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Bone and mineral disorders in pre-dialysis CKD

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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

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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 1α 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

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
Progression of CKD	[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
	[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 TM)	Most inexpensive, antacid properties useful for reflux and peptic ulcer disease	High calcium load
Calcium acetate (PhosLo TM)	Relatively inexpensive, less GI calcium absorption compared with Ca carbonate	May contribute to calcium load and worsens vascular calcification
Aluminum hydroxide (Amphogel TM)	Most effective/potent binder, inexpensive	Aluminum toxicity. Should not be used as maintenance treatment
Sevelamer-HCl (Renagel TM)	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 TM)	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 TM)	No calcium load. Low pill burden	Long-term safety of lanthanum accumulation unknown. Not allowed in liver disease. Chalky taste
Magnesium based (Magnebind TM)	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 ($1,25(\text{OH})_2\text{D}$) [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 Kovessy 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 1 α 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 $\times$ 12 weeks; then monthly OR 500,000 IU as single intramuscular dose
5–15 (12–37)	Mild vitamin D deficiency	50,000 IU/week $\times$ 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 $1,25(\text{OH})_2$ 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.

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References

- Levin A, Bakris GL, Molitch M et al (2007) Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 71:31–38
- Block GA, Klassen PS, Lazarus JM et al (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 15:2208–2218
- Kalantar-Zadeh K, Kuwae N, Regidor DL et al (2006) Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 70:771–780
- Moe S, Drueke T, Cunningham J et al (2006) Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 69:1945–1953
- Yu AS (2004) Renal transport of calcium, magnesium and phosphate. In: Brenner BM (ed) *Brenner & Rector's the kidney*, 7th edn. Saunders, Philadelphia
- Yangawa N, Nakhoul F, Kurokawa K, Lee DB (1994) Physiology of phosphorus metabolism. In: Narins RG (ed) *Maxwell and Kleeman's clinical disorders of fluid and electrolyte metabolism*, 5th edn. McGraw-Hill, pp 307–371
- Portale AA, Booth BE, Tsai HC, Morris RC Jr (1982) Reduced plasma concentration of 1,25-dihydroxyvitamin D in children with moderate renal insufficiency. *Kidney Int* 21:627–632
- Eknoyan G, Levin A, Levin N (2003) Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 42:1–201
- Gupta A, Winer K, Econs MJ et al (2004) FGF-23 is elevated by chronic hyperphosphatemia. *J Clin Endocrinol Metab* 89:4489–4492
- Bricker NS (1972) On the pathogenesis of the uremic state. An exposition of the “trade-off hypothesis”. *N Engl J Med* 286:1093–1099
- Fukagawa M, Kazama JJ (2006) FGF23: its role in renal bone disease. *Pediatr Nephrol* 21:1802–1806
- Gutierrez O, Isakova T, Rhee E et al (2005) Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol* 16:2205–2215
- Mucsi I, Hercz G (1998) Control of serum phosphate in patients with renal failure—new approaches. *Nephrol Dial Transplant* 13:2457–2460
- K/DOQI (2002) Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 39:S1–S266
- Jono S, McKee MD, Murry CE et al (2000) Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res* 87:E10–E17
- Kestenbaum B, Sampson JN, Rudser KD et al (2005) Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 16:520–528
- Menon V, Greene T, Pereira AA et al (2005) Relationship of phosphorus and calcium—phosphorus product with mortality in CKD. *Am J Kidney Dis* 46:455–463
- Voormolen N, Noordzij M, Grootendorst DC et al (2007) High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrol Dial Transplant* 22:2909–2916
- Tonelli M, Sacks F, Pfeffer M et al (2005) Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation* 112:2627–2633
- Chen NX, O'Neill KD, Duan D, Moe SM (2002) Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. *Kidney Int* 62:1724–1731
- Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP (2006) Association of disorders in mineral metabolism with progression of chronic kidney disease. *Clin J Am Soc Nephrol* 1:825–831
- Norris KC, Greene T, Kopple J et al (2006) Baseline predictors of renal disease progression in the African American study of hypertension and kidney disease. *J Am Soc Nephrol* 17:2928–2936
- Barsotti G, Morelli E, Giannoni A et al (1983) Restricted phosphorus and nitrogen intake to slow the progression of chronic renal failure: a controlled trial. *Kidney Int Suppl* 16:S278–S284
- Maschio G, Oldrizzi L, Tessitore N et al (1982) Effects of dietary protein and phosphorus restriction on the progression of early renal failure. *Kidney Int* 22:371–376
- Ibels LS, Alfrey AC, Haut L, Huffer WE (1978) Preservation of function in experimental renal disease by

- dietary restriction of phosphate. *N Engl J Med* 298: 122–126
26. Karlinsky ML, Haut L, Buddington B et al (1980) Preservation of renal function in experimental glomerulonephritis. *Kidney Int* 17:293–302
 27. Lumlertgul D, Burke TJ, Gillum DM et al (1986) Phosphate depletion arrests progression of chronic renal failure independent of protein intake. *Kidney Int* 29:658–666
 28. Kraus ES, Cheng L, Sikorski I, Spector DA (1993) Effect of phosphorus restriction on renal response to oral and intravenous protein loads in rats. *Am J Physiol* 264: F752–F759
 29. Ritz E, Gross ML, Dikow R (2005) Role of calcium-phosphorous disorders in the progression of renal failure. *Kidney Int Suppl* 99:S66–S70
 30. Klahr S, Levey AS, Beck GJ et al (1994) The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of diet in renal disease study group. *N Engl J Med* 330: 877–884
 31. Sampathkumar K, Selvam M, Sooraj YS et al (2006) Extended release nicotinic acid—a novel oral agent for phosphate control. *Int Urol Nephrol* 38:171–174
 32. Llach F, Massry SG (1985) On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. *J Clin Endocrinol Metab* 61:601–606
 33. Salusky IB, Foley J, Nelson P, Goodman WG (1991) Aluminum accumulation during treatment with aluminum hydroxide and dialysis in children and young adults with chronic renal disease. *N Engl J Med* 324:527–531
 34. Thurston H, Swales JD (1971) Aluminium and chronic renal failure. *Br Med J* 4:490
 35. Slatopolsky E, Weerts C, Lopez-Hilker S et al (1986) Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. *N Engl J Med* 315:157–161
 36. Braun J, Oldendorf M, Moshage W et al (1996) Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 27:394–401
 37. Goodman WG, Goldin J, Kuizon BD et al (2000) Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342:1478–1483
 38. Guerin AP, London GM, Marchais SJ, Metivier F (2000) Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 15:1014–1021
 39. London GM, Guerin AP, Marchais SJ et al (2003) Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 18:1731–1740
 40. Kovesdy CP, Mehrotra R, Kalantar-Zadeh K (2008) Battleground: chronic kidney disorders mineral and bone disease—calcium obsession, vitamin D, and binder confusion. *Clin J Am Soc Nephrol* 3:168–173
 41. Mehrotra R, Budoff M, Christenson P et al (2004) Determinants of coronary artery calcification in diabetics with and without nephropathy. *Kidney Int* 66:2022–2031
 42. Mehrotra R, Budoff M, Hokanson JE et al (2005) Progression of coronary artery calcification in diabetics with and without chronic kidney disease. *Kidney Int* 68: 1258–1266
 43. Qunibi WY, Abouzahr F, Mizani MR et al (2005) Cardiovascular calcification in Hispanic Americans (HA) with chronic kidney disease (CKD) due to type 2 diabetes. *Kidney Int* 68:271–277
 44. Russo D, Palmiero G, De Blasio AP et al (2004) Coronary artery calcification in patients with CRF not undergoing dialysis. *Am J Kidney Dis* 44:1024–1030
 45. Tomiyama C, Higa A, Dalboni MA et al (2006) The impact of traditional and non-traditional risk factors on coronary calcification in pre-dialysis patients. *Nephrol Dial Transplant* 21:2464–2471
 46. Russo D, Miranda I, Ruocco C et al (2007) The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int* 72(10):1255–1261
 47. Shantouf R, Budoff MJ, Ahmadi N et al (2007) Effects of sevelamer and calcium-based phosphate binders on lipid and inflammatory markers in hemodialysis patients. *Am J Nephrol* 28:275–279
 48. De Boer IH, Gorodetskaya I, Young B et al (2002) The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. *J Am Soc Nephrol* 13:2762–2769
 49. Fajtova VT, Sayegh MH, Hickey N et al (1995) Intact parathyroid hormone levels in renal insufficiency. *Calcif Tissue Int* 57:329–335
 50. Martinez I, Saracho R, Montenegro J, Llach F (1997) The importance of dietary calcium and phosphorus in the secondary hyperparathyroidism of patients with early renal failure. *Am J Kidney Dis* 29:496–502
 51. Pitts TO, Piraino BH, Mitro R et al (1988) Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. *J Clin Endocrinol Metab* 67:876–881
 52. Reiss E, Canterbury JM, Kanter A (1969) Circulating parathyroid hormone concentration in chronic renal insufficiency. *Arch Intern Med* 124:417–422
 53. St John A, Thomas MB, Davies CP et al (1992) Determinants of intact parathyroid hormone and free 1,25-dihydroxyvitamin D levels in mild and moderate renal failure. *Nephron* 61:422–427
 54. Korkor AB (1987) Reduced binding of [3H]1,25-dihydroxyvitamin D3 in the parathyroid glands of patients with renal failure. *N Engl J Med* 316:1573–1577
 55. Gogusev J, Duchambon P, Hory B et al (1997) Depressed expression of calcium receptor in parathyroid gland tissue of patients with hyperparathyroidism. *Kidney Int* 51: 328–336
 56. Kates DM, Sherrard DJ, Andress DL (1997) Evidence that serum phosphate is independently associated with serum PTH in patients with chronic renal failure. *Am J Kidney Dis* 30:809–813
 57. Yamamoto M, Igarashi T, Muramatsu M et al (1989) Hypocalcemia increases and hypercalcemia decreases the steady-state level of parathyroid hormone messenger RNA in the rat. *J Clin Invest* 83:1053–1056
 58. Llach F, Massry SG, Singer FR et al (1975) Skeletal resistance to endogenous parathyroid hormone in patients

- with early renal failure. A possible cause for secondary hyperparathyroidism. *J Clin Endocrinol Metab* 41: 339–345
59. Fuleihan GE, Gundberg CM, Gleason R et al (1994) Racial differences in parathyroid hormone dynamics. *J Clin Endocrinol Metab* 79:1642–1647
 60. Gupta A, Kallenbach LR, Zasuwa G, Divine GW (2000) Race is a major determinant of secondary hyperparathyroidism in uremic patients. *J Am Soc Nephrol* 11: 330–334
 61. Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K (2007) Obesity is associated with secondary hyperparathyroidism in men with moderate and severe chronic kidney disease. *Clin J Am Soc Nephrol* 2:1024–1029
 62. Vincenti F, Arnaud SB, Recker R et al (1984) Parathyroid and bone response of the diabetic patient to uremia. *Kidney Int* 25:677–682
 63. Hutchison AJ, Whitehouse RW, Boulton HF et al (1993) Correlation of bone histology with parathyroid hormone, vitamin D3, and radiology in end-stage renal disease. *Kidney Int* 44:1071–1077
 64. Malluche HH, Ritz E, Lange HP et al (1976) Bone histology in incipient and advanced renal failure. *Kidney Int* 9:355–362
 65. Rix M, Andreassen H, Eskildsen P et al (1999) Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure. *Kidney Int* 56:1084–1093
 66. Sherrard DJ, Hercz G, Pei Y et al (1993) The spectrum of bone disease in end-stage renal failure—an evolving disorder. *Kidney Int* 43:436–442
 67. Massry SG, Popovtzer MM, Coburn JW et al (1968) Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. *N Engl J Med* 279: 697–700
 68. Rao DS, Shih MS, Mohini R (1993) Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. *N Engl J Med* 328:171–175
 69. Bogicevic M, Stefanovic V (1988) Relationship between parathyroid hormone and pituitary-testicular axis in patients on maintenance hemodialysis. *Exp Clin Endocrinol* 92:357–362
 70. Tonner DR, Schlechte JA (1993) Neurologic complications of thyroid and parathyroid disease. *Med Clin North Am* 77:251–263
 71. Fellner SK, Lang RM, Neumann A et al (1991) Parathyroid hormone and myocardial performance in dialysis patients. *Am J Kidney Dis* 18:320–325
 72. London GM (2002) Left ventricular alterations and end-stage renal disease. *Nephrol Dial Transplant* 1 [17 Suppl]:29–36
 73. Tseke P, Grapsa E, Stamatelopoulos K et al (2006) Atherosclerotic risk factors and carotid stiffness in elderly asymptomatic HD patients. *Int Urol Nephrol* 38:801–809
 74. Kovesdy CP, Ahmadzadeh A, Anderson JE, Kalantar-Zadeh K (2008) Outcomes associated with secondary hyperparathyroidism in men with moderate to severe chronic kidney disease. *Kidney Int* (in press)
 75. Avram MM, Mittman N, Myint MM, Fein P (2001) Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. *Am J Kidney Dis* 38:1351–1357
 76. Fouque D, Guebre-Egziabher F (2007) An update on nutrition in chronic kidney disease. *Int Urol Nephrol* 39:239–246
 77. Mafra D, Farage NE, Azevedo DL et al (2007) Impact of serum albumin and body-mass index on survival in hemodialysis patients. *Int Urol Nephrol* 39:619–624
 78. Massry SG, Smogorzewski M (1994) Mechanisms through which parathyroid hormone mediates its deleterious effects on organ function in uremia. *Semin Nephrol* 14:219–231
 79. Mazzaferro S, Coen G, Bandini S et al (1993) Role of ageing, chronic renal failure and dialysis in the calcification of mitral annulus. *Nephrol Dial Transplant* 8:335–340
 80. Chiu KC, Chuang LM, Lee NP et al (2000) Insulin sensitivity is inversely correlated with plasma intact parathyroid hormone level. *Metabolism* 49:1501–1505
 81. Wareham NJ, Byrne CD, Carr C et al (1997) Glucose intolerance is associated with altered calcium homeostasis: a possible link between increased serum calcium concentration and cardiovascular disease mortality. *Metabolism* 46:1171–1177
 82. Gadallah MF, el-Shahawy M, Andrews G et al (2001) Factors modulating cytosolic calcium. Role in lipid metabolism and cardiovascular morbidity and mortality in peritoneal dialysis patients. *Adv Perit Dial* 17:29–36
 83. Meytes D, Bogin E, Ma A et al (1981) Effect of parathyroid hormone on erythropoiesis. *J Clin Invest* 67:1263–1269
 84. Neves PL, Trivino J, Casaubon F et al (2002) Elderly patients on chronic hemodialysis: effect of the secondary hyperparathyroidism on the hemoglobin level. *Int Urol Nephrol* 34:147–149
 85. Neves PL, Trivino J, Casaubon F et al (2006) Elderly patients on chronic hemodialysis with hyperparathyroidism: increase of hemoglobin level after intravenous calcitriol. *Int Urol Nephrol* 38:175–177
 86. Massry SG, Alexiewicz JM, Gaciong Z, Klinger M (1991) Secondary hyperparathyroidism and the immune system in chronic renal failure. *Semin Nephrol* 11: 186–201
 87. Baczynski R, Massry SG, Kohan R et al (1985) Effect of parathyroid hormone on myocardial energy metabolism in the rat. *Kidney Int* 27:718–725
 88. Amann K, Ritz E (1997) Cardiac disease in chronic uremia: pathophysiology. *Adv Ren Replace Ther* 4: 212–224
 89. Kosch M, Hausberg M, Vormbrock K et al (2000) Impaired flow-mediated vasodilation of the brachial artery in patients with primary hyperparathyroidism improves after parathyroidectomy. *Cardiovasc Res* 47:813–818
 90. Amann K, Tornig J, Flechtenmacher C et al (1995) Blood-pressure-independent wall thickening of intramyocardial arterioles in experimental uraemia: evidence for a permissive action of PTH. *Nephrol Dial Transplant* 10:2043–2048

91. Kamycheva E, Sundsfjord J, Jorde R (2004) Serum parathyroid hormone levels predict coronary heart disease: the Tromsø study. *Eur J Cardiovasc Prev Rehabil* 11:69–74
92. Ichikawa I, Humes HD, Dousa TP, Brenner BM (1978) Influence of parathyroid hormone on glomerular ultrafiltration in the rat. *Am J Physiol* 234:F393–F401
93. Marchand GR (1985) Effect of parathyroid hormone on the determinants of glomerular filtration in dogs. *Am J Physiol* 248:F482–F486
94. Lee K, Brown D, Urena P et al (1996) Localization of parathyroid hormone/parathyroid hormone-related peptide receptor mRNA in kidney. *Am J Physiol* 270:F186–F191
95. Endlich N, Nobiling R, Kriz W, Endlich K (2001) Expression and signaling of parathyroid hormone-related protein in cultured podocytes. *Exp Nephrol* 9:436–443
96. Shigematsu T, Caverzasio J, Bonjour JP (1993) Parathyroid removal prevents the progression of chronic renal failure induced by high protein diet. *Kidney Int* 44:173–181
97. Baker LR, Abrams L, Roe CJ et al (1989) 1,25(OH)₂D₃ administration in moderate renal failure: a prospective double-blind trial. *Kidney Int* 35:661–669
98. Bianchi ML, Colantonio G, Campanini F et al (1994) Calcitriol and calcium carbonate therapy in early chronic renal failure. *Nephrol Dial Transplant* 9:1595–1599
99. Goodman WG, Coburn JW (1992) The use of 1,25-dihydroxyvitamin D₃ in early renal failure. *Annu Rev Med* 43:227–237
100. Martin KJ, Gonzalez EA, Gellens M et al (1998) 19-Nor-1- α -25-dihydroxyvitamin D₂ (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 9:1427–1432
101. Kazama JJ, Maruyama H, Narita I, Gejyo F (2005) Maxacalcitol is a possible less phosphatemic vitamin D analog. *Ther Apher Dial* 9:352–354
102. Goodman WG, Hladik GA, Turner SA et al (2002) The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. *J Am Soc Nephrol* 13:1017–1024
103. Taskapan H, Wei M, Oreopoulos DG (2006) 25(OH) vitamin D₃ in patients with chronic kidney disease and those on dialysis: rediscovering its importance. *Int Urol Nephrol* 38:323–329
104. Saab G, Young DO, Gincherman Y et al (2007) Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. *Nephron Clin Pract* 105:c132–c138
105. Ritter CS, Armbrrecht HJ, Slatopolsky E, Brown AJ (2006) 25-Hydroxyvitamin D₃ suppresses PTH synthesis and secretion by bovine parathyroid cells. *Kidney Int* 70:654–659
106. Teng M, Wolf M, Ofsthun MN et al (2005) Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol* 16:1115–1125
107. Tentori F, Hunt WC, Stidley CA et al (2006) Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 70:1858–1865
108. Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K (2008) Association of treatment with activated vitamin D and mortality in chronic kidney disease. *Arch Intern Med* 168:397–403
109. Shoben AB, Rudser KD, de Boer IH et al (2007) Oral calcitriol use and mortality in non-dialyzed patients with chronic kidney disease [abstract]. *J Am Soc Nephrol* 18:98A
110. Bellows CG, Reimers SM, Heersche JN (1999) Expression of mRNAs for type-I collagen, bone sialoprotein, osteocalcin, and osteopontin at different stages of osteoblastic differentiation and their regulation by 1,25 dihydroxyvitamin D₃. *Cell Tissue Res* 297:249–259
111. Drissi H, Pouliot A, Koolloos C et al (2002) 1,25-(OH)₂-vitamin D₃ suppresses the bone-related Runx2/Cbfa1 gene promoter. *Exp Cell Res* 274:323–333
112. Virdi AS, Cook LJ, Oreffo RO, Triffitt JT (1998) Modulation of bone morphogenetic protein-2 and bone morphogenetic protein-4 gene expression in osteoblastic cell lines. *Cell Mol Biol (Noisy-le-grand)* 44:1237–1246
113. Fraser JD, Otawara Y, Price PA (1988) 1,25-Dihydroxyvitamin D₃ stimulates the synthesis of matrix gamma-carboxyglutamic acid protein by osteosarcoma cells. Mutually exclusive expression of vitamin K-dependent bone proteins by clonal osteoblastic cell lines. *J Biol Chem* 263:911–916
114. Panichi V, De Pietro S, Andreini B et al (1998) Calcitriol modulates in vivo and in vitro cytokine production: a role for intracellular calcium. *Kidney Int* 54:1463–1469
115. Staeva-Vieira TP, Freedman LP (2002) 1,25-dihydroxyvitamin D₃ inhibits IFN-gamma and IL-4 levels during in vitro polarization of primary murine CD4 + T cells. *J Immunol* 168:1181–1189
116. Barrat FJ, Cua DJ, Boonstra A et al (2002) In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. *J Exp Med* 195:603–616
117. Boonstra A, Barrat FJ, Crain C et al (2001) 1 α ,25-Dihydroxyvitamin d₃ has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *J Immunol* 167:4974–4980
118. Aihara K, Azuma H, Akaike M et al (2004) Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. *J Biol Chem* 279:35798–35802
119. Wolf M, Shah A, Gutierrez O et al (2007) Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 72:1004–1013
120. Watson KE, Abrolat ML, Malone LL et al (1997) Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation* 96:1755–1760
121. Bertoli M, Luisetto G, Ruffatti A et al (1990) Renal function during calcitriol therapy in chronic renal failure. *Clin Nephrol* 33:98–102
122. Coen G, Mazzaferro S, Manni M et al (1994) No acceleration and possibly slower progression of renal failure during calcitriol treatment in predialysis chronic renal failure. *Nephrol Dial Transplant* 9:1520
123. Agarwal R, Acharya M, Tian J et al (2005) Antiproteinuric effect of oral paricalcitol in chronic kidney disease. *Kidney Int* 68:2823–2828
124. Nagakura K, Abe E, Suda T et al (1986) Inhibitory effect of 1 α ,25-dihydroxyvitamin D₃ on the growth of the renal carcinoma cell line. *Kidney Int* 29:834–840

125. Penna G, Adorini L (2000) 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol* 164:2405–2411
126. Gysemans C, Van EE, Overbergh L et al (2002) Treatment of autoimmune diabetes recurrence in non-obese diabetic mice by mouse interferon-beta in combination with an analogue of 1alpha,25-dihydroxyvitamin-D3. *Clin Exp Immunol* 128:213–220
127. Li YC, Kong J, Wei M et al (2002) 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 110:229–238
128. Charytan C, Coburn JW, Chonchol M et al (2005) Cinacalcet hydrochloride is an effective treatment for secondary hyperparathyroidism in patients with CKD not receiving dialysis. *Am J Kidney Dis* 46:58–67