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Balancing Nutrition and Serum Phosphorus in Maintenance Dialysis

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Elevated serum phosphorus levels are common in patients with chronic kidney disease and are associated with heart and vascular disease, conditions that in turn are associated with increased mortality. Accurately managing phosphorus intake by restricting dietary protein alone can prove challenging because protein from different sources can contain varying amounts of available phosphorus. Additives used in processed foods frequently are high in inorganic phosphorus, which is readily absorbed, compounding this difficulty. Recent evidence suggests that dietary protein restriction in some cases may do more harm than good in some patients treated with maintenance hemodialysis because protein restriction can lead to protein-energy wasting, which is associated with increased mortality. Accordingly, phosphorus binders are important for managing hyperphosphatemia in dialysis patients. Managing hyperphosphatemia in patients with late-stage chronic kidney disease requires an individualized approach, involving a combination of adequate dietary advice, phosphate-binder use, and adjustments to dialysis prescription. We speculate that increased use of phosphate binders could allow patients to eat more protein-rich foods and that communicating this to patients might increase their perception of their need for phosphate binders, providing an incentive to improve adherence. The aim of this review is to discuss the challenges involved in maintaining adequate nutrition while controlling phosphorus levels in patients on maintenance hemodialysis therapy.

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INDEX WORDS: Diet, protein-restricted; chronic kidney disease; phosphorus, dietary; phosphate binders.

CASE PRESENTATION

A 63-year-old white man with stage 5D chronic kidney disease (CKD) started on maintenance hemodialysis (HD) therapy 2.5 years ago. He presents with the following laboratory measurements (fasting midweek predialysis): serum phosphorus, 6.2 mg/dL (1.90 mmol/L); serum calcium, 10.4 mg/dL (2.60 mmol/L); serum parathyroid hormone (PTH), 280 pg/mL; serum 25-hydroxyvitamin D₃ (25[OH]D₃), 40 ng/mL (100 nmol/L); normalized protein catabolic rate, 1.25 g/kg/d; and serum albumin, 3.8 mg/dL. His medications include Calcijex (intravenous calcitriol, manufactured by Abbvie), 0.5 µg, each HD session; calcium carbonate, 1.5 g/d; and 100,000 units of cholecalciferol every 2 months. His dialysis dose is considered adequate, based on equilibrated Kt/V of 1.35. The patient's biannual food report shows sufficient protein intake of 1.1 g/kg/d and adequate energy intake of 31 kcal/kg/d, and the patient does not report excessive consumption of inorganic phosphate, so is advised not to modify his diet.

This patient has secondary hyperparathyroidism because of end-stage renal disease. He has elevated serum calcium and phosphorus levels, but a normal nutritional vitamin D (25[OH]D₃) level. As a first step toward reducing serum calcium levels, calcitriol treatment is stopped and calcium carbonate is replaced with a noncalcium phosphate binder.

After 3 months, the patient's laboratory values are as follows: serum phosphorus, 6.2 mg/dL (1.90 mmol/L); serum calcium, 8.8 mg/dL (2.20 mmol/L); serum PTH, 300 pg/mL; and serum 25(OH)D₃, 30 ng/mL (75 nmol/L). The patient's serum phosphorus level is still higher than the normal range, at a level that is associated with worse outcomes.¹ He has not adhered to treatment with the noncalcium phosphate binder. During his 6-monthly dietary interview, the patient reports frequently eating processed food and drinking soft drinks every day. The patient is counseled to improve adherence to phosphate binder treatment by discussing ways to fit his medications into his daily routine, as well as helping him understand the importance of taking them as prescribed. The phosphate contents of different foods and drinks also are discussed with

the patient, and he is advised to eradicate processed food from his diet. The patient's serum phosphorus level subsequently decreases to 4.6 mg/dL (1.50 mmol/L) after 3 months.

INTRODUCTION

Serum phosphorus levels tend to be poorly controlled in patients with CKD.¹ Elevated serum phosphorus levels contribute to the disruption of bone metabolism and are associated with heart disease and increased mortality (Fig 1).¹ It therefore is important to control serum phosphorus levels in patients with CKD.

Target levels of serum phosphorus commonly are controlled using a combination of dietary restrictions

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and phosphate-binding drugs, in addition to adjusting dialysis session duration, filter surface, and convection during maintenance HD sessions.² One of the main dietary recommendations for patients with CKD who are not on dialysis therapy is restriction of protein consumption, which helps maintain serum phosphorus at controlled levels.³ The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI 2000) guidelines recommend protein intake of 0.6 g/kg of body weight per day for patients with glomerular filtration rates < 30 mL/min and 1.2 g/kg of body weight per day for patients on maintenance HD therapy.⁴ In patients on maintenance HD therapy, the European Best Practice Guidelines recommend slightly lower dietary protein intake of 1.1 g/kg of ideal body weight per day.³ Recent evidence has shown protein restriction to correlate with increased mortality in patients undergoing maintenance HD, suggesting that reduction of protein in the diet may be detrimental to these patients.⁵ Thus, before maintenance HD therapy, serum phosphorus levels may be controlled by an optimal protein intake of 0.6 g/kg/d. However, after starting dialysis therapy, higher protein intake of 1.1–1.2 g/kg/d is recommended, and other strategies should be introduced to help control serum phosphorus levels. Depending on the extent of hyperphosphatemia and the patient's lifestyle requirements, these measures could include a combination of dietary counseling, phosphate-binder

use, and dialysis prescription. Dietary counseling should be offered in the first instance; however, dietary support may be lacking in some renal wards.

This review discusses the evidence surrounding protein restriction and phosphate control and highlights the challenges of maintaining appropriate nutrition at the same time as controlling serum phosphorus levels in patients undergoing maintenance HD. The review also explores the role of phosphate binders in managing serum phosphorus levels and reviews the potential additional benefits associated with phosphate-binder use.

PROTEIN INTAKE AND SERUM PHOSPHORUS

A common recommendation for the management of hyperphosphatemia is to reduce the amount of phosphorus in the diet.² The NKF-KDOQI guidelines and European Best Practice Guidelines recommend daily phosphorus intake of 800–1,000 mg/d for patients on maintenance HD therapy.^{3,6,7} Foods with high protein content tend to have high phosphorus content, and an increase in dietary protein has been shown to correlate with an increase in serum phosphorus levels (Fig 2).⁸ Limiting dietary phosphorus intake therefore generally involves restricting cheese and dairy products (Box 1).

Spontaneous reduction in food intake and progressive protein-energy wasting may occur in some patients.⁹ Anorexia is the first result of this, followed by the possibility of overhydration, particularly during the long interdialytic interval. Whether limiting phosphorus intake per se will induce protein-energy wasting has not been addressed and deserves further study. However, dietary counseling should caution against excessive restriction. Phosphorus restriction in hyperphosphatemic patients may inadvertently result in a reduction in protein intake, which should be avoided.

Several trials have shown that controlled reduction of protein intake can help ameliorate the onset of the hyperparathyroidism that often is a consequence of CKD.¹⁰ However, the ratio of phosphorus to protein in food is not constant, which can make it difficult to control dietary phosphorus intake accurately purely by reducing the amount of protein in the diet. For example, egg yolk has 15–20 times more phosphorus per gram of protein than egg white.⁸

Bioavailability should be considered when analyzing the relationship between phosphorus level and dietary protein. Animal proteins contain phosphorus primarily as organic phosphoesters, which are readily hydrolyzed and absorbed by the human digestive system.⁸ However, plant foods that are high in protein, such as legumes, nuts, and chocolate, contain phosphorus mostly in the form of phytate or phytic acid, which is not readily broken down in the gut. The bioavailability of plant phosphorus therefore can be as low as 50%.

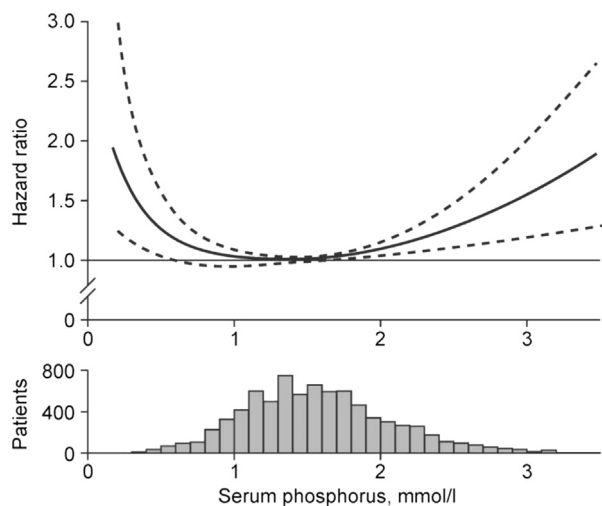


Figure 1. Mortality hazard ratio and serum phosphorus level. The hazard ratio for mortality (95% confidence interval noted by dashed lines) at 30 months after entry to the study, which is derived from Cox regression models adjusted for covariate values at baseline (age, sex, history of cardiovascular disease, diabetes, dialysis vintage, body mass index, serum albumin level, and hemoglobin level) and using fractional polynomials for (top) serum phosphorus level and (bottom) number of patients. Conversion factor for units: phosphorus in mmol/L to mg/dL, $\times 3.097$. Reproduced from Fouque et al,¹ with permission of Oxford University Press.

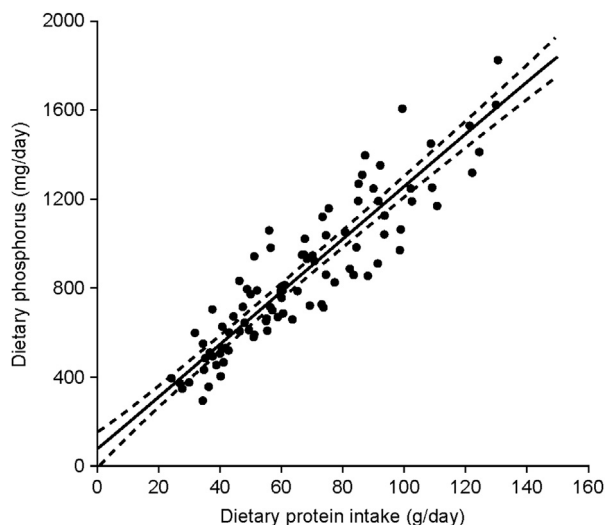


Figure 2. Relationship between dietary protein intake and dietary phosphorus in maintenance hemodialysis (HD) patients. Data from 107 maintenance HD patients shows how increasing dietary protein intake correlates with increasing dietary phosphorus. Regression equation: dietary phosphorus (mg) = $78 + 11.8 \times (\text{protein intake [g]})$ ($r = 0.91$, $F^2 = 0.83$, $P < 0.001$). Dashed lines indicate the predicated confidence interval. Reproduced from Kalantar-Zadeh et al,⁸ with permission of American Society of Nephrology.

Moe et al¹¹ showed in a randomized crossover trial of patients with CKD stage 3 that phosphate intake of 800 mg/d from plant sources was associated with lower phosphaturia and lower serum phosphate levels compared with the same amount of phosphate ingested from animal sources. **Box 1** shows the different phosphate content of proteins and highlights the importance of tailored dietary advice in situations of intractable hyperphosphatemia.

Box 1. Phosphate Content of Foods With High Protein Content

High Phosphate Content

- Egg yolk
- Hard cheeses, ricotta or cottage cheese, fat-free cream cheese
- Soups made with higher phosphorus ingredients (milk, dried peas, beans, lentils)
- Dried peas (split, black-eyed), beans (black, garbanzo, lima, kidney, navy, pinto), or lentils
- Certain types of seafood (shrimp, crab, lobster, oysters)
- Nuts and seeds
- Peanut butter and other nut butters
- Organ meats, walleye, pollock, or sardines

Low Phosphate Content

- Egg white
- Refined grains, including white bread, crackers, cereals, rice, and pasta
- Soups made with lower phosphorus ingredients (broth- or water-based with other lower phosphorus ingredients)
- Low-phosphorus snacks (shortbread cookies)
- Certain types of seafood (sole, sea bass, hake)

A further confounding factor is that the rate of phosphorus absorption can be increased by the presence of vitamin D. This has been shown to stimulate phosphorus transporters in the gut and increase phosphorus uptake.

The way food is prepared also can have an impact on its phosphorus content, and patients on maintenance HD therapy often are advised to boil certain foods to help remove phosphorus. In support of this, Cupisti et al¹² showed that boiling beef for 30 minutes reduces the phosphorus to protein ratio by $>50\%$. In summary, a dietary approach may help patients select protein sources and cooking methods that allow them to reduce their phosphate load without compromising protein intake (**Box 2**).

INORGANIC PHOSPHORUS

Inorganic phosphorus additives are an often-overlooked source of phosphorus in the diet. Compounds that contain inorganic phosphorus frequently are used in the food industry to extend shelf life, enhance flavor, and improve the color of food products; these additives can make the overall phosphorus content very high.¹³ However, it is not a requirement that manufacturers list phosphorus content on food packaging, making the exact levels of phosphorus in these foods difficult to determine. Although it is a requirement that additives are listed on food packaging, they can be lost in the small print and may be difficult for patients to identify. Combined, these factors do not help patients in their assessment of the phosphorus content of food.

Eating processed food instead of freshly prepared food can greatly increase a person's daily phosphorus intake, even without changing the calorie or protein content. One recent study demonstrated that the inclusion of phosphorus-containing additives in cooked meat increased its phosphorus content by up to 70%.¹⁴ Another study showed the phosphorus content of soft drinks to be very variable, ranging from 1-134 mg of phosphorus per 12-oz cup.¹⁵

As well as being prevalent in processed foods, the inorganic phosphorus found in food additives is readily absorbed, adding to serum phosphorus load. The rate of absorption of organic phosphorus is variable, but in an average mixed diet, people tend to absorb $\sim 60\%$ of the phosphorus they consume.¹³ In contrast, phosphorus in an inorganic form is absorbed almost completely.¹³ Hence, food additives present a significant problem for the control of phosphorus levels in patients with CKD.

RISKS ASSOCIATED WITH LOW DIETARY PROTEIN INTAKE

The NKF-KDOQI guidelines suggest that patients receiving HD aim to consume 1.2 g of protein per kilogram per day, and the European Best Practice

Box 2. Key Messages

- There is a contradiction between optimal protein intake and phosphorus intake limitation
- Reduced protein intake is associated with increased mortality in patients on maintenance dialysis therapy; therefore, restricting dietary protein may not be the best method of controlling phosphorus intake in these patients
- Dietary phosphorus absorption is reduced by vegetable fibers
- Hidden inorganic phosphorus added in processed food is readily absorbed and can be as high as 1,000 mg/d
- Phosphate binders have varying equivalent doses and differ in their calcium content and in their potential effects on parathyroid hormone and fibroblast growth factor 23
- Adherence to binder therapy is a cornerstone for the correction of phosphorus level abnormalities, and ways to improve adherence should be encouraged

Guidelines recommend at least 1.1 g of protein per kilogram per day.^{4,7} However, a study of 53,933 patients receiving HD in clinics across the United States showed that >50% of these patients consumed less than this amount.¹⁶ This study further demonstrated that a spontaneous decrease in protein consumption in patients with a normalized protein-nitrogen appearance of 0.8-1.2 g/kg/d in the first 6 months of the study was associated with increasing mortality in the following 18 months.

A subsequent study investigated survival rates of 30,075 patients receiving maintenance HD over the course of 3 years.⁵ These patients were categorized according to whether their protein intake or phosphorus levels increased or decreased during the first 6 months of the study. Patients in whom protein levels decreased had increased mortality regardless of phosphorus levels (Fig 3). These data suggest that the risk of reducing dietary protein may be greater than the benefit gained from lowering phosphorus intake.

In a post hoc analysis of a study of patients receiving maintenance HD, it was found that a prescribed reduction in phosphorus intake correlated with an increase in mortality.¹⁷ Because the specific nutritional advice given to patients was not investigated in this study, an intriguing possibility is that the increased mortality correlated with decreased protein intake. These results therefore could be indicative of the difficulty in maintaining the balance of reduced phosphorus and adequate nutrition by excessive control of dietary intake.

Further trials will be needed to gauge the exact nature of the relationship between reduced protein intake and mortality and determine the impact of other methods of phosphorus control.

PHOSPHATE-BINDER USE AND ADEQUATE NUTRITION

By reducing the amount of dietary phosphorus absorbed from the gut, phosphate binders help control

serum phosphorus levels and are used by 78%-88% of patients receiving HD.^{1,18} Table 1 compares binding capacities and dosages of 4 of the leading phosphate binders in the United States: calcium acetate, calcium carbonate, sevelamer carbonate, and lanthanum carbonate. The values presented are estimates of the dosage that would be required in order to control a relatively modest increase in phosphorus intake of 300 mg per day from food additives.¹⁴ This is a realistic estimate of the exposure of patients on maintenance HD therapy to phosphorus-containing additives.¹⁴ Table 1 shows the differences in phosphate-binding capacity and variation in tablet burden associated with different types of phosphate binder, as well as highlights the additional pill burden related to food additives. In support of this, estimates based on metabolic and urinary studies suggest that similar variation in doses of internationally used phosphate binders would be required to maintain target phosphate levels in patients consuming recommended daily levels of protein.¹⁹

Studies in rat models of CKD (5/6 nephrectomized rats) have shown that the use of phosphate binders can significantly reduce serum phosphorus levels, and clinical trials have confirmed that phosphate binders effectively reduce serum phosphorus levels in healthy

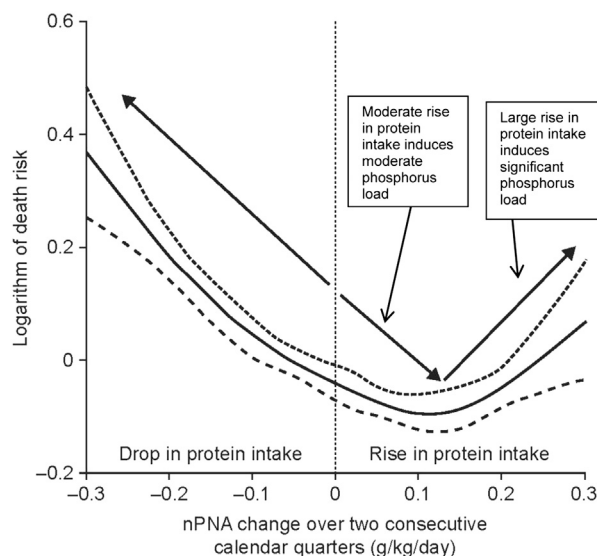


Figure 3. Association between normalized protein nitrogen appearance (nPNA) in maintenance hemodialysis (HD) patients and all-cause mortality. Association between change in average nPNA over 2 consecutive calendar quarters in 30,075 patients on maintenance HD therapy and the logarithm of the risk ratio of all-cause mortality over 3 years based on a multivariable regression spline model, adjusted for case-mix and malnutrition-inflammation complex syndrome. Moderate increases in protein intake are associated with lower mortality than reductions in protein intake. Dashed lines are pointwise 95% confidence levels: upper confidence line small dash, lower confidence line large dash. Adapted from Shinaberger et al⁵ with permission of the American Society of Nutrition.

Table 1. Comparison of Hypothetical Doses of Phosphate Binders Required to Neutralize an Extra Phosphorus Load of 300 mg/d From Additives

Phosphate Binder	Binding Capacity, mg/g (mg/tablet)	Daily Dose, mg/d	Tablets/Day, n
Calcium acetate, 667 mg/tablet	50 (33)	6,000	9
Calcium carbonate, 400 mg/tablet ^a	19 ^b (8)	6,315	16
Sevelamer carbonate, 800 mg/tablet	33 (26)	9,090	12
Lanthanum carbonate, 1,000 mg/tablet	115 (115)	2,610	3

Note: The phosphorus from additives is nearly 100% absorbed.

^aBased on ultra-strength TUMS (GlaxoSmithKline).

^bBased on stool phosphate recovery study in dialysis patient.⁴²

Adapted from Benini et al¹⁴ with permission from Elsevier Inc.

participants, patients not yet undergoing dialysis, and patients receiving long-term dialysis for CKD.²

Given the efficacy of phosphate binders, hyperphosphatemic patients on maintenance HD therapy should receive phosphate binders at the same time as dietary adjustments are advised. This could help control serum phosphorus levels while maintaining adequate protein intake and good nutrition and avoiding the potential for protein-energy wasting and increased mortality associated with protein restriction. In support of this, the DOPPS (Dialysis Outcomes and Practice Patterns Study) showed that phosphate-binder use and increased nutritional status correlated with longer survival in patients on maintenance HD therapy.¹⁸ Prospective interventional studies are needed to confirm this relationship.

ADDITIONAL BENEFITS ASSOCIATED WITH PHOSPHATE BINDERS

One of the complications of CKD is an increased risk of heart disease, and a key risk factor for heart disease is vascular calcification. Although the pathogenesis of vascular calcification in patients with CKD is thought to be multifactorial, hyperphosphatemia is an important risk factor.²⁰ In certain patients, hypercalcemia also may contribute to the progression of calcification, and recent guidelines have suggested that the use of calcium-based phosphate binders is not recommended for some patients.^{2,21} A recent meta-analysis has indicated that there may be beneficial effects associated with the use of non-calcium-based phosphate binders; however, the debate about the potential risks of calcium-based phosphate binders is ongoing.²²

There is some evidence to suggest that the use of non-calcium-based phosphate binders might be associated with reduced vascular calcification in

patients at risk, such as elderly men, postmenopausal women, and patients with diabetes, low bone turnover, prevalent vascular or valvular calcification, or inflammation.²⁰

Studies have shown that the use of sevelamer or lanthanum-based phosphate binders can reduce the occurrence of calcification in laboratory models of CKD. For example, studies of rat vascular smooth muscle cells illustrate that the presence of phosphorus increases the incidence of calcification and that lanthanum can attenuate this increase.²³ Treatment of CKD rats with 3% sevelamer or 3% lanthanum carbonate reduced the calcification of aortic root lesions to similar extents.²⁴

Sevelamer treatment has been shown to attenuate the growth of coronary and aortic calcifications in patients on maintenance HD therapy to a greater extent than treatment with calcium-based phosphate binders.²⁵ Patients receiving lanthanum carbonate showed significantly slower progression of aortic or coronary artery calcification than those treated with other phosphate binders.^{26,27} However, these potential benefits have not been associated with improved survival in large randomized controlled trials.²

Cinacalcet also has been shown to reduce serum phosphorus levels by ~10%, alongside its direct action on PTH levels,²⁸ and this effect is sustained in patients on maintenance HD therapy who have recurrent secondary hyperparathyroidism following parathyroidectomy.²⁹ The mechanism behind this effect is not fully explained, but might be due to a reduction in phosphate bone release in response to a reduction in PTH levels.³⁰ Cinacalcet treatment has been associated with reductions in vascular calcifications, parathyroidectomy, and cardiovascular hospitalization compared with placebo^{31,32}; however, a recent large-scale prospective randomized trial did not see an effect of cinacalcet treatment on mortality or major cardiovascular events compared with placebo control.³³

Serum levels of fibroblast growth factor 23 (FGF-23) also are increased in patients with CKD. This phosphatonin helps regulate phosphorus levels in the blood and elevated FGF-23 levels have been associated with increased morbidity and mortality in patients with CKD, regardless of whether they are undergoing dialysis.³⁴ Recent pharmacologic studies have shown that the use of lanthanum carbonate, sevelamer, or a combination of lanthanum carbonate and calcium carbonate correlates with reductions in serum FGF-23 levels.^{35,36} These data suggest that phosphate-binder use may be important in helping control other critical aspects of late-stage CKD.

PHOSPHATE BINDERS IN CLINICAL PRACTICE

One of the key challenges in the treatment of chronic diseases is patients' adherence to their diet and

Box 3. Treatment Considerations for Patients With CKD and High Serum Phosphate**CKD stages 3-4 and high serum phosphate**

1. Maintain serum phosphate within the normal range²; assess current dietary habits
2. Limit protein intake²
3. Reduce phosphorus intake
 - Ensure patient is aware of the phosphorus content of different foods (Box 1)
 - Suggest limiting intake of processed food and drink, which have high phosphorus content
 - Highlight the need to maintain adequate nutritional intake to avoid protein-energy wasting
4. Consider phosphate-binder prescription
 - Evaluate most appropriate phosphate binder, considering the most appropriate formulation (tablet, powder, liquid) and dose to suit the patient
 - Discuss patient beliefs and concerns about the medication to optimize adherence
 - Discuss the possibility of self-adjusting phosphate-binder dose

CKD stage 5D on maintenance HD with high serum phosphate

1. Lower elevated phosphorus levels toward the normal range²
2. Maintain an optimal protein intake of 1.1 g/kg/d⁷
3. Assess dietary habits and advise on reducing phosphorus intake
 - As above, but with particular emphasis on maintaining adequate protein intake
4. Consider phosphate-binder prescription
 - As above
 - Avoid prescribing calcium-based phosphate binders if patient has hypercalcemia or consistently low parathyroid hormone measurements²
5. Adjust dialysis prescription

Abbreviations: CKD, chronic kidney disease; HD, hemodialysis.

drug regimen. The majority of patients on maintenance HD therapy require phosphate binders; however, on average, 51% of patients are not fully adherent to their prescribed phosphate-binder therapy.³⁷ It therefore is important to consider how best to help patients with CKD follow their often complex therapy regimens.

There are no clear demographic predictors of nonadherence. In a systematic review of 34 studies that investigated adherence to phosphate-binder therapy, no demographic factor (including age, sex, marital status, ethnic group, income, education, employment, or religion) was associated consistently with an increased likelihood of being nonadherent.³⁷

The same review also considered the impact of potential clinical predictors of adherence, including type of dialysis, diabetic status, transplant history, cause of CKD, and regimen complexity. Of these, regimen complexity was the only factor that had a significant impact on adherence, with increased complexity and a high pill burden being associated with lower adherence.³⁷

Simplifying the drug regimens of patients with CKD by reducing the number of pills to be taken therefore could help increase adherence. A lower pill number thus is a crucial point to focus on when prescribing a phosphate binder. Some phosphate binders also are available as powder or liquid formulation; this could be a more convenient way of taking the medication, therefore increasing adherence. Other changes to a regimen, such as arranging for medications to be taken at particular times of day to suit a patient's lifestyle, also can promote adherence.³⁸ Teaching phosphate content of food and self-adjustment of pill number based on simple dietary phosphate units has been shown to increase the number of pills taken and decrease serum phosphate levels in children with various stages of CKD.³⁹

However, regimen changes alone are unlikely to resolve the problem of nonadherence. It is well recognized that in many cases, nonadherence is the result of a conscious decision to take less of the medication than prescribed.⁴⁰ Nonadherence often is related to patients' beliefs about the medication, particularly how they judge their personal need for the medicine relative to their concerns about potential adverse effects.⁴⁰ Studies of long-term conditions have shown that patients' doubts about the necessity of taking daily treatments often are related to their symptom expectations and experiences.⁴¹ Patients are more likely to consider a treatment worthwhile if they perceive significant short- and long-term benefits. Providing a convincing common sense reason for adherence to phosphate-binder therapy is a challenge because the rationale for phosphate-binder therapy is complex and the benefits generally are realized in the long term. Individualized treatment of serum phosphorus levels thus involves a combination of education and treatment tailored to the patient's needs (Box 3).

CONCLUSIONS

Restricting dietary protein to help control phosphorus levels in patients undergoing maintenance HD may be more harmful than beneficial. More importantly, increased awareness of inorganic phosphorus in food additives may lead to significant improvements in dietary phosphorus restriction regimens.

Phosphate binders help maintain serum phosphorus levels in the recommended ranges and have beneficial effects in terms of reducing calcification and serum FGF-23 levels. In addition, taking phosphate binders could help patients manage phosphorus levels without the need to restrict dietary protein.

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