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Review

A Disturbed Phosphate Metabolism in Chronic Kidney Disease Progression and after Kidney Transplantation - What should the Clinicians be Aware of?

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Abstract

Phosphate (P) is an essential element of life and both reduced and elevated serum P levels will reduce lifespan. Kidneys are very important to maintain phosphorus homeostasis. There is sustained evidence showing that high serum phosphate concentration is associated with cardiovascular disease, all-cause and cardiovascular mortality in chronic kidney disease (CKD), basically by vascular aging and altered mineral metabolism both before and after initiation of renal replacement therapy. On the other hand, the hyperphosphatemia was reported to have a detrimental impact on kidney function *per se*. It might have an independent pathogenic role in the onset and progression of CKD and might even attenuate the renoprotective effect of ACE inhibitors in proteinuric CKD patients. The phosphorus reduction has been shown as strongest determinant of improvement in proteinuria. There is some evidence that both post-transplant hypo-and hyperphosphatemia could be the reason of adverse outcome in transplanted patients, but there are still not enough data on disturbed phosphate metabolism that could bring the guidelines that are needed. Enhancing the knowledge on P balance and toxicity is challenging to improve the care of renal patients, to protect the graft and enable longer kidney and patient's survival. A healthy phosphate balanced diet may be important for a healthy life and longevity.

Keywords: phosphate, fibroblast growth factor 23, chronic kidney disease, proteinuria, kidney transplantation

Introduction

Phosphate (P) is an essential element of life. This is a nutrient required for critical biological reactions that maintain the normal homoeostatic control of the cell, an important component of different cellular structures, so both reduced and elevated serum P levels will reduce lifespan [1]. Regulation of the P pool in humans depends on the homeostatic balance between nutritional intake, intestinal absorption, and kidney excretion. Besides, the distribution of P concentrations is highly heterogeneous between body compartments and strictly regulated by hormonal assets [2]. Kidneys are very important to maintain phosphorus homeostasis where tubular handling is a leading regulator of P equilibrium. In normal subjects, about 75 and 10% of the filtered P is reabsorbed in the proximal convoluted tubule, and in the distal convoluted tubule, respectively and around 15% of the filtered P being excreted in the urine. Furthermore, there is an intestinal-glomerular feedback and the 24 h urinary P excretion (UPE) is considered equivalent to daily intestinal absorption (not intake) of P in normal subjects at a steady state [3,4].

Phosphate balance in CKD patients

In chronic kidney disease (CKD) stages 2 and 3 patients, serum phosphate is not usually increased, due to increased fractional excretion of phosphate. The further reduction of GFR, requires compensatory reduction of tubular resorption of P (TRP), which was mediated by fibroblast growth factor 23 (FGF23) [2] which directly enhances tubular excretion of phosphorus and reduce 1-25 hydroxylase activity which in turn reduces calcitriol production and intestinal phosphorus absorption. The determinants of the FGF-23 increase in CKD are still unclear and may involve a low availability of its cofactor Klotho, expressed in the same tubular sites where FGF-23 acts [1,3,5]. Due to the important role of the kidneys in maintaining phosphorus homeostasis, hyperphosphatemia is a common manifestation of advanced CKD. There is sustained evidence showing high serum phosphate concentration is associated with cardiovascular disease, all-cause and cardiovascular mortality in CKD basically by vascular aging and altered mineral metabolism both before and after initiation of renal replacement therapy [6-8]. The maintenance of phospho-

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rus concentrations within an optimum range is considered as a standard of care in this patient population [9].

Hyperphosphatemia and progression of kidney dysfunction

Hyperphosphatemia *per se* was reported to have a detrimental impact on kidney function. Older experimental studies in rats have shown high dietary phosphorus can initiate and/or worsen the progression of kidney dysfunction [10], whereas dietary phosphate restriction reverses and/or restricts the dysfunction [11]. Podocyte injury due to overexpression of pituitary-specific positive transcription factor 1 (Pit-1) was one of the proposed mechanisms which go apart of the effect of phosphorus on inducing calcifications [12]. It is also possible that the deleterious effect of acute phosphorus loading on systemic endothelial function might also extend to the glomerular endothelium. There are few clinical studies about the potential effect of serum phosphorus concentrations on the rate of progression of CKD. Shwarz *et al*. showed that higher serum phosphorus was associated with a significantly higher risk for progression of CKD, even after adjustment for multiple potential confounders supporting earlier studies that showed a beneficial effect of dietary phosphorus restriction on the progression of CKD in experimental animals [13]. The relative risk of developing ESRD was demonstrated to be much higher in CKD patients with serum phosphorus concentrations >1.29 mmol/l in NHANES participants free of CKD [14]. Bellasi *et al*. utilizing the "Prevenzione Insufficienza Renale Progressiva" (PIRP) database, underlined the strong association between serum phosphorus and a rapid decline in the kidney function and mortality [1,15]. Besides, they reported that the relative contribution of hyperphosphatemia in predicting progression to ESRD or death might differ between women, persons with diabetes, older patients, and those in more advanced stages of CKD.
In a post hoc analysis of the Ramipril Efficacy in Nephropathy (REIN) Study, Zoccali *et al*. [16] found that just 1-mg/dl [0.3226 mmol/l] increase in serum phosphate level was associated with an 85% excess risk for progression to ESRD [16]. Their data suggested that phosphate is an independent risk factor for the progression of kidney disease among patients with proteinuric CKD, and high levels of phosphate might even attenuate the renoprotective effect of ACE inhibitors. In addition, it was shown that the strongest determinant of improvement in proteinuria was the phosphorus reduction (either in urine or serum) and not the protein intake per se [17]. One explanation might be the stimulation of the FGF receptor which may activate the RAS. In this way it might facilitate the onset and progression of kidney damage in subjects at risk and, at the same time, might overcome the effects of RAS inhibitors on angiotensin II activity and production, in particular at the tissue level. On the other hand, nitric oxide (NO) production due to direct or indirect effect (through FGF23) of phosphate might also limit or prevent the effects of ACE inhibitor therapy mediated by NO activation. In addition, the coreceptor of FGF23, Klotho, a well recognized renoprotective factor which reduces angiotensin-II-induced renal damage, is downregulated at an early stage in CKD patients. Klotho -/- mice suffer premature aging, and this phenotype may be corrected with a low phosphate diet raising the hypothesis that lower phosphate in CKD patients with reduced Klotho may mitigate the progression of kidney damage and ameliorate the response to ACE inhibition [16-20].
A meta-analysis and systematic review of 12 cohort studies with 25,546 patients published from 1950 to 2014 reported that every 1-mg/dL [0.3226mmol/l] increase in serum phosphorus level was associated independently with increased risk of kidney failure (hazard ratio, 1.36; 95% CI, 1.20-1.55) and mortality (hazard ratio, 1.20; 95% CI, 1.05-1.37) suggesting that large-scale randomized controlled trials should target disordered phosphorus homeostasis in CKD [21].
Dietary phosphate overload never causes persistent hyperphosphatemia unless renal function is critically impaired, because the kidney as it was mentioned above, excretes excess phosphate into the urine (more precisely in the tubular luminal fluid), and maintains phosphate balance [1-3]. Two possible ways exist to increase the amount of phosphate excreted in the urine. One way is due to an increase in the total volume of urine by increasing GFR (hyperfiltration) and the second might be due to increasing the fractional excretion of phosphate (FEP). Being not always able to increase GFR, patients with CKD mostly can increase the FEP per nephron to maintain phosphate balance [22]. This is mediated mainly by increased level FGF23 in early stages but also by PTH later on [20].
In experimental rat studies it was shown that raised phosphate intake and/or decreased nephron number increases the rate of phosphate excretion per nephron, potentially causing calciprotein particle formation in the tubular lumen, epithelial tubular injury, and fibrosis [20,22-25]. In heminephrectomized rats, a high phosphate diet increased phosphaturia resulting in kidney tubular damage associated with inflammation, oxidative stress, and low klotho expression [26]. High FGF23 was found to be associated with a significantly higher risk of end-stage renal disease in patients with relatively preserved kidney function [22] and C-terminal and intact FGF23 was shown that independently predict the progression of CKD after adjustment for age, gender, GFR, proteinuria, and serum levels of calcium, phosphate, and parathyroid hormone [27]. Based on these data a new paradigm for phosphate restriction was proposed suggesting that phosphate binders be used in patients with CKD and an abnormally high FGF 23 level, regardless of serum phosphate level to prevent preventing

histological kidney damage and progression of CKD [20,28]. Decision to treat patients should be based on a risk-benefit assessment taking account harmful side effects of available compounds [28]. Given the potential toxicity of excess phosphate, the general population may also be viewed as a target for phosphate management. Enhancing the knowledge on P balance and toxicity is challenging to improve the care of general population and renal patients [1-3,25]. A healthy phosphate balanced diet may be important for a healthy life and longevity.

Disturbed phosphate metabolism post-transplantation

Phosphate metabolism is changed even after kidney transplantation and could be manifested either as hypophosphatemia (even severe one with phosphate level <0.5 mmol/l) or as hyperphosphatemia (levels >1.5 mmol/l) [29].

In the first three months after kidney transplantation usually hyperphosphaturia and consequent hypophosphatemia occur as the results of high FGF-23 and PTH levels, ischaemia-reperfusion injury, immunosuppressive drugs and metabolic acidosis [29]. Studies have shown that glucocorticoids induce decrease expression of sodium-phosphate (NaPi) cotransporters in the apical membrane of tubular epithelial cells as well as the intestinal NaPi activity, resulting in decreased phosphate absorption in the intestine and reabsorption in the proximal tubule [30-32]. Experimental studies in rats have shown that cyclosporin inhibits NaPi activity [33]. In the similar manner, the usage of calcineurin inhibitors and mTOR (mammalian target of rapamycin) inhibitors is linked to a post-transplant hypophosphatemia [34,35].

In later months after transplantation, hyperphosphatemia can occur as the result of impaired graft function with secondary or tertiary hyperparathyroidism [29].

It is important to know that higher serum phosphate level, calcium-phosphate product and FGF-23 levels after kidney transplantation present a higher risk of graft failure [36-38]. Analysis of the FAVORIT (Folic Acid for Vascular Outcome Reduction in Transplantation) Trial Cohort study indicated that elevation for every 1 mg/dl [0.32 mmol/l] in serum phosphate level increases transplant failure, when adjusted for confounding factors (treatment allocation, traditional cardiovascular disease risk factors, kidney measures, type of kidney transplant, transplant vintage, use of calcineurin inhibitors, steroids and lipid-lowering drugs) [39].

At both 6 and 12 months post-transplant serum phosphate is found to be the independent predictor of graft lost, even when adjusted for age, sex, blood pressure, proteinuria, donor type and HLA mismatches and phosphate level greater than 1.2 mmol/l resulted in worse graft survival [40].

Hyphophosphatemia can be maintained even later after transplantation. Low serum phosphate 1 year post-transplantation is induced by both PTH and FGF23, but with greater impact of persistent hyperparathyroidism [41].

Acute phosphate nephropathy is also described as an entity that could cause graft failure due to phosphate overload and calcium phosphate deposition (with or without hypercalcemia) [42,43]. On the other hand, there are studies that reported no association between serum phosphate, serum calcium and calcium phosphate products with poor patient and graft outcomes during the first year after kidney transplantation [44].

There is some evidence that both post-transplant hypo- and hyperphosphatemia could be the reason of adverse outcome. In the large study on 2786 kidney transplant recipients 1 year after transplantation (with the follow-up of 78.5 months) both, higher (≥5 mg/dl i.e. 1.6 mmol/l) and lower serum phosphate (<2.5 md/dl i.e. 0.8 mmol/l) were associated with death-censored graft failure, but also with patient mortality (exhibiting U-shape association) [45].

Furthermore, it is suggested that higher serum phosphate is a predictor of all-cause mortality in patients with kidney transplant after adjustment for traditional cardiovascular risk factors, estimated glomerular filtration rate, high sensitivity C reactive protein and renal graft failure [46]. Serum phosphate is negatively associated with graft function in CKD stage 4-5 in 990 patients with median 72 months post-transplantation [47].

Treatment of hypo- and hyperphosphatemia after kidney transplantation is very challenging. Phosphate supplementation early post-transplant is recommended when serum phosphate is between 0.5 and 1.0 mmol/l with the presence of muscle weakness [29]. However, it is reported that phosphate supplementation may play a role in the calcification of native or transplanted kidney [48,49]. On the other hand, usage of phosphate binders in patients with transplanted kidney should also be very careful as they can reduce the concentration of mycophenolate mofetil [50].

Compared to the data known for CKD population, in kidney transplant recipients there are still not enough data on disturbed phosphate metabolism that could bring the guidelines that are needed. Therefore, more attention should be paid on the discovering the “nature” of phosphate metabolism in a long run after kidney transplantation and the best approach for treating the potential disturbance in order to protect the graft and enable longer kidney and patient survival.

Conclusion

Exploring the association between serum phosphate levels and renal outcomes based on the available data indicate that phosphate might have an independent pathogenic role in the onset and progression of CKD and might even attenuate the renoprotective effect of ACE inhibitors in proteinuric CKD patients. The phosphorus reduction was shown to be the strongest deter-

minant of improvement in proteinuria. Compared to the data known for CKD population, in kidney transplant recipients there are still not enough data on disturbed phosphate metabolism that could bring the guidelines that are needed. Enhancing the knowledge on P balance and toxicity is challenging to improve the care of renal patients. Finally, a healthy phosphate balanced diet may be important for a healthy life and longevity.

Conflict of interest statement. None declared.

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