INTRODUCTION

New Developments in Hyperphosphatemia Management

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Patients with chronic renal failure have many associated medical problems, including a high propensity for cardiovascular disease (CVD). CVD and stroke are the leading causes of mortality in patients with ESRD (chronic kidney disease stage 5), with a 10- to 20-fold greater risk than in the general population (1,2). These data have generated greater awareness of cardiovascular risk in the chronic renal failure patient, and the most recent National Kidney Foundation guidelines for chronic kidney disease (CKD) state that patients with CKD and kidney transplant recipients should be considered in the *highest risk group* for CVD (3). Indeed, the significance of CVD in this patient population is such that a separate guideline to address the issue of CVD in patients with CKD is in development.

Hyperphosphatemia and Hyperparathyroidism of Renal Failure: A Vicious Cycle with Cardiovascular Consequences

It seems logical that an understanding of the basic pathologic mechanisms underlying the increased cardiovascular risk in CKD could lead to the development of improved treatment paradigms and better outcomes in patients with chronic renal failure. The consequences of progressive renal failure include an imbalance of calcium and phosphorus, which are normally under the tight homeostatic control of the kidneys. The loss of metabolic control of calcium and phosphorus parallels the loss of renal function (4). In early renal failure, a reduction in serum calcitriol and moderate decreases in ionized calcium contribute to an increased synthesis and secretion of parathyroid hormone (PTH). In later stages of renal failure, reduced expression of vitamin D and calcium receptors contributes to glandular resistance to the already decreased calcitriol and calcium, perpetuating the synthesis and secretion of PTH. Independent of these effects, renal failure–mediated phosphate retention and dietary phosphorus lead to increased serum phosphorus levels. Hyperphosphatemia promotes uremia-induced parathyroid gland hyperplasia and PTH synthesis and secretion.

In the past decade, some of the molecular mechanisms of the effects of phosphorus on the parathyroid gland have been determined. Data indicate that high levels of phosphorus can increase parathyroid glandular expression of transforming growth factor-α and promote growth in the gland via activation of mitogen-activated protein kinase cascades (5,6). Conversely, low phosphorus induces the cyclin-dependent kinase inhibitor p21, which inactivates cyclin or cyclin-dependent kinase complexes to specifically induce arrest of growth in the parathyroid gland (6). In sum, hyperphosphatemia associated with progressive renal failure can lead to secondary hyperparathyroidism and accompanying elevated phosphorus and calcium-phosphate product (Ca $\times$ P).

Hyperphosphatemia and secondary hyperparathyroidism are common complications of ESRD (4,7). Importantly, a growing body of evidence suggests that the clinical consequences of altered phosphorus and calcium metabolism and hyperphosphatemia include an increased risk of mortality, CVD, cardiovascular mortality, bone disease, and extraskeletal calcification of soft tissues, including blood vessels, lungs, kidneys, and joints (8–12). Cardiac and vascular calcification is believed to be the underlying common mechanism that mediates such increased risk of morbidity and mortality. Management of hyperphosphatemia thus is a critical issue in the care of patients with renal failure and has the potential to decrease risk for CVD, particularly when instituted with appropriate measures to control other "traditional" cardiovascular risk factors.

Management of Hyperphosphatemia: The Challenge

Although dietary phosphorus restriction and dialysis play important roles in regard to the management of hyperphosphatemia, there is a need for additional support from phosphate-binding therapies. Herein lies the challenge to the clinician. Oral or intravenous administration of vitamin D metabolites can correct secondary hyperparathyroidism (13) but may also lead to enhanced intestinal absorption of calcium and phosphorus, indirectly contributing to vascular calcification.

Other available treatment options include phosphorus-sequestering agents. These agents sometimes contain aluminum or, more typically, calcium, and their use is limited by toxicity in the case of aluminum-containing agents (14,15) or by their potential for increasing calcium load and soft tissue calcification, in the case of calcium-containing phosphate binders (8,16,17). The challenge in the renal failure patient is to reduce effectively and safely serum phosphorus and Ca $\times$ P product without increasing serum calcium levels and the likelihood of vascular calcification. It is in this context that metal-free, calcium-free phosphate binders may have an important role.

In this supplement, we discuss issues critical to the treatment

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of the hyperphosphatemic renal failure patient. Advances in our understanding of the molecular biology of hyperphosphatemia-induced calcification and its clinical consequences are presented and discussed in the context of other well-known cardiovascular risk factors, such as dyslipidemia and oxidative stress.

Molecular Biology and Clinical Correlates of Hyperphosphatemia in the Vasculature

Recent evidence indicates that vascular calcification can occur early in a phosphate-rich environment. Furthermore, hyperphosphatemia-mediated calcification may not be a simple, passive process of deposition of calcium phosphate crystals in vascular walls. Rather, the work of Giachelli and others reviewed in this supplement suggests that calcification may be an active process under exquisite genetic and molecular control. The unfolding *in vitro* data presented by Giachelli paints an active process during which phosphate enters vascular smooth muscle cells via a sodium-dependent phosphate co-transporter–mediated mechanism, inducing the expression of a "master gene"—the Cbfa-1 gene—and setting into process the active deposition of calcium into vascular walls. The end result is a phenotypic cellular change, changing a vascular cell type to an osteogenic cell type (18,19). Calcification is an inherent part of atherosclerosis and is the most frequent cause of CVD in patients with ESRD.

In an accompanying article, London discusses how vascular changes in ESRD not only are related to atherosclerosis and ischemic heart disease but also are associated with vascular stiffening and "remodeling." These latter changes, collectively referred to as "arteriosclerosis," are more ubiquitous, involve calcification of the intima and media of blood vessels, cause a stiffening of the vessel wall (particularly of elastic vessels), and lead to hemodynamic changes, such as increased systolic BP and pulse pressure. These hemodynamic changes eventually lead to left ventricular hypertrophy (LVH), another major cause of cardiovascular mortality in patients with ESRD (20), further highlighting the heightened risk of CVD in patients with ESRD.

Management of Hyperphosphatemia and Reduction of Cardiovascular Risk

It is clear that hyperphosphatemia can facilitate calcification of soft tissues such as blood vessels, with serious clinical consequences. The extent of calcification and the degree of arterial stiffening are independent predictors of mortality. In his article, London also briefly reviews some studies in patients with ESRD that show that attenuation of arterial stiffness can cause regression of LVH and have a favorable impact on patient survival. Although a direct impact of phosphate-binding therapy on LVH has not yet been documented, there is considerable evidence indicating that the use of calcium-free, metal-free phosphate binders can reduce coronary and aortic calcification scores, thereby decreasing some aspects of cardiovascular risk.

In another article, Chertow reviews the impact of phosphate binder use on hyperphosphatemia and the progression of vascular calcification. In a comparative study, Chertow and his colleagues have shown similar phosphate control but lower calcium scores in the aorta and coronary arteries of hemodialysis patients treated with sevelamer (a non–aluminum-, non–calcium-containing binder) compared with patients treated with calcium-containing phosphate binders (21).

It is interesting that a beneficial effect on the lipid profile seems to be a novel advantage of sevelamer treatment. This is exciting, considering the high cardiovascular risk of patients with renal failure. Although the decrease in LDL cholesterol (LDL-C) and increase in HDL cholesterol with sevelamer were not related to calcification scores in Chertow's study, the implications of these data require further investigation.

In reviewing the impact of dyslipidemia in ESRD, Prichard presents a thorough overview of the relative changes in lipids in patients who receive hemodialysis *versus* peritoneal dialysis and shows that dialysis in general can lead to atherogenic changes in lipids. Given this and given the well-established benefits of lipid-lowering treatment in the nondialysis population, Prichard advocates aggressive treatment of dyslipidemia to an LDL-C goal less than 100 mg/dl in patients with renal failure, consistent with the recommendations in the recently released Kidney Disease Outcomes Quality Initiative guidelines on managing dyslipidemias in CKD (22). Whether the benefit on lipids conferred by sevelamer will result in a replacement or reduction of lipid-lowering therapies such as statins in patients with ESRD will need further investigation. The potential benefit in terms of reduction in the number of medications that a patient must take and/or patient compliance is certainly important.

For the future, investigation of the anti-inflammatory potential of drugs such as sevelamer may also provide added insight and benefit, because there is some evidence that calcium deposition in dialysis patients may be triggered by inflammation (23). If additional non–phosphate-related effects of sevelamer are confirmed in further studies, then the multiplicity of beneficial effects of this phosphate binder will indeed be very advantageous in the treatment of patients with hyperphosphatemia. The evidence now points to a relative superiority of sevelamer to calcium-containing phosphate binders in terms of a reduction in vascular calcification and LDL-C levels, with comparable control of hyperphosphatemia, and that evidence indicates that calcium-containing phosphate binders, given their propensity to increase vascular calcification, should be used judiciously.

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