Mineral metabolism and clinical outcomes in dialysis patients
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Disordered mineral metabolism is not a risk factor for loss of residual renal function in dialysis patients

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Submitted for publication
**Background:** Recent studies showed that mineral metabolism disorders are associated with renal function loss in pre-dialysis patients, but their effects in dialysis patients are less well established. We examined associations between parameters of mineral metabolism and loss of residual renal function (RRF) in dialysis patients.

**Study design:** Prospective multicentre cohort study in the Netherlands (NECOSAD).

**Setting and participants:** 1468 incident haemodialysis (HD) and peritoneal dialysis (PD) patients who were not anuric at dialysis initiation.

**Predictors:** Plasma calcium, phosphorus, calcium-phosphorus product, and intact PTH concentrations.

**Outcome:** Total loss of RRF, defined as anuria during the first 3 years of dialysis.

**Measurements:** Cox regression models were applied to calculate relative risks of total loss of RRF. The rate of decline of RRF over time was calculated using general linear mixed models.

**Results:** Mean (SD) age was 59 (15), 62% were men, and 59% were treated with HD. We found that both HD and PD patients with the highest phosphorus \((P < 0.0001)\) and calcium-phosphorus product \((P < 0.0001)\) levels had the lowest baseline residual glomerular filtration rate (rGFR) values. During follow-up, 136 HD (15%) and 67 PD patients (12%) became anuric. After adjustment for baseline rGFR, there were no significant associations between parameters of mineral metabolism and the risk of becoming anuric. There were also no differences in the rate of decline in RRF between categories of plasma concentrations.

**Limitations:** rGFR values could not be calculated for all patients due to missing or unreliable urine collections.

**Conclusion:** Disordered mineral metabolism was neither associated with the risk of becoming anuric, nor with the rate of decline in RRF in dialysis patients. Differences in decline were mainly attributable to the baseline rGFR value.
Introduction

Preserving residual renal function (RRF) is one of the primary goals for nephrologists managing patients with chronic kidney disease (CKD). Also in CKD stage V, after the initiation of dialysis therapy, preservation of RRF remains important. RRF contributes significantly to the overall health and well-being of dialysis patients and the loss of RRF predicts mortality in haemodialysis (HD) and peritoneal dialysis (PD) patients. In addition, loss of RRF contributes significantly to anaemia, inflammation, and malnutrition in patients receiving dialysis treatment.

Disturbances in mineral metabolism, such as secondary hyperparathyroidism and hyperphosphataemia, are common in patients receiving HD or PD therapy and have been suggested as potential causes of decline of RRF. There is some evidence for a role of elevated intact parathyroid hormone (iPTH) levels in the progression of renal failure. In addition, previous studies have shown that a decline in RRF leads to decreased phosphorus removal. Wang et al. reported that residual glomerular filtration rate (rGFR), despite on average being below 2 ml/min/1.73 m², was strongly associated with phosphorus control in PD patients. Although there is evidence that a lower RRF leads to higher plasma phosphorus levels, higher plasma phosphorus levels might lead to a faster decline in RRF as well. In a rat model of CKD, associations between high plasma phosphorus concentration and both decline in renal function and renal morphological changes have been shown. The main external source of plasma phosphorus in humans is protein from the diet. The effect of a protein-restricted diet on decline in renal function has been studied extensively in CKD patients and showed a small benefit. These data support the hypothesis that phosphorus might be associated with the decline in RRF in humans, which was confirmed by some recent studies in pre-dialysis patients. In addition, in one of these studies, a non-significant trend was observed between low plasma calcium levels and decline in RRF.

There are no previous studies that investigated whether hyperphosphataemia, or other disturbances in mineral metabolism, has a deteriorating effect on RRF in patients receiving dialysis therapy. Therefore, we aimed to determine the associations between disordered plasma calcium, phosphorus, calcium-phosphorus (Ca x P) product, and iPTH concentrations, and the decline in RRF in a large prospective cohort of HD and PD patients in the Netherlands.

Methods

Subjects

In the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a large prospective multicentre cohort study, end-stage renal disease patients are followed from the initiation of dialysis until transplantation or death. All incident dialysis patients in 38 dialysis
units in the Netherlands were consecutively invited to participate in the study. Patients had to be 18 years or older with dialysis as their first renal replacement therapy.

For the current analyses we included HD and PD patients new on chronic dialysis treatment between 1997 and 2006. Because we were interested in decline of RRF, patients were excluded when they were already anuric at dialysis initiation. To be included, patients had to have measurements of plasma calcium, phosphorus, and iPTH concentrations available at the time point three months after the start of dialysis (baseline visit). All patients gave informed consent before inclusion and the study was approved by all local medical ethics committees. Patients were followed until transplantation, death, or 1 January 2007.

Data collection

Data on demography, primary kidney disease and comorbidity were collected zero to four weeks before the start of dialysis treatment. During follow-up, data on RRF, biochemistry, and dialysis characteristics were collected at fixed time points, three and six months after the start of dialysis, followed by six-month intervals.

Primary kidney disease was classified according to the codes of the European Renal Association-Dialysis and Transplantation Association (ERA-EDTA). Patients were categorised according to Davies’ comorbidity index as having no, intermediate or severe comorbidity based on the number of comorbid conditions. The nutritional status was scored on the seven-point scale of the Subjective Global Assessment (SGA), which is a standardised method based on the clinical judgment of the dialysis nurse. We defined malnourishment as an SGA score of five or lower. Dialysis dose, expressed as Kt/V urea per week, was calculated as dialysis urea clearance, divided by urea distribution volume (V) according to Watson et al. For HD patients dialysis urea clearance was calculated using a second generation Daugirdas formula and for PD patients peritoneal Kt/V urea was calculated from a 24-hour dialysate collection.

In HD patients blood samples were drawn before and after a monitoring dialysis session and again before the following dialysis session. Urine was collected during the entire interdialytic interval. The plasma concentrations used for the calculation of the GFR, were the mean of the concentration after a monitoring dialysis session, and the concentration before to the next dialysis session. In PD patients, a 24-hour urine and dialysate collection was done prior to a monitoring visit at the outpatient clinic and a blood sample was drawn at that visit. RRF was expressed as rGFR, calculated as the mean of creatinine and urea clearance adjusted for body surface area (ml/min/1.73 m²). rGFR was determined at three and six months after start of dialysis therapy and every six months onwards. The rGFR level was set to zero when urine production was <200 ml/24h. When a patient had a rGFR value of zero at two successive time points, we defined the patient as anuric from the first time point that rGFR was zero.
Plasma calcium, phosphorus, iPTH, and albumin were measured by standard laboratory techniques in the different centres. Calcium concentrations (mg/dl) were corrected for the albumin concentration (g/dl) using the formula \[\text{Corrected Calcium} = \text{Calcium} + 0.8 \times (4 - \text{albumin})\].\(^{26,27}\) To calculate the Ca x P product in mg\(^2\)/dl\(^2\) we multiplied the corrected calcium concentration by the phosphorus concentration, each in mg/dl. Plasma concentrations of calcium, phosphorus, Ca x P product and iPTH were classified into categories less than, at, or greater than the targets recommended in the K/DOQI guideline.\(^{26}\) This guideline recommends serum concentrations of corrected calcium between 8.4 and 9.5 mg/dl (2.10 and 2.37 mmol/l) and serum phosphorus concentrations between 3.5 and 5.5 mg/dl (1.13 and 1.78 mmol/l). Ca x P product concentrations should be less than 55 mg\(^2\)/dl\(^2\) (<4.4 mmol\(^2\)/l\(^2\)) and iPTH concentrations should range from 150 to 300 pg/ml (15.8 to 31.6 pmol/l). Because the greater part of the study period was before publication of the K/DOQI guideline, nephrologists probably did not aim for these targets. The resulting large variation enabled us to study the effects of K/DOQI targets on RRF.

**Statistical analysis**

Standard descriptive statistics were used to examine differences between HD and PD patients. Student’s \(t\)-tests were applied for testing differences in continuous variables and the chi-square test was used to compare distributions of dichotomous or categorical data. All analyses were stratified for treatment modality (HD or PD) as reported three months after start of dialysis. Plasma calcium, phosphorus, Ca x P product, and iPTH concentrations were analysed in categories based on the K/DOQI guideline.\(^{27}\) Patients who had too low or too high plasma concentrations were compared with patients who met the targets (reference category). ANOVA testing was applied to compare baseline rGFR values less than, at, and greater than the advised target ranges.

We evaluated hazard ratios (HRs) for becoming anuric during the first three years of dialysis therapy utilizing Cox proportional hazards models, stratified for treatment modality, and controlling for baseline rGFR, calcium, phosphorus, iPTH, age, sex, comorbid conditions, nutritional status (SGA), systolic and diastolic blood pressure, urinary protein loss, and use of anti-hypertensive drugs. A separate multivariable model was used to calculate the HR for Ca x P product. This model contained the same variables except for calcium and phosphorus.

In addition, generalised linear mixed models for repeated measures were applied to analyse the effects of mineral metabolism, based on the K/DOQI guideline, on the decline of RRF over the first three years of dialysis treatment. The multivariate model contained calcium, phosphorus, iPTH, systolic and diastolic blood pressure, and proteinuria as repeatedly measured variables. Additional adjustments were applied for age, sex, comorbidity score, nutritional status, and use of anti-hypertensive medication as recorded at baseline. A separate
multivariate model, which contained the same variables except for calcium and phosphorus, was applied to analyse the effect of Ca x P product on the decline of RRF.

All statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute; Cary, NC, USA). A P-value <0.05 was considered to indicate statistical significance.

Table 1. Patient characteristics three months after the start of dialysis (n =1468)

<table>
<thead>
<tr>
<th></th>
<th>HD (n =899)</th>
<th>PD (n =569)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>63 (14)</td>
<td>52 (15)</td>
</tr>
<tr>
<td>Gender (% males)*</td>
<td>59</td>
<td>67</td>
</tr>
<tr>
<td>Primary Kidney Disease (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Comorbidity (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>42</td>
<td>61</td>
</tr>
<tr>
<td>Moderate</td>
<td>49</td>
<td>33</td>
</tr>
<tr>
<td>High</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>rGFR (ml/min)*</td>
<td>4.01 (2.70)</td>
<td>4.59 (2.85)</td>
</tr>
<tr>
<td>Dialysis Kt/Vurea (/week)</td>
<td>2.67 (0.80)</td>
<td>1.58 (2.22)</td>
</tr>
<tr>
<td>Urine production (ml/24 h)*</td>
<td>910 (625)</td>
<td>1212 (775)</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>1.77 (2.25)</td>
<td>1.70 (2.22)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)*</td>
<td>149 (19)</td>
<td>140 (21)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)*</td>
<td>80 (10)</td>
<td>85 (12)</td>
</tr>
<tr>
<td>Anti-hypertensive drugs (% yes)*</td>
<td>82</td>
<td>88</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.63 (0.49)</td>
<td>3.64 (0.51)</td>
</tr>
<tr>
<td>Haemoglobin (mmol/l)*</td>
<td>6.71 (0.87)</td>
<td>7.46 (0.98)</td>
</tr>
<tr>
<td>Nutritional status (% malnourished)*</td>
<td>28.9</td>
<td>16.9</td>
</tr>
<tr>
<td>Corrected calcium (mg/dl)*</td>
<td>9.63 (1.04)</td>
<td>9.98 (0.98)</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)*</td>
<td>5.74 (1.67)</td>
<td>5.28 (1.45)</td>
</tr>
<tr>
<td>Ca x P product (mg²/dl²)*</td>
<td>55.3 (16.9)</td>
<td>52.7 (15.5)</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>222 (272)</td>
<td>210 (243)</td>
</tr>
<tr>
<td>Phosphate binders (% yes)</td>
<td>90</td>
<td>91</td>
</tr>
</tbody>
</table>

Mean values (SD) are presented for continuous variables.

* P <0.05, HD versus PD patients.

To convert serum albumin in g/dl to g/l, multiply by 10; plasma calcium in mg/dl to mmol/l, multiply by 0.2495; plasma phosphorus in mg/dl to mmol/l, multiply by 0.3229; plasma iPTH in pg/ml to ng/l, multiply by 1.
Results

Description

From a total of 2004 patients we had to exclude 298 patients because they had not collected urine at any time point in the study. In addition, we excluded 130 patients who were already anuric at the baseline visit. Finally, 104 patients were excluded due to missing information on mineral metabolism at baseline. The remaining 1468 patients were included in the analyses. Compared to the included patients, excluded patients were older and they more often had a high comorbidity score. Other baseline characteristics were not different between in- and excluded patients. The included patients had a mean age of 59 years, 62% were male and 61% were treated with HD. Patient characteristics three months after start of dialysis treatment are summarised in Table 1.

Decline of RRF

At baseline, mean (SD) rGFR was 4.0 (2.7) ml/min/1.73 m² in HD patients and 4.6 (2.9) ml/min/1.73 m² in PD patients ($P <0.0001$). When we compared baseline rGFR values in categories of plasma concentrations as advised in the K/DOQI guideline for bone metabolism and disease, we found that plasma phosphorus concentrations differed significantly between HD and PD patients with plasma phosphorus less than, at, or greater than the target range ($P <0.0001$). Patients with plasma concentrations greater than 5.5 mg/dl had the lowest GFR values. Also HD and PD patients with plasma Ca x P product values >$55 \text{mg}^2/\text{dl}^2$ had lower rGFR values than patients who met the target ($P <0.0001$). GFR values did not differ between categories for calcium and iPTH levels. Results of this analysis are presented in Table 2.

Table 2a. Mean baseline rGFR (ml/min/1.73 m²) in categories of plasma calcium, phosphorus, Ca x P product, and iPTH in HD patients

<table>
<thead>
<tr>
<th></th>
<th>HD ($n = 899$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than</td>
</tr>
<tr>
<td>Calcium</td>
<td>4.10 (3.03)</td>
</tr>
<tr>
<td>% patients</td>
<td>7</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>5.38 (3.16)</td>
</tr>
<tr>
<td>% patients</td>
<td>7</td>
</tr>
<tr>
<td>Ca x P product</td>
<td>-</td>
</tr>
<tr>
<td>% patients</td>
<td></td>
</tr>
<tr>
<td>iPTH</td>
<td>4.07 (2.65)</td>
</tr>
<tr>
<td>% patients</td>
<td>54</td>
</tr>
</tbody>
</table>

Mean (SD) values are presented. $P$-values for ANOVA test.

K/DOQI guideline ranges: calcium 8.4-9.5 mg/dl, phosphorus 3.5-5.5 mg/dl, Ca x P product <$55 \text{mg}^2/\text{dl}^2$, iPTH 150-300 pg/ml.
Table 2b. Mean baseline rGFR (ml/min/1.73 m²) in categories of plasma calcium, phosphorus, Ca x P product, and iPTH in PD patients

<table>
<thead>
<tr>
<th></th>
<th>PD (n = 569)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than</td>
<td>At</td>
<td>Greater than</td>
<td></td>
<td>P-value</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% patients</td>
<td>3.82 (2.55)</td>
<td>4.97 (2.71)</td>
<td>4.49 (2.66)</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>6.56 (2.94)</td>
<td>5.03 (2.81)</td>
<td>3.59 (1.92)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% patients</td>
<td>10</td>
<td>51</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca x P product</td>
<td>-</td>
<td>5.28 (2.88)</td>
<td>3.60 (1.94)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% patients</td>
<td>-</td>
<td>60</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPTH</td>
<td>4.56 (2.56)</td>
<td>4.77 (2.88)</td>
<td>4.58 (2.77)</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>% patients</td>
<td>56</td>
<td>22</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean (SD) values are presented. P-values for ANOVA test.

K/DOQI guideline ranges: calcium 8.4-9.5 mg/dl, phosphorus 3.5-5.5 mg/dl, Ca x P product <55 mg²/dl², iPTH 150-300 pg/ml.

There were 136 out of 899 HD patients (15%) and 67 out of 569 PD patients (12%) who became anuric in the first three years of dialysis treatment. Kaplan-Meier curves for time until loss of RRF in HD and PD patients are shown in Figure 1. The mean (SD) time until patients became anuric was 32.4 (11.5) months for HD patients, and 34.1 (9.1) months for PD patients (P <0.01).

![Figure 1. Kaplan-Meier curves for the time until total loss of RRF in HD and PD patients. Log rank test for HD versus PD patients: P <0.01.](image-url)

Cox proportional hazards models were used to calculate crude and adjusted hazard ratios (HRs) for total loss of RRF in categories of patients that had plasma levels less than, at, or greater than the targets advised in the K/DOQI guideline. In the unadjusted analyses, we found
that PD patients with a baseline plasma calcium concentration above the target range had an elevated risk of becoming anuric [HR: 2.2; 95% confidence interval (CI): 1.1 to 4.2]. HD patients with hyperphosphatemia had a 60% higher risk of becoming anuric within three years after start of dialysis when compared to HD patients who met the target for phosphorus (HR: 1.6; 95% CI: 1.1 to 2.3). Moreover, a Ca x P product concentration greater than 55 mg²/dl² was associated with a significantly elevated HR of 1.7 (95% CI: 1.2 to 2.4) in HD patients, but not in PD patients. We could not detect any statistically significant effects of iPTH on the risk of becoming anuric (data not shown). In the multivariate models containing baseline rGFR, calcium, phosphorus, iPTH, age, sex, co-morbidity, systolic and diastolic blood pressure, albumin, urinary protein, and use of anti-hypertensive drugs, effects of plasma concentrations were no longer statistically significant. Only HD patients with an elevated iPTH levels had a lower risk of becoming anuric compared to patients who met the iPTH-target (HR: 0.5; 95% CI: 0.3 to 1.0). Adjusted HRs are presented in Table 3. We obtained comparable findings after repeating the multivariate analyses with plasma calcium and phosphorus concentrations as continuous variables, instead of applying the K/DOQI cut-off values, or after removing proteinuria from the model. When we removed baseline rGFR from the multivariate model, the observed effects were similar to those from the crude analyses.

Table 3. Adjusted* hazard ratios (HR; 95% confidence interval) for the risk of total loss of RRF in categories of plasma concentrations for HD and PD patients

<table>
<thead>
<tr>
<th></th>
<th>HD (n = 899)</th>
<th>PD (n = 569)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Calcium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 8.4 mg/dl</td>
<td>0.7 (0.3-1.6)</td>
<td>0.39</td>
</tr>
<tr>
<td>8.4-9.5 mg/dl</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 9.5 mg/dl</td>
<td>1.0 (0.6-1.4)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Phosphorus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.5 mg/dl</td>
<td>0.7 (0.2-2.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>3.5-5.5 mg/dl</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 5.5 mg/dl</td>
<td>1.2 (0.8-1.9)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Ca x P product</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55 mg²/dl²</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥ 55 mg²/dl²</td>
<td>1.4 (0.9-2.0)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>iPTH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 150 pg/ml</td>
<td>0.8 (0.5-1.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>150-300 pg/ml</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 300 pg/ml</td>
<td>0.5 (0.3-1.0)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Multivariate model contained: Baseline rGFR, calcium, phosphorus, iPTH, age, sex, comorbidity score, nutritional status (SGA), systolic and diastolic blood pressure, proteinuria, and use of anti-hypertensive drugs.

# Number of patients and events in this category is too low to obtain an effect-estimate.

To convert serum albumin in g/dl to g/l, multiply by 10; plasma calcium in mg/dl to mmol/l, multiply by 0.2495; plasma phosphorus in mg/dl to mmol/l, multiply by 0.3229; plasma iPTH in pg/ml to ng/l, multiply by 1.
Figure 2. Adjusted curves for decline in RRF over time in categories of (A) plasma calcium
d(B) phosphorus, and (C) Ca x P product in HD patients

A. Calcium *

* Multivariate model: time, calcium, calcium* time, phosphorus, iPTH, age, sex, co-morbidity, nutritional status, systolic and diastolic blood pressure, proteinuria, use of anti-hypertensive medication.

B. Phosphorus (P = 0.11)

* Multivariate model: time, phosphorus, phosphorus*time, calcium, iPTH, age, sex, co-morbidity, nutritional status, systolic and diastolic blood pressure, proteinuria, use of anti-hypertensive medication.

C. Ca x P product (P = 0.27)

* Multivariate model: time, Ca x P product, Ca x P product*time, iPTH, age, sex, co-morbidity, nutritional status, systolic and diastolic blood pressure, proteinuria, use of anti-hypertensive medication.

* The groups of HD and PD patients with plasma calcium <8.4 mg/dl were too small to obtain reliable effect estimates after 24 and 30 months, respectively. P-values for differences between categories (main group effect).
Figure 3. Adjusted curves for decline in RRF over time in categories of (A) plasma calcium\textsuperscript{a}, (B) phosphorus\textsuperscript{b}, and (C) Ca x P product\textsuperscript{c} in PD patients.

A. Calcium *

\[ \text{B. Phosphorus } (P = 0.96) \]

\[ \text{C. Ca x P product } (P = 0.70) \]

\textsuperscript{a} Multivariate model: time, calcium, calcium* time, phosphorus, iPTH, age, sex, co-morbidity, nutritional status, systolic and diastolic blood pressure, proteinuria, use of anti-hypertensive medication.

\textsuperscript{b} Multivariate model: time, phosphorus, phosphorus* time, calcium, iPTH, age, sex, co-morbidity, nutritional status, systolic and diastolic blood pressure, proteinuria, use of anti-hypertensive medication.

\textsuperscript{c} Multivariate model: time, Ca x P product, Ca x P product* time, iPTH, age, sex, co-morbidity, nutritional status, systolic and diastolic blood pressure, proteinuria, use of anti-hypertensive medication.
To analyse the decline of RRF over time, we applied general linear mixed models for repeated measures. The multivariate model contained calcium, phosphorus, iPTH, systolic and diastolic blood pressure, proteinuria, age, sex, comorbidity score, nutritional status, and use of antihypertensive medication. Results from these analyses are depicted in Figures 2 and 3. Because the number of HD and PD patients with plasma calcium less than 8.4 mg/dl was too small, effect-estimates from the statistical model after 24 and 30 months, respectively, were unreliable and as a consequence we could not compare the rate of decline in RRF in the three groups. Both in HD and PD patients, there was no significant difference in the rate of decline between the different phosphorus categories. The rate of decline in rGFR was also not significantly different in HD and PD patients who had too high Ca x P product levels when compared to patients who met the target.

To verify whether the results were influenced by baseline rGFR, we repeated all the mixed models-analyses in subgroups of patients with a high or a low baseline rGFR level. Subgroups were defined based on the median rGFR value (HD: 3.48 ml/min/1.73 m²; PD: 4.24 ml/min/1.73 m²). In this additional analysis, we observed similar trends for the rate of decline in the different subgroups (data not shown).

Discussion

This study demonstrates that disordered mineral metabolism is not significantly associated with rate of decline of RRF in HD and PD patients. Differences in decline in RRF between the categories for plasma calcium, phosphorus, Ca x P product, and iPTH concentrations were mainly attributable to the baseline rGFR value. Effects were similar in PD patients when compared to HD patients.

Our study is the first that examines the role of disturbances in mineral metabolism with deterioration of residual renal function in a large cohort of dialysis patients. Several cross sectional studies have shown an association of plasma phosphorus concentration with the level of RRF in patients with rGFR values less than 40 ml/min. A meta-analysis of these studies has shown that a higher protein intake, and consequently a higher phosphorus intake, accelerates the decline in renal function in CKD patients. This finding is in accordance with a study of Schwarz et al. in a historical cohort of male US veterans with CKD stage I to V who were not yet on dialysis. The authors found in this cohort elevated relative risks of progression of CKD (defined as the composite of start of renal replacement therapy or doubling of serum creatinine) in patients with higher serum phosphorus and Ca x P product. In our study, the first performed in dialysis patients, we applied two methods to study both the long term (Cox regression based on baseline values) and short term (general linear mixed models for repeated measurements) effects of disordered mineral metabolism. However, neither of those methods showed any significant associations with decline in RRF. After adjustment for baseline rGFR
Decline of residual renal function

level, associations were no longer statistically significant, while in pre-dialysis patients the
associations were independent of baseline renal function.12-14

We could not detect a significant association between plasma calcium and loss of RRF, while
some other studies found contradictory results. Moist et al. observed in HD and PD patients
that higher serum calcium levels were independently associated with decreased risk of RRF
loss.15 Because only few patients in our study had calcium levels less than 8.4 mg/dl (7% of
HD and 2% of PD patients), we were unable to draw any firm conclusions about the influence
of hypocalcaemia. The only significant finding in this study was that elevated iPTH levels were
associated with a decreased risk of becoming anuric in HD patients. We cannot explain this
finding based on the available literature. Although there is only little direct experimental or
clinical evidence for a role of elevated iPTH on progression of renal failure, it is difficult to
link the presence of (secondary) hyperparathyroidism to a decreased risk of becoming anuric.

There are several other factors related to mineral metabolism that might influence the
progression of CKD, but were not considered in this study. First, there is evidence that 1,25
(OH)2D3 and its analogues attenuate the progression of kidney failure both in non-
inflammatory and inflammatory models of CKD.7,16 Furthermore, an excess of the novel
phosphaturic hormone Fibroblast Growth Factor 23 (FGF-23) might be a potential culprit in
the progression of CKD. A recent study of Fliser et al. demonstrated in a cohort of 227 CKD
patients, that FGF-23 is an independent predictor of progression of renal disease in patients
with non-diabetic CKD.17 Unfortunately, FGF-23 was not measured in our study and data on
vitamin D prescription were only available for a small subset of patients. Also data on other
medications that could interfere in the relationship between mineral metabolism and the
decline of RRF, such as phosphate binders and calcimimetics, were incomplete.

Our study has some additional limitations. First, rGFR levels were not available for each
patient at every time point. Because urine collection was sometimes impossible or unreliable,
rGFR calculations might have been inaccurate in the final phase of ESRD. We believe,
however, that this shortcoming hardly influenced our results, because we considered a patient
as being anuric when urine production was less than 200 ml/24h at two successive time points
in the study and these lowest values of urine production (and rGFR) were not considered in
the analyses. We were also unable to determine the decline in RRF during the first three
months of dialysis treatment. Because rGFR measurements were often missing at the start of
dialysis, we had to apply the rGFR values measured at three months after the start of dialysis as
baseline values. Finally, iPTH measurements were not centrally performed, but by various first
generation immunometric iPTH-assays depending on the different participating centres.

In our study we could not demonstrate that higher plasma phosphorus leads to a faster decline
in RRF in dialysis patients. However, this hypothesis is well-founded by evidence from animal
studies. Animal models of CKD showed that a high plasma phosphorus concentration leads to
the precipitation and deposition of calcium-phosphorus micro crystals in the tubular lumen, peritubular space, capillaries, and the interstitium of the kidney, and is thus responsible for an inflammatory reaction. This leads to interstitial fibrosis and tubular atrophy, resulting in progressive loss of RRF. Additional evidence for a pathophysiological role of phosphorus is provided by a rat model of CKD. Rats with CKD that received phosphate-binding drugs, showed less intra renal calcium-phosphorus deposition and interstitial fibrosis, and less severe renal function loss compared to the rats not receiving such medication.

Mechanisms similar to those observed in animal models could explain the associations of phosphorus concentration with decline in RRF that were observed in studies among pre-dialysis patients. The discrepancies between studies in pre-dialysis patients and our study indicate that the associations between mineral metabolism and RRF are different, depending on the stage of CKD. While disorders of mineral metabolism are important determinants of renal function in the pre-dialysis phase, we can speculate that once dialysis treatment has been started, there are other factors that are dominating. Possible factors might include fluctuations in blood pressure or hypovolemic episodes. Keeping mineral metabolism, especially plasma phosphorus concentrations, in control can delay the deterioration of RRF during the pre-dialysis phase, but not anymore during dialysis treatment. Therefore, it is of major importance to treat disturbances in mineral metabolism thoroughly before the start of renal replacement therapy.

In conclusion, we found that disordered mineral metabolism is not a risk factor for decline of RRF in dialysis patients. Differences between categories of plasma calcium, phosphorus and \(Ca \times P\) product levels were mainly attributable to the baseline rGFR value.

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Decline of residual renal function


