REVIEW ARTICLE

Phosphorus metabolism in chronic kidney disease

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Abstract

The knowledge about the exact mechanisms involved in phosphorus homeostasis and the evolution of secondary hyperparathyroidism in chronic kidney disease (CKD) has improved during the last years. The discovery of Fibroblast Growth Factor 23 (FGF23) has revolutionized our understanding about the links between mineral metabolism, vitamin D and parathyroid hormone (PTH). FGF23 serum levels increase early in CKD before the increase of serum phosphorus or the decrease of vitamin D and there is parathyroid resistance to FGF23 in advanced CKD. Increased levels of serum phosphorus have been related in epidemiological studies with adverse outcomes in patients with CKD, diabetes, coronary artery disease, or even normal adults. In patients with CKD stage 3 or 4, low phosphorus diets have been related with adverse outcomes due to the risk of malnutrition and there are limited data regarding the role of phosphate binders in these patients. Recent studies suggest that increased serum FGF23 levels are associated with mortality, left ventricular hypertrophy and progression of CKD independently of serum phosphorus levels. There is an ongoing debate about the "normal" or "desirable" levels of serum phosphorus in CKD and a new role of FGF23 as a marker of the disturbances of mineral metabolism in CKD is emerging. Hippokratia 2011; 15 (Suppl 1): 50-52

Key words: chronic kidney disease, Fibroblast Growth Factor 23, renal osteodystrophy, parathyroid hormone, phosphorus

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Phosphorus is an important mineral for cell structure and energy. It is mainly intracellular (70%), about 29% resides in the bones and less than 1% circulates in the serum[1-3]. All these three sites are making the "exchangeable phosphorus pool" as suggested by Hruska et al[1]. In normal subjects the skeleton remains neutral (equal exit and entry) regarding phosphorus homeostasis and the kidneys regulate phosphorus balance. Phosphorus is filtered freely in the glomerulus and then it is reabsorbed in the proximal tubule under the effect of various hormones. The amount of reabsorbed phosphorus is the main regulator of the serum phosphorus levels in subjects with normal renal function, or moderately reduced glomerular filtration rate[4].

In Chronic Kidney Disease (CKD) the kidneys fail to excrete the phosphorus and the result is a positive phosphorus balance. However, the skeleton through the disorders of the bone that accompany CKD, contributes to this hyperphosphatemic state as it can not handle the phosphorus excess. So, in this new situation there is a need for a new phosphorus reservoir and this is soft tissue organs including vasculature[1,5]**.** The final result is vascular calcification that is frequently observed in CKD[5-8]. Experimental data have shown that phosphorus is involved in the whole process of vascular calcification leading to a new consensus that has renamed the old term of renal osteodystrophy with CKD mineral bone disorder (CKD-MBD) and emphasizes the almost neglected role of the skeleton in these pathological states[1,2,8,9].

Fibroblast Growth Factor 23 (FGF23)

FGF23 is a 32 kDa protein secreted by osteocytes in bone and regulates phosphorus and vitamin D metabolism[7,10,11]. Its main stimuli are high phosphorus intake, 1,25 vitamin D and perhaps PTH (directly, or through an increase of 1,25 vitamin D)[10,11]. On the contrary, increased serum phosphorus is not a stimulus for FGF23, as it has been observed in the hyperphosphatemia of primary hypoparathyroidism (low PTH and high FGF23 serum levels), indicating that its primary role is net phosphorus balance and not phosphorus serum levels[10]. The exact mechanism by which osteocytes sense phosphorus imbalance and secret FGF23 has not been defined yet. FGF23 increases phosphaturia and decreases renal synthesis of 1, 25 vitamin D. Its action is mediated by klotho[12] which acts as a co-receptor that enhances the binding of FGF23 to its receptors (FGFRs).

Klotho is a transmembrane protein that determines the tissue specificity for FGF23. Although Klotho is expressed in the distal renal tubule, it remain unclear how FGF23 binds on this site and expresses all its actions (phosphaturia and decreased 1,25 vitamin D production) in the proximal tubule. A subsequent distal-proximal tubule interaction has been proposed as a possible explanation[7,12].

The suppressive effect of FGF23 the parathyroid gland may be a) indirect through alterations of serum phosphorus and vitamin D, and b) direct through suppression of PTH synthesis and secretion[7].

In CKD FGF23 serum levels increase early (stage 2-3) and long before phosphorus[10]. Its action through inhibition of 1,25 vitamin D diminishes dietary phosphorus absorption from the alimentary tract, but the net result is a reduction of the 1,25 vitamin D levels rather early and before any evidence of the previously suggested "reduced renal mass" during the progression of CKD. It should ne emphasized that at the moment there is no definite proof that increased FGF23 levels act as a compensatory mechanism in order to maintain the serum phosphate levels and that these increased FGF23 levels may represent increased secretion, decreased degradation or both[10].

Recent data suggest that the failure of increased FGF23 levels to suppress PTH is mainly due to parathyroid resistance by decreased expression of the Klotho-FGFR1 complex in the hyperplastic parathyroid glands[5,7]. Many observational studies have shown increased FGF23 levels in dialysis patients with severe secondary hyperparathyroidism or hyperphosphatemia. This may be due to many reasons such as hyperphospatemia per se, therapy with active vitamin D, or reduced degradation of FGF23[1-10].

Phosphorus Transporters

There are many types of phosphorus transporters in humans with different distributions among organs, different actions and roles and different regulation by various stimuli[1,4,10-12].

Type 1 sodium phosphate co-transporter

There is a type 1 sodium phosphate co-transporter NPT1, which is expressed in the apical membrane of the proximal renal tubular cells and in the liver. It acts as a non specific anionic carrier and its exact role on phosphorus homeostasis remains unknown[1,4,10-12].

Type 2 sodium phosphate co-transporters

There are three type 2 sodium phosphate co-transporters: NPT2a, NPT2b and NPT2c. Among them, the NPT2b co-transporter has not been fully studied regarding its exact localization in the kidney and its role in renal phosphorus reabsorption. It is also expressed in the lung and the small intestine, where it is upregulated by calcitriol.

The NPT2a and NPT2c co-transporters are expressed in the apical side of the proximal renal tubular cells and they reabsorb phosphorus from the glomerular filtrate. Although these two co-transporters have similar affinities for phosphorus they present some differences. The NPT2a co-transporter carries three sodium anions with phosphate, whereas the NPT2c cotransporter carries only two, the expression of the NPT2c is decreasing with age and PTH has different effects on these two contransporters[4].

Type 3 phosphate transporters

These transporters PiT1 and PiT2 are widely expressed in the human body and transport phosphorus with very high affinity. They seem to act in order to supply cells with phosphorus (energy) than to control phosphorus body homeostasis. However, recent studies have shown overexpression of PiT1 in cultures of vascular smooth muscle cells under the influence of a high in phosphorus medium, implicating a role in the mechanisms of pathological vascular calcification.

PTH and Phosphorus transporters

PTH decreases renal phosphorus reabsorption by binding to a type 1 PTH receptor in the proximal tubular cells, by stimulating cAMP synthesis and the phospholipase C pathway and inducing the retrieval of the NPT2a co-transporter from the brush border membrane of the proximal tubular cells with the presence of the sodium-proton exchanger regulatory factor 1 (NHERF1). The exact role of PTH on the NPT2c co-transporter is not completely elucidated[1,4,10].

FGF23 and Phosphorus transporters

FGF23 decreases NPT2a and NPT2c co-transporters RNA and protein expression in the kidney and NPT2b in the intestine. The effect of FGF23 on NPT2b in the intestine is mediated through the reduction of calcitriol levels by the FGF23, as it inhibits 1-α hydroxylase expression in the proximal renal tubule and stimulates the enzyme 24 hydroxylase, that inactivates calcitriol and 25-OH vitamin D. In addition recent data indicate an inhibitory role of FGF23 on the secretion of PTH by the parathyroid glands which can also influence phosphorus excretion as shown above[7,10,12].

Perspectives

Even relatively small elevations of serum phosphorus in the high normal range have been correlated in observational studies with increased cardiovascular and all cause mortality in patients with CKD[13], diabetes[14], coronary artery disease[15], or even normal adults[16]. Phosphate load may be an important driver of vascular calcification, even in the absence of overt hyperphospahatemia[5,8,9].

High serum levels of FGF23 have been associated with increased left ventricular mass[17], increased arterial stiffness[18] and more rapid decline of renal function[19], although its relation with vascular calcification remains rather conflicting[10]. It should be noted that in all these studies the effect of FGF23 was independent of serum phosphate levels indicating that perhaps FGF23 is superior to serum phosphorus levels as a marker of morbidity or mortality in CKD patients[10, 20].

As vitamin D increases FGF23 levels it would sound logical that this kind of therapies might be detrimental for CKD patients. However there are conflicting data, as increased FGF23 serum levels have been associated with increased mortality, whereas vitamin D treatment have been associated better survival in HD patients. Wolf has offered many explanations on this paradox[10].

Current recommendations from various authorities suggest that serum phosphorus levels should be maintained between 2.7- 4.7 mg/dl in patients with CKD 3-4 and 3,5-5,5 mg/dl in CKD 5 via dietary phosphorus restriction or therapy with phosphate binders[1,2]. Although previous studies have shown a beneficial effect of a low in phosphorus diet, recent data indicate that this approach

is frequently accompanied by an excessive risk of malnutrition and should be avoided[21].

The studies regarding therapies with phosphate binders have mainly focused in dialysis patients and there are only a few studies with a limited number of patients in CKD 3-4 patients with sevelamer hydrochloride[22], sevelamer carbonate[23] of lanthanum carbonate[24].

Recently, Isakova et al raised doubts regarding the "optimal" levels of serum phosphorus, as they were based mainly on observational studies with many methodological limitations and there is a need for new well designed multicenter studies with adequate patient populations[20]. They also proposed a possible role for FGF23 as a marker of hyperphosphatemia equal to that of glycosylated hemoglobin in diabetes mellitus, as its levels remain rather stable over long time periods and as a marker of the possible favorable response to vitamin D analogues in severe secondary hyperparathyroidism, or to phosphate binders administration even in patients with serum phosphorus levels among the "normal' levels (2.7- 4.7 mg/dl).

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