INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Chronic Kidney Disease – Mineral and Bone Disorder*

-February 2026-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a clinical review of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) agents. The National Core Formulary (NCF) currently lists any form of vitamin D, any form of calcium (which may function as a phosphate binder), and alendronate. The NCF also includes the non-calcium-based phosphate binder sevelamer, with the included guidance language "for patients on dialysis who cannot use calcium-based phosphate binders due to hypercalcemia." The NPTC voted to **remove guidance language associated with sevelamer** from the NCF.

Discussion:

The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recognize the high prevalence of CKD-MBD in patients with chronic kidney disease (CKD) stages G3a-5D and recommend for these patients periodic monitoring of serum calcium (Ca), inorganic phosphate (Pi), parathyroid hormone (PTH), alkaline phosphatase, and 25(OH)vitamin D - to correct nutrient imbalances and detect the early stages of histologic abnormalities collectively known as renal osteodystrophy. Definitive diagnosis of renal osteodystrophy is generally not possible as the biopsies required are neither palatable to patients nor widely available. Pragmatic diagnosis instead relies on biochemical markers of bone turnover. KDIGO guidelines recommend, and most clinicians still use PTH and bone-specific alkaline phosphatase as bone turnover markers, but the issue of which markers to use remains an area of active controversy and research. Specified cutoffs in these bone turnover markers correlate roughly with high or low-turnover bone disease, i.e. disease with either high or low activity of osteoclasts and osteoblasts.[1,2]

High-turnover bone disease is usually a consequence of secondary hyperparathyroidism. As CKD progresses, renal excretion of Pi declines. PTH reduces reabsorption of Pi at the proximal tubules. While the overall effect of PTH is to reduce the serum concentration of Pi, PTH has pleiotropic effects, including stimulation of osteoclasts. Untreated hyperparathyroidism is associated with osteodystrophy and fractures, plus anemia, heart and vascular complications.[3]

Treatment of high-turnover CKD-MBD focuses on:

- Normalizing 25(OH)vitamin D, which can lower PTH levels, but has no effect on mortality, cardiovascular (CV) death, or fractures[4]
- Phosphorous dietary restriction, which has not consistently resulted in lower PTH in trials
- Phosphate binders, though they are burdensome to take and have not been shown to lower PTH or even serum Pi, much less convey any meaningful clinical benefit[5]
- Calcium correction by avoiding calcium-based Pi binders if hypercalcemic and by using calcium-based binders if hypocalcemic (usually in advanced CKD)

For all these treatments, there is no evidence for either optimal approach or clinically important outcomes.[6]

Treatment of low-turnover CKD-MBD ("adynamic bone disease") focuses on not making it worse by:

- Avoiding calcium-based phosphate binders and active forms of vitamin D (see below) which suppress turnover
- Avoiding bisphosphonates, although the theoretical risk that bisphosphonates could further suppress already-low bone turnover and worsen bone quality has not been validated in clinical trial outcomes[1]
- Allowing PTH to rise, although no target range has been validated

Even these modest measures to avoid doing harm have no evidence for clinical benefit.[2]

Vitamin D receptors bind only to 1,25(OH)vitD (calcitriol), also called "active" vitamin D. Conversion by the kidneys of 25(OH)vitD to calcitriol declines as overall kidney function declines, so it has been hypothesized that patients with advanced CKD should be supplemented with calcitriol rather than vitamin D3 or D2. However, calcitriol has not demonstrated superiority for either the biochemical goal of lowering PTH or any clinical outcomes.[4] It has, however, been associated with hypercalcemia and with inducing adynamic bone disease in low-quality evidence.[6]

Phosphate binders, while equally ineffective for their FDA-approved indication, controlling serum phosphorus, and equally ineffective for lowering PTH and all clinically meaningful outcomes, may still cause harm. Calcium-based binders may cause hypercalcemia, and almost all binders are associated with nausea and constipation, except sucroferric oxyhydroxide, which instead causes diarrhea. Furthermore, while sevelamer does not reduce mortality vs placebo (OR 0.45, 95% CI: 0.13-1.53), it may reduce mortality vs. calcium (OR 0.54, 95% CI: 0.32-0.93).[5] Sevelamer is included on the

NCF, not because of its proven clinical benefits, but to avoid the harms of calcium-based binders when phosphate binders are deemed necessary by clinicians.

Recently, experts have promoted the term “CKD-associated osteoporosis” - an attempt to overcome an overly PTH- and calcium-phosphate–centric approach to bone disease management and turn the focus toward fracture risk. While CKD-osteoporosis may be a distinct form of osteoporosis, bone mineral density testing, such as dual x-ray absorptiometry (DXA), predicts fractures with comparable accuracy in patients with CKD as in the general population, and T-scores predict fracture risk similarly in patients with and without CKD, including in kidney transplant recipients. In addition to United States Preventive Services Task Force criteria, KDIGO recommends DXA when there is biochemical evidence of CKD-MBD (abnormalities in calcium, phosphate, PTH, or alkaline phosphatase).[2]

Whether medications approved for osteoporosis work for CKD stages G4-5D is uncertain as these patients were generally excluded from clinical trials. However, older studies on bisphosphonates used creatinine, rather than creatinine clearance, (CrCl) for their cutoffs, allowing post hoc analysis of a few patients with eGFR<30. A meta-analysis of 9 risedronate trials found no difference in safety and efficacy between mild (CrCl ≥50 to <80 ml/min), moderate (CrCl ≥30 to <50 ml/min), and severe (CrCl < 30 ml/min; mean 26-27 ml/min) renal impairment. In severe renal impairment, risedronate still reduced vertebral fractures by 56% (95% CI: 11-78%, p=0.021).[7] Nevertheless, caution is advised due to the paucity of data, potential exacerbation of low turnover disease, and observational data of worsening renal function.[9]

Denosumab is not cleared by the kidneys, but trials still used an eGFR cutoff (<30 mL/min/1.73 m^2) for exclusion. However, a post hoc analysis found 73 patients with eGFR between 15-29 ml/min were inadvertently included. For these patients, bone mineral density (BMD) increased by 5.9% (95% CI: 3.0–8.7%), but these data were insufficient to analyze fracture incidence or safety.[7] This possible BMD benefit must be weighed against the risk of hypocalcemia. A retrospective cohort study of the 180 days following a denosumab injection found that severe hypocalcemia occurred in 1.6% with eGFR 15-30, and in 15% with eGFR <15.[8]

PTH analogs (teriparatide, abaloparatide) have potential to stimulate bone turnover, so these are theoretically compelling as therapy for low-turnover disease. Unfortunately, the trials for these also excluded patients with eGFR<30. Evidence for use with eGFR <30 is limited to small, inconclusive studies.[9] PTH analogs remain off-label for CKD stages G4-G5D.

Similarly, for romosozumab (humanized monoclonal antibody against sclerostin), evidence is limited to a single uncontrolled case series in dialysis patients, which did demonstrate lumbar spine and femoral neck BMD increases.[9] This very low-quality evidence must be weighed against the black box warning of increased MI, CVA, and CV death.

Findings:

While phosphate binders lack evidence of clinical benefit, they are consistent with current recommendations and widely used. There is reasonable concern for harm due to calcium-based phosphate binders - in particular, mortality vs. sevelamer, and hypercalcemia. To help potentially mitigate these harms, the NPTC voted to remove the current guidance language associated with sevelamer on the NCF. Although treatment of CKD-MBD with vitamin D and calcium supplements is not well supported by evidence, they are consistent with current guidelines—and, of course, remain widely used for osteoporosis treatment and prevention. This review did not find robust evidence for osteoporosis treatments in patients with eGFR<30.

References:

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