Mineral metabolism and clinical outcomes in dialysis patients
Noordzij, M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Mineral metabolism and mortality in dialysis patients: A reassessment of the K/DOQI guideline

Marlies Noordzij
Johanna C. Korevaar
Friedo W. Dekker
Elisabeth W. Boeschoten
Willem J. Bos
Raymond T. Krediet
Patrick M. Bossuyt
and Ronald B. Geskus
for the NECOSAD Study Group
**Background:** Several studies found associations between higher plasma calcium and phosphorus and mortality in dialysis patients. However, different predefined categories and reference values were applied and the precise shape of these relationships remains unclear.

**Methods:** We evaluated 1621 patients from NECOSAD, a prospective multicentre cohort study of incident dialysis patients (60 ± 15 years, 61% male, 64% haemodialysis). We used multivariate Cox regression and restricted cubic spline regression to study effects of time-updated plasma concentrations on mortality in a flexible manner.

**Results:** 486 patients (30%) died during follow-up. Elevated phosphorus concentration was associated with higher mortality ($P=0.0009$). The association of high calcium with mortality was borderline significant ($P=0.07$). Within the studied ranges, we could not identify a threshold where an appreciable change in mortality risk occurred.

**Conclusions:** Mortality risk started to increase at a relatively low phosphorus concentration (4.5 mg/dl). Low-normal calcium combined with low-normal phosphorus concentration was associated with the lowest mortality.
Introduction

Disturbances in mineral metabolism such as hypercalcaemia and hyperphosphataemia are common in patients suffering from chronic kidney disease (CKD). In 2003 the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation published their guideline for bone metabolism and disease in CKD to assist nephrologists in developing an integrated approach to the diagnosis and management of mineral metabolism disorders. This guideline recommends tight control of serum calcium, phosphorus, and calcium-phosphorus product (Ca x P product) concentrations. K/DOQI advises to keep plasma calcium and phosphorus concentrations within a given range, and to keep the Ca x P product below an upper limit, thus assuming that an appreciable change in mortality does not occur until the plasma concentrations exceed a certain threshold.

Recent studies have demonstrated that achievement of these guidelines is low in both haemodialysis (HD) and peritoneal dialysis (PD) patients. The vast majority of patients have plasma concentrations outside the target ranges as recommended by K/DOQI, and especially the proportions of patients with elevated plasma calcium and phosphorus concentrations are distressing. In our previous studies, the proportion of patients with a plasma calcium concentration higher than the target range was almost 60%, and approximately 50% of the patients had plasma phosphorus concentrations above target. These proportions are similar to those found in other international studies. Our findings indicate that maintaining a plasma concentration within the presently advised target ranges is difficult in daily clinical practice.

Several observational studies in dialysis patients, including studies based on data from the United States Renal Data System (USRDS) and the Dialysis Outcomes and Practice Patterns Study (DOPPS), have demonstrated strong associations of abnormalities in mineral metabolism, such as elevated serum calcium, phosphorus, and Ca x P product concentrations, with all-cause and cardiovascular mortality. In these studies, a variety of predefined categories and reference values for plasma concentrations have been applied. However, it should be kept in mind that these associations are dependent on the categorization. Analysis based on a pre-determined categorisation does not allow for an unrestricted assessment of the relationships between plasma calcium and phosphorus concentrations and mortality risk. Therefore, the precise shapes of the curves describing these relationships remain unclear. A smoothing technique such as spline regression, which requires neither categorisation nor an assumption on the shape of the relation between plasma concentration and mortality, is a more appropriate method for exploring these relations.

In the current study we aimed to examine the precise shape of the relationship of plasma calcium, phosphorus, and Ca x P product concentrations with all-cause mortality risk in a prospective cohort of incident dialysis patients in the Netherlands.
Methods

Patients

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a large prospective multicentre cohort study in which ESRD patients are followed from the start of dialysis until transplantation or death. In 38 out of the 50 dialysis units in the Netherlands all ESRD patients who started chronic dialysis treatment between 1997 and 2004 were consecutively invited to participate in the study. To be included, patients had to be 18 years or older and dialysis had to be their first renal replacement therapy. We selected patients who had data on mineral metabolism available three months after the start of dialysis (baseline visit). The study was approved by all local medical ethics committees and all patients gave informed consent before inclusion. Patients were followed until transplantation, death, or 1 January 2005.

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 residual renal function, biochemistry and dialysis characteristics were collected at fixed time points three and six months after the start of dialysis, and at six-monthly intervals thereafter.

Primary kidney disease and causes of death were classified according to the codes of the European Renal Association-Dialysis and Transplantation Association (ERA-EDTA). Patients were classified as having no, intermediate or severe comorbidity based on the number of comorbid conditions according to Davies’ comorbidity index. The nutritional status was scored on the standardised seven-point scale of the Subjective Global Assessment (SGA) which is 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 Kt/V urea was calculated from a 24-hour dialysate collection.

Plasma calcium, phosphorus, intact parathyroid hormone (iPTH), and albumin were measured by standard laboratory techniques in the different centres. Plasma calcium concentrations (mg/dl) were corrected for albumin concentration (g/dl) using the formula recommended by K/DOQI and generally applied in clinical practice \[\text{Corrected calcium} = \text{calcium} + 0.8 \times (4 - \text{albumin})\]. The K/DOQI guideline for bone metabolism and disease in CKD that was published in October 2003, recommends a serum concentration of corrected calcium between 8.4 and 9.5 mg/dl (2.10 and 2.37 mmol/l) and a serum phosphorus concentration between 3.5 and 5.5 mg/dl (1.13 and 1.78 mmol/l). Ca x P product concentration should be less than 55
mg²/dl² (<4.4 mmol²/l²). Because most patients started dialysis treatment before the introduction of the K/DOQI guidelines, nephrologists probably did not aim for these targets. The resulting large variation in plasma concentrations enabled us to study the effects of these plasma concentrations on outcome.

Statistical analysis

Patients were divided into the HD or PD group based on their treatment modality three months after the start of dialysis. To examine differences between HD and PD patients at baseline we applied *t*-tests for continuous variables and chi-square tests for categorical variables. The variable iPTH was skewly distributed and was therefore log-transformed for further analysis.

Time-dependent Cox proportional hazards models were used to estimate relative risks of death associated with time-updated plasma calcium and phosphorus concentrations. In addition, we used restricted cubic spline regression, a flexible statistical technique to evaluate the association between plasma concentrations and mortality. Five knots were used for the analysis and were placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the calcium and phosphorus distributions. Spline functions are used to represent smoothly varying relationships between a predictor (plasma concentration) and the response (mortality risk), which can take on virtually any shape. Moreover, spline functions can help to prevent the problems that result from inappropriate categorisation. Adjustments were made for a number of possible confounding effects selected from the available literature. Covariates included calcium, phosphorus, log iPTH, age, Kt/V urea per week, albumin level, and haemoglobin level as time-updated continuous variables, which were modelled via restricted cubic splines. In addition, the model contained the categorical variables primary kidney disease, Davies’ comorbidity score, and nutritional status at baseline.

We started with a model in which we allowed all effects to be different for HD and PD patients by means of including interactions of dialysis modality with all potential confounding variables in the model. Moreover, we included an interaction of calcium with phosphorus. A test for interaction between dialysis modality and all potential confounding variables was applied. When there was no statistically significant interaction between the confounders and treatment modality, we removed this interaction from the model. The effects of calcium and phosphorus on all-cause mortality risk for specific levels of the other marker were plotted graphically, to determine precisely the shape of the curves that describe the relationships. Median plasma calcium and phosphorus concentrations were utilised as reference values.

Statistical analyses were performed using the R Statistical Package version 2.3.0 (R Foundation for Statistical Computing, Vienna, Austria; URL http://www.R-project.org) and SAS statistical software version 9.1 (SAS Institute, Cary, NC). *P* <0.05 was considered statistically significant.
Chapter 7

Results

Description

From a total of 1753 eligible patients, the number of patients who met the inclusion criteria was 1621. When compared to the included patients, excluded patients had significantly more often renal vascular disease and less often diabetes mellitus and glomerulonephritis as the primary kidney disease. Other baseline characteristics were not different for the included and excluded patients. Baseline characteristics of the included patients are listed in Table 1.

Table 1. Patient characteristics three months after the start of dialysis ($n = 1621$)

<table>
<thead>
<tr>
<th>Treatment modality (% HD)</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>59 (15)</td>
</tr>
<tr>
<td>Gender (% males)*</td>
<td>61</td>
</tr>
<tr>
<td>Primary Kidney Disease (%)*</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>14</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>17</td>
</tr>
<tr>
<td>Comorbidity score (%)*</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>46</td>
</tr>
<tr>
<td>Moderate</td>
<td>45</td>
</tr>
<tr>
<td>High</td>
<td>10</td>
</tr>
<tr>
<td>Dialysis Kt/V urea (/week)</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>2.79 (0.85)</td>
</tr>
<tr>
<td>PD</td>
<td>1.51 (0.41)</td>
</tr>
<tr>
<td>Albumin (g/dl)*</td>
<td>3.61 (0.52)</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)*</td>
<td>11.1 (1.61)</td>
</tr>
<tr>
<td>Nutritional status (% malnourished)*</td>
<td>28.1</td>
</tr>
<tr>
<td>Corrected calcium (mg/dl)*</td>
<td>9.76 (1.02)</td>
</tr>
<tr>
<td>IQR calcium (mg/dl)*</td>
<td>[9.10 ; 10.28]</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)*</td>
<td>5.63 (1.70)</td>
</tr>
<tr>
<td>IQR phosphorus (mg/dl)*</td>
<td>[4.37 ; 6.63]</td>
</tr>
<tr>
<td>Ca x P product (mg^2/dl)*</td>
<td>54.8 (17.1)</td>
</tr>
<tr>
<td>IQR Ca x P product (mg^2/dl)*</td>
<td>[42.8 ; 65.0]</td>
</tr>
<tr>
<td>iPTH (pg/ml)*</td>
<td>123.5</td>
</tr>
<tr>
<td>IQR iPTH (pg/ml)*</td>
<td>[49.4 ; 275.5]</td>
</tr>
</tbody>
</table>

Mean values (SD) are presented for continuous variables.
To convert plasma albumin in g/dl in 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.
* $P < 0.05$, HD versus PD patients.
+IQR, Interquartile Range, lower (p25) and upper quartile (p75) of observations [p25 ; p75]
*Skewly distributed, median is presented.

At baseline, plasma calcium concentrations ranged from 7.6 to 12.7 mg/dl and plasma phosphorus concentrations from 2.6 to 10.6 mg/dl (1st to 99th percentiles). Most patients had higher plasma calcium and phosphorus concentrations than advised in the K/DOQI guideline and only few patients had plasma calcium (6%) and phosphorus (8%) concentrations below
the K/DOQI target range. Percentages of patients who had plasma concentrations below, at, or above the K/DOQI target ranges during follow-up are listed in Table 2.

<table>
<thead>
<tr>
<th>Years after starting dialysis</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N*</td>
<td>1621</td>
<td>1269</td>
<td>859</td>
<td>549</td>
<td>332</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 8.4 mg/dl</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>8.4-9.5 mg/dl</td>
<td>36</td>
<td>26</td>
<td>21</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>&gt; 9.5 mg/dl</td>
<td>59</td>
<td>71</td>
<td>77</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Phosphorus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.5 mg/dl</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>3.5-5.5 mg/dl</td>
<td>43</td>
<td>43</td>
<td>45</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>&gt; 5.5 mg/dl</td>
<td>49</td>
<td>49</td>
<td>47</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>Ca x P product</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55 mg²/dl²</td>
<td>56</td>
<td>52</td>
<td>51</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>≥ 55 mg²/dl²</td>
<td>44</td>
<td>48</td>
<td>49</td>
<td>48</td>
<td>45</td>
</tr>
</tbody>
</table>

*M, number of patients. The percentages for each year represent the distribution among patients alive and in follow-up through this year.

K/DOQI guideline ranges: serum calcium 8.4-9.5 mg/dl, serum phosphorus 3.5-5.5 mg/dl, Ca x P product <55 mg²/dl². To convert plasma calcium in mg/dl to mmol/l, multiply by 0.2495; plasma phosphorus in mg/dl to mmol/l, multiply by 0.3229.

Mortality risk

The maximal follow-up time was 7.8 years (1997-2005). Median follow-up time was 4.2 years (50 months) for HD patients and 6.5 years (78 months) for PD patients. 486 patients (30%) died during the study.

In the most general model, comprising interactions of all possibly confounding variables with treatment modality, the overall interaction effect was not statistically significant ($P = 0.64$) and in the further analyses we did not include these interaction terms. We continued with a model containing only interactions of calcium with phosphorus, and of calcium or phosphorus with treatment modality.

High plasma calcium was significantly related with an increased risk of death in the HD group ($P = 0.038$), but not in the PD group ($P = 0.39$), and the effect of calcium for the total group was borderline significant ($P = 0.07$). Increased plasma phosphorus concentration was significantly associated with a higher all-cause mortality risk ($P = 0.0009$), both in HD ($P = 0.0049$) and in PD patients ($P = 0.025$). No significant interactions between calcium or phosphorus and treatment modality were found ($P = 0.09$) and graphs were created for HD and PD patients combined. We plotted the effects on mortality risk of calcium and
phosphorus for specific levels of the other marker graphically. Smoothed curves with 95% confidence intervals are shown in Figures 1 and 2. Figure 1A demonstrates that mortality risk increased as plasma calcium increased at a low plasma phosphorus concentration of 3.5 mg/dl. However, at higher plasma phosphorus concentrations of 5.5 and 7.0 mg/dl, this effect became less pronounced. The effects of plasma calcium concentration on risk of death appeared to be linear and the null-hypothesis that the relationship between plasma calcium concentration and mortality risk is linear, could not be rejected ($P=0.75$).

![Figure 1](image)

**Figure 1.** Relative risks of mortality for phosphorus concentrations of 3.5 mg/dl (A), 5.5 mg/dl (B), and 7.0 mg/dl (C) according to calcium concentration.

* Multivariate relative risks were estimated from a restricted cubic spline Cox regression model. Point estimates are indicated by a solid line and grey fields represent 95% confidence intervals. The median plasma phosphorus concentration was used as reference point.

As depicted in Figure 2, increasing plasma phosphorus concentrations were associated with an increasing mortality risk and the relative mortality risk already started to increase at a plasma concentration of 4.5 mg/dl (1.45 mmol/l), especially at a low plasma calcium concentration of 8.4 mg/dl. At an elevated plasma calcium concentration of 11 mg/dl this effect was less distinct. The curves in Figure 2 suggest two thresholds, one around 4.5 mg/dl and one around 6 mg/dl. In accordance, the null-hypothesis that the relationship between plasma phosphorus and risk of death is linear, could almost be rejected ($P=0.07$). These graphs show that a low-normal calcium concentration combined with a low-normal phosphorus concentration is optimal to reduce all-cause mortality risk to a minimum.
Reassessment of the K/DOQI guideline

Figure 2. Relative risks of mortality for calcium concentrations of 8.4 mg/dl (A), 9.9 mg/dl (B), and 11.0 mg/dl (C) according to phosphorus concentration.

* Multivariate relative risks were estimated from a restricted cubic spline Cox regression model. Point estimates are indicated by a solid line and grey fields represent 95% confidence intervals. The median plasma calcium concentration was used as reference point.

Given the eight years of enrolment into the study, the analyses were repeated with an additional adjustment for time of study entry (before or after 1 January 2001) to account for unmeasured changes in practice or availability of therapies. These additional adjustments did not alter our findings. Because 19% of the patients switched therapy during the study period we repeated the analyses using a model in which we censored patients at the moment that they switched treatment modality. This additional analysis did not affect our results in any way (data not shown).

Discussion

In the current study we confirmed that high plasma phosphorus concentrations are significantly associated with increased mortality risk in dialysis patients. The effects of plasma calcium concentrations on the risk of death were only borderline statistically significant. We could not identify a certain threshold where an appreciable change in mortality risk occurred within the ranges we studied for plasma calcium and phosphorus concentrations. This finding does not fully support the target thresholds recommended in the K/DOQI guideline for bone metabolism and disease in CKD. Moreover, we demonstrated that the risk of death already started to increase at a plasma phosphorus concentration of 4.5 mg/dl (1.45 mmol/l) and that a low-normal calcium concentration combined with a low-normal phosphorus concentration is optimal to minimise all-cause mortality risk.
These findings suggest that the current K/DOQI guideline might improve by lowering the present upper threshold for phosphorus from 5.5 to 4.5 mg/dl. However, achieving and maintaining such low plasma phosphorus concentrations has proven to be a major problem in daily clinical practice. Although more than 90% of both HD and PD patients used phosphate-binding drugs from the start of dialysis onward, plasma phosphorus concentrations remained elevated (>5.5 mg/dl) in approximately half of the patients. Data on the type and dose of phosphate-binding medication were not available in our study, but since non-calcium-containing phosphate binders were not yet available during the greater part of the study period, we assume that the majority of patients were treated with either calcium acetate or calcium carbonate. Therefore, the elevated plasma calcium and the low iPTH concentrations that we observed could have been caused by the use of calcium-based phosphate binders and vitamin D analogues. Since we did not find any effect of plasma iPTH concentrations on (cardiovascular) mortality risk in our studies,2,10 we focused on plasma calcium, phosphorus and Ca x P product concentrations in the current study.

Our study might have some limitations. First, data on the type and dose of medication related to mineral metabolism, such as phosphate binders and vitamin D analogues, were not available. Second, the numbers of patients that had plasma calcium below 8.4 mg/dl and phosphorus concentrations below 3.5 mg/dl were extremely low. At baseline, only 6% of the patients had hypocalcaemia and 8% had hypophosphataemia. Therefore it was impossible to draw any firm conclusions about the mortality risks that were associated with plasma calcium and phosphorus concentrations in these low ranges.

In the past decade several studies have been performed to determine the association between mineral metabolism and mortality in dialysis patients. In 6407 prevalent HD patients from the USRDS, Block et al. observed increased relative risks of death of 1.27 (P <0.001) for serum phosphorus concentrations above 6.5 mg/dl (2.1 mmol/l) compared to patients with serum concentrations between 2.4 and 6.5 mg/dl (0.8-2.1 mmol/l).6 In DOPPS, a cohort of 17236 HD patients, increased relative risks of cardiovascular death were observed in patients with elevated phosphorus and Ca x P product concentrations.9 Also in our study population we found that elevated plasma phosphorus and Ca x P products, according to the current K/DOQI guideline, were associated with increased mortality risk both in HD and PD patients.2 However, in all the above mentioned studies different predefined cut-off points were applied.

Only a few studies reported associations of low serum calcium and phosphorus concentrations with mortality risk. Two recent studies from the United States found U-shaped associations between calcium and phosphorus and sudden death in HD patients,7,11 but these results were not confirmed in the DOPPS,9 and we could also not detect these effects in our patients. These discrepancies could be due to differences in methodology and the substantially larger
sample size of these American studies. We are not aware of any other publications that studied the effects of hypocalcaemia or hypophosphataemia on mortality risk in PD patients.

In conclusion, increased plasma phosphorus concentrations were significantly associated with higher risk of death in dialysis patients and mortality risk already started to increase at a relatively low phosphorus concentration of 4.5 mg/dl. In addition, the combination of low-normal calcium with low-normal phosphorus concentration was associated with the lowest risk of death. These findings do not fully support the current targets as recommended in the K/DOQI guideline for bone metabolism and disease in CKD.

Acknowledgements

The authors wish to thank the NECOSAD trial nurses and data managers for data collection and management.

References