
Core Curriculum

Management of hyperphosphatemia

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Abstract

Hyperphosphatemia is a well recognized risk factor for cardiovascular mortality in dialysis patients. Despite advanced technology and regular and efficient dialysis treatment the prevalence of hyperphosphatemia is still high. The goal of normalization of serum phosphorus (iP) levels can only be reached by optimization of dialysis prescription in combination with individualized dietary and medical strategies. Due to the unique characteristics of intradialytic iP kinetics, dialysis treatment time and frequency are the most effective factors governing intradialytic iP removal. Although the combination of diffusive and convective removal by hemodiafiltration allows a further increase in iP mass removal, a neutral phosphorus balance without dietary restrictions and the use of phosphate binders has only been achieved by daily nocturnal hemodialysis. Strict dietary phosphate restriction bears the risk of inadequate protein intake and the development of protein/calorie malnutrition. Although phosphate binders (PB) can effectively lower serum iP levels into the normal range, this is rarely achieved in clinical practice probably due to inadequate relation of PB dose to dietary phosphorus intake. Developing methods to enable patients to self-adjust phosphate binder dose to individual meal phosphate content, similar to adjusting insulin dose to carbohydrate intake, may lead to further improvements in phosphate management.

Key words: Phosphate balancer, dialyzer clearance, phosphate binder, diet

INTRODUCTION

Patients with end-stage renal disease (ESRD) are at an increased risk for cardiovascular mortality. Besides classical cardiovascular risk factors that are also present in the general population, disturbances of calcium and phosphate metabolism have been identified as important and modifiable risk factors for this patient population.^{1–3} 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. The long-term consequences of inadequate phosphate control include hyperparathyroidism, metabolic bone disease, calcifying uremic arteriopathy, and cardiovascular calcification. Progressive increases in arterial

calcification are associated with greater rates of mortality.⁴ Adjusted mortality increases by 20% to 40% with extreme increases in iP (up to 4.2 mmol/L) with similar effects reported for $\text{Ca} \times \text{P}$ product > 5.9 (mmol/L).^{2,3} Hyperphosphatemia itself directly induces parathyroid gland hyperplasia with an increase in serum-PTH and a decrease in serum calcitriol levels and at the bone level, contributes to resistance to both PTH and calcitriol.⁵ Besides elevated iP levels, risk factors for coronary calcification even among young dialysis patients include an increase in $\text{Ca} \times \text{P}$ product and high daily calcium intake.⁶ An increased $\text{Ca} \times \text{P}$ product due to elevated iP 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 (HD) patients suggest that coronary calcification may also be predictive of or associated with sudden cardiac death.⁷

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In recognition of these fatal consequences of abnormal calcium and phosphate metabolism, international guidelines have been published, urging for normalization of phosphate levels in ESRD patients.⁸ However, despite advances in dialysis technology and regular and efficient dialysis treatment, the goal of normalization of serum phosphate levels is rarely achieved by extracorporeal therapy alone and hyperphosphatemia is still found in a majority of HD patients. Management of hyperphosphatemia remains a major challenge for all subjects involved in ESRD care, such as doctors, nurses, and—last but not the least—the patients themselves.

EVALUATION OF CURRENT THERAPEUTIC OPTIONS

A comprehensive management of hyperphosphatemia is based on 3 principles: (i) extracorporeal phosphate removal by dialysis, (ii) restriction of dietary phosphorus intake, and (iii) inhibition of gastrointestinal phosphorus absorption.

Phosphate balance in healthy and diseased subjects

Healthy individuals are in neutral phosphorus balance, with phosphorus generation (G_{iP}) from ingested and endogenous proteins almost completely being balanced by renal phosphorus elimination (J_{iP}). In HD patients the lack in renal phosphorus excretion needs to be compensated for by dialytic phosphate elimination and inhibition of gastrointestinal phosphorus absorption. A model of phosphorus mass balance in HD patients (Figure 1) incorporates iP generation, iP removal by phosphate binders (PBs), and iP removal by HD. Phosphorus balance in HD patients necessarily turns positive, whenever G_{iP} exceeds J_{iP} leading to hyperphosphatemia, increased tissue phosphate concentration, and increased risk for tissue calcification.⁹ Phosphate generation rate is closely correlated with dietary phosphorus intake, but may exceed dietary intake in cases of severe secondary hyperparathyroidism, where significant amounts of phosphate may also be released from bone. The difference between iP generation and total removal is the quantity potentially deposited in tissues. In HD patients, overall iP mass balance can be described as follows:

$$\Delta TC_{iP} = G_{iP} - J_{d_{iP}} - J_{b_{iP}} \quad (1)$$

where ΔTC_{iP} is the accumulation of phosphate in the tissue compartment, G_{iP} the phosphorus generation (dietary

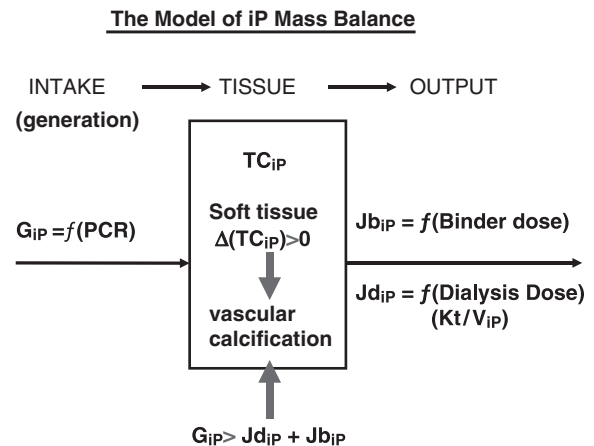


Figure 1 Model of phosphorus mass balance in hemodialysis patients. Phosphorus mass balance is governed by G_{iP} (phosphorus generation by dietary intake), ΔTC_{iP} (variation in tissue phosphorus content), $J_{d_{iP}}$ (removal of iP by dialysis), and $J_{b_{iP}}$ (removal of phosphorus by phosphate binders).

phosphorus intake), $J_{d_{iP}}$ the dialyzer iP removal, and $J_{b_{iP}}$ the phosphate removal by PBs.

Phosphate kinetics during dialysis

Inorganic phosphorus acts like a small molecular weight toxin with a distribution volume that is assumed to be equal to total body water. However, the kinetics of intradialytic phosphate removal differ significantly from classic kinetics reported for urea, a surrogate marker for water-soluble, small molecular weight compounds. During dialysis, blood urea nitrogen concentrations continuously decline and following a short rebound period immediately after termination of the treatment, steadily increase during the interdialytic interval depending on protein intake and urea generation rate. Serum phosphate levels, after an initial relatively steep decline, reach a plateau after about 2 to 2.5 hr into dialysis and, during the second half of the treatment, do not further decline or even slightly increase. Moreover, after termination of treatment, plasma iP levels rebound almost to predialysis values rapidly within a couple of hours. These kinetics were originally described by DeSoi and Umans¹⁰ in 1993 and have recently been confirmed by Gotch et al.¹¹

The intradialytic reduction in phosphate levels during the first half of HD is rapid and leveling off predictably occurs when plasma iP baseline levels decline to about 40% of predialysis values. As dialyzer phosphate clearances do not change during this time, these findings suggest that a substantial fraction of iP removal occurs from the intracellular space and that the transfer rate from the

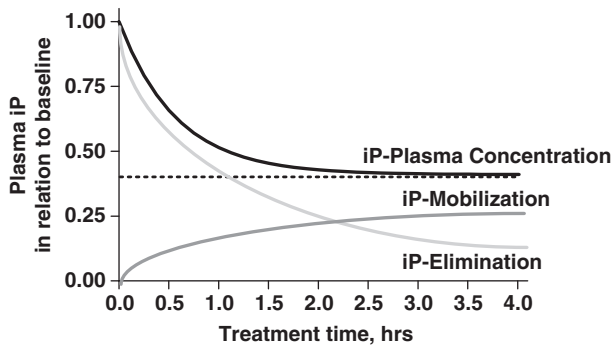


Figure 2 Intradialytic kinetics of plasma phosphate concentration. The observed change in plasma PO levels (black line), which shows a leveling off at about 40% of baseline concentration, may be explained by a combination of classical 2-compartment kinetics (blue line) and the superimposed effect of delayed PO mobilization from at least 2 more compartments (violet line) (see also Figure 3).

intracellular compartment to the plasma compartment determines the rate of change in plasma iP levels during the latter part of HD. As depicted in Figure 2, the observed intradialytic kinetics of plasma phosphate concen-

tration (black line) can be explained as the result of 2 processes: a classical double pool kinetic elimination curve similar to urea kinetics (blue line), and a delayed stimulation of phosphate transfer from other compartments into the plasma compartment (violet line). To describe these *in vivo* phosphate kinetics in more detail, Spalding et al.,¹² have developed a multicompartmental model where extracellular plasma iP initially is replenished by an easily accessible intracellular iP pool with a high mass transfer constant. According to this model, 2 additional iP compartments are activated when intracellular iP depletion is imminent, with one compartment releasing iP directly into the extracellular space, while the other, originally termed the intracellular emergency compartment, releases iP into the intracellular compartment in order to protect the cellular environment from a dangerously low phosphate concentration (Figure 3). The exact site of the various phosphate pools is unknown, but it may be assumed that phosphate is at least partially mobilized from bone, the body compartment with the highest phosphate content. This kinetic behavior of plasma iP levels has to be kept in mind when discussing means to increase dialytic iP removal.

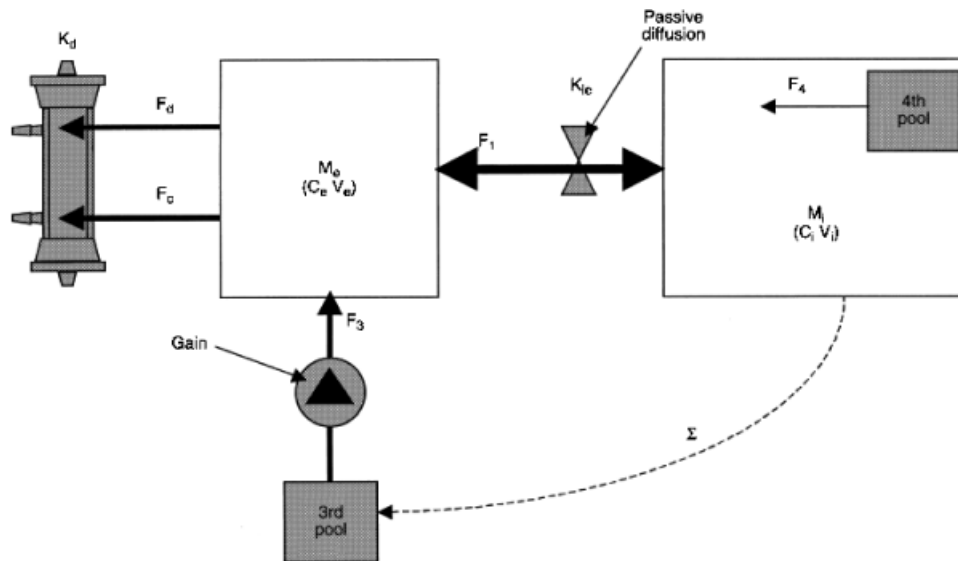


Figure 3 Schematic representation of phosphate 4-pool kinetics. Based on a classical 2-pool kinetic model, additional phosphate flux (F_3) from a third pool occurs in the extracellular space. This occurs in proportion to the phosphate error (Σ) or the difference between the momentary intracellular phosphate concentration and an intrinsic intracellular phosphate target concentration. The magnitude of phosphate generation is dependent on a constant factor termed the gain. When a critically low intracellular phosphate limit is exceeded, an intracellular fourth pool becomes operational until a safe intracellular phosphate level has been re-established. Extracellular mass of solute (M_e), extracellular concentration of solute (C_e), extracellular volume (V_e), intracellular mass of solute (M_i), intracellular concentration of solute (C_i), intracellular volume (V_i), intercompartmental flux (F_1), diffusive flux across dialyzer membrane (F_d), convective flux across dialyzer membrane (F_c), dialyzer clearance (K_d), cell membrane mass transfer coefficient (K_{ie}). Adapted from Mandolfo et al.¹³

Factors affecting intradialytic phosphate elimination

Dialyzer membrane surface area

For any dialyzer membrane, phosphate clearance is generally lower than urea clearance, which is due to a higher diffusive resistance for phosphate in full blood. In contrast to urea, phosphate is not freely diffusible across cell membranes and thus, blood cells act as a diffusion barrier within the dialyzer. Dialyzer phosphate clearance increases with membrane surface area, both in HD and hemodiafiltration (HDF)¹³ (Figure 4). Membrane area is an important factor; if corrected for membrane surface area, there appears to be no difference in phosphate removal between low-flux and high-flux dialyzers.¹⁰ The average removal of phosphate by conventional 4-hr dialysis treatment amounts to 700 to 900 mg. In order to improve phosphate removal, it is recommended to optimize dialyzer membrane surface area.

Blood flow rate (Qb) and dialysate flow rate (Qd)

In general, dialyzer clearance for any substance depends on effective Qb. However, while increasing dialyzer Qb to >250 to 300 mL/min does increase urea Kt/V and potassium removal, this measure has only limited effects on phosphate removal (Figure 5A).¹⁴ In contrast, increasing Qd from 300 to 500 mL/min is associated with a 10% increase in the clearance of phosphate, as well as urea and creatinine (Figure 5B), but not for β_2 microglobulin.^{13,15} A further increase of Qd to 800 mL/min increases in vivo urea clearance and Kt/V by another 10%,¹⁶ however, no

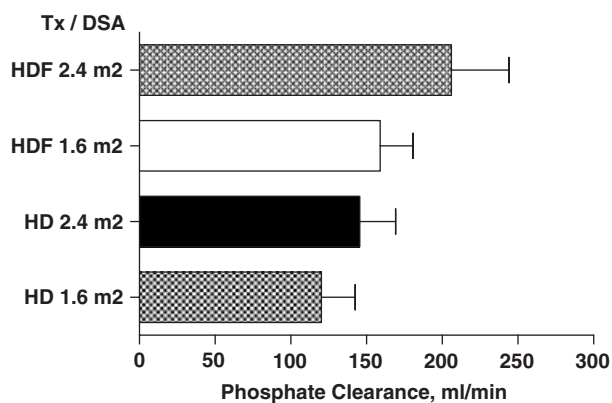


Figure 4 Effect of dialyzer membrane surface area (DSA) on dialyzer phosphate clearance in hemodialysis (HD) and hemodiafiltration (HDF).

clinical data exist for phosphate removal under these conditions.

Treatment time (t)

Treatment time is the most important factor influencing phosphate elimination. Extending dialysis time increases phosphate mass removal even when Kt/V is not changed. This was shown in a study on 9 HD patients by Vaithilingam et al.¹⁷ Weekly dialysis time was increased from 12 (3 × 4) to 15 (3 × 5) hr, while urea Kt/V was kept constant by reduction in Qb. Under these conditions, phosphate mass removal increased by 13% (Figure 5C). Data from the dialysis unit in Tassin also demonstrate that extended treatment times are associated with better phosphate control. The fact that blood phosphate levels reach a plateau during dialysis actually favors longer treatment times. While fractional urea mass removal during dialysis declines with increasing dialysis time due to a steady fall in blood urea concentration and a diminished concentration gradient across the dialyzer membrane, in contrast, due to the plateau reached in plasma iP levels after the first half of dialysis, the diffusion gradient for phosphate does not decline during the second half of dialysis, resulting in a sustained iP mass removal. It is therefore evident that phosphate removal benefits much more from extended treatment times than urea removal.

Hematocrit

The clearance of any substance among other factors also depends on the effective distribution volume within the blood stream. While for urea this is total blood water and for creatinine plasma water volume and 61% of erythrocyte volume, for phosphate it is plasma water volume alone. As plasma water volume depends on hematocrit and albumin levels, phosphate clearance declines with increasing hematocrit.¹⁵

Physical activity

It is established that physical activity before or during dialysis treatment increases urea Kt/V through improved perfusion of muscle, the main urea-containing body compartment. Similar effects have been described for phosphate removal with predialysis physical activity increasing phosphate removal by 6% and intradialytic activity even by 9% (Figure 5D).¹⁷

Hemodiafiltration

The addition of convective transport has been shown to enhance phosphate removal and in the long term reduce

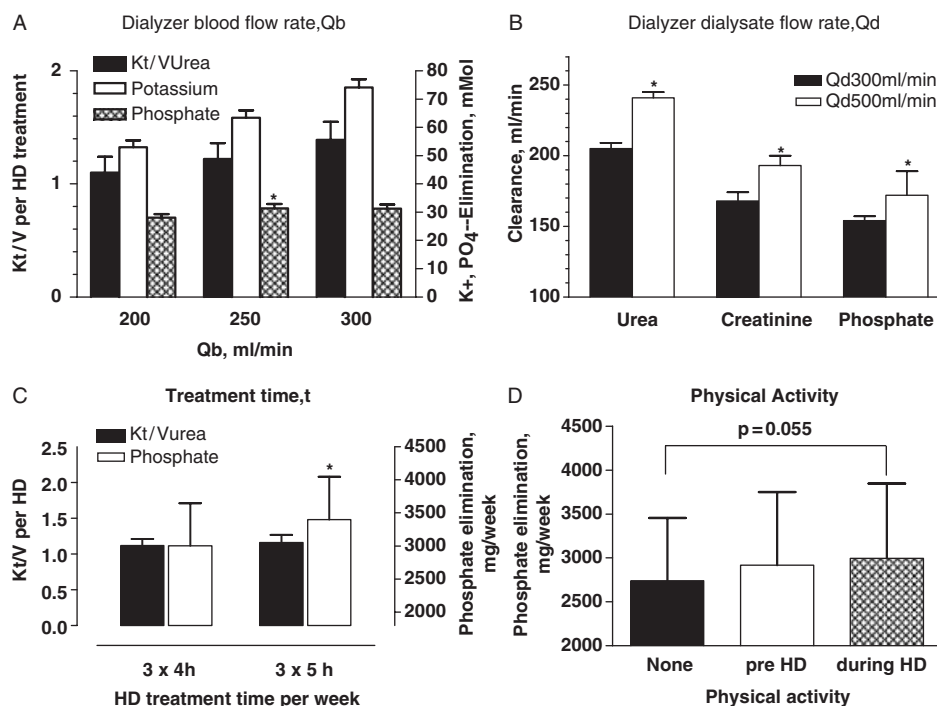


Figure 5 Effects of dialyzer blood flow rate Qb (A), dialysate flow rate Qd (B), treatment time (C), and physical activity before or during dialysis (D) on the elimination of phosphorus and some other compounds.

plasma iP concentrations. With HDF, the convective removal is increased. This proves highly effective for substances with middle and high molecular weight, while it is less important for low-molecular-weight substances. Several clinical studies demonstrated a positive effect of HDF on total phosphate removal. Minutolo et al., showed that post-dilution HDF resulted in an increase of phosphate clearance from 800 to 1170 mg/treatment.¹⁸ Similar data were reported by Zehender et al.,¹⁹ where phosphate clearance was increased by 32% to 41% during HDF compared with conventional low-flux dialysis and by Mandolfo et al.¹³ (Figure 4). Minutolo, in his study, reported a faster and steeper phosphate rebound observed after HDF. This may be explained by a stronger stimulation of phosphate mobilization by higher removal rates. Despite the higher phosphate rebound, predialysis serum phosphate levels steadily declined during the 6-month follow-up in Minutolo's study, indicating a reduction in total body phosphate burden.

Dialysis frequency

Increasing dialysis frequency from 3 to 5 or 6 times/week appears to be an attractive alternative treatment schedule that may be associated with an increased quality of life

and potentially better outcome and phosphate control.²⁰ Phosphate control will, under these conditions, depend on the effective duration of each HD session.

a) Daily nocturnal HD (DNHD). Several small studies report the effects of daily nocturnal HD on phosphate removal. Pierratos et al.,²¹ in a study comparing 3 × 4 vs. 6 × 8 hr HD, demonstrated a significantly improved phosphate elimination despite unchanged urea mass removal. Although urea Kt/V was not different in the 2 treatment groups, due to a limitation of Qds to 100 mL/min in the 6 × 8 hr group, phosphorus elimination was significantly higher in DNHD. In addition, prescription of PBs was completely stopped despite significantly increased dietary protein and phosphorus intake in the DNHD patients. It is evident that daily nocturnal HD with a conventional Qd of 300 to 500 mL/min would even further increase phosphate removal, which may then be well in excess of daily dietary phosphorus intake.²² In these cases, it may be necessary to add phosphorus to the dialysate in order to avoid phosphate depletion.

b) Short daily HD (SDHD). The concept of SDHD allows for more frequent dialysis at a shorter treatment duration. The ability to control phosphate levels without the use of

PBs, however, will depend on the duration of each HD session. With a regimen of 6×2 to 2.5 hr, about 400 to 500 g of phosphate are removed per session, which will be inadequate to balance daily phosphorus intake of about 1000 mg/day. In almost all studies on SDHD published so far, patients had to continue to take PBs.^{20,23} In order to achieve phosphate control without the use of PBs, a longer treatment duration, such as 6×3 hr may be necessary. However, it may be discussed whether the term SHORT daily HD is appropriate in this setting. In a recent study by Ayus et al.,²⁴ seventy-seven HD patients were treated with either conventional thrice-weekly dialysis (3×4 hr; N=51), or with short daily HD (6×3 hr; N=26). A significant decrease in serum phosphorus levels was seen in the SDHD group (6.3 ± 2.57 mg/dL at baseline, 4.61 ± 0.6 mg/dL at 6 months of treatment, and 4.0 ± 1.19 mg/dL at 12 months of dialysis treatment, $p < 0.004$) that was not seen in the patients on conventional HD. This reduction in serum phosphorus occurred despite the withdrawal of PBs in 73% of the SDHD group. The normalization of phosphate levels was accompanied by a significant reduction in PTH levels of 55% and 40% in the SDHD and conventional dialysis groups, respectively. Improved phosphate removal and a reduction in PB dosage have also been reported for short daily HDF (6×2 –2.5 hr).²⁵

Dietary phosphorus restriction

Emphasis on therapy was initially directed toward limitation of dietary phosphorus intake, which comes from 3 major sources, the natural phosphorus content, from phosphate-containing additives for preservation, and from phosphate-containing dietary supplements. It is usually assumed that dietary phosphorus intake is strictly related to protein intake, but it has been reported recently that phosphorus intake from additives may amount to 1000 mg/day.²⁶ These phosphorus additives are highly absorbable, with almost 100% being taken up into the circulation. Manufacturers are not required to list phosphorus content on the food label, thus making it even more difficult for patients to identify those high-phosphorus foods. The phosphorus content of beverages may vary substantially and a list containing phosphorus content of a large number of beverages available in the United States has been published electronically recently.²⁷

The average phosphorus concentration in protein is ~ 15 mg/g, with dairy proteins having a somewhat higher phosphorus concentration per gram protein. The recommended daily dietary protein intake for dialysis patients is 1.0 to 1.2 g/kg body weight,²⁸ which, in a 70 kg patient,

will result in an ingestion of about 1000 mg of phosphorus per day. Given a gastrointestinal absorption rate of 60% to 70%, the phosphorus burden will be 4200 to 4900 mg/week. Dietary phosphorus restriction will inevitably lead to a reduction in protein intake, thereby increasing the risk for development of malnutrition, which by itself increases the mortality risk of dialysis patients. Of course, excess phosphorus intake without the adequate dose of PBs needs to be avoided and this is an important issue for renal dieticians.

Assuming an average dietary phosphorus intake of 1000 mg/day with a gastrointestinal absorption rate of 60% and an average phosphate mass removal of 800 mg during one standard dialysis treatment with a classical $3 \times$ /week regimen, phosphate balance is positive with about 1800 mg/week. In order to achieve a neutral phosphate balance, roughly 250 mg of phosphorus from daily dietary intake remain to be bound by PBs (Table 1). It has to be pointed out that a neutral phosphorus balance can generally be achieved by the use of PBs, as has been demonstrated in the Treat-To-Goal-Study²⁹ and other studies. However, on average, 10 PB pills and in many cases even higher doses were necessary to achieve phosphate targets. Still, there is considerable room for improvement in dietary phosphate management.

Phosphate binders tend to be prescribed in fixed doses, such as 2-2-2, without taking into account potential day-to-day and meal-to-meal variations in dietary phosphorus intake. It may be assumed that inadequate dosing of PBs, together with incompliance, is a major common barrier to neutral phosphorus balance in HD patients. To overcome these barriers, the author has recently developed a new concept (Phosphate Education Program [PEP]) to enable patients to self-adjust PB dose to the phosphorus content of each individual meal. This can only be achieved when assessment of meal phosphorus content is quick and simple without involving multi-page food tables, booklets, or even computers. The innovative concept is based on the introduction of the phosphorus unit (PU) to indicate food

Table 1 Phosphorus balance in HD patients

Recommended dietary intake	1000 mg/day \times 7 = 7000 mg/week
Assumed gastrointestinal absorption (60%)	7000 mg/week \times 0.6 = 4200 mg/week
Average elimination by hemodialysis (HD)	800 mg/HD \times 3 = 2400 mg/week
Phosphorus balance =	1800 mg/week
Phosphorus mass to be bound by phosphate binders	1800 mg: 7 days = 250 mg/day

phosphorus content, with 1 PU assigned per 100 mg of phosphorus per serving size. As different food components of a similar food group have similar phosphorus content, this new concept allows to assign PU values to food groups (meat, fish, cheese, vegetables, diaries, etc.) instead of individual food components, e.g., any fish filet (serving size: 150 g)=4 PU, any meat (serving size: 150 g)=3 PU. The new concept bears the advantage that patients do not have to memorize the phosphorus content of each individual food component, but only the PU value for a limited number of food groups. After eye-estimating meal PU content, patients self-adjust the PB dose according to a PB/PU ratio as prescribed by the physician. After introduction of the PEP concept to the patient, the PB/PU ratio is titrated to the patient's individual needs by repeatedly measuring predialysis serum phosphate levels and re-adjusting the PB/PU ratio until phosphate targets have been achieved. (The phosphate education program (PEP) is the first concept applying the idea of patient empowerment to the management of hyperphosphatemia in dialysis patients. Currently, PEP (www.pep-ernaehrungsprogramm.de) is available in Germany, Austria, and Switzerland, and in the near future also in Eastern European countries.

Phosphate binders

For many years, calcium carbonate was the phosphate binder of choice. The 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, that offers an improved binding efficiency. Recent literature, however, is packed with reports on the ill effects of calcium-based binders, including increased rate of hypercalcemic events, and risk of increased Ca × P product leading to vascular and extravascular calcifications and increased mortality rates.^{6,30} Aluminum and magnesium salts are available as non-calcium-based PBs, but these compounds are only used sporadically and even then only for short periods due 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 was demonstrated with the use of this PB.^{30–32} A beneficial further effect of sevelamer is its effects in reducing low-density lipoprotein cholesterol levels.^{33,34} Another non-calcium-based PB, lanthanum chloride, has been investigated recently.³⁵ The effect on phosphate levels appears to be similar to those of sevelamer and no adverse effects on bone have been reported over a 2-year period. Other polymers, sold initially

as bile acid sequestrants, are also being studied as iP binders, as is iron oxide, which may also be useful. A detailed discussion of the use of PBs in dialysis patients, which is beyond the scope of this article, can be found in a recent excellent reviews by Nolan and Qunibie³⁶ and Bellasi et al.³⁷

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