HHS Public Access

Author manuscript

Semin Dial. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Semin Dial. 2015 November ; 28(6): 610–619. doi:10.1111/sdi.12412.

Novel Therapeutic Options for the Treatment of Mineral Metabolism Abnormalities in End Stage Renal Disease

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Abstract

Abnormalities in mineral metabolism are a universal complication in dialysis patients and are associated with an increased risk of cardiovascular disease and mortality. Hyperphosphatemia, increased fibroblast growth factor 23 levels and secondary hyperparathyroidism are all strongly associated with adverse outcomes in end stage renal disease (ESRD) and most treatment strategies target these parameters. Over the past few years, new therapies have emerged for the treatment of abnormalities of mineral metabolism in ESRD and many are promising. This article will review these new therapeutic options including the potential advantages and disadvantages compared to existing therapies.

End stage renal disease (ESRD) is a major public health problem. It is associated with significant morbidity and mortality and high healthcare costs. Despite advances in dialysis care, only 54% of hemodialysis patients and 65% of peritoneal dialysis patients are alive three years after ESRD onset (1). Abnormalities in mineral metabolism are a universal complication in dialysis patients and are associated with an increased risk of cardiovascular disease and mortality. Treating disordered mineral metabolism is a key strategy in ESRD care. Hyperphosphatemia, increased fibroblast growth factor 23 (FGF23) levels and secondary hyperparathyroidism are all strongly associated with adverse outcomes in ESRD and most available treatment strategies target these parameters. Recently, several new therapies have emerged for the treatment of disordered mineral metabolism. This article will review these new therapeutic options including the potential advantages and disadvantages compared to existing therapies.

Management of Hyperphosphatemia

Phosphate excess in dialysis patients is managed by low dietary phosphate intake, oral phosphate binders and by dialysis dose and frequency. Since dietary modifications are difficult to follow and conventional dialysis does not completely correct serum phosphate, phosphate binders are the mainstay of therapy in ESRD. Nearly all dialysis patients are

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prescribed phosphate binders. Despite widespread prescribing of these medications, phosphate control remains challenging in patients with ESRD. Phosphate binders must be taken several times per day with meals leading to a large pill burden for most patients. Additionally, there are side effects to the medications further decreasing patient adherence. In a meta-analysis of 13 trials of dialysis patients, the mean prevalence of nonadherence to phosphate binders was 51% (2). Before discussing newly developed phosphate binders, we will briefly review binders currently in use to gain insights into whether new phosphate binders could provide advantages over existing ones.

The current phosphate binders available work by binding phosphate in the gastrointestinal tract (GI) and allowing excretion in the feces. However, some of the binders are absorbed by the GI tract, which can lead to adverse effects. Current binders are based on metals (aluminum, lanthanum), calcium and/or magnesium, or polymers (sevelamer). Advantages and disadvantages of the currently available binders are shown in Table 1.

Calcium-Based Binders

Calcium-based binders are the most widely used binder since they are highly effective and inexpensive. The downside to these binders is the risk of hypercalcemia, calcification, adynamic bone disease and gastrointestinal side effects (3,4). Data regarding the effect of calcium-based binders on vascular calcification are conflicting (5–8). Some studies have found progression of arterial calcification in patients on calcium-based binders compared to non-calcium based binders, whereas others have not. However, concerns about the calcium load with calcium-based binders have led the Kidney Disease Improving Global Outcomes (KDIGO) to recommend restricting the dose of calcium-based binders in patients with hypercalcemia and/or arterial calcification (4). Many experts still recommend calcium-based phosphate binders as first-line therapy for hyperphosphatemia given their high tolerability and low cost (9).

Magnesium-Calcium-Based Binders

Magnesium-based phosphate binders have been used since the mid-1980s and were initially introduced to replace aluminum-containing binders. Magnesium hydroxide use was complicated by diarrhea and mild hyperkalemia (10). Magnesium carbonate has proven to be more effective than the original magnesium formulations and has resulted in fewer side effects (11). There is currently one commercially available magnesium-based binder (magnesium carbonate/calcium acetate) but it is not available in the US. It was shown to be non-inferior to sevelamer at controlling serum phosphate (9,12).

Interest in magnesium in dialysis grew after several small retrospective studies showed that patients with higher serum magnesium concentrations had less progression of vascular calcification (13,14). A study in 44 peritoneal dialysis patients evaluated for progression of vascular calcification by radiographs of the hands and feet demonstrated that patients who did not progress had higher serum magnesium concentrations (3.0 ± 0.5 vs. 2.7 ± 0.5 mg/dl) than those who progressed (13). There was no difference in calcium, phosphorus or parathyroid hormone levels between groups.

The only prospective evaluation of vascular calcification in magnesium-supplemented dialysis patients was small and nonrandomized. Seven patients were treated with magnesium containing phosphate binders with a goal of elevating serum magnesium concentration. Patients were evaluated by electron beam computed tomography at baseline, 6, 12 and 18 months for coronary artery and aortic calcification (15). These investigators found minimal progression over 18 months in these patients despite the presence of vascular calcification at study entry, a finding significantly different than reported in the literature for patients receiving calcium-based phosphate binders. A potential disadvantage of magnesium-based binders is the risk of mild-to-moderate hypermagnesemia. Their long-term consequences on bone, blood and vessels need further study.

Metal-Based Binders

Aluminum was the earliest phosphate binder used. Aluminum hydroxide is a very effective, inexpensive binder. Since aluminum is absorbed from the GI tract the risk of systemic aluminum toxicity (encephalopathy, anemia, osteomalacia) led to discontinuation of its use (4). Today, lanthanum is the most widely used metal-based binder. Lanthanum is a resin-free, non-calcium based binder with a high binding potential. Although lanthanum is poorly absorbed there are still concerns regarding long-term complications of low-grade accumulation; however, lanthanum monotherapy has been shown to be effective and well tolerated for up to 6 years with no evidence of safety concerns or increased frequency of adverse events (16–18). Additionally, lanthanum is expensive and the need to chew the pills poses difficulty for some patients. A powder-based formulation is now available which can be mixed with food. It appears pharmacologically equivalent to the chewable form but this still needs to be proven in patients with ESRD (17).

Polymer-Based Binders

Sevelamer is the most common polymer-based binder used and is available as sevelamer hydrochloride or sevelamer carbonate. Sevelamer is an anion-exchange polymer resin that binds phosphate and bile acids. In addition to being an effective phosphate binder, sevelamer has pleiotropic effects including reducing low-density lipoprotein cholesterol, inflammation and uric acid (19). Disadvantages include high cost, high pill burden, GI side effects, metabolic acidosis (sevelamer hydrochloride) and the potential for interference with absorption of vitamins D and K (4). A systematic review and meta-analyses examining the effect of calcium and non-calcium containing binders demonstrated decreased mortality in ESRD patients using sevelamer compared to calcium-based binders (20). This difference in mortality was attributed to a decreased risk of vascular calcification. However, due to limitations of existing studies, uncertainty remains regarding the effects of sevelamer on clinical endpoints. Given its significant cost, it cannot be indisputably recommended over calcium-based binders at this time except in patients with high calcium levels or arterial calcifications.

Even though currently available phosphate binders are effective, they are associated with high pill burden and side effects leading to poor adherence. Lack of adherence and tolerability in patients remain important factors in the poor phosphate control in ESRD patients. The ideal phosphate binder would be highly effective, inexpensive, have minimal

systemic absorption, low pill burden and few or no side effects. Toward this end, new iron-based phosphate binders have been developed.

Iron-Based Phosphate Binders

The phosphate-binding capacity of iron was first recognized in experimental and animal studies (21–23). Iron is a cation that binds phosphate in the GI tract and results in increased phosphate excretion in feces. Two iron-based phosphate binders have been recently approved by the FDA: sucroferric oxyhydroxide and ferric citrate.

Sucroferric oxyhydroxide

Sucroferric oxyhydroxide, formerly known as PA21, is a stabilized polynuclear iron (III)-oxyhydroxide based binder. Each chewable tablet contains 500 mg of elemental iron in 2,500 mg of sucroferric oxyhydroxide (24). The addition of sucrose to the iron-hydroxide prevents the compound from aging and maintains its phosphate binding capacity. Sucroferric oxyhydroxide has high phosphate binding over a wide pH range. In a Phase I study of 8 hemodialysis patients, 8 non-dialysis dependent chronic kidney disease (CKD) patients, and 8 healthy subjects, the binder was well-tolerated (25). Iron absorption over the course of one week was minimal and notably lower in CKD patients than in healthy controls: 0.02% for hemodialysis patients, 0.06% for non-dialysis CKD patients and 0.43% for healthy controls (25). A Phase II study of 154 hemodialysis patients randomized to sucroferric oxyhydroxide in doses of 1.0–2.5 g/day (based on iron content) or sevelamer found that sucroferric oxyhydroxide reduced serum phosphate with similar efficacy to sevelamer (26).

An open-label, randomized, active-controlled (sevelamer carbonate), parallel-group, multicenter phase III study was performed in 1,059 dialysis patients (n=968 hemodialysis patients, n=86 peritoneal dialysis patients) over 24-weeks (27). Patients were randomized in a 2:1 fashion of sucroferric oxyhydroxide:sevelamer. The dose of both medications was adjusted according to serum phosphate. The study demonstrated that sucroferric oxyhydroxide was non-inferior to sevelamer for control of serum phosphate despite 62% fewer tablets than with sevelamer. In the sucroferric oxyhydroxide group, transferrin saturation increased with a trend towards increased ferritin levels More treatment-emergent adverse events leading to study withdrawal were observed in the sucroferric oxyhydroxide group (15.7% vs. 6.6%). The most frequent adverse events with sucroferric oxyhydroxide were diarrhea and discolored stools.

The long-term effects of sucroferric oxyhydroxide were examined in a 28-week extension study of the phase III study in 644 patients (28). The same treatment and binder dose (sucroferric oxyhydroxide (n=384) or sevelamer carbonate (n=260) used at the end of the initial study was continued. Serum phosphate remained within the KDOQI target range for both treatment groups throughout the study. Both groups saw no notable change in serum phosphate levels from the start of the extension study to week 52. The number of daily tablets was lower in the sucroferric oxyhydroxide group (mean ± SD 4.0 ± 1.5 tablets/day) compared to sevelamer (mean ± SD 10.1 ± 6.6 tablets/day).

Importantly, there was no evidence of iron accumulation over the 1-year period of treatment. Mean ferritin concentrations increased in both groups more noticeably but not more significantly in the sucroferric oxyhydroxide group. There were no significant changes in transferrin saturation, iron or hemoglobin concentrations. Treatment-emergent adverse events were more common with sucroferric oxyhydroxide compared to sevelamer (14.6% vs. 9.0%). As were adverse events leading to study withdrawal (8.2% vs. 4.9%). The most common reason for study withdrawal in both groups was hyperphosphatemia

Overall, sucroferric oxyhydroxide appears to be effective in lowering serum phosphorus in dialysis patients, with similar efficacy to sevelamer, a lower pill burden, and with a good adherence. The recommended starting dose is one tablet per meal (1,500 mg/day) and the maximum dose is 3,000 mg/day (24). Tablets must be chewed but they are soft and disintegrate rapidly which should not result in a problem for patients with dental issues. Sucroferric oxyhydroxide inhibits GI absorption of levothyroxine which may pose a problem for patients with hypothyroidism. There are no human studies in pregnancy but no adverse effects have been observed in animal studies, hence the pregnancy category is B. The long-term side effects beyond 1-year are. In animal studies, doses 5 to 10-fold higher than the recommended human dose over 2 years resulted in inflammation of the GI tract and epithelial hyperplasia (24).

Ferric Citrate

Ferric citrate has been studied as a phosphate binder in both animal and human studies. It is estimated that the phosphate-binding capacity is 85–100 mg of phosphorus per gram of elemental ferric iron (21). Ferric citrate has already been in use in Japan and was recently approved by the US FDA.

The first study examining ferric citrate as a binder was performed over 10 years ago in a prospective, randomized crossover trial of 54 hemodialysis patients (29). Patients were randomized to ferric citrate or calcium carbonate for 4 weeks. Ferric citrate was efficacious at lowering phosphate and well tolerated. The most frequent adverse event was discoloration of feces. A phase III, multicenter, open-label randomized clinical trial of 151 hemodialysis patients randomized to 1, 6, or 8 g/day of ferric citrate demonstrated that ferric citrate reduced phosphate in a dose dependent manner (30).

In a large, phase III, long-term study of over 400 dialysis patients randomized to ferric citrate or active control (sevelamer carbonate or calcium acetate) for 56 weeks, ferric citrate was as effective as sevelamer and calcium acetate in controlling serum phosphate levels (31). The mean ± SD serum phosphate at the end of the study period was 5.4 ± 1.6 mg/dL in the ferric citrate group, 5.4 ± 1.7 mg/dL in the sevelamer carbonate group, and 5.3 ± 1.4 mg/dL in the calcium acetate group. Ferric citrate had a lower average pill burden (8 tablets/day) compared with sevelamer (9 tablets/day, p=0.01) but not calcium acetate (7.7 tablets/day, p=0.28). More patients in the ferric citrate group discontinued the study drug compared to the active control in the first weeks of the study (21% vs. 15%) most commonly for nonserious GI side effects. Thirty-nine percent of patients in the ferric citrate group experienced a serious adverse event compared to 49% in the active control group. GI serious adverse events were more common in the active control group compared to the ferric citrate

group (12.8% vs. 6.9%). There were fewer cardiovascular serious adverse events (SAEs) in the ferric citrate group (7.3%) versus the active control group (12.1%) (31).

At study entry, the use of erythropoietin stimulation agents (ESA) and intravenous iron was similar between the two groups. During the study, ferric citrate increased serum ferritin and transferrin saturation compared to active control (32). These differences persisted throughout the follow-up period, with mean differences of 282 ± 43 ng/mL ($p<0.001$) and 9.6% ± 1.6% ($p<0.001$) for ferritin and transferrin saturation, respectively, at 52 weeks. Additionally, ferric citrate reduced both intravenous iron ($p <0.001$) and ESA ($p=0.04$) usage. Fewer patients in the ferric citrate group needed intravenous (IV) iron compared to the active control group: at week 52, 85.4% of the ferric citrate group was not receiving any IV iron compared to 69.0% of the active control group ($p<0.001$). In the ferric citrate group, 19.8% had at least one serum ferritin level >1500 ng/mL during the study whereas only 9.5% of the active control group had a ferritin level that high. Three patients had ferric citrate discontinued because of elevated serum ferritin. Cumulative median ESA use was lower in the ferric citrate group compared to active control (5303 vs 6954 units/week, $p=0.04$). Hemoglobin levels remained stable throughout the study period and were slightly higher in the ferric citrate group compared to active control (11.42 ± 0.10 g/dL vs. 11.14 ± 0.12 g/dL, $p=0.02$). The study did not perform radionuclide-tagged balance studies or organ biopsies to examine them for iron accumulation. However, there were few SAEs in the organ systems typically considered vulnerable to iron overload thereby suggesting there was no clinically significant iron overload (32).

Overall, ferric citrate appears to be an effective phosphate binder with minimal side effects. Additionally, it reduces IV iron and ESA use. In the currently available commercial form, each ferric citrate tablets contains 210 mg of ferric iron (1 gm of ferric citrate) (33). The recommended starting dose is 2 tablets three times per day with meals. The maximum daily dose is 12 tablets per day. It is unknown whether ferric citrate can cause fetal harm and currently it is labeled as Pregnancy Category B. Additionally, it may not be safe in nursing women, as data from rat studies have shown transfer of iron into milk. Long-term effects beyond 52-weeks have not yet been determined.

New Therapeutic Options for the Management of Hyperparathyroidism

Secondary hyperparathyroidism develops early in the course of chronic kidney disease and the frequency increases as kidney function declines. Treatment of secondary hyperparathyroidism has primarily consisted of dietary phosphate restriction, phosphate binders, calcitriol and its analogues, parathyroidectomy, and more recently, the use of calcimimetics. We will review changes in the use of calcitriol and its analogues and will discuss the new IV calcimimetic, AMG 416.

Vitamin D

Nutritional vitamin D, calcitriol and vitamin D analogues are all used in patients with chronic kidney disease to prevent and treat secondary hyperparathyroidism. Despite theoretical benefits of raising 25-hydroxyvitamin D levels with nutritional vitamin D (e.g. ergocalciferol and cholecalciferol) in dialysis patients there are no large long-term

randomized controlled trials supporting an improvement in parathyroid hormone levels (PTH) (34–36). Calcitriol and its analogues are effective at lowering serum PTH levels and are well tolerated but often result in elevations in serum phosphate and calcium levels, which limit their use. Recently, some dialysis units have changed from administering the IV form of calcitriol and its analogues to administering the oral form to dialysis patients three times per week. Due to a lack of comparative data, no conclusions regarding the preferred routes of administration can be determined. A meta-analysis done in 2007 found that the IV form of vitamin D was superior to the oral form in reducing PTH levels (37). However, when one study that used very high doses of IV vitamin D was removed, there were no differences in the PTH levels between the IV and oral groups. Additionally, no differences were found between daily and less-frequent (usually 3 times per week) dosing. Therefore, for cost savings, many dialysis units have changed to using oral forms of calcitriol and its analogues.

Calcimimetics

Cinacalcet was approved by the FDA in 2004 for the treatment of secondary hyperparathyroidism in dialysis patients. Cinacalcet is well tolerated and highly effective. Its downside is that it has to be given orally on a daily basis which increases the pill burden for patients, a very common reason for noncompliance in patients on dialysis. AMG 416 is a novel, long-acting 8-amino-acid peptide calcimimetic that is administered IV in dialysis patients. AMG 416 binds to and activates the calcium sensing receptor on the parathyroid gland in the presence or absence of serum calcium. Over the past year, data from Phase 3 trials have been released from AMGEN showing positive results, but have not yet been published (38–40).

The safety and efficacy of AMG 416 was evaluated in a 26-week, randomized, double-blind, placebo-controlled study of 515 dialysis patients with secondary hyperparathyroidism (38). Patients received AMG 416 or placebo IV three times per week with each hemodialysis treatment. The dose ranged from 2.5 mg to 15 mg. Patients also received standard of care which could include calcium supplementation, vitamin D sterols, and phosphate binders. The primary endpoint was the percentage of patients with >30% reduction from baseline in PTH levels. Seventy-five percent of patients achieved a >30% reduction in PTH levels compared to 9.6% in the placebo arm. Serum phosphate levels also were significantly reduced in the AMG 416 group compared to placebo (mean change −9.63% and −1.60%, respectively). Calcium levels did fall significantly in the AMG 416 group compared to placebo (mean change −6.69% and 0.58%, respectively). Treatment-emergent adverse events were reported in 91.7% and 81.1% of patients who received AMG 416 and placebo, respectively. The most common adverse events with AMG 416 were decreased serum calcium (66.7%), diarrhea (14.3%) and muscle spasms (11.1%). Symptomatic hypocalcemia was observed in 6.6% of patients receiving AMG 416. Serious adverse events were similar between the two groups (AMG 416: 24.6%, placebo: 27.4%).

A second Phase 3 trial with AMG 416 was performed in 508 hemodialysis patients and found similar results (39). Seventy-four percent of patients in the AMG 416 group had >30% reduction in PTH levels compared to only 8.3% in the placebo arm. Again, serum

phosphate and calcium levels were significantly lower in the AMG 416 group. Treatment-emergent adverse events were reported in 91.1% and 78.7% of patients who received AMG 416 and placebo, respectively. The most common adverse events were decreased serum calcium, diarrhea and muscle spasms.

A 26-week, randomized, active-controlled, double-blind, double-dummy study compared AMG 416 with cinacalcet in 683 hemodialysis patients (40). Patients randomized to treatment with AMG 416 received IV doses of AMG 416 three times per week at the end of each dialysis treatment plus daily oral doses of placebo tablets. Patients randomized to cinacalcet received daily oral doses of cinacalcet tablets and IV doses of placebo three times per week at the end of each dialysis treatment. Patients also received standard of care which could include calcium supplementation, vitamin D sterols and phosphate binders. At the end of the study, AMG 416 was non-inferior to cinacalcet in reducing PTH levels by >30%. Additionally, AMG 416 was superior to cinacalcet in the proportion of patients achieving >50% reduction in PTH levels (52.4% for AMG 416 vs. 40.2% for cinacalcet). There was no difference in nausea or vomiting in the first 8 weeks between the two groups, which was another secondary endpoint. Treatment-emergent adverse events were reported in 92.9% and 92.0% of patients receiving AMG 416 and cinacalcet, respectively. The most common adverse events were (AMG 416 vs. cinacalcet, respectively): decreased serum calcium (68.9% and 59.8%), nausea (18.3% and 22.6%), vomiting (13.3% and 13.8%), and diarrhea (6.2% and 10.3%). Symptomatic hypocalcemia was reported in 5.0% of patients on AMG 416 versus 2.3% in the cinacalcet group. Serious adverse events were similar between the two treatment groups.

The results position AMG 416 as a promising new treatment for secondary hyperparathyroidism in hemodialysis patients. Compared to cinacalcet. Additionally, it is not an inhibitor or inducer of the hepatic cytochrome P450 enzyme, which makes it more compatible with other medications. Long-term studies have not been performed but are currently ongoing. Additionally, no data exist regarding AMG 416 and hard clinical endpoints such as mortality or cardiovascular events. AMG 416 is not yet FDA approved but may be approved within the next year.

Fibroblast Growth Factor 23 (FGF23) Lowering Therapies and FGF Receptor Blockers

FGF23 is a 251 amino acid protein secreted by osteoblasts and osteocytes. FGF23 plays a key role in the control of serum phosphate, vitamin D metabolism and secondary hyperparathyroidism. FGF23 inhibits phosphate reabsorption in the proximal tubule causing increased phosphate excretion and inhibits 1-α-hydroxylase activity resulting in decreased calcitriol production (41). FGF23 levels rise early in the course of kidney disease in order to maintain normal serum phosphate levels. FGF23 levels progressively rise as kidney function decreases and are highest among dialysis patients (42). Numerous studies have demonstrated an increased risk of mortality and cardiovascular disease in patients with elevated FGF23 levels (42–45). Hence, targeting FGF23 levels may be a potential new strategy for improving outcomes in patients with CKD.

FGF23 is a member of the FGF family. The FGFs consist of 23 proteins that regulate cell proliferation, migration, differentiation, and survival (46). FGF23 was initially presumed to only be active in tissues that also contain the co-receptor klotho, including the kidney and parathyroid gland (41). However, the effects of FGF23 on the cardiovascular system appear to be independent of klotho; FGF23 directly induce left ventricular hypertrophy (LVH) in mice (47). These findings suggest that elevated FGF23 may direct contribute to cardiovascular disease in patients with CKD. The question of whether reducing or neutralizing FGF23 levels may improve outcomes has stimulated recent studies examining different therapies targeting FGF23 levels, including phosphate binders, calcimimetics and FGF23 neutralization.

Phosphate Binders and FGF23

Numerous studies have examined the effect of various phosphate binders on circulating FGF23 levels in CKD patients and the results have been conflicting. In a study of 100 patients with CKD stage 4, sevelamer carbonate, but not calcium acetate, decreased FGF23 levels by 27.1% from baseline (48). A small study of 39 patients with CKD stages 3 or 4 found that the combination of a low phosphate diet plus lanthanum carbonate reduced FGF23 levels whereas diet or lanthanum carbonate alone did not (49). In patients on dialysis, short-term studies have not shown a benefit of phosphate binders on FGF23 levels, but long-term studies have (50, 51). A recent open-labeled, controlled randomized parallel group study of 50 hemodialysis patients randomized to calcium acetate or sevelamer for 48 weeks found that sevelamer significantly reduced FGF23 levels but calcium acetate did not (51). Given the conflicting findings, further studies are needed to determine if phosphate binders can lower FGF23 levels. Additionally, it remains unknown whether lowering FGF23 levels with phosphate binders will improve clinical outcomes.

Cinacalcet and FGF23

Cinacalcet effectively lowers PTH, calcium and phosphate levels in patients with secondary hyperparathyroidism. Given the complexity of mineral bone disorders in CKD and the key role of FGF23, several studies have examined the role of cinacalcet on FGF23 levels. In a small study of 55 hemodialysis patients, cinacalcet significantly reduced FGF23 levels from 14,750 pg/mL [IQR, 3055–23,991 pg/mL] to 5121 pg/mL [IQR, 1869–18,315 pg/mL] at 12-weeks and maintained the reduced levels after 52 weeks (52). In 91 patients randomized to either active vitamin D alone or active vitamin D plus cinacalcet, FGF23 levels were reduced in the group receiving cinacalcet after 27 weeks (53). Another small study of 58 hemodialysis patients found that cinacalcet reduced FGF23 levels after 6 months of treatment, but only in 52% of the patients (54). In addition to the small sample size, there was also no placebo-treated group.

While these studies are suggestive that cinacalcet may reduce FGF23 levels, it is unclear whether the decrease is due to cinacalcet per se, to less use of active vitamin D analogues, to better control of secondary hyperparathyroidism or to other mechanisms. Additionally, it is important to note that in the EVOLVE study there was no improvement in cardiovascular events or mortality in dialysis patients receiving cinacalcet compared to placebo (55). Thus, it remains unclear if lowering FGF23 levels will result in improved clinical outcomes.

FGF23 Neutralization and FGF Receptor Inhibition

There are four FGF receptors (FGFR 1, 2, 3 and 4) that are members of the receptor tyrosine kinase family (46). FGF23 can bind the FGFR isoforms with varying affinity. Thus, receptor and receptor signaling antagonists are logical candidates for neutralizing FGF23.

Several experimental studies have been performed examining the effect of FGFR inhibitors and anti-FGF23 antibodies on various outcomes. In a study by Faul et al, PD 173047 (a FGFR 1–3 inhibitor) blocked CKD induced LVH in 5/6 nephrectomized rats but did not alter renal function, serum FGF23 levels or blood pressure (47). These results support the notion that FGF23 directly induces LVH and that blocking its receptors can inhibit LVH.

However, another study examining antibodies to the FGF23 molecule did not find similar results. Shalhoub et al (56) administered monoclonal FGF23 antibody to 5/6 nephrectomized rats for 6 weeks. The anti-FGF23 antibody blocked the ability of FGF23 to bind and signal through its receptors. Neutralization of FGF23 decreased serum PTH, increased both serum vitamin D and calcium and normalized bone markers. However, a dose-dependent increase in serum phosphate and aortic calcification was seen and there was an increased risk of mortality in rats treated with the anti-FGF23 antibody. The increase in mortality was attributed to hyperphosphatemia and the resulting aortic calcification. Ventricular hypertrophy was minimal in both the treated and control rats.

The differing results compared to the Faul et al. study may be due to several reasons: 1) the rats in both studies were fed different diets (Faul et al: normal chow vs. Shalhoub et al: high phosphate diet); 2) the anti-FGF23 antibody was started 6 weeks after the 5/6 nephrectomy whereas the FGFR inhibitor was started 1-hour after the 5/6 nephrectomy in the Faul et al. study; 3) the 5/6 nephrectomized rats from the Shalhoub et al. study were not hypertensive compared to the control rats whereas in the Faul et al. study they were markedly hypertensive compared to control; 4) in the Shalhoub et al. study, the 5/6 nephrectomized rats had minimal to no LVH whereas the rats in the Faul et al. study had significant LVH; and 5) finally, blocking the FGFR and neutralizing the actual FGF23 molecule are likely to differ in their effects.

What will happen if we neutralize FGF23 or inhibit FGFR in patients with CKD? Hypothetically, in patients with CKD not yet on dialysis, neutralizing FGF23 or its inhibitor may increase serum phosphate and worsen tissue mineralization. Once patients have ESRD there is no longer a mechanism for phosphate reabsorption (i.e., patients are anuric) so theoretically, there should not be an increase in serum phosphate levels. Whether neutralization will improve calcitriol levels, reduce PTH levels, reduce renal osteodystrophy and improve LVH and clinical outcomes remains to be seen. In cancer treatment, blockade of FGF/FGFR signaling is gaining momentum as a therapeutic approach. (57). FGFs and FGFRs are emerging as oncogenes that drive proliferation and several small-molecule FGFR kinase inhibitors are currently in development and being tested in clinical trials. However, one the most frequent adverse events has been hyperphosphatemia due to blockade of FGFR1 (57). The nephrology research community should examine the possibility of administering FGFR inhibitors in ESRD.

Conclusion

Abnormalities in mineral metabolism are associated with an increased risk of cardiovascular disease and mortality in ESRD patients. Lack of adherence of patients to treatments remains an important factor in mineral metabolism control. Over the past several years, new therapies have emerged for the treatment of abnormalities of mineral metabolism in ESRD and many are promising. The new iron based binders and IV calcimimetic may improve compliance with medications as they lower pill burden. However, it is important to remember that there is not a single “magic bullet” that will effectively treat disorders of mineral metabolism. Treatment of disordered mineral metabolism is complex and requires a multifaceted approach. Future studies should take this into account and combine various interventions. Whether or not improvements in mineral metabolism control results in improved clinical outcomes remains unclear.

Acknowledgments

Support: This work was supported by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) grants K23 DK087859 and 1R01DK081473-01.

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Table 1

Comparison of the Currently Available Phosphate Binders

Binder	Advantages	Disadvantages	Forms	Dosage (mg)
Calcium Carbonate	• Effective • Inexpensive • Readily available (over the counter) • Long-term experience	• Potential hypercalcemia • Potential for progression of vascular calcification • GI side effects • Low-turnover bone disease	• Tablet, chewable • Capsule • Liquid • Gum	• Contains 40% elemental calcium (200mg elemental calcium per 500mg)
Calcium Acetate	• Effective • Inexpensive • Readily available • Long-term experience • Potentially less calcium absorption than calcium carbonate	• Potential hypercalcemia • Potential for progression of vascular calcification • GI side effects • Low-turnover bone disease	• Tablet • Capsule • Liquid	• Contains 25% elemental calcium (160mg elemental calcium per 667 mg capsule) • Total dose of elemental calcium should not exceed 2,000–2,500 mg/day
Magnesium Carbonate/Calcium Acetate	• Effective • Inexpensive • Decreased calcium load compared with calcium-based binders	• Potential hypermagnesemia • Potential hypercalcemia • GI side effects • No long-term experience	• Tablet	• 235 mg/435 mg • Maximum dose is 3–6 pills/day
Aluminum hydroxide	• Very effective • Inexpensive	• Potential for aluminum toxicity • GI side effects • Altered bone mineralization • Anemia	• Tablet • Capsule • Liquid	• 300–600 mg 3 times per day • Aluminum content varies from 100 to >200 mg per tablet • Limit use to no more than 4 weeks
Lanthanum Carbonate	• Effective • Calcium free	• Expensive • Potential for lanthanum	• Tablet, Chewable • Powder	• 500–1,000 mg (3–6 chewable tablets) 3

Binder	Advantages	Disadvantages	Forms	Dosage (mg)
		accumulation in bone and tissue • GI side effects • No long-term data		times per day
Sevelamer hydrochloride	• Effective • Calcium free • Pleiotropic effects	• Expensive • GI side effects • Metabolic acidosis • Potential interferes with vitamin D and vitamin K absorption • Potentially decreased vascular calcification	• Tablet	• 800–1600 mg 3 times per day • Maximum dose studied 13 grams/day
Sevelamer Carbonate	• Effective • Calcium free • Pleiotropic effects • No metabolic acidosis	• Expensive • GI side effects • Potential interferes with vitamin D and vitamin K absorption • Potentially decreased vascular calcification	• Tablet • Powder	• 800–1600 mg 3 times per day • Maximum dose studied 14 grams/day
Sucroferric Oxyhydroxide	• Effective • Calcium free • Less pill burden than sevelamer • Potential to raise transferrin, iron and hemoglobin levels	• Expensive • GI side effects • Cannot be prescribed with oral levothyroxine or paricalcitol • Long-term side effects unknown • Unknown if iron accumulation long-term	• Tablets, chewable	• 500 mg (1 tablet) 3 times per day • Maximum dose is 3,000 mg/day
Ferric Citrate	• Effective • Calcium free • Less pill burden than sevelamer • Potential to raise transferrin, iron and hemoglobin levels • Potential to decrease iron and ESA usage	• Expensive • GI side effects • Long-term side effects unknown • Unknown if iron accumulation long-term	• Tablets	• Each tablet contains 210 mg ferric iron • Starting dose: 2 tablets 3 times per day • Maximum dose is 12

Binder	Advantages	Disadvantages	Forms	Dosage (mg)
				tablets per day

Mg= milligrams; GI= gastrointestinal; ESA= erythropoietin stimulation agents