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

Nora Voormolen¹, Marlies Noordzij², Diana C. Grootendorst¹, Ivo Beetz¹, Yvo W. Sijpkens³, Jeannette G. van Manen¹, Elisabeth W. Boeschoten⁴, Roel M. Huisman⁷, Raymond T. Krediet⁶, Friedo W. Dekker¹ and the PREPARE study group⁷

¹Department of Clinical Epidemiology, Leiden University Medical Center, ²Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, ³Department of Nephrology, Leiden University Medical Center, Leiden, ⁴Hans Mak Institute, Naarden, ⁵Department of Nephrology, University Medical Center Groningen, Groningen, ⁶Department of Nephrology, Academic Medical Center, Amsterdam and ⁷the PREPARE study group consists of: P. Gerlag, Maxima Medical Centre, Veldhoven; C.J. Doorenbos, Deventer Ziekenhuizen, Deventer; K. Jie, Groene Hart Hospital, Gouda; A. Schraaer-van der Meer, Rijnland Ziekenhuis, Leiderdorp; C. Verburgh, Kennemer Gasthuis, Haarlem, The Netherlands

Abstract

Background. Herephosphataem is associated with increased mortality in patients with chronic kidney disease (CKD) stage IV or on dialysis. Furthermore, in animal studies, elevated plasma phosphate 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 phosphate with renal function loss and mortality in CKD stage IV–V pre-dialysis patients with GFR <20 ml/min/1.73 m².

Methods. Incident pre-dialysis patients were included between 1999 and 2001 in the multi-centre 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 (5.4) ml/min/1.73 m², decline in renal function 0.38 (0.95) ml/min/month]. Phosphate concentration at baseline was 4.71 (1.16) mg/dl, calcium 9.25 (0.77) mg/dl and calcium–phosphate product 43.5 (10.9) mg²/dl². For each mg/dl higher phosphate concentration, the mean (95% CI) decline in renal function increased with 0.154 (0.071–0.237) ml/min/month. After adjustment, this association remained [β 0.178 (0.082–0.275)]. Seven percent of the patients died. Crude mortality risk was 1.25 (0.85–1.84) per mg/dl increase in phosphate, which increased to 1.62 (1.02–2.59) after adjustment.

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

Keywords: CKD; decline: mortality; renal function; serum phosphate

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 [1]. 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 [2]. In addition to these factors, plasma phosphate has been suggested for many years as a potential risk factor for a more progressive decline in renal function [3].

Recently, a direct association between plasma phosphate 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 phosphate showed a faster decline in renal function compared with rats fed with a low phosphate diet [4]. In humans, the main external source of plasma phosphate 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 [3,5,6]. Together, these data support the hypothesis that phosphate 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 [7–10]. In pre-dialysis and haemodialysis (HD) patients, hyperphosphatemia has been shown to be associated with accelerated atherosclerotic lesion formation and cardiovascular morbidity [11]. Furthermore, several observational studies have shown an association between plasma phosphate and mortality in dialysis patients and in patients with a creatinine clearance between 30–60 ml/min [7–9,12,13] However, the association of plasma phosphate with mortality in pre-dialysis patients remains to be determined.

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

Methods

Patients

Incident patients with CKD stage IV–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 glomerular filtration rate (eGFR) was <20 ml/min, and the need for renal replacement therapy (RRT) was expected within 1 year. Patients who spent less than 1 month on pre-dialysis care or with prior RRT were excluded. Additional inclusion criteria for the present analysis included the availability of serum phosphate 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 conducted 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 the 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 [14]. Calcium-phosphate product was calculated as the corrected calcium concentration multiplied by the phosphate concentration, and expressed in mg²/dl². Estimated GFR (eGFR) formula was calculated by abbreviated Modification of Diet in Renal Disease (MDRD) formula. The daily protein intake was determined by calculating the normalized protein equivalent of nitrogen appearance (nPNA) in a subgroup of 238 out of 448 patients from three centres with available 24 h 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 1 month after start of RRT was assessed from the paper medical records and hospital databases. Causes of death were classified according to ERA-EDTA guidelines [17].

Analysis

Data are expressed as mean (SD). Differences between groups were examined by independent sample t-tests for continuous variables and chi-square test for categorical variables. Phosphate, calcium and other variables included in multivariate analysis were baseline values assessed at entry in the pre-dialysis clinics. Additional analysis using mean plasma phosphate during the first 3 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 phosphate and calcium phosphate product. In multivariate analysis, variables associated with decline in kidney function as mentioned in the 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 [2,18,19]. 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 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, phosphate 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 phosphate 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 31–1442). 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/1.73 m² at baseline. The mean plasma phosphate concentration was 4.71 mg/dl (1.16) (Figure 1), plasma calcium was 9.25 (0.77) mg/dl and calcium-phosphate product was 43.5 (10.9) mg²/dl². Phosphate 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 [20]. Hyperphosphataemia was found in 216/448 (48%) patients and hypophosphataemia only in 9/448 (2%) patients. From the hyperphosphataemic patients 157/216 (73%) had been referred to the pre-dialysis outpatient clinic by a nephrologist. Of these patients, 68% had been attending nephrological care for >6 months, which is comparable with 64% of 194 out of 232 (84%) patients without hyperphosphataemia.

The majority, 364 out of 448 (81%) of the patients had a calcium–phosphate product <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 PTH was determined in the majority of patients at baseline [n = 144 out of 182 (79%)] as recommended in these guidelines. Mean (SD) PTH in this subgroup was 28 [33]. At entry in a pre-dialysis care clinic, 63% (n = 288 out of 448) of patients were prescribed a phosphate binding drug. In the patients with a normal plasma phosphate level this was 59%, in the hyperphosphataemic patients only 68% were prescribed a phosphate-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 pre-dialysis care was determined in 81% of patients (n = 238 out of 293). Mean (SD) nPNA was 1.01 (0.26).

Plasma phosphate level was associated with baseline eGFR \( (\beta = -2.09, P < 0.001) \). After correction for baseline eGFR, higher plasma phosphate was associated with higher PTH, more proteinuria, younger age and the presence of glomerulonephritis or polycystic kidney disease.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 448</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 15</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>56</td>
</tr>
<tr>
<td>Primary kidney disease (%)^a</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 o. u. o.</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>eGFRb (ml/min/1.73 m²)</td>
<td>13 ± 5.4</td>
</tr>
<tr>
<td>eGFR decline (ml/min/month)</td>
<td>-0.38 ± 0.95</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>BMI (kg/m²)c</td>
<td>25.7 ± 4.6</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></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>Phosphate (mg/dl)^d^</td>
<td>4.71 ± 1.16</td>
</tr>
<tr>
<td>Calcium (mg/dl)^d^</td>
<td>9.25 ± 0.77</td>
</tr>
<tr>
<td>Calcium × Phosphate (mg²/dl²)</td>
<td>43.5 ± 10.9</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>39 ± 5.4</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>11.0 ± 1.0</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)^e^</td>
<td>2.78 ± 2.74</td>
</tr>
</tbody>
</table>

Mean values (± SD) are given for continuous variables; o. u. o. of unknown origin.
^a According to European Renal Association classification.
^b eGFR calculated with MDRD formula.
^c available in 402 patients.
^d corrected for albumin concentration.
^e available in 408 patients.

Plasma phosphate concentration at the start of pre-dialysis care can be converted from milligram/decilitre to millimol/litre 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).

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.

Fig. 1. Distribution of plasma phosphate concentration at the start of pre-dialysis care. Plasma phosphate can be converted from milligram/decilitre to millimol/litre 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).
Calcium, 0.1 mg/dl

Decline in renal function

The median number of eGFR determinations per patient during the first half year of pre-dialysis care was 7 (range 2–44, 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/1.73 m²), baseline phosphate of 4.23 (1.03), age of 66.1 years (15.1), 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 vs 17% in the whole group), renovascular disease (16 vs 22%) and polycystic kidney disease (5 vs 13%) and more often interstitial nephritis (23 vs 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 the start of dialysis, while only 31% started dialysis.

Plasma phosphate was significantly associated with decline in renal function: each milligram/millilitre higher plasma phosphate was associated with a 0.154 ml/min/month steeper slope of the renal function (95% CI: 0.082–0.275) ml/min/month, Table 2). Further adjustment for albumin or nPNA at the start of pre-dialysis care did not influence the rate of decline in renal function [β (95% CI) 0.178 (0.081–0.275) and 0.128 (0.020–0.236) ml/min/month, respectively].

To check the robustness of the results, additional analyses were performed. First, the mean plasma phosphate during the first 3 months after start of pre-dialysis care was calculated for each patient. The median (minimum, maximum) number of phosphate measurements during this period was three [2,19] and the mean (SD) concentration 4.74 (1.18) mg/dl. This value of plasma phosphate was independently associated with decline of renal function as well [β 0.249 (0.154–0.345) ml/min/month]. Second, 51 patients had a high plasma phosphate level (>4.6 mg/dl) at entry, which decreased to normal values within 3 months, whereas an additional 51 patients had normal plasma phosphate (≤4.6 mg/dl) at entry, which increased to >4.6 mg/dl after 3 months. Compared with patients with stable plasma phosphate ≤4.6 mg/dl during these first 3 months of pre-dialysis care, patients with normalization of plasma phosphate...
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 phosphate level with 1 mg/dl was 1.25 (95% CI; 0.85–1.84). After adjustment for age, sex and baseline renal function, this relation did not change substantially [RR (95% CI) 1.37 (0.91–2.05)]. After additional correction for primary kidney disease, the risk increased to 1.59 (95% CI 1.01–2.48). Vasculitis (mainly SLE) as primary kidney disease was associated with a substantially increased risk of dying, while the phosphate 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 1.02–2.59, Tables 2 and 3). Further adjustment for albumin at the start of pre-dialysis care did not influence the mortality risk substantially [RR 1.56 (0.99–2.47)]. Cardiovascular specific mortality could not be analysed reliably due to the low number of events.

When dichotomized on cut-off points as defined in the K/DOQI guidelines, the adjusted RR for plasma phosphate concentration above 4.6 mg/dl was 1.23 (95% CI 0.56–2.73). 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 1.01–9.27).

Discussion

In this population of pre-dialysis patients, high plasma phosphate 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 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 phosphate level with faster deterioration of renal function, independent of absolute renal function. Previously, several cross-sectional studies have shown an association of plasma phosphate concentration with the level of renal function at GFR levels <40 ml/min [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 [5], thereby shortening the time to start of dialysis [6]. Together with the presented data, these studies support the hypothesis that plasma phosphate 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 phosphate 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 phosphate 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 phosphate, but high mortality. This corrected mortality risk is higher than the 1.33 per mg/dl found by Kestenbaum et al. [7].

### Table 3. Association of serum phosphate (mg/dl) with mortality

<table>
<thead>
<tr>
<th>Model of phosphate corrected for:</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1.25 (0.85–1.84)</td>
<td>0.262</td>
</tr>
<tr>
<td>Age, sex</td>
<td>1.31 (0.87–1.99)</td>
<td>0.193</td>
</tr>
<tr>
<td>Baseline renal function</td>
<td>1.37 (0.91–2.05)</td>
<td>0.130</td>
</tr>
<tr>
<td>Primary kidney disease</td>
<td>1.59 (1.01–2.48)</td>
<td>0.043</td>
</tr>
<tr>
<td>Malignancy, diabetes–cardio- and cerebrovascular disease</td>
<td>1.56 (0.98–2.47)</td>
<td>0.060</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>1.62 (1.02–2.59)</td>
<td>0.042</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, gender, primary kidney disease, eGFR, diabetes, cardio- and cerebrovascular disease, malignancy and pulmonary disease.
and substantially higher than the approximately 1.05 found in HD patients [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/1.73 m² are not treated by a nephrologist [24]. This may limit generalizability of our results. Second, an advantage of investigating predialysis 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 phosphate level was merely 3.6%. However, the variance explained by all other traditional risk factors together was only 7.3%, to which phosphate 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 [18]. Fourth, a low plasma phosphate concentration is possibly associated with an increased mortality in HD patients [8,25]. However, since very few patients had a low plasma phosphate 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–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 [RR (95% CI) 1.57 (1.05–2.36)]. 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 phosphate and endpoints was technically not realizable. This analysis would be important, especially if pre-dialysis care has a large impact on plasma phosphate 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 6 months to a nephrologist. Furthermore, after 3 months of care, 22.6% of patients who had initially normal phosphate levels became hyperphosphataemic at 6 months, while 9.8% started dialysis. Of the patients with hyperphosphataemia, 22.6% had a normal phosphate level after 6 months, while 6.0% started dialysis. Therefore, it is unlikely that this will influence our results in a major way.

The association between plasma phosphate concentration and the decline in renal function can be explained pathophysiologically by the ‘precipitation–calcification hypothesis’ [26]. Animal models of CKD have shown that a high plasma phosphate concentration leads to the deposition of calcium phosphate 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 [27,28]. Further evidence for a pathophysiological role of phosphate is provided by a rat model of CKD. When given phosphate-binding drugs, these rats with CKD show less intrarenal calcium phosphate deposition and interstitial fibrosis, and less severe renal function loss compared with the rats not receiving such medication [29]. In our study, the effect of phosphate and the calcium-phosphate 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 phosphate concentration and because hypocalcaemia was rare. Therefore, the association of phosphate concentration with progressive decline in our study could be due to mechanisms similar to those observed in animal models.

Alternatively, the association of phosphate and decline in renal function could be due to the incapability of the metabolism to adapt to long-term high phosphate levels. Factors contributing to deregulation of the calcium phosphate balance may be a rapid renal function loss with massive phosphate retention or a direct imbalance in calcification inhibiting factors caused by the severity of renal disease [30]. In a subgroup of our patients, phosphate concentration was closely related to PTH concentration, independently of baseline renal function and calcium level (data not shown). However, even if plasma phosphate 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 between phosphate and (cardiovascular) mortality is thought to be mediated through an increase in cardiovascular disease [31]. The relation of phosphate and cardiovascular disease is supported by the fact that patients with CKD and hyperphosphataemia have increased vascular calcification of large and small arteries [13,32]. This is further supported by recently developed mouse models with a defect in the klotho or fibroblast growth factor 23 (FGF23)-genes [33]. Both of these genes are linked to phosphate homoeostasis, possibly through the same pathway [33]. Interestingly, klotho-defect mice, who are fed a phosphate-containing diet, develop cardiovascular calcification similar to those seen in dialysis patients. When phosphate is restricted from the diet, klotho-defect mice develop normally, which confirms
an important role of phosphate in increased cardiovascular mortality in CKD patients [34]. Furthermore, FGF23 seems to be a promising determinant of phosphate homeostasis since it has been linked to inhibition of phosphate reabsorption in the kidney in in vitro studies and is elevated in patients with chronic renal failure [35].

Our data have clinical implications. Several guidelines have been developed for the optimal regulation of phosphate 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 the National Kidney Foundation—Kidney Disease Outcomes Quality Initiative (K/DOQI)—multi-disciplinary 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 pre-dialysis patients is not only a risk factor for higher mortality, but also for increased decline in renal function. The present data underline the importance of plasma phosphate concentrations within the normal range in pre-dialysis patients.

Acknowledgements. Trial nurses, data managers and students from the Hans Mak Institute are gratefully acknowledged for their assistance in data collection. Furthermore, we thank all the laboratory information system managers who invested time and effort to supply laboratory data, and all supporting staff who helped tracing records of (eventually) every patient. This study was supported by an unrestricted grant from Amgen BV.

Conflict of interest statement. The PREPARE study is an independent academic study designed and carried out by the Department of Clinical Epidemiology from the Leiden University Medical Center in collaboration with the Hans Mak Institute (Naarden) and the participating hospitals. This study was funded by an unrestricted grant from AMGEN BV (The Netherlands and Switzerland). The sponsor of the study was not involved in study design, collection of data, statistical analysis, interpretation of data, writing of the manuscript or in the decision to submit the paper for publication. None of the authors have declared a conflict of interest.

References
23. Block GA, Hulbert-Shareon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate...


34. Morishita K, Shirai A, Kubota M et al. The progression of aging in klotho mutant mice can be modified by dietary phosphorus and zinc. *J Nutr* 2001; 131: 3182–3188


Received for publication: 11.12.06
Accepted in revised form: 16.4.07