Original Article

Phosphate Intake and Removal in Predominantly Vegetarian Patients on Twice-Weekly Hemodialysis

Abstract

Background: Hyperphosphatemia is linked to increased mortality and morbidity in patients on hemodialysis. Currently, the phosphate intake and dialytic removal in predominantly vegetarian patients on twice-weekly dialysis is not well studied. **Materials and Methods:** This prospective, study recruited patients on twice-weekly dialysis of at least 3 months duration. Baseline clinical variables were measured. Dietary protein and phosphorus intake was assessed using a validated food frequency questionnaire. Phosphate binder use was assessed, hourly blood was collected for serum phosphorus during dialysis, and spent dialysate was collected to estimate cumulative phosphorus removal during the session. **Results:** Forty (67%) of the 60 patients studied were vegetarians. Twenty-eight (48%) were hyperphosphatemic, and 15 (25%) had serum parathormone (PTH) >500 pg/ml. The mean phosphorus intake was 1247 (±312) mg/day, the mean serum phosphorus was 5.49 (±2.01) mg/dl, and the mean dialytic phosphorus removal was 910 (±383) mg/session. Up to 67% of the study population took calcium-based phosphate binders, 25% took sevelamer carbonate, and 40% took activated vitamin D preparation. The lowest tertiles of phosphorus intake correlated with low energy-adjusted protein intake and hypoalbuminemia. Hyperphosphatemic subjects had better nutritional indices (mid-upper arm circumference and body mass index). Dietary intake and serum phosphorus levels were not mutually associated, but both were strongly correlated with total phosphorus removal in the spent dialysate. Serum phosphorus levels fell by 32% by the first hour of hemodialysis. **Conclusion:** Twice-weekly dialysis is often practised in resource-limited Asian countries. However, due to a predominantly vegetarian diet, hyperphosphatemia was noted only in up to half of the patients, despite twice-weekly hemodialysis schedules. This reinforces the fact that plant-based dietary phosphate is less well absorbed.

Keywords: *Hyperphosphatemia, phosphate binders, phosphate removal, secondary hyperparathyroidism, twice-weekly hemodialysis*

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Introduction

Chronic kidney disease–associated mineral bone disorder (CKD-MBD) is consistently associated with mortality and hospitalization in patients on dialysis.[1] Even in thrice-weekly hemodialysis schedules as practised in the developed countries globally, CKD-MBD is a prevalent problem, contributing up to half of the pill burden in these patients.[2] In an analysis of over 26,000 prevalent patients on dialysis, only one-third of them were found to have target concentrations of serum calcium, phosphorus, and intact parathyroid hormone (iPTH), and an increase of each one of the out-of-target concentrations was linked to an increase in death and hospitalization rates.[3] In a study based on data from Dialysis Outcomes and Practice Patterns Study (DOPPS) that tracks hemodialysis patients longitudinally in over 20 countries, the hazard ratio of cardiovascular mortality increased from 1.61 to 1.81 when the serum phosphorus increased from 6.00–6.99 to >7.00 mg/dl.[4] This signifies the importance of recognizing and managing hyperphosphatemia in patients on dialysis. The intake of phosphorus from diet varies widely, based on region, education, socioeconomic status, amount and source of protein intake, and consumption of packaged foods and beverages.[5] The removal of phosphorus via hemodialysis is a function of both the frequency and duration of sessions and is, therefore, intuitively lower in twice-weekly dialysis sessions, as practised in several regions in the developing world, and in those opting for incremental hemodialysis.

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A daily dietary phosphorus consumption of 1000 mg with up to 70% absorption will lead to an approximate weekly phosphorus burden of 5000 mg. A standard 4-h dialysis session removes 700–900 mg of phosphorus; therefore, twice-weekly dialysis amounting to only 1800 mg removal would result in larger phosphate burden compared to conventional thrice-weekly dialysis regimens.[6] Only strict adherence to phosphate binders can optimize the phosphorus balance, which is often difficult to achieve. Therefore, it appears that most patients on twice-weekly dialysis schedules would suffer inevitable phosphorus loading. The present study was undertaken to examine the dietary phosphorus intake, phosphate binder use, and dialytic phosphorus removal in a prevalent dialysis population on twice-weekly hemodialysis, as these would help in formulating strategies to achieve target serum phosphorus values in similar settings.

Methods

The study was planned as a single-center, observational study. The study was approved by the institute's ethical committee and registered before commencement (CTRI/2019/05/019383). All the procedures were conducted conforming to the provisions of the Declaration of Helsinki. The study was carried out in the hemodialysis unit of a public sector tertiary care teaching hospital in a study population consisting of patients aged 18 years or more with end-stage kidney disease (ESKD) and on maintenance hemodialysis (MHD) twice weekly for at least last 3 months, after written informed consent was obtained from them. Patients who had intervening hospitalizations and gastrointestinal disturbances precluding adequate dietary intake in the preceding 3 months were excluded. Also, patients with early terminated sessions or those patients who were prescribed intradialytic parenteral nutrition or blood product transfusions were also excluded.

All the study participants were administered a 54-item food frequency questionnaire (FFQ) once for longitudinal phosphorus, protein, and energy intake assessment (for the preceding 3 months) by a trained dietician in the same week as the study dialysis session.[7] Also, all the patients received instructions on filling diary entries for reporting the dose and timing of phosphate binders and vitamin D analogues, which were filled on two predialysis days in a 14-day period. Anthropometric (body mass index [BMI in kg/m^2] mid-upper arm circumference [MUAC in cm]) and the most recent laboratory parameters (haemoglobin, serum albumin, calcium, and iPTH levels) were noted (once during the study) by trained dialysis nurses.

All the patients underwent dialysis with low-flux dialyzers, with a dialysate flow rate of 500 ml/min and a duration of 4 h. The sessions after the longer interdialytic interval were chosen for the study. Blood was drawn for the estimation of serum phosphorus levels just before the start of the session, then hourly till the end of dialysis, and the last sample was taken 30 min after dialysis termination. Blood urea estimation was also performed in the predialysis and 30-min post-dialysis samples. Spent dialysate was collected by partial dialysate collection method, as described by Cheng *et al*.[8] Phosphorus estimation in serum and dialysate was done using Beckman Coulter AU 480 kit. Dialysis adequacy was calculated using the Daugirdas formula: sp Kt/V = − ln (R − 0.03) + [(4 − 3.5R) × (UF/W)], where UF is the ultrafiltrate volume removed (in l), W is the post-dialysis weight, and R is the ratio of post-dialysis to predialysis blood urea nitrogen (BUN).[9] Urea reduction ratio (URR) was calculated as (predialysis BUN – post-dialysis BUN/ predialysis BUN), where BUN is expressed in mg/dl.[10] Total phosphorus removal (in g) was calculated as dialysate phosphorus concentration (mg/ml) × [dialysate flow rate (ml/min) × duration of dialysis (min) + ultrafiltrate removed (ml)]/1000.

Statistical analysis

All the data were expressed as means with standard deviations or medians with interquartile range. Data normality was tested using the Shapiro–Wilk test. For continuous variables, Student's *t*-test or Mann–Whitney test was performed. For comparison of more than two groups, one-way analysis of variance (ANOVA) was used. For categorical variables, Pearson's Chi-square test or Fisher's exact test was performed, as appropriate. Linear regression analysis was done to derive predictors for dialytic phosphorus removal. A P value of <0.05 was considered significant. All the tests were performed using Statistical Package for the Social Sciences (SPSS) software version 16.0 (IBM Corp., Chicago, IL, USA).

Results

The recruitment of the study began in August 2019 and was carried out till February 2020. During this period, 67 patients were recruited in the study after informed consent was taken from them. A total of 79 dialysis sessions were carried out as part of the study. However, three sessions had to be excluded due to incomplete dialysis sessions. Two sessions were excluded due to more than one missing blood collection, and seven were excluded due to inappropriate dialysate collection. Seven patients were excluded due to incomplete FFQ and drug entries in the diary provided. The data on the dialysis sessions of these seven patients were not analyzed further. Therefore, a total of 60 patient sessions were analyzed. To check for compliance to the prescribed medications, 18 of the 60 self-filled diary sheets were compared to the corresponding month's prescription by the investigator. Compliance to calcium-containing binder and vitamin D analogue was >80% for both, and the compliance to sevelamer carbonate was only 57%.

The study population was predominantly young (mean age of 39 years), male (44 males and 16 females), and

had a mean dialysis vintage of 30 months. Diabetes as a comorbidity was prevalent in up to 24% of the study population. Forty patients (67%) were vegetarians (did not consume meat or any animal products other than the dairy products). The rest of the patients (n = 20) consumed meat products (chicken, fish, and mutton); 12 (60%) reported once-weekly consumption, five (25%) twice weekly, and three (15%) reported fortnightly consumption of one or more meat products, with chicken being consumed most commonly. The mean BMI of the study population was 21.8 kg/m^2.

The mean dietary phosphorus intake of the whole group was 1247 mg/day (from the FFQ-based estimation). Dietary phosphorus intake correlated with dietary protein intake, serum albumin levels, calcium-containing phosphate binder use, and total dialytic phosphorus removal. Phosphate binder use and calcitriol use were the lowest in the lowest tertiles of phosphorus intake. Table 1 presents the median values for clinical, laboratory, and dialytic parameters in each tertiles of phosphorus intake.

Hyperphosphatemia was defined as a serum phosphorus value of ≥5.5 mg/dl. The study subjects with hyperphosphatemia were then compared to those with normal serum phosphate levels. Hyperphosphatemia was significantly associated with a longer dialysis vintage, higher (though in normal range) BMI, MUAC, and serum albumin values, and a higher energy-adjusted protein intake, but not with dietary phosphorus intake [Table 2]. Table 3 shows the higher use of phosphate binders and vitamin D analogues in patients with hyperphosphatemia. In terms of fall in serum phosphorus levels, the first hour of dialysis accounted for around 32% reduction from predialysis serum phosphorus levels, with normophosphatemia displaying nearly normal serum values at the end of first hour, but the hyperphosphatemics showed a steep fall in serum phosphorus levels at the first hour, followed by a gradual fall in serum phosphorus values continuing at later time points [Figure 1]. With regard to dialysis-related parameters, patients with hyperphosphatemia achieved lower Kt/V and URR values than normophosphatemic patients and also experienced a smaller fall in serum phosphorus levels in the first hour of hemodialysis. The total amount of dialytic phosphorus removal was greater in the group with hyperphosphatemia, as shown in Table 4. Linear regression was performed to predict phosphorus removal during a dialysis session, and a model comprising dietary phosphorus intake and serum phosphorus levels could explain 32.7% of the variance in dialytic phosphorus removal.

Discussion

Hyperphosphatemia is unquestionably linked to higher mortality in ESKD.[1,4] This has prompted guidelines to prescribe reduction in serum phosphorus levels with the use of dietary phosphate restriction, phosphate binders, and

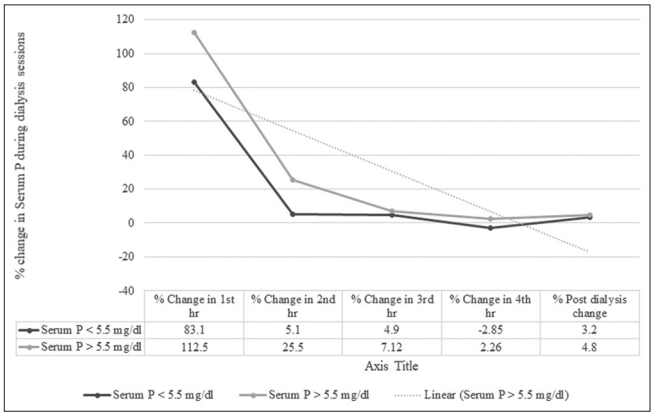

Figure 1: Changes in serum phosphorus levels in the groups with and without hyperphosphatemia

Table 1: Dietary phosphorus intake (by tertiles) and its correlation with clinical and laboratory parameters

Characteristic	Tertiles 1 (n=19)	Tertiles 2 (n=19)	Tertiles 3 (n=22)	P
Age (years)	42	36.5	39	0.19
Dialysis vintage (months)	32	24	27	0.08
Body mass index (kg/m^2)	18.8	23.7	22.1	0.51
Mid-upper arm circumference (cm)	21.5	24.8	25.2	0.12
Hemoglobin (g/dl)	8.9	9.1	9.0	0.46
Serum albumin (g/dl)	3.2	3.6	3.4	0.04
Serum intact parathyroid hormone levels (pg/ml)	138	334	343	0.12
Serum phosphorus (mg/dl)	5.1	4.8	5.9	0.36
Energy-adjusted protein intake (g/day)	46.8	52.1	53.3	0.01
Ultrafiltration removed (ml/4 h)	2000	3100	3000	0.10
sp Kt/V	1.32	1.39	1.30	0.47
Urea removal ratio	0.66	0.67	0.67	0.38
Total dialytic phosphorus removal (mg/4 h)	595	998	1065	0.001
Median dose of calcium-containing phosphate binder (mg/day)	0	1000	1000	0.07
Median dose of sevelamer carbonate (mg/day)	0	0	0	0.10
Median dose of calcitriol use (mg/day)	0	0.25	0	0.03

Table 2: Comparison of clinical and laboratory parameters between subjects with and without hyperphosphatemia

Characteristic	Serum *P*≤5.5 mg/dl Median (IQR) (*n*=32)	Serum *P*≥5.5 mg/dl Median (IQR) (*n*=28)	*P*
Age (years)	38 (28-50)	39 (28-49)	0.95
Sex (M: F)	21:11	23:5	0.12
Presence of diabetes mellitus	8 (25%)	6 (21%)	0.15
Dialysis vintage (months)	28 (18-34)	33 (21-38)	0.036
Body mass index (kg/m2)	18.7 (16.9-22.4)	23.5 (19.2-24.4)	0.02
Mid-upper arm circumference (cm)	22.8 (20.7-24.3)	25.7 (22.5-27.1)	0.03
Hemoglobin (g/dl)	8.9 (8.1-10.4)	9.1 (7.8-11.1)	0.91
Serum albumin (g/dl)	3.3 (3.1-3.5)	3.5 (3.3-3.7)	0.000
Serum intact parathyroid hormone levels (pg/ml)	203 (90.5-443)	409 (238.5-595)	0.005
Serum phosphorus levels (mg/dl)	4.1 (3.6-4.9)	6.5 (6.1-7.7)	0.000
Daily energy intake (kcal/day)	1668 (1307-1810)	1534 (1274-1765)	0.53
Energy-adjusted daily protein intake (g/day)	46.3 (41.1-55.4)	50.3 (48.4-73.7)	0.03
Daily protein intake/kg body weight (g/kg)	0.84 (0.74-0.98)	1.03 (0.88-1.21)	0.05
Daily phosphorus intake (mg/day)	1211 (890-1392)	1337 (1063-1549)	0.12
Daily phosphorus-to-protein intake (mg/g)	25.7 (17.1-32.9)	28.6 (18.6-34.5)	0.07

IQR: Interquartile range

Table 3: Comparison of phosphate binder and calcitriol use between subjects with and without hyperphosphatemia

Characteristic	Serum *P*<5.5 mg/dl Median (IQR) (*n*=32)	Serum *P*≥5.5 mg/dl Median (IQR) (*n*=28)	*P*
Median daily dose of calcium-containing phosphate binder (mg)	0 (0-1000)	1000 (1000-1500)	0.000
Median daily dose of sevelamer carbonate (mg)	0 (0-0)	800 (0-1600)	0.01
Median daily dose of calcitriol (mg)	0 (0-0.25)	0.25 (0.25-0.50)	0.005

IQR: Interquartile range

Table 4: Comparison of dialysis-related parameters between subjects with and without hyperphosphatemia

Characteristic	Serum *P*<5.5 mg/dl Median (IQR) (*n*=32)	Serum *P*≥5.5 mg/dl Median (IQR) (*n*=28)	*P*
Ultrafiltration removal/session (ml/4 h)	2500 (1500-3500)	3100 (1400-4000)	0.21
Total phosphorus removal/session (mg/4 h)	822.8 (478.8-1063.0)	1044.0 (740.3-1291.3)	0.002
sp Kt/V	1.48 (1.16-1.83)	1.29 (0.97-1.46)	0.06
URR (%)	69 (63-76)	64 (57-69)	0.07
Fall in serum phosphorus in the first hour of dialysis as a % of total session fall	66 (59.5-77)	55.5 (49-60.5)	0.000

IQR: Interquartile range, URR: Urea reduction ratio

hemodialysis.[11] To our knowledge, this is the first study to examine phosphate kinetics, namely, intake and removal, in patients on twice-weekly dialysis schedules. The present study, conducted in 60 patients on twice-weekly hemodialysis, found a high (>1 g/day) dietary phosphate intake, nearly 50% prevalence of hyperphosphatemia, and up to 25% prevalence of secondary hyperparathyroidism in the study population.

The mean phosphorus removal per session of hemodialysis was around 910 mg. This is higher than the prescribed dietary phosphorus of 800 mg/day, but higher dietary phosphorus intake was not associated with the development of hyperphosphatemia. This discrepancy is likely explained by the dependence of phosphorus absorption on the source of phosphorus in the diet, that is, organic phosphorus from animal or plant sources is absorbed to a lesser extent (40%–60%) compared to inorganic phosphorus (up to 100%) in processed foods such as cheese and cola drinks.[11] The recent guideline from Kidney Disease Improving Global Outcomes (KDIGO) suggests limiting dietary phosphate intake to manage hyperphosphatemia, however, with a cautionary note that the source of phosphorus must be checked while making dietary recommendations.[12] A recently published Malaysian study in 435 dialysis patients revealed that a pattern of higher intake of beverages with sweeteners (high in inorganic phosphorus) was significantly associated with hyperphosphatemia. Home food–based diets, even when these diets had animal proteins, did not result in similar elevations in serum phosphorus levels.[13] These findings are pertinent, as predominantly plant-based sources contribute to both dietary protein and phosphorus content of a majority of dialysis patients in our region.[14] Only a few earlier studies have assessed dietary phosphorus intake in this region and none have assessed it

in the dialysis population. Regarding phosphorus intake, our group developed and validated an FFQ for dialysis patients in Lucknow, Uttar Pradesh, situated in northern India.[7] In our previous study, up to half of the cumulative protein and phosphorus intake comprised just five items: *roti* (a flattened wheat bread staple of North Indian diet), *milk, paneer* (cottage cheese), *red gram,* and *rice*. Even in that study, while 45% of the study subjects consumed meat, the consumption was insufficient to contribute to 50% of cumulative variance in dietary phosphorus intake.

Hitherto, Noori *et al*.[15] analyzed dietary phosphorus intake in relation to mortality in patients on hemodialysis. In their study, dietary phosphorus intake was found to be associated with 5-year mortality, independent of serum phosphorus and PTH levels. The lack of correlation between dietary phosphorus intake and predialytic serum phosphorus levels is a common feature for the study by Noori *et al*.[15] and the present study. Serum phosphorus is known to fluctuate with respect to time of the day, dietary nutrient intake, dose and schedule of dialysis session, residual renal function, as well as net bone resorption. A more precise estimate of phosphorus exposure may be gained by time averaged through the day or week. Therefore, Noori *et al.* hypothesized that dietary phosphorus intake provides a more representative estimate of the body's phosphorus exposure than a single measurement of serum phosphorus, and therefore, both measures may not show correlation.[15] So, based on the aforementioned FFQ, the patients in the present study were divided into tertiles of phosphorus intake. The associations of low phosphorus intake with lower protein and poorer nutritional indices (BMI, MUAC, serum albumin levels) were weak, and dietary phosphorus intake was not associated with either serum phosphorus or iPTH levels. However, dietary phosphorus intake was significantly associated with total phosphorus removed by a session of dialysis. The weak association of dietary phosphorus intake with serum levels could also be secondary to poorer absorption of predominantly plant-based organic phosphorus, losses during cooking, and general overestimation due to FFQ-based dietary assessment.[5] FFQs tend to overestimate nutrient intakes, when compared to food diaries and other short-term recall methods.[16]

With regard to phosphate binder use, median intake of calcium as part of calcium-containing phosphate binders was 1 g, which corresponds to binding of 40–45 mg phosphorus. Poor prescription compliance as well as cost factor possibly contributed to the overall low use of sevelamer carbonate. Vitamin D analogue was being taken by 36 of the study subjects, and prevalent secondary hyperparathyroidism correlated strongly with vitamin D analogue intake.

The mean phosphorus removal per dialysis session in the entire group was 909 mg, and therefore, the weekly dialytic removal would be nearly 2 g. This is only the second study, to our knowledge, to assess single-session phosphorus removal in the spent dialysate. In their 2018 study, Elias *et al*.[17] noted that while serum phosphorus levels normalize by the first hour of dialysis, only a quarter of dialytic phosphorus removal occurs by that time point. Similar to the present study, hyperphosphatemic subjects had greater mass removal of phosphorus in the spent dialysate when compared to those with normal serum phosphorus levels. As spent dialysate assessment was done *en masse* (at the end of 4 h) and not at the end of 1 h, our study cannot confirm the degree of phosphorus removal in the first hour as a fraction of the total session removal. However, the degree of fall of serum phosphorus levels in the first hour was 32%, somewhat lower than the 45% reported in the previous study. In the present study, both the dietary intake as well as serum phosphorus (though not mutually associated) were significantly associated with the magnitude of phosphorus removal per session, providing indirect support to Noori's hypothesis that dietary intake, in addition to serum phosphorus levels, be assessed to gauge the body phosphorus load in dialysis patients.[15] This also supports the use of total dialytic phosphorus removal as a marker for body phosphorus exposure, as dialytic phosphorus removal is affected by both dietary intake and serum levels. Further studies may be planned to associate total dialytic phosphorus removal with the incidence of mortality, cardiovascular events, and mineral bone disease.

Another interesting observation in the present study was that hyperphosphatemia correlated with a higher protein intake (1.0 g/kg/day), as well as higher BMI, MUAC, and serum albumin level (measures of nutritional status). Proposed management strategies for hyperphosphatemia in patients on twice-weekly hemodialysis schedules could include protein intake of up to 1 g/kg/day, adhering to diets with optimal protein to phosphorus ratios, ensuring maximal compliance to phosphate binders, and increasing time on dialysis. As the study did not measure dialytic phosphorus removal at various time points during dialysis, this study does not answer whether individual dialysis session should be prolonged or the frequency of sessions be increased, in order to achieve higher phosphorus removal. While the present study demonstrates optimal BMI, MUAC, serum albumin levels in patients with a protein intake of under 1 g/kg/day, this has not been well studied for its effects on mortality and other intermediate and long-term events, or the risks of developing protein–energy wasting with this approach.

The primary strength of the study derives from the use of an FFQ developed and validated in a similar population. Also, the use of dialysate collection for estimation of phosphorus clearance provided robust information regarding dialytic phosphorus removal in the context of the given dietary phosphorus intake and twice weekly hemodialysis. The study also throws light on phosphate kinetics in a

predominantly vegetarian population with low inorganic phosphorus intake. The important limitations of the study include the small number of patients, lack of hourly collection of spent dialysate (to study phosphorus removal as a function of time), methodologic issues such as no information collected on residual renal function, including only single dialysis sessions for each patient (which would provide more accurate phosphorus removal data), and also, not performing measurement of formal nutritional assessment scores to look for associations with the patients' phosphate kinetics.

Conclusion

In a cohort of dialysis patients who were predominantly vegetarian (67%), despite twice-weekly dialysis, hyperphosphatemia was noted only in up to a half of the patients. Though phosphate intake correlated with increasing protein intake, it was not associated with elevated serum phosphorous levels, suggesting poor gastrointestinal absorption. Also, patients with hyperphosphatemia exhibited a slower fall in serum phosphorus levels during dialysis than those with normal serum phosphorus levels.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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