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Hyperphosphatemia of chronic kidney disease

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Observational studies have determined hyperphosphatemia to be a cardiovascular risk factor in chronic kidney disease. Mechanistic studies have elucidated that hyperphosphatemia is a direct stimulus to vascular calcification, which is one cause of morbid cardiovascular events contributing to the excess mortality of chronic kidney disease. This review describes the pathobiology of hyperphosphatemia that develops as a consequence of positive phosphate balance in chronic kidney disease and the mechanisms by which hyperphosphatemia acts on neointimal vascular cells that are stimulated to mineralize in chronic kidney disease. The characterization of hyperphosphatemia of chronic kidney disease as a distinct syndrome in clinical medicine with unique disordered skeletal remodeling, heterotopic mineralization and cardiovascular morbidity is presented.

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Hyperphosphatemia is associated with significant pathophysiology in chronic kidney disease (CKD). This pathophysiology contributes to the high rates of mortality observed in CKD.[1] Approximately 11–15% of Americans have CKD,[2–4] and their risk of death due to a cardiovascular event-related cause is higher than their risk of surviving and needing renal replacement therapy for end-stage kidney disease (ESKD).[1,2,4] The mortality rates of patients surviving CKD and receiving hemodialysis are extremely high such that a 30-year-old patient with ESKD has a life expectancy similar to that of a 90 year old with normal renal function.[2] The mechanisms of this excess risk of cardiovascular disease are not completely understood. The well-characterized risks of cardiovascular disease in the general population do not explain the increased risk in CKD.[1,3] Observational studies suggest that the well-known propensity of ESKD patients to develop heterotopic mineralization of soft tissues, including the vasculature, is an important component of the cardiovascular risks of ESKD.[5,6] Furthermore, several observational studies demonstrate that hyperphosphatemia is an independent cardiovascular risk factor in CKD.[7–9] Hyperphosphatemia has been linked to vascular calcification.[5,10,11]

PATHOGENESIS

To consider the pathogenesis of hyperphosphatemia in CKD, it is useful to review the mechanisms of phosphate homeostasis (Figure 1). We ingest approximately 1000–1200 mg of phosphorus in the average American diet of 2007. Of this, a net weight of about 800 mg is absorbed into the exchangeable phosphorus pool. This pool consists of intracellular phosphorus (70%), the skeletal mineralization front (29%), and the serum phosphorus ($<1\%$). Exit from the exchangeable pool occurs through skeletal deposition, renal excretion, and intestinal secretion (Figure 1). Exit from the exchangeable pool into the skeleton is matched by entry from the skeleton into the pool in adulthood, and therefore, we do not normally think of the skeleton as a key contributor to the level of phosphorus concentration in the pool, but in CKD, as will be shown in the sections below, it is very important. Regulation of phosphorus excretion by the kidney is the key mechanism of maintaining phosphate balance in normal day-to-day life. Kidney injury impairs the ability of mammals to maintain phosphorus balance, and in human CKD,

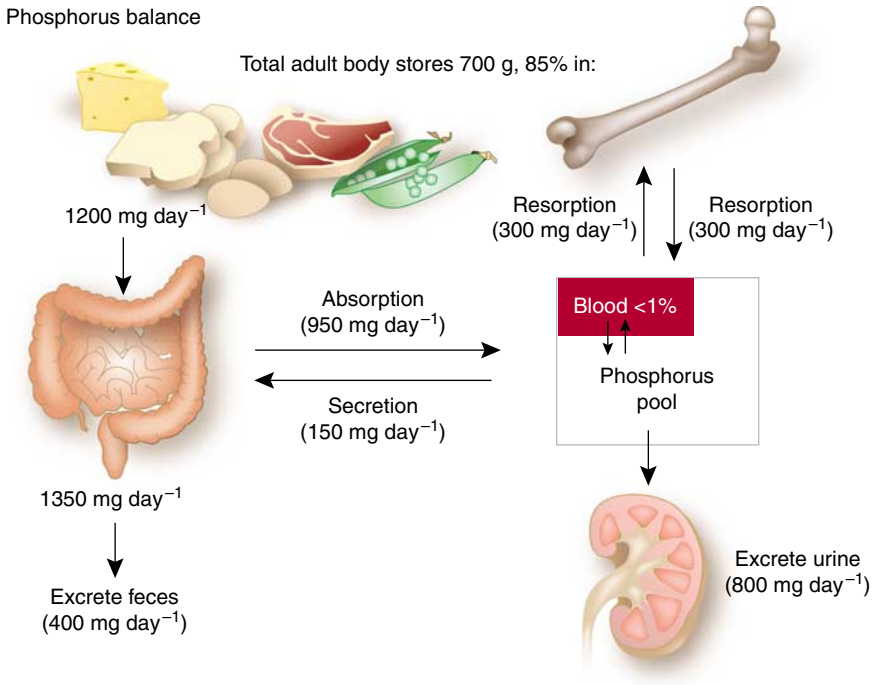

Figure 1 | Phosphorus balance in normal physiology. The kidney is the main regulator of human phosphate homeostasis. In adulthood, exit from the exchangeable phosphorus pool into the skeleton (bone formation) is roughly equal to entry into the exchangeable pool due to bone resorption. The skeleton is a storage depot for Pi and contains 85% of the total body phosphorus.

phosphorus homeostasis is lost and positive phosphate balance occurs in the later stages (4 and 5) of kidney diseases.[12,13] Loss of phosphorus homeostasis due to excretion failure in CKD results in hyperphosphatemia[14] due to positive balance increasing the concentration in the exchangeable phosphorus pool, often when the pool size is reduced as in the adynamic bone disorder (ABD) (Figure 2). Surprisingly, and not generally adequately considered, the skeleton contributes to hyperphosphatemia in CKD and ESKD through the effects of disordered bone remodeling. There are multiple skeletal remodeling disorders in CKD that have been discussed in the sections below, but all of them are associated with excess bone resorption compared with bone formation. Thereby, they contribute to hyperphosphatemia and effectively block the skeleton from exerting its normal reservoir function when positive phosphate balance occurs.

The normal function of the skeleton as a reservoir when phosphate balance is positive is seen in several syndromes of hyperphosphatemia in mammalian pathophysiology (Table 1). All of these, except immobilization and CKD, are associated with increased skeletal mass and mineralization due to phosphorus deposition into the skeletal storage reservoir (see section 'Other Hyperphosphatemic Syndromes'). In CKD, there is a complex set of losses and adaptations in skeletal function that produce bone disorders that complicate the state (see section 'Renal Osteodystrophy'). Recent discoveries characterize all forms of skeletal function disorder in CKD as having excess bone resorption rates compared with bone formation rates (see section 'Osteoporosis in CKD'). Therefore, the skeleton is contributing to hyperphosphatemia in CKD, and the reservoir function of the skeleton that is supposed to act in the presence of positive phosphorus balance is blocked. The outcome of this change in physiology to a new pathophysiology requires that a new phosphate reservoir for the positive balance be established. This new reservoir is soft tissue organs, including the vasculature (Figure 2). The problem with establishing the new reservoirs of phosphate storage is that they produce disease.

Regulation of phosphate balance during CKD before loss of balance occurs is complex. Loss of calcitriol production capacity is an important factor leading to a decrease in Ca absorption, hypocalcemia, and stimulation of parathyroid hormone (PTH) secretion (Figure 3). The increase in PTH levels reduces the fraction of the filtered phosphate load and maintains phosphate excretion at normal levels despite the reduction in the filtered load of phosphorus due to the decrease in glomerular filtration. The decrease in calcitriol production also represents a decrease in the signal to the osteocytes and osteoblasts for the production of fibroblast growth factor 23 (FGF23).[15] However, the tendency for decreased production is overcome by the fact that FGF23 is normally catabolized by glomerular filtration and proximal tubular degradation. Thus, the protein levels increase in CKD as the glomerular filtration rate decreases.[16,17] This is a second potent stimulus to phosphorus excretion as kidney function is diminished. The relative contributions PTH and FGF23 make to phosphate homeostasis during CKD have not been determined, but in the absence of either, homeostasis is lost. A third stimulus for increased phosphate excretion is

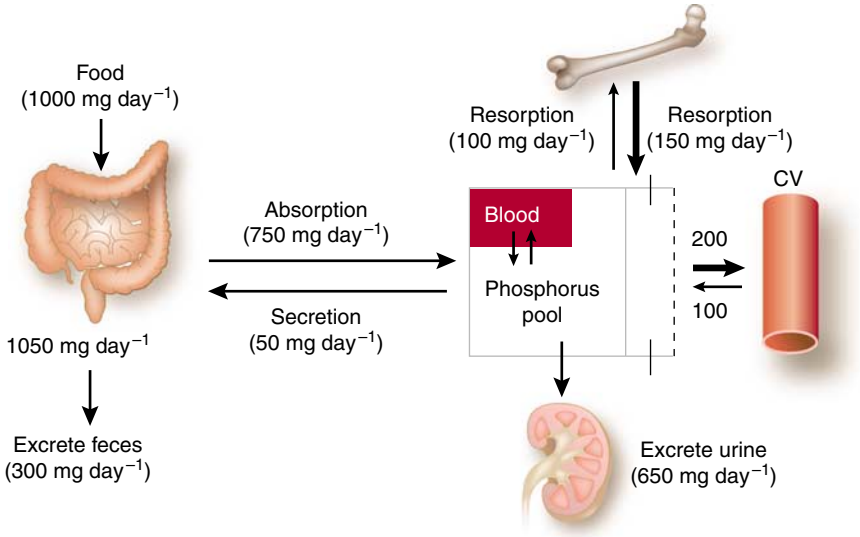

Figure 2 | Phosphorus homeostasis is lost in CKD due to failure of excretion. Despite reductions in the fraction of filtered phosphorus that is reabsorbed, eventually the filtered load becomes insufficient to maintain homeostasis and positive phosphorus balance ensues. Kidney disease decreases the exchangeable phosphorus pool size by inhibiting bone formation. The skeletal mineralization fronts at the sites of new bone formation are significant components of the exchangeable phosphorus pool. Positive phosphate balance is associated with establishment of heterotopic mineralization sites in soft-tissue organs and the vasculature. Exit from the exchangeable phosphorus pool into the vasculature is portrayed as a bidirectional process because we have been able to demonstrate that stopping the exit into the vasculature results in diminishment of established vascular calcification levels.

Table 1 | Hyperphosphatemic syndromes

Increased intake
Transcellular shifts from intracellular to extracellular spaces
Excess bone resorption
Decreased renal excretion
Idiopathic hyperparathyroidism
Pseudohypoparathyroidism
FGF23 deficiency
Tumoral calcinosis
Chronic kidney disease
Acromegaly
Artifactual

FGF, fibroblast growth factor.

phosphate itself, which also potently inhibits the activity of the proximal tubular sodium-dependent Pi transport proteins (Na/Pi co-transporters, NaPi2a, and NaPi2c[18,19]).

The sodium-dependent phosphate transport protein, NaPi2a (approximately 70% of proximal tubular phosphate transport), is regulated mainly by endocytic vesicle cycling in an out of the apical membrane of the epithelial cell.[19,20,21] It is directly regulated by Pi concentrations.[18,20,21] Low Pi increases decreases vesicular retrieval from the plasma membrane, whereas high Pi concentrations stimulate the same.[20] A late effect of Pi concentration is a slight change in gene transcription of NaPi2a with greater effects on protein levels, and stimulation of transcription of NaPi2a-associated proteins (such as diphor-1) by low and inhibition by high Pi.[20,22] Similar experiments have not been performed for the minor, but very important NaPi2c of the proximal tubule. NaPi2b of the duodenal enterocyte is a transcriptional target of the vitamin D receptor and dietary phosphorus,[23] but calcitriol deficiency or hyperphosphatemia in CKD does not result in decreased intestinal phosphate absorption, because the decrease in active duodenal transport is compensated by passive transport through enterocyte paracellular pathways in the rest of the intestine.

One of the new reservoirs for phosphate deposition established when excretion is no longer sufficient to maintain balance, the vasculature (Figure 2), is especially disease causing. Vascular calcification in CKD is not well tolerated, as it produces blood vessel stiffness (Figure 4). There are two forms of vascular calcification prominent in CKD, calcification of atherosclerotic neointimal plaques and arterial medial calcification. CKD markedly stimulates both forms. The atherosclerotic calcification is especially appreciated in the coronary arteries, as it is measured by the increasingly popular imaging techniques for determining coronary artery calcification.[24,25] However, arterial medial calcification is as clinically important, as it is the likely the most important factor in vascular stiffness and increased pulse pressure in CKD.

To study the mechanisms of CKD-stimulated vascular calcification, we developed a translational animal model. We started with a model of atherosclerosis that develops cardiac valvular and atherosclerotic neointimal plaque calcification, the low-density lipoprotein receptor-deficient mouse (LDLR−/−) fed a high-fat diet. To the model we added ablation-induced kidney failure and demonstrated marked stimulation of aortic atherosclerotic calcification.[26] We discovered that bone morphogenetic protein-7 (BMP-7) prevented development of CKD-stimulated vascular calcification.[26] Furthermore, the high-fat-fed CKD mice exhibited

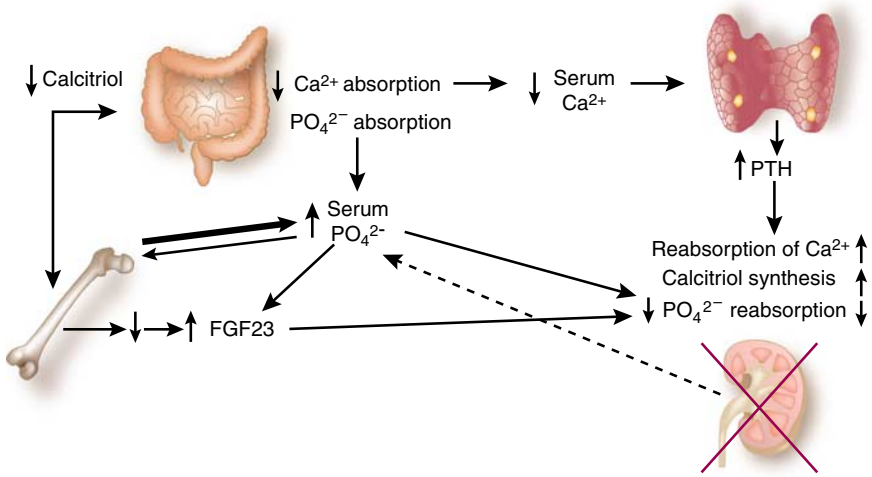

Figure 3 | Regulation of phosphorus balance in CKD. Regulation of phosphorus homeostasis is complex. In CKD, a decrease in calcitriol production leads to a decrease in calcium absorption, hypocalcemia, and hyperparathyroidism. Hyperparathyroidism is one factor contributing to the decrease in the fraction of filtered phosphorus reabsorbed (decrease in the tubular reabsorption of phosphorus (TRP)). Additionally, high levels of FGF23 and hyperphosphatemia itself contribute to reducing the TRP. However, when kidney failure becomes too severe, hyperphosphatemia ensues.

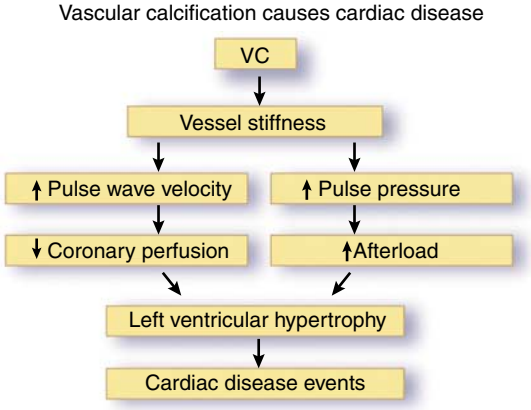

Figure 4 | Vascular calcification causes cardiac morbidity and mortality in CKD. Vascular calcification increases arterial stiffness, leading to an increase in pulse wave velocity and pulse pressure both of which contribute to development of cardiac ischemia, and left ventricular hypertrophy and cardiac failure.

hyperphosphatemia that was corrected by BMP-7.[27] While investigating the mechanism of hyperphosphatemia correction by BMP-7, we found that bone formation was stimulated correcting the ABD that complicates the kidney failure in these mice.[27] Renal phosphate excretion was not increased, and we questioned how much of the effect of BMP-7 on vascular calcification was due to bone formation-induced correction of hyperphosphatemia. To examine this, we added phosphate binders to the high-fat diet in an attempt to isolate hyperphosphatemia correction as a single entity separate from the other actions of BMP-7. To our surprise, phosphate binders were very effective in preventing vascular calcification. We first used $CaCO_3$,[27] but subsequently have studied sevelamer carbonate (Figure 5)[28] and $LaCO_3$ with similar results.

The LDLR−/−, high-fat-fed mouse is characterized by obesity, hypertension, and insulin resistance that progresses to diabetes and severe hypercholesterolemia. Thus, the mouse model is relevant to the human metabolic syndrome, and the development of kidney disease in obese diabetics. Even the renal osteodystrophy complicating CKD, the ABD, is the same as that observed in patients with diabetic nephropathy. The vascular calcification of the model was discovered by Towler and Semenkovich.[29] They found that osteoblastic transcriptional activity was present in the aorta, and their model is the starting point to which we add CKD. At the beginning, in other words our high-fat-fed, sham-operated animals expressed BMP-2, BMP-4, Runx2, Msx2, osteocalcin, and osteopontin in the vasculature, especially the aorta. This is relevant because several investigators have demonstrated that the vasculature of patients with CKD/ESKD expreshyphen-qj;ses osteoblastic markers.[30–33] However, our high-fat-fed, sham-operated animals had a low level of vascular calcification that was stimulated two- to fourfold by induction of CKD.[26]

To further investigate the mechanisms of atherosclerotic calcification, we developed an *in vitro* model to study in cell culture with the strategy of confirming discoveries made *in vitro* using our animal model. We began by obtaining primary cultures of human vascular smooth-muscle cells (VSMCs) from areas of aortic atherosclerotic plaques, which were expanded and then exposed to an increase in media phosphorus concentrations (Figure 6). We demonstrated that the starting tissue and the primary cultures in regular media expressed BMP-2, BMP-4, Runx2, Msx2, osteocalcin, and osteopontin. Thus, it appeared that BMP-2 and BMP-4 as bone morphogens were stimulating an osteoblastic-differentiation program in vascular cells directed by the osteoblast-specific transcription factors. These data are in agreement with those of other investigators,[34] including those

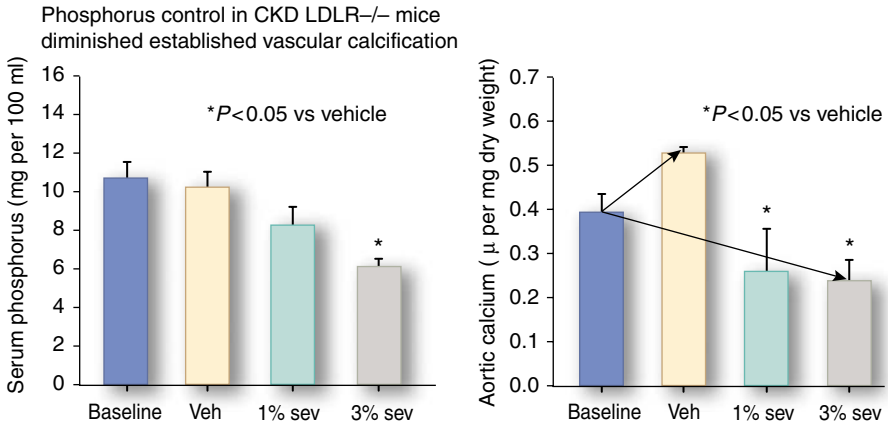

Figure 5 | Control of hyperphosphatemia in translational studies results in reduction of established vascular calcium levels. LDLR−/− mice on high-fat diets with CKD have established vascular calcification at 22 weeks (baseline), which increases in vehicle-treated animals killed at 28 weeks (veh). However, in animals treated with sevelamer carbonate (1 and 3% sev), aortic calcium levels were significantly reduced compared with baseline, as the hyperphosphatemia was controlled.[28]

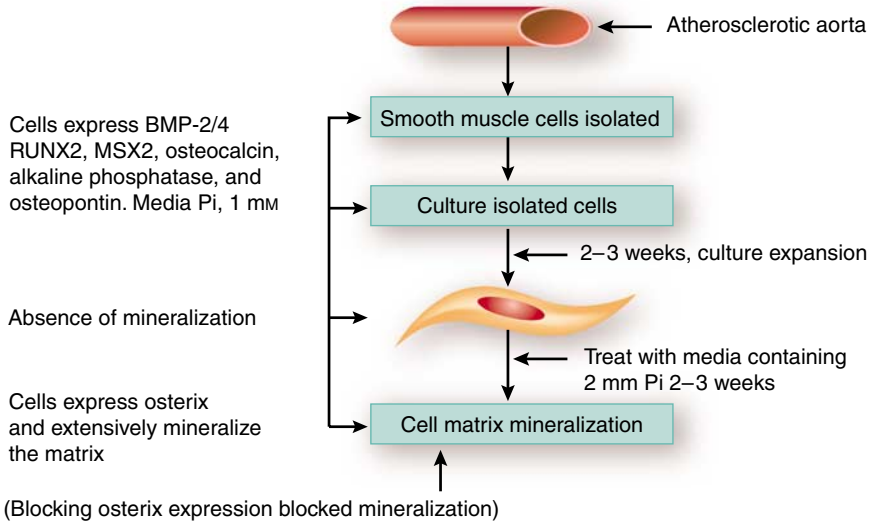

Figure 6 | Schematic representation of the experimental scheme for *in vitro* studies demonstrating that high phosphorus level causes vascular calcification and osteoblastic gene expression. Human VSMCs derived from atherosclerotic aortas expressed increased levels of morphogens, specific transcription factors, and biomarkers of the osteoblast, and decreased levels of those corresponding to contractile human VSMCs. Yet the cells did not mineralize until media Pi was increased from 1 to 2 mM. High level of Pi in the media stimulated osterix expression, and when osterix expression was diminished in the presence of high media Pi level, there was no mineralization.[38]

who reported increased levels of BMP-2 and BMP-4 in atherosclerotic lesions.[35,36] However, the primary human VSMC cultures did not mineralize the extracellular matrix as osteoblast cultures do (Figure 6).[37] When media phosphorus was increased by 1 or 2 mM to 2 or 3 mM (equal to a serum phosphorus of 6–9 mg per 100 ml), heavy matrix mineralization ensued. Analysis of the osteoblastic transcription program revealed that the very low levels of osterix expression in the starting cultures were increased several fold by the increase in media phosphorus. Blocking the increase in osterix expression in high-phosphate media prevented matrix mineralization.[38] Both our translational model *in vivo* and our cell culture model *in vivo* represent mineralization due to the atherosclerotic process. We observe mainly neointimal calcification *in vivo*, and the medial calcification we observe is in proximity to atherosclerotic plaques.

When we examined aortas from our various groups of high-fat-fed LDLR−/− animals, we found that the sham-operated, high-fat-fed animals had low or undetectable levels of osterix expression that were increased several fold when CKD was induced.[38] Most importantly, treatment of CKD high-fat-fed hyperphosphatemic animals with phosphate binders inhibited osterix expression (Figure 7).[38] As expected

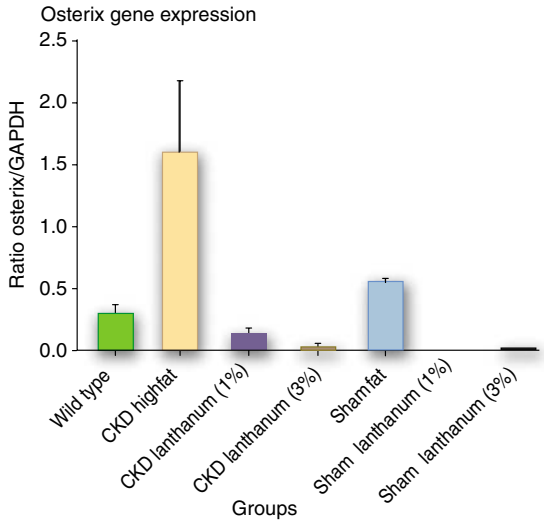

Figure 7 | Expression of osterix in the aortas of LDLR−/−, high-fat-fed mice. High-fat feeding had a small effect to increase aortic osterix expression in sham-operated animals (sham fat) compared with wild-type mice. Induction of CKD (CKD high fat) produced a several fold increase in osterix expression, which was eliminated by treatment with phosphate binders, in this case 1 or 3% $LaCO_3$ added to the diet.[38]

without a critical osteoblastic transcription factor, matrix mineralization (neointimal calcification) was severely compromised similar to results shown in Figure 5.

The mechanism of phosphorus stimulation of matrix mineralization *in vitro* has been studied by Jono *et al.*[39] and Li *et al.*[40] in VSMCs and by Beck *et al.*[41,42] in osteoblastic cells. These authors have demonstrated that the effect of media phosphorus was through activation of ERK1/2, and was blocked by an inhibitor of sodium-dependent phosphate transport proteins, phosphonoformic acid (PFA). However the effects of PFA are relatively specific to the type-2 Na/Pi co-transporters.[43] A sodium-dependent phosphate transport protein of the VSMCs is Pit-1, and an RNAi to Pit-1 also inhibited the actions of high-phosphorus media.[40,43] The effects of PFA in VSMC mineralization may have been due to the role of phosphonates to inhibit phosphate crystal formation, although NaPi2a has recently been found in osteoblast-like cells.[43,44] Other recent studies of Pi transport in VSMCs indicate that Pit-1 and Pit-2 account for sodium-dependent transport, which is only modestly inhibited by high concentrations of PFA.[45] In subsequent studies reported in abstract form at this writing, the authors demonstrate that these concentrations of PFA induce cytotoxicity.[46] Despite the recent clarification regarding the effects of PFA on VSMCs, the studies with RNAi to Pit-1[40,45] indicate that the effects of blocking the actions of high-phosphorus culture media *in vitro* are similar to those of lowering serum phosphorus *in vivo*, that of inhibiting osteoblastic stimulation of matrix mineralization.

Thus, phosphorus is more than a stimulator of vascular calcification acting through an elevated calcium–phosphorus product in CKD and ESKD. It is a signaling molecule serving to complete osteoblastic differentiation in the aorta, and an important component of the action of CKD to stimulate atherosclerotic calcification. The results of the translational animal studies and the studies *in vitro* just discussed are in agreement with a new clinical consensus that has led to renaming of renal osteodystrophy by the KDIGO Foundation as the CKD mineral bone disorder (CKD-MBD) in recognition of the roles of the skeleton in hyperphosphatemia and vascular calcification.[47]

OTHER HYPERPHOSPHATEMIC SYNDROMES

Hyperphosphatemic syndromes occur due to a variety of causes (Table 1). Hyperphosphatemia due to intravenous hyperalimentation (total parenteral nutrition (TPN)) in an immobilized patient is the most common cause of hyperphosphatemia in clinical medicine. Here, the phosphate content of the TPN prescription equivalent to normal dietary intake is associated with hyperphosphatemia, leading to removal of phosphate from the parenteral alimentation. Sometimes removal of phosphate intake does not correct the hyperphosphatemia and patients require inhibition of bone resorption to correct the hyperphosphatemia. The immobilization syndrome has at least two key features in common with the hyperphosphatemia of CKD. The first is severe inhibition of bone formation associated with immobilization that resembles inhibition of bone formation in the ABD of CKD/ESKD. The second is excess bone resorption contributing to hyperphosphatemia. The major difference from hyperphosphatemia of CKD may be duration of the syndrome, which in the case of immobilization is insufficient to calcify the vasculature and produce cardiac events due to the hyperphosphatemia.

Transcellular shifts of phosphate associated with catabolism, tumor lysis, or rhabdomyolysis are also relatively common causes of hyperphosphatemia (Table 1). Hyperphosphatemic syndromes due to decreased renal excretion besides CKD are uncommon in clinical medicine. Of these, FGF23 deficiency genetically produced in the mouse is especially instructive. FGF23-null mice exhibit hyperphosphatemia, elevated calcitriol levels, and increased skeletal mineralization, including chondrosseous junctions, the primary spongiosa, and heterotopic sites such as various organs and the vasculature.[48] The mice die at about 13 weeks due to cardiovascular complications. The phenotype of the FGF23-null mice is rescued by production of a double genetic deficiency for FGF23 and 25 hydroxycholecalciferol-1-alpha hydroxylase.[49] This demonstrates the role of excess calcitriol in the FGF23-null phenotype. Interestingly, the vascular calcification of this phenotype is also rescued by low-phosphate diets.[50]

FGF23 is a recently discovered phosphaturic hormone responsible for autosomal dominant hypophosphatemic rickets through an activating mutation.[51] The recent discovery that inactivating mutations cause the rare human disease of familial tumoral calcinosis completes the picture presented by the FGF23-null mice due to similarities in the

phenotypes. The premature cardiac death in FGF23-deficient mice is reminiscent of the early coronary artery disease in Klotho mice.[52,53] Klotho has recently been discovered to function as a co-receptor for FGF23 in the proximal tubule,[54] and its inactivation has also been found to cause familial tumoral calcinosis.[55] Thus, the role of hyperphosphatemia in stimulating heterotopic mineralization has clearly been demonstrated in mice and humans. The unique aspect of hyperphosphatemia in CKD is that the skeletal response to hyperphosphatemia, increased deposition of phosphate, is blocked.

RENAL OSTEODYSTROPHY

There are several disorders of bone remodeling that complicate CKD and ESKD. These have been characterized histomorphometrically and are correlated to PTH levels to estimate bone turnover rates. This process has to be replaced in order to monitor the skeleton more closely as is necessary to optimize cardiovascular therapy in CKD. Our current practice of using PTH levels to correlate with bone turnover is insufficient in terms of sensitivity and fails to detect excess bone resorption. Presently, high PTH levels ($>500\,pg\,ml^{-1}$ with an intact hormone assay) are thought to indicate increased skeletal remodeling due to secondary hyperparathyroidism. Although this is generally correct, it does not measure the impact of elevated remodeling in CKD on bone mass or strength. The elevated remodeling associated with secondary hyperparathyroidism, produces an osteoblast phenotype that has reduced secretion of type-1 collagen and increased production of RANK ligand, the critical osteoclast differentiation factor. This results in bone resorption outpacing bone formation. In addition, the high remodeling rates are characterized by insufficient replacement of newly formed atypical 'woven' bone with bone formed on collagen lamellae. Thus, even with normal bone mass, skeletal frailty may be problematic in high turnover osteodystrophy in CKD/ESKD.

A secondary effect of hyperphosphatemia in CKD is stimulation of nodular hyperplasia of the parathyroid glands.[56–59] Hyperplastic chief cells from the nodular areas are of clonal origin demonstrating less of cell-cycle control.[60] Clinically, this phenomenon accounts for the loss of control of the adaptive function of secondary hyperparathyroidism in CKD, and results in highly elevated PTH levels that are difficult to treat and clinical manifestations of severe secondary hyperparathyroidism. This often leads to parathyroidectomy in order to treat the clinical complications of the uncontrolled PTH levels.

With prevalent administration of high doses of vitamin D analogs in CKD/ESKD, a newer (discovered in the 1980s) low-turnover form of renal osteodystrophy has become increasingly common, termed the ABD.[61–63] The ABD was originally thought to be due to suppression of osteoblast function with high doses of vitamin D analogs.[61,63] The finding that vitamin D analogs stimulate, and not inhibit, bone formation and osteoblast function has put this contention to rest.[64–66] What is likely the case is that the negative effects of CKD on skeletal anabolism are uncovered by suppression of PTH. This demonstrates that higher than normal levels of PTH are required to maintain bone remodeling in CKD.[67] Many different mechanisms of resistance to the actions of PTH in CKD have been proposed, including desensitization of the PTH receptor by persistent high PTH levels.[68] While this is likely, another mechanism is probably central and critical. The endosteal osteoblast forms the niche of the hematopoietic stem cell,[69–71] and loss of osteoblast surface and number as a result of loss of skeletal anabolism due to kidney injury threatens hematopoiesis. There are three principles that regulate the hematopoietic stem cell niche, the BMPs, the Wnts, and PTH.[69,71] Loss of the influence of BMP or Wnt as a result of kidney injury would lead to a need for higher levels of PTH to protect niche function and skeletal remodeling. The point that is well established is that in ESKD, higher than normal levels of PTH are required to maintain normal rates of skeletal remodeling, that is, PTH levels recommended in the KDOQI guidelines.

The loss of skeletal remodeling after renal injury produces a mechanism of increasing PTH secretion due to the decrease in the exchangeable phosphorus pool size (Figure 2). Now boluses of phosphorus, as with meals, distribute in a smaller pool and produce intermittent short-lived stimuli to increased PTH secretion either through secondary effects on serum Ca or due to direct effects of transient increases in serum phosphorus that may be within the normal range. All this occurs in the face of normal fasting levels of Ca and PO_4. Renal osteodystrophy begins early in CKD. It is often first detected by elevated PTH levels in the face of normal Ca, PO_4 and calcitriol levels.[14] In this setting, the cause of the increase in PTH levels is a decrease in the exchangeable PO_4 pool size due to a loss of the skeletal mineralization front that occurs when the normal stimulus to bone formation is lost due to kidney injury. Despite recent studies, the role of FGF23, which is increased before changes in Ca, Pi, or calcitriol, in PTH secretion is unclear.[72] The underpinning of renal osteodystrophy by a loss of skeletal anabolic potential due to kidney injury is poorly appreciated, but it is often uncovered when PTH levels are suppressed to near-normal levels, producing the ABD.[62,63,73]

OSTEOPOROSIS IN CKD

The balance between bone formation and resorption may be either negative or positive in CKD. When positive, osteosclerosis results, but this is rare in modern medicine. In the case of negative bone balance, bone loss occurs in cortical and cancellous bone, and is more rapid when bone turnover is high. In those cases, bone densitometry will detect osteopenia or osteoporosis. The prevalence of osteoporosis in the population with CKD exceeds the prevalence in the general population.[74–76] Osteoporosis is observed in CKD before dialysis is required for end-stage kidney failure.[77] When bone turnover is high, as in secondary hyperparathyroidism with osteitis fibrosa, bone resorption rates are in excess of bone

formation and osteopenia progressing to osteoporosis may result. When bone turnover is low, although both bone formation rates and bone resorption may be reduced, resorption is in excess and loss of bone mass occurs. Thus, osteoporosis may be observed with either the high-turnover[77–80] or low-turnover[81] forms of osteodystrophy. When bone resorption exceeds bone formation rates in CKD, phosphorus and calcium release contribute to hyperphosphatemia and hypercalcemia. The increase in skeletal mineral deposition that should result from hyperphosphatemia or hypercalcemia is blocked, and heterotopic mineralization is stimulated, especially in the vasculature. The failure of the skeleton to absorb positive phosphate balance in CKD is an important stimulus to heterotopic mineralization, and links the skeleton and osteoporosis in CKD to cardiovascular events and mortality. This link between osteoporosis and vascular calcification, now partly defined in CKD, is not specific to CKD. Type-2 osteoporosis is strongly associated with vascular calcification, and perhaps, the mechanisms defined in CKD related to the serum phosphorus as a signal and positive phosphate balance also apply.

The discussion of osteoporosis in CKD above is focused on osteoporosis caused by CKD itself. However, many patients with CKD have osteoporosis independent of CKD. These patients may be elderly or may have post-menopausal osteoporosis. In addition, it is clear that gonadal hormone deficiency, as in post-menopausal osteoporosis, is also caused by CKD and is another factor in the pathogenesis of osteoporosis in CKD. Thus, osteoporosis in CKD presents a difficult differential diagnosis between the type-2 osteoporosis of aging, gonadal hormone deficiency, and excess bone resorption associated with the CKD-MBD.

CONCLUSION

In conclusion, hyperphosphatemia in CKD is a distinct syndrome. It represents one component of the increased risk of cardiovascular disease in CKD that has been analyzed successfully. Hyperphosphatemia in CKD represents a signal that heterotopic sites of mineralization are being used to compensate for the failure of reservoir function of the skeleton in positive phosphate balance. In fact, hyperphosphatemia itself is one of the signals activating heterotopic deposition sites, and functions as a signaling molecule in stimulating atherosclerotic neointimal mineralization that is markedly increased in CKD. The unique features of hyperphosphatemia in CKD, especially failure of the skeletal reservoir function, qualify it as a distinct syndrome characterized by phosphate excretion failure, contribution of the skeleton to hyperphosphatemia, heterotopic mineralization, including the vasculature, and severe cardiovascular disease leading to morbid cardiac events and often to demise.

DISCLOSURE

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