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CKD-MBD in stage 4 and 5 CKD: What we know in 2015

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Abstract

Patients with CKD stages 4 and 5 experience and are treated for biochemical derangements associated with Chronic Kidney Disease- Mineral Bone Disorder (CKD-MBD). 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 to 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.

Keywords

FGF-23; hyperphosphatemia; mortality; vascular calcification; hyperparathyroidism; phosphate binders; metabolic acidosis

Introduction

Patients with chronic kidney disease (CKD) stages 4 and 5 begin to exhibit biochemical manifestations of chronic kidney disease- mineral bone disorder (CKD-MBD) with elevations in phosphate and 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 end-stage renal disease, 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.

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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 risk found in CKD.²

Parathyroid hormone (PTH) levels are also elevated at lower 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, 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 upon by expert panels based on available data.^{4,5}

Ideal PTH levels

The current KDIGO guidelines for CKD suggest that the optimal level of PTH is not known in people with GFR <45 ml/min/1.73m².⁴ 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 shows that PTH values start increasing likely with an eGFR <60 ml/min/1.73m² and that by the time the GFR is less than 30 ml/min/1.73m² approximately 70% of patients will have an elevated PTH.⁶ The reason there is no consensus on the optimal level of PTH in stage 4 and 5 CKD is due to the dearth of data on clinical outcomes in this patient population. Higher PTH levels have been associated poor clinical outcomes in end-stage renal disease.⁷ In the general population, a meta-analysis of observational data revealed an association between higher PTH levels and cardiovascular events.⁸ However, recent clinical trials, including PRIMO and OPERA, in patients with CKD stages 3–5 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) and from dietary supplement use. Currently available nutritional vitamin D formulations in the United States include ergocalciferol (D₂) calcifediol (D₃) and cholecalciferol (D₃). In 2001–2006, 32% of US population had 25-hydroxyvitamin D levels <20 ng/mL, a level which 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, etc). 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 non-calcemic 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 renal-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 non-dialysis CKD patients, PTH levels decreased significantly, -31.5 pg/ml (95% 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 3–5, 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

The Use of Activated Vitamin D (1,25-dihydroxyvitamin D use)

Currently available activated forms of vitamin D (pre-cursors or analogs of 1,25-dihydroxyvitamin D) include calcitriol, paricalcitol and doxercalciferol. Two Cochrane reviews^{25,26} showed that in both dialysis and pre-dialysis 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 pre-dialysis 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 pre-

dialysis patients.^{25,26} Two recently published trials tried to evaluate the effects of activated vitamin D on left ventricular hypertrophy. The OPERA trial was conducted in 60 patients with stage 3–5 CKD and left ventricular (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 cardiovascular related hospitalizations in the paricalcitol group (0 in the paricalcitol group vs. 5 in the placebo group).⁹ Essentially this trial showed that paricalcitol doesn't cause regression of LV mass in patients with CKD and LVH.

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 left ventricular mass index, was not different between the randomized groups.¹⁰ Interesting, similar to the OPERA trial, there were fewer cardiovascular related hospitalizations in the paricalcitol group in PRIMO, 1 in the paricalcitol group, 7 in the placebo group.¹⁰ A post-hoc analysis of the PRIMO trial, published separately, revealed that therapy with paricalcitol significantly decreased left atrial volume.²⁷ Thus, the findings of fewer cardiovascular hospitalizations in both studies suggest the need for another clinical trial with CV hospitalizations as the primary outcome. However, until such a trial is done, evidence shows no differences between activated vitamin D and placebo.

One possible worrisome finding of the PRIMO trial was the faster decline in eGFR in the paricalcitol group (creatinine based: $-4.1 \text{ ml/min/1.73m}^2$ (standard deviation (SD) 0.9; cystatin C based: -9.5 (SD 2.7)) compared to the placebo group (creatinine based: $-0.1 \text{ ml/min/1.73m}^2$ (SD 0.7); cystatin C based: -3.8 (SD 2.7)) ($p < 0.001/p = 0.06$).¹⁰ Activated vitamin D increases creatinine levels without decreasing GFR, therefore the investigators used a cystatin C based estimate as well.²⁸ Even the cystatin C based eGFR estimates showed faster decline in the paricalcitol group, although this was not statistically significant ($p = 0.06$). The paricalcitol group had a lower mean eGFR ($31 \text{ ml/min/1.73m}^2$) at baseline compared to the placebo group ($36 \text{ ml/min/1.73m}^2$) and more patients initiated chronic dialysis in the paricalcitol group (6 vs. 1). It is hard to know whether this difference was due the paricalcitol itself or due to the baseline imbalances between the groups. Clinicians should be aware that activated vitamin D compounds increase creatinine levels and should watch for this effect. If patients quickly lose kidney function on an activated vitamin D (1,25-dihydroxyvitamin D) agent, it is probably prudent to stop the agent and re-assess.

The Use of Cinacalcet

Cinacalcet HCl is a calcimimetic agent that effectively suppresses parathyroid hormone secretion by acting as a modulator of the calcium-sensing receptor on the parathyroid chief cell, causing the chief cell to decrease production of parathyroid hormone. It is used in ESRD to control secondary hyperparathyroidism. As such, the effect of PTH on bone is decreased, resulting in better preserved mineral metabolism while calcium and phosphorus homeostasis is optimized. Can the same principal apply to pre-dialysis patients with varying degrees of GFR?

In a short-term study of 18 weeks, Cinacalcet was effective in decreasing PTH in predialysis patients as compared to placebo, when given with vitamin D sterols.²⁹ Serum phosphorus levels increased while urinary excretion of phosphate decreased significantly in the cinacalcet group as compared with the placebo group. Use of phosphate binders was increased in the cinacalcet group. Cinacalcet was associated with increased serum phosphorus in a 32 week RCT in both CKD 3 and CKD 4 patients, while achieving a reduction in PTH (30%).³⁰ Urinary excretion of phosphorus was decreased in the cinacalcet group.

Since the kidney in ESRD is terminally diseased or may not even be present, PTH cannot affect phosphate handling in the renal tubule. This is not the case in pre-dialysis patients: Phosphate homeostasis is at least partially dependent on PTH effect on the kidneys. Suppressing PTH secretion results in decreased PTH effect on the proximal convoluted tubule, decreased activation of adenylyl cyclase and NaPi2 transporter systems, decreased phosphate secretion into urine, and ultimately retention of phosphorus in the serum, causing hyperphosphatemia. Hyperphosphatemia is an adverse outcome that is to be avoided in patients with declining renal function. On the other hand, decreasing PTH with cinacalcet has been shown to prevent parathyroid proliferation in animal models,³¹ which may be ultimately beneficial in avoiding the sequelae of secondary hyperparathyroidism.

Ideal Phosphate Level

Phosphate levels increase in stage 4 and 5 CKD due to decreased renal reserve and because compensatory mechanisms, such as elevated FGF-23 and PTH are no longer able to offset for the loss of nephrons. The 2009 KDIGO guidelines suggest maintaining the serum phosphate level in the normal range in stage 4 and 5 CKD. Some suggest that in the future we may use FGF-23 to target our phosphate therapy because phosphate elevation happens so late in the course of CKD. Thus, while we do not know what the ideal phosphate levels are, it is important to note that multiple observational studies have revealed an association between elevated phosphate levels and cardiovascular events and mortality in patients with CKD.^{7,32} Basic science evidence reveals that upon contact with elevated phosphate levels, vascular endothelial cells become osteoblast-like cells which may lead to the vascular calcification so common in patients with kidney disease.³³ Thus, because elevated phosphate levels, probably both directly and through effects on FGF-23, are associated with increased morbidity and mortality, phosphate levels should probably be maintained as close to normal as possible in patients with CKD stages 4 and 5.

Phosphate lowering therapy in CKD stage 4–5: Diet

The first line of phosphate lowering therapy should be dietary phosphate restriction. Phosphate is contained in multiple different foods, such as protein (meat), dairy products, nuts, beans and peas, dark cola drinks, bran and packaged foods where phosphate is used as a preservative. Dietary restriction of protein is controversial in kidney disease due to the risk of malnutrition³⁴ and inconsistent outcome data.^{35,36} Interestingly, a study in patients with stage 3 and 4 CKD showed that a vegetarian diet lowers phosphorus levels more than a meat diet with the same amount of protein.³⁷ Thus, dietary phosphate intake as well as the type of

protein containing the phosphate probably affects serum phosphate levels. If dietary restriction is not enough, phosphate binders can be used.

Phosphate lowering therapy in CKD stage 4–5: Binders

Usually dietary restriction is not sufficient to lower phosphate levels, and therefore phosphate binders must be used. There has not been a large, randomized clinical trial comparing phosphate binders to placebo to evaluate patient-level outcomes. Therefore, we must rely on observational studies and meta-analyses of smaller trials to guide our clinical practice. Observational studies suggest that patients on phosphate binders, at least those on hemodialysis, have better survival.³⁸ A recent meta-analysis evaluating whether drug effects on the surrogate markers of phosphate, PTH and calcium revealed that drug effects on biomarkers are weakly correlated with all-cause and cardiovascular deaths in CKD.³⁹ One interesting study which was not powered to look at outcomes, suggested that phosphate binder use compared to placebo decreased phosphate levels and 24 hour urinary phosphorus but that phosphate binders increased coronary artery and abdominal aortic calcification.⁴⁰ Although a small study, it was well-designed and the results were the opposite of what was expected. Much further research is needed in this area.

Phosphate binders: Is one better than the others?

There are now multiple different phosphate binders available on the market. All of them are approved for dialysis patients. Traditionally, they are divided into calcium based binders and non-calcium based binders which include sevelamer, lanthanum, aluminum and the newly approved iron based binders (Table 1 for selected clinical trial information). Several studies in dialysis and non-dialysis patients with kidney disease have been recently summarized in a meta-analysis.⁴¹ This meta-analysis combined data from 18 studies (11 randomized clinical trials) and found that non-calcium based phosphate binders were associated with a 22% lower risk of all-cause mortality (Risk ratio 0.78 (95% confidence intervals (CI): 0.61 to 0.98)).⁴¹ They also found less vascular calcification in the patients on non-calcium based phosphate binders.⁴¹ Interestingly, there was no difference in phosphate levels between the different binder groups, suggesting that potentially phosphate is so tightly regulated that although phosphate levels were not different, upstream regulators (such as FGF-23 or PTH) may explain the differential mortality risk between the groups. A differential effect on the levels of FGF-23 exists, with the calcium based phosphate binders leading to an increase in FGF-23 levels whereas non calcium based binders such as sevelamer and iron based phosphate binders caused a decrease in the levels and lanthanum did not cause the levels to change significantly.^{40,42,43} Thus, while definitive data is lacking, the current evidence suggests that phosphate binder use definitely lowers serum phosphate levels. The bulk of the evidence suggests that non-calcium based phosphate binders are likely better than calcium based phosphate binders.

Ideal Bicarbonate Levels

Many patients with stage 4 and 5 CKD develop a metabolic acidosis due to the kidney's decreased capacity to excrete ammonia. Approximately 30–50% of patients with eGFR <30

ml/min/1.73m² have a serum bicarbonate level <22 meq/L.^{44,45} Current guidelines suggest keeping serum bicarbonate levels >22 meq/L in order to prevent overt acidemia.⁴⁶ Since bone is the major of chronic acidosis, bicarbonate therapy in patients with CKD may aid to preserve bones. Low serum bicarbonate levels are associated with lower bone mineral density in older adults.^{47,48} Other associations between low bicarbonate levels and clinical outcomes include a faster progression of chronic kidney disease, insulin resistance, and possibly mortality.^{49–52} Evidence of faster progression of CKD is derived from both observational and animal studies showing complement activation and tubular injury with metabolic acidosis.^{49,50} Interestingly, there is also observational evidence showing that a high serum bicarbonate level (>26 meq/L) are associated with a higher risk of heart failure.⁵³ Thus, the ideal bicarbonate level is still unknown but likely lies between 22 and 26 meq/L.

Bicarbonate therapy: Possible benefits?

Small clinical trials show that treatment with sodium bicarbonate may decrease the rate of progression of CKD.^{54,55} One of these trial was an open label, randomized trial showing slower decline in creatinine clearance (5.93 vs. 1.88 mL/min per 1.73 m²; p < 0.0001) and fewer cases of ESRD seen in 134 patients with CKD stage 4 and serum bicarbonate levels of 16–20 mEq/L and randomized to receive oral sodium bicarbonate when compared to controls receiving usual care.⁵⁵ Interestingly, an alkaline diet high in fruits and vegetables may be able to achieve similar results.^{56,57} In addition, in chronic kidney disease, treatment with sodium bicarbonate has been shown to be safe and may improve muscle function.⁵⁸ While evidence is not definitive, it appears that treatment with sodium bicarbonate is safe and may have benefits in patients with CKD.

Summary

Patients with stage 4 and 5 CKD are unique because they start manifesting most of the biochemical derangements of CKD-MBD. However, there is not as much randomized clinical trial evidence to guide clinicians and guideline makers as in patients with end-stage renal disease. Current evidence suggests that phosphate binder use (probably non-calcium containing) may be associated with improved outcomes. The use of activated and nutritional vitamin D compounds and cinacalcet for control of PTH levels are not currently backed by randomized clinical trial evidence of efficacy on patient outcomes. If using vitamin D compounds or cinacalcet, clinicians must be aware of possible elevations in serum creatinine with vitamin D compounds and hyperphosphatemia with both vitamin D compounds and cinacalcet. Treatment of metabolic acidosis in CKD either with an alkaline diet or sodium bicarbonate appears to be safe and may have beneficial effects on kidney disease progression.

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Clinical Summary

Patients with CKD stages 4 and 5 experience hyperphosphatemia and secondary hyperparathyroidism which are both associated with poor clinical outcomes. Current therapy for secondary hyperparathyroidism includes the use of nutritional vitamin D (precursors of 25-hydroxyvitamin D) (ergocalciferol, calcifediol or cholecalciferol), 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 of metabolic acidosis appears to be safe.

Selected clinical trials of phosphate binder therapy in patients with chronic kidney disease stages 4 and 5.

Table 1

Study	Study Design	Sample size	CKD stage	Study duration	Drugs	Primary end point	Results
Russo et al (2007)	RCT	90	Stage 3–5	2 years	Calcium carbonate vs. sevelamer vs. placebo	Total calcium scores (TCS) and CAC	TCS (initial vs. final) Controls (369±115 vs. 547±175); ($p<0.001$) Ca treated (340±38 vs. 473±69); ($p<0.001$) Sevelamer (415±153 vs. 453±127); NS
Scaria et al (2009)	Randomized, open label cross over study	26	Stage 4	12 weeks	Lanthanum carbonate vs. calcium acetate	Serum phosphorus, calcium, Ca × P product, Serum alkaline phosphate	The mean serum phosphorus concentrations showed a declining trend with lanthanum carbonate (from pre-drug levels of 7.88 ± 1.52 mg/dL– 7.14 ± 1.51 mg/dL) and calcium acetate (7.14 ± 1.51 mg/dL) and calcium acetate (7.14 ± 1.51 mg/dL). A statistically significant difference was seen when comparing the change in serum calcium produced by these drugs ($P<0.05$)
Gulati et al (2009)	Randomized control study	22	Stage 3–4	12 weeks	Sevelamer HCl vs. calcium acetate	Decrease in serum phosphorus level	The adjusted mean serum phosphate levels at 12 weeks did not differ significantly between calcium acetate– (5.3 mg/dl) and sevelamer-treated subjects (6.1 mg/dl) (P adjusted Means = 0.6).
Di Lorio et al (2012)	randomized, multicenter, nonblinded pilot study	212	Stage 3–4	36 months	Sevelamer vs. calcium carbonate	All-cause mortality	The rate of all-cause mortality, dialysis inception, and the composite end point was significantly less frequent (log-rank test = 11.46; $P<0.01$) among patients randomized to sevelamer
Block et al (2012)	Randomized controlled trial	N = 176	Stage 3b–4	9 months	Calcium acetate vs. lanthanum carbonate vs. sevelamer carbonate vs. placebo	Change in mean serum phosphorus	Baseline mean serum phosphorus active and placebo – 4.2mg/dl At End of Active therapy – 3.9mg/dl At end of Placebo – 4.1mg/dl $P = 0.03$ (final active vs final placebo)

Study	Study Design	Sample size	CKD stage	Study duration	Drugs	Primary end point	Results
Kathleen M. Hill et al (2013)	randomized cross-over placebo controlled study	N – 8	stage 3–4	Two 3 week periods	Calcium carbonate vs. placebo	Calcium and phosphorus balances and calcium kinetics	Calcium carbonate= positive calcium balance and significantly higher than placebo (508 vs. 61 mg/d, respectively, $p=0.002$) Phosphorus balance was not significantly different from zero on placebo and did not differ between calcium carbonate and placebo (153 vs. 95 mg/d, $p=0.2$)
Block et al (2014)	Double-blind, placebo-controlled randomized trial	N – 149	stage 3–5	12 weeks	Ferric citrate vs placebo	TSAT and serum phosphate level	mean TSAT in ferric citrate increased from $22\% \pm 7\%$ (SD) to final $32\% \pm 14\%$ vs placebo $21\% \pm 8\%$ to $20\% \pm 8\%$ ($p < 0.001$) serum phosphate levels reduced in ferric citrate from 4.5 ± 0.6 to 3.9 ± 0.6 mg/dL vs placebo $4.7 (4.7 \pm 0.6$ to 4.4 ± 0.8 mg/dL ($p < 0.001$))
Keitaro Yokoyama et al (2014)	multicenter, double blind, randomized trial	N – 90	eGFR = 9.21 ± 5.72 ml/min per 1.73 m^2	12 weeks	2:1 to ferric citrate hydrate vs placebo	change in serum phosphate from baseline to the end of treatment	Ferric citrate hydrate mean S. phosphorus change from baseline – 21.29 mg/dl (95% CI, – 1.63 to – 0.96 mg/dl) Placebo group mean S. phosphorus change from baseline – 0.06 mg/dl (95% CI, – 0.20 to 0.31 mg/dl) ($P < 0.001$ for difference between groups)