THE EVOLVING WORLD OF CHRONIC KIDNEY DISEASE MINERAL BONE DISORDER

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ABSTRACT

Chronic kidney disease - mineral and bone disorder (CKD-MBD) is associated with a significant morbidity and mortality. *In vitro* and animal models suggest that phosphorous, calcium, parathyroid hormone, and vitamin D abnormalities, mediate the cardiovascular and bone diseases that characterise CKD-MBD and increase the risk of death. Currently, mineral abnormalities are corrected through phosphorous restriction, phosphate binders, calcimimetics and vitamin D administration. Nonetheless, data in humans that support the use of these compounds are still scarce, mainly based on observational studies. Thus, a considerable number of doubts and questions still challenge clinicians dealing with CKD patients and mineral metabolism imbalances. We herein critically review clinical evidence that support the use of different drugs in CKD-MBD.

Keywords: CKD-MBD, dialysis, outcome, management, needs.

INTRODUCTION

Calcium, phosphate, vitamin D and parathyroid hormone (PTH) have been repeatedly recognised as predictors of outcome in chronic kidney disease (CKD).[1-4] Though the mechanisms are still poorly understood, numerous studies suggest that mineral homeostasis abnormalities are associated with bone and cardiovascular (CV) diseases that portend a poor survival.[5] Hence, biochemical, CV, and bone abnormalities are now considered part of the multifaceted CKD-MBD syndrome (Figure 1).[5]

In spite of convincing preclinical data linking mineral metabolism imbalances to cardiovascular and bone diseases, clinical evidence is still far from conclusive[4,6] and a considerable number of doubts and questions still challenge clinicians dealing with CKD patients and mineral metabolism imbalances. CKD-MBD is currently treated with nutritional interventions, native and active vitamin D phosphate binders, and calcimimetics administration (Figure 2). The aim of this review is to critically evaluate and summarise available evidence as well as highlight
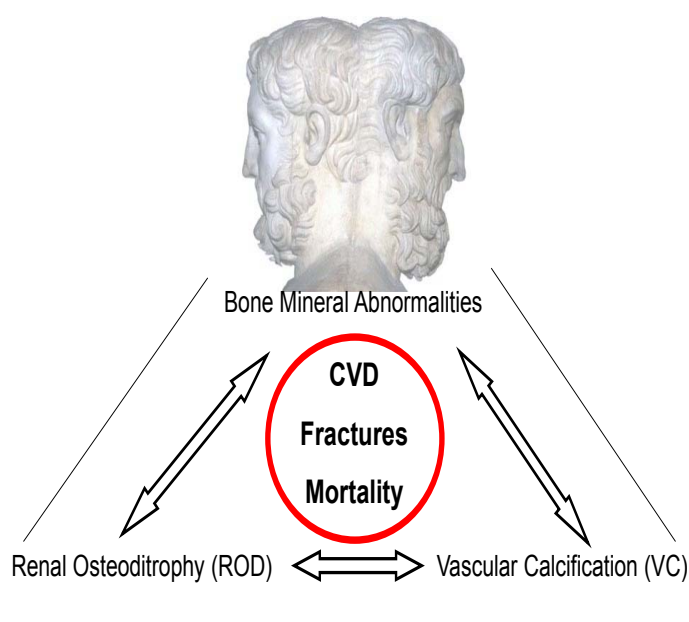

Figure 1. CKD-MBD a multifaceted syndrome characterised by serum parameters abnormalities, bone and cardiovascular marker of disease and associated with poor outcome.
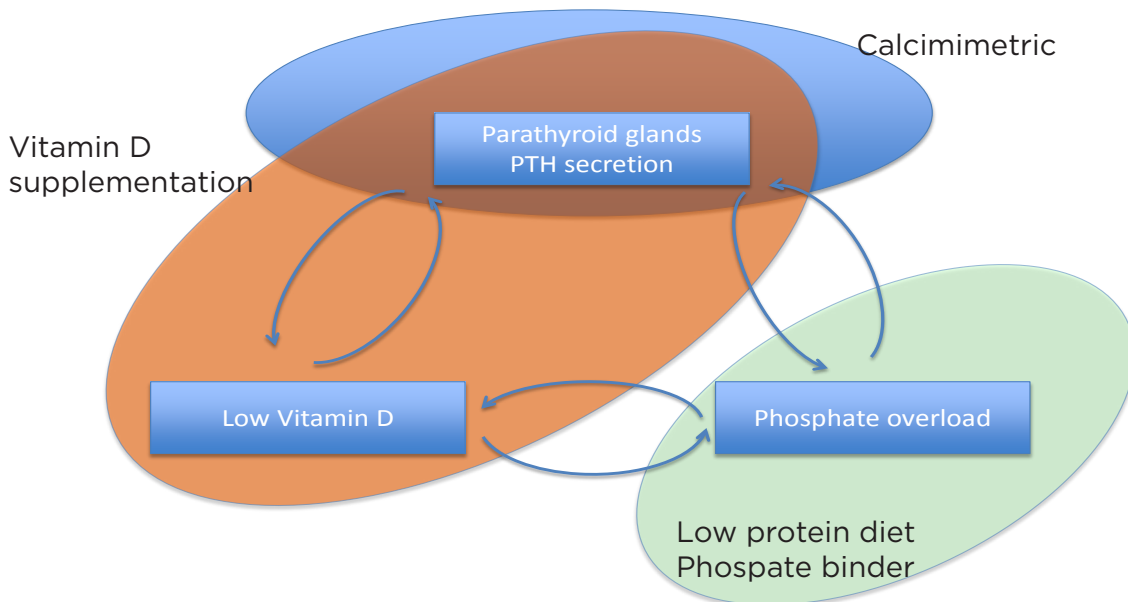
Figure 2. CKD-MBD pathophysiology is characterised by phosphate overload, PTH hypersecretion and vitamin D depletion. Our armamentarium is composed by low protein diet and phosphate binder (light green circle) to lower phosphate overload; different forms of vitamin D (orange circle) to overcome vitamin D deficiency and inhibit PTH production and secretion; calcimimentics (light blue circle) to reduce PTH secretion

the numerous unanswered clinical questions on CKD-MBD management.

Diet: Facts, Promises and Expectations

Hyperphosphatemia control is perceived by nephrologists as one of the most relevant targets to achieve in CKD.[4] Indeed, numerous studies have reported a close association between serum phosphorus levels and the risk of death in both subjects from the general population[7,8] as well as subjects with varying degrees of renal function impairment.[1-4] Furthermore, a large body of evidence suggests a direct link between phosphorous and the cardiovascular and bone systems.[5] Thus, it is commonly accepted that phosphorus is a uraemic toxin, and current guidelines on mineral metabolism management recommend maintaining it within the range of normality.[9-10]

As kidney function declines, urinary phosphate excretion becomes insufficient and eventually hyperphosphataemia ensues if the phosphate daily intake remains constant.[11] It is estimated that the daily phosphate intake in a standard diet in Western countries is about 1500 mg/day.[11,12] Considering that faecal excretion is about 600 mg/day of which about 200 mg/day are secreted by the intestine, the amount of phosphorous absorbed by the gastrointestinal tract may approach 1100 mg/day (Figure 3).[11,12] To maintain phosphorous homeostasis and keep serum levels within the range of normality, renal excretion should match the daily intake at the expense of increasing the tubular workload of each functional nephron.[13] Notably, the average phosphate level in the general population varies according to sex and menopausal status[14,15] and data suggest an increased risk of unfavourable outcomes for phosphorous levels within the range of normality[8,15] further corroborating the notion that serum phosphorus may not adequately reflect phosphorous balance.

Two different strategies to lower phosphorous intake are available: low phosphate diet and phosphate binders. A low phosphorous intake can be achieved via protein restriction and quality selection.[5] Indeed, Moe et al.[16] showed that a vegetarian rather than a meat-based diet significantly reduces serum phosphorous and the phosphaturic factor fibroblast growth factor 23 (FGF23). Notably, these differences were independent of the circadian serum and urine phosphorous changes, suggesting that phosphorous contained in the vegetarian diet is less adsorbable in the gastrointestinal tract which is possibly due to the phosphate binding to phytate.[16]

Cooking method and food additives are two other factors that significantly affect phosphorous intake.[17-22] Cupisti and coworkers[18] reported that 20-30 minutes boiling significantly reduce (30-50%) phosphorous burden at the expense of a minimal reduction of the protein content (9-17%).
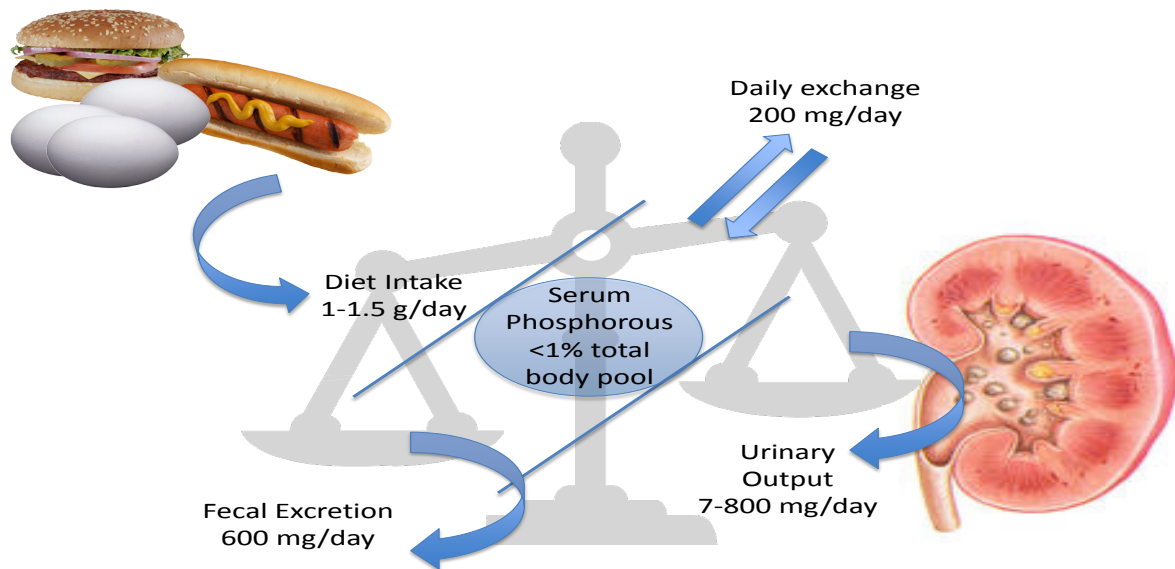
Figure 3. Phosphorous balance is the net results of intake (diet), quota exchanged with bones and output (urine, faeces).

Food additives are another source of phosphorous in prepared meals. A recent survey of best-selling processed groceries concluded that phosphorus additive-containing foods averaged 67 mg phosphorus/100 g more than matched non-additive-containing foods (about 736 mg more phosphorus per day compared with meals consisting of only additive-free foods).[23] Phosphorous-based additives (phosphoric acid, tetrasodium pyrophosphate, tricalcium phosphate, disodium phosphate, monopotassium phosphate, etc.) are used to enhance taste and consistency of different foods such as baked goods (baking powder, cakes, frozen dough, etc.), beverages (colas, chocolate milk, buttermilk, fruit juices, sport drinks, canned milk, soy beverages), cereals, dairy, meat and egg products, fruit and vegetables, and pasta and noodles.

Inorganic phosphorous contained in food additives is highly bioavailable and adsorbed in the gastrointestinal tract to a greater extent than the organic phosphorous. It is estimated that as much as 90% versus 60% of the ingested inorganic (food additives) and organic (vegetable and meat protein) phosphorous is absorbed, respectively.[21,22]

Though the mechanisms are still unclear, accumulating evidence suggests the high serum levels of phosphorous are associated with increased levels of FGF23 that in turn, have been independently associated with a significant risk of endothelial dysfunction,[24] left ventricular hypertrophy,[25] CKD progression and all-cause mortality.[26] In the absence of a randomised controlled clinical trial (RCT), it is unclear whether elevated serum phosphorous or FGF23 mediates the toxicity[1,26] or, alternatively, both factors contribute to the organ damage and poor survival in CKD-MBD.[27]

A balanced nutritional program should control both serum phosphorous and FGF23. Di Iorio et al.[28] showed that a very low protein diet (0.3 g/kg of ideal body weight per day) supplemented with alpha-chetoanalogues and essential aminoacids significantly reduces FGF23 and phosphoremia. In 32 CKD subjects randomised to cross-over sequential treatments with either standard low protein diet (60-70 g of protein/day) or very low protein diet (25-30 g of protein/day), they reported a significant 33.5%, 12% and 34% reduction of FGF23, serum and urinary phosphorous levels associated with very low protein diet (VLPD), respectively.[28] Of note, the two diet regimens did not differ only in the total protein intake but also in the animal/vegetal protein ratio (VLPD regimen based on vegetable protein only) and phosphorous content (350-420 mg/day versus 600-700 in VLPD and standard diet, respectively).[28] Other groups have confirmed that phosphorous restriction with or without phosphate binders, is effective in controlling FGF23.[29,30]

Low phosphate and protein diet has also been associated with proteinuria and CKD progression reduction.[19,31,32] In a seminal paper by Brunori at al.,[32] it was demonstrated that life expectancy among old patients with end-stage renal disease (ESRD) was similar if patients were randomised to VLPD and conservative treatment or haemodialysis.

The most important drawback of low protein and phosphorous diet is the potential for malnutrition.[33] Indeed, a balanced nutritional program should be tailored to each individual and should provide the patient with the right amount of calories and nutrients.[34] In this regard, an observational study suggests that protein malnutrition maybe more detrimental than phosphorous intake and that the ideal nutritional regime should provide enough protein with minimal phosphorous burden.[33]

Future RCT studies should investigate the safety and the impact of low protein and VLPD on long-term survival and CKD progression, in both CKD patients not receiving and receiving dialysis. In consideration of the substantial increase of the mean age of dialysis patients, it is to be established if the recommended protein intake by current guidelines is still adequate in light of the considerable number of patients with increased levels of serum phosphorous.[35] Finally, a pharmacoeconomic analysis should evaluate the cost burden connected to aproteic foods, chetoanalogue or essential aminoacid supplements.

Phosphate Binders: Facts, Promises and Expectations

Phosphate binders are another strategy for reducing phosphate intake. These compounds share the property to bind phosphorous in the intestinal lumen, prevent its absorption and increase the faecal excretion. Various drugs are now available on the market with this indication.[36,37] For ease, these compounds can be divided into two different groups: calcium-based phosphate binders (calcium carbonate and calcium acetate) and calcium-free phosphate binders (aluminium hydroxide, lanthanum carbonate, magnesium carbonate, sevelamer hydrochloride, and sevelamer carbonate). Alternatively, these compounds can be divided into absorbable (calcium-based binders, aluminium hydroxide, lanthanum carbonate, magnesium carbonate) and not absorbable (sevelamer hydrochloride, and sevelamer carbonate) in the gastrointestinal tract. Though all these compounds might have different affinity for phosphorous in the gastrointesinal tract and different doses have to be administered,[38] clinical studies suggest that they all effectively lower serum phosphorous.[36,39,40] Nonetheless, due to the different adsorbability in the gastrointestinal tract, the safety profile of these compounds can be profoundly different. Indeed, the prolonged use of aluminum-based phosphate binder is not indicated due to its accumulation and toxicity.[41]

The debate on calcium-containing versus calcium-free phosphate binders has characterised the last decade.[36,42] Preclinical data suggest that both phosphorous and calcium can actively induce vascular calcification,[43-45] a marker of vascular disease[46] and a risk factor for arterial stiffness[47] and mortality.[46,48] A seminal paper by Cozzolino and coworkers[49] demonstrated that the use of sevelamer was associated with a similar phosphate control but lower extraosseous calcification than calcium-based phosphate binder. Observational data suggest that excessive calcium intake may result in a positive calcium balance that in turn has been associated with arterial stiffness and vascular calcification,[50,51] adynamic bone disease[52,53] and, in some but not all studies, excessive mortality.[35,54]

RCTs have also yielded somehow conflicting results. To date, three studies have tested the impact of calcium-free and calcium-containing phosphate binders on vascular calcification, CKD progression and all-cause mortality in moderate CKD.[55-57] In the first study ever published on this topic, Russo and coworkers[55] observed a significant reduction of coronary calcification (CAC) progression among patients with CKD stage 3-4 treated with sevelamer as compared to patients treated with calcium carbonate or low-protein diet.[55] Considering that the dose of both binders was based on a similar reduction in urinary phosphate excretion (i.e. phosphate binding equivalency), it is plausible that the different impact of sevelamer and calcium carbonate on vascular calcification is due to the excessive calcium load in the calcium carbonate-treated arm. Indeed, recent evidence suggests that a calcium intake greater than that usually ingested in a normal Western country diet (about 800 mg/day) can induce a positive calcium balance in moderate CKD.[58] However, it is also possible that the additive effects of sevelamer on FGF23, fetuin-A, lipids, C-reactive protein, and uric acid[59,60] may account for some of these results. Block and coworkers[56] recently failed to confirm the beneficial effect of non-calcium-containing phosphate binders (sevelamer carbonate, lanthanum carbonate) on vasculature. Though the study was designed to address the phosphate lowering efficacy of calcium and non-calcium-containing phosphate binders versus placebo in mild to moderate CKD, authors report among treated patients on a worrisome increase in CAC, measured as secondary endpoint.[56] However, it is unclear whether calcium or non-calcium-containing phosphate binders drive this result. The limited statistical power of the study further limits the interpretation of this finding.[56]

A third RCT designed to test the impact of sevelamer versus calcium carbonate on hard outcomes (all-cause mortality and CKD progression) in mild to moderate CKD patients (mean creatinine clearance 30 ml/min) with hyperphosphatemia supports the notion that non-calcium-containing phosphate binders may be associated with a more favourable renal and life survival rate.[57] In this study, a significant CAC progression attenuation was also noted.[57] Although sevelamer-treated patients showed a higher CAC prevalence and burden at baseline (prevalence of CAC 62.6% versus 47.6%; P=0.02; median CAC score: 122 AU [IQR, 0–180] versus 0 AU [IQR, 0–215]; P=0.01 in the sevelamer and calcium carbonate group respectively), at study completion a significantly lower risk of CAC progression or *de novo* onset (12.8% in sevelamer-treated patients and 81.8% in calcium carbonate–treated patients) was noted.[57]

Other studies in ESRD patients new to[48] or on maintenance dialysis[61] have also investigated the differential impact of calcium salts and calcium-free phosphate binders on vascular calcification or hard outcome.[48,62] Though the majority of these trials point toward a harmful potential of calcium-containing phosphate binders, metanalyses have repeatedly failed to confirm this hypothesis.[39,63,64] A recent study by Di Iorio et al.[65] unfolds an almost 10-fold reduction of CV and all-cause mortality associated with sevelamer versus calcium carbonate in a large cohort (N=466) of patients new to dialysis.

Though these data suggest a different effect of calcium-free phosphate binders on the cardiovascular system and survival, no study has ever tested whether serum phosphorous-lowering is associated with a survival benefit. In light of the many adaptive mechanisms to hyperphosphataemia such as increased PTH and FGF23 that can modulate phosphorous toxicity and the potential calcium toxicity,[66,67] future studies should address when to start in the course of CKD and to what serum phosphorus target should we aim when prescribing phosphate binders. Finally, cost-effectiveness analyses of these compounds are needed in light of the expanding epidemiology of CKD.[68]

Native Vitamin D: Facts, Promises and Expectations

Native vitamin D has received growing interest in the last ten years. Every year, hundreds of manuscripts on native vitamin D associations with a variety of diseases such as osteoporosis,[69] hypertension,[70] cardiovascular disease,[71,72] insulin resistance,[73] infections,[74] cancer[75] and mortality[76] are published. Similarly, nephrologists have traditionally linked native vitamin D deficiency to CKD progression,[77] secondary hyperparathyroidism (SHPT)[78] and survival[79] in renal patients. The widespread association between native vitamin D and unfavourable outcomes in the general population, as well as in selected diseased sub-cohorts, together with the emerging knowledge of the extra-renal activation of native vitamin D, support the hypothesis that vitamin D deficiency is an etiologic factor rather than a mere biomarker of frailty.[80]

The term 'native Vitamin D' refers to the 25 hydroxlate vitamin D (25(OH)D) forms. Vitamin D precursors ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are synthesised by the UV radiation in yeast and in animals starting from ergosterol and 7-dehydrocholesterol, respectively.[81] In turn, vitamin D precursors are hydroxylated in the liver to form 25(OH)D2 and 25(OH)D3, respectively.[81] These are the substrates that are subsequently activated to $1\text{-}25(OH)_2D$ (calcitriol) by the renal and, to a lesser extent, by the extra-renal 1 alpha hydroxylase.[82] Of note, humans do not synthesise vitamin D2[81] and almost 80% of vitamin D is obtained by UVB irradiation with only a minor contribution of diet intake.[82]

Though it is commonly prescribed as a supplement, we currently ignore what is the desirable level of 25(OH)D.[69,83] It is commonly accepted that levels of 25(OH)D above 30 ng/ml, between 21 and 29 ng/ml and below 20 ng/ml define vitamin D sufficiency, insufficiency and deficiency, respectively.[82]

Native vitamin D deficiency is highly prevalent in the general population as well as in CKD and is almost ubiquitous in dialysis patients (greater than 80%).[84] Three drugs are currently available for vitamin D supplementation (ergocalciferol, cholecalciferol and calcifediol) based on the precursor from which they are originated. A few subtle pharmacologic differences have been described.[85,86] Several studies observed that ergocalciferol is less potent than cholecalciferol in restoring 25(OH)D levels,[86] possibly due to a stronger affinity of cholecalciferol to the vitamin D binding protein.[86] Moreover, the activated form of vitamin D (1,25OHD – calcitriol), originated from cholecalciferol, induces a sustained activation of the vitamin D receptor (VDR) due to a higher affinity of its catabolite 1-24-25(OH)D3 to the VDR than the ergocalciferol-derived catabolite 1-24-25(OH)D2.[85] Thus, it is commonly accepted that

50.000 IU of ergocalciferol are pharmacologically equivalent to 5-15.000 IU of cholecalciferol.[87] However, whether or not these two forms of vitamin D may have different clinical implications is still unknown. Two RCTs are currently recruiting patients to compare the effect of vitamin D2 versus Vitamin D3 on mineral metabolism in CKD stage 2-5 (NCT01633853, NCT01173848) to shed light on which 25(OH)D form is better suited in CKD. Current evidence suggests a potential role for 25(OH)D as PTH lowering agent. Indeed, a recent meta-analysis by Kandula and colleagues[88] concludes, based on the available observational studies, that 25(OH)D compared to placebo reduces PTH levels in CKD (about 25 pg/ml) as well as in ESRD (about 60 pg/ml) patients. However, the heterogeneity of the studies precludes speculation on what could be the best 25(OH)D regimen in CKD. Whether 25(OH)D can be used instead of VDR activator for PTH suppression in CKD is still under debate, though preliminary data suggest that paricalcitol and doxercalciferol induce a stronger PTH reduction compared to ergocalciferol and cholecalciferol in CKD 3-4[89,90] and ESRD patients,[86] respectively. Similarly, data concerning PTH reduction by the co-administration of native and active vitamin D are still inadequate, mainly based on observational and retrospective studies.[91-93] Further evidence is advocated before recommending the implementation of this combined approach.

In spite of the many pleiotropic effects described in the past decades and the substantial increase in the risk of death associated with low 25(OH)D levels,[75] only a few studies have investigated the impact of native vitamin D on surrogate endpoints such as renal osetodystrophy, vascular calcification, proteinuria, LVH or survival. However, numerous RCTs are currently investigating the effect of native vitamin D on left ventricular hypertrophy (NCT01323712), insulin resistance (NCT00893451), erythropoietin dosing (NCT01395823), proteinuria (NCT01426724), immunity (NCT00892099), ateriovenous fistulae maturation (NCT00912782) and physical and cognitive performance (NCT00511225, NCT01229878) to shed light on the potentials of this treatment. Finally, the NUTRIVITA study is actively randomising dialysis patients to 25(OH)D versus placebo treatment to test the effect of 25(OH)D on survival, fatal myocardial infarction, and non-fatal stroke (NCT01457001).

Due to the scarce data available, current guidelines on mineral metabolism management,[10] suggest 25(OH)D deficiency replenishment as the first step to correct SHPT in CKD stage 3-5,[10] whereas no suggestion is provided for dialysis patients. These statements are 'not graded' and based on expert opinion rather than on evidence.[10] A considerable ongoing and future effort is needed to clarify the impact of 25(OH)D administration to CKD and dialysis patients.

Vitamin D Analogues: Facts, Promises and Expectations

Repeated observational data described an independent association between PTH levels and unfavourable outcomes in CKD stage 3-5[94,95] as well as in ESRD.[2,3] However, no RCTs have yet proven that an active reduction of PTH values improves such patient-centred hard outcomes as hospitalisations, cardiovascular events, CKD progression, and survival. Thus, the optimal PTH target is still uncertain in CKD as well as in ESRD subjects. KDIGO guidelines provide a low-grade suggestion to maintain PTH levels into the range of normality in CKD stage 3-5 and between two and nine-times the normal range in ESRD.[10]

The reduction of calcitriol levels, together with hypocalcemia and hyperphosphataemia, are the leading causes of increased PTH levels. Thus, KDIGO guidelines suggest the use of vitamin D in case of increased PTH values and its tailoring in case of PTH over-correction, hypercalcemia or hyperphosphataemia.[10] The risks related to high doses of vitamin D are mainly due to phosphate and calcium overload that possibly contribute to the low achievement rate of calcium and phosphate recommended targets[96] and to a poor survival in dialysis patients.[3] However, selective vitamin D receptor activator (VDRA), with a stronger effect on PTH and a lesser impact on calcium and phosphate load, may improve the global achievement of serum PTH, calcium and phosphate targets reducing the vitamin D toxicity.[97-99]

In recent years industries have provided multiple synthetic vitamin D2 (paricalcitol and doxercalciferol) and vitamin D3 analogues (alfacalcidol, falecalcitriol and maxacalcitol). However, comparison data of different vitamin D analogues on mineral metabolism control, surrogate and patient-centred outcomes are currently still scarce.

Several studies suggest that VDRAs are superior to placebo and calcitriol in controlling PTH, calcium and phosphate, but the few available head-to-head comparisons between VDRAs led to heterogeneous

and inconclusive results. Alfacalcidol was similar to calcitriol in suppressing PTH values with equal change in phosphate and calcium levels,[100,101] however recent data by Hansen et al.[102] did not observe significant differences between alfacalcidol and paricalcitol on similar targets. Joist et al.[103] observed that paricalcitol at very high doses suppressed PTH with lower elevation of phosphate and calcium levels compared to doxercalciferol. However, Fadem and coworkers[104] could not detect any difference in PTH, calcium and phosphorous control when haemodialysis patients were switched from intravenous paricalcitol to doxercalciferol. No clinical data comparing doxercalciferol with alfacalcidol in humans are currently available.

More recently, a growing interest for vitamin D pleiotropic effects, related to the widespread regulation of the human genome played by VDR activation, has been observed. Albuminuria, left ventricular hypertrophy (LVH) and cardiac remodelling have all been tested as potential targets of vitamin D analogues. The activation of VDR can regulate the expression of several genes involved in glomerular and myocardial inflammation as renin,[105] TGF-beta,[106] antioxidant molecules,[107] NFκB and RANTES.[108] The VITAL study, a randomised placebo controlled trial in diabetic CKD patients, documented a dose dependent trend toward reduction of albuminuria when paricalcitol was added to RAAS inhibitors.[109] Though the PRIMO study failed to demonstrate a significant LVH reduction,[110] a post-hoc analysis documented a lower increase of brain natriuretic peptide and left atrial index in diabetic CKD patients receiving paricalcitol on top of ACE-I or ARBs compared to placebo.[111] Interestingly, paricalcitol was associated with lower risk of hospitalisation in those patients with more severe LVH.[110] However, no RCT has tested the effect of different forms of vitamin D or VDRA on hard patient-centred outcomes.

Numerous, albeit not all, observational studies suggest potential benefits beyond mineral metabolism control linked to VDRA use on hospitalisation, cardiovascular events, and mortality. Kalantar-Zadeh and coworkers[3] reported a 14% reduction in all-cause hospitalisation among patients receiving paricalcitol compared to those treated with calcitriol in a large cohort of 58,058 haemodialysis patients.[3] Paricalcitol[112-114] and doxercalciferol[114] use were both associated with lower mortality risk compared to calcitriol in other large series of patients on chronic haemodialysis. Recently

published results from the Italian FARO survey[115] unexpectedly showed a better survival in dialysis patients receiving vitamin D also in the presence of PTH ≤150 pg/ml. However, the Dialysis Outcome and Practice Pattern Study (DOPPS) investigators failed to report on vitamin D improved survival after adjustment for confounders and different practice patterns.[116] Hence, these encouraging observational data have to be confirmed in RCTs prior to orient stronger recommendations on vitamin analogues prescription.

Future studies should shed definitive light on whether the use of VDRAs improve survival in CKD and ESRD as well as surrogate outcomes such as albuminuria and LVH. Finally, in consideration of the growing number of CKD patients and the high-cost burden connected to CKD management, future studies should also verify the cost-effectiveness of the use of VDRA in different stages of CKD.

Cinacalcet: Facts, Promises and Expectations

The existing body of evidence suggests that cinacalcet effectively lowers serum PTH, phosphorous, and calcium levels in ESRD modulating the parathyroid calcium sensing receptor affinity to serum calcium.[6,117-125] Phase two and three studies show that, on average a 40-50% (250-350 pg/ml) serum PTH, a 5-8% (0.5-0.8 mg/dl) serum calcium and a 5-10% (0.2-1.0 mg/dl) serum phosphorous reduction is expected when cinacalcet is administered.[6,117-125] It is conceivable that the calcium-PTH setpoint shift and the metabolic change in bone metabolism induced by this drug explain these results.[126,127]

Whether calcimimetics are superior to VDRAs in controlling CKD-MBD is another unanswered question. Two large RCTs, the ACHIEVE[119] and the IMPACT[128] study investigated this issue in haemodialysis patients. The first study[119] concluded for a better PTH control with cinacalcet, while the second study[128] showed a better PTH control among patients treated with intravenous paricalcitol. However, some major differences in the two study designs may account for some of the discrepant results: 1) in the ACHIEVE study both paricalcitol and doxercalciferol were allowed as VDRAs, while paricalcitol was the only VDRA administered in the D arm of the IMPACT study; 2) cinacalcet was admitted as a rescue therapy for hypercalcemia during VDRA treatment in the IMPACT study, whereas it was not allowed in the ACHIEVE study; 3) treatment algorithms for cinacalcet or VDRA dose modulation were different in the two trials. In light of these study

design differences it is unclear whether one of these two approaches is superior, though answering this question might be of limited clinical utility in light of the different pharmacological profile of calcimimetic and VDRAs.

The presence of calcium-sensing receptors in different tissues other than the parathyroid glands, could explain the positive impact of cinacalcet on the bones and vasculature detected in numerous preclinical data.[129] *In vitro* and animal evidence suggest that a reduction of functional calcium-sensing receptors is associated with vascular calcification,[129,130] blood pressure,[131] proteinuria,[132] CKD progression,[132] arterial stiffness and endothelial dysfunction improvement.[133] Large cohort prospective studies show that calcium-sensing receptor modulation is associated with favourable clinically meaningful outcomes. Cunningham and coworkers[134] showed a significant reduction in the risk of cardiovascular disease, bone fracture, parathyroidectomy incidence, and a parallel improvement in the general health perception among dialysis patients with secondary hyperparathyroidism. Block et al.[135] documented a substantial risk reduction in all-cause and cardiovascular mortality associated with cinacalcet in a large cohort of 25,292 chronic haemodialysis patients independent of several confounders.

However, the clinical impact of cinacalcet on hard outcome is far from being established in light of the recently published results of the ADVANCE[124] and EVOLVE[6] trials. The ADVANCE trial was conducted to investigate whether cinacalcet in combination with low dose of vitamin D (<6 mcg paricalcitol equivalent/ week) versus flexible doses of vitamin D attenuates coronary, aorta, and cardiac valves calcification progression in a cohort of 360 prevalent haemodialysis patients. After a relatively short period of follow-up of 12 months, a trend toward CAC reduction in the cinacalcet arm (Agatston CAC scores % change: 24% (95% confidence interval: - 22%, 119%) and 31% (- 9%, 179%), in the cinacalcet and flexible vitamin D group, respectively, P=0.073) was noted. Notably the trend was consistent across all CV sites investigated for vascular calcification.[124] Furthermore, the large dose of calcium-containing phosphate binders and vitamin D administered in the calcimimetic arm may contribute to explain these results.[136] Finally, the EVOLVE trial was designed to test the survival benefit of cinacalcet hypothesised by observational data in haemodialysis patients. At study completion, a statistically non-significant trend toward reduction (relative hazard in the cinacalcet group vs. the placebo group, 0.93; 95% confidence interval, 0.85 to 1.02; P=0.11) of the composite endpoint (time until death, myocardial

Treatment	Type of evidence	Head-to-head comparisons between drugs of the same class	Mineral metabolism control	Tissue marker of organ damage	Survival data	Pharmacoeconomic evaluation
Low phosphate diet	Observational studies	NA	YES	NO	NO	NA
	RCTs	NA	YES	NO	NO	NO
Phosphate binders	Observational studies	YES	YES	YES	YES	NA
	RCTs	YES	YES	YES	YES	NO
Native vitamin D	Observational studies	YES	YES	YES	YES	NA
	RCTs	NO	NO	NO	NO	NO
Activated forms of vitamin D (VDRA)	Observational studies	YES	YES	YES	YES	NA
	RCTs	NO	YES	YES	NO	NO
Cinacalcet	Observational studies	YES	YES	YES	YES	NA
	RCTs	NA	YES	YES	YES Inconclusive	NO

Table 1. Available knowledge is mainly based on observational and inconclusive RCTs.

infarction, hospitalisation for unstable angina, heart failure, or a peripheral vascular event) was reported.[6] However, the lower than anticipated event rate, the high drop-in and out rate during follow-up (about 20%),[6] significantly affected the statistical power (0.54)[6] and the interpretability of this inconclusive RCT.

In essence, data support the notion that cinacalcet is a safe and effective drug to lower PTH in secondary hyperparathyroidism. Nonetheless, future research projects should indentify the ideal candidate that would likely increase survival and quality of life while on this treatment. Finally, though the use of cinacalcet in predialysis stages of CKD is not approved because of the risk of hypocalcemia, future studies should evaluate its efficacy and safety in CKD not dialysis dependent cases of secondary hyperparathyroidism, characterised by normal-high calcium and high phosphate in which vitamin D may further aggravate phosphorous and calcium balance.

CONCLUSION

Treatment of CKD-MBD is currently based largely on opinion rather than evidence, and many questions about CKD-MBD await answers. A tremendous effort has been performed in the attempt to clarify the natural history and pathogenic mechanisms that trigger CKD-MBD and modulate the astonishing risk connected to it. Nonetheless, a substantial degree of uncertainty on the clinical relevance and use of different serological and tissue biomarkers used to individualise, and titrate treatments still exists and affects patient care. Furthermore, the incompleteness (Table 1) and inconclusiveness due to various methodological flaws in the few available RCTs complicate the interpretation of the available evidence and lead to a heterogeneous use of the different drugs we have in our armamentarium.[96]

Future effort is therefore needed to elucidate mechanisms and treatment of these imbalances that, at least observational data, link to a substantial risk burden[2] in CKD patients.

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