Phosphorus kinetics in patients with chronic renal failure on hemodialysis

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Abstract

Introduction: Hyperphosphatemia is one of the factors associated with high mortality in patients with chronic renal failure in dialysis programs. The objective of the present study was to perform intra- and postdialysis serum phosphorus (P) kinetics, taking into account factors such as dialysis time and extracorporeal flow (Qs).

Methods: This cross-sectional study was conducted from September 2018 to January 2019. Baseline phosphate levels were analyzed 60, 120, 180, and 240 intradialytic and 1 and 2 hours posthemodialysis. A descriptive analysis is performed. Linear regression was performed to determine factors associated with posthemodialysis serum P levels.

Results: Fifty-six patients were included, 48 ± 13 years old, 30 women (53%), 46 with catheters (82%), and 27 (48%) who received treatment for 240 minutes. Qs of 300 ml/min in 11%, 350 ml/min in 65%, 400 ml/min in 26% of cases. pH 7.3 ± 0.6, hemoglobin 9.4 ±1.6 gr/dL. Basal P, at 60, 120, 180 and 240 minutes, was 5.3, 3.5, 2.9, 2.7 and 2.6 mg/dl, respectively. The P at 60 and 120 minutes post HD were 3.5 and 3.75 mg/dl, respectively. Factors associated with the phosphorus level at 120 min post hemodialysis were hemoglobin P=0.004 Standardized beta coefficient (CBE) 0.247 (95% CI 0.04-0.219) and phosphorus removal at 240 min P=0.001, CBE=0.503, (CI95% 0.265-0.905).

Conclusions: The decrease in phosphate in the study group was 50.9%, with a rebound elevation at 2 hours of 21.82%. Hemoglobin above 11 gr/dl is a factor associated with hyperphosphataemia. The intensity of phosphorus removal at 240 minutes is associated with serum phosphorus levels.

Keywords:

MESH: renal dialysis; Hemodiafiltración; Phosphorus metabolism disorders; Hyperphosphatemia; Kinetics.
Approximately 2 million people have end-stage chronic kidney disease (ESRD) worldwide. The use of renal replacement therapy with maintenance hemodialysis or peritoneal dialysis continues to increase, and despite continuing technological advances, the mortality rate for these patients remains unacceptably high.

Evidence suggests that bone mineral metabolism disorders contribute to the high burden of death in ESRD patients [1]. Elevated serum phosphate is a fundamental factor in the hormonal dysregulation that underlies bone and mineral metabolism disorders in chronic kidney disease. Numerous observational studies have reported an independent association between disorders in mineral metabolism (hyperphosphatemia, hyperparathyroidism, elevated fibroblast growth factor 23, deficient calcitriol levels) and increased morbidity and mortality in people with advanced chronic kidney disease [2].

While most attention has focused on using noncalcium phosphate binders such as sevelamer and lanthanum, modification of conventional dialysis regimens to improve phosphate clearance is an alternative approach that remains relatively unstudied [3]. The clinical practice guideline of the Japanese Society of Dialysis (JSDT) recommends that dialysis patients maintain serum phosphate levels within 3.5-5.5 mg/dL, with phosphorus correction being a priority, followed by calcium and then calcium. PTH [4].

A three-pronged approach is commonly used to control serum phosphorus in dialysis patients: (1) removal of phosphorus with dialysis, (2) restriction of dietary phosphate intake, and (3) use of orally administered phosphate binders to limit the absorption of ingested phosphate from the intestinal contents.

Serum P levels in one-third to one-half of dialysis patients exceed 5.5 mg/dL; this is attributed to the fact that phosphate elimination during a hemodialysis session is 800 mg to 1,000 mg; therefore, a triweekly treatment is insufficient to eliminate the recommended daily intake of phosphorus. It is difficult to limit phosphate intake without limiting the recommended daily protein intake for chronic hemodialysis patients to 1.1 to 1.3 g/kg body weight. Another factor is lack of adherence, dialysis patients must take multiple medications, and phosphate binders increase the patient’s pill load, are large, are difficult to swallow, or, if chewed during a meal, can distort the sense of taste, with accompanying gastrointestinal complaints that decrease appetite. Another factor is calcitriol, or its analogs, which increase phosphate absorption from the small intestine. The other factor is decreased intestinal free phosphate concentration, either by dietary restriction or chelator use, a known stimulus to increase phosphate absorption in the small intestine [5].

When seeking to improve the elimination of any solute during dialysis, several strategies are used: (a) increase in session duration, (b) increase in blood flow; (c) increase in dialyzer size; and (d) higher dialysate flow rate [2]; however, these strategies are not fully supported: M. Albalate et al. (2003) found that as the primary determinant of phosphorus removal at initial plasma concentration, none of the changes made to the composition of the bath improved the amount of P removed. In this study, the surface area of a low-permeability dialyzer was increased from 2 to 2.6 m²; although it improves Kt/V, it does not increase P elimination, and the increase in Qd did not induce modifications [4].

P. Gallar et al. (2007) selected 108 hemodialysis patients. Seventy-eight percent had an AVF, and 22% had a tunneled catheter. The dialyzer membrane was polysulfone with high permeability in 31 (30%) and medium permeability in 77 (70%). The dialyzer surface was 1.7 m²:17 (16%); 1.8 m²:77 (71%); and 2.1 m²:113 (13%). Dialysis fluid flow: 500 ml/min: 55 patients; 700 ml/min: 53 patients. Session duration: 4.14 ± 0.41 (range 3.5-5 hours). Eighty-five percent underwent dialysis between 4 and 5 hours. They concluded that phosphorus clearance in a hemodialysis session involves, in addition to plasma phosphorus, the amount of purified blood, which is generally higher when vascular access is an AVF. Other factors, such as the session duration and the dialyzer’s surface area, ultrafiltration, dialysis fluid flow, membrane permeability, or the online hemodiafiltration technique, do not significantly increase phosphorus clearance [6].

Tonelli et al. (2009) studied three strategies to increase phosphate removal in patients: increasing session duration from 4.0 to 4.5 hours, increasing dialysate flow or using two dialyzers in parallel. Of the three strategies, only using the two dialyzers in parallel was the only strategy that significantly impacted phosphorus removal [7]. Daugirdas (2012) analyzed short daily hemodialysis sessions and nocturnal hemodialysis, which reduced serum phosphorus levels by 0.6 and 1.6 mg/dL, respectively, relative to 3 sessions. In the short-daily hemodialysis arm, intensive HD significantly reduced the estimated dose of phosphate binder per day, whereas in the overnight arm, intensive HD caused binder discontinuation in 75% of patients. However, intensive HD does not significantly affect serum concentrations of calcium and parathyroid hormone. In conclusion, intensive HD, especially nocturnal HD, lowers serum phosphorus levels and decreases the need for phosphate binders [8]. Jenan G et al. (2015), comparing hemodiafiltration and HD, did not observe any difference in serum phosphate levels [9].

Bertocchio JP et al. (2016) concluded that modulation of serum bicarbonate may play a role in the control of the phosphate compartment, noting that in an attempt to correct metabolic acidosis during hemodialysis, excess alkaline may impair phosphate mobilization clearance [10]. Due to these antecedents, the objective of the present study was to carry out phosphorus kinetics taking into account intradialytic factors and posthemodialysis rebound in a group of patients with renal insufficiency undergoing chronic treatment.
Materials and methods

Study design
This study is cross-sectional and analytical.

Scenery
The study was carried out in the hemodialysis unit of the Hospital de Especialidades "Dr. Bernardo Sepúlveda," Centro Médico Nacional Siglo XXI, Mexico City, in patients with chronic renal failure on hemodialysis during the period from September 2018 to January 2019.

Participants
Patients older than or equal to 18 years were included, with a diagnosis of chronic kidney disease in stage 5-D, in a three-week hemodialysis programme, with a minimum duration of 9 hours per week, with serum phosphorus levels >5.5 mg/dL and with accesses semi-permanent or functional permanent. Patients who did not agree to participate in the study had an acute or chronic infectious process, and an active neoplastic process was excluded. Additionally, cases with acute vascular access dysfunction during the sampling or patients who did not complete the scheduled blood collection or revoked their informed consent were eliminated.

Variables
The variables were age, sex, type of vascular access, session duration, extracorporeal flow, pH, serum hemoglobin, and albumin. Baseline serum phosphorus, 60 minutes intradialytic, 120 minutes intradialytic, 180 minutes intradialytic, 240 minutes intradialytic, 60 minutes postdialysis, and 120 minutes postdialysis.

Data sources/measurements
The source was direct, and a questionnaire with the variables was applied. The study analyzed two hemodialysis sessions in the middle of the week, one of 180 minutes and another of 240 minutes. Blood samples of 2 ml were taken through the arterial line of the vascular access before starting treatment. At 60, 120, 180, and 240 minutes of the session, 2 ml samples were taken through the arterial line of the extracorporeal circuit. At 1 hour and 2 hours posthemodialysis, a 2 ml blood sample was taken through the peripheral route. All samples were taken with a sterile syringe, placed in a biochemical tube with BD Vacutainer SST (R) REF368159 gel, centrifuged at 3500 revolutions for 15 minutes, stored at 4 degrees Celsius, processed in a period not exceeding 2 hrs with PHOS2(R) reagent and analyzed by Roche/Hitachi COBAS c701/702.

Biases
To avoid possible interviewer, information, and memory biases, the data were guarded at all times by the principal investigator with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period above were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their agreement was verified.

Study size
The sample was nonprobabilistic, census type. For convenience, all possible cases were selected.

Quantitative variables
Inferential descriptive statistics were used. Scaled results are expressed as the means and standard deviations. Categorical data such as sex are presented as proportions.

Statistical analysis
Descriptive statistics were performed, and the results were expressed as medians and ranges, as well as means and standard deviations, depending on the data distribution. Linear regression was performed to determine factors associated with posthemodialysis serum phosphorus levels after data normalization by logarithmic transformation. A Mann–Whitney U analysis was performed to analyze pre, intra, and posthemodialysis phosphorus values. The statistical package used was SPSS 24.0 for PC (IBM Corp. Released 2016. Armonk, NY.)

Results

Participants
Fifty-six patients entered the study. The diagram of the participants is presented in Figure 1.

Characteristics of the study population
Fifty-six patients whose demographic characteristics are shown in Table 1 were included. The average age was 48 ± 13 years; 54% of the population was women (n=30), with a body mass index (BMI) of 24.9 ± 3.5 kg/m2. Of the total vascular accesses, 82% were semi-permanent, and 18% were fistulas. A total of 51.7% received an HD session lasting 180 minutes, and the rest received a 240-minute session. The blood flows varied according to the vascular access; 11% were prescribed flows of 300, 63% with 350, and 26% with 400 ml/min. Serum pH levels at the start of the HD session were 7.3 ± 0.6, Hb 9.4 ± 1.6 g/dl, and albumin 3.7 ± 0.5 mg/dl.
Pre, intra, and posthemodialysis measurements
The median P levels at the start of the HD session were 5.3 mg/dl, with a progressive decrease to a minimum value of 2.7 mg/dl in 180-minute sessions and 2.6 mg/dl in 240-minute sessions. A posthemodialysis rebound of a maximum value of 3.75 mg/dl at 2 hours was observed (Figure 2 and Table 2).

Multiple linear regression of phosphorus levels pre, intra, and posthemodialysis
The factors influencing blood phosphorus levels were hemoglobin nines, serum phosphorus level, and extracorporeal flow (Table 2). There was a significant association between hyperphosphatemia and an increase in hemoglobin above a value of 11 gr/dl (Figure 3).

Subanalysis
The factors that influenced serum P levels 60 minutes after the HD session were Qs (P = 0.21, 95% CI 0.001 - 0.016), basal P levels (P = 0.000, 95% CI 0.237 - 0.438), P180 (P=0.021, 95% CI 0.084 - 0.94), P240 levels (P = 0.00, 95% CI 0.448 - 1.03), and Hb levels (P=0.032 (95% CI 0.09 - 0.19)).

The factors influencing serum P levels 120 minutes after the HD session were P at baseline (P = 0.00, 95% CI 0.313-0.505), P 180 (P = 0.002, 95% CI), P 240 (P=0.001, 95% CI 0.265 - 0.905) and Hb levels (P=0.004, 95% CI 0.041-0.219 0.262-1.021), P 240 (P =0.001, 95% CI 0.265 - 0.905) and Hb levels (P=0.004, 95% CI 0.041-0.219).

P levels at the end of the 180-minute HD session increased at PR + 60 0.84 mg/dl (P = 0.001) and at PR + 120 0.34 (P < 0.0001). P levels at the end of the 240-minute session increased at PR +60 0.72 mg/dl (P = 0.001) and at additional PR + 120 0.30 mg/dl (P = 0.001).

Table 1. Demographic characteristics of the population.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of cases = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>48 ± 13</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24.9 ± 3.5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>26 (46%)</td>
</tr>
<tr>
<td>Woman</td>
<td>30 (54%)</td>
</tr>
<tr>
<td>vascular access</td>
<td></td>
</tr>
<tr>
<td>Semipermanent</td>
<td>46 (82%)</td>
</tr>
<tr>
<td>FAVI</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>180 minutes</td>
<td>29 (52%)</td>
</tr>
<tr>
<td>session duration</td>
<td></td>
</tr>
<tr>
<td>240 minutes</td>
<td>48 (48%)</td>
</tr>
<tr>
<td>extracorporeal flow</td>
<td></td>
</tr>
<tr>
<td>Qs 300 ml/min</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Qs 350 ml/min</td>
<td>35 (63%)</td>
</tr>
<tr>
<td>Qs 400 ml/min</td>
<td>15 (26%)</td>
</tr>
<tr>
<td>pH</td>
<td>7.3±0.6</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.4 ± 1.6</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.7±0.5</td>
</tr>
</tbody>
</table>

BMI: body mass index, AFV: internal arteriovenous fistula

Table 2. Pre, Intra, and post hemodialysis phosphorus concentration.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures of dispersion</th>
<th>% decrease from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline P (mg/dl)</td>
<td>5.3 (3.1-12.7)</td>
<td></td>
</tr>
<tr>
<td>P60 (mg/dl)</td>
<td>3.5 (2.2-7.5)</td>
<td>-1.80 (33.96%)</td>
</tr>
<tr>
<td>P120 (mg/dl)</td>
<td>2.9 (1.8-5.7)</td>
<td>-2.40 (43.28%)</td>
</tr>
<tr>
<td>P180 (mg/dl)</td>
<td>2.7 (1.8-5.1)</td>
<td>-2.60 (49.05%)</td>
</tr>
<tr>
<td>P240 (mg/dl)</td>
<td>2.6 (1.6-3.9)</td>
<td>-2.70 (50.90%)</td>
</tr>
<tr>
<td>PR+60 (mg/dl)</td>
<td>3.5 (2.17)</td>
<td>-1.80 (33.96%)</td>
</tr>
<tr>
<td>PR+120 (mg/dl)</td>
<td>3.75 (2.38)</td>
<td>-1.55 (29.08%)</td>
</tr>
</tbody>
</table>

P60 phosphatemia at 60 minutes intradialytic; P180: at 180 min intradialytic. P240 to 240 minutes. PR+60 phosphoramide 60 min post hemodialysis. RP+120: phosphoramide 120 minutes post hemodialysis.

Table 3 Regression linear multiple of the determinants of the levels of phosphorus of a 120 minutes post hemodialysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized Beta coefficient</th>
<th>P</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.163</td>
<td>0.244</td>
<td>2.29 – 10.08</td>
</tr>
<tr>
<td>Sex</td>
<td>0.022</td>
<td>0.161</td>
<td>0.822 - 1.44</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.247</td>
<td>*0.004</td>
<td>0.04 - 0.219</td>
</tr>
<tr>
<td>P basal</td>
<td>0.721</td>
<td>*&lt;0.0001</td>
<td>0.313-0.505</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.0017</td>
<td>0.196</td>
<td>0.281 - 0.342</td>
</tr>
<tr>
<td>BMI</td>
<td>0.112</td>
<td>0.417</td>
<td>-0.038 - 0.091</td>
</tr>
<tr>
<td>Q's</td>
<td>0.390</td>
<td>0.118</td>
<td>0.052 - 0.808</td>
</tr>
<tr>
<td>HD Duration</td>
<td>0.023</td>
<td>0.145</td>
<td>0.075-14.08</td>
</tr>
<tr>
<td>P180</td>
<td>0.641</td>
<td>*0.002</td>
<td>0.262 - 1.021</td>
</tr>
<tr>
<td>P240</td>
<td>0.503</td>
<td>0.001</td>
<td>0.265-0.905</td>
</tr>
<tr>
<td>pH</td>
<td>0.042</td>
<td>0.247</td>
<td>2.29 – 10.08</td>
</tr>
</tbody>
</table>

The basal level during the first hour, with a progressive decrease of 44.4, 48.4, and 49.2% at the second, third, and fourth hour of the session, respectively. At the end of the session, there was an increase in baseline P of 66 and 71% in the first and second hours, respectively. There is an association between hemoglobin levels: anemia is associated with hypophosphatemia, and hemoglobin levels >11 g/dl are associated with hyperphosphatemia. DeSoi et al. [11] evaluated P kinetics in high-flow HD, finding a precipitous decline in P levels in the early stages, reaching the lowest level at 30–150 minutes, subsequently with lower rates of decline until reaching a plateau. Moreover, a prehemodialysis P value was reached four hours after the end of the session. Leypold et al. [12] described a significant decrease in serum P during the first 60 minutes of HD with a subsequent decrease in concentration that continued until the end of treatment. P kinetics were determined by pre- and posthemodialysis levels, blood flow, hemoglobin, and albumin.

We found a significant negative correlation between prehemodialysis P levels and P levels at the end of the session, with a more significant decrease in the 240-minute sessions. Kjellstrand et al. [13] studied the dynamics of P considering the following variables: number of sessions, duration, blood flows, dialysate flows, and type of membrane with serum measurements before and after hemodialysis, finding a negative correlation between the P removed and the predialysis concentrations ($P=0.0001$). The highest levels of Hb were associated with higher serum levels of intra- and posthemodialysis phosphorus, possibly related to the fact that intradialytic P levels remain low and that P is almost exclusively removed from the plasma in its passage through the dialyzer, which reduces P clearance relative to urea (which is cleared from plasma and blood cells). This effect is potentiated by hematocrit levels, as described by Daugirdas et al. [2].

Descombres et al. [14] performed in vivo and in vitro mass balance and equilibrium studies to examine the diffusion kinetics of P, where they showed that dialysate clearance is very close to plasma dialysate. Basal and immediate posthemodialysis P levels were determined at 60 and 120 minutes posthemodialysis P levels. Agar et al. [15] analyzed P levels 60 minutes after hemodialysis in sessions of 2 and 4 hours and found no difference in the percentage of postdialysis P ($P = 0.001$). Leypold et al. [16] proposed that P mobilization from tissues is proportional to the difference between predialysis serum levels and final concentrations.

Concerning the prescribed Qd, we did not observe statistically significant differences in the reduction of P. Leclerc M et al. [17] carried out a prospective study where they evaluated the impact of the Qs rate on the dialysis dose with low dialysate flows and found that the reduction percentage of P increases from 0.46 ± 0.1 to 0.49 ± 0.07 when increasing the Qs from 300 to 450 mL/min, respectively. Increasing the blood pump

**Discussion**

This study describes the kinetics of phosphorus during a hemodialysis session, which shows a decrease of 33.8% with respect.
flow by 1 mL/min resulted in an increase of 0.00017% (P = 0.28, 95% CI −0.0001 - 0.0005). Although some reports indicate that the extension of weekly dialysis time improves P removal and even decreases the need to use P binders, in the present study, no statistically significant correlation was found for sessions of 180 or 240 minutes, a situation contrary to what was described by Tonelli et al. [7] in HD sessions of 4.5 hours compared to a 4-hour session (P =0.04), and Eloot et al. [18] showed a greater clearance in HD sessions of 4, 6 and 8 hours (P=<0.001).

Constant intradialytic serum P levels were identified, regardless of the duration of HD, as reported by Spalding et al. [19]. They observed that serum P levels did not decrease to critically low levels, probably associated with P transport from sites according to their four-compartment P kinetic model. Regarding albumin levels, we found higher posthemodialysis P levels in the 240-min session (2.57 vs. 3.15 mg/dl) with albumin levels below 3.5 and above 4 mg, respectively; this is probably related to the fact that up to 10% of P is bound to proteins, and the rest is ultrafiltrate [20].

The results of this study were limited by the small number of patients, the lack of control over serum changes in pH, bicarbonate, and temperature, which could modify the intracellular movement of P, and the lack of control over the use of chelators and adherence. The diet could influence kinetics. New evaluations are required to standardize a model explaining P’s kinetics during hemodialytic therapy.

Conclusions
Phosphorus kinetics in hemodialysis shows that the most significant decrease in this ion is in the first hour of the session and during the first posthemodialysis hour, as predictive factors, as expected, baseline serum phosphorus levels (prehemodialysis), together with other factors, including posthemodialysis serum levels of P, hemoglobin and albumin.

Abbreviations
P: phosphorus.

References

HD: hemodialysis.
Qs: extracorporeal flow.

Supplementary information
Supplementary materials have not been declared.

Acknowledgments
Does not apply.

Author contributions
Juan Manuel Duran: Conceptualization, Data Curation, Formal Analysis, Fundrais-ing, Research, Methodology, Project Management, Resources, Software, Writing – original draft.
Maria Inés Gil Arredondo: conceptualization, supervision, validation, visualization, and writing: review and editing.
Pedro Trinidad Ramos: conceptualization, supervision, validation, visualization, and writing: review and editing.
All authors read and approved the final version of the manuscript.

Financing
The authors provided research expenses. Laboratory studies and serum phospho-rus measurements were performed at institutional cost after approval of the proto-col; they were not extra costs for the patients.

Availability of data or materials
The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable academic request.

Statements
Ethics committee approval and consent to participate
The local health research committee approved this study 3601 with registration number 170109015034 before CDEPIS and registration number before CONBIOETICA 09 CEI 023 2017082. The clinical research was conducted following the principles expressed in the Declaration of Helsinki (64th Assembly General, FOr-taleza, Brazil, October 2013).

Consent to publication
It does not apply when images or photographs of the physical examination or X-rays/tomographies/MRIs of patients are not published.

Conflicts of interest
The authors report having no conflicts of interest.


DOI: Digital Object Identifier. PMID: PubMed Identifier.

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