Phosphate Clearance in Peritoneal Dialysis: Automated PD Compared with Continuous Ambulatory PD

Although dialytic removal of phosphate significantly contributes to the management of phosphate levels in end-stage renal disease, many patients on peritoneal dialysis (PD) still do not reach optimal phosphate control. The present review discusses the impact of PD modality—continuous ambulatory (CAPD) or automated (APD)—on phosphate removal. Relevant factors are the diffusive properties of the phosphate anion and the kinetics of phosphate distribution in various body compartments. Confounders that potentially affect comparisons of phosphate clearances in CAPD and APD are differences in residual renal function, membrane transport status, and prescribed dialysis dose. The evidence reviewed here is not strong enough to clearly determine if one modality has a clear advantage with respect to phosphate removal. In the absence of final proof, the data suggest that, given the same residual renal function and dialysis dose, CAPD might be slightly more effective than APD at peritoneal phosphate clearance, especially in low transporters.

Key words
APD, CAPD, phosphate clearance

Introduction
Dialytic removal of phosphate is a key aspect of managing phosphate levels in end-stage renal disease. However, many patients (about 40%) on peritoneal dialysis (PD) still have higher-than-normal phosphate levels (1), suggesting that phosphate management in those patients is not optimal. One factor that may affect phosphate clearance is the prescribed PD modality.

Discussion

Phosphate clearance properties
It is important to understand the properties of phosphate that govern its clearance in dialysis. Dialytic removal of phosphate depends on diffusive and convective transport of phosphate across the peritoneal membrane (2,3). Phosphate clearance is also time-dependent and affected by the kinetics, molecular size, and compartmental distribution of the phosphate anion.

One peculiarity of phosphate is that it seems to exhibit elimination characteristics different from those of other small-molecular-weight toxins (2–5). For instance, peritoneal clearance of phosphate [molecular weight (MW) 95] can be up to 50% lower than that of urea (MW 60) and almost 20% lower than that of creatinine (MW 113). One factor that contributes to this dissimilarity of phosphate from other small-MW molecules is the aqueous shell that surrounds the phosphate anion (Figure 1). The shell tends to...
increase the effective MW and molecular radius of the phosphate ion (6). In the shell, at least one water molecule can form weak hydrogen bonds with each of the four oxygen molecules in the phosphate anion. Pribil and colleagues (6) showed that approximately 13 water molecules can participate in making up the shell closest to the phosphate ion. In their study, those authors demonstrated that the mean distance between adjacent water molecules was, on average, 3.9 Å. In addition, in contrast to urea, phosphate does not readily diffuse across cell membranes (2,4,5), possibly because approximately 5% of the circulating phosphate is a component of sodium, calcium, or magnesium salts.

**Phosphate kinetics**
The kinetics of phosphate depend on phosphate movement from the various pools within the body. To assess phosphate movement from the various phosphate pools, Spalding and colleagues conducted an extensive modeling study based on patient data (7). Their findings suggest that phosphate behavior depends on serum phosphate levels.

Under healthy conditions, phosphate kinetics were shown to follow a 4-compartment model. The model comprises 4 distinct phosphate pools, of which mainly the first 2 pools are the most relevant for hyperphosphatemic dialysis patients. In such patients, phosphate levels rarely decline below the physiologic range; therefore, release of phosphate from the 3rd and 4th pools is usually not activated. Therefore, in dialysis patients, phosphate kinetics tend to follow a 2-compartment or a pseudo 1-compartment model (8). The 1st compartment is the inaccessible compartment (for example, bone). The 2nd compartment is the accessible compartment or the miscible pool. The authors propose that the accessible pool is in equilibrium with the plasma during the intradialytic and post-dialytic periods. Phosphorus mobilization into that compartment comes from the larger inaccessible pool at a rate proportional to dialytic phosphate clearance. Because the inaccessible compartment is relatively large, its phosphorus concentration is assumed to be constant over time and equal to the pre-dialytic plasma phosphorus concentration, making the 2-compartment model mathematically identical to the pseudo 1-compartment model. Thus, during dialysis, phosphate is removed primarily from the miscible pool.

**Phosphate mass removal and clearance in CAPD and APD**

Very few data comparing the removal of phosphate across PD modalities are available. A review of the existing literature revealed only six studies that investigated the total mass removal of phosphate in PD (3,9–13). In CAPD, the overall mass removal of phosphate by PD was determined to range from 2 g to 3 g per week (Table I).

In an early study performed in 9 patients (14), Twardowski and colleagues demonstrated that, compared with APD (n = 3), CAPD (n = 6) provided better clearance of small solutes, including phosphate. In that study, the CAPD regimen consisted of four 2-L exchanges, and the APD regimen involved exchanges of 13 – 24 L in-center over 8 hours during the daytime. The study was limited by its small number of patients and the absence of appropriate controls for transport status. Further, clearance in APD was affected by very short cycles involving 10-minute dwells and 27-minute fill/drain times.

A later study by Sedlacek et al. (15) showed that the average weekly phosphate clearance did not significantly differ between CAPD (56.4 ± 16 L, n = 20) and APD (51 ± 21 L, n = 36). Notably, 18 of the patients in that study had residual renal function (RRF). The
authors speculated that larger dialysate volumes in APD might have been offset by the shorter dwell times.

Badve et al. (16) conducted a 2-year cross-sectional retrospective study of 129 prevalent PD patients, of whom 62 were on CAPD (52 with RRF) and 67 were on continuous cycling PD (37 with RRF). Their daily dialysate volumes were 8.2 ± 1.6 L for CAPD and 14.4 ± 3.5 L for APD (p < 0.001). In their analysis across modalities, the authors did not find a significant difference in weekly peritoneal phosphate clearance between CAPD and continuous cycling PD (38.3 ± 12 L/1.73 m$^2$ vs. 40.9 ± 10.4 L/1.73 m$^2$, p = 0.199).

Data from Bernardo and colleagues (17) and Botelho et al. (13) support the study by Badve and coworkers, in that the overall phosphate clearance did not differ between PD modalities (p = 0.928 and 0.926 respectively). In contrast, a study by Gallar et al. (18) showed that peritoneal phosphate clearance was higher in APD than in CAPD. Those authors discussed how plasma phosphate levels, daily dialysate volume, and peritoneal membrane characteristics were factors that affected peritoneal phosphate clearance, but the effect of membrane status was not assessed.

Evenepoel and colleagues (9) compared phosphate mass removal and phosphate clearance between 16 CAPD patients (14 with RRF) and 34 APD patients (27 with RRF). Although weekly total phosphate removal was not significantly different between CAPD and APD (2.7 g vs. 2.8 g, p = 0.4), weekly peritoneal phosphate clearance was significantly better with CAPD than with APD (40.2 ± 13.0 L/1.73 m$^2$ vs. 32.7 ± 14.8 L/1.73 m$^2$, p < 0.0001), despite the larger dialysate volume in APD (11.7 L vs. 9 L on average). However, the study did not adjust for the group differences in transport status and RRF.

Based on the quality of the available studies comparing phosphate clearance between APD and CAPD, it is quite difficult to assess whether modality choice actually affects phosphate clearance. The available studies are limited by their small sample size, their design, and their lack of adjustment for confounders. What the studies bring to light, however, is that many factors play a role in determining phosphate clearance. It appears that when choosing a PD modality with the aim of optimizing or improving phosphate clearance, transport status and the presence of RRF are crucial factors that should be considered.

### Confounders of phosphate clearance in PD

Assessing phosphate removal in CAPD compared with APD is challenging because of a substantial bias by indication attributable to differences in RRF, transport status, and required dialysis dose. In the presence of RRF, adequate fluid balance is maintained, overall systemic inflammation is lower, and renal endocrine functions and elimination mechanisms are protected to varying degrees (19–25). Importantly, RRF also contributes significantly to adequate Kt/V and phosphate removal. At the start of dialysis, RRF may account for up to 65% of total phosphate clearance, adding up to 40–50 mmol of clearance daily. As RRF declines, there is a greater need for an increased dialysis dose. That situation often leads to an intensified PD prescription and use of APD, resulting in higher ultrafiltration (UF), increased peritoneal Kt/V, and consequently, better phosphate clearance. A prospective study by Granja and colleagues (1) supports that theory. Of phosphate removed in APD patients, 11% was because of net UF, with a significant correlation between the UF rate and phosphate removal ($r = 0.81$). However, Botelho and colleagues did not find a

### Mass phosphate removal in continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD)

<table>
<thead>
<tr>
<th>Reference</th>
<th>APD</th>
<th>CAPD</th>
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<tbody>
<tr>
<td>Messa et al. (3)</td>
<td>2028±1257 (n=35; 4×2 L)</td>
<td>2941 (n=35, 4×3 L)</td>
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<tr>
<td>Evenepoel et al. (9)</td>
<td>2739±1042 (n=34)</td>
<td>2790±1022 (n=16)</td>
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<tr>
<td>Delmez et al. (10)</td>
<td>2170 (4×2 L)</td>
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<tr>
<td>Winchester et al. (11)</td>
<td>3250 (4×3 L)</td>
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<tr>
<td>Botelho et al. (13)</td>
<td>3024 (renal plus peritoneal), 1862 (peritoneal alone)</td>
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**Confounding factors:**

1. **Fluid balance:** Adequate fluid balance is maintained in the presence of RRF, reducing overall systemic inflammation and protecting renal endocrine functions.
2. **Ultrafiltration (UF):** As RRF declines, UF becomes increasingly important to maintain phosphate clearance. This can lead to intensified PD prescriptions.
3. **Peritoneal Kt/V:** Higher UF results in increased peritoneal Kt/V, contributing to better phosphate clearance.

**Conclusion:** The presence of RRF significantly affects phosphate clearance in PD, making modality choice less straightforward. Monitoring these factors is crucial for optimizing phosphate management.
correlation between net UF and phosphate clearance. They showed that UF accounted for only 5.9% of the phosphate removed by the peritoneum (13). Interestingly, those investigators also determined that total daily phosphate removal correlated negatively with peritoneal Kt/V urea.

In another study, 22 of 24 patients who started on CAPD were switched to APD with an increased dialysis dose as RRF declined (5). The authors demonstrated that peritoneal phosphate clearance increased and appeared to compensate for the loss of renal function during the study period. Thus, patients on APD might have lower renal function but higher peritoneal phosphate clearance because of three synergistic mechanisms: the increase in dialysis dose, structural changes in the peritoneal membrane toward high transport characteristics over time, and convective transport because of increased UF. Although the follow-up period in the study was short (median: 7.2 months), the investigators concluded that implementation of APD could increase clearance of water-soluble toxins such as phosphate. However, whether the effect was independent of dose could not be determined from the data.

To understand the effect of an increased dialysis dose on phosphate removal in APD, Juergensen et al. (26) studied 10 patients who were high or high-average transporters. They showed a 19% increase in phosphate clearance when the dialysate volume was increased by 71% ($p < 0.005$). That increase in phosphate clearance translates into less than 50 mg of net phosphate removal in 9 hours, assuming a serum phosphate of 6 mg%/.

In a pediatric study ($n = 87$), Schmitt and colleagues (27) also showed that dialytic phosphate clearance correlated positively with total and nighttime fluid turnover, the number of cycles, total cycle time, and net UF. In fact, PD fluid turnover was found to be the major determinant of phosphate clearance. The study determined that, for every liter of PD fluid replaced per square meter, the daily peritoneal clearance of phosphate increased by 0.7 L/1.73 m$^2$. Those results support similar previous reports in adults, which showed that 8 – 8.8 mmol phosphate could be removed for every liter of fluid replaced (3,11). Although the foregoing observations are interesting, and clearly, loss of RRF could be counterbalanced by APD and an increased dialysis dose, the efficiency of increasing phosphate removal is low and comes with the burden of significantly increased costs.

Transport status is another important confounder of phosphate clearance in PD. High (“fast”) transporters tend to show better phosphate clearance than do low (“slow”) transporters. They are also more likely to be on APD because of their need for short cycles. Schmitt and colleagues showed that high transporters had better clearance of phosphate and creatinine (27). In their study, dialysate-to-plasma (D/P) creatinine and creatinine clearance correlated well with D/P phosphate ($r = 0.27$) and phosphate clearance ($r = 0.52$), although compared with D/P creatinine, D/P phosphate was clearly a better predictor of phosphate clearance. The authors further suggested that patients with a D/P phosphate of less than 0.27 after 2 hours (or less than 0.41 after 4 hours) could be considered low phosphate transporters.

Sedlacek et al. (15) concluded that the main determinant of peritoneal phosphate clearance was transport status, as determined by a peritoneal equilibration test (PET). Compared with slow transporters, fast transporters had significantly better phosphate clearance ($p = 0.0003$). Although phosphate clearance in slow transporters was slightly better with CAPD, it did not reach significance. When Badve et al. (16) adjusted for transport status, modality choice was not an important factor for high transporters ($p = 0.72$). In contrast, high-average and low to low-average transporters had significantly better phosphate clearance with CAPD ($p = 0.01$ and 0.034 respectively). In general, compared with the other transport groups, high transporters had better phosphate clearance. With respect to transport status, Bernardo et al. (17) concluded that, for fast and fast-average transporters, there was no difference in the phosphate cleared by APD or CAPD. For slow and slow-average transporters, however, their results indicated that CAPD might be a more favorable option for improving phosphate clearance ($p = 0.006$ for slow-average, $p = 0.049$ for slow transporters).

**Summary**

The quality of the available studies is insufficient to ultimately prove an independent effect of CAPD or APD on peritoneal phosphate clearance. Several confounders—including RRF, dialysis dose, transport status, and UF—limit interpretation of the study outcomes. Higher transport status, dialysis dose, and UF are associated with higher phosphate removal regardless of modality. Weighing the foregoing evidence,
and giving special consideration to the confounders in each study, CAPD seems to be slightly favored over APD with respect to peritoneal phosphate clearance, especially in low transporters.

Disclosures
All authors are employees of Fresenius Medical Care North America.

References


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