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Narrative Review

Intensive Hemodialysis, Mineral and Bone Disorder, and Phosphate Binder Use

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Mineral and bone disorder is a common complication of end-stage renal disease. Notably, hyperphosphatemia likely promotes calcification of the myocardium, valves, and arteries. Hyperphosphatemia is associated with higher risk for cardiovascular mortality and morbidity along a gradient beginning at 5.0 mg/dL. Among contemporary hemodialysis (HD) patients, mean serum phosphorus level is 5.2 mg/dL, although 25% of patients have serum phosphorus levels of 5.5 to 6.9 mg/dL; and 13%, >7.0 mg/dL. Treatment of hyperphosphatemia is burdensome. Dialysis patients consume a mean of 19 pills per day, half of which are phosphate binders. Medicare Part D expenditures on binders for dialysis patients approached $700 million in 2013. Phosphorus removal with thrice-weekly HD (4 hours per session) is ~3,000 mg/wk. However, clearance is unlikely to counterbalance dietary intake, which varies around a mean of 7,000 mg/wk. Dietary restriction and phosphate binders are important interventions, but each has limitations. Dietary control is complicated by limited access to healthy food choices and unclear labeling. Meanwhile, adherence to phosphate binders is poor, especially in younger patients and those with high pill burden. Multiple randomized clinical trials show that intensive HD reduces serum phosphorus levels. In the Frequent Hemodialysis Network (FHN) trial, short daily and nocturnal schedules reduced serum phosphorus levels by 0.6 and 1.6 mg/dL, respectively, relative to 3 sessions per week. A similar effect of nocturnal HD was observed in an earlier trial. In the daily arm of the FHN trial, intensive HD significantly lowered estimated phosphate binder dose per day, whereas in the nocturnal arm, intensive HD led to binder discontinuation in 75% of patients. However, intensive HD appears to have no meaningful effects on serum calcium and parathyroid hormone concentrations. In conclusion, intensive HD, especially nocturnal HD, lowers serum phosphorus levels and decreases the need for phosphate binders.
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INDEX WORDS: Chronic kidney disease; mineral and bone disorder (MBD); calcium; cinacalcet; daily dialysis; end stage renal disease (ESRD); Frequent Hemodialysis Network; home dialysis; intensive hemodialysis; nocturnal hemodialysis; parathyroid hormone; phosphate binder; phosphorus; secondary hyperparathyroidism; short daily hemodialysis; vascular calcification; review.

Mineral and bone disorder (MBD) is an inevitable complication of chronic kidney disease.[1] In the earliest stage of chronic kidney disease, a decrease in glomerular filtration rate leads to phosphate retention. Excess phosphate load likely first signals increased production of fibroblast growth factor 23 (FGF-23), a phosphaturic hormone, by osteocytes. Because FGF-23 inhibits 1-α-hydroxylase, decreased synthesis of 1,25-dihydroxycholecalciferol (ie, calcitriol) results.[2] Together, the increase in FGF-23 production, decrease in calcitriol synthesis, and decrease in ionized calcium levels (due to binding with retained phosphate) stimulate increased parathyroid hormone (PTH) secretion from the parathyroid glands, resulting in secondary hyperparathyroidism. PTH stimulates the release of calcium from bones and the production of calcitriol, which enhances calcium absorption in the small intestine. Still, as chronic kidney disease progresses, calcitriol production diminishes, usually resulting in hypocalcemia (in the absence of pharmacologic intervention).

As the collective result of these derangements, large excursions from target serum concentrations of calcium, phosphorus, and PTH may occur in dialysis

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patients. In an analysis of more than 26,000 prevalent hemodialysis (HD) patients in a single dialysis provider organization (and in receipt of multiple treatments, including vitamin D sterols, phosphate binders, and cinacalcet hydrochloride), only 34.5% of patients were in target ranges of serum calcium, phosphorus, and intact PTH, with respective targets of 8.4 to 10.2 mg/dL, 3.5 to 5.5 mg/dL, and 150 to 600 pg/mL for the mean values of all serum measurements during a 4-month interval.[3] Meanwhile, 25.7% of patients had in-target calcium and intact PTH levels, but elevated phosphorus levels; and 10.7% of patients had in-target calcium levels, but both elevated phosphorus and intact PTH levels. In total, 40.9%, 20.9%, and 3.7% of patients had 1, 2, and 3 out-of-target concentrations, respectively. As the number of out-of-target concentrations increased, the unadjusted rate of cardiovascular-related events (ie, death and hospitalization) increased.[3] In addition to these associations, FGF-23 level is independently associated with risk for death in dialysis patients.[4]

There are a number of pharmacologic interventions for MBD, including vitamin D sterols, in either oral or intravenous formulation; phosphate binders, including calcium acetate, lanthanum carbonate, and sevelamer (with carbonate or hydrochloride salt); and cinacalcet hydrochloride, a calcimimetic indicated for the treatment of secondary hyperparathyroidism. Dialysate calcium concentration can also be manipulated. In contrast to antihypertensive agents, which are generally inexpensive, both phosphate binders (particularly sevelamer) and cinacalcet are tremendously expensive. In dialysis patients with Medicare Part D coverage in 2013, cumulative costs for phosphate binders were $692 million, and for cinacalcet, were $407 million.[5] (For frame of reference, cumulative Part D costs in dialysis patients were $1.97 billion.) From a clinical perspective, the efficacy of these treatments is constrained by adherence, which is notoriously poor for phosphate binders.[6] Although a number of strategies to improve adherence have been assessed, the core impediment of high pill burden remains.[7] Poor adherence to both phosphate binders and cinacalcet is also motivated by gastrointestinal adverse effects.[8,9] Clearly, novel strategies are needed to address MBD, particularly hyperphosphatemia.

Although the pathophysiology of MBD is clearly complex, hyperphosphatemia, in the absence of residual kidney function, undeniably reflects an imbalance between the dietary intake and dialytic clearance of phosphorus. Therefore, increasing dialysis frequency or duration may constitute an effective strategy for correcting hyperphosphatemia and limiting the need for phosphate binders. In this review, we describe the epidemiology of hyperphosphatemia, mechanics of phosphate intake and excretion, efficacy and limitations of oral phosphate binders, and effects of intensive HD on both serum phosphorus levels and phosphate-binder use. We also briefly examine the effects of intensive HD on both calcium and PTH levels, as well as gaps in the existing literature. We show that both short daily HD and nocturnal HD can effectively lower serum phosphorus levels and markedly reduce the use of phosphate binders, but have unclear effects on other biochemical parameters, as well as the incidence of clinical consequences of MBD.

EPIDEMIOLOGY OF HYPERPHOSPHATEMIA

Prevalence of Hyperphosphatemia

Hyperphosphatemia is common in dialysis patients despite prescribed treatment with phosphate binders. In the DOPPS (Dialysis Outcomes and Practice Patterns Study) surveillance population, as of December 2015, mean serum phosphorus level, as calculated during a 3-month interval, was 5.18 mg/dL.[10] The 50th, 75th, 90th, and 95th percentiles of serum phosphorus levels were 5.00, 5.82, 6.90, and 7.70 mg/dL, respectively. More than 36% of HD patients had serum phosphorus levels persistently above the target range of 3.5 to 5.5 mg/dL (Fig 1).[10] Also notably, another 15% to 20% of patients had serum phosphorus levels of 5.0 to 5.5 mg/dL, an interval that is considered to be within target, but that is nonetheless associated with increased cardiovascular risk.[11]

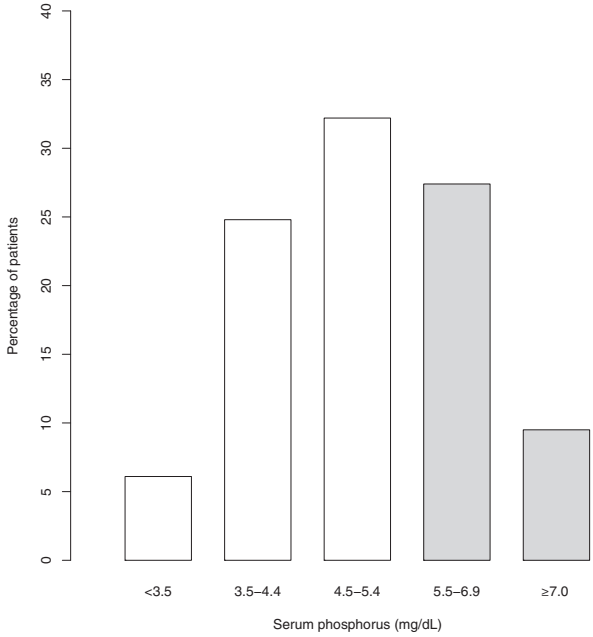

Figure 1. Distribution of 3-month mean serum phosphorus levels in the Dialysis Outcomes and Practice Patterns Study Practice Monitor, December 2015.[10]