CKD-Mineral Bone Disorder in Stage 4 and 5 CKD: What We Know Today?

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Patients with CKD stages 4 and 5 experience biochemical derangements associated with CKD-mineral bone disorder. Some of the key abnormalities are hyperparathyroidism, hyperphosphatemia, hypocalcemia, and metabolic acidosis. We review the available treatments for these conditions and the evidence behind the treatments. We conclude that there is greater evidence for treating hyperphosphatemia than hyperparathyroidism. Treatment of metabolic acidosis in small clinical trials appears to be safe. We caution the reader about side effects associated with some of these treatments that differ in patients with CKD Stages 4 and 5 compared with patients on dialysis. The use of cinacalcet has been associated with hyperphosphatemia in patients with functioning kidneys. Activated vitamin D therapy has been associated with elevated creatinine levels, which may or may not be a reflection of true decrement in kidney function. Finally, the use of non-calcium–containing phosphate binders may be associated with improved clinical outcomes in patients; however, many more clinical trials are needed in this important area of medicine.

Key Words: FGF-23, Hyperphosphatemia, Vascular calcification, Hyperparathyroidism, Metabolic acidosis

INTRODUCTION

Patients with CKD Stages 4 and 5 begin to exhibit biochemical manifestations of CKD-mineral bone disorder (MBD) with elevations in phosphate and parathyroid hormone (PTH). CKD-MBD is a systemic disorder that involves abnormal biochemical tests, bony abnormalities, and vascular calcification. The pathophysiology of CKD-MBD is complex, and our understanding of it is rapidly evolving. As patients near ESRD, if untreated, they develop hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism. In this review, we will discuss our evolving understanding of CKD-MBD, its consequences, and treatments.

CKD-MBD PATHOPHYSIOLOGY

Calcium and phosphate levels are kept within normal as the kidneys fail by a variety of mechanisms. The first abnormality appears to be an elevation in FGF-23 levels.[1] FGF-23 is a hormone made by the bone and causes phosphaturia (leading to lower serum phosphate levels) and decreases 1-alpha hydroxylase activity in the kidney (leading to lower 1,25-dihydroxyvitamin D levels). As the kidneys fail, FGF-23 levels remain elevated, and this elevation likely becomes maladaptive, whereby it is associated with and may contribute to the increased cardiovascular (CV) risk found in CKD.[2]

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PTH levels are also elevated at lower glomerular filtration rates (GFRs).[3] PTH is made in the parathyroid gland chief cells in response to fluctuations in calcium via the calcium-sensing receptors on the chief cells. PTH promotes release of phosphorus and calcium from bone and increases vitamin D production in the kidney and urinary secretion of phosphorus. The signals for elevation of PTH in CKD are numerous including low calcium levels, high phosphate levels, and low 1,25-dihydroxyvitamin D levels. Historically, therapy for CKD-MBD has focused on keeping calcium, PTH, and phosphate levels within a range agreed on by expert panels based on available data.[4,5]

IDEAL PTH LEVELS

The current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for CKD suggest that the optimal level of PTH is not known in people with GFR < 45 mL/min/1.73 m^2.[4] They do suggest that patients with elevated PTH should be evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. Why is there controversy about the ideal levels of PTH? We know that in dialysis patients, the recommended levels of PTH are 2× to 9× the upper limit of normal in the laboratory.[4] These recommendations, from the same guidelines, were based on an evidence review performed by KDIGO, but they acknowledge that the evidence in support of this recommendation was not very strong (Grade 2C—"we suggest" with low quality of evidence).[4] In the general population, PTH levels should be below the upper limit of the laboratory normal. The transition point between these recommendations occurs somewhere around CKD Stages 3, 4, and 5. Data show that PTH values start increasing likely with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and that by the time the GFR is less than 30 mL/min/1.73 m^2, approximately 70% of patients will have an elevated PTH.[6] The reason why there is no consensus on the optimal level of PTH in Stages 4 and 5 CKD is due to the dearth of data on clinical outcomes in this patient population. Higher PTH levels

have been associated with poor clinical outcomes in ESRD.[7] In the general population, a meta-analysis of observational data revealed an association between higher PTH levels and CV events.[8] However, recent clinical trials, including Paricalcitol Capsules Benefits Renal Failure Induced Cardiac Morbidity in Subjects With Chronic Kidney Disease Stage 3/4 (PRIMO) and Oral Paricalcitol in Stage 3 - 5 Chronic Kidney Disease (OPERA), patients with CKD Stages 3 to 5 treated with vitamin D analogs did not show a clinical benefit on the primary outcomes from lowering PTH levels.[9,10] Therefore, clinicians are left in a quandary about what PTH levels to target in patients with CKD Stages 4 and 5.

THE USE OF NUTRITIONAL VITAMIN D (25-HYDROXYVITAMIN D USE)

Nutritional vitamin D (precursors or analogs of 25-hydroxyvitamin D) is obtained from either exposure to sunlight, vitamin D–containing foods (such as fish and fortified dairy products), or dietary supplement use. Currently available nutritional vitamin D formulations in the United States include ergocalciferol (D_2), calcifediol (D_3), and cholecalciferol (D_3). In 2001 to 2006, 32% of US population had 25-hydroxyvitamin D levels <20 ng/mL, a level that most agree is inadequate.[11] Patients with CKD are more likely to have low vitamin D levels due to proteinuria, less outdoor physical activity, and dietary restrictions.[12] 25-hydroxyvitamin D gets converted to 1,25-dihydroxyvitamin D in the kidney and other tissues where the 1-alpha hydroxylase functions (such as monocytes, and so forth). Theoretically, patients with CKD may require nutritional vitamin D (25-hydroxyvitamin D) as a substrate for production of 1,25-dihydroxyvitamin D in sites other than the kidney, and this conversion may have noncalcemic actions, such as actions on the immune system, the heart, the pancreas, and others.[13-16] Another area of 25-hydroxyvitamin D research at particular interest for nephrologists is possible kidney-protective effects of higher 25-hydroxyvitamin D levels.[17-20] Multiple observational studies have shown an association between low 25-hydroxyvitamin D levels and a faster progression of CKD.[17-21] The mechanism underlying the renal protection may be related to effects on the renin-angiotensin system, reduction of albuminuria, or others.[22,23] However, convincing interventional studies in patients with CKD are lacking.

So, where is the evidence in 2015? We now know that in Stage 4 CKD and even Stage 5, nutritional vitamin D (25-hydroxyvitamin D) therapy may decrease PTH levels. A meta-analysis of nutritional vitamin D compounds was recently performed and found that in 4 randomized clinical trials including both dialysis and nondialysis CKD patients, PTH levels decreased significantly, −31.5 pg/mL (95% confidence interval [CI]: −57 to −6.1).[24] There was no evidence regarding patient outcomes.[24] This is a small decrease in PTH, but in patients with CKD Stage 4, where PTH levels are not extremely elevated, nutritional vitamin D (25-hydroxyvitamin D) may keep PTH levels closer to normal. KDIGO guidelines suggest that in patients with CKD Stages 3 to 5, clinicians should measure 25-hydroxyvitamin D levels.[4] If low 25-hydroxyvitamin D levels are discovered, patients should receive nutritional vitamin D (25-hydroxyvitamin D) per recommendations for the general population.[4] This topic was recently reviewed in a National Kidney Foundation initiative, and the panel concluded that there was currently not enough evidence to make recommendations for ideal vitamin D levels or supplementation in patients with CKD.[12]

CLINICAL SUMMARY

- Patients with CKD Stages 4 and 5 experience hyperphosphatemia and secondary hyperparathyroidism both of which are associated with poor clinical outcomes.
- Current therapy for secondary hyperparathyroidism includes the use of nutritional vitamin D (precursors of 25-hydroxyvitamin D; ergocalciferol, cholecalfierol, and calcifediol), activated vitamin D (1,25-dihydroxyvitamin D and its analogs; calcitriol, paricalcitol, or doxercalciferol), and cinacalcet.
- Phosphate levels are controlled through dietary restriction and the use of phosphate binders.
- Treatment with sodium bicarbonate appears to be safe.

THE USE OF ACTIVATED VITAMIN D (1,25-DIHYDROXYVITAMIN D USE)

Currently available activated forms of vitamin D (precursors or analogs of 1,25-dihydroxyvitamin D) include calcitriol, paricalcitol, and doxercalciferol. Two Cochrane reviews[25,26] showed that in both dialysis and predialysis CKD patients, calcitriol and activated vitamin D analogs decrease PTH (−196 pg/mL, 95% CI: −298 to −94 in dialysis patients; −49 pg/mL, 95% CI: −86 to −13 in predialysis patients) but increase serum phosphate and calcium levels. Not enough data exist from randomized clinical trials to make conclusions about patient outcomes such as fractures, mortality, or need for dialysis in predialysis patients.[25,26] Two recently published trials tried to evaluate the effects of activated vitamin D on left ventricular (LV) hypertrophy. The OPERA trial was conducted in 60 patients with Stage 3-5 CKD and LV hypertrophy by echocardiographic criteria.[9] The trial did not find any difference in LV mass index, the primary end point, between the randomized groups after 52 weeks of paricalcitol 1 mcg daily.[9] Paricalcitol, as expected, decreased PTH and alkaline phosphatase levels. Interestingly, there were fewer CV-related hospitalizations in the paricalcitol group (0 in the paricalcitol group vs 5 in the placebo group).[9] Essentially, this trial showed that paricalcitol does not cause regression of LV mass in patients with CKD and LV hypertrophy.

The PRIMO study, a larger trial, randomized 227 patients with CKD Stages 3 and 4 to paricalcitol 2 mcg or identical placebo for 48 weeks.[10] The primary end point in this trial, change in LV mass index, was not different between the randomized groups.[10] Interestingly, similar to the OPERA trial, there were fewer CV-related hospitalizations in the