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Phosphate removal and hemodialysis conditions

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Phosphate removal and hemodialysis conditions. Hyperphosphatemia is frequently found in hemodialysis patients, and the association with an increased risk of mortality has been demonstrated. Other authors have linked hyperphosphatemia to increased cardiovascular mortality. The normalization of phosphate plasma levels is therefore an important goal in the treatment of end-stage renal disease patients. Absorption of phosphate from the food exceeds the elimination through a hemodialysis treatment, and this leads to a chronic phosphate load for the majority of hemodialysis patients. This imbalance should be improved by either a reduction of phosphate absorption or an increased removal of phosphate. A reduction of phosphate absorption can be achieved by reducing the amount of phosphate in the diet or by the administration of phosphate binders. Unfortunately, these measures imply practical difficulties, for example, a lack of patient compliance or other side effects. When considering modifications of the hemodialysis treatment, an essential understanding of the kinetics of dialytic phosphate removal is mandatory. Phosphate is unevenly distributed in different compartments of the body. Only a very small amount of phosphate is present in the easily accessible plasma compartment. The major part of phosphate removed during hemodialysis originates from the cytoplasm of cells. A transfer from intracellular space to the plasma and further from the plasma to the dialysate is necessary. However, if we consider improvement to phosphate removal by dialysis procedures, full dialyzer clearance is effective in only the initial phase of the dialysis treatment. After this initial phase, the transfer rate for phosphate from the intracellular space to the plasma becomes the rate-limiting step for phosphate transport. Attempts to improve this transfer rate have recently been investigated by acidosis correction, but turned out not to be consistently successful. Furthermore, modifications of the treatment schedule have been described in the literature as measures to influence the phosphate balance consistently. Successful improvements of the phosphate balance can be achieved specifically through increasing the frequency of the dialysis treatments.

For patients with end-stage renal disease (ESRD), hemodialysis is the most widely used and established treatment. During hemodialysis, the functions of the natural kidney are partly taken over, specifically the removal of uremic toxins. Removal of uremic toxins depends on both treatment conditions (for example, dialyzer type, treatment time, or frequency) and patient characteristics (for example, distribution volumes, diet, age, and comorbidities). If a specific uremic toxin is unevenly distributed in blood, interstitium and intracellular space transport kinetics between these compartments determine, together with the transport kinetics across the dialyzer membrane, the overall transport kinetics during the hemodialysis treatment.

Phosphate is one of the most widely accepted uremic toxins, and hyperphosphatemia is frequently found in hemodialysis patients, where an increased risk of mortality has been clearly attributed to elevated phosphate levels [1]. Furthermore, plasma concentrations of calcium, phosphate, and parathyroid hormone are closely related through physiological regulatory systems, with the kidney playing an important part. During the progression of chronic renal failure, these regulatory systems are disturbed, one common consequence being the development of secondary hyperparathyroidism [2]. Hyperphosphatemia is also linked to an increased cardiovascular mortality [3, 4].

The normalization of the phosphate plasma levels is therefore considered to be an important goal in the treatment of ESRD patients.

PHOSPHATE BALANCE IN HEMODIALYSIS PATIENTS

Phosphate balance is disturbed in the majority of hemodialysis patients whereby the absorption of phosphate from the diet exceeds the elimination through hemodialysis treatment. The phosphate balance of a typical patient can be estimated according to Mucsi and Hercz as follows [5]:

The daily nutritional phosphate intake is within the range of 18 and 36 mmol. Assuming an intestinal resorption between 40 and 80%, the effective daily intake varies from 10 to 30 mmol, which is equivalent to a weekly intake between 100 and 210 mmol. The PO_4 removal during dialysis for a patient without residual renal function is between 20 and 40 mmol per hemodialysis session. This is equivalent to a weekly removal between 60 and 120 mmol of PO_4. Thus, standard hemodialysis patients have a positive phosphate balance.

Key words: dialysis frequency, hyperphosphatemia, cardiovascular mortality, end-stage renal disease, uremic toxins.

Table 1. Reduction of phosphate concentration in end-stage renal disease patients: Possibilities and limitiations

Action	Limit
Reduction of phosphate content of the ingested food	Food with the necessary protein content typically also contains phosphate
Phosphate binder to limit the intestinal absorption of phosphate	Side-effects Aluminum intoxication (aluminum salts) Hypercalcemia (calcium salts) Gastrointestinal problems
More efficient dialysis due to higher clearance for phosphate	Phosphate removal limited after an initial phase of ~1 hour due to limited transport from intra- to extracellular space
Prolongation of treatment time	Organizational problems and/or patient preferral for short treatment time
Increased frequency of dialysis treatments	Higher cost of treatment

This positive phosphate balance is further confirmed by the analysis of two special studies published by the United States Renal Data System (USRDS): Case Mix Adequacy Study in 1990 (CMAS, $N = 3738$) and the Dialysis Morbidity and Mortality Study, Wave 1 in 1993 (DMMS; $N = 2669$) [1].

The median levels of PO_4 concentration in both studies are virtually identical: CMAS, 6.2 mg/dL, and DMMS, 6.3 mg/dL, which is also true for the distributions of phosphate among the investigated patients. The extent of the elevation of the phosphate concentrations is impressive, when we realize that the normal range for phosphate is between 2.6 and 4.5 mg/dL. The USRDS further investigated over a period of two years whether there is a link between the risk of mortality and either the PO_4 concentration, the Ca^{2+} concentration, or the ion product of phosphate and calcium.

Patients were grouped into quintiles for each of the three parameters, and the relative risk was assessed for those quintiles as reference, which were closest to the normal range. With regard to phosphate, the two quintiles with the highest PO_4 concentration showed an increased relative risk of mortality, whereas no statically significant difference was found for the other three quintiles. Thus, an elevated phosphate concentration is associated with an increased risk of mortality. An analogous analysis of the effect of calcium concentration did not show any significant effect. The results for the ion product of calcium and phosphate were similar compared with the results for phosphate.

THERAPEUTIC REDUCTION OF PLASMA PHOSPHATE

Some possibilities to reduce the phosphate concentration in ESRD patients are listed in Table 1, together with limits in their practical application. These therapeutic approaches can be separated into two groups: reducing the PO_4 absorption or improving PO_4 removal by hemodialysis.

One chance to reduce phosphate absorption is, of course, through reduced PO_4 intake. This approach is difficult to achieve because protein-rich diets typically contain increased levels of PO_4. Practically, absorption of ingested phosphate is approached by the use of phosphate binders, which unfortunately show the known adverse effects. For this reason, calcium-based phosphate binders (calcium acetate, calcium carbonate) currently have replaced aluminum-based phosphate binders.

Table 2. Distribution of phosphate in the human body

	Phosphate *mmol*	Total %
Bone	19000	85.00
Soft tissues	3200	14.00
Teeth	100	0.50
Interstitial fluid	10	0.05
Plasma	3.5	0.02
Erythrocytes	6.5	0.03

Data are from the *Oxford Textbook of Clinical Nephrology* [6]. Used with permission.

IMPROVED PHOSPHATE REMOVAL WITH HEMODIALYSIS

The second approach focuses on an increased removal of phosphate through hemodialysis by increasing the removal of absolute PO_4 mass. For a better understanding of this procedure, phosphate kinetics during dialysis have to be considered in more detail.

Phosphate is preferentially found intracellularly. Only a small percentage is distributed in the extracellular space. The distribution of phosphate in the body compartments is given in Table 2 [6]. It clearly shows that only 3.5 mmol of plasmatic phosphate are directly available for dialytic removal.

Comparing the quantity of PO_4 in plasma with that quantity, which is standardly removed during hemodialysis (20 to 40 mmol PO_4 per session), shows that PO_4 pools other than plasma must contribute to the overall PO_4 to be removed during dialysis. Part of this phosphate may originate from the interstitial fluid compartment, which contains about 10 mmol of phosphate. However, we consider the greatest contribution to come from the intracellular space.

Prior to dialysis treatment, phosphate concentrations

are unevenly distributed between the intracellular and extracellular space: The intracellular phosphate concentration is approximately 50 times higher than its extracellular counterpart [7], which indicates a rather high impermeability of the cell membrane for PO_4.

Although there is no change of the concentrations over time, phosphate is exchanged between these two compartments at a certain rate. When dialysis is started, the plasma concentration of phosphate is reduced rapidly during the first phase of the hemodialysis treatment, typically lasting 60 to 90 minutes [8]. After this initial phase, the plasma phosphate concentration is lower, reducing the diffusion gradient over the dialyzer membrane and thus the amount of phosphate removed per time unit via the dialyzer for the rest of the dialysis treatment. Phosphate has to be transferred from the intracellular space to the extracellular space and then via the dialyzer out of the patient.

The rate-limiting step in this phase is the transfer from the intracellular space to the extracellular space and not the phosphate clearance of the dialyzer. After the dialysis treatment is completed, the transport within the patient is continuing, leading to a new balanced situation. This is the large rebound of the phosphate concentration seen after dialysis. The time for completion of the rebound is certainly longer than 30 minutes [9] and can be estimated to be some hours.

In consequence, phosphate removal must not be considered to follow simple one-compartment kinetics. The model must at least consist of an extracellular compartment and an intracellular compartment.

With these kinetics in mind, we must search for possibilities of how to increase PO_4 removal during dialysis. In theory, three methods may be useful: (*1*) increasing PO_4 clearance by higher blood flows or by using a dialysis membrane with a higher PO_4 permeability; (*2*) increasing PO_4 transport between the intracellular and extracellular space through, for example, correction of acidosis (discussed later in this article); and (*3*) increasing PO_4 removal by prolongation and/or increased frequency of hemodialysis treatments.

INCREASED CLEARANCE

The influence of dialyzer clearance on PO_4 removal has been investigated by Chauveau et al for five high-flux [10] and by Kerr et al for six low-flux dialyzers [11].

Chauveau et al showed that differences in dialyzer phosphate clearance do not lead to differences in phosphate removal [10]. The dialyzer phosphate clearances under in vitro conditions (manufacturer's data sheet) varied from 130 to 166 mL/min (blood flow 200 mL/min, dialysate flow 500 mL/min). In vivo investigations were performed under standardized conditions, including a crossover design, blood flow 300 mL/min, and dialysate flow 500 mL/min. In vivo clearances were calculated from the total removed amount of phosphate (dialysate collection) and the pretreatment and post-treatment plasma phosphate concentrations, making the simplified assumption of a linear decreasing phosphate plasma concentration during the treatment. The in vivo clearances ranged from 80.9 to 104.5 mL/min, showing statistically significant differences between the dialyzers. The total amount of phosphate removed per treatment was in the narrow range between 29.4 and 32.9 mmol, with no statistically significant differences between the dialyzers.

Kerr et al investigated six different types of low-flux dialyzers [11], looking at three different parameters for phosphate kinetics: the phosphate reduction ratio in the midweek dialysis, the instantaneous clearance after one hour of treatment in the midweek session, and the weekly phosphate removal. Although Kerr et al found some statistically significant differences between the dialyzers, these were inconsistent and lead the authors to the conclusion that "*no one membrane appeared consistently better at clearing phosphate, and... this criterion is unable to separate the membranes*" [11].

DELAYED CORRECTION OF ACIDOSIS

It has been discussed that a slow correction of metabolic acidosis during hemodialysis treatment may lead to an increased phosphate removal. This is assumed to be due to enhanced transport of phosphate from the intracellular space to the extracellular space. There is still controversy as to whether this holds true for all patients [8, 12]. However, it has been shown that a good correction of acid-base balance reduces hyperparathyroidism and, consequently, improves the patients status [13, 14] (abstract; Movilli et al, *Nephrol Dial Transplant* 14:A37, 1999).

DURATION AND FREQUENCY OF HEMODIALYSIS TREATMENT

Treatment time in hemodialysis has proved to be an important determinant of dialysis dose whereby a prolongation of dialysis treatment time enhances removal of uremic toxins. Knowing the kinetics of phosphate, an increased treatment time does not contribute proportionally to increased phosphate removal. This is the consequence of the high PO_4 removal rate in the first hour of treatment and the reduced removal rates at later stages.

An increase of hemodialysis frequency above the mostly used thrice weekly schedule has been suggested as early as in 1972 [16]. The higher frequency avoids large fluctuations of solute concentrations and comes close to the physiological situation with continuously working kidneys.

The effect of from three times per week to six or seven

times per week increased frequency of hemodialysis has been investigated by several groups [17–19]. As a result, an easier control of phosphate concentration was found. The phosphate binder dosage in these cases was reduced or even discontinued.

A Canadian group used nocturnal home hemodialysis, treating the patients 8 to 10 hours for six to seven times per week and compared this treatment schedule to a conventional four-hour, three times weekly treatment. In addition, the dialyzer surface area had been reduced to 0.7 m^2 compared with the former 1.8 m^2. The dialysate flow rate was reduced to 100 mL/min compared with 500 mL/min. Dialysate sodium was increased from 135 to 140 mmol/mL, and dialysate bicarbonate was decreased from 35 to 30 mmol/mL. These changes were made in order to limit the small molecular weight clearance and to avoid a possible deficiency of important nutrients, like amino acids. As no problems were observed, in a more recent study from the same group, some of these preventive measures were no longer consequently applied, with the dialyzer surface area ranging in the later study from 1.1 to 1.8 m^2 and dialysate flow rate typically from 200 to 300 mL/min and in individual patients up to 800 mL/min [20]. This described treatment change led to an improved phosphate metabolism. Over the prolonged treatment period, removal of phosphate was gentle, and a rebound after dialysis was avoided. For a single treatment, the quantity of PO_4 removed was similar for the two compared treatment modes. Because of the increased frequency, the weekly removal of phosphate was more than doubled. In consequence of this increased removal, plasma phosphate concentrations were reduced ($P < 0.05$ after 1 month and $P < 0.001$ after 5 months), and phosphate binders could be discontinued in all patients. The phosphate content of the diet was increased in parallel [17].

A French group also increased the frequency of dialysis but kept the weekly treatment time constant. This lead to an increased Kt/V_{urea}, a stop of antihypertensive drugs, an improved nutrition, a reduced need of EPO and an easier control of phosphate balance [18].

One Dutch group increased the frequency of dialysis and shortened the individual treatments in a manner that kept the weekly Kt/V_{urea} constant [19]. This modification of the dialysis treatment schedule proved to be still advantageous. A major effect was the better hemodynamic control because fluctuations of the fluid status were reduced. Changes in the metabolic status were only minor in this study, but the authors reported a reduction of serum phosphate levels and reduced dosage of PO_4 binders.

Combining the outcome of these three experiences, one can assume that an increased frequency of dialysis is the most effective measure in improving dialytic phosphate removal in hemodialysis patients. This effect is only partly explained by the increased weekly dose of dialysis (Kt/V_{urea}); increased treatment frequency itself contributes to better PO_4 control.

CONCLUSION

Hyperphosphatemia is a severe problem for ESRD patients. When restricted to the conventional dialysis schedule of three times for four to five hours per week, measures to improve this situation are: reducing the ingested amount of phosphate with an adequate diet, reducing the absorption of phosphate with phosphate binders, and providing as much dialysis treatment as possible. A more frequent dialysis schedule will result in a better control of hyperphosphatemia.

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