Prevention and Control of Phosphate Retention/
Hyperphosphatemia in CKD-MBD: What Is Normal,
When to Start, and How to Treat?
Kevin J. Martin and Esther A. González

Summary
Phosphate retention and, later, hyperphosphatemia are key contributors to chronic kidney disease (CKD)—mineral and bone disorder (MBD). Phosphate homeostatic mechanisms maintain normal phosphorus levels until late-stage CKD, because of early increases in parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23). Increased serum phosphorus, and these other mineral abnormalities, individually and collectively contribute to bone disease, vascular calcification, and cardiovascular disease. Earlier phosphate control may, therefore, help reduce the early clinical consequences of CKD-MBD, and help control hyperphosphatemia and secondary hyperparathyroidism in late-stage CKD. Indeed, it is now widely accepted that achieving normal phosphorus levels is associated with distinct clinical benefits. This therapeutic goal is achievable in CKD stages 3 to 5 but more difficult in dialysis patients. Currently, phosphate control is only initiated when hyperphosphatemia occurs, but a potentially beneficial and simple approach may be to intervene earlier, for example, when tubular phosphate reabsorption is substantially diminished. Early CKD-MBD management includes dietary phosphate restriction, phosphate binder therapy, and vitamin D supplementation. Directly treating phosphorus may be the most beneficial approach because this can reduce serum phosphorus, PTH, and FGF-23. This involves dietary measures, but these are not always sufficient, and it can be more effective to also consider phosphate binder use. Vitamin D sterols can improve vitamin D deficiency and PTH levels but may worsen phosphate retention and increase FGF-23 levels, and thus, may also require concomitant phosphate binder therapy. This article discusses when and how to optimize phosphate control to provide the best clinical outcomes in CKD-MBD patients.


Introduction
Chronic kidney disease (CKD) is a leading cause of morbidity and mortality worldwide—an important contributor to this disease burden is the associated mineral and bone disorder (MBD). Phosphate retention and later hyperphosphatemia are central to the development of CKD-MBD.

Phosphate retention is an inevitable consequence of the gradual decline in renal phosphate clearance that starts at an early stage of CKD (1). Hyperphosphatemia is, however, prevented until the later stages of CKD by two major forces that control phosphate homeostasis, parathyroid hormone (PTH) (2), and fibroblast growth factor-23 (FGF-23) (3). In the early stages of CKD, phosphorus retention stimulates FGF-23 and PTH secretion, which in turn suppress renal phosphate reabsorption and augment renal phosphate excretion. FGF-23 also suppresses PTH secretion in normal parathyroids (4,5), resistance to the effect of FGF-23 appears as kidney function declines because of decreased Klotho expression in the parathyroid (6) and kidney (7). Thus, as CKD progresses to late stages, these homeostatic mechanisms are inevitably overwhelmed, hyperphosphatemia ensues, and the levels of PTH and FGF-23 increase progressively.

The adaptive responses involved in phosphate homeostasis in early CKD typically keep increases in phosphorus levels relatively small and within the normal range, but result in abnormally low 1,25D and high PTH (8–10), as well as high FGF-23 (11,12). These abnormalities, together with reductions in urinary calcium, individually and collectively contribute to renal bone disease, vascular calcification, and cardiovascular disease (CVD) (1,13,14).

Although the exact (patho)physiologic roles and interactions of phosphorus, FGF-23, and PTH are, at present, areas of intense interest, identification and treatment of early mineral abnormalities are an even more important consideration in clinical practice. Early treatment of phosphate retention or hyperphosphatemia may prevent or slow development of CKD-MBD that is linked to poor clinical outcomes. This article outlines the practical issues around management of phosphate retention and hyperphosphatemia in CKD and emphasizes considerations about when and how to optimize phosphate control to benefit clinical outcomes in patients with CKD-MBD.
What to Consider as Normal when Assessing Serum Phosphorus in CKD-MBD

It is important to consider what serum phosphorus levels should be targeted or maintained. A wealth of experimental and human observational data provide guidance on serum phosphorus targets.

A number of large epidemiologic studies consistently show high serum phosphorus levels (even within normal range) are associated with increased CVD morbidity and/or mortality in dialysis patients (15,16), in CKD stage 3 to 5 patients (17), and in those with normal renal function with or without CVD as summarized in Table 1 (18–22). These data suggest values >3.5 to 4.0 mg/dl seem to be associated with adverse effects. More recent observational data in ESRD have identified the existence of an inflection point, the point where survival significantly deteriorates appears to be somewhat higher, at phosphorus levels around approximately 5.5 to 6.0 mg/dl. However, exact estimates have varied and include 5.0 to 5.5 (15), >5.5 (23), 6.0 to 7.0 (24), and >6.5 mg/dl (25).

The relationship between serum phosphorus and CVD morbidity and mortality is complex but may involve direct effects of increased phosphorus on renal bone disease and extraskeletal calcification (26,27). It also may involve effects of secondary hyperparathyroidism (SHPT) on bone and vascular calcification (15,16,28) and high FGF-23 levels that correlate with increased CVD morbidity and mortality (29–31). Regardless of the underlying mechanisms, it is essential to consider phosphorus levels as a key contributor to CKD-MBD outcomes. The observation that phosphorus restriction improves survival of Klotho deficient mice is further support for this issue (32).

Based on the best available data, the Kidney Disease Outcomes Quality Initiative 2003 guidelines recommended targeting a normal phosphorus range of 2.7 to 4.6 mg/dl in patients with CKD stage 3 to 4 and a target of 3.5 to 5.5 mg/dl in those with CKD stage 5 and 5D, in whom normal phosphorus levels were considered largely unachievable (33). The Kidney Disease Improving Global Outcomes 2009 guidelines evaluated more recent data and reaffirmed the need for treatment to normalize phosphorus levels in CKD stage 3 to 5 and toward normal serum phosphorus levels in CKD stage 5D patients, although these guidelines refrained from recommending specific targets (34).

The current guidelines consider both the evidence on optimal phosphorus levels for best clinical outcomes and how achievable these targets are in practice. Treatment to maintain/achieve normal targets is likely to provide the greatest clinical benefits. However, because this is not always achievable in ESRD, it is also important to note that phosphorus control “toward” the normal range is recommended.

When to Start Treating Phosphate Retention in CKD-MBD?

In addition to considering what normal serum phosphorus levels may be, it may also be useful to consider whether to start phosphate control early based on any changes within the normal range and/or other potential biomarkers of early phosphate retention. In current clinical practice, dietary phosphate control is inconsistently prescribed in the early stages of CKD to moderate phosphate intake, and more effective phosphate binder therapy is reserved.
Table 1. Association of higher serum phosphorus with cardiovascular events

<table>
<thead>
<tr>
<th>Study</th>
<th>Serum Phosphorus (mg/dl)</th>
<th>Higher Serum Phosphorus Is Associated With:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Atherosclerosis Risk in Communities (ARIC)</td>
<td>3.5</td>
<td>CVD events and mortality</td>
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<tr>
<td>Study (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-Ethnic Study of Atherosclerosis (MESA)</td>
<td>&gt;4.0</td>
<td>High ankle brachial index among individuals without clinically recognized CVD</td>
</tr>
<tr>
<td>Study (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham Offspring Study (FOS) (19)</td>
<td>3.5 to 6.2</td>
<td>Increased CVD risk in individuals free of CKD and CVD in the community</td>
</tr>
<tr>
<td>Third National Health and Nutrition Examination</td>
<td>&gt;4.0</td>
<td>CV events, which are unlikely to be a result of differences with dietary intake or</td>
</tr>
<tr>
<td>Survey (NHANES III) (18)</td>
<td></td>
<td>traditional CV risk factors, and when GFR was &lt;30 ml/min per 1.73 m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Each 1 mg/dl higher serum phosphorus levels was associated with a 31% increase of a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>first major CV event</td>
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<tr>
<td>Cholesterol and Recurrent Events (CARE) study</td>
<td>≥3.5</td>
<td>An increased risk of new heart failure, myocardial infarction, and the composite of</td>
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<tr>
<td>(22)</td>
<td></td>
<td>coronary death or nonfatal myocardial infarction, but not the risk of stroke</td>
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<tr>
<td></td>
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<td>Each 1 mg/dl higher serum phosphorus levels was associated with a 27% increase in all-</td>
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<tr>
<td></td>
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<td>cause mortality</td>
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</tbody>
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until frank hyperphosphatemia is observed. However, it may be appropriate to initiate phosphate binders at earlier stages when phosphate retention has begun, as shown by elevations in PTH and FGF-23 levels, but before hyperphosphatemia occurs. This may help maintain stable phosphorus well within normal serum levels and limit even small rises that may lead to early mineral and bone disturbances. Indeed, there are early experimental observations that provide compelling support for this approach (Figure 2) (35). In these studies in uremic dogs, dietary phosphorus reduction in proportion to the reduction in GFR was effective in preventing the development of hyperparathyroidism during a period of 2 years of observation.

Currently, emphasis is placed on detection, monitoring, and treatment of serum phosphorus above the normal serum levels. Although this is obviously a clinically important consideration, changes in serum phosphorus, even within the normal range, may be insensitive to clinically relevant changes in mineral and bone metabolism (36). Thus, it may be important to consider not only phosphorus measurements but other markers for mineral and bone abnormalities as an indication for treatment to control phosphorus in early stage CKD, before the onset of hyperphosphatemia.

Figure 2. | The effect of dietary phosphorus intake on the development of secondary hyperparathyroidism in dogs with CKD. The solid line represents the levels of PTH in animals with CKD receiving 1200 mg phosphorus per day (CKD). The dashed line shows the PTH values in dogs with CKD whose dietary phosphorus intake was reduced in proportion to the reduction in GFR (CKD-PPR). (Modified from Rutherford et al. J Clin Invest 60: 332–341, 1977 with permission.)
PTH levels are already used as a clinically relevant indicator for CKD-MBD treatment targeted at SHPT. This measure may be currently somewhat limited by issues related to inconsistent sample collection/processing between laboratories, lack of assay standards, and variability between the various assays in current use (37). FGF-23 has been advocated as a novel and potentially useful biomarker of early phosphate retention (3). Its use may in the future become widespread, but at this time, is limited because a standard assay for FGF-23 has not been established for use in clinical practice.

Until better biomarkers are available, a simple but effective approach may be to measure tubular reabsorption of phosphate (TRP) in patients with CKD stage 3 to 4 as an integrated index of phosphaturic homeostatic mechanisms. To avoid hyperphosphatemia as glomerular filtration declines, increases in PTH and FGF-23 augment phosphaturia by reducing the fraction of filtered phosphate that is reabsorbed. Thus, when TRP falls below normal (<80), it may be beneficial to initiate interventions to limit phosphate retention and avoid the ensuing elevation of serum phosphorus. TRP can be easily determined by calculating the ratio of phosphate clearance to creatinine clearance as follows: %TRP = 1 – [(U_P / P_P) × (P_Cr / U_Cr)] × 100, where U_P and P_P are plasma and urine phosphate and U_Cr and P_Cr are plasma and urine creatinine (38). This may also be used to monitor the response to intervention and to possibly help to avoid phosphate depletion that may contribute to the development of osteomalacia. The clinical utility of this approach needs to be tested, as well as the use of other indices of phosphate excretion such as maximum tubular reabsorption of phosphorous.

**How to Treat Early CKD-MBD: Phosphate Control, 1,25D Therapy, or Both?**

Once it has been decided that CKD-MBD treatment is needed, it is important to consider how best this is achieved to provide greatest clinical benefits. The main approaches used in the later stages of CKD before onset of dialysis include dietary phosphate restriction or oral phosphate binder use to reduce phosphate retention and/or 1,25D treatment to improve 1,25D deficiency and SHPT.

**Dietary Phosphate Restriction**

A number of clinical studies on the effects of dietary phosphate and protein control in patients with CKD stages 4 and 5 have shown some short-term control of SHPT (39–44). Few studies, however, have evaluated how this impacts on bone disease or vascular calcification. One study found dietary phosphate restriction alone was insufficient to slow vascular calcification (45). Another reported dietary phosphate control could normalize bone parameters in most patients with late-stage CKD not yet on dialysis over 1 to 5 years (46,47). Importantly, the means used to achieve phosphate restriction may be important because a recent observational study suggested that protein restriction as a means of achieving a reduction in phosphate may not be beneficial to overall patient outcomes (48).

Despite the potential usefulness of dietary intervention, it is not always practical for patients to achieve phosphate control. The phosphate content of many foods is substantial and is not adequately described on nutritional labeling (49–51). It has been shown, however, that careful attention to food labels describing the food additives is effective in improving hyperphosphatemia (51) In addition, the risks of protein malnutrition must be carefully monitored (48). Thus, dietary modifications alone may be unsuitable to reduce phosphorus intake sufficiently in many CKD patients.

**Phosphate Binder Therapy**

It is, today, widely accepted that phosphate binders reduce serum phosphorus levels, which should equate to improved clinical outcomes in CKD patients. Despite a lack of direct evidence of clinical benefits from interventional trials, this seems logical, given the clear and consistent evidence of the association of phosphorus levels and outcomes. This is further supported by a recent prospective study that showed phosphate binder use is linked to clinical benefits in dialysis patients (52).

Many clinical trials show that phosphate binders are effective at reducing serum phosphorus levels, and some show that they can affect bone and calcification outcomes (53–57). Importantly, recent evidence suggests phosphate binders not only reduce phosphorus and PTH, but also FGF-23 (58,59). This may offer additional benefits, beyond simply treating SHPT and renal bone disease, which include improvements in FGF-23–related patient outcomes, especially at earlier stages of CKD.

The decision to use a phosphate binder should be followed by consideration of which currently available phosphate-binding agent is suitable for the patient. Despite often being the default phosphate binder therapy in those with some kidney function, calcium salts may not always be most appropriate and should be used cautiously (60). Calcium intake is assumed to be readily excreted; however, urinary calcium excretion tends to be low even after large calcium intakes in CKD patients, partly as a consequence of their elevated PTH. Calcium use can, therefore, potentially cause harmful calcium retention, which may promote vascular calcification. It is not well understood how calcium balance is controlled and where excess calcium goes in CKD patients. Consequently, although calcium-based and calcium-free phosphate-binding agents have similar phosphate-lowering efficacy, they can have differential effects on serum calcium and risk of hypercalcemia. This is an important issue that requires further study in patients with CKD. Although large doses of calcium salts should probably be avoided, modest doses (<1.5 g of elemental calcium) may be reasonable. In addition, there are several non–calcium-containing binders available that offer effica-
cious alternatives to calcium-based binders, without the potential risk of added calcium.

1,25D Treatment

Clinical trials in predialysis and dialysis patients have shown treatment with 1,25D or its analogs can reduce PTH levels but at the expense of potential increases in serum phosphorus and calcium (61,62). There is, however, insufficient clinical data across the spectrum of CKD to determine how these effects impact on CVD and mortality outcomes (61,62), although observational data have suggested 1,25D use is associated with lower PTH and improved clinical outcomes (63,64).

Although 1,25D treatment can offer benefits through control of SHPT, its elevating effects on calcium and phosphorus may be associated with increased risks of calcification. It is, therefore, logical that it be limited in those patients whose calcium or phosphorus are near the upper limit of normal to avoid potential risks of hypercalcaemia and hyperphosphataemia (65). In addition, it is possible that increases in serum phosphorus levels stimulated by 1,25D treatment may exacerbate phosphate retention and elevated FGF-23 levels, which are potentially associated with poor patient outcomes. Concomitant therapy with phosphate binders may therefore be required.

Conclusion

Phosphate retention eventually leads to increases in serum phosphorus and hyperphosphataemia, which are associated with poor clinical outcomes in CKD patients. Thus, phosphate control is an important part of CKD-MBD management. Current clinical guidelines, therefore, emphasize the importance of normal phosphorus levels in predialysis patients and toward normal in dialysis patients.

Importantly, it is now thought that increases in PTH and FGF-23 occur as early as CKD stages 3 to 4 to compensate for phosphate retention and are observed before hyperphosphataemia develops. PTH and FGF-23 are themselves associated with poor outcomes, which suggests phosphate retention may be important to treat at earlier stages of CKD. Early treatment may also help maintain near-normal phosphorus for longer as CKD progresses. Thus, although current practice is to wait until serum phosphorus is elevated before taking steps to manage phosphate as part of CKD-MBD treatment, it may be more appropriate to treat earlier. For example, an effective approach could be to initiate phosphate control early in CKD when TRP is reduced, a measurement that represents a “bio-assay” of the integration of the effects of compensatory phosphaturic factors on the kidney. This measurement could also potentially provide a guide for the titration of dosing. Phosphate binders will also be required if vitamin D sterols are used to try to combat any increase in intestinal phosphate absorption induced by vitamin D sterols. Clinical trials of the efficacy of such an approach would be useful.

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Disclosures

None.

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