Prevention and treatment of hyperphosphatemia in chronic kidney disease

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Hyperphosphatemia has consistently been shown to be associated with dismal outcome in a wide variety of populations, particularly in chronic kidney disease (CKD). Compelling evidence from basic and animal studies elucidated a range of mechanisms by which phosphate may exert its pathological effects and motivated interventions to treat hyperphosphatemia. These interventions consisted of dietary modifications and phosphate binders. However, the beneficial effects of these treatment methods on hard clinical outcomes have not been convincingly demonstrated in prospective clinical trials. In addition, exposure to high amounts of dietary phosphate may exert untoward actions even in the absence of overt hyperphosphatemia. Based on this concept, it has been proposed that the same interventions used in CKD patients with normal phosphate concentrations be used in the presence of hyperphosphatemia to prevent rise of phosphate concentration and as an early intervention for cardiovascular risk. This review describes conceptual models of phosphate toxicity, summarizes the evidence base for treatment and prevention of hyperphosphatemia, and identifies important knowledge gaps in the field.

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Abnormal phosphate metabolism is one of the key disturbances in chronic kidney disease (CKD). It is now recognized that overt hyperphosphatemia occurs rather late in the process of CKD progression, usually at stage 4 and onward.[1] However, adaptive mechanisms, particularly high concentrations of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23), antedate the development of overt hyperphosphatemia, promoting kidney phosphate excretion.[2] Because these adaptive mechanisms may be directly involved in uremia-associated pathologies, it is difficult to untangle assumed phosphate toxicity from pathogenetic effects of these adaptive responses. Moreover, a reduction of phosphate exposure by dietary intervention or inhibition of intestinal phosphate absorption does not normalize elevated concentrations of PTH and FGF23. Other factors such as vitamin D deficiency, inflammation, and autonomous overproduction of these hormones may explain the limited effects of phosphate-targeted intervention on their circulating levels.

Maintaining normal phosphate balance is of crucial importance for many physiological processes including bone mineralization. Phosphate homeostasis is determined by modulation of intestinal uptake of dietary phosphate, renal phosphate reabsorption of ultrafiltered phosphate, and the shift of intracellular phosphate between extracellular and bone storage pools (Figure 1).[3,4] It is well established that phosphate is one of the major factors in the maintenance of bone health and that phosphate deficiency results in bone pathology, as seen in patients with specific monogenic diseases, leading to isolated renal phosphate wasting syndromes.[5]

Hyperphosphatemia *per se* usually is asymptomatic. Morbidity associated with hyperphosphatemia is the consequence of acquired structural or functional[6] abnormalities, including vascular calcification, which has been recently summarized[7] but is beyond the scope of the current review. This is important because the justification for treating hyperphosphatemia is based on the assumption that associated abnormalities are caused by abnormal phosphate homeostasis. The second assumption is that a reduction in phosphate concentration over time toward the normal range is accompanied by a parallel decline in morbidities and death. Comparable assumptions formed the base to restore hemoglobin concentration in renal anemia to near normal levels by epoetin, aiming to improve clinical outcome, but proved untrue.[8]

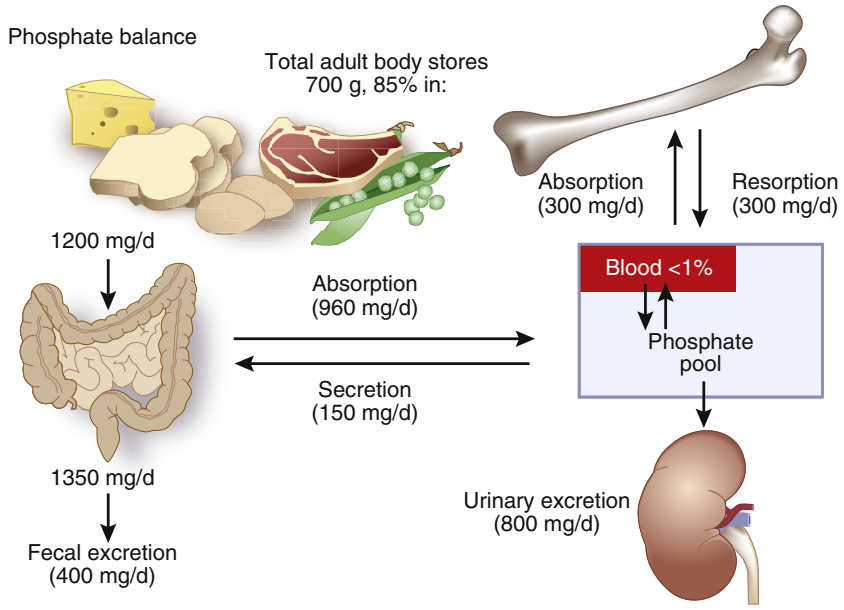

Figure 1 | Phosphate homeostasis. Phosphate balance by phosphate intake, absorption, storage, and excretion. Used with permission from Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of chronic kidney disease. *Kidney Int.* 2008;74:148–157. Copyright © 2008 International Society of Nephrology.[4]

Epidemiological evidence in support of the role of phosphate in clinical events

The assumptions described above are based on numerous observational studies that generally reported on the risk for mortality or cardiovascular disease of higher serum phosphate concentrations across the entire spectrum of CKD, ranging from normal or slightly decreased kidney function to dialysis-dependent end-stage kidney disease. Large studies in non-CKD populations, collectively encompassing over 39,000 subjects all found an association between phosphate, even in the normal range, and all-cause mortality,[9,10] cardiovascular events,[11] or cardiovascular mortality.[12] Also in patients with CKD, an association between phosphate and adverse events exists. In an analysis of 1203 patients, Eddington *et al.* found a stepwise positive association of serum phosphate concentration and mortality in CKD stages 3 and 4 but not stage 5.[13] Voormolen *et al.*,[14] however, analyzing patients with stage 5 (nondialysis) CKD did find an increased relative risk for mortality of 1.62 for patients with an average eGFR of 13 (±5.4) ml/min per 1.73 m^2 and serum phosphate concentration of 4.71 (±1.16) mg/dl.[14] Although an analysis of the Modification of Diet in Renal Disease (MDRD) study (n = 840) could not confirm this association,[15] the largest study to date, from the Veterans Affairs Medical Centers (n = 3490) by Kestenbaum *et al.*[16] found a linearly increasing mortality risk for patients with CKD, above a threshold serum phosphate concentration of 3.5 mg/dl (1.13 mmol/l).[16] Finally, in patients undergoing dialysis, numerous studies have consistently reported the independent association between hyperphosphatemia and mortality risk.[17–23]

Phosphate pools or serum phosphate concentration?

Generally, hyperphosphatemia is considered indicative for overall phosphate burden. However, routine clinical observations demonstrate that this view is an oversimplification, as hyperphosphatemia is widely prevalent in CKD, even in individuals with low bone mass, in which the tissue contains approximately 85% of total body phosphate. In fact, phosphate resides in different compartments, of which plasma and interstitial fluids represent very small fractions (Figure 2).[24] Among these compartments, a rather rapid exchangeable pool must exist, which is responsible for the rebound of serum phosphate after dialysis, which is both rapid and high, reaching a 40% increase within 60 minutes after its hemodialysis-induced nadir.[25] This phosphate pool of unknown residence, which is responsible for the rebound, can probably be depleted by intensified hemodialysis therapy, especially by extended duration dialysis schedules.[26,27] Importantly, the magnitude of this phosphate pool is difficult to estimate, and therefore, no report has been able to demonstrate an association between serum phosphate concentration and the amount of phosphate in this or other phosphate reservoirs. The implication is that phosphate may accumulate in CKD, initially without causing hyperphosphatemia. Remarkable observations for instance from the Framingham offspring cohort, as described above, indicate that serum phosphate even within the normal range is associated with increased risk for cardiovascular events.[9,11] This may be explained by the assumption that differences in the amount of stored phosphate in pools is much larger than suggested by corresponding serum concentrations. Based on these observations, authors have speculated about the potential of phosphate toxicity in the absence of overt hyperphosphatemia.[24,28] It is possible that serum phosphate concentration is just an unreliable reflection of phosphate stores and that these stores are the true "phosphate culprit" causing cardiovascular disease (Figure 3, left side). This