International Journal of Clinical Nutrition, 2017, Vol. 5, No. 1, 18-23
Available online at http://pubs.sciepub.com/ijcn/5/1/4

DOI:10.12691/ijcn-5-1-4

Phosphate Nutritional Intake Control between Patient Undergoing Conventional Thrice Weekly and Infrequent Hemodialysis

Piergiorgio Bolasco*, Andrea Galfré, Stefania Caria, Patrizia Scotto, Stefano Murtas

Territorial Nephrology and Dialysis Unit of ASSL Cagliari, Italy
*Corresponding author: pg.bolasco@tin.it

Abstract Introduction. It is largely agreed that preservation of residual kidney function (RKF) has a directly proportional effect on general and, in particular, cardiovascular mortality. Unlike the oligoanuric patient undergoing thrice weekly hemodialysis (TDH) evaluation of patients on infrequent (once-weekly or twice-weekly) hemodialysis (ID) shows the importance of phosphaturia and residual diuresis are frequently underestimated. Indeed, the native kidney preserves the ability to eliminate not only toxic molecules but also achieve a significant output of phosphate despite a severe decrease in RKF. But without a tailored hypoproteic-hypophosphoric nutritional approach it was not possible to recruit patients for whatever programs of infrequent hemodialysis. Aim. The aim of our study was to assess phosphate balance in patients on ID compared to those on conventional THD with no residual kidney function. Methods. In each group the proteic/phosphoric intake was estimated. Thirty-seven patients were recruited: 12 on THD, 15 on twice-weekly dialysis and 10 on once-weekly dialysis with a combined diet dialysis program (CDDP). A total of 36 urine samples were collected from 36 THD patients and grouped according to dialysis method employed: high efficiency dialysis (HDH), post-dilution on-line hemodiafiltration (postHDF), or pre-dilution hemodiafiltration (preHDF). Fifty-seven urine samples were obtained from patients on TWD, and 109 from CDDP. Results. Compared to THD patients, patients on ID were characterized by a negative or neutral balance between input/output of phosphates. Weekly balance: THD: +4.45; TWD: - 0.73; CDDP: - 0.38. Conclusions. A tailored ID, together with a low-protein – low-phosphorus diet may delay the need for THD and prolong patients' quality of life and cardiovascular survival, being proportionally linked to a lack of accumulation of dietary phosphate.

Keywords: *hypoproteic nutrition, infrequent hemodialysis, phosphaturia, residual kidney function*

Cite This Article: Piergiorgio Bolasco, Andrea Galfré, Stefania Caria, Patrizia Scotto, and Stefano Murtas, "Phosphate Nutritional Intake Control between Patient Undergoing Conventional Thrice Weekly and Infrequent Hemodialysis." *International Journal of Clinical Nutrition*, vol. 5, no. 1 (2017): 18-23. doi: 10.12691/ijcn-5-1-4.

1. Introduction

In patients affected by advanced chronic kidney disease (CKD5), the preservation by all possible means of residual kidney function (RKF), even with a glomerular filtration rate (GFR) of less than 5 ml/min/1.73 sqm, is fundamental in delaying onset of dialysis and lowering the frequency of hemodialysis sessions (HD) [1]. Indeed, in patients undergoing hemodialysis treatment (HD) should be combined with a tailored low-protein diet; patients show good compliance may be considered as candidates for Infrequent Hemodialysis (ID) [2]; the concept of ID was borrowed from peritoneal dialysis as recently confirmed by Sandrini et Al. [3,4]. The potential strength of infrequent dialysis is based not only of preservation of RKF and the underestimated value of phosphaturia, but also on the fundamental influence of a low-protein diet that provides a controlled intake of phosphates.

The impact of preserving RKF on mortality is already well known [5,6]. This strategy was first acknowledged by the Giovannetti Italian School [7] and by Mitch et al [8], and the efficacy of this approach was subsequently confirmed by several Authors [9,10]. However, the inverse relationship between frequency of dialysis sessions and duration of a sufficient RKF should always be taken into account [11,12]. Moreover a rapid loss of residual RKF produces a marked impact on mortality rate [13,14]. The underlying causes may be varied, including micro-inflammation resulting from extracorporeal circulation, particularly in sessions using membranes with a lower biocompatibility and poor quality dialysis water [15,16], as well as reduced urinary output of protein-bound uremic toxins [17]. A series of clinical experiences have highlighted the importance of phosphate balance and its output, particularly in view of the increased risk in patients with CKD5 and CKD5D.

Using the model proposed by Neves KR et al [18] in 5/6 parathyroidectomized (PTx) and nephrectomised rats (Nx), in addition to myocardial hypertrophy, and excluding the potential effects produced by secondary uremic hyperparathyroidism, hyperphosphatemia alone was found to induce a deterioration in RKF compared to

groups of PTx + Nx + low phosphorous (LP), and sham + HP rats, with higher levels of anemia and elevated Ca X P product. The leading causes of kidney damage have long been acknowledged [19], being largely correlated with calcification of the renal microcirculation and consequent tubular-interstitial lesions, also due to the presence of high levels of hydroxyapatite crystals in the intraluminal and tubular renal tissues, particularly the cortico-medullary junction. Numerous literature reports have demonstrated a clear correlation between hyperphosphatemia, or increased phosphorus levels with mortality starting with conservative management of CKD since stage of dialytic treatments (CKD5D) [20-27].

Recently, the Study group of the Italian Society of Nephrology underlined how the control of protein intake is mandatory in conservatively managed patients (CKD5) and those on CKD5D [28]. To date, no studies have been undertaken to establish the extent of phosphaturia in dialysis patients; only Iwasawa et al, in a study of 79 patients on thrice-weekly dialysis, [26] reported a phosphaturia of 283 mg/day in patients with GFR > 3.0 ml/min, and 119 mg/day in patients with GFR < 3.0 ml/min.

The aim of this study therefore was to determine phosphate balance in oligoanuric patients on thrice-weekly HD (THD) and patients on twice-weekly HD (TWHD) and once-weekly HD (CDDP), with RKF.

2. Material and Methods

2.1. Phosphorus Intake in A Range of Low-protein Dietary Programs

The hypoproteic-hypophosphoric intake was a (0.6 g/Kg/die/1.73 smq) and 800 – 900 mg/die respectively in total tailored synergy with Residual Kidney Function; It was calculated using the formula of Urea Nitrogen Appearance from the indications suggested by Maroni et al [29] and later confirmed and used by Massud et al [30].

Largely speaking, protein intake by compliant CKD5 or CKD5D patients may be used as a basis for rough calculations of the availability of phosphates for intestinal adsorption in a western diet;subsequently, by taking into account the relevant variables, the method proposed by Sherman et al [31] may be applied, whereby 1g protein/day is taken as containing 14.6 mg of phosphates (Table 1).

Table 1. Phoshorus intake from different hypoproteic diet prescription

Protein intake 0.6 gr/Kg/70 kg = phosphorus intake: 613.2 mg/day
Protein intake 0.8 gr/Kg/70 kg = phosphorus intake: 817.6 mg/day
Protein intake 1.0 gr/Kg/70 kg = phosphorus intake: 1,022 mg/day
Protein intake 1.2 gr/Kg/70 kg = phosphorus intake: 1, 226 mg/day

2.2. Reduction of Intestinal Adsorption of Phosphate by Specific Binding Substances

Although this topic has been addressed in numerous publications, it is not an easy task to determine the degree of activity carried out by a given phosphate binder, irrespective of calcium content. Important meta-analyses published recently have failed to reach a satisfactory conclusion due to the numerous efficacy-related issues. In a study conducted on 12,562 patients, of which only 212 at CKD stage 3-4, Palmer et al [32] assessed the following: calcium carbonate, calcium acetate, sevelamer hydrochloride or carbonate, ferric citrate, lanthanum carbonate, nicotinic acid, colestilan, bixalomer. However, a low-protein diet does not necessarily contain low levels of phosphorus, largely due to a scarce nutritional education and to a lack of information on the amount of phosphate-based additives contained in foods and drinks. Studies conducted to compare a daily dose of 3,000 mg/day calcium acetate, 1,500mg/day lanthanum carbonate, 3,400 mg/day sevelamer, and 1,500 mg/day sucroferric oxyhydroxide demonstrated an efficacy of phosphorus binding ranging from 21% to 53% [33]. There is a general consensus that a binding rate of 25-35% should be accepted with caution [34,35,36,37]. However, to avoid an overly optimistic assessment and considering the unavoidable contents of phosphates additivies in many foods we opted for a phosphate underestimate binding capacity of 25%.

2.3. Phosphate Removal by Hemodialysis

The removal of phosphates by hemodialysis may be affected by a series of obstacles [38]. Although several authors have attempted to determine phosphate removal rates, we here refer to the paper by Lornoy et al [39], the findings of which have been confirmed by numerous authors Indeed, in spite of the presence of a series of membranes, both during high-efficiency hemodialysis (HED) and post-dilution hemodiafiltration (postHDF), an extremely limited phosphate removal rate is achieved. The few literature reports refer to a phosphate output corresponding in HD to approximately 1.5 g/session, and in postHDF to 2.1 g/session. For this aim we create an original method for assessing the hemodialytic output of phosphates in both on-line postdilution HDF and on-line predilution HDF, and collected a small share of dialysate extracted continuously at the same speed (1 mL/min) from the start to the end of the extracorporeal session with spillage of the dialysate exiting the filter by a proportional pump used to administrated drugs i.v. (Volumat Mc Agilia – Fresenius Kabi AG) for metering and dosing.

In our study group, otal phosphate mass (*Tpm*) was calculated by means of the following equation: $Tpm = Ex_{spill}\ (V_d + V_{inf} + V_{uf})$ where Ex_{spill} is the extracted phosphate concentration withdrawn by the spilling-pump; V_d is the total dialysate volume passed through the dialyzer; V_{inf} is the total infusion volume; V_{uf} is the total ultrafiltration volume. Ultrafiltration volume was set according to interdialytic body weight gain and ideal dry weight of the patient. Prescribed total infusion flow in ultra-pure on-line postHDF was set for all patients at 30% of dry body weight and, in the absence of clear indications in the literature, equal to the amount of body water in on-line ultra-pure preHDF (> 60% of the dry weight) [44]. We thus determined the weekly phosphate output for each patient, except for anuric THD patients, by adding phosphate nutritional intake + phosphaturia + output by dialysis.

Indications: Patients were required to have a dialysis vintage ≥ 6 months, metabolic steady state, good dietary compliance, protein intake in THD of 1.2-1.4 g/kg/day/1.73 s.m.; TWD 0.8-0.9 g/kg/day/1.73 s.m., CDDP 0.6 g/kg/day/1.73 s.m; no age limits were applied. THD patients with diuresis < 200 mL/die were excluded because the phosphaturia amount would be paltry.

A study was set up to investigate phosphate content in urine samples collected during interdialytic period from patients undergoing TWD although it was observed that in these patients, unlike ID patients, diuresis was not reduced immediately following dialysis. In CDDP patients, urine samples were collected on the second and fourth day dialysis days, and over the 24 hours immediately prior to the next dialysis day. Data from ID patients were compared to the findings obtained in THD patients.

Both the day of dialysis session and the following day were excluded from calculations of weekly phosphaturia in the presence of diuresis of less than 0.15 ml/min.

Thirty-seven patients were recruited, of which 15 on TWD, 12 on THD, and 10 on CDDP. Table 2 summarizes patient data and vintages of each treatments,. THD patients had been on the same dialysis regimen for at least 24 months; of the fifteen TWD patients, 7 had started dialysis on a twice-weekly basis (46.6%), whilst 8 of the 10 CDDP patients (80%) had started on once-weekly dialysis. The remaining patients on ID had initially started with thrice-weekly hemodialysis; following routine clinical follow-up these two patients had displayed a progressively increased diuresis that prompted us to evaluate RKF, resulting in a reduction of dialysis sessions and marked improvement of patient wellbeing. Dialysis efficiency: an equilibrated Kt/V ≥ 1.2 was obtained in all patients.

All patients signed an informed consent form.

3. Results

Table 2 summarized the patient recruitment. The findings obtained for serum calcium and phosphatemia (mg/dL), iPTH (µg/mL), RKF (mean 24-hours average of urea/creatinine clearance mL/day/1.73 sqm), urine volume (ml/day), and number of urine samples collected are illustrated in Table 3.

3.1. Efficiency of Phosphate Removal by Hemodialysis

The removal of phosphates by hemodialysis was determined on dialysate collected from the filter in both HDF and THD. All methods employed focused on the collection of 12 samples over a one-month period at the 1st, 2nd and 3rd weekly session and subsequent calculation of mean weekly output of phosphates. The duration of the dialysis session was standardized for all methods to 240 minutes.

Dry weight of patients on THD was 68.0 ± 3.4 kg, on TWD 69.3 ± 14.4 kg, and on CDDP 67.8 ± 13.3 kg. Interdialytic weight gain in THD patients 2.6 ± 0.7 L/session.

The 15 THD patients had carried out 8 HED, 4 postHDF, e 3 preHDF; the 12 TWD patients: 6 HED, 3 postHDF, 3 preHDF; the 10 CDDP patients: 2 HED, 8 postHDF. In postHDF patients, a value of 22.7 ± 2.9 L/session corresponded to total infusion volume plus the interdialytic weight gain corresponding to 33.3 % of dry body weight.

Values 45.2 ± 7.9 L/session were estimated for preHDF patients, corresponding to total infusion volume plus the interdialytic weight gain corresponding to 65.8 % of dry body weight.

The average dialytic removal of phosphate for session was: HED: 0.8 ± 0.2 g/week, postHDF: 0.9 ± 0.3, preHDF: 1.0 ± 0.3.

3.2. Mass Phosphate Balance

Calculated phosphate balances are reported in Table 4.

In addition to the above parameters, assessment of the urine samples was completed as illustrated in Table 5.

Table 2. Patient and dialysis vintage data

Patients	Recruited	Sex	Age, years	Dialysis vintage, months	Vintage methodology
Thrice-weekly hemodialysis	12	10 M/2F	70.0 ± 10.0	121.8 ± 94.7	121.8 ± 94.7
Twice-weekly hemodialysis	15	10 M/5F	67.8 ± 12	38.5 ± 17.5	28.4 ± 19.5
Once-weekly hemodialysis	10	8 M/2F	71.0 ± 13.7	31.2 ± 21.8	20.4 ± 14.1

M: males; F: females.

Table 3. Main biochemical and functional data

THD: serum calcium: 8.8 ± 0.6 , phosphatemia: 5.6 ±0.7, iPTH 445.5 ± 135.2, RKF : 0.0 Average protein intake: 1.35 g. 24 hours diuresis: 1386 ± 640; TWD: serum calcium: 9.1 ± 0.4 , phosphatemia: 5.1 ± 0.6, iPTH 331.5 ± 142.5, RKF : 8.3 ± 0.8, Average protein intake: 0.76 ± 0.1 g/24 hours; daily diuresis: 1386±640, number of urine samples collected: 57;

CDDP: serum calcium: 8.6 ± 0.4, phosphatemia 4.8 ± 0.8, iPTH: 446.2 ± 195.6, RKF : 10.6 ± 2.3, Average Protein intake: 0.69 ± 0.11 g/24 hours ; diuresis: 1677 ± 550, number of urine samples collected: 109.

Table 4. Weekly phosphate balances according to different dialysis strategies

Hemodialysis sessions/week	phosphate intake, g/week (seven days)	average output HD, g/all sessions	phosphate binder adsorption (-25%), g/week	phosphaturia, g/week	Phosphate balance, g/week
Thrice-weekly HFD	9.38	2.30 ± 0.36	7.03	-	+ 4.73
Thrice-weekly postHDF	9.38	2.47 ± 1.05	7.03	-	+ 4.66
Thrice-weekly preHDF	9.38	3.06 ± 1.10	7.03	-	+ 3.97
Twice-weekly (°°)	5.82	3.6 (°)	4.37	1.14 (°°)	- 0.37
Once-weekly	4.8	1.8 (°)	3.6	2.18 (°°)	- 0.38

(°) average of THD, postHDF and preHDF methodologies.
(°°) the mean obtained over three days was estimated as total weekly output phosphate output.

Table 5. Other urinary data in Infrequent Hemodialysis

	Calciuria, mg/dL	Proteinuria, g/24 h	Natriuresis, mmol/L
TWD	29.2 ± 13.9	0.72 ± 0.48	58.9 ± 43.4
CDDP	44.6 ± 25.9	0.91 ± 0.4	79.2 ± 33.5

Statistical methods:

It was not necessary to use elaborated formula because of the absence of statistical comparison. So It had been calculated only the Average and ± Standard Deviation.

4. Discussion

The milestone to preserve residual renal function and especially allow infrequent dialysis rhythms is compulsorily prescribe and monitor closely and regularly protein-phosphate nutritional intake [1-7]. It is widely acknowledged that dialysis produces a negative impact on RKF: the higher the intensity and frequency of hemodialysis, the greater the loss of RKF [6,45]. It is largely agreed that preservation of RKF has a directly proportional affect on general, and in particular cardiovascular, mortality. Indeed, the native kidney preserves the ability to eliminate toxic molecules [46], a task the modern membranes are as yet incapable of reproducing.

The strategy of preserving residual kidney function for as long as possible and not waiting until GFR is excessively low (>5 mL/min/.73 sqm) to initiate dialysis, has focused increasing attention on trials conducted using the so-called “incremental dialysis”, underlining the beneficial effects achieved in CKD5D patients with a good metabolic steady state and dietetic compliance and so using an RKF-tailored hemodialysis approach. The protective effect on RKF is further potentiated by a limited dietary intake of phosphorus [47-50]. Indeed, hyperphosphatemia alone was found to induce a deterioration in residual kidney function (RKF) directly damaging renal microcirculation and tubular-interstitial system [19-51]. The role of FGF-23 is fundamental as it stimulates phosphaturia by down-regulating sodium-phosphate co-transporters in the proximal tubules [52]. Indeed, high levels of FGF-23 have been detected in the later stages of CKD and in hemodialysis patients [53,54]. Although a low-protein diet may contribute to a certain degree to reducing FGF-23 levels, particularly when adhering to a vegetarian diet, as reported by Moe et al [55], these findings are still viewed as controversial.

Although natriuresis and calciuria were beyond the scope of the present study, briefly, the observed changes in sodium-phosphate exchange in the proximal renal tubule may explain the finding in patients with advanced CKD of moderately low urinary sodium levels. In fact, in these patients type II sodium-dependent phosphate (Na/Pi) co-transporter (NPT2) is the major molecule in the renal proximal tubule and is regulated by hormones and non hormonal factors [56]. Progression of CKD is known to result in a reduction in phosphaturia, although clearly in patients at stage CKD5D the tubular action of the FGF-23/K axis prevails. Undeniably, FGF-23 serum concentrations may rise enormously in CKD5D patients, with levels increasing up to 100,000 RU/mL in dialysis patients [53,54,57]. The finding of hypocalciuria in patients on ID may have been influenced by iPTH levels and/or prescribed treatments, vitamin D and diuretics [58]. Failure to measure FGF-23 levels be viewed as a weakness of this study; however, the aim of the study was not to justify the reasons for opting to maintain phosphaturia in CKD5D, but rather to demonstrate how the latter has been grossly overlooked as a key factor in maintaining phosphate balance and reducing cardiovascular mortality. The THD patients with diuresis <200 mL/day were selected by random to emphasize the phosphate buildup when diuresis progressively lose. Besides this dialysis-nutritional strategy responds in part to the doubts about the usefulness and safety of the taliored ID expressed recently by Basile and Casino [59].

The importance of implementing infrequent dialysis sessions was first reported in literature by the Californian group led by Kalantar-Zadek [60,61], who challenged the advisability of conventional thrice-weekly hemodialysis [62,63].

5. Conclusions

Accordingly, the mandatory contribution of the low-protein nutritional requirement in selected and collaborating patients was demonstrated by the CDDP although infrequent dialysis sessions should always be viewed as a time-lag bridging treatment prior to the inevitable start of a conventional hemodialysis regimen, residual kidney function should be assessed and closely monitored. The latter would not only enable patients to be enrolled in a tailored ID program, but also, as suggested by the findings of our group, would result in a decreased morbidity and mortality. Increasing mildly the focus on protein-phosphoric intake especially with particular attention to the food additives it could obtain a neutral phosphate balance in selected and compliant patients.

Conflict of Interest

All the Authors declare any conflict of interest.

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