BoneKEy-Osteovision. 2005 June;2(6):5-16
http://www.bonekey-ibms.org/cgi/content/full/ibmske;2/6/5
DOI: 10.1138/20050164

PERSPECTIVES

The Phosphatonins and the Regulation of Phosphorus Homeostasis

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June 2005

The Importance of Phosphorus in Mammalian Physiology

Phosphorus plays an important role in several metabolic processes, such as intracellular signaling, enzyme function, energy metabolism, cell membrane integrity, nucleic acid chemistry, and bone mineralization (1-9). Phosphorus is an integral component of hydroxyapatite in bone (4). Severe hypophosphatemia from any cause can result in serious metabolic disorders, such as muscle weakness, rhabdomyolysis, hemolysis, neutrophil and platelet dysfunction, cardiomyopathy, and rickets or osteomalacia (10-25).

Adaptations to Changes in Dietary Phosphorus in Mammals

Mammalian organisms have developed the capacity to adapt to a low dietary intake of phosphorus by increasing the efficiency of phosphorus absorption in the intestine and reducing the amount of phosphorus excreted in the urine (26-31). Conversely, when dietary phosphorus is present in adequate or large amounts, the efficiency of phosphorus absorption in the intestine is reduced, and increased amounts of phosphorus are excreted by the kidney. The movement of inorganic phosphate across the apical borders of the intestinal absorptive cell and the proximal tubular cell is mediated by sodium-phosphate (Na^+-Pi) cotransporters that move sodium and phosphate ions together from the lumen into the cell (32-45). This uptake of phosphate is a secondary active process, powered primarily by the activity of the sodium-potassium ATPase present along the basolateral surface of absorptive epithelial cells. The number of Na^+-Pi transporters in the intestinal absorptive cell and proximal tubular cell is directly proportional to the amount of phosphate needed to preserve homeostasis.

It is important to remember that although various circulating factors and hormones play a role in regulating the efficiency of phosphate absorption in the intestine and kidney, a number of nonhormonal, locally produced or intrinsic factors are also important in altering the efficiency of phosphate transport in the kidney and intestine (46;47). The major hormones involved in the regulation of phosphate transport in the intestine or kidney include 1α,25 dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$], parathyroid hormone (PTH), growth hormone (GH), and insulin-like growth factor 1 (IGF-1) (35;48-81). The primary effect of 1α,25$(OH)_2D_3$ is to increase the efficiency of both phosphorus absorption in the jejunum and ileum and phosphate reabsorption by the proximal tubule of the kidney (48;51;53;54;57-59;64;81-92). In addition, 1α,25$(OH)_2D_3$ increases bone mineral mobilization and serum phosphate concentration (48;53). The primary effect of PTH with respect to phosphate homeostasis is to decrease the efficiency of phosphate reabsorption in the proximal tubule (26;35;41;61;63;68;70;71;93-100). PTH indirectly influences phosphate absorption in the intestine by increasing both the activity of the 25$(OH)D_3$ 1α-hydroxylase and synthesis of 1α,25$(OH)_2D_3$ (101). PTH also enhances bone mineral mobilization,

thereby increasing the amount of phosphate entering the extracellular fluid space. The net effect of the acute administration of PTH, however, is a reduction in serum phosphate concentration mediated by an increase in the fractional excretion of phosphate in the kidney, the effects of $1\alpha,25(OH)_2D_3$ being offset by the increases in phosphate excretion in the kidney directly mediated by PTH. GH and IGF-1 increase the reabsorption of phosphate primarily through renal mechanisms (67;73-80).

Sequence of Metabolic Events That Occur With a Change in Dietary Phosphorus Intake

A reduction in the dietary intake of phosphorus is associated with a decrease in serum phosphate concentration, a reciprocal increase in serum calcium concentration, a decrease in PTH release from the parathyroid gland, and direct stimulation of $25(OH)D_3$ 1α-hydroxylase activity, which results in an increase in the synthesis of $1\alpha,25(OH)_2D_3$ (48;56;81;82;102). The reduction in circulating PTH concentration results in a decrease in the fractional excretion of phosphorus by the kidney. The increase in the synthesis of $1\alpha,25(OH)_2D_3$ results in an increase in both phosphorus absorption in the intestine and phosphate retention by the kidney. These two events, namely a reduction in circulating PTH concentration and an increase in $1\alpha,25(OH)_2D_3$ concentration, increase overall phosphate retention and absorption and thus counteract the reduction in dietary phosphate. An increase in dietary phosphate is associated with an increase in PTH concentration and a reduction in the synthesis of $1\alpha,25(OH)_2D_3$.

The Phosphatonins and Phosphate Homeostasis

In 1994, based on experiments performed with tumor cells derived from a patient with hypophosphatemia associated with oncogenic osteomalacia (OOM), we postulated the existence of a phosphate-regulating substance that had properties distinct from that of PTH and other unknown phosphate-regulating factors (103). This substance, called “phosphatonin,” increased renal losses of phosphate and inhibited the synthesis of $1\alpha,25(OH)_2D_3$ (104). Both of these biological properties resulted in hypophosphatemia, and consequently, in osteomalacia. At least four phosphaturic peptides have now been identified in tumors associated with OOM -- fibroblast growth factor 23 (FGF-23), secreted frizzled-related protein 4 (sFRP-4), matrix extracellular phosphoglycoprotein (MEPE), and fibroblast growth factor 7 (FGF-7) (105-110). Of these, FGF-23 and sFRP-4 have also been shown to inhibit the $25(OH)D_3$ 1α-hydroxylase activity that should normally increase in the face of hypophosphatemia. Thus, only FGF-23 and sFRP-4 can be appropriately classified as "phosphatonins" (111). Both of these peptides inhibit the reabsorption of phosphate in the proximal tubule of the kidney *in vivo* and in cells in culture by enhancing the internalization of Na+-Pi cotransporters in renal cells (111). They also inhibit $25(OH)D_3$ 1α-hydroxylase activity, thereby reducing the synthesis of $1\alpha,25(OH)_2D_3$ and inhibiting the obstruction of phosphate in the intestine and kidney (106;109;112).

Phenotypic Similarity in Oncogenic Osteomalacia, Autosomal Dominant Hypophosphatemic Rickets, and X-linked Hypophosphatemic Rickets

OOM (also known as tumor-induced osteomalacia), autosomal dominant hypophosphatemic rickets (ADHR), and X-linked hypophosphatemic rickets (XLHR) are characterized by a similar biochemical phenotype of low serum phosphate concentration, phosphaturia, and a decreased tubular maximum for phosphate (despite a reduction in serum phosphate); normal or low normal serum calcium concentration; generally normal PTH concentration,; reduced serum concentration of 1α, 25 dihydroxyvitamin D_3; and the presence of osteomalacia or rickets (111;113;114). ADHR has been shown to be caused by activating mutations of the gene for FGF-23, which results in the formation of an FGF-23 variant that is lacking a furin protease site and thus resistant to proteolysis (108;115). Mutations in the endopeptidase PHEX are found in patients with XLHR and the murine model of

the disease, the Hyp mouse (116). It is hypothesized that inactivating mutations in the PHEX protein prevent the proteolysis of a phosphaturic substance, perhaps FGF-23.

Clinical Conditions Associated With Hypophosphatemia and Altered FGF-23 Concentration

Several clinical conditions associated with hypophosphatemia have now been shown to be associated with elevated FGF-23 concentration. Some (but not all) patients with OOM have an elevated FGF-23 serum concentration (117-119). Following removal of a tumor, FGF-23 concentration generally returns to normal. Some patients with XLHR also have an elevated concentration of FGF-23 (119-121). An elevated FGF-23 concentration is seen in patients with humoral hypercalcemia of malignancy, chronic renal failure, and fibrous dysplasia (111;122-126). Patients with primary hyperparathyroidism have a marginally elevated FGF-23 concentration that is not substantially altered following parathyroidectomy (122;127-129). Of interest, patients with stage III and IV ovarian cancer who have no alteration in serum phosphate concentration also have an elevated FGF-23 concentration (130). Conditions associated with hyperphosphatemia are also associated with increases in FGF-23. These conditions include chronic renal failure, tumoral calcinosis, hypoparathyroidism, and hyperthyroidism (125;131-134). In these latter conditions, it is thought that the FGF-23 concentration is elevated to reduce persistent hyperphosphatemia.

Regulation of FGF-23 by Phosphate and $1\alpha,25(OH)_2D_3$

From a physiological perspective, it would be appropriate for FGF-23 concentration to be regulated by the intake of dietary phosphorus and serum phosphate concentration. When the serum phosphate concentration is elevated, FGF-23 concentration might be expected to increase, and the opposite would be predicted to occur when the serum phosphate concentration is diminished. Additionally, because $1\alpha,25(OH)_2D_3$ increases phosphate retention and serum phosphate concentration, such increases might be mitigated by an increase in FGF-23. Studies in both humans and animal models have begun to shed light on the regulation of FGF-23 by phosphate and $1\alpha,25(OH)_2D_3$.

In humans, short-term alterations in dietary phosphate intake do not seem to influence FGF-23 concentration. Larsson *et al.* (125) fed human subjects normal, high-, or low-phosphate diets for 72 hours. FGF-23 concentration did not change substantially in this study, suggesting that dietary phosphate did not regulate FGF-23 concentration. In a subsequent study (135), a high- or low-phosphate diet was given to humans with concomitant changes in dietary calcium designed to minimize changes in PTH. In this study, modest decreases or increases (well within normal range) in FGF-23 were observed following the administration of a low- or high-phosphate diet, respectively. In neither of the two studies were short-term changes in urinary phosphate excretion evaluated to determine whether temporal changes in the renal excretion of phosphate directly correlated with temporal changes in FGF-23. Thus, in humans, it seems that dietary variation in phosphate intake has no (or at most an extremely modest) effect on phosphate excretion in the kidney. In neither study was the effect of dietary phosphate on $1\alpha,25(OH)_2D_3$ or the effect of $1\alpha,25(OH)_2D_3$ on FGF-23 examined.

Recent information regarding the regulation of FGF-23 by $1\alpha,25(OH)_2D_3$ in rats has become available. Saito *et al.* (136) showed that serum FGF-23 concentration increased following the administration of $1\alpha,25(OH)_2D_3$ to intact rats in a dose-dependent manner. A dose of 10 ng/kg/rat, given intravenously three times a week for two weeks, elicited no change in serum FGF-23 concentration. No changes in serum phosphorus were noted at this dose. However, a dose of 30 ng/kg/rat, given intravenously three times a week for two weeks, was associated with a modest increase in serum FGF-23 and a clearly measurable increase in serum phosphorus concentration. Marked changes in serum FGF-23 concentration were noted following the administration of 100 ng/kg/rat

three times a week for two weeks. There was a direct correlation between serum phosphorus and serum FGF-23 concentration. In thyroparathyroidectomized rats, $1\alpha,25(OH)_2D_3$ also increased serum FGF-23 concentration. Of interest, in thyroparathyroidectomized rats, serum FGF-23 concentration was at the low end of normal, despite an elevated serum phosphorus concentration. This response is different than that observed in hypoparathyroid humans, where serum FGF-23 concentration is elevated (134). Saito *et al.* (136) next tested the effect of diets containing different amounts of phosphate on serum FGF-23 concentration in rats that had undergone a 5/6 nephrectomy. In these animals, a high-phosphate diet was associated with a substantial increase in serum FGF-23 concentration, when compared with that observed in rats fed a normal or low-phosphate diet. There was a direct correlation between serum phosphate and serum FGF-23 concentration in nephrectomized rats. No results were reported for the effects of dietary phosphate on serum FGF-23 in rats with normal renal function. Reports have appeared in abstract form, suggesting that the amount of phosphate in the diet regulates serum FGF-23 concentration in rats with normal renal function (137).

What conclusions can be drawn concerning the regulation of FGF-23 by $1\alpha,25(OH)_2D_3$ and dietary phosphate in humans and rats? When $1\alpha,25(OH)_2D_3$ concentration is elevated in an effort by the organism to provide more calcium and phosphate for bone mineralization, there is clearly no advantage to driving the serum phosphate level down by increasing FGF-23. FGF-23 may decrease or turn off the synthesis of $1\alpha,25(OH)_2D_3$ after the demands for calcium and phosphate have been satisfied, thus complementing local factors, such as an increase in tissue 24-hydroxylation of $1\alpha,25(OH)_2D_3$ (138). With respect to the regulation of FGF-23 by dietary phosphate, one must conclude at present that the effect of dietary phosphate intake on FGF-23 serum concentration in humans is modest. Furthermore, there is no information concerning correlations between phosphate excretion measured over shorter periods of time (*i.e.*, < 72 hours), variations in dietary phosphate, and changes in serum FGF-23 concentration. In rodents with renal failure, the effect of dietary phosphate on serum FGF-23 concentration seems to be more marked than in humans, and it is possible that FGF-23 plays a more important role in phosphate homeostasis in the rodent than in humans. The role of other tumor-derived phosphaturic factors (*i.e.*, sFRP-4, MEPE, and FGF-7) in adaptations to dietary phosphate have not been explored. Clearly, further studies examining the influence of dietary and serum phosphate on serum FGF 23, sFRP-4, MEPE, and FGF-7 concentration and the renal handling of phosphate need to be performed to precisely determine the role of phosphatonins in human phosphate physiology.

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