Self-adjustment of phosphate binder dose to meal phosphorus content improves management of hyperphosphataemia in children with chronic kidney disease

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Abstract

Background. Hyperphosphataemia in patients with chronic kidney disease (CKD) is associated with mineral and bone disorder and increased cardiovascular mortality. Despite phosphate binders (PB), nutrition counselling and dialysis therapy, the prevalence of hyperphosphataemia remains unacceptably high. It was hypothesized that an inadequate relation of PB dose to meal inorganic phosphorus (iP) content may be an important factor for failure of phosphate management.

Methods. The innovative ‘Phosphate Education Program’ (PEP) bases on patient empowerment to eye-estimate meal iP content by newly defined ‘Phosphate Units’ (PU; 1 PU per 100 mg phosphorus) and self-adjust PB dosage to dietary iP intake by an individually prescribed PB/PU ratio (PB pills per PU). In a prospective study, 16 children (aged 4–17 years) with CKD and their parents were trained with the PEP concept and followed up for 24 weeks for changes in serum electrolyte levels, dietary behaviour and PB dose.

Results. Within 6 weeks after PEP training, the percentage of children with serum phosphate (PO) >1.78 mmol/l dropped from 63% (10/16) to 31% (5/16). Mean serum PO level decreased from 1.94 ± 0.23 at baseline to 1.68 ± 0.30 (SD) mmol/l in Week 7–12 (P = 0.02) and to 1.78 ± 0.36 (SD) mmol/l in Week 19–24 (P = 0.2), whereas serum calcium [2.66 ± 0.3 vs 2.60 ± 0.23 (SD) mmol/l in Weeks 7–12 (P = 0.45) and 2.66 ± 0.23 (SD) mmol/l in Week 19–24 (P = 0.21)] and serum potassium [4.69 ± 0.48 vs 4.58 ± 0.68 (SD) mmol/l in Week 7–12 (P = 0.40) and 4.65 ± 0.49 (SD) mmol/l in Week 19–24 (P = 0.73)] remained unchanged. The mean daily PB dose rose from 6.3 ± 2.9 to 8.2 ± 5.4 (SD) pills during observation period with an increased meal-to-meal variability (P = 0.04). Dietary iP intake was not affected by PEP concept.

Conclusion. The empowerment of children with CKD and their parents to self-adjust PB dose to eye-estimated meal iP content significantly improved management of hyperphosphataemia without reducing dietary iP intake.

Keywords: children; chronic kidney disease; hyperphosphataemia; phosphate units; renal diet

Introduction

Chronic kidney disease (CKD) causes derangements of mineral metabolism. In 2003, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for bone metabolism and disease highlighted the fundamental importance of preventing hyperphosphataemia in CKD [1]. Hyperphosphataemia is not only associated with secondary hyperparathyroidism and renal osteodystrophy, but also with increased cardiovascular calcification. In numerous studies, elevated serum phosphate (PO) level has been identified as a significant independent risk factor for cardiovascular morbidity and mortality in patients with advanced CKD [2–6]. Disturbances of calcium and phosphate metabolism pose an important threat especially to younger CKD patients [7–9], because childhood and adolescence are crucial times for development of the skeletal and vascular system. Various studies have documented that young adults (aged 20–40 years) with end-stage renal disease (ESRD) already show significant cardiovascular calcification related to hyperphosphataemia and cumulative calcium load [10,11].

Although the importance of an adequate management of serum PO is generally emphasized [1,12], the prevalence of hyperphosphataemia remains critically high. The international Dialysis Outcome and Practice Pattern Study (DOPPS) suggested that fewer than 50% of the patients met the target value for serum PO [13,14].

Management of hyperphosphataemia is based on three principles: (i) phosphate removal by dialysis, (ii) restriction of dietary inorganic phosphorus (iP) intake and (iii) inhibition of gastrointestinal iP absorption by phosphate binders [15,16].

Dietary iP restriction is frequently not well tolerated, especially by paediatric patients because of prohibition of
Materials and methods

Study design and patients

The protocol of the ‘junior PROPHET’ study (‘Phosphate Reduction by Phosphate Education Program’ in paediatric CKD patients) was approved by the Ethics Committee of the Medical School of Hannover, Germany. ‘Junior PROPHET’ was designed as a non-randomized prospective study with a one group, pre-test/post-test intervention design, using each subject as his or her own control. The primary end point of the study is the mean serum PO level in Week 3–6, 7–12, 13–18 and 19–24 after PEP training in comparison to the mean serum PO level at baseline. The calculation of sample size was performed for a two-tailed test with the following considerations: The effect was considered as relevant, if the pre-test/post-test difference of serum PO is 0.2 mmol/l. It was assumed that the standard deviation was 0.25 mmol/l. Using an alpha error level of 5% and a sample size of 15 patients, the statistical power would be 87%. Secondary end points are PB dose, dietary habits and patient satisfaction.

Patients were recruited from the outpatient clinic of the Department of Paediatric Nephrology of the Medical School of Hannover, Germany. Patients aged <18 years with various stages of CKD (either pre-dialysis, or on haemodialysis, or on peritoneal dialysis) and treated with PBs for management of hyperphosphataemia for at least 12 weeks were eligible for participation. Patients were excluded from the study if (i) they received dietary supplements, (ii) they did not require PB medication for control of hyperphosphataemia or (iii) the patients or their caregivers were unwilling to participate. Written informed consent was given. A total of 18 patients were chosen for the ‘junior PROPHET’ study (Table 1). However, after PEP training, two patients were excluded from the study because of the start of dialysis during the initial observation period: A 13-year-old boy (Patient 18) starting peritoneal dialysis about 5 weeks before PEP training, and a 15-year-old boy (Patient 17) starting haemodialysis during the second study week. Accordingly, 16 paediatric patients with CKD were included: 2 on haemodialysis, 4 on peritoneal dialysis and 10 on predialysis (Table 1). The patient age ranged between 4 and 17 years (median 13 years), and 50% of the subjects were male (n = 8).

Concept of PEP

The recently developed PEP allows CKD patients to self-adjust PB dose in relation to the iP content of each individual meal [18]. The concept is comparable with adjusting insulin dose to carbohydrate intake (carbohydrate counting) in the treatment of diabetes mellitus [19]. The innovative PEP concept is based on eye-estimation of the meal iP content by PU. The PB dose results from an individually prescribed PB/PU ratio (number of PB pills per PU) (Figure 1). One PU is defined per 100 mg of iP per given serving size (Figure 2). Since different components of the same food group have similar iP content, the PEP concept allows to categorize major food groups by their iP content and to assign the same PU value to all sorts of one food group (e.g. a 150-g serving size of any fish fillet = 4 PU or of any meat sort = 3 PU). Therefore, the patients do not have to memorize the exact iP content of each food component but only the PU value for a limited number of food groups.

PEP training

Detailed instruction on the new PEP concept was given in the form of PEP workshops for smaller groups of study participants (4–9 paediatric patients with their parents per workshop). The meetings were held by one paediatrician.
Self-adjustment of phosphate binder dose to phosphorus intake

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (year)</th>
<th>Sex</th>
<th>CKD stage</th>
<th>Dialysis treatment</th>
<th>Δ Creatinine (pre/post) (mmol/l)</th>
<th>Vitamin D medication (calcitriol; daily dose)</th>
<th>Phosphate binders (PB)</th>
<th>Adjustments of PB/PU ratio</th>
<th>Follow-up (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>♀</td>
<td>V</td>
<td>HD</td>
<td>+ 208</td>
<td>1 μg</td>
<td>No</td>
<td>No</td>
<td>1×</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>♂</td>
<td>V</td>
<td>HD</td>
<td>+ 208</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>♀</td>
<td>V</td>
<td>PD</td>
<td>- 50</td>
<td>0.13 μg</td>
<td>No</td>
<td>No</td>
<td>3×</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>♀</td>
<td>V</td>
<td>PD</td>
<td>- 112</td>
<td>No</td>
<td>No</td>
<td>O</td>
<td>3×</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>♂</td>
<td>V</td>
<td>PD</td>
<td>+ 292</td>
<td>0.25 μg</td>
<td>0.25 μg</td>
<td>2×</td>
<td>2×</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>♀</td>
<td>V</td>
<td>PD</td>
<td>- 322</td>
<td>No</td>
<td>No</td>
<td>O</td>
<td>1×</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>♀</td>
<td>V</td>
<td>V</td>
<td>- 55</td>
<td>0.5 μg</td>
<td>0.25 μg</td>
<td>O</td>
<td>3×</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>♂</td>
<td>V</td>
<td>V</td>
<td>+ 65</td>
<td>0.5 μg</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>♀</td>
<td>V</td>
<td>V</td>
<td>+ 120</td>
<td>0.5 μg</td>
<td>No</td>
<td>No</td>
<td>1×</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>♂</td>
<td>IV</td>
<td>Ω</td>
<td>+ 4</td>
<td>0.5 μg</td>
<td>0.5 μg</td>
<td>O</td>
<td>2×</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>♀</td>
<td>V</td>
<td>Ω</td>
<td>+ 7</td>
<td>0.25 μg</td>
<td>0.25 μg</td>
<td>O</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>♂</td>
<td>IV</td>
<td>Ω</td>
<td>+ 144</td>
<td>0.25 μg</td>
<td>0.5 μg</td>
<td>O</td>
<td>3×</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>♀</td>
<td>V</td>
<td>V</td>
<td>- 184</td>
<td>No</td>
<td>0.25 μg</td>
<td>0.25 μg</td>
<td>1×</td>
</tr>
<tr>
<td>14</td>
<td>13</td>
<td>♀</td>
<td>V</td>
<td>Ω</td>
<td>0</td>
<td>0.25 μg</td>
<td>0.25 μg</td>
<td>O</td>
<td>3×</td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td>♂</td>
<td>V</td>
<td>Ω</td>
<td>+ 42</td>
<td>0.25 μg</td>
<td>0.5 μg</td>
<td>O</td>
<td>2×</td>
</tr>
<tr>
<td>16</td>
<td>13</td>
<td>♂</td>
<td>V</td>
<td>Ω</td>
<td>+ 151</td>
<td>0.25 μg</td>
<td>0.25 μg</td>
<td>O</td>
<td>3×</td>
</tr>
<tr>
<td>17</td>
<td>15</td>
<td>♀</td>
<td>Ω</td>
<td>Ω; HD</td>
<td>Excluded</td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>18</td>
<td>13</td>
<td>♂</td>
<td>Ω</td>
<td>PD</td>
<td>Excluded</td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

Dialysis therapy: HD, haemodialysis; PD, peritoneal dialysis; Ω, no dialysis. Type of phosphate binder: O, at study start; x, at study end; Φ, at study start and end; Δ Creatinine, the difference between s-creatinine values at baseline and at end of the study.

Data collection

Baseline data for the 6 weeks directly prior to the PEP workshop were obtained prospectively from medical records. The follow-up period after PEP training was 24 weeks, subdivided into four intervals of 6 weeks. Changes in serum phosphate, calcium, potassium, creatinine and parathyroid hormone concentrations after PEP training were compared to the baseline data. Blood chemistry data derived during the first 2 weeks after the PEP training or during a hospital stay were not included in the analysis. Follow-up was incomplete in five patients due to either successful renal transplantation (Patient 2, 6, 8 and 13) or start of haemodialysis (Patient 9), with a minimum follow-up of 7 weeks (Table 1).

Prescription of PB

Instead of a fixed dosing regimen, PBs were strictly prescribed as individual PB/PU ratio (= number of PB pills per PU). The first PB/PU ratio for each patient was calculated from individual dietary diaries (2-3 days per person) and actual serum PO levels: the total intake of PUs per day was estimated by analysing the dietary records. The number of PUs per day was related to the previous daily intake of PBs. The resulting PB/PU ratio indicated the number of PB pills per PU (for example 1 PB/2 PU = one tablet of PB per two PU) (Figure 1). One PB pill was defined as either 500 mg calcium acetate or 500 mg calcium carbonate or 800 mg sevelamer hydrochloride. After PEP training, the PB/PU ratio was adjusted to the patient’s individual needs by repeating measures the serum PO levels.

Table 2. Definition of the ‘Phosphate Unit’ (PU)

<table>
<thead>
<tr>
<th>Phosphorus content (mg)</th>
<th>Phosphate Unit (PU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–50</td>
<td>0</td>
</tr>
<tr>
<td>50–100</td>
<td>1</td>
</tr>
<tr>
<td>100–200</td>
<td>2</td>
</tr>
<tr>
<td>200–300</td>
<td>3</td>
</tr>
<tr>
<td>300–400</td>
<td>4</td>
</tr>
<tr>
<td>400–500</td>
<td>5</td>
</tr>
<tr>
<td>500–600</td>
<td>6</td>
</tr>
</tbody>
</table>

The inorganic phosphorus (iP) content of different food components is categorized by ‘Phosphate Units’ (PU). One PU is assigned per 100 mg of iP per defined serving size.

Definition of hyperphosphataemia

The National Kidney Foundation (NKF) recommends target serum PO levels 5.17 mmol/l for adults with advanced CKD [1]. However, target serum PO levels during infancy and early childhood differ from adults [12]: Serum PO levels of newborns average 2.0 mmol/l (range 1.55–2.39) and gradually decrease during infancy [20]. At 4 years of age, normal serum PO levels are in the range of 1.4 mmol/l (range 0.97–1.81), and during the following childhood and adolescence, serum PO does not differ significantly from adults. The youngest patient of our study group was 4 years old. Therefore, hyperphosphataemia was defined as serum PO levels >1.78 mmol/l in accordance with the KDOQI guidelines for adults [1].

Statistical analysis

All data are expressed as mean ± standard deviation (SD) and/or as median. The differences of serum phosphate levels >1.78 mmol/l at baseline and after PEP training were examined by Pearson’s chi-square. The follow-up data on serum phosphate, serum calcium, serum potassium, meal iP content, PB intake and patient satisfaction were analysed by two-tailed paired or unpaired t-test or Mann–Whitney test. Normal distribution was
confirmed by the Kolmogorov–Smirnov test. Significance was set at a level of \( P < 0.05 \).

## Results

### Follow-up of serum phosphate levels and other electrolytes after PEP training

During the 6-week period preceding the PEP training, hyperphosphataemia, defined as serum PO levels > 1.78 mmol/l, was prevalent in 62.5% (10/16) of our study group. Within 6 weeks after PEP training, the percentage of children with hyperphosphataemia has dropped to 31% (5/16) (\( P = 0.08 \)) (Figure 2, Table 3). After the PEP workshop, the mean serum PO level significantly decreased from 1.94 ± 0.23 at baseline to 1.65 ± 0.30 (SD)mmol/l in Week 3–6 (\( P = 0.01 \)) and to 1.68 ± 0.30 (SD)mmol/l in Week 7–12 (\( P = 0.02 \)). Within the following 12 weeks (13th–24th week after PEP training), mean serum PO levels increased slightly but still remained below baseline levels [1.70 ± 0.35 (SD)mmol/l in Week 13–18 (\( P = 0.10 \)) and 1.78 ± 0.36 (SD)mmol/l in Week 19–24 (\( P = 0.20 \)).

However, due to the limited number of study subjects in Week 13–18 (\( n = 13 \)) and in Week 19–24 (\( n = 11 \)), the differences from baseline did not reach statistical significance. Because of a successful kidney transplantation or start of dialysis, five children (Patient 2, 6, 8, 9 and 13) dropped out of the study after 7, 10, 11, 15 and 18 weeks (Table 1). Regarding only those eleven patients followed up for 24 months, mean serum PO level decreased from 1.91 ± 0.21 at baseline to 1.76 ± 0.21 (SD)mmol/l in Week 3–6 (\( P = 0.10 \)) and to 1.78 ± 0.36 (SD)mmol/l in Week 19–24 (\( P = 0.2 \)).

In accordance to the follow-up of serum PO, the mean calcium × phosphate product was significantly improved [5.13 ± 0.64 vs 4.32 ± 0.89 (SD)mmol²/l² in Week 3–6 (\( P = 0.01 \)); Table 3]. While the serum PO level and calcium × phosphate product decreased significantly after PEP training, no significant changes in mean serum calcium [2.66 ± 0.3 at baseline vs 2.60 ± 0.23 (SD)mmol/l in Week 7–12 (\( P = 0.45 \)) and 2.66 ± 0.23 (SD)mmol/l in Week 19–24 (\( P = 0.69 \)) vs baseline].

### Table 3. Follow-up of mean serum phosphate, calcium, calcium × phosphate product and parathyroid hormone at baseline and during the 24-week follow-up after PEP training

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline (( n = 16 ))</th>
<th>Before PEP</th>
<th>After PEP training</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–6</td>
<td>1.94 (10/16)</td>
<td>1.65 (5/16)</td>
<td>1.68 (5/16)</td>
</tr>
<tr>
<td>7–12</td>
<td>2.66 (15/16)</td>
<td>2.61 (15/16)</td>
<td>2.6 (15/16)</td>
</tr>
<tr>
<td>13–18</td>
<td>5.13 (13/16)</td>
<td>4.32 (9/16)</td>
<td>4.36 (6/16)</td>
</tr>
<tr>
<td>19–24</td>
<td>16.7 (2/16)</td>
<td>13.2 (0/16)</td>
<td>14.2 (0/16)</td>
</tr>
</tbody>
</table>

\( (n/n) \), proportion of patients exceeding the upper limit of KDOQI guidelines; Ca × PO product, calcium × phosphate product.
Table 3] and mean serum potassium concentration 4.69 ± 0.48 vs 4.58 ± 0.68 (SD) mmol/l in Week 7–12 (P = 0.40) and 4.65 ± 0.49 (SD) mmol/l in Week 19–24 (P = 0.73) were observed. For the most part, serum calcium is beyond the KDOQI guidelines partially caused by the widely used medication of calcium-containing PBs. In paediatric nephrology, calcium-free PBs were established only in recent years. Prior to study start, calcium-containing PBs have already been decreased, and several patients have been switched to sevelamer due to high serum calcium levels. Some children had high serum calcium levels even without calcium-containing PBs.

Parathyroid hormone (Table 3) and vitamin D medication (Table 1) did not show significant changes during the study period.

In contrast to the majority of our study group, four patients showed persistent hyperphosphataemia after PEP training in association with a significant increase in serum creatinine level indicating a concomitant impairment of residual renal function and/or efficiency of dialysis (Table 1).

**Dietary habits**

Dietary habits were evaluated by comparing dietary diaries during the baseline period with those in Month 2–4 after PEP training (each with 2–3 days per patient). Two children (Patient 6 and 10) failed to record nutrition protocols during the follow-up period. Accordingly, a total of 74 daily food records of 14 patients were available for analysis: 37 before the PEP workshop and 37 after.

The dietary diaries showed a remarkable day-to-day variation in meal iP content both before and after the PEP workshop (Figure 3A and B): The iP content of the main dishes (breakfast, lunch, dinner) ranged between <50 and 687 mg before PEP training and between <50 and 572 mg.

![Fig. 3. Individual meal phosphorus content before (A) and after (B) introduction of the PEP concept. Meal inorganic phosphorus (iP) content of 14 children with CKD was derived from 37 dietary diaries (2–3 days per patient) during baseline period (A) compared to 37 dietary diaries (2–3 days per patient) during the second to the fourth month after introduction of the PEP concept (B). Average iP content is indicated.](https://academic.oup.com/ndt/article-abstract/25/10/3241/1870403)
During the baseline period, the mean meal iP content was 138 ± 125 (SD)mg for breakfast, 214 ± 135 (SD)mg for lunch and 265 ± 154 (SD)mg for dinner (Figure 3A). The snacks contributed significantly to the daily iP intake (up to 438 mg per snack): A total of 61 snacks (on average 1.6 snacks per day) were documented with a mean iP content of 88 ± 91 (SD)mg. Among the recorded days, there were 46% with one snack, 32% with two snacks and 14% with ≥3 snacks, but only 8% without any snack (3/37). After the PEP workshop, the dietary iP consumption did not show any significant change (P = 0.25): Mean meal iP content was 173 ± 115 (SD)mg for breakfast, 274 ± 130 (SD)mg for lunch, 244 ± 141 (SD)mg for dinner and 110 ± 97 (SD)mg for snacks (Figure 3B). With a total of 50 snacks, the average daily frequency of snacks was similar to the baseline period (1.4 snacks per day): No snacks were consumed in 22% of recorded days, one snack in 35%, two snacks in 30% and ≥3 snacks in 13%. This data documents that dietary behaviour and total dietary iP consumption have not significantly changed after introduction of the PEP concept.

**PB medication**

Before PEP training, PB medication was mainly prescribed in fixed doses (e.g. 3 × 2 pills per day). Depending on the serum calcium concentration, the paediatric patients received calcium-containing or calcium-free PBs: At the beginning of our study, 1 patient (6%) was on calcium carbonate, 14 patients (88%) on calcium acetate and 5 patients (31%) on sevelamer hydrochloride; among these five patients, four received a combination of calcium acetate and sevelamer (Table 1). At the start of the study, the previously fixed PB dose was replaced by an individual PB/PU ratio. The individual PB/PU ratios ranged from 1 PB pill per 3.5 PU to 1 PB pill per 0.5 PU. During the active study period, the PB/PU ratio had to be adjusted on average 1.6 times per patient (a total of 26 modifications in 16 patients) (Table 1): During the first 6-week under observation, 62.5 % of our study group (10/16) required an adjustment of the PB/PU ratio, and during the following 6-week periods, the PB/PU ratio was adjusted only in four and six patients, respectively. While in the cases of serum PO levels <1.1 mmol/l, the PB/PU ratio was reduced, and PB medication was not discontinued in any patient.

At the end of follow-up, one patient (6%) was still on calcium carbonate, 12 patients (75%) on calcium acetate and 6 patients (38%) on sevelamer hydrochloride; among these six patients, three received a combination of calcium acetate and sevelamer (Table 1).

At baseline, the average daily PB dose was 6.3 ± 2.9 pills per day. After PEP training, the mean intake of PB pills significantly increased to 8.2 ± 5.4 pills per day (mean ± SD) during the observation period (P = 0.04).

The analysis of the PB documentation of the dietary diaries showed that the distribution of daily PB dose was changed after the introduction of the PEP concept: Before the PEP workshop, the mean PB dose for breakfast, lunch and dinner was 2.0 ± 1.1, 2.1 ± 1.1 and 2.1 ± 0.9 pills (mean ± SD), respectively, but significantly less for snacks (0.1 ± 0.5 pills) (Figure 4). The majority of patients did not take any PB pills with snacks: Only 6.6% of snacks (4/61) were covered with PB pills. This data is indicative for a predominantly fixed dosing regimen for PBs with an almost exclusive focus on main dishes (e.g. 3 × 2 pills per day). In contrast, the PEP concept resulted in an increased meal-to-meal and day-to-day variation of PB dose, as indicated by a higher standard deviation of PB dose per meal (Figure 4). The mean BP dose taken during breakfast, lunch and dinner increased significantly to 2.6 ± 2.1, 4.0 ± 2.8

**Fig. 4.** Consumption of phosphate binders per meal before and after introduction of the PEP concept. The number of phosphate binder pills per meal at baseline (open bars) and during the second to the fourth month after PEP training (solid bars) was derived from dietary diaries of 14 paediatric patients (37 dietary diaries before PEP training versus 37 afterwards). Data is given as mean ± SD; significance (P < 0.05) versus baseline data as asterisks.
and 4.1 ± 3.9 tablets (mean ± SD), respectively (P = 0.14, P = 0.0003, P = 0.004). Notably, the number of PBs taken with snacks rose to 1.2 ± 1.5 tablets (p < 0.0001). Accordingly, dietary diaries documented that, after PEP training, 62% of snacks (31/50) were covered with PBs.

Patient compliance and acceptance of PEP

Patient compliance was assessed by questionnaires in Month 2-4. The analysis of questionnaires indicated that our paediatric patients and their parents reliably remembered PU calculation and PB intake nearly at each meal, including most of the snacks (median 8.0 points on a scale 1–10). The majority of children and parents assessed the PEP concept as easy and suitable for daily use [median 8.4 points on a scale from 1 (very difficult) to 10 (very easy)]; even the 11-year-old boy (Patient 11) considered that the PU calculation is very easy (10 points on a scale 1–10), and his parents confirmed that the boy applied PEP on his own authority. Accordingly, questioning demonstrated that the children and parents had to only occasionally consult the PEP manual (at an average of once a day).

Patient satisfaction

The questionnaire replies of the paediatric CKD patients and their parents in Month 2-4 showed that PEP improved patient satisfaction related to eating: After PEP training, the children had to give up significantly less favourite foods (P = 0.0002) and showed a tendency to greater pleasure in eating (P = 0.16; data not shown). Furthermore, we analysed the favourite foods of our paediatric study group: 56% (9/16) ranked meat as favourite food, 56% (9/16) fast food (e.g. burgers, kebabs, pizza), 50% (8/16) chocolate; all other foods were chosen by <40% of our paediatric patients. Those food groups most frequently named (by ≥50% of our patients) are all high in phosphate.

Discussion

In the present prospective study (‘junior PROPHET’), the introduction of a novel concept for the management of hyperphosphataemia resulted in a significant improvement of serum PO levels in paediatric patients with CKD.

The inadequate relation of PB dose to dietary iP intake seems to be a critical point of management of hyperphosphataemia. In clinical practice, PBs are preferentially prescribed in a fixed dosing regimen, such as 3 × 2 pills per day. This pattern is based on the assumption that dietary iP intake is relatively stable and predictable. However, our analysis of paediatric dietary diaries revealed a strong meal-to-meal and day-to-day variability of dietary iP intake. With regard to this variability, the PB prescription in fixed doses is obviously inappropriate offering no possibility for PB adjustment to actual iP intake. In addition, the conventional fixed PB dosing regimen normally takes only main dishes into account. However, the dietary diaries of our paediatric study group indicated that even snacks, which were mostly not covered by PBs, are an important source of additional iP intake. The PEP concept enables a flexible, individual adjustment of PB dose to variable iP content of each meal, including both, all main dishes and all snacks. Thus, after PEP training, we found an increased meal-to-meal and day-to-day variability of PB dose, similar to the fluctuant meal iP content. In contrast to a fixed PB dosing regimen, the majority of snacks were covered with PBs.

A further cause of limited efficiency of conventional fixed PB prescription is poor patient compliance including complete neglect of PB pills and inadequate timing of PB intake: Many patients take their PB pills thrice daily without considering mealtimes [16]. However, the synchronization with mealtimes is crucial for the adequate binding of dietary iP. It is well established that unsynchronized intake of PBs significantly increases the absorption of ingested iP when compared to concomitant intake of PBs with meals [21,22]. In this regard, the PEP concept offers the condition for more adequate timing of PB intake: By relating meals directly with eye-estimation of iP content and calculation of PB dose, patients are automatically reminded of the necessity to take PBs with every meal. Accordingly, our paediatric patients and their parents confirmed that they remembered PU calculation and PB intake nearly at each meal.

In addition to the improved adjustment of PB dose, the introduction of the PEP concept resulted in an increase of PB consumption. Several randomized controlled trials on the efficacy of PBs in ESRD have demonstrated that an adequate lowering of serum PO levels into the target range is generally possible with all phosphate-binding substances, but only at the price of a higher total daily PB dose [23–26].

Besides the phosphate-binding medication, the management of hyperphosphataemia is based on the restriction of dietary iP intake. During the PEP workshop, detailed information about food iP content was provided, which by itself might result in improved phosphorus awareness, reduced dietary iP intake and lowered serum PO levels. However, the comparison of dietary diaries before and after PEP training did not show any significant reduction of daily iP intake. Therefore, we suggest that the increased knowledge of food iP content alone made only a small contribution to the success of the ‘junior PROPHET’ study. Recently, Blaszak et al. also reported on a dietary education programme in children receiving peritoneal dialysis, where in spite of intensive patient education, they found no effect on serum PO level or PB consumption [27].

In general, restriction of dietary phosphorus intake is badly tolerated; especially, children often refuse the phosphorus reduced diet since their favourite food is usually rich in phosphorus. During childhood and adolescence, patients respond to uncompromising dietary limits and cumulative prohibitions with frustration and defiance, provoking a complete refusal to eat and take pills. The PEP concept offers an alternative to strict prohibitions. Instructing patients to self-adjust PB dose to estimated meal iP content is a novel concept which integrates patient empowerment for the first time in the management of hyperphosphataemia in CKD [15,16,18]. Hence, PEP improved patient satisfaction since the patients had to give up favourite foods significantly less. Additionally, our patients...
showed an increased reliability in taking PB pills, possibly due to the concept of patient empowerment.

Furthermore, dietary phosphate restriction may even be harmful to patients due to an increased risk of development of protein malnutrition: Due to the close relation between food iP and protein content, patients adhering strictly to dietary iP restriction may severely reduce dietary protein intake [17]. Shinaberger et al. recently demonstrated that, in adult patients in whom serum PO levels were normalized at the expense of dietary protein intake, the mortality risk was significantly higher than in those in whom serum PO targets were achieved while dietary protein intake was maintained or even increased [28]. Consequently, it is difficult to find the balance between dietary phosphate restriction and adequate protein intake. The conventional estimation of ingested phosphate using phosphorus tables, booklets and electronic calculators is complicated, cumbersome and time-consuming. The patients are mostly overtaxed by an abstract calculation with triple-digit milligram-numbers and millilitre-quantities. Moreover, in childhood and adolescence, there is no general recommendation for daily phosphate consumption, since the allowed phosphate intake is dependent on age, body height, weight, growth rate, residual renal function and dialysis dose. Therefore, the PEP concept was developed combining a novel method for eye-estimation of meal iP content with an innovative PB dosing strategy. In contrast to abstract, triple-digit milligram-numbers, the newly defined PU are easy, single-digit numbers related to serving sizes (e.g., one glass, two slices, a tablespoonful). Patients are not required to memorize the iP content of each individual food component, but only one PU value for each major food group. Hence, PU calculation is applicable everywhere and easy to memorize. The paediatric patients and their parents assessed the PEP concept as feasible and suitable for daily use. PEP offers the basis for an individual phosphate-conscious diet instead of an inflexible, strict phosphate-reduced diet. A similar concept of patient empowerment and self-adjustment of medication has been successfully established in the management of insulin-dependent diabetes (carbohydrate counting), even in childhood [19,29,30].

In spite of the considerable advantages, the patient empowerment of the PEP concept carries the risk of uncontrolled excessive PB intake. An excessive intake of calcium-based PBs can lead to an undesirable hypercalcemia and progression of vascular calcification [22,31] linked with increased risk of death [4]. Accordingly, it was found that treatment with calcium-containing PBs was associated with increased mortality compared to sevelamer [32,33]. Clinical trials have shown that sevelamer in not generating hypercalcemia reduced the risk of cardiovascular calcification [23]. Therefore, in case of elevated serum calcium, we treated our paediatric patients with sevelamer or with a combination of sevelamer and calcium acetate. However, overdosing of calcium-free PBs, such as sevelamer, aluminium hydroxide or lanthanum carbonate, will either have some economic impact (sevelamer, lanthanum carbonate) or increase the risk of substance accumulation (lanthanum or aluminium) or the development of metabolic acidosis (sevelamer) [22,25,31,34,35]. To prevent an excessive PB consumption after PEP training, we decided to limit the total daily intake of calcium acetate, calcium carbonate and sevelamer, respectively. The maximum prescription of PB pills per day was assessed depending on the age and body weight. Hence, our patients showed no significant increase in mean serum calcium levels in spite of an increased mean daily PB intake.

Although the majority of our paediatric study group showed an improved phosphate management during the observation period, we found four patients with persistent hyperphosphataemia despite introduction of the PEP concept. However, their disappointing results are probably caused by concomitant impairment of residual renal function or dialysis efficiency. Moreover, we suppose that insufficient patient and parent cooperation contributed to the disappointing serum PO levels of some patients. Based on the concept of patient empowerment, an essential requirement for successful PEP management is the willingness to cooperate. Accordingly, in cases of distinct non-compliance, PEP is not promising.

Concerning the course of the mean serum PO level during the study period, a slow but steady increase was found: Compared to the baseline, mean serum PO levels were significantly lower during the first 12 weeks, while statistical significance was not achieved during the following 12 weeks. Due to the small sample size, dropout and heterogeneous response to interventions significance were not verifiable at all levels. Potentially, the tendency of serum PO concentration to slowly increase may also point to a need for a retraining after 3 months in order to ensure motivation and adherence.

Altogether, after introduction of the PEP concept, the improvement of serum PO levels resulted in higher mean daily PB consumption and increased meal-to-meal variability of PB dose, whereas the dietary iP intake and parathyroid hormone have not significantly changed during the study period. The success of the PEP concept seems to be predominantly caused by patient empowerment and a flexible, individualized PB dosing regimen.

The ‘junior PROPHET’ study was designed as a non-randomized prospective study with a one group, pre-test/post-test intervention design. This design did not allow us to completely distinguish the effects of pure participation in a trial from those of the new PB dosing concept. However, the finding that both, an increase in total daily PB dose and a higher meal-to-meal variability of BP dose, occurred in parallel, can only be explained as a direct result of the PEP intervention.

In conclusion, this is the first trial using the innovative PEP concept in patients with CKD. The ‘junior PROPHET’ study proves that management of hyperphosphataemia may be significantly improved by individual self-adjustment of PB dose to variable meal iP content. In view of the promising results of this paediatric study, a future randomized trial applying the PEP concept in a large cohort of adults is urgently warranted.

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References


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