Published in final edited form as:

Curr Opin Nephrol Hypertens. 2016 March ; 25(2): 120–126. doi:10.1097/MNH.0000000000000203.

Optimal management of bone mineral disorders in chronic kidney disease and ESRD

Andrew L. Lundquist, MD, PhD and Sagar U. Nigwekar, MD, MMSc

Division of Nephrology, Massachusetts General Hospital, Boston, MA

Abstract

Purpose of review—This review summarizes recent studies on chronic kidney disease-mineral bone disorders, with a focus on new developments in disease management.

Recent findings—The term chronic kidney disease-mineral bone disorder has come to describe an increasingly complex network of alterations in minerals and skeletal disorders that contribute to the significant cardiovascular morbidity and mortality seen in patients with chronic kidney disease and ESRD. Clinical studies continue to suggest associations with clinical outcomes, yet current clinical trials have failed to support causality. Variability in practice exists as current guidelines for management of bone-mineral disorders are often based on weak evidence. Recent studies implicate novel pathways for therapeutic intervention in clinical trials.

Summary—Mineral-bone disorders in chronic kidney disease arise from alterations in a number of molecules in an increasingly complex physiological network interconnecting bone and the cardiovascular system. Despite extensive associations with improved outcomes in a number of molecules, clinical trials have yet to prove causality and there is an absence of new therapies available to improve patient outcomes. Additional clinical trials that can incorporate the complexity of mineral bone disorders and with the ability to intervene on more than one pathway are needed to advance patient care.

Keywords

CKD-MBD; FGF23; secondary hyperparathyroidism

INTRODUCTION

Chronic kidney disease-mineral bone disorder (CKD-MBD) was coined in 2006 by the Kidney Disease Improving Global Outcomes (KDIGO) working group in recognition that the mineral and skeletal disorders caused by CKD are critical contributors to the high cardiovascular morbidity and mortality seen in patients with kidney disease. The typical biochemical profile of altered mineral metabolism includes early and progressive FGF-23 elevation, decreasing calcitriol, increasing parathyroid hormone and a gradual rise in

Author of correspondence. Name: Andrew Lundquist, MD, PhD, Address: 165 Cambridge Street, Suite 302, Boston, MA 02114, Telephone number: 617-726-5050, alundquist@mgh.harvard.edu.

Conflicts of interest

None

phosphate, with associated bone disease, vascular calcification, and left ventricular hypertrophy. Despite extensive research and compelling observational studies, no large scale randomized controlled trial modifying these factors has shown clinical benefit and clinical guidelines were developed where little evidence exists. There is a significant need to describe and modify the morbidity and mortality related to CKD-MBD. This review will focus on developments in management of CKD-MBD over the past year. It will not discuss advances in CKD-MBD in transplant or pediatric patients.

Hyperphosphatemia

Current KDIGO guidelines for the management of hyperphosphatemia include reduced phosphate intake and oral phosphate binding medications. It is assumed that reduced phosphate intake will benefit CKD and ESRD patients equally, though Selamet *et al* [1] found no relationship between 24-hour urine phosphate excretion (a surrogate for oral phosphate intake) and all cause mortality in pre-dialysis patients, suggesting that phosphate intake is not directly linked to serum phosphate levels as it is in dialysis patients. Despite widespread use of oral phosphate binding medications, no clinical trial data support benefit on bone strength, cardiovascular events or death [2]. Observational studies suggest non-calcium binders minimize vascular calcification, but again clinical trial data are lacking. A new class of iron based phosphate binders offers the potential for both phosphate and iron management. Van Buren *et al* [3] found comparable safety and efficacy with ferric citrate (FDA approved in 2014) compared to sevelamer carbonate or calcium acetate in dialysis patients. Lewis *et al* [4] showed that ferric citrate is effective, increased iron stores and decreased IV iron and ESA usage (a yearly savings of ~\$2,000 / patient) compared to standard phosphate binders. It is important to remember that common medications (amlodipine, lisinopril and Paxil) can contribute to phosphate burden and selection of vitamin D supplementation (paricalcitol appears less phosphatemic than calcitriol) can influence phosphate control [5].

Vitamin D

Goals for vitamin D measurement and supplementation are complicated by genetic variation that affects vitamin D binding protein (DBP) and thus measured levels of 25(OH)D [6]. DBP regulates the bioavailability and hydroxylation of 25(OH)D and may have future relevance in CKD-MBD management, though a well validated assay for DBP is needed [7]. Van Ballegoijen *et al* [8] found that associations of 25(OH)D with BMD were strongest among White and Chinese participants and null among Black and Hispanic participants. Further studies are needed to determine optimal vitamin D measurements for bone health in all ethnic groups, as management of 25(OH)D in non-white patients with CKD is not clear at this time.

A number of clinical trials examined the putative role of vitamin D repletion and are summarized in Table 1. Two trials [9, 10] assessed the use of oral vitamin D in dialysis patients, both showing safety and efficacy with improvement in levels of 25(OH)D and hints at possible mortality benefit [9] and reduced fracture risk [10]. With limited novel therapies that improve dialysis survival, larger studies appear worth pursuing to determine if nutritional supplementation of vitamin D leads to clinical benefit. Arguing that prior

associations were not causal, two clinical trials [11, 12] were unable to show a reduction in blood pressure in hypertensive patients with oral vitamin D supplementation. In accordance with the PRIMO study [16], Wang *et al* [13] found no difference in LV mass in with paricalcitol in stage 3–5 CKD patients. Suggesting that endothelial dysfunction is at least partially reversible in CKD patients and vitamin D supplementation may yet exert favorable effects on the cardiovascular system, two trials identified improvement in endothelial function with paricalcitol use [14, 15]. Consistent with prior studies suggesting that vitamin D can reduce proteinuria both through RASS-dependent and RAAS-independent pathways [17], Molina *et al* [18] identified a significant decrease in proteinuria in CKD patients treated with cholecalciferol for 6 months. Thus, despite a number of negative trials with vitamin D supplementation, recent data indicate possible benefit on endothelial dysfunction and albuminuria.

FGF23

FGF23 is regulated by a number of factors and acts to increase urinary phosphate excretion, inhibit hydroxylation of 25(OH)D and is associated with cardiovascular morbidity. Some have proposed FGF23 as an early biomarker of CKD. In contrast to serum phosphate, FGF23 levels do not vary within individuals during the day or with short-term variations in dietary intake. Rebholz *et al* [19] found that baseline elevation of FGF23 was associated with a 5-fold increased risk of ESRD, independent of baseline kidney function and hyperphosphatemia. The association of elevated FGF23 with future ESRD persisted in subjects with eGFR > 90 ml/min per 1.73 m². Similarly, Speer *et al* [20] report that a pre-operative FGF-23 level predicted mortality in a prospective cohort of 859 patients scheduled for elective cardiac surgery, with FGF23 outperforming the 18 variable EuroSCORE II system. While neither of these studies prove causation, baseline FGF23 level may have utility as a biomarker in specific circumstances.

It remains unclear if FGF23 is a marker of phosphate excess, a marker of klotho deficiency, or if FGF23 directly promotes left ventricular hypertrophy and vascular calcification. In a secondary analysis of the EVOLVE trial, Moe *et al* [21] report that cinacalcet use resulted in a more frequent reduction in FGF23 at 20 weeks (68% vs. 28%) compared to control. Among patients on cinacalcet, those with a $\geq 30\%$ reduction in FGF23 had reduced cardiovascular death and cardiovascular events (interestingly, patients in the control group with $\geq 30\%$ reduction in FGF23 did not). As the study was not designed to assess causality, additional studies in humans targeting FGF-23 levels appear warranted. Accordingly, Isakova *et al* [22] proposed the COMBINE Study to determine if reduced dietary phosphate, nicotinamide (aimed to counteract NPT2b upregulation with phosphate binder use) and lanthanum carbonate will safely reduce serum phosphate and FGF23 levels in patients with stage 3–4 CKD. Of note, an experimental human antibody to FGF23 successfully increased phosphate and 1,25(OH)D in patients with X linked hypophosphatemia and may have future utility if reduction of FGF23 levels improves clinical outcomes [23]. However, there are currently no clinical trial data to recommend active reduction of FGF23.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism (SHPT) is associated with high-turnover bone disease and possibly increased mortality. Available therapy for SHPT includes phosphate binders, vitamin D receptor activators, calcimimetics and surgical parathyroidectomy. In 2009, the KDIGO guidelines suggested maintenance of phosphorus and calcium in the normal range and serum PTH in the range of 2–9 times the upper limit of normal. In a prospective study of ~6300 European dialysis patients, Fernandez-Martin *et al* [24] found that serum phosphate, calcium and PTH were all associated with increased mortality with a U shaped curve. Importantly, in patients with serum phosphate >5.2 mg/dL or serum Ca >9.5 mg/dL, decreases towards the “safest ranges” were associated with a lower relative risk of mortality, one of the first demonstrations that active reduction in serum phosphate leads to decreased mortality. Tentori *et al* [25] analyzed data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) to assess trends in PTH and SHPT therapies over the past 15 years. Compared with PTH 150–300 pg/mL, all-cause mortality was higher for PTH 301–450 pg/mL and > 600 pg/mL, with PTH > 600 also associated with increased risk of cardiovascular mortality and cardiovascular hospitalizations. PTH < 50 pg/mL was associated with adverse outcomes and a high proportion of these patients were continued on therapy for SHPT increasing their risk of adynamic bone disease. With a suggestion that a PTH > 300 ng/ml is associated with increased risk of death and hospitalization, the trend towards increased PTH in dialysis patients worldwide may have clinical consequences.

The European Renal Best Practice group recently released recommendations against routine use of calcimimetic therapy in dialysis patients [26] noting that treating 1000 people with cinacalcet for 1 year has no effect on mortality, prevents 3 patients from surgical parathyroidectomy and leads to ~60 episodes of hypocalcemia and ~150 episodes of nausea. However, in a pre-specified age based subgroup analysis of the EVOLVE trial, Parfrey *et al* [27] reported a reduced risk of death and major cardiovascular events in older (age > 65), but not younger, dialysis patients on cinacalcet. Thus, although cinacalcet was not formally proven to improve cardiovascular or all cause mortality, neither has a positive effect been formally ruled out [28, 29]. Cinacalcet continues to be used for management of SHPT and its secondary effects on bone in ESRD. In the PARADIGM trial, Wetmore *et al* [30] noted only modest reductions in PTH with cinacalcet (–12%) and vitamin D analogs (–7%) as monotherapy. In an exploratory analysis of PARADIGM, cinacalcet use was associated with hypocalcemia and reduced FGF-23, while vitamin D analogs were associated with hypercalcemia, hyperphosphatemia and increased FGF23 [31]. Finally, administration of a novel IV calcimimetic (AMG-416), yet to be approved by the FDA, resulted in significant PTH reductions, with over 50% of dialysis patients experiencing a > 30% decrease [32]. If larger studies do not implicate unwanted side effects, AMG-416 may prove useful for management of SHPT in dialysis patients.

In the setting of a PTH > 600 ng/ml despite medical therapy, many consider surgical parathyroidectomy. Komaba *et al* [33] reported a 34% and 41% lower risk for 1 year all-cause and cardiovascular mortality, respectively, following parathyroidectomy in ~4500 Japanese dialysis patients. A nested index-referent study of Swedish dialysis patients also noted a reduced risk of death following parathyroidectomy [34], while a USRDS study

identified a 2% 30 day mortality and a 24% re-hospitalization rate (30% of these required ICU care) within 30 days of discharge following parathyroidectomy [35]. Differences in the overall health of the various populations (more diabetes in the US population for example) may partially explain the disparate results described above and selection bias is a concern in retrospective studies. It may be that older, sicker patients benefit more from cinacalcet than parathyroidectomy, consistent with the recent subgroup analysis of the EVOLVE trial [27].

Calciophylaxis

Calciophylaxis (a.k.a. calcific uremic arteriolopathy) is a rare condition seen in patients with advanced kidney disease that is associated with high morbidity and mortality [36, 37]. The current understanding of the pathogenesis and risk factors of calciophylaxis is limited and unfortunately, at present, there are no effective and well-studied prevention or treatment strategies. The annual incidence of calciophylaxis is <1% in chronic hemodialysis patients; however the frequency of calciophylaxis may be on the rise [38]. The proposed calciophylaxis risk factors are summarized in Table 2. A multi-modal and multi-disciplinary approach that incorporates wound and pain management, sodium thiosulfate, optimization of mineral bone parameters, bisphosphonates, and avoidance of risk factors such as vitamin K antagonist has been advocated in the latest reports and this approach is described in detail in a recent review by S. U. Nigwekar [36]. A recent case series of 46 calciophylaxis patients has reported the efficacy of hyperbaric oxygen therapy in over 50% of calciophylaxis patients when it was added as a “last resort” therapy after failure to respond to other potential therapies [39]. It is also noteworthy that The EVOLVE trial demonstrated relative calciophylaxis risk reduction of 69–75% in the cinacalcet arm compared to the placebo arm; [40] however, the low event rate of calciophylaxis introduces a possibility that findings may have been due to chance.

Fracture and Renal Osteodystrophy

ESRD is associated with a 2–4 fold increase in fracture risk compared to the general population and the incidence of fracture in the CKD population is increasing. Current strategies to minimize fracture risk focus normalizing levels of calcium, phosphorus, PTH and 25(OH)D and consideration of available bone modifying therapies. Tetracycline labeled bone biopsy remains the gold standard for classification of bone disease in CKD, though less invasive methods are needed. A number of recent studies showed utility of dual energy x-ray absorptiometry scans in patients with CKD causing KDIGO to re-examine recommendations regarding routine BMD testing [41]. Haarhaus *et al* [42] report that increased levels of the bALP isoform B1x (exclusively found in patients with CKD) are diagnostic of biopsy proven low bone turnover, while elevated levels of bALP and PTH levels are suggestive of non-low bone turnover. DKK1 and sclerostin (a Wnt inhibitor) [43] may be additional biomarkers for CKD-MBD, but widespread use of bALP isoform B1x, DKK1, and sclerostin is currently limited by assay availability and reliability.

Behets *et al* [44] characterized bone histology after treatment with cinacalcet in dialysis patients with biopsy proven high turnover bone disease, noting improvement in bone formation and biochemical markers. While no patients had normal bone histology at baseline, 20/77 patients had a normal bone biopsy after 12 months of cinacalcet use. A number of therapeutic agents for management of bone disease now exist including anabolic

(teriparatide, romosozumab) or antiresorptive (bisphosphonates, denosumab) drugs, though limited data exist on the antifracture efficacy (and sometimes safety) of these agents in CKD populations. Palcu *et al* [45] reported safe use of teriparatide over 24 months in a single dialysis patient with improvement in pain, bone biopsy and BMD. In a retrospective study of 13 patients with CKD4–5 treated with denosumab, Dave *et al* [46] identified severe hypocalcemia in 8/13 patients. A prospective study of denosumab in 11 dialysis patients with low bone mass identified an increase in BMD following one dose of denosumab, complicated only by asymptomatic hypocalcemia and a compensatory increase in PTH [47]. Both of these studies were observational and small, but suggest that denosumab might be safe to use in dialysis patients with aggressive repletion of calcium and vitamin D. Finally, the sclerostin inhibitor romosozumab is an exciting new agent that improved bone mineral density via both bone formation and decreased bone resorption over 12 months in post-menopausal women, though utility in patients with CKD is unknown [48]. Overall, despite reasonable consensus that these agents may be used in patients with CKD1–3 use in more advanced CKD requires additional study and close monitoring [41, 49].

CONSLUSIONS

Significant effort is placed on management of CKD-BMD, yet many questions remain. The current KDIGO guidelines remain the standard of care, though evidence to support many of the recommendations is poor and begs for additional clinical trials. As past discoveries resulted in the re-branding of the field (CKD-MBD), the current multitude of inter-related factors in CKD-MBD requires novel investigative methodologies. Instead of focusing on the perturbation of one or two substrates (which often leads to unwanted alterations of other related parameters), future studies will need to measure all of these molecules simultaneously and likely intervene on multiple pathways to produce a desired clinical effect. Methodologies borrowed from systems biology and pathway or network analysis are likely to be of benefit as they are able to incorporate the increasing complexity of CKD-MBD.

Acknowledgments

None

Financial support and sponsorship

Sagar U. Nigwekar has received funding support from the American Heart Association's NCRP Winter 2015 Fellow-to-Faculty Transition Award (15FTF25980003) and from the KL2/Catalyst Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 TR001100). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

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Key Points

- CKD related mineral bone disorders contribute to the high cardiovascular morbidity and mortality seen in patients with CKD and ESRD.
- A number of observational studies have defined associations with changes in CKD-MBD parameters and improved clinical outcomes, though clinical trials have yet to prove causality in most cases.
- There is a need for new clinical trials that can account for the increasing complexity of the CKD-MBD axis and intervene on more than one pathway.

Table 1

Recent clinical trials assessing vitamin D therapy

Trial	Population	Intervention	Results
DIVINE [9]	ESRD with 25(OH)D < 32 ng/ml, N = 105	Ergocalciferol 50,000 IU weekly or monthly for 12 wks	-Safe (minimal changes in Ca, Pi, PTH) and effective (increased mean 25(OH)D)
VitaDial [10]	ESRD with 25(OH)D < 30 ng/ml, N = 55	Cholecalciferol 25,000 IU weekly for 13 wks	-Safe and effective method to increase 25(OH)D and 1,25(OH)D
Styrian Vitamin D Hypertension Trial [11]	Hypertensive patients with 25(OH)D < 30ng/ml, N = 200	Cholecalciferol 2800 IU daily for 8 wks	-No effect on 24 hour SBP or any other cardiovascular outcome
DAYLIGHT [12]	Mild hypertension with 25(OH)D < 25 ng/ml, N = 534	Cholecalciferol 4000 IU versus 400 IU daily over 6 mo	-No reduction in blood pressure
OPERA [13]	Stage 3–5 CKD with LV hypertrophy, N = 60	Paricalcitol 1ug daily for 52 wks	-No change in LV structure or function, reduced PTH
PENNY [14]	Stage 3–4 CKD and PTH > 65 pg/mL, N = 88	Paricalcitol 2ug daily for 12 wks	-Increased endothelium – dependant vasodilation
Lundwall <i>et al</i> [15]	Stage 3–4 CKD, N = 36	Paricalcitol 1 or 2 ug daily for 3 mo	-Attenuated decline in endothelial function

Table 2

Proposed calciphylaxis risk factors

Category	Risk factors
Demographic characteristics	Female sex and white race
Co-morbid conditions	Diabetes mellitus, obesity, autoimmune diseases, hypercoagulation disorders, liver disease, hypoalbuminemia, and increased serum aluminum levels
Mineral bone abnormalities	Hypercalcemia, hyperphosphatemia, elevated calcium-phosphate product, hyperparathyroidism, and adynamic bone disease
Dialysis related characteristics	Increased dialysis vintage, unmet dialysis adequacy parameters, and high dialysate calcium bath
Medications	Warfarin, calcium supplements, calcium based phosphate binders, vitamin D analogues, iron therapy, corticosteroids, and subcutaneous injections

Source: from Curr Opin Nephrol Hypertens. 2015 Nov;24(6):531–7