Mineral metabolism and clinical outcomes in dialysis patients

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High plasma phosphorus as a risk factor for decline in renal function and mortality in pre-dialysis patients

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**Background:** Hyperphosphataemia is associated with increased mortality in patients with chronic kidney disease (CKD) stage IV or on dialysis. Furthermore, in animal studies elevated plasma phosphorus has been shown to be associated with an accelerated decline in renal function. The aim of this study was to determine the association of plasma phosphorus with renal function loss and mortality in CKD stage IV and V pre-dialysis patients with a glomerular filtration rate (GFR) <20 ml/min/1.73m².

**Methods:** Incident pre-dialysis patients were included between 1999 and 2001 in the multicentre PREPARE study, and followed until 2003 or death. Rate of decline in renal function for each patient was calculated by linear regression using the Modification of Diet in Renal Disease (MDRD) formula to estimate GFR (eGFR).

**Results:** A total of 448 patients were included [mean (SD) age 60 (15) years, eGFR 13 (5.4) ml/min, decline in renal function 0.38 (0.95) ml/min/month]. Phosphorus concentration at baseline was 4.71 (1.16) mg/dl, calcium 9.25 (0.77) mg/dl and calcium-phosphorus (Ca x P) product 43.5 (10.9) mg²/dl². For each mg/dl higher phosphorus concentration, the mean (95% confidence interval) decline in renal function increased with 0.154 (0.071 to 0.237) ml/min/month. After adjustment, this association remained [β 0.178 (0.082 to 0.275)]. Seven percent of patients died. Crude mortality risk was 1.25 (0.85 to 1.84) per mg/dl increase in phosphorus, which increased to 1.62 (1.02 to 2.59) after adjustment.

**Conclusions:** High plasma phosphorus is an independent risk factor for a more rapid decline in renal function and a higher mortality during the pre-dialysis phase. Plasma phosphorus within the normal range is likely of vital importance in pre-dialysis patients.
Introduction

In patients with severe chronic kidney disease (CKD), a preserved renal function not only postpones dialysis, but once dialysis is initiated, the residual renal function is associated with survival as well. Several risk factors for more rapid progression of renal function loss have been identified, including primary kidney disease, race, baseline renal function, proteinuria, blood pressure, poor glycaemic control and smoking. As inconclusive factors dyslipidaemia and anaemia are mentioned. In addition to these factors, plasma phosphorus has been suggested for many years as a potential risk factor for a more progressive decline in renal function.

Recently, a direct association between plasma phosphorus concentration and both decline in renal function and renal morphological changes has been shown in a rat model of CKD. Rats fed with a diet rich in phosphorus showed a faster decline in renal function compared with rats fed with a low phosphorus diet. In humans, the main external source of plasma phosphorus is protein from diet. The effect of a protein-restricted diet on decline in renal function has been studied extensively in CKD patients and shows a small benefit. Together, these data support the hypothesis that phosphorus is associated with decline in renal function in humans, especially in patients with severe CKD.

Hyperphosphataemia is present in about 50% of dialysis patients and 8% of patients with stage IV CKD. In pre-dialysis and haemodialysis (HD) patients, hyperphosphataemia has been shown to be associated with accelerated atherosclerotic lesion formation and cardiovascular morbidity. Furthermore, several observational studies have shown an association of plasma phosphorus and mortality in dialysis patients and in patients with a creatinine clearance between 30 and 60 ml/min. However, the association of plasma phosphorus with mortality in pre-dialysis patients remains to be determined.

The aim of this study was to assess the association of plasma phosphorus with decline in renal function in incident pre-dialysis patients with CKD stage IV and V with glomerular filtration rate (GFR) <20 ml/min/1.73m². Second, the association of plasma phosphorus with mortality risk was assessed in these patients.

Methods

Patients

Incident patients with CKD stage IV and V at the outpatient clinics of eight hospitals were included in the years 1999-2001 when referred to pre-dialysis care. Patients had been referred to these outpatient clinics when estimated GFR (eGFR) was <20 ml/min/1.73m², and the need for renal replacement therapy (RRT) was expected within one year. Patients who spent
less than one month on pre-dialysis care or with prior RRT were excluded. Additional inclusion criteria for the present analysis included the availability of serum phosphorus levels at the start of pre-dialysis and at least two measurements of serum creatinine during pre-dialysis care. The study was approved by the Institutional Review Boards of the participating hospitals, and in concordance with Good Clinical Practice Guidelines.

Study Design

This study was a retrospective follow-up study. The clinical course of incident pre-dialysis patients was followed through the medical charts until start of dialysis, death or 1 January 2003, whichever was earliest. Pre-defined data on demography, anthropometry and clinical symptoms were extracted from medical records at inclusion and at end of follow-up by specially trained trial nurses and medical students. All available data concerning laboratory measurements during the pre-dialysis period were extracted from the Hospital Information Systems.

Clinical laboratory

Calcium levels were corrected for plasma albumin level. Calcium-phosphorus (Ca x P) product was calculated as the corrected calcium concentration multiplied by the phosphorus concentration, and expressed in mg²/dl². eGFR was calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula. The daily protein intake was determined by calculating the normalised protein equivalent of nitrogen appearance (nPNA) in a subgroup of 238 out of 448 patients from three centres with available 24-hour urine samples and corrected for total body water according to Watson et al.15,16

Endpoints

The decline in renal function was estimated as the slope of the linear regression line through available eGFRs in each individual patient. All available eGFRs collected during follow-up were used. Death during pre-dialysis care or within one month after start of RRT was assessed from the paper medical records and hospital databases. Causes of death were classified according to the ERA-EDTA guidelines.17

Statistical analysis

Data are expressed as mean (SD). Differences between groups were examined by independent samples t-tests for continuous variables and chi-square tests for categorical variables. Phosphorus, calcium and other variables included in multivariate analysis were baseline values assessed at entry in the pre-dialysis clinics. Additional analysis using mean plasma phosphorus during the first three months of pre-dialysis care and in subgroups of patients were performed.
to test the robustness of the results. Linear regression analysis was used to assess the relation between the decline in renal function and phosphorus and Ca x P product. In multivariate analysis, variables associated with decline in kidney function as mentioned in the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (K/DOQI) review were used. These included baseline eGFR, primary kidney disease, haemoglobin level, systolic blood pressure and smoking. Other factors corrected for were age, gender and proteinuria. Cox proportional hazard analysis was used to estimate crude and adjusted mortality risk during the pre-dialysis period. Time from the first pre-dialysis visit until the start of dialysis, death, or end of follow-up was used in these models. Variables included in the multivariate model were age, gender, kidney function, primary kidney disease and main comorbidities (diabetes, cardiovascular disease and malignancy). Data were analysed with SPSS version 12.

Results

A total of 547 incident pre-dialysis patients were identified in the participating hospitals. At initiation of pre-dialysis care, phosphorus levels were available in 448 patients. Demographic, biochemical and comorbidity characteristics of the included patients are listed in Table 1. At least two measurements of eGFR between inclusion and end of follow-up were present in 432 out of the 448 patients, allowing calculation of the decline in renal function during pre-dialysis care in these patients. Patients with available plasma phosphorus levels at start of pre-dialysis care were not different from patients without this data with regard to age, sex, and primary kidney disease. Median follow up time was 337 days (range 31 to 1442). During follow up 32.4% started HD and 31.7% peritoneal dialysis, 2.9% were primarily transplanted, 6.7% died and 8.9% were referred to a different outpatient clinic (lost to follow-up), while 17.4% remained on pre-dialysis care until end of follow-up.

Baseline

For the total group, mean (SD) eGFR was 13 (5.4) ml/min/1.73m² at baseline. The mean plasma phosphorus concentration was 4.71(1.16) mg/dl (Figure 1), plasma calcium was 9.25 (0.77) mg/dl and Ca x P product was 43.5 (10.9) mg²/dl². Phosphorus within the target range as defined by the K/DOQI guidelines for CKD stage IV (between 2.7 and 4.6 mg/dl) was present in 223 out of 448 (50%) of patients. Hyperphosphataemia was found in 216 of 448 (48%) patients and hypophosphataemia only in 9 of 448 (2%) patients. From the hyperphosphataemic patients 157 of 216 (73%) had been referred to the pre-dialysis outpatient clinic by a nephrologist. Of these patients, 68% had been attending nephrological care for more than six months, which is comparable with 64% of the 194 out of 232 (84%) patients without hyperphosphataemia. The majority, 364 out of 448 (81%) of the patients had a Ca x P product below 55 mg²/dl², the target defined in the K/DOQI guidelines. These guidelines advise measurement of parathyroid hormone (PTH) in all pre-dialysis patients. However, laboratory files with PTH measurements at baseline were only available in five centres, where
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PTH was determined in the majority of patients at baseline \( n = 144 \text{ out of } 182 \ (79\%) \) as recommended in these guidelines.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>( n = 448 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60 ± 15</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>56</td>
</tr>
<tr>
<td>Primary kidney disease (%)*</td>
<td></td>
</tr>
<tr>
<td>Renal vascular disease/nephrosclerosis</td>
<td>22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>15</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>13</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>11</td>
</tr>
<tr>
<td>CRF (unknown origin)</td>
<td>11</td>
</tr>
<tr>
<td>Multi-system disease</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td>CrCl(^1) (ml/min)</td>
<td>17 ± 6.3</td>
</tr>
<tr>
<td>CrCl decline (ml/min/month)</td>
<td>-0.51 ± 0.90</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>152 ± 28</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84 ± 14</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>36</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>22</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>15</td>
</tr>
<tr>
<td>Malignancy</td>
<td>11</td>
</tr>
<tr>
<td>Smokers and quitters &lt;1 year before inclusion (%)</td>
<td>57</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4.71 ± 1.16</td>
</tr>
<tr>
<td>Calcium (mg/dl)(^†)</td>
<td>9.25 ± 0.77</td>
</tr>
<tr>
<td>Ca x P product (mg²/dl²)</td>
<td>43.5 ± 10.9</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>39 ± 5.4</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.0 ± 1.0</td>
</tr>
<tr>
<td>Proteinuria (g/24h)</td>
<td>2.78 ± 2.74</td>
</tr>
</tbody>
</table>

Mean values ± SD are given for continuous variables;

*According to European Renal Association classification;

\(^1\)CrCl, creatinine clearance calculated with the Cockcroft-Gault formula;

\(^†\)corrected for albumin concentration.

At entry in a pre-dialysis care clinic, 63% \( n = 288 \text{ out of } 448 \) of patients were prescribed a phosphate-binding drug. In the patients with a normal plasma phosphorus level this was 59%, in the hyperphosphataemic patients only 68% was prescribed a phosphorus-binding drug. Mainly calcium-containing phosphate-binding drugs were used. Fifty-five percent of the patients were prescribed a protein-restricted diet, with the same distribution among normo- and hyperphosphataemic subjects. There were nPNA measurements available in three centres where nPNA at the start of dialysis was determined in 81% of patients \( n = 238 \text{ out of } 293 \). Mean (SD) nPNA was 1.01 (0.26).
Mineral metabolism in pre-dialysis patients

Plasma phosphate concentration at start of predialysis care (mg/dl)

Figure 1. Distribution of plasma phosphorus concentrations at start of pre-dialysis care.

Plasma phosphorus can be converted from mg/dl to mmol/l by multiplying with 0.323. Bold lines indicate the margins of K/DOQI guideline CKD stage III-IV (2.7-4.6 mg/dl), thin lines indicate the margins of K/DOQI guideline CKD stage V (3.5-5.5 mg/dl).

Plasma phosphorus level was associated with baseline eGFR ($\beta =-2.09$, $P <0.001$). After correction for baseline eGFR, higher plasma phosphorus was associated with higher PTH, more proteinuria, younger age and the presence of glomerulonephritis or polycystic kidney disease ($P <0.01$ for all). Gender, haemoglobin concentration, nPNA and calcium were not associated with phosphorus level after correction for baseline eGFR ($P >0.10$ for all).

Decline in renal function

The median number of eGFR determinations per patient during the first half year of pre-dialysis care was 7 (range 2 to 44, mean: 9). Mean (SD) decline in renal function was 0.38 (0.95) ml/min/month for the total group. Remarkably, some patients had an improvement in renal function during the pre-dialysis care period (Figure 2). The 39 patients who had >0.5 ml/min/month increase in renal function had a similar baseline renal function [14.9 (5.7) ml/min/1.73m²], baseline phosphorus of 4.23 (1.03) mg/dl, age of 66.1 (15.1) years, and time on pre-dialysis care 519 (448) days as patients with stable or declining function. Main primary kidney disease was less often diabetes (8% versus 17% in the whole group), renovascular disease (16% versus 22%) and polycystic kidney disease (5% versus 13%) and more often
interstitial nephritis (23% versus 15%). Twenty-six percent of these patients were referred to an internal medicine outpatient clinic, 31% remained stable on pre-dialysis care and 13% died before start of dialysis, while only 31% started dialysis.

**Figure 2.** Association between plasma phosphorus concentration at the start of pre-dialysis care and subsequent decline in renal function during follow-up.

The solid line indicates the regression line for the relation between decline in renal function and plasma phosphorus level, dashed lines the upper and lower limit of the 95% confidence interval of the regression line.

Plasma phosphorus was significantly associated with decline in renal function: each mg/dl higher plasma phosphorus was associated with a 0.154 ml/min/month steeper slope of the renal function [95% confidence interval (CI): 0.071 to 0.237]. When the rate of decline was adjusted for known risk factors for a faster decline, higher phosphorus remained independently associated with a more rapid rate of decline [β (95% CI) 0.178 (0.082 to 0.275) ml/min/month, Table 2]. Further adjustment for albumin or nPNA at the start of pre-dialysis did not influence the rate of decline in renal function [β 0.178 (0.081 to 0.275) and 0.128 (0.020 to 0.236) ml/min/month, respectively].

To check the robustness of the results, additional analyses were performed. First, the mean plasma phosphorus during the first three months after start of pre-dialysis care was calculated for each patient. The median (minimum, maximum) number of phosphorus measurements during this period was three (2, 19) and the mean (SD) concentration 4.71 (1.18) mg/dl. This value of plasma phosphorus was independently associated with decline of renal function as
well [$\beta$ 0.249 (0.154 to 0.345) ml/min/month]. Second, 51 patients had a high plasma phosphorus level (>4.6 mg/dl) at entry, which decreased to normal values within three months, whereas an additional 51 patients had normal plasma phosphorus (≤4.6 mg/dl) at entry, which increased to >4.6 mg/dl after three months.

**Table 2.** Associations of phosphorus and Ca x P product with rate of decline in renal function and mortality.

<table>
<thead>
<tr>
<th></th>
<th>Crude $\beta$ (95%CI) per ml/min/month decline</th>
<th>$P$</th>
<th>Adjusted $\beta$ (95%CI) per ml/min/month decline</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus (mg/dl)$^a$</td>
<td>0.196 (0.104 to 0.288)</td>
<td>&lt;0.001</td>
<td>0.187 (0.082 to 0.293)$^*$</td>
<td>0.001</td>
</tr>
<tr>
<td>Ca x P (mg$/^2$/dl)$^b$</td>
<td>0.018 (0.009 to 0.028)</td>
<td>&lt;0.001</td>
<td>0.018 (0.007 to 0.029)$^†$</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium (0.1 mg/dl)$^b$</td>
<td>-0.051 (-0.189 to 0.087)</td>
<td>0.466</td>
<td>0.028 (-0.11 to 0.167)$^§$</td>
<td>0.693</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Crude HR (95%CI)</th>
<th>$P$</th>
<th>Adjusted HR (95%CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus (mg/dl)$^a$</td>
<td>1.25 (0.85 to 1.84)</td>
<td>0.262</td>
<td>1.72 (1.06 to 2.78)$^‡$</td>
<td>0.028</td>
</tr>
<tr>
<td>Ca x P (mg$/^2$/dl)</td>
<td>1.03 (0.99 to 1.07)</td>
<td>0.173</td>
<td>1.06 (1.01 to 1.12)$^‡$</td>
<td>0.014</td>
</tr>
<tr>
<td>Calcium (0.1 mg/dl)$^b$</td>
<td>1.11 (0.91 to 1.35)</td>
<td>0.317</td>
<td>1.13 (0.86 to 1.47)$^‡$</td>
<td>0.379</td>
</tr>
</tbody>
</table>

N.B. a negative beta is equivalent to an improvement in renal function;
$^a$ A one mg/dl change in plasma phosphorus is equivalent to 0.32 mmol/l change;
$^b$ A one mg/dl change in plasma calcium is equivalent to 0.25 mmol/l change;
$^*$ Adjusted for age, gender, primary kidney disease, baseline CrCl, systolic blood pressure, proteinuria, haemoglobin and plasma calcium;
$^†$ Adjusted for age, gender, primary kidney disease, baseline CrCl, systolic blood pressure, proteinuria and haemoglobin;
$^§$ Adjusted for age, gender, primary kidney disease, baseline CrCl, systolic blood pressure, proteinuria, haemoglobin and plasma phosphorus;
$^‡$ Adjusted for age, gender, primary kidney disease, baseline CrCl and comorbidity at baseline (diabetes, cardiovascular disease, malignancy and pulmonary disease).

Compared with patients with stable plasma phosphorus ≤4.6 mg/dl during these first three months of pre-dialysis care, patients with normalisation of plasma phosphorus showed a trend towards an improvement in the decline in renal function [β 0.172 (-0.127 to 0.472) ml/min/month]. In contrast, those patients in whom plasma phosphorus increased during the first 3 months, had a significantly steeper decline compared with patients with stable plasma phosphorus [β -0.386 (-0.688 to -0.084) ml/min/month]. The proportion of patients using phosphorus binders at entry in the stable-phosphorus group was 61.2%. In the ‘normalised-phosphorus’ group, 64.7% of patients were prescribed phosphorus-binding drugs, while this was 70.5% in the ‘increasing-phosphorus’ group of patients.

Third, in the subgroup of patients from five centres where PTH was available in the majority of patients, there was no association between PTH level and decline in renal function [adjusted β 0.000 (-0.006 to 0.007)]. Finally, when dichotomised on cut-off points as defined in the K/DOQI guidelines, patients with a plasma phosphorus concentration above 4.6 mg/dl had a 0.187 (0.397 to -0.022) steeper decline of renal function than patients with levels below this.
cut-off point. When the target for dialysis patients of 5.5 mg/dl was used as cut-off point, this decline was faster when compared with patients below this target [$\beta = 0.263 (-0.009$ to $0.518)$].

**Mortality**

During pre-dialysis care, 30 out of 448 patients died (6.7%). Causes of death according to ERA-EDTA classification in this population were cardiovascular (37%), uraemia (4%), malignancy (3%) and unknown (53%). One patient had a car accident. The overall mortality risk during pre-dialysis care for each increase of phosphorus level with 1 mg/dl was 1.25 (95% CI: 0.85 to 1.84). After adjustment for age, sex and baseline renal function this relation did not change substantially [hazard ratio (HR): 1.37; 95% CI: 0.91 to 2.05]. After additional correction for primary kidney disease, the risk increased to 1.59 (95% CI: 1.01 to 2.48). Vasculitis (mainly SLE) as primary kidney disease was associated with a substantially increased risk of dying, while the phosphorus level was relatively low in these patients. After adjustment for age, sex, eGFR at baseline, primary kidney disease and important markers of comorbidity (diabetes mellitus, cardiovascular disease, COPD and malignancy in medical history) the mortality risk increased to 1.62 (95% CI: 1.02 to 2.59, Tables 2 and 3). Further adjustment for albumin at the start of pre-dialysis care did not influence the mortality risk substantially (HR: 1.56; 95% CI: 0.99 to 2.47). Cardiovascular specific mortality could not be analysed reliably due to the low number of events.

**Table 3. Association of serum phosphorus (mg/dl) with mortality.**

<table>
<thead>
<tr>
<th>Model of phosphorus adjusted for:</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1.25 (0.85 to 1.84)</td>
<td>0.262</td>
</tr>
<tr>
<td>Age, sex</td>
<td>1.31 (0.87 to 1.99)</td>
<td>0.193</td>
</tr>
<tr>
<td>+ Baseline renal function</td>
<td>1.42 (0.93 to 2.17)</td>
<td>0.103</td>
</tr>
<tr>
<td>+ Primary kidney disease</td>
<td>1.68 (1.05 to 2.69)</td>
<td>0.030</td>
</tr>
<tr>
<td>+ Malignancy, diabetes, cardio- and cerebrovascular disease</td>
<td>1.70 (1.05 to 2.75)</td>
<td>0.030</td>
</tr>
<tr>
<td>+ Pulmonary disease</td>
<td>1.72 (1.06 to 2.78)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Models were constructed stepwise, with addition of confounders by row. The final model (lowest row) included all confounders, i.e. age, sex, baseline renal function, primary kidney disease, malignancy, diabetes, cardio- and cerebrovascular disease and pulmonary disease.

When dichotomised on cut-off points as defined in the K/DOQI guidelines, the adjusted HR for plasma phosphorus concentration above 4.6 mg/dl was 1.23 (95% CI: 0.56 to 3.31). When the target for dialysis patients of 5.5 mg/dl was used as cut-off point, this risk increased to 3.06 (95% CI: 1.01 to 9.27).

**Discussion**

In this population of pre-dialysis patients, high plasma phosphorus level was identified as a risk factor for more rapid decline in renal function. This association remained after adjustment for
other important risk factors of renal function loss including proteinuria, baseline renal function and blood pressure, and therefore, seems to be of significant clinical importance. Furthermore, hyperphosphataemia was clearly associated with an increased mortality risk. Notwithstanding the known detrimental consequences of hyperphosphataemia and the availability of treatment options, 45% of our pre-dialysis patients had hyperphosphataemia at the start of pre-dialysis care, while only 60% of these patients were prescribed phosphate-binding drugs. Our data imply that more attention for this complication of CKD is necessary.

This is one of the first studies in a large cohort of pre-dialysis patients, showing an association of plasma phosphorus level with faster deterioration of renal function, independent of absolute renal function. Previously, several cross-sectional studies have shown an association of plasma phosphorus concentration with the level of renal function at GFR levels <40 ml/min.\textsuperscript{21,22} Furthermore, a meta-analysis has shown that a higher protein intake, which increases phosphate intake, accelerates the decline in renal function in CKD patients,\textsuperscript{5} thereby shortening the time to start of dialysis.\textsuperscript{6} Together with the presented data, these studies support the hypothesis that plasma phosphorus is a risk factor for more progressive decline in renal function in CKD patients in general and in pre-dialysis patients in particular.

In our patients, an increased mortality risk was associated with a high plasma phosphorus concentration. Although the crude risk was 1.25, after correction for primary cause of kidney disease and comorbidities this risk increased to 1.62 for each mg/dl increase in plasma phosphorus concentration independent of age and gender. This was mostly due to patients with multi-system disease or malignancy in their medical history, who had a relatively low serum phosphorus, but high mortality. This corrected mortality risk is higher than the 1.33 per mg/dl found by Kestenbaum \textit{et al.},\textsuperscript{7} and substantially higher than the approximately 1.05 found in HD patients.\textsuperscript{8,9,12,23} The discrepancies in relative risks found in these studies can be explained by the cross-sectional design of the previous studies, which might have induced a survival bias. Furthermore, in these studies data were collected from large (national) databases, which might not record clinical characteristics of patients as precisely as the nephrologists' medical records of patients which may have resulted in a less precise correction for potential confounders.

The present study has potential limitations. Only patients with the most advanced stage of renal disease before RRT were included in this study. It has been estimated that between 36% and 65% of patients with an eGFR <15 ml/min/1.73m\textsuperscript{2} are not treated by a nephrologist.\textsuperscript{24} This may limit generalisability of our results. Second, an advantage of investigating pre-dialysis patients is the large variation in both decline in renal function and biochemical abnormalities due to uraemia. This increases the likelihood to detect risk factors, which may be too weak to be detected in patients with less severe disease. The variance explained by phosphorus was merely 3.6%. However, the variance explained by all other traditional risk factors together was only 7.3%, to which phosphorus added an additional 3.1%. This seems a substantial
contribution. Moreover, hyperphosphataemia is a potentially treatable risk factor, deserving extra attention. Third, we assumed the decline in renal function to be linear in this late stage of renal function loss. Although on theoretical grounds an exponential decline could be expected, linearity is a reliable assumption in this latest stage of renal function loss as previously shown by others. Fourth, a low plasma phosphorus concentration is possibly associated with an increased mortality in HD patients. However, since very few patients had a low plasma phosphorus concentration, it was impossible to investigate this association in our study. Fifth, the number of patients dying in our pre-dialysis population was lower than expected in a population with CKD stage IV and V. It can be argued that those patients who died during the first month after initiation of dialysis should be attributed to pre-dialysis care. However, when including these deaths, the relative mortality risk remained unchanged (HR: 1.57; 95% CI: 1.05 to 2.36). Finally, due to the retrospective method of data collection, with unfixed time points resulting in an unbalanced design, a time averaged or time varying analysis of the association of plasma phosphorus and endpoints was technically not realisable. This analysis would be important, especially if pre-dialysis care has a large impact on plasma phosphorus level. However, the majority of patients were known to a nephrologist previously, with no difference in prevalence of hyperphosphataemia between patients known longer or shorter than six months to a nephrologist. Furthermore, after three months of care, 22.6% of patients who had initially normal phosphorus levels became hyperphosphataemic at six months, while 9.8% started dialysis. Of the patients with hyperphosphataemia 22.6% had normal phosphorus after six months, while 6.0% started dialysis. Therefore it is unlikely that this will influence our results in a major way.

The association between plasma phosphorus concentration and the decline in renal function can be explained pathophysiologically by the ‘precipitation-calcification hypothesis’. Animal models of CKD have shown that a high plasma phosphorus concentration leads to the deposition of calcium phosphorus crystals in either the mitochondria of tubular cells or renal interstitium. This may cause cell damage and mitogenesis of fibroblasts, resulting in progressive loss of renal function. Further evidence for a pathophysiological role of phosphorus is provided by a rat model of CKD. When given phosphate-binding drugs, these rats with CKD show less intrarenal calcium phosphorus deposition and interstitial fibrosis, and less severe renal function loss compared to the rats not receiving such medication. In our study, the effect of phosphorus and the Ca x P product on the decline in renal function was comparable. This can easily be explained by the fact that the product term is mainly driven by the phosphorus concentration and because hypocalcaemia was rare. Therefore, the association of phosphorus concentration with progressive decline in our study could be due to mechanisms similar to those observed in animal models.

Alternatively, the association of phosphorus and decline in renal function could be due to the incapability of the metabolism to adapt to long-term high phosphorus levels. Factors contributing to deregulation of the calcium phosphorus balance may be a rapid renal function
loss with massive phosphorus retention or a direct imbalance in calcification inhibiting factors caused by the severity of renal disease. In a subgroup of our patients, phosphorus concentration was closely related to PTH concentration, independently of baseline renal function and calcium level (data not shown). However, even if plasma phosphorus would be merely a marker of rapidly progressive disease rather than a pathophysiological agent itself, it is an important and available parameter to identify patients at high risk for progression of renal function loss.

The association of phosphorus and (cardiovascular) mortality is thought to be mediated through an increase in cardiovascular disease. The relation of phosphorus and cardiovascular disease is supported by the fact that patients with CKD and hyperphosphataemia have increased vascular calcification of large and small arteries. This is further supported by recently developed mouse models with a defect in the klotho or fibroblast growth factor 23 (FGF-23)-genes. Both of these genes are linked to the phosphorus homeostasis, possibly through the same pathway. Interestingly, klotho-defect mice, who are fed a phosphate-containing diet, develop cardiovascular calcification similar to those seen in dialysis patients. When phosphorus is restricted from the diet, klotho-defect mice develop normally, which confirms an important role of phosphorus in increased cardiovascular mortality in CKD patients. Furthermore, FGF-23 seems to be a promising determinant of phosphorus homeostasis since it has been linked to inhibition of phosphorus reabsorption in the kidney in vivo studies and is elevated in patients with chronic renal failure.

Our data have clinical implications. Several guidelines have been developed for the optimal regulation of phosphorus in both stage IV and V CKD, because of the serious implications of long-standing hyperphosphataemia, and the availability of various treatment options. In the framework of K/DOQI, multidisciplinary work groups based their guidelines for CKD stage IV partly on studies in dialysis patients and partly on expert opinion, due to the absence of evidence in pre-dialysis patients. The present study shows that hyperphosphataemia in predialysis patients is not only related to a higher mortality, but also to an increased decline in renal function. The present study underlines the importance of plasma phosphorus concentrations within the normal range in pre-dialysis patients.

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