Phosphate Removal With Several Thrice-Weekly Dialysis Methods in Overweight Hemodialysis Patients

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Background: Currently available phosphate binders are associated with either hypercalcemia or high costs, which limit their use in hemodialysis patients. Whether modifying dialysis prescription to intensify small-solute clearance also leads to better phosphate clearance is unknown.

Study Design: Randomized crossover trial.

Participants: Large patients (>80 kg; N = 18) who could not achieve adequate Kt/V during a standard 4-hour thrice-weekly prescription of maintenance hemodialysis.

Intervention: 2 high-flux dialyzers in parallel for 4 hours in comparison to 3 other dialysis modalities (4 hours of standard hemodialysis, 4.5 hours of hemodialysis, and 4 hours of hemodialysis with increased dialysate flow).

Outcomes: (1) Predialysis serum phosphate level, (2) postdialysis phosphate level, (3) phosphate clearance, and (4) phosphate removal, all assessed during the last midweek session for each of the 4 different modalities.

Results: Mean baseline predialysis serum phosphate level was 5.95 ± 1.95 mg/dL. Using 2 dialyzers in parallel was associated with a significant decrease in predialysis serum phosphate level compared with standard hemodialysis (1.33 mg/dL lower; $P = 0.01$). Mean serum postdialysis serum phosphate levels during the last treatment of the double-dialyzer period were also lower by 0.43 and 0.74 mg/dL than during the last treatment of the standard-hemodialysis ($P = 0.05$) and increased-dialysate-flow ($P < 0.001$) periods, respectively. The double-dialyzer strategy also was associated with greater phosphate clearance (113.4 mL/min; 95% confidence interval [CI], 101.4 to 125.3) than the other 3 strategies (83.9 mL/min; 95% CI, 71.6 to 96.2; 86.6 mL/min; 95% CI, 73.8 to 99.3; and 83.0 mL/min; 95% CI, 71.1 to 94.9), but not greater phosphate removal.

Limitations: Small sample size, short study duration, and results of phosphate removal analysis inconclusive.

Conclusion: Use of 2 dialyzers in parallel for 6 weeks in overweight hemodialysis patients led to substantially lower predialysis phosphate levels. Future studies should explore the potential contribution of increased dialyzer surface area to better control of serum phosphate levels in maintenance hemodialysis patients.

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INDEX WORDS: Hemodialysis; phosphate; obesity; kinetic studies; randomized trial.

Greater serum phosphate levels are independently associated with increased risk of death in hemodialysis patients.[1,2] Although it is unknown whether better control of hyperphosphatemia would improve clinical outcomes, current practice guidelines recommend tight control of serum phosphate levels.[3]

Calcium-based phosphate binders traditionally have been the cornerstone of treatment for hyperphosphatemia. However, recent data support an association between vascular calcification and accelerated cardiovascular disease in patients with end-stage renal disease,[1,4-14] and observational data suggest that greater doses of calcium-based phosphate binders may contribute to vascular calcification.[15] Therefore, there has been considerable interest in controlling serum phosphate levels while minimizing oral calcium load. Although most attention has focused on the use of such non–calcium-containing phosphate binders as sevelamer and lanthanum,[16] modifying conventional dialysis regimens to improve phosphate clearance is an alternative approach that is relatively unstudied.

We used data from a previously conducted randomized trial[17] to test the hypothesis that more intensive hemodialysis would improve phosphate clearance and decrease serum phosphate concentrations in large hemodialysis patients. Three methods of intensifying a thrice-weekly hemodialysis regimen were considered: greater dialysate flow,[18,19] extended dialysis duration, and use of 2 dialyzers in parallel,[20,21] all compared with standard thrice-weekly hemodialysis.

METHODS

Patients

We performed a randomized crossover study in 6 university-affiliated dialysis units. The protocol was approved by the health ethics review board at each institution. Inclusion criteria were as follows: patients on a stable regimen of hemodialysis for 3 months or longer, dry weight of 80 kg or greater, Kt/V of 1.2 or less on 2 occasions in the previous 6 months or requirement for longer than 12 hours of hemodialysis weekly because of a history of inadequate dialysis, and blood flow rate of 350 mL/min or greater through a well-functioning access. Patients were excluded if they had renal transplantation scheduled in the next 6 months, had a contraindication to intradialytic anticoagulation, required more than 4.5 hours of hemodialysis 3 times weekly for the purpose of volume removal because of excessive interdialytic weight gains or intradialytic hypotension/cramping, and failure to provide informed consent. All patients who met inclusion/exclusion criteria and were not already receiving a hemodialysis regimen consisting of 4 hours thrice weekly were switched to this modality for 4 weeks before entry into the active treatment part of the study.

Study Design

Each participant received 4 different hemodialysis regimens in a randomized crossover fashion, each lasting 6 weeks (Fig 1). To permit blinding of patients to dialysis treatment modality, all dialysis sessions were 4.5 hours; for the 3 strategies that included active dialysis for only 4 hours, dialysate flow was stopped and no dialysis occurred for the last 30 minutes of the run. The standard hemodialysis prescription consisted of 4 hours of hemodialysis 3 times weekly. Hemodialysis was undertaken by using the same high-flux high-efficiency polysulfone dialyzer during the entire study period. The F80A (Fresenius Inc, Walnut Creek, CA; in vivo mass transfer area coefficient for urea, 945 mL/min) and Optiflux F160 dialyzers (Fresenius Inc; in vivo mass transfer area coefficient for urea, 1,063 mL/min) were used by 13 and 5 patients during the study, respectively. Prescribed blood flow was 350 to 400 mL/min, and dialysate flow was 500 mL/min. During increased-dialysate-flow treatment, patients received standard dialysis for 4 hours 3 times weekly, but dialysate flow rate was 800 mL/min rather than 500 mL/min. The third modality was increased dialysis duration at 4.5 hours 3 times weekly using dialysate flow of 500 mL/min. Last, in the final dialysis modality consisting
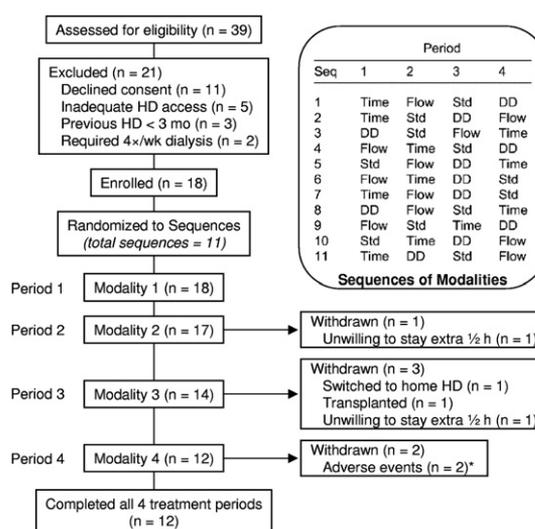
Figure 1. Trial flow. Each sequence denotes the period (1, 2, 3, and 4) in which the modalities (Time [4.5-hour dialysis], Std [4-hour dialysis + 0.5-hour ultrafiltration], Flow [4-hour dialysis at increased dialysate flow], and DD [4-hour dialysis using double dialyzer]) were administered. Each modality occurred once per sequence. Abbreviation: HD, hemodialysis. *One adverse event was treatment related.

of 2 dialyzers in parallel, patients received hemodialysis for 4 hours 3 times weekly with dialysate flow of 800 mL/min and 2 dialyzers connected by a Y-connector in a parallel configuration, which is expected to split blood flow equally between the dialyzers.[21]

During all study dialysis sessions, dialysis machines were sequestered behind a curtain in an attempt to blind patients to the dialysis strategy they were receiving.

Study Measures

The primary outcome of the original study was health-related quality of life. The present study reports a prespecified secondary analysis that assessed the impact of the different dialytic strategies on the following indices of serum phosphate control and phosphate removal: (1) predialysis serum phosphate level (primary outcome), (2) postdialysis phosphate level, (3) phosphate clearance ([total dialysate volume × dialysate phosphate concentration]/[time × mean serum phosphate concentration]),[22] and (4) phosphate removal (using fractional dialysate collection).[23] We assessed each outcome during the last midweek session for each of the 4 different modalities. Therefore, for each participant, there were 4 measures of each outcome (1 for each of the 4 modalities). All measurements were performed on midweek dialysis sessions. Predialysis and postdialysis serum phosphate samples were drawn from the arterial needle. Postdialysis blood samples were drawn 2 minutes after decreasing the pump speed to 50 mL/min (ie, at 4 hours for 3 of the strategies and at 4.5 hours for the increased-dialysis-time strategy). Serum phosphate measurements were obtained from 2 central laboratories.

Statistical Analysis

Sample size calculations were based on the primary study outcome, which required 18 patients to show a clinically relevant improvement in quality of life. Baseline characteristics are presented as mean ± SD (or median and first and third quartiles, when appropriate) for continuous variables and proportion for dichotomous variables. To determine the association between dialysis treatment regimens and serum phosphate/phosphate clearance/phosphate removal, we used a linear mixed-effects model that takes into account the correlation of data caused by repeated measurements for each participant given the crossover design of the study.[24,25] This analysis is robust to missing data, provides an assessment of within-participant treatment comparisons (to determine the effect of the treatment), and also permits assessment of between-participant sequence comparisons (to determine the influence of the order of the treatments) and participant-by-sequence effects (to assess for potential carryover effects).

The assumption that response variables were normally distributed was tested and met. Initially, treatment, treatment period, and treatment sequence were modeled as fixed effects with participants modeled as random effects. Least-squares means with SEs were computed for each treatment, adjusting for other effects in the model. There was no evidence of period or carryover effects; therefore, the primary analysis did not include terms for treatment period or treatment sequence. All analyses adjusted for predialysis serum phosphate level obtained during the previous treatment period ("rolling baseline" serum phosphate level) as a fixed effect. All analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline characteristics of the 18 study participants are listed in Table 1, with trial flow in Fig 1. Mean baseline predialysis serum phosphate level for patients receiving 4 hours of hemodialysis 3 times weekly before enrollment was 5.95 ± 1.95 mg/dL. Mean prestudy serum calcium level was 9.06 ± 0.91 mg/dL, and mean prestudy calcium-phosphate product was 53.92 ± 19.21 mg²/dL².

As previously reported,[17] both increased dialysis duration (1.41; 95% confidence interval [CI], 1.32 to 1.50) and using 2 dialyzers in parallel (1.41; 95% CI, 1.33 to 1.49) led to significantly greater Kt/V than standard dialysis (1.27; 95% CI, 1.19 to 1.35). Mean Kt/V delivered in treatments with increased dialysate flow (1.31; 95% CI, 1.22 to 1.39) was similar to that for standard dialysis.

Using 2 dialyzers in parallel was associated with a significant decrease in predialysis serum phosphate level compared with standard hemodialysis (Fig 2). Mean predialysis serum phosphate

Table 1. Participant Characteristics

Characteristic	N = 18
Age (y)	58 (44, 66)
Men	17 (94.4)
White	13 (72.2)
Body mass index (kg/m²)	32.0 (30.1, 36.1)
Time on dialysis therapy (mo)	21.5 (16.0, 30.0)
Baseline Kt/V for patients while receiving 4-h dialysis*	1.23 ± 0.10
Baseline predialysis serum phosphate for patients receiving 4-h dialysis (mg/dL)	5.95 ± 1.95
Cause of end-stage renal disease	
Diabetes	11 (61.1)
Glomerulonephritis	4 (22.2)
Polycystic kidney disease	1 (5.6)
Other	2 (11.2)
Charlson comorbidity score	4 (3, 7)
Diabetes mellitus	14 (77.8)
Coronary artery disease	8 (44.4)
Congestive heart failure	5 (27.8)
Cerebral vascular disease	3 (16.7)
Peripheral vascular disease	4 (22.2)

Note: Results presented as median (first, third quartiles), number (percent), or mean ± SD. Conversion factor for serum phosphate in mg/dL to mmol/L, ×0.3229.
*n = 13.

level while using 2 dialyzers in parallel was 1.34 mg/dL less than with standard hemodialysis (P = 0.01; Table 2).

Mean serum postdialysis serum phosphate level measured while using 2 dialyzers in parallel was also lower by 0.43 and 0.74 mg/dL than with the standard-hemodialysis (P = 0.05) and increased-dialysate-flow (P < 0.001) strategies, respectively. Longer dialysis time of 4.5 hours also significantly reduced postdialysis serum phosphate level by 0.45 mg/dL compared with the increased-dialysate-flow modality (P = 0.04).

Using 2 dialyzers in parallel also was associated with greater phosphate clearance than the other 3 strategies (Fig 3; Table 3). However, total phosphate removal was not significantly different between treatments (all P ≥ 0.5). Similarly, heparin dose was not significantly different among the 4 dialytic regimens (all P ≥ 0.6).

Results were similar in sensitivity analyses that adjusted for prerandomization predialysis serum phosphate level rather than the rolling baseline measure of predialysis serum (data not shown).

Figure 2. Effect of dialysis modality (Time [4.5-hour dialysis], Std [4-hour dialysis + 0.5-hour ultrafiltration], Flow [4-hour dialysis at increased dialysate flow], and DD [4-hour dialysis using double dialyzer]) on predialysis and postdialysis serum phosphate levels. Values expressed as mean ± SE. All comparisons are adjusted for rolling baseline serum phosphate level. Conversion factor for serum phosphate in mg/dL to mmol/L, ×0.3229.
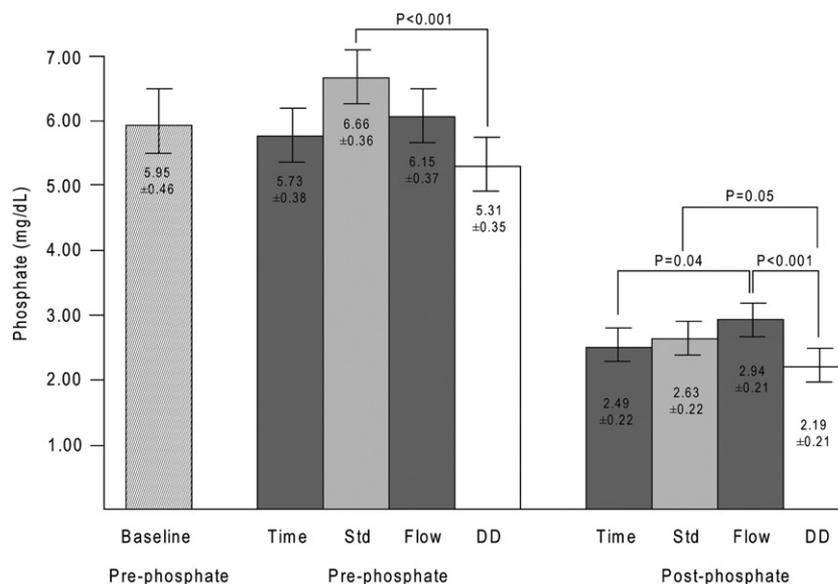
DISCUSSION

Multiple recent publications and practice guidelines promote the need to achieve better control of serum phosphate and calcium-phosphate product levels in hemodialysis patients.[3-5,9-14] Although it remains to be confirmed that achieving tighter control of either serum phosphate or calcium-phosphate product levels will improve patient outcomes,[26] considerable time and money currently are spent in pursuit of this goal.[27] Contemporary approaches to decreasing serum phosphate levels center on the choice and dose of oral phosphate binders, and minimizing intake of calcium-based agents has become an important secondary objective for clinicians. Although it appears that substantially increasing dialysis time (as in frequent nocturnal hemodialysis) allows markedly better control of serum phosphate levels,[28-30] this modality is not an option for the majority of hemodialysis patients, and few

data address the potential benefits of modifying conventional hemodialysis to achieve this objective.

We found that use of 2 dialyzers in parallel for a 6-week period led to better phosphate control in large hemodialysis patients, reflected by a 1.34-mg/dL decrease in predialysis serum phosphate level compared with conventional hemodialysis. In contrast, increasing dialysate flow or prolonging dialysis treatment from 4 to 4.5 hours did not lead to significantly better phosphate clearance or control.

The relative lack of interest in enhancing phosphate clearance during conventional hemodialysis probably occurs because most phosphate is intracellular and thus perceived to be unavailable for removal by hemodialysis. Although many nephrologists assume that intradialytic serum phosphate concentrations parallel those of urea, it appears that phosphate kinetics are consider-

Table 2. Serum Phosphate Level by Dialytic Regimen

Characteristic	Predialysis Serum Phosphate (mg/dL)	Postdialysis Serum Phosphate (mg/dL)
Baseline (prerandomization)	5.95 (4.98-6.92)	
Standard hemodialysis	6.66 (5.94-7.38)	2.63 (2.19-3.07)
Increased dialysis time	5.73 (4.96-6.50)	2.49 (2.04-2.93)
Increased dialysate flow	6.14 (5.40-6.89)	2.94 (2.51-3.37)
2 Dialyzers in parallel	5.31 (4.61-6.01)	2.20 (1.78-2.61)

Note: N = 18. Values expressed as mean (95% confidence interval). Adjusted for rolling baseline serum phosphate level. Serum phosphate expressed in mg/dL; conversion factor for mmol/L, ×0.3229.
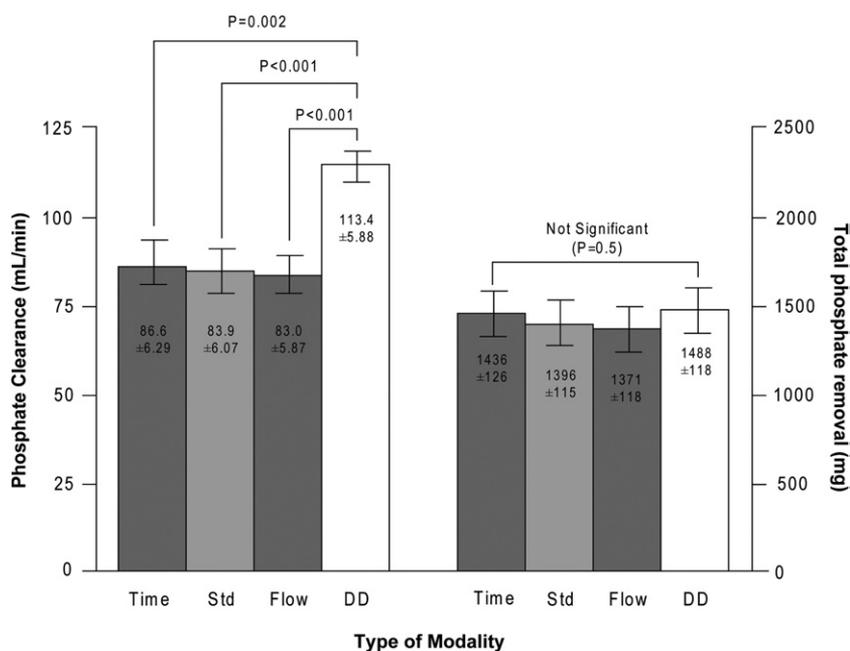
Figure 3. Effect of dialysis modality (Time [4.5-hour dialysis], Std [4-hour dialysis + 0.5-hour ultrafiltration], Flow [4-hour dialysis at increased dialysate flow], and DD [4-hour dialysis using double dialyzer]) on phosphate clearance and phosphate removal. Values expressed as mean ± SE. All comparisons are adjusted for rolling baseline serum phosphate level. Conversion factor for serum phosphate in mg/dL to mmol/L, ×0.3229.

ably more complex.[31] Serum phosphate levels decrease sharply during the first 60 to 120 minutes of dialysis and remain relatively constant thereafter, apparently independent of dialyzer blood flow and type of dialyzer membrane.[32-34] Mathematical modeling suggests that the constant blood levels during the latter part of dialysis are most consistent with mobilization of phosphate from an extracellular compartment that does not equilibrate freely with serum.[31] Factors governing the release of phosphate from this third compartment are unknown, but it may be triggered by a decrease in serum phosphate level to less than 1.1 to 1.2 mmol/L (<3.4 to 3.7 mg/dL).[35] A fourth compartment also may exist, serving to defend against critically low intracellular phosphate concentrations by releasing phosphate into the intracellular space from an unknown reservoir.[35] This putative compartment may reduce the amount of phosphate available for removal by hemodialysis by altering the ratio of intracellular to extracellular phosphate, although this is speculative.

Taken together, these theoretical considerations suggest that: (1) the rate-limiting step for intradialytic phosphate removal is equilibration between the intracellular and extracellular space, (2) factors that enhance dialytic clearance of urea will not necessarily lead to greater phosphate clearance, and (3) factors that predispose to low intradialytic phosphate levels (such as very rapid dialyzer blood flow rates, low body size, or low predialysis serum phosphate levels) may reduce capacity for net phosphate removal.

Consistent with these theoretical considerations, increasing dialyzer surface area (by using 2 dialyzers) was effective for decreasing serum phosphate levels. In contrast, increasing dialysis

Table 3. Phosphate Clearance and Phosphate Removal by Dialytic Regimen

Characteristic	Phosphate Clearance (mL/min)	Phosphate Removal (mg)
Standard hemodialysis	83.9 (71.6-96.2)	1,395.8 (1,163.6-1,628.1)
Increased dialysis time	86.6 (73.8-99.3)	1,435.7 (1,179.9-1,691.5)
Increased dialysate flow	83.0 (71.1-94.9)	1,371.4 (1,132.0-1,610.7)
2 Dialyzers in parallel	113.4 (101.4-125.3)	1,487.8 (1,248.6-1,727.1)

Note: N = 18. Values expressed as mean (95% confidence interval). Adjusted for rolling baseline serum phosphate level. Serum phosphate expressed in mg/dL; conversion factor for mmol/L, ×0.3229.

duration from 4 to 4.5 hours increased urea clearance, but did not significantly improve phosphate clearance or control. The tighter phosphate control presumably was caused by enhanced clearance of serum phosphate, although there was no significant increase in total phosphate removal as reflected by dialysate collection, perhaps because of insufficient statistical power. Alternatively, some of the apparent increase in dialyzer clearance (but not removal) might be caused by adsorption to the dialysis membrane, which would not be reflected in collections of spent dialysate. Future studies should confirm that larger dialyzer surface area decreases predialysis serum phosphate levels and use larger sample sizes to determine whether increased removal is responsible.

The cost of using a second high-flux dialyzer is approximately $7,100 per annum, substantially more than the annual cost of any available phosphate binder (including calcium acetate, $85 per annum; and sevelamer, $4,211 per annum).[36] In a North-American setting, these costs generally would be borne by the dialysis provider (rather than the patient) and might be lower in settings in which dialyzers are reused. However, as with sevelamer, the double-dialyzer strategy currently cannot be recommended for use given the lack of data showing that it would improve clinical outcomes. Rather, our results suggest the need for further investigation of methods for enhancing intradialytic removal of phosphate. Because the incremental cost of using very large dialyzers may be relatively small compared with currently available alternatives, this strategy appears worthy of further investigation. Given the findings of several other small trials, the potential merits of hemofiltration as a means of reducing serum phosphate levels also should be studied further.[37-39]

Although our study was randomized and conducted by using rigorous experimental and statistical methods, it has some limitations that should be considered. First, the number of patients was relatively small, all patients were overweight; and enrollment occurred at only 2 Canadian centers. Therefore, our results may not be generalizable to all maintenance hemodialysis patients. Second, although we found no evidence of sequence or carryover effects, we used a crossover design, which has well-known limitations.

Third, duration of follow-up was relatively short (3 months), and future studies should examine the impact of dialytic strategies for a longer period. Fourth, the increased duration was only 30 minutes longer than the standard treatment, and 6- or even 7-hour treatments may have been required to observe significant decreases in serum phosphate levels compared with a standard 4-hour treatment.[40] However, these longer treatments may have been less acceptable to many patients. Although 4 or 4.5 hours might lead to better control of serum phosphate levels compared with 3-hour sessions (which are common practice in the United States), this speculation requires confirmation in additional studies. Fifth, collecting information about equilibrated postdialysis phosphate levels would have permitted calculation of blood-side phosphate clearances, which unfortunately were not available in the present study. Sixth, our study was not large enough to determine whether there was a significantly increased risk of adverse events associated with the double-dialyzer strategy. However, as we previously reported, 1 patient had a serious adverse event (intravascular hemolysis) that likely was caused by the Y-tubing associated with the double-dialyzer configuration.[17] If our findings are confirmed, this would argue in favor of developing single dialyzers with substantially larger surface area (to obviate the need to connect dialyzers in parallel). Finally, this study was not designed or statistically powered to examine the effect of the various dialytic modalities on such clinically relevant outcomes as mortality, cardiovascular events, hospitalization, or quality of life. Given the emphasis that is placed in contemporary nephrology practice on achieving better phosphate control without increasing oral calcium load, there is great need for trials that test whether achieving this objective (by modification of dialysis regimens or other means) is helpful to patients.

In conclusion, use of 2 dialyzers in parallel for 6 weeks in overweight hemodialysis patients led to substantially lower predialysis phosphate levels than those associated with conventional hemodialysis. Future studies should investigate the biochemical and clinical benefits of other dialytic strategies aimed at reducing serum phosphate levels, especially the use of single dialyzers with large surface area.

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