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Dietary phosphate restriction in dialysis patients: A new approach for the treatment of hyperphosphataemia

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Abstract *Background and Aim:* Elevated serum phosphate and calcium–phosphate levels play an important role in the pathogenesis of vascular calcifications in uraemic patients and appear to be associated with increased cardiovascular mortality. We aimed to evaluate the effects of a partial replacement of food protein with a low-phosphorus and low-potassium whey protein concentrate on phosphate levels of dialysis patients with hyperphosphataemia.
Methods and Results: Twenty-seven patients undergoing chronic haemodialysis were studied for a 3-month period. In the intervention group ($n = 15$), food protein were replaced by 30 or 40 g of low-phosphorus and low-potassium protein concentrate aimed at limiting the phosphate intake. In the control group ($n = 12$) no changes were made to their usual diet. Anthropometric measurements, biochemical markers and dietary interviews were registered at baseline and during the follow-up period. From baseline to the end of the study, in the intervention group, serum phosphate and circulating intact parathyroid hormone levels lessened significantly (8.3 ± 1.2 mg/dL vs 5.7 ± 1.4 mg/dL and 488 ± 205 pg/ml vs 177 ± 100 pg/ml respectively; $p < 0.05$) with decreasing of phosphate and potassium intake. No significant differences were found in the control group. No significant changes were observed in serum albumin, calcium, potassium, *Kt/V*, body weight and body composition in both the intervention and control groups.
Conclusion: Dietary intake of phosphate mainly comes from protein sources, so dietary phosphorus restriction may lead to a protein/energy malnutrition in a dialysis patient. A phosphorus-controlled diet plan including a nutritional substitute resulted in serum phosphate and intact parathyroid hormone decrease without nutritional status modifications in dialysis patients.

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Controlling hyperphosphataemia is crucial to prevent the development of a secondary hyperparathyroidism and renal osteodystrophy in chronic kidney disease patients. In addition, hyperphosphataemia, causing soft-tissue calcifications, is emerging as an independent risk factor of cardiovascular mortality in dialysis patients [1–3]. However, a positive phosphate balance frequently occurs in conventional dialysis patients. High dietary phosphate intake (>1200 mg/day) is the most significant contributor to high serum phosphate levels [4]. Because of standard haemodialysis removing ~900 mg of phosphate three times per week, more than 90% of patients with uraemia require phosphate binders to avoid hyperphosphataemia [5]. Therefore, both the use of phosphate binders and the limitation of phosphate dietary intake may represent the main approaches for good phosphate control in dialysis patients [6]. A restricted dietary intake should be the most effective method to prevent this condition. However, dietary phosphate is strictly related to dietary protein content [7] and the conflict between adequate protein and phosphate intake is a well-known problem in the clinical practice [8]. A highly significant correlation between dietary phosphate and protein intake has been demonstrated [9]. For an optimal daily protein intake (1–1.2 g/kg/day), the phosphate intake is 778–1444 mg d^{-1}; therefore, because of protein contributing to a significant percentage of the total dietary phosphate intake, dialysis patients need to markedly limit their protein intake. To achieve the least phosphate intake with an adequate protein intake, an accurate selection of foods is needed. A diet including foods with a low phosphate content per gram of protein should be followed [4]. Despite the dietary phosphate restriction and the use of phosphate binders, serum phosphate levels remain significantly high in approximately 65% of the dialysis population [10].

The purpose of the present study was to evaluate the effects of a partial replacement of food protein with a low-phosphorus and low-potassium whey protein concentrate on phosphate levels of dialysis patients with hyperphosphataemia.

Methods

This study was performed on 27 chronic haemodialysis patients (15 male and 12 female, mean age 50.2 ± 9.0 years) for a 3-month period. Inclusion criteria were haemodialysis treatment for at least 6 months; no allergy to cow's milk protein and hyperphosphataemia (serum phosphate ≥6.5 mg/dl) with stable dialysis dose and modality, dietary intakes, body weight and biochemical markers for at least 3 months. All patients were on thrice weekly 4 h standard bicarbonate haemodialysis, and were clinically stable and without other illness. Subjects with diabetes, liver disease, malignancy, parathyroidectomy or psychiatric disease and those who were non-collaborative were excluded. Most patients received both phosphate binders (sevelamer, lanthanum carbonate, calcium carbonate and aluminium hydroxide) and vitamin D analogues. No patient had anabolic steroids or different protein supplements. No changes in dialysis prescription, medications or body weight were mandated. Eating habits, energy and protein intake were estimated in all patients. As the compliance to dietary restrictions on high-phosphate foods is sometimes difficult, patients were asked not to change their eating habits and they were instructed to keep unchanged their total protein and energy intake throughout the study. No patient, initially assessed for inclusion into the study, refused to enter the study. Patients were randomly assigned to either maintain their usual diet (control group, $n = 12$) or partially replace dietary protein intake with a low-phosphorus and low-potassium whey protein concentrate (intervention group, $n = 15$) for a 3-month period. Patients in the intervention group were instructed to consume 30 or 40 g of the low-phosphorus and low-potassium protein concentrate powder (PROther®, DMF Dietetic Metabolic Food) (Table 1) dissolved in 150–200 mL of water or some other liquid in place of usual daily portion sizes of protein-rich foods including milk consumed at breakfast and meat, fish, eggs or dairy and poultry products consumed at lunch time. They were supplied with adequate amounts of sugar and/or oil, depending on usual energy intake. Dietary adherence was monitored monthly in all patients. Compliance with the diet was ascertained through interviews conducted by an expert dietician using a detailed food-frequency questionnaire including 130 foods and beverages [11]. All patients continued to consume their phosphate binders.

Table 1 Nutritional composition of the low-phosphorus and low-potassium whey protein concentrate (Prother®).

	100 g
Energy kcal (kJ)	369 (1550)
Protein g	89.0
Carbohydrate g	1.0
Fat g	0.8
Phosphorus g	0.21
Calcium g	0.6
Sodium g	0.25
Potassium g	0.4
Iron mg	9.3

Table 2 Baseline characteristics in the intervention and control groups.

	Intervention	Control
Number	15	12
M/F	8/7	7/5
Age (years)	50.2 ± 9.0	48.7 ± 9.7
Dialysis age (months)	20.3 ± 19.5	19.7 ± 16.3
Body weight (kg)	69.9 ± 13.6	70.2 ± 8.4
Height (cm)	160.3 ± 9.1	162.1 ± 9.7
Body Mass Index (kg/m^2)	27.2 ± 6.4	27.0 ± 5.3
Phosphate (mg/dl)	8.1 ± 0.9	8.2 ± 0.7
Sevelamer use (n [%])	8 (53)	6 (50)
Aluminium hydroxide use (*n* [%])	3 (20)	3 (25)
Lanthanum use (n [%])	2 (13)	1 (8)
Calcium carbonate use (*n* [%])	1 (7)	1 (8)
Multiple binders use (*n* [%])	1 (7)	1 (8)
Active vitamin D derivative use (*n* [%])	7 (47)	6 (50)

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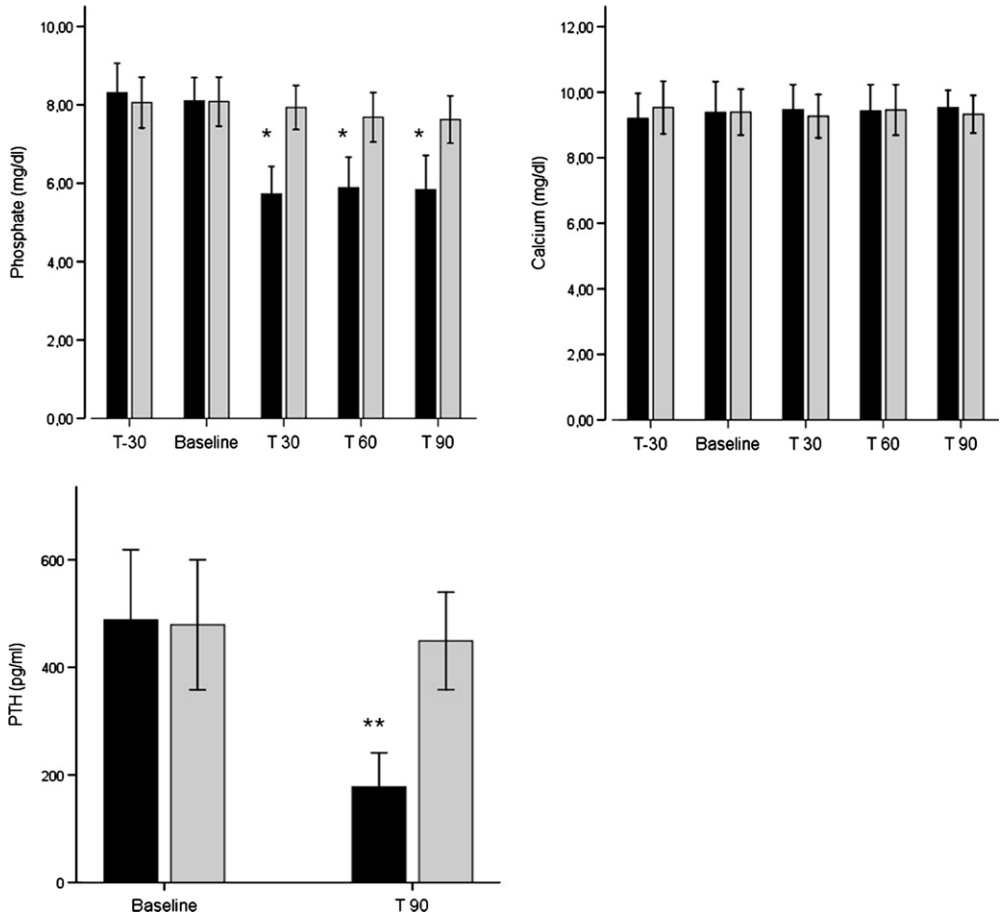

Figure 1 Serum phosphate and calcium levels before *the trial* (T-30), at baseline (T0) and after 1, 2 and 3 months (T30, T60 and T90, respectively) and serum *parathormone* (PTH) levels at baseline and after 3 months, in Intervention (black) and Control (gray) groups. *$p = 0.000$ vs T-30 and baseline (ANOVA with a Bonferroni *post hoc* test), **$p < 0.001$ vs baseline (Student's paired test).

Blood samples were drawn before the dialysis session of the patients to measure serum calcium, phosphate, albumin (Behring Nephelometer, Dade Behring Inc, Newark, DE), creatinine, intact parathyroid hormone (iPTH) and the plasma levels of urea (reported as blood urea nitrogen, BUN). A sample was also obtained at the end of the dialysis session to measure the BUN value. The Kt/V, which is a measure of the dialysis dose, was calculated by the following equation: $-\ln(R - 0.008 \times Td) + (4 - 3.5R)\, UF/W$, where: R = BUN post-HD/BUN pre-HD, Td = HD time (hours), UF = ultrafiltration volume, W = body weight at end of dialysis session (kg). Kt/V is a dimensionless measure of dialytic dose, where K is the urea dialytic clearance (expressed in ml/ml), t is treatment time (in minutes) and V is the body volume cleared by urea at a rate K (V approximately equals total body water, that is, 58% of dry weight) [12]. iPTH was measured by immunoradiometric assay (IRMA, Scantibodies Laboratory Inc., Santee, CA; normal range, 10 to 65 pg/mL).

Anthropometric measurements and biochemical nutritional markers were registered before the trial, at baseline and after 1, 2 and 3 months. Body weight was always measured at the end of the of haemodialysis session. Body mass index (BMI) was calculated as the ratio body weight/height^2 (kg/m^2) [13]; body composition was qualitatively evaluated according to the patterns of bioelectrical impedance vector analysis [14]; resistance (Rs) and reactance (Xc) were directly measured in ohms (Ω) at 50 kHz using the bioelectrical impedance analyser (BIA 101 RJL, Akern Bioresearch, Firenze, Italy) according to the standard tetrapolar technique [15,16]. Measurements were carried in standardised conditions 30 min after the end of the dialysis session. Rs and Xc measurements were normalised by the stature of the patient and plotted as point vector on the gender-specific 50th, 75th and 95th tolerance ellipses calculated from the reference healthy population [14]. The vector's length (Z) indicates the changes in tissue hydration and was calculated as $|Z| = \sqrt{[(R/H)^2 + (Xc/H)^2]}$. The phase angle has been found to be a sensitive indicator of malnutrition depending on body cell mass changes and was calculated as the arctan (Xc/R) in degrees. The same investigators performed anthropometry and bioelectrical impedance (BIA) measurements.

The study was approved by the Ethical Committee of the Medical School of the University Federico II of Naples and all subjects gave their informed consent.

Statistics

Values are given as mean $\pm$ standard deviation. The independent Student's t-test was used to compare differences

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Table 3 Body weight and biochemical markers before the trial (T-30), at baseline (T0) and after 1, 2 and 3 months (T30, T60 and T90, respectively) in intervention and control groups.

	Intervention group ($n = 15$)						Control group ($n = 12$)					
	T-30	T0	T30	T60	T90	*p* value	T-30	T0	T30	T60	T90	*p* value
BW (kg)	70.4 ± 17.2	69.9 ± 13.6	70.5 ± 17.2	70.3 ± 17.5	70.7 ± 17.4	1.00	70.9 ± 18.2	70.2 ± 8.4	70.8 ± 16.5	71.3 ± 18.7	71.7 ± 19.6	1.00
Potassium (mEq/l)	6.2 ± 0.8	6.1 ± 0.9	5.7 ± 0.6	5.7 ± 0.6	5.6 ± 1.0	0.15	6.1 ± 0.7	6.0 ± 0.9	5.9 ± 0.8	5.9 ± 0.7	5.8 ± 1.2	0.93
T. Protein (g/dl)	6.8 ± 0.5	6.8 ± 0.5	6.7 ± 0.3	6.7 ± 0.4	6.6 ± 0.3	0.64	6.9 ± 0.6	6.9 ± 0.7	6.8 ± 0.7	6.8 ± 0.5	6.7 ± 0.6	0.92
Albumin (g/dl)	3.92 ± 0.3	4.01 ± 0.4	4.01 ± 0.5	3.97 ± 0.2	3.89 ± 0.2	0.82	3.95 ± 0.5	3.97 ± 0.3	4.04 ± 0.7	4.02 ± 0.3	3.85 ± 0.5	0.88
Hemoglobin (g/dl)	11.6 ± 1.4	11.9 ± 1.4	11.6 ± 1.3	11.7 ± 1.2	11.6 ± 1.2	0.96	11.5 ± 1.5	11.8 ± 1.4	11.7 ± 1.7	11.7 ± 1.6	11.7 ± 1.3	0.97
Creatinine (mg/dl)	12.3 ± 3.4	12.4 ± 2.5	11.8 ± 1.9	11.6 ± 2.3	11.0 ± 2.4	0.56	11.9 ± 3.5	12.0 ± 2.4	11.5 ± 1.6	11.7 ± 2.9	11.5 ± 2.3	0.98
BUN (mg/dl)	88.6 ± 23.2	88.5 ± 29.6	83.2 ± 18.6	92.1 ± 18.0	87.0 ± 10.8	0.84	90.6 ± 24.3	91.5 ± 29.3	93.1 ± 18.8	94.1 ± 19.0	90.0 ± 11.6	0.98
Kt/V	1.35 ± 0.12	1.40 ± 0.15	1.42 ± 0.16	1.35 ± 0.15	1.43 ± 0.12	0.36	1.35 ± 0.16	1.37 ± 0.17	1.43 ± 0.18	1.43 ± 0.14	1.44 ± 0.15	0.54

between control and intervention groups at baseline and the paired Student's *t*-test was used to analyse the difference from baseline to the end of the study. Analysis of variance (ANOVA) for repeated measurements and the Bonferroni *post hoc* test were used for comparison of the dependent variables in the different time periods. $P < 0.05$ was considered statistically significant.

Results

Baseline data are shown in Table 2. Demographic and anthropometric data, mean serum phosphate and iPTH levels, concomitant vitamin D and the use of phosphate binders gave similar results between intervention and control groups. All patients completed the study and no patient discontinued the treatment prematurely. At the end of follow-up, patients of the intervention group showed a significant decrease in mean serum phosphate and iPTH levels (8.3 ± 1.2 mg/dL vs 5.7 ± 1.4 mg/dL, $p = 0.000$, and 488 ± 205 pg/ml vs 177 ± 100 pg/ml, $p < 0.001$, respectively), while no significant changes were found in the control group. No significant changes in serum albumin, calcium, potassium, *Kt/V* and body weight were observed in both, the intervention and control groups (Fig. 1 and Table 3). Interdialytic weight gain and pre-dialytic blood pressure did not change significantly in both intervention and control groups. Moreover, our findings show that no statistically significant differences were observed in *Rs*, *Xc*, phase angle and in the vector length measures, as assessed by BIA between baseline and the end of the study in both groups (Table 4).

At the end of follow-up, patients of the intervention group showed a significant decrease in phosphate (−37% vs. baseline, $p < 0.05$) and potassium (−23% vs. baseline, $p < 0.05$) intake, whereas no significant differences were observed for energy and protein intake. A decrease of the dietary phosphate−protein ratio (−37% vs. baseline, $p < 0.05$) also occurred. In the control group, conversely, no significant differences in phosphate, potassium, energy and protein intake were observed at the end of the study (Table 4).

Discussion

In a recently published study of 40,538 haemodialysis patients, higher serum phosphate levels were consistently associated with increased death risks [2]. Similarly, a rise in serum phosphate over time is associated with increasing mortality [3].

Dietary restrictions to control serum phosphate are recommended in dialysis patients and are usually associated with a reduction in protein intake, as phosphate and protein intakes are related. This may lead to malnutrition and poor survival in the patients [17,18]. Therefore, dietary phosphate restriction should always be considered according to an adequate protein intake of >1 g/kg/day. Without any phosphate binders, an average of 60−80% of the phosphate intake is absorbed in the gut [19]. If binders are employed, the phosphate absorbed could be reduced to 40% [20−23]; in these circumstances, 642 mg of phosphate is absorbed and this value should be a critical amount.

The present study shows that a partial replacement of natural foods, which are naturally high in phosphate, with

Table 4 Bioelectrical impedance data and mean dietary intakes in Intervention and Control groups at baseline (T0) and after 3 months (T90).

	Intervention group $n = 15$			Control group $n = 12$		
	T0	T90	p value	T0	T90	p value
Resistence (Ohm)	527 ± 88	509 ± 90	0.58	530 ± 68	515 ± 8	0.64
Reactance (Ohm)	62 ± 15	58 ± 15	0.47	57 ± 12	59 ± 16	0.73
Phase Angle (°)	6.8 ± 1.7	6.4 ± 1.2	0.46	6.7 ± 1.9	6.9 ± 1.3	0.76
Vector length (Ohm/m)	332 ± 64	320 ± 63	0.60	330 ± 59	350 ± 60	0.42
Energy intake (kcal/kg[a])	39.2 ± 8.5	(36.7 ± 9.3) + (2.2 ± 0.3)[b]	0.92	39.9 ± 7.2	39.7 ± 10.2	0.96
Protein intake (g/kg[a])	1.3 ± 0.2	(0.8 ± 0.1) + (0.5 ± 0.1)[b]	1.00	1.3 ± 0.5	1.3 ± 0.3	1.00
Phosphate intake (mg/day)	1070.0 ± 143.6	672.3 ± 119.8	0.000	1100.3 ± 115.6	1098.7 ± 119.7	0.97
Potassium intake (mg/day)	1675.4 ± 363.6	1291.8 ± 278.0	0.000	1695.4 ± 333.8	1705.0 ± 293.3	0.91
Phosphorus/protein intake	11.6 ± 3.1	7.3 ± 1.5	0.000	12.0 ± 3.5	11.9 ± 2.7	0.94

[a] kg of ideal body weight.
[b] From protein concentrate (PROther®).

a low-phosphorus protein concentrate, does affect serum phosphate levels in dialysis patients with hyperphosphataemia (Fig. 1). Our data are in keeping with the chance to reduce dietary phosphate content without change in protein intake, limiting the phosphate load. In addition, natural foods, such as uncooked meat and poultry, may contain additives that increase phosphorus and potassium content by as much as almost two- and threefold, respectively [24]. Educating patients to avoid processed and fast foods prepared with phosphorus-containing additives results in clinically significant improvements in serum phosphate levels [25]. Therefore, even though food additives are another significant source of phosphate, this study was focussed on examining the contribution of phosphate that is naturally present in food on serum phosphate levels.

In dialysis patients, a neutral phosphate balance could be reached only by a marked dietary protein restriction [7] that may induce malnutrition [17,18]. However, although a significant decrease of dietary phosphate intake was obtained in the intervention group, no modification of total energy and protein intake was observed. A quite low phosphate-to-protein ratio in all patients at baseline is due to general dietary recommendations by nephrologists in an attempt to reduce phosphorus intake; however, a significant decrease of the dietary phosphate—protein ratio occurred only in the intervention group. Nutritional status was also maintained unchanged during the study period, as demonstrated by the constancy of both body weight and biochemical markers (Table 4). In addition, no modification in body composition was observed, as assessed by BIA. In fact, either phase angle (representative of body cell mass) or vector length (representative of hydration status) remained unchanged after 3 months of follow-up in the intervention group (Table 4). These findings also support the safety of this diet.

'Moreover, phosphate retention is a main factor in the development of secondary hyperparathyroidism [20,26]. The increase in iPTH levels causes osteitis fibrosa, which in the past was the most frequent form of bone disease observed in the dialysis population. Serum iPTH levels significantly decreased in the intervention group at the end of the 3-month study period. In contrast, no significant difference was observed in the control group (Fig. 1). This result suggests that a controlled serum phosphate concentration could be partially responsible for lowering iPTH levels already after a 3-month period in dialysis patients. Nevertheless, this important finding must be cautiously interpreted because of the small simple size.

Furthermore, patients showed good diet compliance because they found the nutritional substitute in their diet quite satisfactory. None of the treated patients dropped out of the study. This low-phosphorus and low-potassium protein concentrate may help patients maintain normal serum potassium levels as well; this is very important for low mortality in haemodialysis patients [27].

The major limitation of this study is the small sample size that decreased the statistical power of statistical tests. Moreover, the estimates obtained from this study can be used while designing future studies.

In conclusion, this study indicates that innovative strategies in addition to both traditional dietary and pharmacological therapy may be useful in hyperphosphataemia management in dialysis patients. This plan could also lead to a reduction in the needed dosage of phosphate binders, ameliorating their compliance and tolerability. We believe that a phosphate-controlled diet is a very important therapeutic approach to hyperphosphataemia in compliant and motivated dialysis patients, and the nutritional substitute is a valid integrated method to achieve it.

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Disclosures

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