

**Fe**  
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CLINICAL UPDATE

# CKD-MBD and Anemia

BENEFITS AND RISKS ASSOCIATED WITH COMMON THERAPIES

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## Introduction

Chronic kidney disease is associated with multiple comorbid conditions including disturbances in mineral and bone metabolism, anemia, and cardiovascular disease (CVD). More specifically, most patients on dialysis have hyperphosphatemia and are iron deficient. While the established therapeutic approaches for serum phosphate management and repletion of iron stores have benefits, they also have limitations and may increase risk for adverse events.

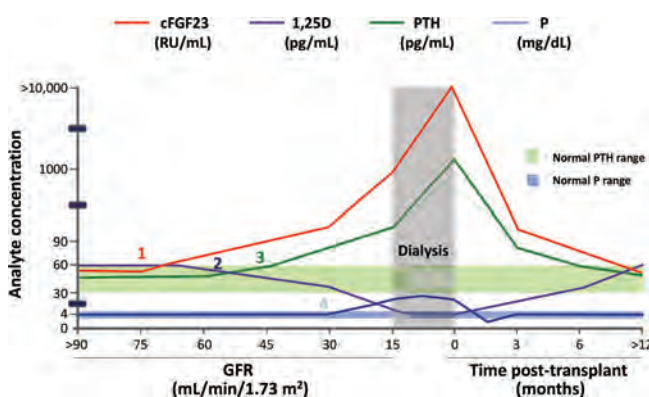
## Chronic Kidney Disease-Mineral and Bone Disorder

### Altered Mineral Metabolism

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a complex metabolic abnormality that affects the majority of the CKD population. The processes causing CKD-MBD have their onset in the early stages of CKD, and continue throughout the progressive loss of kidney function.

The earliest detectable alteration in mineral metabolism in CKD is an increase in circulating levels of fibroblast growth factor (FGF) 23.<sup>1</sup> FGF-23 production is stimulated by phosphorus retention as the kidneys become less able to handle phosphorus load. Gradually increasing FGF-23 levels cause a decline in 1,25-dihydroxyvitamin D levels, followed by a reduction in serum calcium levels and elevated parathyroid hormone secretion. This pathological sequence of events occurs long before increases in serum phosphate levels are evident.<sup>2</sup> (Figure 1) CKD-MBD puts patients at risk for bone abnormalities and vascular calcification, which can contribute to bone fractures, CVD and mortality.<sup>3,4</sup> Elevated FGF-23 is also an independent risk factor for progressive kidney disease in patients with CKD and a predictor of mortality in patients with CKD stages 2 through 5D.<sup>5,6</sup>

Figure 1. Progression of CKD-MBD<sup>2</sup>



CKD-MBD is assessed by monitoring serum levels of phosphate, calcium, iPTH, alkaline phosphatase activity and 25-hydroxyvitamin D beginning in CKD stage 3.<sup>3,4</sup> The cornerstone of CKD-MBD management is treating hyperphosphatemia along with secondary hyperparathyroidism. Standard treatments for these conditions include dietary phosphate restriction, phosphate binders, calcitriol and vitamin D analogues, and calcimimetics.

## Phosphate Management

Clinical practice guidelines suggest maintaining serum phosphate in the normal range in patients with CKD stages 3–5, and lowering elevated phosphate levels toward the normal range in patients with CKD stage 5D.<sup>3,4</sup> Phosphate-restricted diets in combination with oral phosphate binders are well established treatments in the management of hyperphosphatemia in patients with CKD stages 3–5D. Counseling patients about the hidden sources of phosphate (additives/preservatives), as well as the protein sources of phosphate may improve serum phosphate outcomes. A study that focused on protein source showed that patients consuming a vegetarian diet (lower phosphate bioavailability) had lower serum phosphate and FGF-23 levels compared to patients on a meat diet (higher phosphate bioavailability), even though the protein and phosphate content of the diets were the same.<sup>7</sup>

The percentage of patients on dialysis prescribed a phosphate binder is 83%.<sup>8</sup> There are several risks and limitations associated with established phosphate binder treatments. Aluminum binders are known to cause aluminum toxicity.<sup>9</sup> Calcium salts, including carbonate and acetate salts, are used frequently, but evidence suggests that the chronic use of high doses is associated with vascular calcification and hypercalcemia.<sup>10,11</sup> Calcium also raises FGF-23 levels.<sup>12</sup> Therefore, dietary calcium should be carefully assessed before adding to the calcium load. The use of non-calcium-based phosphate binders may offer advantages over traditional calcium-based binders in patients on dialysis.<sup>13,14</sup> In a study of patients with CKD, who had normal or near-normal serum phosphate levels, calcium-based and non-calcium-based binders lowered serum and urinary phosphate and attenuated progression of secondary hyperparathyroidism. However, use of calcium based binders was associated with increases in FGF-23 and accelerated vascular calcification.<sup>15</sup> Also, a recent meta-analysis showed non-calcium based binders are associated with decreased risk of all-cause mortality compared with calcium-based binders.<sup>16</sup>

## Anemia

### Iron Deficiency

Anemia is common in patients with CKD and is associated with adverse outcomes including hospitalization, CVD, cognitive impairment, and mortality.<sup>17,18</sup> Low hemoglobin (Hb) concentration that is characteristic of anemia can lead to many symptoms, such as fatigue and weakness, which can negatively impact quality of life. Iron deficiency frequently coexists with erythropoietin deficiency as a cause of anemia in patients undergoing hemodialysis. Iron deficiency in this population is mainly due to increased iron loss during dialysis treatment (retention of blood in dialyzer and blood lines), frequent blood draws for laboratory testing, surgical procedures, accidental blood loss (vascular access), and gastrointestinal blood loss. Other causes include interference with iron absorption due to medications such as phosphate binders and gastric acid inhibitors, reduced iron absorption due to inflammation, elevated hepcidin levels, and increased requirements during erythropoietin therapy for effective erythropoiesis to occur.<sup>19</sup> Untreated iron deficiency is an important cause

of hyporesponsiveness to erythropoiesis-stimulating agent (ESA) treatment. Therefore, managing iron deficiency can reduce the severity of anemia in CKD.

### Iron Management

Iron status is measured by iron saturation (TSAT) and ferritin; and directs the indication for iron replacement therapy. Clinical practice guidelines suggest the use of iron if TSAT is  $\leq 30\%$  and ferritin is  $\leq 500\text{ng/m}$ , but caution to balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia related symptoms against the risks of harm in individual patients.<sup>17</sup> While ESA doses in the U.S hemodialysis population have decreased since the addition of a black box warning to the labeling and commencement of a bundled reimbursement policy, the use of intravenous (IV) iron has concurrently escalated, perhaps in an effort to lower ESA dosing requirements. According to the USRDS, more than 50 percent of patients receive monthly IV iron in the first six months of dialysis treatment, which is a record high. Another 20 percent receive IV iron in five of the first six months of dialysis therapy.<sup>20</sup> The percentage of patients on dialysis in the U.S prescribed IV iron each month is 67-70%.<sup>8</sup>

IV iron is effective in maintaining iron balance and reducing ESA requirements, but because it bypasses the biological safeguards associated with oral iron, it has been suggested that it may increase progression of cardiovascular disease, worsen viral hepatitis, promote microbial infections, and exacerbate diabetes and diabetic complications.<sup>21</sup> This is in addition to the potential acute adverse reactions to IV iron including anaphylaxis, hypotension, and gastrointestinal symptoms.

Boluses of IV iron (typically 100-1000mg) exceed the capacity of iron-binding proteins and represent a much larger amount in contrast to the 1 to 2 mg/day of intestinal iron absorption over the course of 3 to 4 meals. Large doses of IV iron lead to increased plasma levels of catalytically active iron and the rise in biomarkers of oxidative stress and inflammation.<sup>21</sup> Recent data show that IV iron dose is also an important consideration with regard to mortality. The Dialysis Outcomes Practice Patterns Study (DOPPS) reports elevated mortality among dialysis patients given higher doses of IV iron ( $\geq 300\text{ mg/month}$  and  $\geq 6\text{ mg/kg}$  per month over 4 months).<sup>22</sup>

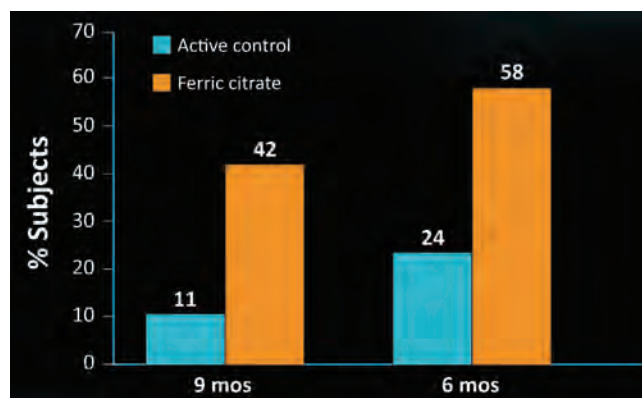
### Novel Phosphate Binder Therapies

New approaches to phosphate management recently include iron-based phosphate binders. One of them, sucroferric oxyhydroxide, is a polynuclear iron oxyhydroxide which is part sucrose, part iron, and part starch. In clinical trials, sucroferric oxyhydroxide was effective at reducing serum phosphate; at its highest dose of 2.5g/day serum phosphate was reduced by 1.7mg/dL. Iron absorption appears to be minimal with sucroferric oxyhydroxide administration since the effect on measured iron indices is negligible. At the highest doses (2g/day and the 2.5g/day) changes in serum ferritin and TSAT from baseline were negative to slightly positive, but essentially neutral.<sup>23</sup>

A different iron-based phosphate binder called ferric citrate coordination complex has recently been approved for clinical use. In clinical trials, ferric citrate effectively controlled serum phosphate and significantly reduced FGF-23, while simultaneously increasing serum ferritin and TSAT levels, and sustaining Hb concentration.<sup>24</sup> The increase in serum iron parameters reduced the need for ESA and IV iron.<sup>25</sup> Clinicians need to monitor iron indices in patients receiving ferric citrate. Ferric Citrate is contraindicated for patients with iron overload syndromes such as hemochromatosis.<sup>26</sup>

A clinical trial showed that since ferric citrate delivered much larger doses of elemental iron with food (up to 2520 mg/d) compared with previous oral preparations, TSAT increased from  $\sim 30\%$  up to  $\sim 40\%$  within 12 weeks, and sustained this level over the course of the year. Subsequently, nearly 60% of patients did not require IV iron therapy over the last 6 and 9 months of the study period, ESA usage was reduced, and slightly higher Hb concentration was achieved compared with controls.<sup>27</sup> (Figure 2) This study also showed a plateau of TSAT over 52 weeks and a decreased rate of rise in ferritin in subjects on ferric citrate suggesting that the gastrointestinal iron absorption from ferric citrate was regulated.<sup>27</sup> These are important findings that will provide additional treatment options and have the potential to improve patient outcomes.

Figure 2. Ferric Citrate Reduces Need for IV Iron<sup>27</sup>



Last 6 and 9 months with no IV iron in the study

### Summary

When treating altered mineral metabolism and iron deficiency associated with CKD it is critical to consider the risks and benefits of all therapies. Calcium-based phosphate binders are linked with vascular calcification, increased FGF-23 levels, and increased mortality. Escalating use of IV iron therapy is associated with oxidative stress and other tissue damage. A novel phosphate binder, ferric citrate, has a positive effect on iron repletion in addition to lowering phosphate, thereby reducing the need for IV iron and ESA, with the potential for cost savings in the care for patients on dialysis.

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## DISCLAIMER

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