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Evidence Basis for Integrated Management of Mineral Metabolism in Patients with End Stage Renal Disease

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Abstract

Purpose of Review: Treatment of mineral metabolism is a mainstay of dialysis care including some of its most widely used and costly pharmaceuticals. Although many mineral metabolites are associated with increased risk of mortality, cardiovascular disease, and other morbidities, few clinical trials are available to guide therapy and most focus on single drug approaches. In practice, providers manage many aspects of mineral metabolism simultaneously in integrated treatment approaches that incorporate multiple agents and changes in the dialysis prescription. This review discusses the rationale and existing evidence for evaluating integrated, as opposed to single drug, approaches in mineral metabolism.

Recent Findings: Drugs used to treat mineral metabolism have numerous, and sometimes, opposing effects on biochemical risk factors, such as fibroblast growth factor 23 (FGF23), calcium and phosphorus. While vitamin D sterols raise these risk markers when lowering parathyroid hormone (PTH), calcimimetics lower them. Trials demonstrate that combined approaches best ‘normalize’ the mineral metabolism axis in end-stage renal disease (ESRD). Observations embedded within major trials of calcimimetics reveal that adjustment of calcium-based binders and dialysate calcium is a common approach to adverse effects of these drugs with some initial, but inconclusive, evidence that these co-interventions may impact outcomes.

Summary: The multiple, and often opposing, biochemical effects of many mineral metabolism drugs provides a strong rationale for studying integrated management strategies that consider combinations of drugs and co-interventions as a whole. This remains a current gap in the field with opportunities for clinical trials.

Keywords

Mineral metabolism; vitamin D; cinacalcet; phosphorus; parathyroid hormone

Introduction

Integrated management of mineral metabolism in patients with end-stage renal disease (ESRD) on dialysis embraces its complex physiology to focus on multi-pronged interventions. Over the past 4 decades a wide armamentarium of mineral metabolism drugs

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have emerged including a steady progression from vitamin D and calcitriol to calcium-based phosphorus binders, synthetic vitamin D sterols, non-calcium-based phosphorus binders, calcimimetics and, most recently, novel iron-based phosphorus binders. Simultaneous with these evolving pharmacologic options have been systematic changes in dialysis practices including changes in common dialysate calcium concentrations, dialysis duration, parathyroid hormone (PTH) and phosphorus targets, and iron administration patterns, often driven by changes in practice guidelines, dialysis payment or quality benchmarks (Figure 1).^{1,2} Each of these shifts in dialysis care may impact the mineral metabolism axis.

Because most mineral metabolism drugs received marketing approval based on biochemical endpoints, without robust data on hard clinical outcomes, critical evidence gaps remain in understanding potential risks and benefits of mineral metabolism therapies in ESRD. As these drugs have been widely adopted into practice, our opportunity to conduct placebo-controlled trials has waned, leaving comparative effectiveness and biochemical “target” trials as the most feasible approaches to developing evidence-based practices. Integrated mineral metabolism therapy goes a step further to consider interactions between classes of mineral metabolism agents, but also other features such as dialysate prescriptions and intensity of treatment targets, in an effort to identify optimal holistic treatment practices in ESRD. This growing focus on integrated management is reflected in the updated Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines for Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) that newly emphasizes the need to consider mineral metabolites in concert (Guideline 4.1.1).³ On this backdrop, the current manuscript reviews the landscape of clinical trials in mineral metabolism and related areas in ESRD, and considers the case for further studies of integrated mineral metabolism therapy as an area for future clinical trials.

Integrated Physiology in Mineral Metabolism

Mineral metabolism in untreated ESRD is characterized by elevation in serum phosphorus and its regulatory hormones fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH), as well as low levels of 1,25-dihydroxyvitamin D (1,25-D), serum calcium and expression of α -klotho, the co-receptor for FGF23. The prevailing view is that the genesis of these abnormalities centers on a reduced capacity to excrete phosphorus as kidney disease worsens.⁴ To counteract this reduced capacity, FGF23 rises. In addition to promoting phosphorus excretion, FGF23 inhibits the hydroxylation of 25-hydroxyvitamin D to the active form of 1,25-D, leading to falling levels. Low 1,25-D results in lower serum calcium and klotho. Both low 1,25-D and calcium drive progressive increases in PTH, completing the constellation of abnormalities (Figure 2).^{5,6} Treatment to reverse these changes has been a central component of dialysis management for decades largely to prevent severe bone disease, vascular disease and deformity that was previously widespread without therapy.^{7,8}

Over the last 2 decades there has been growing recognition of the role the mineral metabolism axis may play in the development of less overt forms of cardiovascular disease, prompting calls to treat this axis more aggressively. Robust *in vitro*, *in vivo*, and mostly observational human studies link higher phosphorus concentrations to vascular calcification and dysfunction in ESRD; high FGF23, high PTH, and low klotho to changes in cardiac

structure and function, such as left ventricular hypertrophy and myocardial fibrosis; and change in serum calcium to vascular calcification and arrhythmia (Figure 2).^{9–17} Therapies focused on lowering serum phosphorus and PTH, and treating 1,25-D deficiency can reverse some of these biochemical changes, but haven't convincingly demonstrated efficacy in reducing clinical cardiovascular toxicities.^{18–26} This uncertainty is, in part, due to the lack of high quality placebo-controlled trials.

However even where trials exist, generalizing from single-agent studies to full management strategies that better reflect the care delivered by providers is challenging because of the complex physiologic interaction of the treatment targets in mineral metabolism. For instance, treatment with calcitriol or active vitamin D sterols lowers PTH but also raises FGF23, serum calcium and phosphorus.^{22,23,27,28} Theoretically, some of these potential risks could be offset by the impact of vitamin D to boost endogenous klotho expression, potentially directing the higher FGF23 away from purported adverse cardiovascular effects which depend on klotho-independent signaling.^{29,30} On the other hand, calcimimetics lower FGF23 along with PTH and reduce serum calcium and phosphorus.³¹ The adverse calcium and phosphorus related effects of vitamin D agents and calcimimetics can be somewhat attenuated by selection of phosphorus binders with or without calcium, or adjustment of the dialysis duration or calcium concentration.^{32,33} The sometimes opposing biological impacts of these different therapies and co-interventions underscore the importance of considering the full approach to mineral metabolism in design and interpretation of future studies.

Integrated Treatment Targets in Mineral Metabolism

Due to the inherent biological connections between mineral metabolites discussed above, it may not be ideal to evaluate each abnormality in isolation. Data from a large cohort of prevalent dialysis patients identified common mineral metabolism 'phenotypes', characterized by combinations of serum calcium, phosphorus and PTH. In this study many phenotypes that included hypercalcemia or common phenotypes, such as high PTH alone or concomitant elevation of PTH and phosphorus, were associated with increased risk of death and cardiovascular disease.³⁴ Further analyses of this cohort evaluated a simplified metric that quantified the number of mineral metabolites above guideline-based ranges. In this study having 2 or more mineral metabolite above range is both common and associated with high risk of adverse outcomes, thereby identifying a group in need of focused attention.³⁵ Mineral metabolism related drugs are among the most widely prescribed and costly drugs in dialysis care, thus focusing efforts on this high risk, common group could be beneficial from a population health management perspective.³⁶

However, both of these prior studies were limited because patients were already being treated with mineral metabolism therapies in most cases. Therefore, these results may reflect improved outcomes among patients who are responsive, as opposed to refractory, to therapy. Additionally these studies do not consider the drugs that are being used to manage mineral metabolism. In addition to controlling serum calcium, phosphorus and PTH, many mineral metabolism drugs have opposing effects on biochemical risk factors that are not currently measured in practice, such as FGF23 and klotho, as well as other unknown or unmeasured beneficial and adverse effects. In lieu of studies focused on achieved biochemical values as

treatment targets, studies focused on comparing different treatment approaches may better answer questions about optimal therapy.

Evidence-Based and Principles for Single Drug Approaches

Most of the existing evidence guiding treatment approaches for mineral metabolism in dialysis is focused on single drug approaches to care as reviewed below.

Phosphorus Binders

Phosphorus binders have been used for decades to reduce gastrointestinal phosphorus absorption in ESRD and prevent severe hyperphosphatemia. Based on risks extrapolated from observational and animal studies, guidelines advocated more stringent control of serum phosphorus levels resulting in a large number of approved products for phosphorus lowering.^{3,37–41} None of these products have been shown to lower risk of hard clinical outcomes in placebo controlled trials. A recent trial in approximately 100 individuals with ESRD on hemodialysis demonstrated the feasibility of achieving higher and lower phosphorus targets using a binder titration algorithm.⁴² This and other studies are building momentum for trials that could evaluate phosphorus binders versus placebo, with rescue therapy for severe hyperparathyroidism, or higher versus lower serum phosphorus targets among patients using binders.

A small number of randomized trials have evaluated the comparative effectiveness of different classes of phosphorus binders particularly calcium-based vs. sevelamer based binders.^{43–47} The largest of these studies, the Dialysis Clinical Outcomes Revisited (DCOR) was plagued by frequent drop out and loss to follow up, ultimately yielding non-definitive results.⁴⁴ However, leveraging a passive follow up mechanism via linkage with mortality and ESRD registries, a longer-term analysis demonstrated no difference between binder types.⁴⁸ Meta-analyses have pooled this study along with smaller studies not powered for mortality and found a small but statistically significant benefit of non-calcium based binders.^{49,50} Largely based on these findings and concerns about calcium balance in ESRD, the updated KDIGO Guidelines for CKD-MBD recommends limiting the total dose of calcium-based phosphorus binders.³ However, since most of the included studies in these meta-analyses were neither designed for survival outcomes nor registered, small study and publication biases could significantly contribute to this finding. Additionally, these studies were largely conducted in an era when active vitamin D sterols were the dominant approach to manage secondary hyperparathyroidism. Because the risk associated with calcium-based binders may be due to excessive calcium loading and vascular calcification, calcium-based binders may not confer the same risks if coupled with calcimimetics for treatment of secondary hyperparathyroidism or in the setting of lower dialysate calcium. In fact, in recent trials of calcimimetics, increased intake of calcium-based phosphorus binders is a common approach to mitigate their hypocalcemic effects.^{33,51} Trial data on the safety and efficacy of calcium-based phosphorus binders in the setting of calcimimetic use, specifically, are not available but this could be evaluated as a component of an integrated management approach.

Novel phosphorus binding agents, such as iron based binders, have recently emerged as a therapeutic option.⁵² In addition to lowering phosphorus many binders in this class have the

additional potential benefit of lowering FGF23 and reducing erythropoietin and iron requirements.⁵³ Neither placebo-controlled, nor comparative effectiveness trials have been conducted to evaluate the impact of these binders on clinical outcomes, such as mortality, cardiovascular events or fracture.

Calcitriol and Vitamin D Sterols

Use of calcitriol or other active vitamin D sterols in patients with ESRD on dialysis and secondary hyperparathyroidism clearly improves PTH, prevents parathyroidectomy and improves bone histology.^{22,23} Observational studies suggest benefits of treatment with vitamin D agents in ESRD, including reduction in mortality, but these benefits have never been confirmed in trials.^{54–56} Currently, active vitamin D sterols are used in the majority of patients on dialysis worldwide and thus placebo-controlled trials are unlikely. Dose escalation trials focused on alternate fixed doses or titration to a target PTH could provide evidence for a dose-response effect solidifying their role in cardiovascular disease prevention.

Comparative effectiveness trials have evaluated calcitriol and vitamin D sterols head-to-head focusing on biochemical endpoints in ESRD. In sum, these studies largely have demonstrated fewer episodes of clinically relevant hypercalcemia with the use of synthetic vitamin D sterols compared to calcitriol in some studies, and similar or superior effects on PTH reduction and bone outcomes.^{32,57} Comparisons of alternative sterols have demonstrated similar efficacy in PTH reduction, although most were not designed with *a priori* non-inferiority or equivalence criteria.^{28,58} Long-term comparisons utilizing randomized designs are not available, however observational comparative effectiveness studies report similar long term outcomes with different agents, such as paricalcitol versus doxercalciferol.⁵⁶ Novel, investigational vitamin D sterols with different routes of administration, pharmacokinetics and possibly increased selectivity for bone and parathyroid gland are under development.⁵⁹

Calcimimetics

Cinacalcet received US Food and Drug Administration (FDA) approval in 2004 as the first-in-class calcimimetic based on its ability to lower PTH in short term placebo-controlled trials of patients on dialysis.^{19,25,60,61} Pooled results from these trials demonstrated better achievement of guideline based targets for PTH, phosphorus and calcium with addition of cinacalcet compared to placebo.⁶² A post-hoc meta-analysis of these and other placebo-controlled cinacalcet trials suggested a reduced risk of parathyroidectomy, fracture, and cardiovascular hospitalization when cinacalcet was added to standard of care.⁶³ The included trials were not designed for these endpoints and often restricted titration of standard of care medications. Nonetheless, their pooled results helped lay the groundwork for the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, which tested cinacalcet versus placebo in addition to standard of care on the primary composite outcome of all-cause mortality, myocardial infarction, unstable angina, heart failure and peripheral vascular event in over 3,000 patients on hemodialysis.²⁶ Secondary outcomes included parathyroidectomy and fracture. In contrast to the preceding meta-analysis in which therapies other than cinacalcet were generally not titrated, the design

of EVOLVE included titration of standard of care medication, such as active vitamin D sterols and phosphorus binders, to conform with contemporary practice targets. The combined results of EVOLVE did not reveal a statistically significant benefit of cinacalcet on the primary outcome although a benefit was seen in adjusted analyses and analyses that censored follow up 6 months after discontinuation of the study drug. Rates of parathyroidectomy and severe tertiary hyperparathyroidism were lower in the cinacalcet group, but reduction in fracture was only observed after adjustment for baseline characteristics.^{26,64}

Drop out was a major limitation of many studies evaluating mineral metabolism approaches including over 60% drop out in the cinacalcet group within EVOLVE and 20–30% drop out in earlier studies.^{65–68} A newer intravenous calcimimetic, etelcalcetide, recently received FDA approval for treatment of secondary hyperparathyroidism in patients with ESRD on dialysis due to PTH reduction in placebo-controlled trials.³³ In a comparative effectiveness non-inferiority trial, etelcalcetide achieved even greater PTH and FGF23 lowering than cinacalcet in the short-term. It is not clear if this is due to greater efficacy of the formulation or greater investigator control of treatment adherence due to its ease of administration during hemodialysis. Adverse gastrointestinal effects were similar despite the intravenous route of administration.⁵¹

The PARADIGM trial is the first to compare management of secondary hyperparathyroidism with calcitriol or active vitamin D analogs versus cinacalcet monotherapy. PARADIGM studied approximately 300 participants on hemodialysis for up to 1 year.⁶⁹ Vitamin D and cinacalcet based strategies demonstrated similar efficacy at reducing PTH. Post-hoc studies suggest that they have opposite effects on other biochemical risk factors, such as FGF23, phosphorus and calcium.²⁷ Subgroup analyses with PARADIGM demonstrated that the PTH reduction with cinacalcet was greater when associated with a calcium-based phosphorus binder or a higher dialysate calcium, perhaps by mitigating additional stimulation of PTH by hypocalcemia.⁶⁹ Although this study was expressly designed to study monotherapy, these biological interactions with other mineral metabolism co-interventions imply the need to study complete or integrated mineral metabolism strategies to best optimize therapy.

Evidence-Base and Principles for Integrated Therapeutic Approaches

A growing body of literature is evaluating multi-drug therapy and considering drug treatment in the context of other aspects of dialysis care. These types of studies recognize the complexity of mineral metabolism physiology and represent the full “practice style” of different treating providers who simultaneously manage many aspects of mineral metabolism.^{3,38,70} In the setting of limited guidance from trials and international organizations on best strategies, a variety of styles abound.^{71,72}

Combined Pharmacologic Approaches

In the ACHIEVE trial, 173 patients with secondary hyperparathyroidism were randomized to cinacalcet plus low dose active vitamin D sterols versus titration of active vitamin D sterols alone. The results demonstrated that a higher proportion of patients achieved guideline-based targets for PTH, calcium and phosphorus in the cinacalcet plus vitamin D

arm,⁶⁷ and that this arm resulted in a lower FGF23 than vitamin D alone.⁷³ These effects on improved PTH, calcium and phosphorus may translate into reduced burden of vascular calcification, as suggested in the ADVANCE study. In ADVANCE, 360 participants were again randomized to cinacalcet plus low dose vitamin D sterols versus low dose vitamin D sterols alone for 52 weeks. The primary outcome was proportion of participants with >15% progression in coronary artery calcification score as determined by computed tomography. There was a trend towards less progression of calcification in the cinacalcet plus low dose vitamin D group that was not statistically significant in the unadjusted analysis ($p=0.09$), but was stronger with adjustment for baseline imbalances between groups, including higher serum phosphorus in the cinacalcet plus vitamin D group ($p=0.01$).⁶⁸ In each of the above studies the achieved PTH was lower in the cinacalcet plus vitamin D group compared to vitamin D alone making it difficult to discern effects of specific drug classes from more intensive management of secondary hyperparathyroidism.

The OPTIMA trial evaluated a clinical protocol favoring cinacalcet as a central agent, but that also added or titrated active vitamin D sterols and phosphorus binders in response to changes in calcium, phosphorus or over-suppression of PTH, in order to achieve simultaneous control of multiple parameters.⁷⁴ IMPACT SHPT used a similar approach of protocol driven care combining cinacalcet and active vitamin D sterols in the treatment arm, but unlike OPTIMA also provided a clear protocol for dose titration in the active vitamin D alone arm achieving more standardized care in both groups. In OPTIMA, biochemical outcomes were improved with a cinacalcet based approach, whereas the vitamin D arm (paricalcitol) had lower rates of treatment discontinuation and achieved better PTH results in IMPACT SHPT.⁷⁵ Neither study was designed to evaluate clinical outcomes.

Dialysate Management

Although changes in dialysate calcium and time may help mitigate adverse effects of active vitamin D sterols and cinacalcet, only a few studies have evaluated the impact of dialysate management in conjunction with mineral metabolism drugs. In a secondary analysis of the EVOLVE trial, cinacalcet therapy was associated with lower risk of the primary outcome among those using higher dialysate calcium (>2.5 mEq/L), but not among those with lower dialysate calcium although the interaction was not statistically significant.⁷⁶ Cinacalcet also demonstrated stronger PTH reduction in PARADIGM among those using higher dialysate calcium.⁶⁹ It is possible that low dialysate calcium coupled with hypocalcemic effects of cinacalcet may offset some of the benefits of therapy due to risks related to hypocalcemia or additional stimulation of PTH.⁷⁷

Other Drugs and Aspects of Dialysis Care

In addition to the primary drug classes and dialysate composition, other aspects of dialysis care can contribute to control of mineral metabolism. Extension of dialysis treatment time can improve dialytic phosphorus removal, potentially impacting serum phosphorus and other downstream mineral metabolites.^{78,79} Investigational mineral metabolism treatments currently in phase 3 trials may provide additional tools in the treatment arsenal if approved for use. For instance, tenapanor, a small molecular inhibitor of gastrointestinal phosphorus absorption, lowered serum phosphorus and FGF23 in patients with ESRD on dialysis in

short-term trials. Future trials will clarify possible roles in an integrated strategy for mineral metabolism.⁸⁰

Conclusion

The 2017 (KDIGO) Guidelines for CKD-MBD highlight uncertainty about best agents and targets to use for treatment of mineral metabolism in ESRD.³ With limited evidence from comparative effectiveness studies, no clear consensus has emerged about the best pharmacologic options for treating mineral metabolism, including calcitriol and other active vitamin D sterols, calcimimetics or combinations, or a growing number of classes of phosphorus binders.³ In the meantime our biological understanding of the role of a wide variety of mineral metabolites in the pathogenesis of cardiovascular and bone disease and their inherent biological tradeoffs underscore the potential folly of studies that consider treatments in isolation. Classifying mineral metabolism approaches by only one aspect of care cannot easily characterize them in a mutually exclusive way, as illustrated schematically in vignettes in Figure 3, and will require an alternative integrated scheme. By analogy, similar approaches have been embraced in other complex fields, such as nutrition, in which interaction between nutrients turned the paradigm towards studying dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) pattern, as opposed to isolated nutrient targets.⁸¹ In mineral metabolism, although growing biological insights and single agent studies can guide hypotheses about holistic strategies, ultimately confirmatory trials of different treatment approaches will be needed to translate this high impact area into the best care practices for our patients.

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References

1. Clark EG, Zimmerman DL. Dialysate Calcium in Limbo: How Low Can You Go? *Am J Kidney Dis.* 2015;66(4):558–560. [PubMed: 26408235]
2. Fuller DS, Robinson BM. Facility Practice Variation to Help Understand the Effects of Public Policy: Insights from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol.* 2017;12(1):190–199. [PubMed: 28062678]
- *3. Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Mineral and Bone Disorder Working Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl.* 2017;7:1–59. New guidelines for CKD-MBD released by KDIGO provide some changes relevant to this review on integrated mineral metabolism management in ESRD. First recommendation 4.1.1 was revised to emphasize that treatment should be based on CKD-MBD measurements “considered together.” In addition, recommendation 4.2.4 recognizes the uncertainty of optimal agents for management of secondary hyperparathyroidism including potentially “calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs.”
4. Vervloet MG, Sezer S, Massy ZA, Johansson L, Cozzolino M, Fouque D. The role of phosphate in kidney disease. *Nat Rev Nephrol.* 2017;13(1):27–38. [PubMed: 27867189]

5. Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie H, Appleby D, Nessel L, Bellocovich K, Chen J, Hamm L, Gadegebeku C, Horwitz E, Townsend RR, Anderson CA, Lash JP, Hsu CY, Leonard MB, Wolf M. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int.* 2011;79(12):1370–1378. [PubMed: 21389978]
6. Block GA, Ix JH, Ketteler M, Martin KJ, Thadhani RI, Tonelli M, Wolf M, Juppner H, Hruska K, Wheeler DC. Phosphate homeostasis in CKD: report of a scientific symposium sponsored by the National Kidney Foundation. *Am J Kidney Dis.* 2013;62(3):457–473. [PubMed: 23763855]
7. Ritz E, Kremzien B, Mehls O, Malluche H. Skeletal abnormalities in chronic renal insufficiency before and during maintenance hemodialysis. *Kidney Int.* 1973;4(2):116–127. [PubMed: 4790866]
8. Parfitt AM. Soft-tissue calcification in uremia. *Arch Intern Med.* 1969;124(5):544–556. [PubMed: 4899444]
9. Scialla JJ, Lau WL, Reilly MP, Isakova T, Yang HY, Crouthamel MH, Chavkin NW, Rahman M, Wahl P, Amaral AP, Hamano T, Master SR, Nessel L, Chai B, Xie D, Kallem RR, Chen J, Lash JP, Kusek JW, Budoff MJ, Giachelli CM, Wolf M. Fibroblast growth factor 23 is not associated with and does not induce arterial calcification. *Kidney Int.* 2013;83(6):1159–1168. [PubMed: 23389416]
10. Chen NX, O'Neill KD, Duan D, Moe SM. Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. *Kidney Int.* 2002;62(5):1724–1731. [PubMed: 12371973]
11. Faul C, Amaral AP, Oskoue B, Hu MC, Sloan A, Isakova T, Gutierrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, Sutton M St John, Ojo A, Gadegebeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro OM, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest.* 2011;121(11):4393–4408. [PubMed: 21985788]
12. Touchberry CD, Green TM, Tchikrizov V, Mannix JE, Mao TF, Carney BW, Girgis M, Vincent RJ, Wetmore LA, Dawn B, Bonewald LF, Stubbs JR, Wacker MJ. FGF23 is a novel regulator of intracellular calcium and cardiac contractility in addition to cardiac hypertrophy. *Am J Physiol Endocrinol Metab.* 2013;304(8):E863–873. [PubMed: 23443925]
13. Amann K, Tornig J, Kugel B, Gross ML, Tyralla K, El-Shakmak A, Szabo A, Ritz E. Hyperphosphatemia aggravates cardiac fibrosis and microvascular disease in experimental uremia. *Kidney Int.* 2003;63(4):1296–1301. [PubMed: 12631346]
14. Watanabe Y Effects of calcium and sodium concentrations on atrioventricular conduction: experimental study in rabbit hearts with clinical implications on heart block and slow calcium channel blocking agent usage. *Am Heart J.* 1981;102(5):883–891. [PubMed: 6272562]
15. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnhen-Dechent W, Weissberg PL, Shanahan CM. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. *J Am Soc Nephrol.* 2004;15(11):2857–2867. [PubMed: 15504939]
16. Pun PH, Horton JR, Middleton JP. Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. *Clin J Am Soc Nephrol.* 2013;8(5):797–803. [PubMed: 23371957]
17. Hu MC, Shi M, Cho HJ, Adams-Huet B, Paek J, Hill K, Shelton J, Amaral AP, Faul C, Taniguchi M, Wolf M, Brand M, Takahashi M, Kuro OM, Hill JA, Moe OW. Klotho and phosphate are modulators of pathologic uremic cardiac remodeling. *J Am Soc Nephrol.* 2015;26(6):1290–1302. [PubMed: 25326585]
18. Tonelli M, Pannu N, Manns B. Oral phosphate binders in patients with kidney failure. *N Engl J Med.* 2010;362(14):1312–1324. [PubMed: 20375408]
19. Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, Hercz G, Cunningham J, Abu-Alfa AK, Messa P, Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCarty LC, Zani VJ, Olson KA, Drueke TB, Goodman WG. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med.* 2004;350(15):1516–1525. [PubMed: 15071126]
20. Lindberg JS, Culleton B, Wong G, Borah MF, Clark RV, Shapiro WB, Roger SD, Husserl FE, Klassen PS, Guo MD, Albizem MB, Coburn JW. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a

- randomized, double-blind, multicenter study. *J Am Soc Nephrol.* 2005;16(3):800–807. [PubMed: 15689407]
21. Martin KJ, Gonzalez EA, Gellens M, Hamm LL, Abboud H, Lindberg J. 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.* 1998;9(8):1427–1432. [PubMed: 9697664]
 22. Martin KJ, Gonzalez EA. Vitamin D analogues for the management of secondary hyperparathyroidism. *Am J Kidney Dis.* 2001;38(5 Suppl 5):S34–40.
 23. Andress DL, Norris KC, Coburn JW, Slatopolsky EA, Sherrard DJ. Intravenous calcitriol in the treatment of refractory osteitis fibrosa of chronic renal failure. *N Engl J Med.* 1989;321(5):274–279. [PubMed: 2631697]
 24. Quarles LD, Sherrard DJ, Adler S, Rosansky SJ, McCary LC, Liu W, Turner SA, Bushinsky DA. The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. *J Am Soc Nephrol.* 2003;14(3):575–583. [PubMed: 12595492]
 25. Lindberg JS, Moe SM, Goodman WG, Coburn JW, Sprague SM, Liu W, Blaisdell PW, Brenner RM, Turner SA, Martin KJ. The calcimimetic AMG 073 reduces parathyroid hormone and calcium x phosphorus in secondary hyperparathyroidism. *Kidney Int.* 2003;63(1):248–254. [PubMed: 12472790]
 26. Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med.* 2012;367(26):2482–2494. [PubMed: 23121374]
 27. Cozzolino M, Ketteler M, Martin KJ, Sharma A, Goldsmith D, Khan S. Paricalcitol- or cinacalcet-centred therapy affects markers of bone mineral disease in patients with secondary hyperparathyroidism receiving haemodialysis: results of the IMPACT-SHPT study. *Nephrol Dial Transplant.* 2014;29(4):899–905. [PubMed: 24500308]
 28. Hansen D, Rasmussen K, Pedersen SM, Rasmussen LM, Brandi L. Changes in fibroblast growth factor 23 during treatment of secondary hyperparathyroidism with alfacalcidol or paricalcitol. *Nephrol Dial Transplant.* 2012;27(6):2263–2269. [PubMed: 22140123]
 29. Hu MC, Kuro-o M, Moe OW. Klotho and chronic kidney disease. *Contrib Nephrol.* 2013;180:47–63. [PubMed: 23652549]
 30. Grabner A, Amaral AP, Schramm K, Singh S, Sloan A, Yanucil C, Li J, Shehadeh LA, Hare JM, David V, Martin A, Fornoni A, Di Marco GS, Kentrup D, Reuter S, Mayer AB, Pavenstadt H, Stypmann J, Kuhn C, Hille S, Frey N, Leifheit-Nestler M, Richter B, Haffner D, Abraham R, Bange J, Sperl B, Ullrich A, Brand M, Wolf M, Faul C. Activation of Cardiac Fibroblast Growth Factor Receptor 4 Causes Left Ventricular Hypertrophy. *Cell Metab.* 2015;22(6):1020–1032. [PubMed: 26437603]
 31. Sprague SM, Wetmore JB, Gurevich K, Da Roza G, Buerkert J, Reiner M, Goodman W, Cooper K. Effect of Cinacalcet and Vitamin D Analogs on Fibroblast Growth Factor-23 during the Treatment of Secondary Hyperparathyroidism. *Clin J Am Soc Nephrol.* 2015;10(6):1021–1030. [PubMed: 25873267]
 32. Wesseling-Perry K, Pereira RC, Sahney S, Gales B, Wang HJ, Elashoff R, Juppner H, Salusky IB. Calcitriol and doxercalciferol are equivalent in controlling bone turnover, suppressing parathyroid hormone, and increasing fibroblast growth factor-23 in secondary hyperparathyroidism. *Kidney Int.* 2011;79(1):112–119. [PubMed: 20861820]
 33. Block GA, Bushinsky DA, Cunningham J, Drueke TB, Ketteler M, Kewalramani R, Martin KJ, Mix TC, Moe SM, Patel UD, Silver J, Spiegel DM, Sterling L, Walsh L, Chertow GM. Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: Two Randomized Clinical Trials. *JAMA.* 2017;317(2):146–155. [PubMed: 28097355]
 34. Block GA, Kilpatrick RD, Lowe KA, Wang W, Danese MD. CKD-mineral and bone disorder and risk of death and cardiovascular hospitalization in patients on hemodialysis. *Clin J Am Soc Nephrol.* 2013;8(12):2132–2140. [PubMed: 24052218]

35. Danese MD, Halperin M, Lowe KA, Bradbury BD, Do TP, Block GA. Refining the definition of clinically important mineral and bone disorder in hemodialysis patients. *Nephrol Dial Transplant*. 2015;30(8):1336–1344. [PubMed: 25817224]
36. Yusuf AA, Howell BL, Powers CA, St Peter WL. Utilization and costs of medications associated with CKD mineral and bone disorder in dialysis patients enrolled in Medicare Part D. *Am J Kidney Dis*. 2014;64(5):770–780. [PubMed: 24833203]
37. Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Mineral and Bone Disorder Working Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int*. 2009;76(Suppl 113):S1–S130.
38. Foundation NK. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42, Supplement 3:1–201.
39. Cannata-Andia JB, Fernandez-Martin JL, Locatelli F, London G, Gorriz JL, Floege J, Ketteler M, Ferreira A, Covic A, Rutkowski B, Memmos D, Bos WJ, Teplan V, Nagy J, Tielemans C, Verbeelen D, Goldsmith D, Kramar R, Martin PY, Wuthrich RP, Pavlovic D, Benedik M, Sanchez JE, Martinez-Cambor P, Naves-Diaz M, Carrero JJ, Zoccali C. Use of phosphate-binding agents is associated with a lower risk of mortality. *Kidney Int*. 2013;84(5):998–1008. [PubMed: 23823605]
40. Isakova T, Gutierrez OM, Chang Y, Shah A, Tamez H, Smith K, Thadhani R, Wolf M. Phosphorus binders and survival on hemodialysis. *J Am Soc Nephrol*. 2009;20(2):388–396. [PubMed: 19092121]
41. Lopes AA, Tong L, Thumma J, Li Y, Fuller DS, Morgenstern H, Bommer J, Kerr PG, Tentori F, Akiba T, Gillespie BW, Robinson BM, Port FK, Pisoni RL. Phosphate Binder Use and Mortality Among Hemodialysis Patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS): Evaluation of Possible Confounding by Nutritional Status. *Am J Kidney Dis*. 2012;60(1):90–101. [PubMed: 22385781]
42. Wald R, Rabbat CG, Girard L, Garg AX, Tennankore K, Tyrwhitt J, Smyth A, Rathe-Skafel A, Gao P, Mazzetti A, Bosch J, Yan AT, Parfrey P, Manns BJ, Walsh M. Two phosphate tarGets in End-stage renal disease Trial (TARGET): A Randomized Controlled Trial. *Clin J Am Soc Nephrol*. 2017;12(6):965–973. [PubMed: 28550080]
43. Chertow GM, Burke SK, Raggi P, Treat to Goal Working G. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*. 2002;62(1):245–252. [PubMed: 12081584]
44. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, Ling BN, Chasan-Taber S, Dillon MA, Blair AT, Burke SK. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int*. 2007;72(9):1130–1137. [PubMed: 17728707]
45. Di Iorio B, Bellasi A, Russo D, Investigators IS. Mortality in kidney disease patients treated with phosphate binders: a randomized study. *Clin J Am Soc Nephrol*. 2012;7(3):487–493. [PubMed: 22241819]
46. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int*. 2007;71(5):438–441. [PubMed: 17200680]
47. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, Raggi P. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int*. 2005;68(4):1815–1824. [PubMed: 16164659]
48. St Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. *Am J Kidney Dis*. 2008;51(3):445–454. [PubMed: 18295060]
49. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, Lok CE, Fitchett D, Tsuyuki RT. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet*. 2013;382(9900):1268–1277. [PubMed: 23870817]
50. Palmer SC, Gardner S, Tonelli M, Mavridis D, Johnson DW, Craig JC, French R, Ruospo M, Strippoli GF. Phosphate-Binding Agents in Adults With CKD: A Network Meta-analysis of Randomized Trials. *Am J Kidney Dis*. 2016;68(5):691–702. [PubMed: 27461851]

- *51. Block GA, Bushinsky DA, Cheng S, Cunningham J, Dehmel B, Drueke TB, Ketteler M, Kewalramani R, Martin KJ, Moe SM, Patel UD, Silver J, Sun Y, Wang H, Chertow GM. Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: A Randomized Clinical Trial. *JAMA*. 2017;317(2):156–164. [PubMed: 28097356] This trial included >600 patients with end-stage renal disease on hemodialysis to compare the effectiveness of a new intravenous calcimimetic, etelcalcetide, versus cinacalcet. Although the study was designed for noninferiority, at 6 months, patients treated with etelcalcetide demonstrated superior rates of >30% reduction in PTH with a similar side effect profile. Etelcalcetide received market approval in 2017.
52. Shah HH, Hazzan AD, Fishbane S. Novel iron-based phosphate binders in patients with chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2015;24(4):330–335. [PubMed: 26050119]
53. Chertow GM, Block GA, Neylan JF, Pergola PE, Uhlig K, Fishbane S. Safety and efficacy of ferric citrate in patients with nondialysis-dependent chronic kidney disease. *PLoS One*. 2017;12(11):e0188712. [PubMed: 29186198]
54. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med*. 2003;349(5):446–456. [PubMed: 12890843]
55. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernan MA, Camargo CA, Jr., Thadhani R. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol*. 2005;16(4):1115–1125. [PubMed: 15728786]
56. Tentori F, Hunt WC, Stidley CA, Rohrscheib MR, Bedrick EJ, Meyer KB, Johnson HK, Zager PG. Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int*. 2006;70(10):1858–1865. [PubMed: 17021609]
57. Sprague SM, Llach F, Amdahl M, Taccetta C, Battle D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int*. 2003;63(4):1483–1490. [PubMed: 12631365]
58. Xie Y, Su P, Sun Y, Zhang H, Zhao R, Li L, Meng L. Comparative efficacy and safety of paricalcitol versus Vitamin D receptor activators for dialysis patients with secondary hyperparathyroidism: A meta-analysis of randomized controlled trials. *BMC Nephrology*. 2017;18(1).
59. Thadhani R, Zella JB, Knutson DC, Blaser WJ, Plum LA, Clagett-Dame M, Buck RD, Deluca HF. 2MD (DP001), a Single Agent in the Management of Hemodialysis Patients: A Randomized Trial. *Am J Nephrol*. 2017;45(1):40–48. [PubMed: 27880946]
60. Goodman WG, Frazao JM, Goodkin DA, Turner SA, Liu W, Coburn JW. A calcimimetic agent lowers plasma parathyroid hormone levels in patients with secondary hyperparathyroidism. *Kidney Int*. 2000;58(1):436–445. [PubMed: 10886592]
61. Goodman WG, Hladik GA, Turner SA, Blaisdell PW, Goodkin DA, Liu W, Barri YM, Cohen RM, Coburn JW. The Calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. *J Am Soc Nephrol*. 2002;13(4):1017–1024. [PubMed: 11912261]
62. Moe SM, Chertow GM, Coburn JW, Quarles LD, Goodman WG, Block GA, Drueke TB, Cunningham J, Sherrard DJ, McCary LC, Olson KA, Turner SA, Martin KJ. Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. *Kidney Int*. 2005;67(2):760–771. [PubMed: 15673327]
63. Cunningham J, Danese M, Olson K, Klassen P, Chertow GM. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int*. 2005;68(4):1793–1800. [PubMed: 16164656]
64. Moe SM, Abdalla S, Chertow GM, Parfrey PS, Block GA, Correa-Rotter R, Floege J, Herzog CA, London GM, Mahaffey KW, Wheeler DC, Dehmel B, Goodman WG, Drueke TB. Effects of Cinacalcet on Fracture Events in Patients Receiving Hemodialysis: The EVOLVE Trial. *J Am Soc Nephrol*. 2015;26(6):1466–1475. [PubMed: 25505257]
65. Chertow G, Block G, Correa-Rotter R, Drueke T, Floege J, Goodman W, Herzog C, Kubo Y, London G, Mahaffey K, Mix T, Moe S, Trotman M, Wheeler D, Parfrey P. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*. 2012;367:2482–2494. [PubMed: 23121374]

66. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. *J Am Soc Nephrol.* 2004;15(8):2208–2218. [PubMed: 15284307]
67. Fishbane S, Shapiro W, Corry D, Vicks S, Roppolo M, Rappaport K, Ling X, Goodman W, Turner S, Charytan C. Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone: the ACHIEVE study results. *Clin J Am Soc Nephrol.* 2008;3:1718–1725. [PubMed: 18945995]
68. Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, Moustafa M, Goodman WG, Lopez N, Downey G, Dehmel B, Floege J. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant.* 2011;26(4):1327–1339. [PubMed: 21148030]
69. Wetmore JB, Gurevich K, Sprague S, Da Roza G, Buerkert J, Reiner M, Goodman W, Cooper K. A Randomized Trial of Cinacalcet versus Vitamin D Analogs as Monotherapy in Secondary Hyperparathyroidism (PARADIGM). *Clin J Am Soc Nephrol.* 2015;10(6):1031–1040. [PubMed: 25904755]
70. Uhlig K, Berns JS, Kestenbaum B, Kumar R, Leonard MB, Martin KJ, Sprague SM, Goldfarb S. KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD). *Am J Kidney Dis.* 2010;55(5):773–799. [PubMed: 20363541]
71. Tentori F, Wang M, Bieber BA, Karaboyas A, Li Y, Jacobson SH, Andreucci VE, Fukagawa M, Frimat L, Mendelssohn DC, Port FK, Pisoni RL, Robinson BM. Recent Changes in Therapeutic Approaches and Association with Outcomes among Patients with Secondary Hyperparathyroidism on Chronic Hemodialysis: The DOPPS Study. *Clin J Am Soc Nephrol.* 2015;10(1):98–109. [PubMed: 25516917]
72. Tentori F, Zepel L, Fuller DS, Wang M, Bieber BA, Robinson BM, Pisoni RL. The DOPPS Practice Monitor for US Dialysis Care: PTH Levels and Management of Mineral and Bone Disorder in US Hemodialysis Patients. *Am J Kidney Dis.* 2015;66(3):536–539. [PubMed: 26300197]
73. Wetmore JB, Liu S, Krebill R, Menard R, Quarles LD. Effects of cinacalcet and concurrent low-dose vitamin D on FGF23 levels in ESRD. *Clin J Am Soc Nephrol.* 2010;5(1):110–116. [PubMed: 19965548]
74. Messa P, Macario F, Yaqoob M, Bouman K, Braun J, von Albertini B, Brink H, Maduell F, Graf H, Frazao J, Bos W, Torregrosa V, Saha H, Reichel H, Wikie M, Zani V, Molemans B, Carter D, Locatelli F. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. *Clin J Am Soc Nephrol.* 2008;3:36–45. [PubMed: 18178780]
75. Ketteler M, Martin KJ, Wolf M, Amdahl M, Cozzolino M, Goldsmith D, Sharma A, Marx S, Khan S. Paricalcitol versus cinacalcet plus low-dose vitamin D therapy for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: results of the IMPACT SHPT study. *Nephrol Dial Transplant.* 2012;27(8):3270–3278. [PubMed: 22387567]
- *76. Pun PH, Abdalla S, Block GA, Chertow GM, Correa-Rotter R, Dehmel B, Drueke TB, Floege J, Goodman WG, Herzog CA, London GM, Mahaffey KW, Moe SM, Parfrey PS, Wheeler DC, Middleton JP. Cinacalcet, dialysate calcium concentration, and cardiovascular events in the EVOLVE trial. *Hemodial Int.* 2016;20(3):421–431. [PubMed: 26564024] In this secondary analysis of the EVOLVE trial the authors evaluate whether clinical outcomes with cinacalcet depend upon the prescribed dialysis calcium level. Although the interaction was not statistically significant, among those using a higher dialysate calcium (>2.5 mEq/L) participants randomized to cinacalcet had lower risk of the composite outcome. Risk was not statistically lower among those using lower dialysate calcium levels.
77. Brunelli SM, Sibbel S, Do TP, Cooper K, Bradbury BD. Facility Dialysate Calcium Practices and Clinical Outcomes Among Patients Receiving Hemodialysis: A Retrospective Observational Study. *Am J Kidney Dis.* 2015;66(4):655–665. [PubMed: 26015274]
78. Daugirdas JT. Removal of Phosphorus by Hemodialysis. *Semin Dial.* 2015;28(6):620–623. [PubMed: 26358370]

79. Daugirdas JT, Chertow GM, Larive B, Pierratos A, Greene T, Ayus JC, Kendrick CA, James SH, Miller BW, Schulman G, Salusky IB, Klinger AS. Effects of frequent hemodialysis on measures of CKD mineral and bone disorder. *J Am Soc Nephrol*. 2012;23(4):727–738. [PubMed: 22362907]
- *80. Block GA, Rosenbaum DP, Leonsson-Zachrisson M, Astrand M, Johansson S, Knutsson M, Langkilde AM, Chertow GM. Effect of Tenapanor on Serum Phosphate in Patients Receiving Hemodialysis. *J Am Soc Nephrol*. 2017;28(6):1933–1942. [PubMed: 28159782] This trial of ~160 patients with hyperphosphatemia on hemodialysis evaluated a novel NHE3 inhibitor, tenapanor, on serum phosphorus over 4 weeks. As anticipated tenapanor lowered serum phosphorus meaningfully compared with placebo (up to 2 mg/dl in the highest dose group), but also reduced FGF23. Future agents like tenapanor may have a role in future integrated mineral metabolism treatment strategies by helping to control multiple biochemical risk factors.
81. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336(16):1117–1124. [PubMed: 9099655]

Key Points

- Management of mineral metabolism in ESRD involves simultaneous management of multiple classes of pharmacologic agents and co-interventions, such as vitamin D sterols, calcimimetics, phosphorus binders, and the dialysate prescription.
- Different pharmacologic options often having opposing effects on biochemical risk factors, such as the impact of vitamin D sterols to raise, and calcimimetics to lower, FGF23, phosphorus and calcium.
- Combinations of agents and rational selection of co-interventions, such as use of calcium or non-calcium based phosphorus binders or adjustment of dialysate time and calcium, may be able to best normalize the physiologic milieu in ESRD.
- Few trials adequately powered for clinical events have been conducted testing mineral metabolism drugs in isolation, and none have evaluated an integrated strategy characterized by its combination of drugs and co-interventions.

Figure 1. Timeline of Introduction of New Pharmaceuticals, Guidelines and Policies Affecting Mineral Metabolism Therapy.

A growing armamentarium of new mineral metabolism related drug classes has transformed the landscape over the last several decades requiring a new emphasis on studying combinatorial drug therapy. Drug selection and biochemical treatment targets have also been influenced by changes in national and international guidelines occurring in 2003, 2009, and 2017, implementation of bundled dialysis payment through the Center for Medicare & Medicaid Services (CMS) Prospective Payment System in 2011, and inclusion of monthly serum calcium and phosphorus measurement in the CMS Quality Improvement Program (QIP) in 2014, followed by hypercalcemia as a clinical QIP metric in 2016.

Figure 2. Simplified Schematic Presenting Complementary Pharmaceutical Agents, their Physiologic Targets and Potential Downstream Toxicities in Mineral Metabolism.

Three major types of pharmaceutical agents are available to target mineral metabolism including vitamin D sterols, calcimimetics and gastrointestinal phosphorus binders. Each of these control mineral metabolites at different points within its integrated physiology. For instance, phosphorus binders limit the gastrointestinal absorption of phosphorus, lowering serum levels and partially helping to maintain normal parathyroid hormone (PTH) and possibly fibroblast growth factor 23 (FGF23). Certain classes of phosphorus binders, such as iron-based binders, have proven effects to lower FGF23 in part by replenishing iron stores. Calcimimetics directly lower PTH as partial agonists of the calcium sensing receptor. Due to the feed forward effects of PTH on FGF23 transcription and vitamin D activation, these drugs also lower FGF23 and serum phosphorus. By lowering the ability of PTH to respond to falling calcium, hypocalcemia is a major adverse effects. Vitamin D sterols consisting of calcitriol and its analogs lower PTH through feedback inhibition. However they directly raise FGF23, as well as calcium and phosphorus. Not pictured, these agents also promote endogenous klotho expression, the co-receptor for FGF23. By promoting klotho it is plausible that vitamin D sterols help ameliorate the adverse cardiovascular effects of FGF23 that appear to depend upon klotho-independent signaling. Hypothesized toxic downstream effects of these physiologic changes are depicted in the column to the right. Overall, this

schematic illustrates the complexity of mineral metabolism and provides a theoretical justification for a multi-target intervention.

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Figure 3. Hypothetical Patient Scenarios Illustrating Different Approaches to Mineral Metabolism Therapy from an Integrated Perspective.

These panels indicate 4 hypothetical patients with different treatment approaches to mineral metabolism. Most prior studies have evaluated one component of mineral metabolism at a time. From this single agent perspective, both patients 1 and 2 may be classified as patients using a vitamin D alone approach, although they have differences in control of calcium and phosphorus due to their selection of phosphorus binders and dialysis treatment time. Both patients 3 and 4 would be considered calcimimetic users, however the use of calcimimetics along with vitamin D in patient 4 results in higher serum phosphorus and calcium. Patients 1, 2 and 4 each use a dialysate calcium of 2.5 mEq/L versus 3.0 mEq/L in patient 3. However, they achieve quite different serum calcium due to different use of calcium-based binders, cinacalcet and vitamin D. Finally, patients 2 and 3 achieve lower serum phosphorus targets versus patients 1 and 4, but via different approaches, with one patient using cinacalcet and 2 phosphorus binders and the other using one high dose binder and longer dialysis time. Given the biological interactions of mineral metabolites and mineral metabolism drugs as presented in Figure 1, trials of drugs and targets in mineral metabolism

should comparative effectiveness of a full, or integrated, intervention that provides a consistent global approach to mineral metabolism.

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