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Factors for Increased Morbidity and Mortality in Uremia: Hyperphosphatemia

Nathan W. Levin, Frank A. Gotch, and Martin K. Kuhlmann

Hyperphosphatemia is a metabolic abnormality present in the majority of patients treated by dialysis. Inorganic phosphorus (iP) can be categorized as a true uremic toxin given its known in vivo and in vitro effects and the ability to reduce these effects by normalizing iP levels. However, despite regular and adequate dialysis treatment, the goal of normalization of phosphorus levels rarely is achieved. This article briefly evaluates the significance of hyperphosphatemia in hemodialysis patients, current therapeutic approaches, and describes a new model for evaluating the dialysis prescription for iP balance.
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Original epidemiologic studies[1] have suggested that approximately 70% of patients have increased inorganic phosphorus (iP) levels greater than 1.58 mmol/L, with approximately 17% greater than 2.58 mmol/L. Increased awareness of this issue and intensive education during recent years have had an effect on the incidence of hyperphosphatemia. In a recent analysis of Renal Research Institute units treating over 6,000 patients, only 34.6% of patients had an iP value greater than 1.7 mmol/L. The new National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease[2] may contribute further to better phosphate management in dialysis patients. However, despite advances in dialysis technology, there is little doubt that the management of hyperphosphatemia is not accomplished easily.

The long-term consequences of inadequate phosphorus control include hyperparathyroidism, metabolic bone disease, calcific uremic arteriolopathy, and cardiovascular calcification. Progressive increases in arterial calcification are associated with greater degrees of mortality.[3] The adjusted mortality increases by 20% to 40%, with extreme increases in iP levels (up to 4.2 mmol/L), with similar effects reported for Ca × P product > 5.9 $(mmol/L)^2$.[1] Hyperphosphatemia itself directly induces parathyroid gland hyperplasia, with an increase in serum PTH level and a decrease in serum calcitriol levels, and at the bone level it contributes to resistance to both PTH and calcitriol.[4] Besides increased iP levels, risk factors for coronary calcification even among young dialysis patients include an increase in Ca × P product and high daily calcium intake.[5] An increased Ca × P product owing to increased phosphorus levels in conjunction with normal or high calcium levels is associated with calcium-phosphate precipitations, mainly in the form of hydroxyapatite, in blood vessels, myocardium, and heart valves, resulting in structural dysfunction. Cardiac dysfunction is manifested by hemodynamic changes, arrhythmia, heart failure, and cardiac decompensation. Recent studies in nonhemodialysis patients suggest that coronary calcification also may be predictive of or associated with sudden cardiac death.[6] Sudden death among hemodialysis patients may be a particularly common effect, but the occurrence of heart failure caused by a variety of mechanisms also is common.

Of particular interest is the now well-established finding of vascular calcification being an actively regulated process akin to bone mineralization. Recently, Jono et al[7] have reported that human aortic smooth muscle cells in culture that are exposed to physiologic iP levels (1.4 mmol/L) grow normally, whereas cells grown in the presence of higher iP concentrations (up to 2.0 mmol/L) show an approximate 5-fold increase in calcium deposition. Vascular smooth muscle cells undergo phenotypic conversion to osteogenic cell types in the presence of hyperphosphatemia in both animals and humans. Pro-osteogenic effects of increased iP levels are mediated by a sodium-dependent phosphate cotransporter facilitating the entry of phosphorus into vascular cells. The activity of these transporters may be increased in a uremic environment and in hyperphosphatemia. In cell culture, selective

Renal Research Institute, New York, NY.
Nathan W. Levin, MD, Medical and Research Director, Renal Research Institute, 207 E 94th St, Suite 303, New York, NY 10128. E-mail: nlevin@rriny.com

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inhibition of these transporters inhibits phosphorus uptake and also phosphate-induced osteogenic gene expression.[8]

Evaluation of Current Therapeutic Options

It is evident that a major goal in reducing cardiovascular mortality should be the normalization of iP levels. Prevention and therapy of hyperphosphatemia is based on 3 principles: (1) restriction of dietary phosphorus intake, (2) inhibition of gastrointestinal phosphorus absorption by phosphate binders, and (3) phosphorus removal by dialysis.

Dietary Phosphorus Restriction

Emphasis on therapy initially was directed toward limitation of dietary phosphorus intake. However, dietary phosphorus intake strictly is related to protein intake. Dietary phosphorus is found mainly in proteins but also in colas, chocolate, and so forth. The average concentration of iP in protein is approximately 15 mg/g, but dairy proteins have somewhat higher concentrations per g/protein. The recommended daily dietary protein intake for dialysis patients is 1.0 to 1.2 g/kg body weight.[9] Consequently, in a 70-kg patient this will result in an ingestion of 1,000 to 1,200 mg/d of phosphorus. Given a gastrointestinal absorption rate of 70% to 80%, the phosphorus burden will be 4,200 to 4,800 mg/wk. Dietary phosphorus restriction inevitably will lead to a reduction in protein intake, thereby increasing the risk for development of malnutrition, which by itself increases the mortality risk for dialysis patients. Of course, excess phosphorus intake needs to be avoided and this is an important issue for renal dieticians.

Phosphate Binders

For many years calcium carbonate was the phosphate binder of choice. Advantages of this substance included inhibitory effects on PTH secretion, low cost, and good tolerability. Meanwhile, the emphasis had shifted from calcium carbonate to calcium acetate owing to improved binding efficiency. Recent literature, however, is packed with reports on the ill effects of calcium-based binders, including increased rate of hypercalcemic events,[10] and risk for increased Ca × P product, leading to vascular and extravascular calcifications and increased mortality rates.[5] Aluminum and magnesium salts are available as non–calcium-based phosphate binders, but these compounds are used only sporadically and even then only for short periods owing to a number of potentially severe side effects. More recently, phosphate-binding polymers such as sevelamer were developed. Reduced progression or even improvement of vascular calcifications were shown with the use of this phosphate binder.[11-13] A beneficial further effect of sevelamer is its effects on reducing low-density lipoprotein cholesterol levels.[14,15] Another non–calcium-based phosphate binder, lanthanum chloride, has been investigated recently.[16] The effect on phosphate levels appears to be similar to those of sevelamer and no adverse effect on bone has been reported over a 2-year period. However, the question of accumulation in the bone has been raised but not excluded as a problem. Other polymers, sold initially as bile acid sequestrants, also are being studied as iP binders, as is iron oxide, which also may be useful. However, there are many problems occurring with the use of phosphate binders including inadequate patient compliance owing to a high number of tablets and side effects, inappropriate timing of medication, and a potential lack of relation between actual phosphorus intake and dose of phosphate binder.

The use of new more expensive phosphate binders is limited and calcium-based binders still are prescribed widely. Measures to reduce the calcium load associated with calcium-containing phosphate binders and also calcium blood levels currently are being investigated, including the use of low calcium dialysate. Currently, dialysate calcium concentrations prescribed are decreasing, but it is not clear how safe a calcium concentration of 1 to 1.25 mm is. The possibility of a negative calcium balance and reduced inhibition of PTH production both exist.[17-19]

Clearly, the ideal binder will be one that is highly effective, for example, fewer tablets or capsules, has few side effects (such as those affecting the gastrointestinal tract), does not accumulate in bone, and is inexpensive.

Phosphate Removal by Dialysis

The cardinal report by DeSoi and Umans in 1993 established that concentration profiles of iP were virtually identical despite substantial differences in dialyzer clearances. Their results suggested that after an initial rapid decrease in iP concentration, plasma levels subsequently are maintained by one or more pools opening to maintain plasma iP concentrations. These data recently have been confirmed by others.[20] Average removal of phosphorus by dialysis with low-flux dialyzers amounts to 700 to 900 mg per treatment (ie, 2,100-2,700 mg/wk) and may be increased by hemodiafiltration to almost 1,200 mg per treatment.[21] Similar results should be obtained with high-flux dialyzers. An appropriate way to increase phosphate removal further is by increasing dialysis frequency. In patients undergoing daily nightly hemodialysis, protein intake increased, while at the same time phosphate-binder medication was stopped completely without development of hyperphosphatemia.[22]

A new approach could be the use of larger highly efficient dialyzers to remove clinically important quantities of iP, thus reducing the need for phosphate binders with resultant better compliance, both with drugs and diet. Appropriate prescription of such dialytic therapy, however, requires knowledge of the effects of iP removal on steady state.

Kinetic Model to Estimate iP Intake and Removal by Hemodialysis and Phosphate Binders

The model of phosphorus mass balance (Fig.1) incorporates major components of generation of iP (from protein), re-

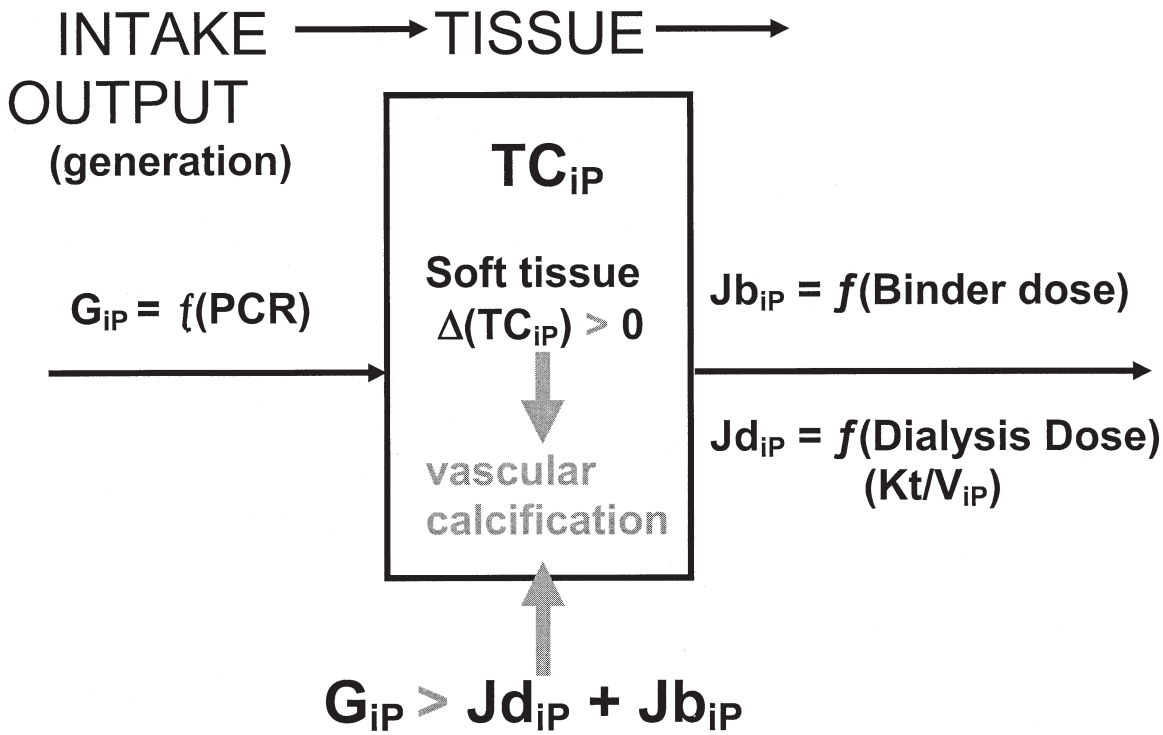

Figure 1 Model of phosphorus mass balance in hemodialysis patients. Phosphorus mass balance is governed by GiP, △ TciP, JdiP, and JbiP.

moval by phosphate binders, and removal by dialysis. The difference between generation and removal is the quality deposited in tissues (as mentioned earlier). Overall iP mass balance thus can be described as follows:

$$\triangle \text{TciP} = \text{GiP} - \text{JdiP} - \text{JbiP}$$

where △TciP (variation in tissue phosphorus content) equals the accumulation of phosphate in the tissue compartment, GiP (phosphorus generation by dietary intake) equals the phosphorus generation (dietary phosphorus intake), JdiP equals the dialyzer iP removal (removal of iP by dialysis), and JbiP (removal of phosphorus by phosphate binders) equals the phosphate removal by phosphate binders.

In determining a kinetic model of phosphate balance the following assumptions were made: for iP generation, the iP content is 15 mg/g protein with gastrointestinal absorption of 80% and protein intake derived from the protein catabolic rate; and for iP removal by binders, each unit (tablet, capsule) binds 24 mg.

To model dialysis iP removal it is essential to know the number of dialysis treatments per week, the duration of each treatment, the dialyzer clearance of phosphate, and the time-averaged iP concentration during dialysis (TAC_{iP}). Therefore, it was necessary to examine profiles of the iP concentration curves during dialysis and determine the time-averaged concentration normalized for the predialysis iP concentration ($nTAC_{iP}$). Serum concentration of iP was measured every 30 minutes as a function of the predialysis iP concentration (ie, normalizing the latter to 100%) over the total period of the dialysis treatment. If the $nTAC_{iP}$ were predictable in the individual patient, then the total removal of iP during dialysis might be established accurately with knowledge of the predialysis iP concentration, the dialysis schedule, and the dialyzer clearance. Calculated and measured iP concentrations in the dialysate were virtually identical. The time-averaged iP concentration turned out to be a predictable mathematic function of the Kt/V for iP.[23] Calculation of $nTAC_{iP}$ was improved further by including for each patient 2 coefficients (β and α) describing the individual iP profiles for intradialytic iP removal (with β being variable and α being close to a flat line) (Fig. 2). These 2 coefficients can be calculated from 2 data points taken before and after dialysis. It is unknown whether the pool that is mobilized rapidly to sustain iP levels during later stages of dialysis is derived from normal body components only or from previously deposited Ca × P precipitations.

If the profiles in individual patients are stable, which is under current investigation, then it should be possible by examining the balance of iP to determine the extent of the need for iP binders and to predict the effects of further increases in dialytic iP clearance on serum iP concentrations.

K/DOQI Guidelines

The recently developed K/DOQI guidelines on Bone Metabolism and Disease in Chronic Kidney Disease[2] recommend following treatment modalities for patients with end-stage renal disease (stage 5):

1. Both calcium-based phosphate binders and other non–calcium-, non–aluminum-, non–magnesium-containing

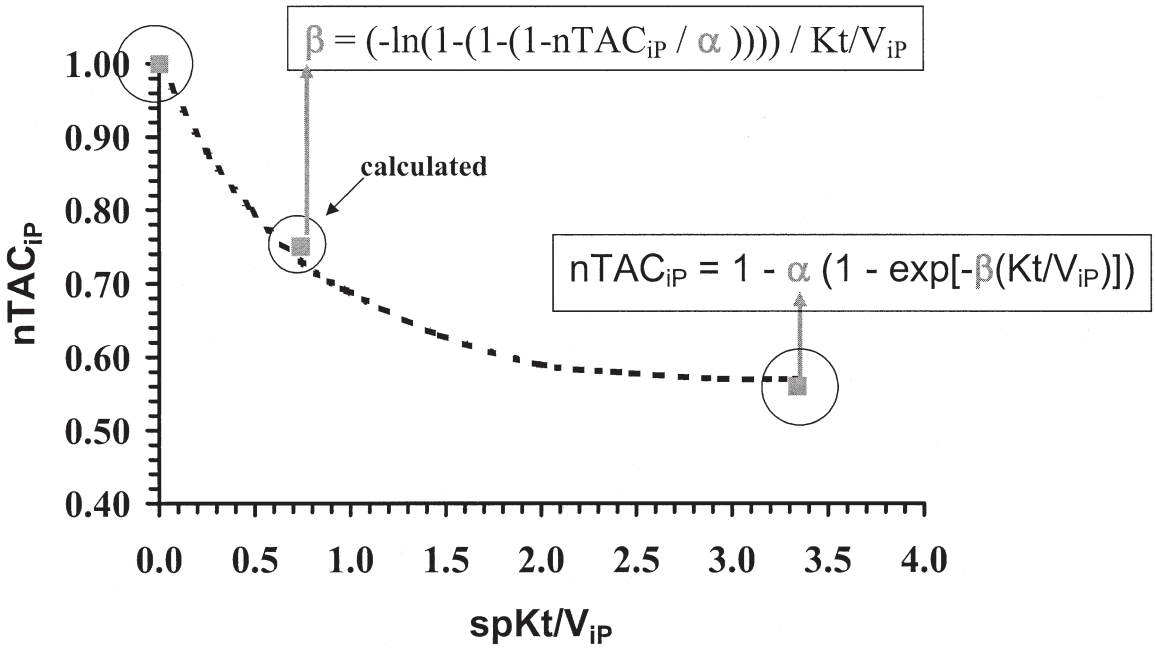

Figure 2 Method to determine individual patient coefficients describing the $nTAC_{iP}$ profile in relation to $spKt/V_{iP}$ (single pool Kt/V for iP) during dialysis from 2 data points (pre- and postdialysis). The $nTAC_{iP}$ profile is determined by 2 individual coefficients (α and β) describing an initial steep decline (coefficient β) and a later phase of flattening (coefficient α). Coefficient β can be calculated from pre- and postdialysis iP values without an additional intradialytic blood sample.

phosphate-binding agents (such as sevelamer HCl) are effective in decreasing serum phosphorus levels (EVIDENCE) and either may be used as the primary therapy.

2. In dialysis patients who remain hyperphosphatemic (serum phosphorus levels >1.78 mmol/L) despite the use of either calcium-based phosphate binders or other non–calcium-, non–aluminum-, non–magnesium-containing phosphate-binding agents, a combination of both should be used.
3. The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/d, and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/d in our opinion.
4. Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium concentration of >2.54 mmol/L), or whose plasma PTH levels are less than 16.5 pmol/L on 2 consecutive measurements (EVIDENCE).
5. Non–calcium-containing phosphate binders are preferred in dialysis patients with severe vascular and/or other soft-tissue calcifications in our opinion.
6. In patients with serum phosphorus levels greater than 2.26 mmol/L, aluminum-based phosphate binders may be used as a short-term therapy (4 wk), and for one course only, to be replaced thereafter by other phosphate binders in our opinion. In such patients, more frequent dialysis also should be considered (EVIDENCE).

Conclusion

Hyperphosphatemia remains one of the major problems in end-stage renal disease. The K/DOQI guidelines recommend normalization of phosphorus levels in all patients. However, despite advances in dialysis technology and intensified phosphate-binder therapy, increased phosphate levels are found in more than one third of patients. Better understanding of phosphate kinetics during hemodialysis, development of highly efficient dialyzers, and/or a switch to more frequent dialysis treatments will be necessary to achieve the K/DOQI goals.

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