Title

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Journal

International Urology and Nephrology, 40(2)

ISSN

0924-8455

Authors

Kovesdy, Csaba P

Kalantar-Zadeh, Kamyar

Publication Date

2008-06-01

DOI

10.1007/s11255-008-9346-7

Int Urol Nephrol (2008) 40:427–440
DOI 10.1007/s11255-008-9346-7

REVIEW

Bone and mineral disorders in pre-dialysis CKD

Csaba P. Kovesdy · Kamyar Kalantar-Zadeh

Received: 15 January 2008 / Accepted: 29 January 2008 / Published online: 27 March 2008

Abstract Disorders in calcium, phosphorus, and parathyroid hormone (PTH) are common in chronic kidney disease (CKD) and may be associated with poor outcomes including a higher rate of CKD progression and increased death risk. Although these abnormalities have been examined extensively in patients with CKD stage 5 who are receiving chronic maintenance dialysis, they have not been studied to the same extent at earlier stages of CKD, in spite of the much larger numbers of patients in the early CKD population. We summarize the available literature on outcomes associated with bone and mineral disorders in patients with CKD not yet receiving maintenance dialysis. We have reviewed novel data linking fibroblast growth factor 23 (FGF-23) to phosphorus and vitamin D homeostasis. More rapid CKD progression is linked to hyperphosphatemia and its associated hyperparathyroidism and vitamin D deficiency. Hence, hyperphosphatemia may play a central role in the diverse disorders characterizing CKD. We provide a brief overview of the available treatment recommendations for bone and mineral disorders, with an emphasis on areas needing further research.

Keywords Chronic kidney disease · Parathyroid hormone · Hyperphosphatemia · Mortality · FGF-23 · 1,25-Dihydroxy-cholecalciferol

C. P. Kovesdy (✉)
Division of Nephrology, Salem VA Medical Center, 1970 Roanoke Boulevard, Salem, VA 24153, USA
e-mail: csaba.kovesdy@va.gov

C. P. Kovesdy
University of Virginia, Charlottesville, VA, USA

K. Kalantar-Zadeh
Harold Simmons Center for Kidney Disease Research and Epidemiology, Torrance, CA 90502, USA

K. Kalantar-Zadeh
Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA 90502, USA

K. Kalantar-Zadeh
David Geffen School of Medicine at UCLA, Torrance, CA 90502, USA

Abbreviations

CKD	Chronic kidney disease
PTH	Parathyroid hormone
FGF-23	Fibroblast growth factor 23
MHD	Maintenance hemodialysis
MBD	Mineral and bone disorder
SHPT	Secondary hyperparathyroidism
GFR	Glomerular filtration rate
MDRD	Modification of diet in renal disease
CV	Cardiovascular
AASK	African American study of hypertension and kidney Disease
1,25(OH)2D	1,25-Dihydroxycholecalciferol
ESRD	End stage renal disease

Introduction

Disorders of mineral and bone metabolism are common in patients with chronic kidney disease (CKD) [1] and have been implicated as a novel risk factor in the high mortality seen in patients receiving maintenance hemodialysis (MHD) therapy [2, 3]. Several abnormalities are grouped under the currently preferred term of CKD mineral and bone disorder (MBD), [4] including secondary hyperparathyroidism (SHPT), renal osteodystrophy, disorders of vitamin D metabolism, hyperphosphatemia, hypo- and hypercalcemia, and vascular calcification. While several of the abnormalities characterizing CKD-MBD develop during earlier stages of CKD, the outcomes associated with these abnormalities, along with the potential benefits of their treatment, are much less thoroughly studied in this patient population. The few studies that examined CKD-MBD at earlier stages of CKD have indicated that the adverse outcomes associated with hyperphosphatemia and SHPT in CKD stage 5 are also present at these earlier stages. Furthermore, in patients with CKD who are not yet on dialysis (hereinafter referred to as CKD) mortality is not the only outcome of interest; in these patients the impact of various risk factors on progression of CKD deserves to be assessed separately.

This review examines the available literature on the association between abnormalities of CKD-MBD and outcomes in the CKD population. While outcomes associated with abnormalities in phosphorus, calcium, and PTH metabolism, including the novel link via FGF-23 will be discussed separately, they often occur simultaneously, and need to be addressed as such in clinical practice. Treatment recommendations in CKD are limited by the paucity of clinical trials, but suggestions for future research are provided based on potential benefits suggested by observational data.

Hyperphosphatemia in CKD

Phosphorus is an essential building block of the human body as a component of the bony skeleton, adenosine triphosphate, nucleic acids, phospholipid membranes and blood and urinary buffers [5]. A complex regulatory system ensures the maintenance of phosphorus homeostasis under usual circumstances [6]. The kidneys play a pivotal role in this system as the main organs responsible for phosphorus excretion, and abnormalities affecting phosphorus are one of the centerpieces of CKD-MBD.

The FGF-23 axis

As the glomerular filtration rate (GFR) decreases several changes occur that affect phosphorus balance, the most important ones being a decrease in calcitriol level due to deficient 1α hydroxylation [7] (and with consequently lower intestinal calcium absorption, hypocalcemia, and stimulation of PTH production) and a decrease in the filtered amount of phosphorus (with consequent hyperphosphatemia, hypocalcemia and stimulation of PTH and fibroblast growth factor-23 [FGF-23] production) [8 9]. The higher PTH levels will enhance urinary clearance of phosphorus by lowering proximal tubular reabsorption, thus ensuring normal plasma levels, albeit at the expense of secondary hyperparathyroidism (the classical trade-off hypothesis [10]), and also a higher FGF-23 level, which in itself inhibits the 1-α hydroxylation of 25-OH-vitamin D, resulting in further lowering of calcitriol levels and more stimulation of PTH production (Fig. 1) [11, 12]. This regulatory mechanism is unable to compensate for phosphorus retention once the GFR falls below approximately 40 ml/min; this is when a subtle rise in serum phosphorus occurs, albeit mostly without manifest hyperphosphatemia [5]. Frank hyperphosphatemia becomes common once patients with CKD reach the need for dialysis where the lack of substantial kidney function combined with the inefficiency of thrice weekly dialysis treatments in facilitating phosphorus clearance [13] result in a persistent positive phosphate balance unless the amount of absorbed phosphorus is diminished.

Outcomes associated with serum phosphorus levels in CKD

Much attention has focused on hyperphosphatemia and its consequences in dialysis patients [3], even though they represent only a minority of all patients with CKD [14]. The lesser attention devoted to this issue in patients with CKD may be explained by the

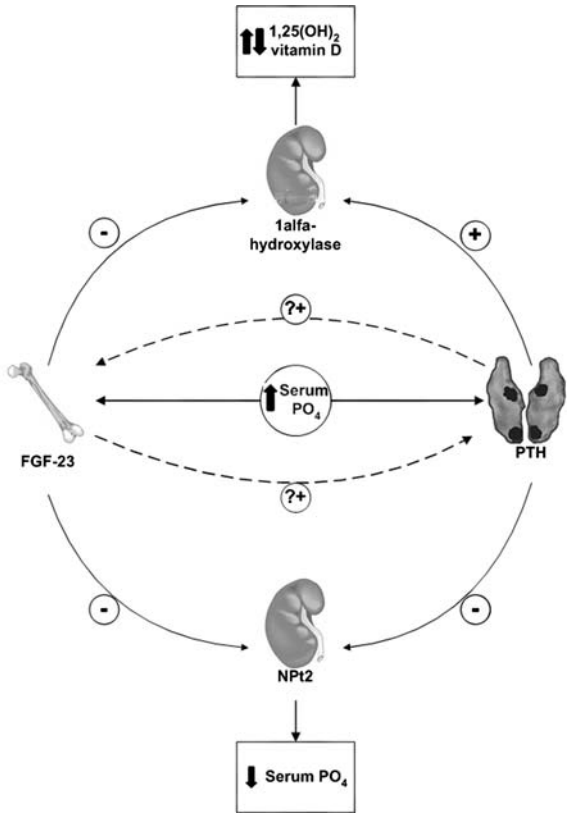

Fig. 1 Mechanism of action whereby fibroblast growth factor-23 and parathyroid hormone participate in the regulation of phosphorus and activated vitamin D metabolism

lack of available data sources, but also by the differences in the bone–mineral milieu between patients with CKD and those on dialysis: as detailed above, serum phosphorus levels in patients with CKD are in general much lower until CKD reaches stage 5. In vitro data suggest that the phenotypic transformation of aortic smooth muscle cells into osteoblast-like cells that is thought to be involved in the soft tissue and cardiovascular calcification mediated by hyperphosphatemia occurs at ambient phosphorus concentrations of about 6 mg/dl and above [15]. Such elevated plasma phosphorus levels are unusual in CKD, and it is hence possible that the cardiovascular effects of hyperphosphatemia are more subtle at earlier stages of CKD, and thus more difficult to detect. A distinct challenge in CKD is the presence of competing end points: while mortality is still of major interest, progression of CKD is also regarded as a separate end point and is in fact the main focus of nephrologists' clinical practice.

Mortality and phosphorus level in CKD

Following several studies showing a significant association between hyperphosphatemia and mortality in dialysis patients [2, 3], three studies have examined the same issue in patients with CKD, and one in a non-CKD population (Table 1). Kestenbaum et al. [16] examined 3,490 US veterans with CKD and showed that higher phosphorus was associated with higher mortality. The second study was a secondary analysis from the Modification of Diet in Renal Disease (MDRD) study: Menon et al. [17] examined 839 mostly non-diabetic patients and showed an association between higher phosphorus and all-cause and cardiovascular (CV) mortality, but the associations were not statistically significant. The third study, by Voormolen et al. [18], examined 448 patients with CKD stage 4–5 and found a hazard ratio for all-cause mortality of 1.62 (95% CI: 1.02–2.59) associated with a 1-mg/dl higher phosphorus level. The fourth study was by Tonelli et al. [19], who examined 4,127 participants with normal kidney function enrolled in the Cholesterol and Recurrent Events study, and showed that higher plasma phosphorus level was associated with higher all-cause mortality, CV mortality, fatal or non-fatal myocardial infarction, and new onset congestive heart failure. The putative mechanism(s) behind the observed associations could be the calcification-inducing effects of phosphorus on the vascular bed [15, 20], or the concomitant deleterious effects of other factors linked to hyperphosphatemia, such as secondary hyperparathyroidism [3].

Phosphorus and progression of CKD

Three observational studies have examined the association between higher phosphorus and progression of CKD (Table 1). We examined the association between phosphorus level and the incidence of dialysis or doubling of serum creatinine in 985 male US veterans with CKD and found that higher phosphorus was associated with a higher incidence of the renal end point (Fig. 2); a 1-mg/dl higher phosphorus level was associated with an adjusted hazard ratio of 1.29 (95% CI: 1.12–1.48, $P < 0.001$) [21]. A second study by Norris et al. [22] examined risk factors for progression of CKD in 1,094 black patients enrolled in the African American Study of

Table 1 Outcomes associated with plasma phosphorus level in chronic kidney disease

End point	Study reference	Number of patients	Kidney function	Main results	Comments
All-cause mortality	[16]	3,490	Mean creatinine clearance 47.2 ml/min	A 1-mg/dl higher PO_4 level associated with a hazard ratio for all-cause mortality of 1.23 (95% CI: 1.12–1.36)	Patients were mostly males and mostly Caucasian
	[17]	839	Mean GFR: 33 ± 12 ml/min/1.72 m^2	A 1-mg/dl higher PO_4 level associated with a hazard ratio for all-cause mortality of 1.10 (95% CI: 0.86–1.40); and for CV mortality of 1.27 (0.94–1.73)	Low mortality rate, limited external validity
	[18]	448	Mean estimated GFR: 13 ± 5.4 ml/min/1.72 m^2	A 1-mg/dl higher PO_4 level associated with a hazard ratio for all-cause mortality of 1.62 (95% CI: 1.02–2.59)	Only 6.7% of patients died
	[19]	4,127	Normal or nearly normal kidney function (no overall mean value available)	A 1-mg/dl higher PO_4 level associated with a hazard ratio for all-cause mortality of 1.27 (95% CI: 1.02–1.58)	Also showed higher associations for congestive heart failure and cardiovascular events
Progression of CKD	[21]	985	Mean estimated GFR: 37.0 ± 17.5 ml/min/1.72 m^2	A 1-mg/dl higher PO_4 level associated with a hazard ratio of renal composite outcome of 1.29 (95% CI: 1.12–1.48)	All patients were males
	[22]	1,094	Mean GFR: 46.4 ± 13.6 ml/min/1.72 m^2	A 0.3-mg/dl higher PO_4 level associated with a hazard ratio of renal composite outcome of 1.07 (95% CI: 1.00–1.15)	Association maintained when composite of renal events and death was examined as the end point
	[18]	448	Mean estimated GFR: 13 ± 5.4 ml/min/1.72 m^2	A 1-mg/dl higher PO_4 level associated with a 0.178 ml/min/month higher progression (95% CI: 0.082–0.275)	Examined ordinary least squares regression slopes of estimated GFR as a marker of progression

GFR: glomerular filtration rate

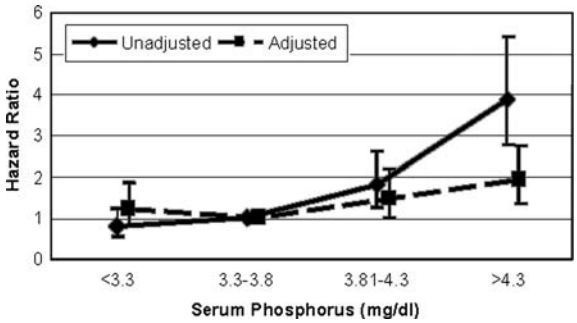

Fig. 2 Hazard ratio (95% confidence interval) of the composite outcome of end stage renal disease and doubling of serum creatinine associated with quartiles of serum phosphorus, unadjusted and after adjustment for age, race, systolic and diastolic blood pressure, diabetes, smoking status, estimated glomerular filtration rate, serum albumin, calcium, bicarbonate, blood urea nitrogen, hemoglobin, 24-h urine protein, and use of calcium-containing phosphate binders and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. The group with serum phosphorus 3.3–3.8 mg/dl served as a reference. Based on data presented in Schwarz et al. [21]

Hypertension and Kidney Disease (AASK) and found phosphorus level to be one of several independent predictors of progressive CKD. The third study by Voormolen et al. [18] described an association between higher serum phosphorus levels and faster decline in renal function (by examining slopes of estimated GFR) in 432 patients with CKD. The plausibility of these findings is strengthened by the results of studies in patients with CKD [23, 24] and in laboratory animals [25–27], which showed an attenuation of the progression of CKD after dietary restriction of phosphorus. Several mechanisms could be responsible for the observed associations: renal parenchymal calcification, a deleterious effect of SHPT, hemodynamic alterations, and derangements in cellular energy metabolism have been suggested as plausible explanations [27–29].

Treatment of hyperphosphatemia in CKD

The rationale for lowering phosphorus level in CKD is not necessarily to treat frank hyperphosphatemia (given the relative infrequency of it), but rather to treat secondary hyperparathyroidism. Given the association of higher phosphorus levels with mortality and progression of CKD, it is also possible that lowering plasma phosphorus may be beneficial in lowering these outcomes, but this would have to be proven in clinical trials first.

Strategies to lower plasma phosphorus in CKD include dietary phosphate restriction and the application of medications that inhibit the intestinal absorption of phosphorus. Dietary protein restriction (with concomitant restriction of phosphate intake) is already one of the strategies applied to alleviate progression of CKD [30]. Medications that inhibit the absorption of phosphorus include phosphate binders (calcium, magnesium, iron and lanthanum salts, and sevelamer hydrochloride) and inhibitors of intestinal mucosal phosphate transport (nicotinamide [31]) (Table 2). None of these medications has been formally approved for therapy of hyperphosphatemia in CKD; thus, their "off-label" use would be based on data and experience drawn mostly from dialysis patients. It is also worth remembering that the application of either one of the above treatments should be applied with the understanding that there is currently no consensus about what an ideal plasma phosphorus level should be in CKD. The K/DOQI (Kidney Disease Outcomes Quality Initiative) guidelines on bone and mineral disorders recommend a plasma phosphorus concentration of 2.7–4.5 mg/dl [8], which in fact corresponds to what is currently regarded as the "normal" range of plasma phosphorus, but it does not address the results of more recent studies that suggest a graded increase in the risk of adverse outcomes associated with higher levels of phosphorus, even within this "normal" range (Table 1). One could also argue that it is not only the plasma phosphorus level that should serve as a therapeutic target in CKD, but also the plasma PTH level and/or the amount of phosphorus excreted in the urine. Further research is warranted to clarify these issues. Another issue worth discussing is the safety of the calcium containing medications in CKD; we will discuss this topic in the following section.

Serum calcium level and calcium intake in CKD

Before the early-to-mid 1980s hyperphosphatemia was managed with aluminum-containing phosphorus binders and dietary phosphorus restriction [32]. Following the emergence of data on the untoward consequences of aluminum-based binders (dementia, refractory anemia, and osteomalacia) [33, 34], calcium-based

Table 2 Phosphorus binders that may be used off-label in a chronic kidney disease population not on dialysis

	Pros	Cons
Calcium carbonate (Tums™)	Most inexpensive, antacid properties useful for reflux and peptic ulcer disease	High calcium load
Calcium acetate (PhosLo™)	Relatively inexpensive, less GI calcium absorption compared with Ca carbonate	May contribute to calcium load and worsens vascular calcification
Aluminum hydroxide (Amphogel™)	Most effective/potent binder, inexpensive	Aluminum toxicity. Should not be used as maintenance treatment
Sevelamer-HCl (Renagel™)	Calcium and metal-free binder; may have ancillary benefits beyond phosphorus control, such as lipid lowering, uric acid lowering, anti-inflammatory effect	Expensive, may worsen metabolic acidosis and hyperchlorhydria, GI symptoms such as diarrhea. High pill burden
Sevelamer carbonate (RenVela™)	Calcium and metal-free binder; may have ancillary benefits beyond phosphorus control (see above), no metabolic acidosis. Improved GI tolerance	Probably expensive. Limited/no post-marketing experience
Lanthanum carbonate (Fosrenol™)	No calcium load. Low pill burden	Long-term safety of lanthanum accumulation unknown. Not allowed in liver disease. Chalky taste
Magnesium based (Magnebind™)	No calcium load. Anti-constipating	Potential for hypermagnesemia, diarrhea
Trivalent iron-containing binders	No calcium load	Limited information available
Niceritrol (inhibitors of intestinal phosphate transport)	Different mechanism of action, inexpensive	Poorly tolerated. Limited data available as a binder

medications became the binders of choice. These agents also offered the added benefit of further suppressing parathyroid hormone production [35]. Subsequently, vascular calcification was described to be prevalent in MHD, and it was found to be associated with poor survival in these patients [36, 37]. Once vascular calcification was found to be associated with higher serum calcium level and higher calcium intake [37–39], and once higher serum calcium levels were also associated with higher mortality [2, 3] in CKD patients receiving MHD, the use of calcium-containing binders in this patient population diminished, although their role continues to be a matter of intense debate [40].

Contrary to studies of patients receiving MHD, observational studies in CKD have in general failed to establish an association between higher serum calcium levels and coronary calcification [41–45]. The reason for the discrepant findings between studies in CKD and those examining MHD patients are unclear. One explanation could be the better calcium homeostasis provided by residual kidney function and the lack of additional calcium intake from dialysate sources in CKD; hypercalcemia is in fact uncommon, even in advanced stages of CKD [1].

Compared with MHD patients, much less is known about the role of calcium intake in CKD. A recent small clinical trial in patients with CKD compared coronary calcification in untreated hyperphosphatemic patients and in patients treated with calcium carbonate or sevelamer hydrochloride [46]. This study showed less progression of coronary calcification with calcium carbonate compared with untreated patients, but the progression was lowest in the group treated with sevelamer hydrochloride; this latter group also showed no significant changes in blood lipid levels [46]. It thus appears from this study that untreated hyperphosphatemia portends a poor prognosis, which can be improved by the administration of a calcium-containing phosphate binder. The finding of an even better outcome associated with using a non-calcium-containing binder may suggest that calcium could have had an additional deleterious effect that diminished its benefit of phosphate lowering. Further studies would be needed to clarify outcomes in the context of using other phosphate binders, including calcium-containing products with a lower absorbable calcium-load, and also different non-calcium-containing binders in order to differentiate between the potential effects of some binders that are unrelated to phosphate lowering [47].

Secondary hyperparathyroidism in CKD

Elevated PTH levels develop early in the course of CKD and progressively rise with advancing stages of this disease [1, 48–53]. SHPT develops as a result of a combination of events: deficiency of 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$) [1, 7], decreased expression of the vitamin D receptor [54] and the calcium-sensing receptor [55], hyperphosphatemia [56], hypocalcemia [57], and PTH resistance [58] are believed to contribute to it. More recently, fibroblast growth factor 23 (FGF-23) has emerged as a new regulator that may also play an important role in PTH regulation (Fig. 1) [11]. In addition to these CKD-specific factors, PTH levels are also influenced by various demographic [59, 60], anthropometric [61], and co-morbidity characteristics [62].

Secondary hyperparathyroidism is associated with a variety of complications including bone disease [63–66], uremic pruritus [67], refractory anemia [68], and cognitive and sexual dysfunction [69, 70]. In patients receiving MHD, SHPT has been associated with increased cardiovascular morbidity [48, 71–73] and mortality [2, 3]. The association of SHPT with mortality or with progression of kidney disease in CKD has not been well characterized. In a recent study of 515 male patients with CKD stages 3–5 (none receiving MHD), higher PTH level was associated with increased all-cause mortality (Fig. 3);

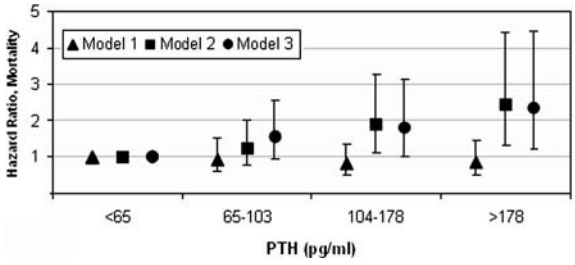

Fig. 3 Hazard ratios of all-cause mortality associated with different levels of intact parathyroid hormone level, unadjusted (Model 1), and after adjustment for case mix variables (age, race, body mass index, systolic and diastolic blood pressure, smoking status, comorbidity index, diabetes mellitus and use of activated vitamin D, calcium containing and non-calcium containing phosphate binders; Model 2), and case mix variables plus laboratory parameters (estimated glomerular filtration rate, calcium, phosphorus, albumin, cholesterol, hemoglobin, white blood cell count, percentage of lymphocytes in white blood cells and 24-h urine protein; Model 3). Based on data presented in Kovesdy et al. [74]

a serum intact PTH level of >65 pg/ml (compared with ≤65 pg/ml) was associated with an adjusted hazard ratio for all cause mortality of 1.59 (95% CI: 1.02–2.49) [74]. Interestingly, the higher risk of mortality in this study was already evident at PTH levels above the upper limit of the normal range (>65 pg/ml). Currently, the K-DOQI bone and mineral metabolism guidelines recommend an intact PTH level of 70–110 pg/ml for patients with CKD stage 4 [8]. This is an opinion-based guideline, and the results of the above study suggest that higher PTH levels, even within this range, could be associated with worse mortality; further research will be needed to clarify what the ideal treatment targets should be for SHPT. The lack of a lower threshold level for mortality risk in the above study is also in contrast to studies in MHD patients, in which the association of PTH level with mortality was U-shaped [3, 75]. A significant proportion of the higher mortality seen with lower PTH levels in MHD patients was, however, related to confounding by markers of malnutrition and inflammation [3], which themselves have been linked to higher mortality [76, 77].

The mechanism behind the higher mortality observed in patients with higher PTH remains speculative. Elevated PTH levels have been shown to cause a wide range of cardiovascular, metabolic, hematologic, and immunologic abnormalities. These include lower cardiac contractility, myocardial calcium deposition, hypertrophy and fibrosis and vascular calcification, [78] mitral annular calcification, [79] impaired insulin sensitivity [80] and glucose intolerance, [81] abnormal lipid metabolism, [82] bone marrow fibrosis [68] with ineffective erythropoiesis [83–85], and abnormal immune function [86]. Animal models showed that PTH increases myocardial calcium content and adversely affects energy utilization in myocardial tissue [87] and that it could play a role in myocardial fibrosis [88], impaired vasodilatation [89], and blood pressure-independent wall thickening of the intramyocardial arterioles [90]. In a population-based cross-sectional study, a higher PTH level was predictive of coronary heart disease [91]. It is important to emphasize that the link between SHPT and mortality in CKD remains associative; a cause–effect relationship can only be proven by clinical trials showing a benefit from lowering PTH levels. Thus far, we are unaware of any plans for such trials.

Progression of CKD and SHPT

The effect of SHPT on the progression of CKD is unclear. Animal studies have suggested that PTH may have an effect on podocytes [92, 93], which express PTH receptors [94, 95]. In a remnant kidney model PTH accelerated progression of CKD in animals that received a high protein diet, and parathyroidectomy attenuated the increase in serum creatinine [96]. Data in humans on the role of SHPT in the progression of CKD are even sparser. The study by Kovesdy et al. [74] detailed above found a significant association with a higher MHD initiation rate only in unadjusted models, but this association became nonsignificant once adjusting for confounding variables. No prospective trials have examined whether lowering PTH levels in CKD can retard the progressive loss of kidney function.

Treatment of SHPT in CKD

The complex pathophysiology of SHPT (vide supra) offers several options for correcting this abnormality. We have already discussed the potential role of phosphorus lowering in the treatment of SHPT in the section about phosphorus control; this benefit could be directly related to a phosphorus-lowering effect in the case of non-calcium-containing medications, with an added calcium-related effect provided by calcium-containing binders. Treatment of SHPT remains, nevertheless, an "off-label" indication for phosphate binder medications. In common practice secondary hyperparathyroidism in MHD has been managed by the provision of supplemental calcium (in the form of oral supplementation and through dialysate calcium) and active vitamin D; the latter initially in the form of synthetic calcitriol (in the US) and alfacalcidol (in Europe) [97–99], and more recently in the form of various analogs of activated vitamin D such as paricalcitol, doxercalciferol [100], and maxacalcitol [101]. Our armamentarium was further diversified with the recent introduction of the first calcium-sensing receptor agonist, cinacalcet [102]. Yet another therapeutic option could be the supplementation of 25(OH) vitamin D [103], the levels of which are low in patients with CKD [104], and the administration of which was able to suppress PTH production in vitro by virtue of direct stimulation of the vitamin D receptor and a slow tissue-level 1α hydroxylation [105]. Current guidelines recommend routine assessment of 25(OH) vitamin D and its replacement in the case of deficiency (Table 3) [8].

Mortality and activated vitamin D in CKD

In spite of the above plethora of various therapeutic options, presently only activated vitamin D and its analogs are explicitly approved as a treatment for SHPT in CKD. Administration of activated vitamin D and its analogs in MHD patients has been associated with improved survival compared with patients not receiving such treatments [3, 106, 107]. Similar studies in patients with CKD have not been available until recently. In a study of 520 male patients with CKD the administration of 0.25 mcg/day of oral calcitriol was associated with significantly better all-cause mortality, even after adjustment for multiple potential confounders [108]. The multivariable adjusted incidence rate ratio of all-cause mortality in

Table 3 Recommended supplementation schedule for 25(OH) vitamin D deficiency and insufficiency in CKD stages 3 and 4. Adapted from the National Kidney Foundation Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease [8]

Serum 25(OH) level, ng/ml (nmol/l)	Definition	Ergocalciferol dose (Vitamin D2)
<5 (12)	Severe vitamin D deficiency	50,000 IU/week orally × 12 weeks; then monthly OR 500,000 IU as single intramuscular dose
5–15 (12–37)	Mild vitamin D deficiency	50,000 IU/week × 4 weeks, then 50,000 IU/month
16–30 (40–75)	Vitamin D insufficiency	50,000 IU/month orally

treated versus untreated patients was 0.35 (0.23–0.54, $P < 0.001$) and for combined death and dialysis initiation it was 0.46 (0.35–0.61); this study also found a non-significant trend between calcitriol treatment and a lower incidence of end stage renal disease (ESRD) [108]. The above benefits were present in all the studied subgroups, including patients with lower pre-treatment PTH, and higher calcium and phosphorus levels. Similar findings were reported in another study examining the association of calcitriol therapy in mostly male patients with CKD [109].

The mechanism of action behind the higher survival associated with activated vitamin D therapy in the aforementioned studies remains unclear. As detailed earlier in this article, SHPT in itself is associated with higher cardiovascular morbidity [48, 71] and mortality [2, 3], which could explain why suppression of PTH concentrations with activated vitamin D would lead to lower mortality. The impact of activated vitamin D treatment may nevertheless be much wider ranging. The vitamin D receptor is ubiquitous, and its stimulation with vitamin D analogs has been shown to directly impact on the cardiovascular system by inhibiting the production of proteins implicated in arterial calcification [110–112], by stimulating the production of proteins that are inhibitors of arterial calcification [110, 113], by inhibiting the production of cytokines that are involved in calcification and atheroma formation [114, 115] and stimulating the production of cytokines that are inhibiting it [116, 117], and by preventing thrombosis [118]. Furthermore, activated vitamin D deficiency was associated with higher all-cause and cardiovascular mortality in a large cohort of hemodialysis patients [119], and lower $1,25(OH)_2$ vitamin D levels have been associated with worsened coronary calcification [120], also suggesting a PTH-independent link between vitamin D and survival.

In spite of the uniformity of the observational studies in MHD and at the earlier stages of CKD, and in spite of the plausible mechanisms of action detailed above, there have been no attempts to examine the benefit of activated vitamin D in randomized controlled trials. It is also unclear, as detailed above, how much of the benefit observed with activated vitamin D therapy can be ascribed to the lowering of PTH, and thus it is unclear whether similar benefits can be expected from other types of therapy.

Activated vitamin D therapy and progression of CKD

The application of activated vitamin D in CKD has been subject to concerns over their potential to hasten the decline of kidney function [99], which has been attributed to hypercalciuria and nephrocalcinosis, although hyperphosphatemia could also play a role [21]. Studies employing lower (non-hypercalcemic) doses of calcitriol did not show worsened renal outcomes [121]; in fact, one study indicated a tendency towards slower progression of CKD in a group treated with 0.25 mcg/day of calcitriol compared with placebo [122]. A study of 520 male patients with CKD examined the association between calcitriol therapy and the incidence of ESRD, and found a tendency towards a lower incidence of ESRD in the calcitriol-treated group [108], which raises the possibility of a renoprotective effect. Such an effect is indeed conceivable since therapy with paricalcitol, a selective vitamin D analog, has been shown to lower proteinuria [123]. The mechanism of a renoprotective effect from activated vitamin D could be related to their inhibition of cell proliferation [124] and inflammation [125, 126], or to suppression of renin production [127]. Prospective studies examining the renoprotective effect of activated vitamin D have not yet been performed in patients with CKD.

Conclusions

The various disorders that characterize CKD MBD are common in CKD. Recent evidence suggests that both hyperphosphatemia and SHPT are associated with deleterious outcomes in CKD, similar to what has been described in patients receiving MHD. The impact of hypercalcemia and calcium intake on outcomes in CKD is still unclear. Lowering plasma phosphorus levels in CKD can be beneficial in treating SHPT, and could become an additional therapy to lower mortality and to alleviate progressive loss of kidney function. Treatment of SHPT with calcitriol is associated with lower all-cause mortality, and may also have a renoprotective effect.

Several questions remain unanswered. It is unclear what the net benefit is from therapeutic agents that treat one aspect of CKD-MBD while worsening another. Such effects could occur when treating

hyperphosphatemia with calcium-containing binders (which could have the undesirable effect of hypercalcemia), or when treating SHPT with activated vitamin D (undesirable effects: hypercalcemia and hyperphosphatemia) or calcium receptor sensitizing agents (undesirable effect with cinacalcet in CKD: hyperphosphatemia [128]). It is also unclear what outcomes are associated with the use of 25(OH) vitamin D in the treatment of SHPT in CKD. More research is desirable to strengthen the conclusions of observational studies linking CKD-MBD to unfavorable outcomes in CKD, and randomized controlled trials will be needed before any of the therapies mentioned can be recommended as a means of improving mortality or progression of kidney disease in CKD.

Acknowledgements *Conflict of interest* Csaba P. Kovesdy and Kamyar Kalantar-Zadeh have received grants and/or honoraria from Amgen (manufacturer of Sensipar™), Abbott (manufacturer of Calcijex™ and Zemplar™), Genzyme (manufacturer of Hectorol™, Renagel™ and Renvela™), and/or Shire (manufacturer of Fosrenol™).

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