Protecting Calcium and Phosphate Balance in Chronic Renal Disease

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In its earliest stages, chronic kidney disease (CKD) is associated with a failure to regulate phosphate balance optimally. Multiple aspects of normal renal physiology—from maintenance of an adequate GFR to responsiveness of the nephron to systemic and local signals that regulate phosphate secretion—underlie the deterioration in phosphate control as CKD progresses. The human organism is endowed with several adaptive mechanisms that attempt to counter the kidneys’ early and continuous decline in the functioning pathways that are normally involved in the regulation of phosphate excretion (1).

Two components are central to these adaptive mechanisms. The first is the inexorable increase in circulating parathyroid hormone (PTH) prompted by minimally perceived increases in phosphate levels. Increased PTH concentrations stimulate the remaining nephrons to excrete phosphate more efficiently in the face of a continually decreasing nephron mass as CKD progresses. The second is the role of calcium in facilitating phosphate removal via nonrenal mechanisms. In the intestine, available free calcium binds readily with ingested phosphate to form a less soluble salt that is removed easily via normal bowel function. In soft tissue, free calcium binds with excessive phosphate and is deposited within the tissue. Although effective in the short-term, this adaptive response ultimately leads to progressive soft tissue calcification, a trade-off that is associated with a significant increase in cardiovascular risk. It follows that a secondary adaptive response that is intended to protect calcium homeostasis ensues. PTH mobilizes needed calcium from bone reserves, producing another unfavorable trade-off, ubiquitous metabolic bone disease in patients with CKD and ESRD.

Why would the adaptive, compensatory mechanisms that protect phosphate and calcium homeostasis have such ultimately devastating consequences for these patients? Tight control of both phosphate and calcium homeostasis is essential to the normal functioning of virtually all life-sustaining, physiologic processes. Cell phosphate is at the core of all energy-dependent physiologic processes. Cell calcium and its ubiquitous binding protein are the triggers that initiate virtually all cellular functions. Thus, compromising the tight regulation of these two ions, even short term, carries an immediate risk to the highly integrated physiologic systems that are critical to sustaining essentially all biologic process. Viewed in that context, a trade-off that maintains biologic systems for years but ultimately leads to life-threatening conditions later in patients with CKD and ESRD is understandable.

Unfortunately for the patient with early CKD, these adaptive mechanisms are so successful that even though GFR is significantly compromised, serum phosphate does not become elevated until the late stages of renal disease, at which time health care providers recognize the need to respond. By that time, parathyroid hyperplasia is irreversible, bone loss is significant, and soft tissue calcification, even if not grossly evident, is already well established. Historically, the foundation of the therapeutic approach to this clinical situation has been the use of calcium-containing phosphate binders (CCPB). Although not typically appreciated, this traditional approach when viewed in the context of the origins and consequences of the hyperphosphatemia of CKD and ESRD as outlined above is both logical and physiologically appropriate. Using CCPB to control phosphate provides the biologically appropriate agent to bind phosphate in the intestine while ensuring sufficient calcium systemically to downregulate PTH secretion and avoid mobilization of the organism’s endogenous calcium reserves from bones.

Unfortunately, in the past few years, the logic and appropriateness of using CCPB in the management of phosphate balance in ESRD and CKD have been challenged. Essentially one study (2) and its putative documentation that using CCPB in dialysis patients actually contributes to coronary calcifications and thus cardiovascular risk have been used to convince nephrologists of this presumed association as well as to influence strongly the new practice guidelines of the National Kidney Foundation. Thoughtful review of the evidence first from this one study (3,4) and then the preponderance of evidence accumulated over the past five decades of clinical and basic research in the realm of mineral metabolism in CKD and ESRD argue strongly against the approach championed by Chertow et al. (2) and Block et al. (5). These authors, as well as those involved in the Dialysis Clinical Outcomes Revisited (DCOR) trial (6), have argued that physicians who care for patients with renal disease should no longer rely on the well-established, cost-effective approach of using CCPB to manage phosphate balance. As we have called for, what is most needed in this field is a longitudinal, randomized, controlled trial of CCPB in the earliest stages of CKD to document that much of the metabolic and cardiovascular consequences of disarrayed mineral metabolism in CKD and ESRD can be attenuated if not prevented by the...
early introduction and continuous use of CCPB throughout the clinical course of CKD.

The five articles included here address the increased cardiovascular risks associated with CKD and ESRD while reviewing the most current evidence as to what underlies these risks and how best to respond therapeutically. In his review of cardiovascular disease in CKD, Dr. Dennis describes the multiple factors that increase cardiovascular heart disease risk in these patients and highlights the need for early traditional interventions as means of reducing this risk. Dr. Qunibi discusses the multiple sequelae of CKD that contribute to the high prevalence of cardiovascular calcification in this population and the available means of their amelioration. Dr. Coladonato discusses the high incidence of hyperphosphatemia among patients with ESRD and both the available and the emerging therapies for its management. Dr. McCullough addresses the relationship between the lipid profile and coronary artery calcification, validating the importance of achieving and maintaining optimal lipid levels in slowing calcification progression. The harsh economic and social realities of ESRD and approaches to improving them are described by Dr. Nolan in his assessment of the consequences of renal disease and their treatment options, costs, and access barriers.

Bringing clarity to managing phosphate balance in CKD and ESRD is an urgent need in nephrology (1). The clinical confusion prompted by the illogical assumption that CCPB use is a primary contributor to coronary calcifications may in the end prove constructive if it stimulates thoughtful, comprehensive, and critical review of the current scientific evidence and prompts the necessary definitive clinical trials earlier in CKD to determine the safety and efficacy of CCPB in managing mineral metabolism and cardiovascular risk in our patients.

References