Phosphate Homeostasis

Subjects: Nutrition & Dietetics

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Phosphorus is an essential nutrient that is critically important in the control of cell and tissue function and body homeostasis. Phosphorus excess may result in severe adverse medical consequences.

phosphorus intake | phosphaturia | hyperphosphatemia | diabetic kidney disease | chronic kidney disease | CKD progression

1. Phosphate Homeostasis

Phosphorus accounts for ~1% of whole body mass and is essential for cellular function. It is a main constituent of teeth and bones, but also critically contributes to the generation and storage of cell energy at the molecular level (in the form of ATP (Adenosine triphosphate)) [1]. Most body phosphorus is deposited in the bone as a hydroxyapatite. The gastrointestinal (GI) tract, bones and the kidneys are the key players in regulation of phosphorus homeostasis, whereas parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23) and other phosphatonins, klotho protein and vitamin D remain key hormones precisely controlling this homeostasis. Dietary phosphate intake (especially with high-phosphate containing products such as processed food) is a critical factor determining its gut absorption, kidney reabsorption, bone deposition and tissue content. Since several toxicities can be attributed to the phosphate excess, fine-tuned regulation of phosphate balance is essential to keep normal body homeostasis. The amount of phosphorus absorbed from the GI, reabsorbed into the kidney and eliminated in the urine, as well as deposited in the bone tissue, must be precisely balanced in order to avoid potential toxicities. Phosphorus is absorbed from the GI lumen using sodium- dependent and sodium-independent pathways and is largely regulated by active forms of vitamin D [2][3]. Sodium-dependent absorption is provided mostly using NaPi-IIb (Npt2b) protein upon the control of calcitriol. Mechanisms of transcellular and paracellular, sodium-independent phosphate transport have not been fully elucidated. It seems that these pathways are calcitriol independent (which could explain increased absorption of phosphorus in patients with advanced chronic kidney disease, i.e., the condition of severe vitamin D depletion) [3][4]. Renal phosphate reabsorption is provided by sodium-dependent co-transporters localized in the luminal membranes of proximal tubular cells. They include: sodium–phosphate co-transporter type IIa (NaPi-IIa, Npt2a), IIc (NaPi-IIc, Npt2c) and sodium–potassium co-transporter type III (Pit-2, Ram-1) [5]. FGF (fibroblast growth factor) 23 and PTH (parathyroid hormone), key phosphaturic hormones increase phosphaturia by inhibition of Npt2a. FGF23, phosphatonin released by osteocytes, needs klotho protein as a co-factor to act on the proximal tubule phosphate absorption. Several other factors are involved in phosphate homeostasis in the kidney and include: growth hormone, insulin-like growth factor (IGF-1), insulin, thyroid hormones, secreted frizzled-related protein 4 (sFRp-4)

and FGF 7. Phosphate (and calcium) deposition and resorption in and from the bones is also precisely regulated by several hormones acting on the osteoclasts and osteoblasts [3][6].

2. Abnormalities of Phosphate Homeostasis in Chronic Kidney Disease (CKD)

Mineral and bone disorders of chronic kidney disease (CKD-MBD) are considered the key homeostatic abnormalities of CKD. It should be emphasized that the dysregulation of calcium and phosphate balance develops far before the development of overt uremic toxicity (uremia)—it may be detected as early as in CKD stage 2 and then progress further with decreasing glomerular filtration rate (GFR). Most of the abnormalities (both at the laboratory and the clinical level) can already be identified in CKD stage 3b (i.e., when GFR falls to the range of 30–45 mL/min/1.73m^2). CKD-MBD affects almost all aspects of metabolism, beyond the bone turnover (historically, clinicians and researchers were focused mainly on this aspect of described abnormalities, referred to as “renal osteodystrophy”). Due to their abundance, advancement and clinical importance, cardiovascular (CV) consequences of CKD-MBD are now included in the definition of this clinical entity [7]. Phosphate retention directly translates into increased risk of CV events and mortality, as well as the risk of bone fractures and faster progression of CKD. Since the normal serum phosphate concentration is a homeostatic priority in order to avoid the consequences of hyperphosphatemia, it is kept within the normal range until the late stages of CKD owing to significantly diminished reabsorption in remaining (functioning) nephrons (i.e., markedly increased single nephron phosphaturia). It is achieved at the expense of significantly elevated serum FGF23 and PTH [8]. Since healthy kidney tissue is the most important source of klotho (co-factor of FGF23 receptor), CKD progression leads to the renal FGF-23 resistance, which additionally boosters synthesis and release of this phosphatonin. FGF23 at supraphysiologic concentrations (needed to maintain phosphaturia), interacting with FGF23 receptor without klotho, influences the tissues normally out of its control (for example triggers heart injury and hypertrophy and activates renin-angiotensin-aldosterone axis) [9]. Along with CKD progression (and progressive loss of nephrons), an excess of phosphaturic hormones fails to control phosphate level and hyperphosphatemia develops. Since phosphate intake is a potentially modifiable factor that impacts on phosphate homeostasis, the reduction of an excess phosphate intake with phosphate binders has long been recognized as one of the key therapeutic strategies in CKD. Indeed, many observational studies demonstrated the relationship between dietary phosphate and CV events and outcome [10]. On the other hand, it should be kept in mind that hypophosphatemia and low phosphate intake may also result in an increased mortality. Malnutrition seems the most obvious way to interpret such a finding. However, as shown by Chang et al., a relationship between low phosphate and mortality persists also after adjustment for nutritional markers, suggesting other possible mechanisms. Interestingly, the mortality increment curve was steeper for decreasing than for increasing phosphate level [11].

Recent trials however demonstrated that the correlation between phosphate intake and serum phosphate is relatively weak [12][13]. Selamet et al. analyzed the outcome of 795 patients with CKD stage G3a-G5 who were included into the Modification of Diet in Renal Disease (MDRD) trial (with mean follow-up of 16 years). The authors analyzed the relationship between phosphatemia, phosphate intake based on 3-day dietary recall and phosphate

loss with 24-h urine and found that the correlation between these parameters is rather weak. Twenty four hour urine phosphate loss did not correlate with the risk of end-stage renal disease (ESRD), CV death or all cause-death, whereas a strong correlation was found between the serum phosphate and all-cause mortality [14]. This study confirmed the importance of hyperphosphatemia as predictor of CV and renal end-points but did not show the importance of phosphate intake as a contributor to hyperphosphatemia. The concept of preventing or treating hyperphosphatemia with dietary restrictions has also been challenged recently by the data suggesting that decreased phosphorus intake may significantly increase the efficacy of its intestinal absorption—the percentage or fraction of phosphate absorbed vs ingested (mechanism physiologically designed to keep normal bone homeostasis in periods of dietary phosphorus depletion). Such an increase in absorption may potentially counterbalance the potentially harmful effects of dietary phosphate deficiency on bone quality. These discoveries may in the future shift the main strategy of prevention and treatment of hyperphosphatemia from reduced intake and use of phosphate binders into the use of compounds that inhibit passive paracellular and active sodium-dependent transcellular phosphate transport in the intestinal epithelium. Tenapanor, the inhibitor of sodium—protein exchanger 3 (NHE3) located in the intestine, has already been registered in the United States as a promising agent to effectively prevent hyperphosphatemia in advanced CKD by means of reduced GI absorption [15][16][17]. This novel strategy may be of great importance since most therapeutic approaches used to date are of the limited efficacy concerning the “hard” endpoints, despite their positive impact on the CKD-MBD lab profile. Whether the new generation of phosphate-controlling agents would influence the patient outcome remains to be demonstrated. The latest data on pharmacological treatment of diabetes additionally challenged the traditional view on the role of phosphate homeostasis on outcome. Namely, it has been shown that SGLT2 Sodium-glucose co-transporter type 2) inhibitors (such as dapagliflozin) promote phosphate retention, increase serum FGF23 and PTH, and decrease serum 1.25 $(OH)_2D_3$ [18][19]. Although this change in a biomarker profile clearly goes in the “wrong” direction when mineral metabolism is considered, SGLT2i are both cardio- and renoprotective and life-saving drugs for patients with and without diabetes and across CKD stages 1–4 [20][21][22][23][24][25][26][27][28].

3. Interactions between Glucose and Phosphate Homeostasis

Chronic inflammation, the hallmark of diabetes, obesity and CKD, contributes to the synthesis of FGF23 [29]. It has been demonstrated in animal models that insulin inhibits FGF23 synthesis. Bär et al. analyzed the relationship between plasma insulin concentration following oral glucose load and FGF23 in healthy volunteers, showing an inverse correlation between these two hormones. Such a relationship may suggest a potential impact of hyperinsulinemia on renal phosphate retention [30]. Garland et al. have demonstrated that insulin resistance is significantly associated with FGF23 increase in multivariable linear regression analysis—HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) and eGFR (estimated glomerular filtration rate) decline were the only parameters out of broad spectrum of bone-turnover biomarkers, indices of inflammation and “classical” parameters reflecting the risk of atherosclerosis that influenced serum FGF23 in patients with CKD stages 3–5 [31]. Similar results were obtained by Hanks et al., who found an independent relationship between FGF23 and several indices of insulin resistance, which were much more apparent in subjects with normal kidney function as compared to

patients with CKD stages 3–5; in the same study the authors confirmed a strong relationship between analyzed interleukins (IL6, IL10), C reactive protein and serum FGF23 [32]. Animal experiments have proven an essential role of phosphate in the normal secretion of insulin by pancreatic beta cells [33]. This finding has also been confirmed in humans—Haap et al. found that in 881 healthy subjects (non-obese, without diabetes) serum phosphate and glucose are inversely correlated and that serum phosphate was correlated positively with insulin sensitivity, but not with insulin secretion [34]. On the other hand, incidence of the type two diabetes was significantly higher in those subjects from the group of 71,270 participants followed in the French E3N-EPIC (Etude Epidémiologique auprès de femmes de l'Education Nationale study) cohort, who ingested diet with high phosphate content. In second, third and fourth quartile of phosphate intake there was a progressive and significant increase in the hazard ratio of T2D (1.18, 1.41., 1.54 vs. first quartile, respectively; with all increases being statistically significant). It is worth to mention that the mean intake of phosphorus in this study equaled 1477 ± 391 mg/day, which should be considered quite high (almost fifty percent higher than an average recommended daily intake). Neither GFR value nor serum creatinine were provided in the paper, but due to the population-based, observational design and very low prevalence of comorbidities (for example hypertension present in less than 13.5%), normal or near-normal renal function among study participants could be assumed [35]. This study highlights the importance of phosphate intake as another lifestyle-related risk factor for the development of T2D, probably not appreciated by most practitioners.

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