A shift in focus: international insights into the optimal management of CKD-MBD

How high is high enough? 25(OH)D adequacy in non-dialysis CKD-MBD patients

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Although a patient like Marie (see case study) may be symptom free, the five-year period when she was lost to follow up is problematic, potentially limiting both life span and the opportunity for effective clinical intervention.

Case study of Marie: a 50-year-old, white female with advancing CKD, 25(OH)D deficiency and SHPT

Lab values over time:

2011 eGFR = 52 mL/min/1.73m^2

2015 eGFR = 45 mL/min/1.73m^2⇒**referred to nephrologist**

- 25(OH)D = 36 ng/mL (90 nmol/L)
- PTH = 67 pg/mL (67 ng/L)

Lost to follow-up for nearly 5 years

2020 eGFR = 38 mL/min/1.73m^2

2020 eGFR = 38 mL/min/1.73m2

- PTH = 97 pg/mL (97 ng/L)

2021 eGFR = 34 mL/min/1.73m^2

CKD, chronic kidney disease; 25(OH)D, 25-hydroxyvitamin D; SHPT, secondary hyperparathyroidism; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

Patient case provided by Professor Wetmore, USA.

Clinical management of Secondary hyperparathyroidism (SHPT) in the non-dialysis CKD population includes regular and early monitoring of PTH (from CKD stage 3a) and correcting vitamin D [25(OH)D] deficiency/insufficiency. However, neither the target for optimal PTH, nor the level of 25(OH)D needed to achieve sufficient reduction of PTH are well defined.[1]

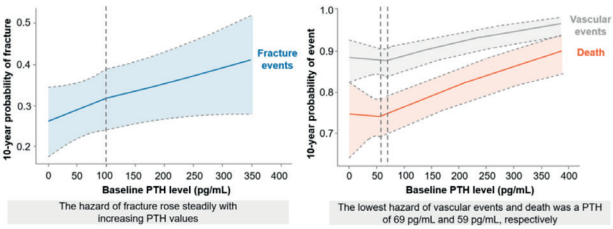

Figure 1.
PTH levels independently predict fracture, vascular events and death in Stage 3-4 CKD. Adapted from Geng S, *et al. Osteoporos Int* 2019;30:2019–25.

There is strong evidence to support early intervention. Early treatment of SHPT may interrupt the natural history of the development of gland hypertrophy, hyperplasia and autonomous function, and decrease the risk of CV and bone outcomes.[2,3] An observational study of 5,108 patients with stage 3-4 CKD show that SHPT is associated with an increased risk of facture, vascular events and death with rising PTH levels (see fig 1).[2]

As SHPT manifests early in CKD, with prevalence and severity increasing as kidney function declines, early diagnosis and treatment of SHPT is crucial.[4]

The mainstay of treatment is correcting vitamin D [25(OH)D] insufficiency.[5] Views on target vitamin D levels have changed from 20-30 ng/mL

to something closer to 100 ng/mL, or at least 50 ng/mL.[6]

Slowly increasing 25(OH)D levels with the aim of reaching >50 ng/mL[7] should allow:

- A reliable increase in 25(OH)D levels
- A minimal increase in 24,25$(OH)_2$D levels
- A physiological controlled adaption of 1,25$(OH)_2$D levels
- A physiological controlled reduction of PTH
- A minimal increase in serum Ca and P

An optimal treatment to control SHPT would increase 25(OH)D and reduce PTH with negligible effects on serum calcium, phosphate and fibroblast growth factor 23 (FGF-23),[8,9] but there are important unmet medical needs with current treatment options.

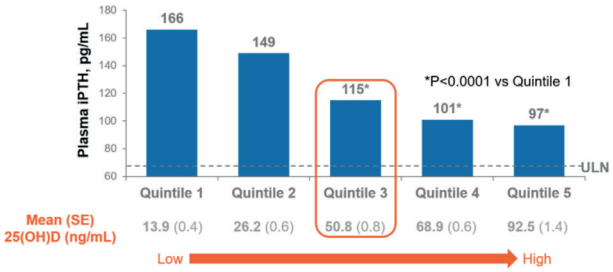

Figure 2.
Plasma PTH at weeks 20-26 as a function of post-treatment 25(OH)D quintile. Adapted from Strugnell SA, *et al. Am J Nephrol* 2019;49:284–93.

Nutritional vitamin D (cholecalciferol) and immediate release (IR) calcifediol both increase the level of 25(OH)D, but neither treatment consistently and reliably reduces PTH, and IR calcifediol also has a detrimental effect on FGF-23 levels. While active vitamin D/analogues are associated with a highly beneficial reduction in PTH, they also reduce 25(OH)D and have a highly detrimental effect on levels of calcium, phosphate and FGF-23.[9]

Extended-release calcifediol (ERC) may provide a beneficial treatment option. In phase 3 studies, it increased serum 25(OH)D levels and lowered plasma PTH consistently and steadily over time.[10,11]

At the end of the clinical trial, the investigators grouped the patient data into five quintiles of achieved level of 25(OH)D. Lower plasma PTH was observed for each quintile with increasing 25(OH)D levels (see fig 2).[7]

This represents a new paradigm in the treatment of SHPT: to raise the 25(OH)D level to the point where there is reciprocal reduction in PTH.

The favorable efficacy and safety profile of ERC has been confirmed in a real-world setting. Stage 3-4 CKD patients with SHPT and vitamin D insufficiency (n=174) were treated with ERC. Over 26-weeks of follow up, patients achieved a mean 23.7 ng/mL (P<0.001) increase in 25(OH) D and a 34.1 pg/mL (P<0.001) reduction in PTH, with no associated increase in serum calcium or phosphate levels.[12]

In the same study, 122 patients (70.1%) achieved 25(OH)D levels ≥30 ng/mL, 70 (40.2%) achieved ≥30% reduction in PTH and 53/90 patient (58.9%), whose baseline 25(OH)D was <20 ng/mL, achieved 25(OH)D ≥30 ng/mL.[12]

So, what did the results mean for the case study Marie? She commenced treatment with ERC in February 2020 and her 25(OH)D increased to about 70-75 ng/mL (175-188 nmol/L) and PTH decreased from about 90 pg/mL (70 ng/L) to about 70 pg/mL (70 ng/L) over the course of 12 months. After this there was no further reciprocal reduction in PTH, suggesting that each individual has their own physiologic 'setpoint' for PTH, and no further reduction will be seen once 25(OH)D is adequately repleted.

The PORTRAY study is a real-world evidence study led by an expert CKD-MBD steering committee from five countries. It will collect data on the use of ERC in a routine clinical setting in European patients. For more information about the PORTRAY study, contact Ingrid Gerber (Ingrid.Gerber@cernerenviza.com).

Controlling serum phosphate levels: a focus on CKD patients on dialysis

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An analysis of the European Fresenius database showed an association between serum phosphate and mortality in European hemodialysis (HD) patients, with the lowest risk of mortality (HR≤1.1) at 1.41 [1.08-1.80] mmol/L. Higher and lower phosphate levels were both associated with a higher risk of mortality.[13]

A more telling analysis from COSMOS (Current Management Of Secondary Hyperparathyroidism Study), looked not only at the relationship between phosphate and mortality, but also at what happens when you change phosphate levels. If baseline phosphate is well controlled, but either increases of decreases a few months later, mortality increases in both scenarios. Likewise, when baseline phosphate is high (>5.2 mg/dL) and then increases further, mortality increases; but importantly, when high baseline phosphate decreases, mortality also decreases to some degree.14 This is one of the first pieces of evidence that demonstrates a likely beneficial effect of phosphate control.

The source of phosphate is also important as plant phosphate cannot be digested or absorbed to the same extent as meat-based phosphate. In a highly controlled cross-over study, 9 patients with a GFR of about 30 mL/min consumed either a meat-based or a purely vegetarian diet for 7 days. Phosphate intake was similar across both groups (810 ± 27 mg/day and 795 ± 51 mg/day for the meat-based and vegetarian diets respectively), but serum phosphate increased with the meat-based diet (from 3.5 ± 0.6 to 3.7 ± 0.6 mg/dL) and decreased with the vegetarian diet (from 3.5 ± 0.6 to 3.2 ± 0.5 mg/dL) after 7 days, with a significant difference between the two groups (p=0.02). These results were reflected in FGF-23 levels: after 7 days, more FGF-23 was needed to excrete the additional phosphate for those on the meat-based diet compared to the vegetarian diet (101 ± 83 pg/mL and 61 ± 35 pg/mL respectively).[15]

A diet consisting of mainly fresh rather than processed foods is also important as phosphate additives in processed foods are readily absorbed. In a study, 10 healthy volunteers consumed a diet containing 900 mg of phosphate and no phosphate additives for the first week, followed by a diet containing the same level of calories and the same composition (% fat, protein and carbohydrates), but consisting mostly of processed foods for the second week. The additive-enhanced diet was associated with significantly higher levels of phosphate (1677 ± 167 vs 1070 ± 58 mg/day; p<0.001) and sodium (148 ± 28 vs 89 ± 28 mmol/day; p<0.05) compared to the low additive diet.[16]

High levels of phosphate have been shown to accelerate calcification. In an interventional study from Turkey, dialysis patients were given either a 1.25 or a 1.75 mmol/L calcium dialysate bath. After 2 years, coronary artery calcification was measured, and no significant difference between the two groups. When the results were stratified by phosphate (<4.7 vs ≥ 4.7 mg/dL), there was a tendency for people with higher phosphate to have more coronary artery calcification, but it was not significant. It was not until the two parameters were combined (i.e. the group that was both loaded with calcium through the dialysate and had poorly controlled phosphate) that very rapid progress of coronary artery calcification of up to 500 Agatston score points over 2 years was seen.[17]

There are many effective phosphate binders available, but there are key differences between classes in terms of pill burden, pleiotropic effects, accumulation and cost (see Fig 3).[18]

The 2017 KDIGO guidelines recommend restricting the dose of calcium-based phosphate binders in adult patients with CKD stages 3a-5D receiving phosphate-lowering treatment,19 but it is also important to think about the patient when considering treatment to decrease phosphate levels. For example, bringing phosphate levels down, avoiding coronary artery calcification and staying healthy are much more important in a 20- or 30-year-old who is a candidate for transplant than in an 80-year-old with an average life expectancy of 1.3 years. Controlling phosphate in elderly patients is often not the priority: it is more important for them to eat, enjoy life and be active.

Sucroferric oxyhydroxide (Fe-Oxyhydroxide) is a newer phosphate binder that is effective, has a low pill burden, no pleiotropic effects and does not accumulate – the iron is not taken up. Sucroferric oxyhydroxide also dissolves more readily than lanthanum, which has to be chewed, as the tablets are starch based.[18]

In a phase 3 study, sucroferric oxyhydroxide reduced phosphate as well as sevelamer after a wash-out over 52 weeks of treatments.[20,21] Serum ferritin was increased from baseline in both the sucroferric oxyhydroxide and sevelamer groups, although the result with sevelamer was an artefact of the situation in the United States, where reimbursement switched to product bundling, leading to greater use of iv iron instead of erythropoietin. Similar results with sevelamer were not seen in the EU or other countries.[20,22]

Sucroferric oxyhydroxide gives a small increase in iron uptake, usually in those patients who are iron deficient at the outset and, unlike ferric citrate, there are no documented cases of oral iron overload induction, so it is a small but perceivable benefit.

	Effective	Pill burden	Pleiotropic effects	Accumulation	Cost
Aluminium			Ø		
Calcium-Ac/Carb			Ø		
Sevelamer					
Lanthanum			Ø		
Ca-Mg			Ø		
Colestilan*					
Fe-Citrate			Ø		?

Figure 3. Overview of phosphate binders. Adapted from Floege J. *J Nephrology* 2016;29:329-40.
*Colestilan was removed from the market in the European Union. Green denotes benefit or advantage, orange potential or established disadvantage. Grey box, no known pleiotropic effects. Ac, actetate; Ca, calcium; Carb, carbonate; Fe, iron; Mg, magnesium.

The main benefit of sucroferric oxyhydroxide compared to sevelamer is the pill burden. In the first 24 weeks of the phase 3 study, average daily dose of sucroferric oxyhydroxide and sevelamer were 1.5 ± 0.6 g/day vs. 6.5 ± 2.5 g/day respectively, which translates to 3.1 pills of sucroferric oxyhydroxide and 7-8 pills of sevelamer each day.[20] There are some patients who can adapt their dose of a phosphate binder to their meal, but many are unable to do that, and it is easy for them to remember to take one tablet per meal.

In the phase 3 trial, the key adverse effect with sucroferric oxyhydroxide was diarrhea – mostly in the form of loose stools rather than watery diarrhea – and this was clustered in the very first phase.20,21 The likely explanation for this is the adaptation of the intestinal microbiome to iron.

Dr Floege and colleagues looked at this in the oral cavity and found a different microbiome after one week of treatment with sucroferric oxyhydroxide, but that it quickly reverted to normal. It is likely that the same effect is causing the short-term incidence of diarrhea with sucroferric oxyhydroxide in the phase III study. For many patients that is a perceived benefit because they often experience constipation.
The other key adverse effect, reported by 15.4% of patients taking sucroferric oxyhydroxide, was discoloration of the feces, although it is likely that this effect was significantly under reported in the study.[20,21]

Real world data also show that, following a switch from sevelamer to sucroferric oxyhydroxide, the number of patients with well-controlled phosphate increased over 12 months, and the number with previously poorly controlled phosphate decreased markedly.[23] An interesting observation in this study is that albumin divided by phosphate increases over the 12 months following initiation of sucroferric oxyhydroxide,23 so patients can have a little more nutritional liberty as their diet does not have to be restricted to the same extent to achieve a reduction in phosphate.

Further readings

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