intracellular to extracellular shift: Tumor lysis syndrome, rhabdomyolysis, hemolysis, hyperthermia, profound catabolic stress, acute leukemia

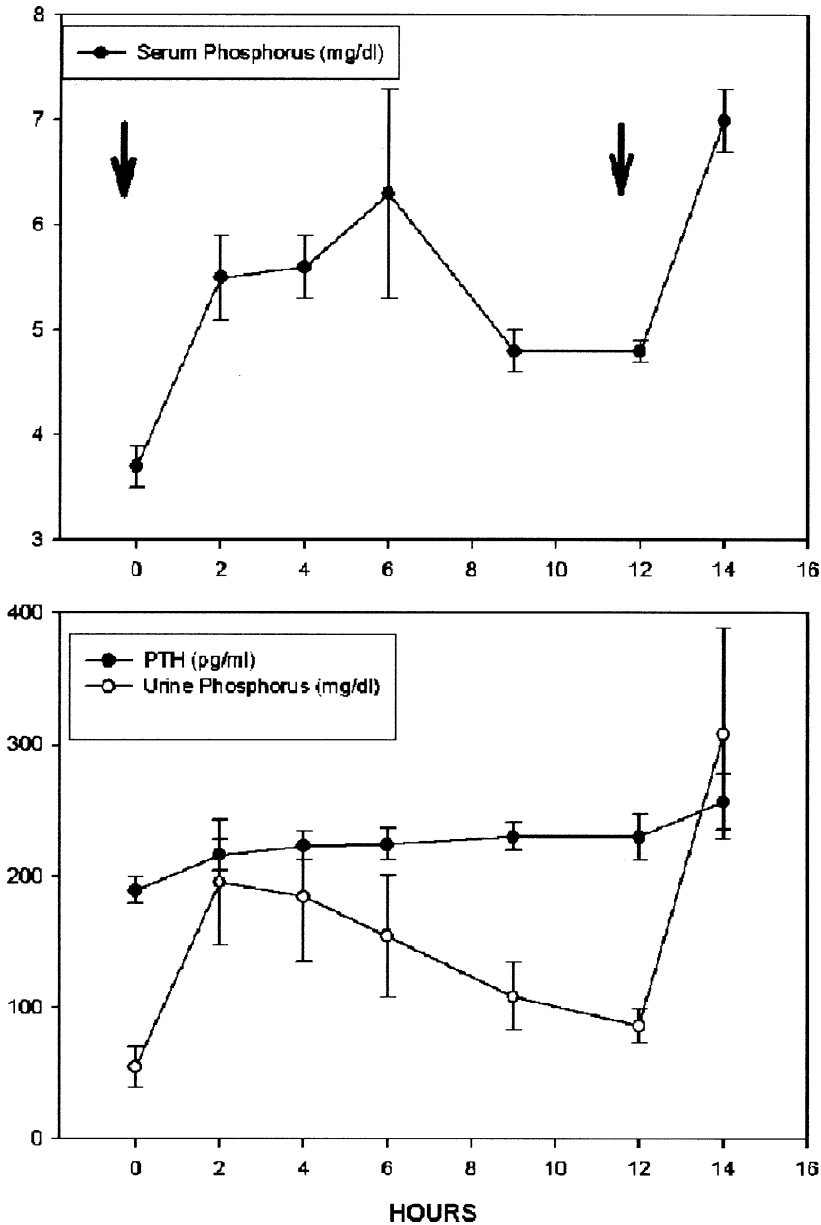


Figure 2-4. Adaptive response to phosphorus intake. Rapid response to phosphate load in the form of sodium phosphate bowel enema administered 12 hours apart (arrows, upper panel). The serum P_i increases (upper panel), and there is a very rapid increase in urinary P_i excretion (lower panel). In addition, there is a later, more modest increase in parathyroid hormone (PTH; lower panel). Thus, changes in serum P_i induce a rapid change in P_i excretion. (Adapted from ref. 15.)

Acute hyperphosphatemia generally does not cause symptoms unless there is precipitation of calcium \times P_i , although chronic hyperphosphatemia seen in CKD is associated with adverse sequelae (see later). Treatment of acute hyperphosphatemia includes volume expansion, dialysis, and phosphate binders, although in the setting of normal, or even mild to moderate kidney disease it is usually self-resolving owing to the continued ability of the kidney to excrete a P_i load.

VIII. Disorders of P_i In CKD Patients

As should be apparent from the preceding discussion, hyperphosphatemia is a common problem in patients with CKD. Levels of P_i are above the normal range in most subjects once the GFR is less than 15 to 30 ml/min.¹⁶ The reason that serum levels are often maintained within the normal range at abnormal GFR is because of a compensatory secondary hyperparathyroidism, which then increases the urinary P_i excretion. This will lead to normal serum levels until the maximum excretion per nephron is reached AND there is a decrease in the number of functioning nephrons. This rise in serum PTH at the expense of maintaining normal serum P_i is believed to be a major mechanism by which secondary hyperparathyroidism develops in patients with CKD (Fig. 2-5)¹⁷ and is often referred to as the “trade-off hypothesis.”¹⁸ Support for this hypothesis is generated by animal studies in which P_i restriction can slow or halt the progression of secondary hyperparathyroidism in CKD.¹⁹ In addition, despite the maintenance of serum P_i in the normal range in patients with CKD stage 3 (GFR 60–30 ml/min), there is a gradual increase in the serum levels,^{20,21} indicating a new “steady state” of slightly higher serum P_i and increased PTH. For example, in a recent national cross-sectional study, the mean serum P_i level

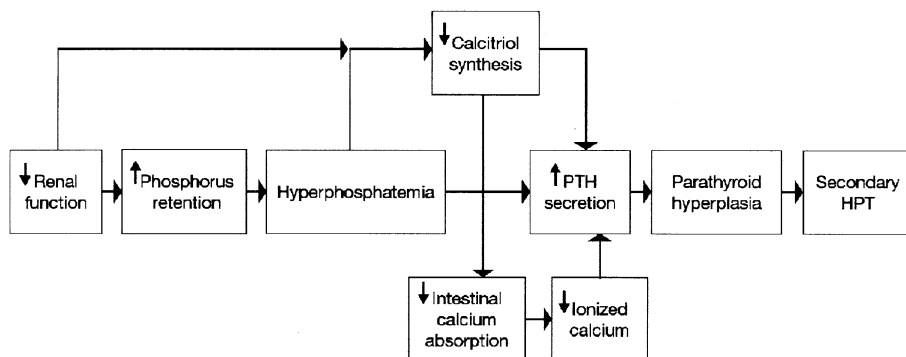


Figure 2-5. The pathogenesis of secondary hyperparathyroidism. (Reprinted from ref. 17 with permission.)

in patients with CKD stage 3 was 3.5 ± 0.5 mg/dl ($n = 65$); in stage 4, was 4.1 ± 1.1 mg/dl ($n = 113$); and in stage 5 not on dialysis 4.4 ± 1.1 ($n = 22$).²¹

P_i has a direct effect on the synthesis of PTH. In addition, P_i retention will inhibit the conversion of 25-(OH) vitamin D to 1,25-(OH)₂D by inhibiting the 1 α -hydroxylase enzyme in the kidney, and will lower the ionized calcium by complexing with free calcium. Together these factors contribute to the pathogenesis of secondary hyperparathyroidism in CKD (Fig. 2-5). The therapeutic approach to treat secondary hyperparathyroidism includes control of P_i load through the use of dietary restriction, phosphate binders, administration of vitamin D, and normalizing serum calcium levels. These options are further discussed in Chapter 3.

IX. Dialytic Removal of Phosphate

Unfortunately, standard dialysis is ineffective in clearing P_i , owing to only a small percentage of total body P_i present in the extracellular space. The extracellular serum levels decrease during a single hemodialysis treatment, but immediately after a hemodialysis treatment there is a rapid equilibration of intracellular P_i to the extracellular space resulting in a “rebound” of the serum levels to near predialysis values within 2 to 4 hours after the treatment.²² Increasing the blood flow or using larger dialyzers has little effect on overall clearance of P_i during hemodialysis.²³ Similarly, peritoneal dialysis can remove some P_i , but not enough to keep up with normal daily intake.²⁴ As a result, more than 90% of patients on standard thrice weekly hemodialysis or peritoneal dialysis require phosphate binders. Unfortunately, patients have a difficult time remaining compliant with phosphate binders owing to the large number of pills required and the frequency of administration (with each meal).²⁵ However, reducing the dietary intake of P_i from 1500 mg to 900 mg per day can reduce the number of binders needed by nearly one half. Thus, a combination of dietary restriction and phosphate binders are needed with standard dialysis regimens.

The overall clearance of P_i is increased with more frequent dialysis or longer sessions. Continuous forms of dialysis such as slow nocturnal hemodialysis, in which patients are dialyzed over an 8- to 10-hour period each night is highly effective in removing P_i such that patients no longer require phosphate binders and some even require P_i supplementation.²⁶ Similarly, patients undergoing short daily dialysis also have significant reductions in phosphate binder requirements.²⁷ Further supporting that increased frequency of dialysis is important in P_i removal are data showing that serum P_i levels are highest after the longest interdialysis interval (i.e., Mondays for patients dialyzed on Monday, Wednesday, and Friday).²⁸ Given the significant morbidity and

mortality associated with hyperphosphatemia, these new dialytic therapies may improve P_i control in the future if they become more utilized.

X. Consequences of Hyperphosphatemia

Cross-sectional studies have demonstrated that hyperphosphatemia is associated with all cause and cardiovascular mortality in one study of patients with CKD stages 3 and 4 (GFR 15 to 60 ml/min),²⁹ and in several studies in patients on hemodialysis in the United States^{30–32} and throughout the world^{33,34} (Fig. 2-6). The level of P_i at which there is an increased mortality depends on the study design and the reference range set. The first study used a “normal” range of 5 to 7 mg/dl and found levels greater than those that were associated with increased mortality when adjusted for multiple confounding factors.³⁰ Subsequent studies have used even lower levels as the reference

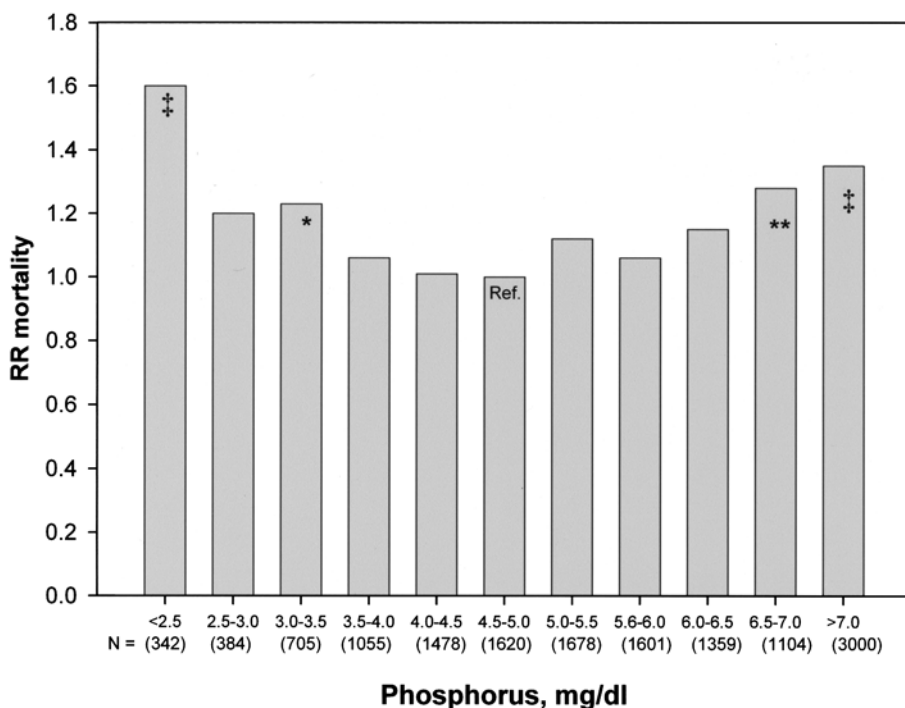


Figure 2-6. Association between all-cause mortality and serum phosphorus concentration, stratified by country and adjusted for serum concentrations of calcium and PTH, dialysate calcium concentration, age, gender, race, duration of ESRD, hemoglobin, albumin, Kt/V, and 14 summary comorbid conditions. * $p < 0.05$; ** $p < 0.01$; † $p < 0.001$; ‡ $p < 0.0001$. (Reprinted with permission from ref. 34.)

range (5.0 mg/dl) and have found levels above that increase the risk of all cause and cardiovascular mortality.³¹ A study by Block et al.³¹ found a 4% increase in mortality per 1 mg/dl (0.32 mmol/L). Another study in Canada, after adjustment for demographic variables, dialysis type and adequacy, hemoglobin, and albumin, found that serum P_i independently predicted mortality with a relative risk of 1.56 per 1 mmol/L.³⁵ Thus, the target P_i level in CKD patients should be less than 5.0 mg/dl, and preferably in the normal range for the general population. However, very low levels of P_i (< 2.5 mg/dl) are associated with osteomalacia and bone disease, and can even induce rhabdomyolysis and therefore should be avoided. However, whether low levels of P_i are associated with increased mortality or are only a marker for malnutrition is controversial.^{31,34} Although these data are compelling, it is important to emphasize that the cross-sectional nature of these studies cannot confer a true cause-and-effect relationship. There are no prospective trials demonstrating that reduction in serum P_i is associated with increased survival. However, observational data confirm that P_i is a modifiable risk factor, control of which predicts long-term survival.³⁶

What are the potential mechanisms by which hyperphosphatemia can cause cardiovascular disease and death? P_i is an important component of cell membranes, and its intracellular:extracellular ratio is tightly controlled. Hyperphosphatemia may hasten the decline in kidney disease based on animal models,³⁷ presumably owing to deposition in the renal tubules or calcification of the arteries causing glomerular ischemia. High levels of P_i , but in the range observed in many dialysis patients, can induce vascular smooth muscle cells to transform, or dedifferentiate to osteoblast (bone-like) cells in culture.³⁸ These differentiated cells express the factor *Cbfa1* (core binding factor alpha 1), an important transcription factor that directs a pluripotent mesenchymal stem cell to become an osteoblast. Once transformed, these cells can lay down a matrix of collagen and noncollagenous bone proteins that can become calcified.³⁹ High levels of both calcium and P_i can induce vascular smooth muscle cells to mineralize in vitro, and the effects of both are additive.^{40,41} This transformation is further accelerated by other uremic toxins.⁴² There are additional data that in humans with CKD, hyperphosphatemia is associated with vascular calcification, and vascular calcification is associated with increased cardiovascular and all cause mortality.^{39,43} The risk of vascular calcification increases with advancing age, duration of dialysis, and in patients with diabetes mellitus,³⁹ all risk factors for poor survival. Thus, there is biologic plausibility based on in vitro data and some human studies that hyperphosphatemia may lead to increased cardiovascular mortality by inducing vascular calcification.

In addition to the effects on vascular calcification, hyperphosphatemia is a major factor in the pathogenesis of secondary hyperparathyroidism. Elevated levels of PTH are also associated with increased all cause mortality and

cardiovascular mortality,^{31,33,34} as well as increased hospitalizations,³¹ hip fractures,⁴⁴ and cardiac dysfunction.⁴⁵ PTH directly affects the intracellular calcium concentration of nearly all cells, and can thereby adversely affect many cellular functions.⁴⁶

XI. Conclusions

P_i is a key ion in the body, with important diverse functions. The maintenance of serum P_i levels is dependent on normal kidney function. As a result, patients with kidney disease are often hyperphosphatemic. Elevations in serum P_i are associated with increased morbidity and mortality in patients with CKD, may hasten loss of residual renal function, and can cause secondary hyperparathyroidism. Unfortunately, current removal of P_i with thrice weekly hemodialysis or daily peritoneal dialysis is not adequate for normal dietary intake. As a result, phosphate binders are a mainstay of therapy in patients with CKD.

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