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Mineral metabolism and cardiovascular morbidity and mortality risk: peritoneal dialysis patients compared with haemodialysis patients

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Abstract

Background. The K/DOQI guideline for bone metabolism and disease in chronic kidney disease is predominantly based on studies in haemodialysis (HD) patients. However, in clinical practice, this guideline is also applied to peritoneal dialysis (PD) patients. To validate the implementation of this guideline in PD patients, we evaluated the associations between plasma concentrations outside the K/DOQI-targets and the risk of cardiovascular morbidity and mortality in incident PD patients compared with HD patients.
Methods. In a large prospective multicentre study in the Netherlands (The Netherlands Cooperative Study on the Adequacy of Dialysis, NECOSAD), we included patients starting PD or HD between 1997 and 2004. Relative risk of cardiovascular morbidity and mortality were estimated using time-dependent Cox regression modelling.
Results. We included 586 PD patients with mean age 52 ± 15 years (66% males) and 1043 HD patients with mean age 63 ± 14 years (58% males). Cardiovascular disease (CVD) was the reason for hospitalization in 102 PD and 271 HD patients. In HD patients, the relative risk of CVD-related hospitalization increased with elevated plasma calcium concentrations (hazard ratio: 1.4; 95% CI: 1.1–1.9). Cardiovascular mortality was significantly higher for phosphorus concentrations above the K/DOQI-threshold in PD (2.4; 95% CI: 1.3–4.2) and HD patients (1.5; 95% CI: 1.1–2.1), and for elevated $Ca \times P$ in PD (2.2; 95% CI: 1.3–3.8) and HD patients (1.5; 95% CI: 1.1–2.1).
Conclusions. Plasma calcium concentrations above the K/DOQI-threshold increase the relative risk of CVD-related hospitalization in HD patients. Associations with cardiovascular mortality were more pronounced. Both in PD and HD patients with elevated plasma phosphorus and $Ca \times P$ concentrations, the cardiovascular mortality risk is increased. Therefore, it seems appropriate to adopt the current guideline in PD patients.

Keywords: calcium; cardiovascular disease; dialysis; mineral metabolism; mortality; phosphorus

Introduction

Disorders of mineral metabolism such as hypercalcaemia, hyperphosphataemia and secondary hyperparathyroidism are common among patients suffering from end-stage renal disease (ESRD). Several observational studies have demonstrated a strong association of abnormalities in mineral metabolism and all-cause mortality [1–5]. In addition, growing evidence suggests that altered mineral metabolism contributes to the development of cardiovascular disease (CVD) and cardiovascular mortality [2–4,6].

Cardiovascular mortality is 10–20 times higher in dialysis patients than in the age- and sex-matched general population [7,8]. Because CVD causes about 50% of mortality in dialysis patients [9] and has been proven to be related to disturbances in mineral metabolism, management of mineral metabolism has become an issue of major importance. In 2003, the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation introduced a guideline for bone metabolism and disease in chronic kidney disease (CKD) to assist nephrologists in developing an integrated approach to the diagnosis and management of mineral metabolism disorders [10]. This guideline recommends a tight control of serum calcium, phosphorus, calcium–phosphorus product ($Ca \times P$) and intact parathyroid hormone (iPTH)

concentrations. This guideline was predominantly based on studies in haemodialysis (HD) patients.

Previous cross-sectional studies of prevalent HD patients found that elevated phosphorus, Ca × P and iPTH levels increase cardiovascular mortality risk [1,3,4,6]. In addition, Block et al. [2] observed recently that hyperphosphataemia and hyperparathyroidism were significantly associated with cardiovascular hospital admission rates in prevalent HD patients in the US. These studies so far examined only the effects of disordered mineral metabolism on the development of cardiovascular morbidity and mortality in HD patients. However, in clinical practice, the K/DOQI guideline is applied to peritoneal dialysis (PD) patients as well, and evidence is needed to validate the implementation of the guideline in this group of patients. Since the associations between disordered mineral metabolism, according to the K/DOQI guideline, and cardiovascular morbidity and mortality have never been studied before in PD patients, the objective of our study was to evaluate these associations in incident PD patients in comparison with HD patients.

Subjects and methods

Subjects

In the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a large prospective multicentre cohort study, ESRD patients are followed from the initiation of dialysis until transplantation or death. In 38 out of the 50 dialysis units in the Netherlands, all new ESRD patients were consecutively invited to participate in the study. To be eligible for the study, patients had to be 18 years or older and dialysis had to be their first renal replacement therapy. The study was approved by all local medical ethics committees and all patients gave informed consent before inclusion. Patients were followed until transplantation, mortality or 1 January 2005.

For this analysis, we selected patients who had started on chronic PD or HD treatment in the period between January 1997 and July 2004. Patients who had measurements of plasma calcium, phosphorus, iPTH and albumin concentrations available at 3 months after the start of dialysis (baseline) were included. Since most of our patients had started on dialysis treatment before the publication of the K/DOQI guidelines (2003), nephrologists probably were not aiming for these targets. The resulting large variation in plasma concentrations enabled us to study the effects of K/DOQI-targets on outcome.

A total of 229 patients (14%) switched from treatment modality during the study. There were 174 PD patients who switched to HD therapy and the median time until the first switch of therapy was 620 days for these patients. Besides, there were 55 HD patients who switched to PD treatment during the study and the median time until modality switch was 540 days in this group of patients.

Data collection

Data on demography, primary kidney disease and comorbidity were collected 0–4 weeks before the initiation of dialysis treatment. During follow-up, data on residual renal function, biochemistry and dialysis characteristics were collected at fixed times, i.e. at 3 and 6 months after the start of dialysis and subsequently at 6-month intervals.

Reasons for hospital admission were classified as CVD in case of a diagnosis of myocardial infarction, cerebrovascular accident, coronary artery disease, cardiac failure, peripheral vascular disease, hypertension or other cardiac disease. Primary kidney disease and causes of death were classified according to the codes of the European Renal Association-Dialysis and Transplantation Association (ERA-EDTA). Cardiovascular mortality was defined as any death attributed to myocardial ischaemia and infarction, cardiac failure, cardiac arrest (cause unknown), cerebrovascular accident, fluid overload, hyper- and hypokalaemia, haemorrhage from a ruptured aneurism or mesenteric infarction. Whenever the cause of death was uncertain or could not be determined, we classified it as cardiovascular because these patients in general died acutely. All other causes of death were classified as non-cardiovascular.

Patients were classified as having no, intermediate or severe comorbidity based on the number of comorbid conditions according to Davies' comorbidity index [11]. The nutritional status was scored on the standardized 7-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 5 or lower. Residual renal function was expressed as residual glomerular filtration rate (rGFR), calculated as the mean of creatinine and urea clearance adjusted for body surface area (ml/min/ $1.73 \, m^2$). Dialysis dose, the Kt/V_{urea} per week, was calculated as dialysis urea clearance, divided by urea distribution volume (V) according to Watson et al. [12]. 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 h dialysate collection [13].

Laboratory variables were evaluated in reference to the targets advised in the K/DOQI guideline for bone metabolism and disease in CKD. 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 × P concentrations should be $<55 \, mg^2/dl^2$ ($<4.4 \, mmol^2/l^2$) and iPTH concentrations should range from 150 to 300 pg/ml (15.8–31.6 pmol/l). Plasma calcium, phosphorus 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 [corrected calcium = calcium + 0.8 × (4 − albumin)] [10]. The Ca × P in mg^2/dl^2 was calculated by multiplying the corrected calcium concentration by the phosphorus concentration, both in mg/dl. Measurements of iPTH were performed by various first-generation immunometric iPTH-assays depending on the different participating centres.

Statistical analysis

Patients were classified as HD or PD based on the treatment modality reported 3 months after the start of dialysis. To explore the differences between PD and HD patients, we used standard descriptive statistics. We used a time-dependent

Cox proportional-hazards model for recurrent events to examine the relative risk of CVD-related hospital admission. To correct for the dependency between repetitive hospitalizations within the same patient, we added a frailty term to the statistical model [14]. The underlying logic of frailty models is that some patients are intrinsically more or less prone to develop CVD. Hazard ratios (HRs) for cardiovascular and non-cardiovascular mortality were calculated using time-dependent Cox proportional-hazards regression models. In all time-dependent analyses, the most recently measured plasma concentrations were used to predict the effects on outcome in the subsequent period of 6 months. The analyses were stratified for treatment modality (PD or HD) and plasma concentrations were categorized into categories below, on or above the K/DOQI targets. Patients with plasma concentrations that were either too low or too high were compared with patients who met the target (reference category). Adjustments were made for a number of possible confounding effects selected from the available literature. These included age, Davies' comorbidity score, primary kidney disease and SGA as recorded at baseline, and albumin level, Kt/V_{urea} and haemoglobin level as time-dependent variables. Supplementary adjustments for laboratory parameters related to mineral metabolism were made for phosphorus and iPTH in analyses on the effects of calcium. We made similar additional adjustments for calcium and iPTH in analyses of phosphorus, for iPTH in analyses of $Ca \times P$, and for calcium and phosphorus in analyses of iPTH. All statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute, Cary, NC), except for the frailty analysis, which was performed using the S-plus statistical software version 6.0.

Results

Description

Of the 1753 eligible patients, 1629 met the inclusion criteria. We had to exclude 124 patients due to missing plasma calcium, phosphorus, iPTH or albumin levels at baseline. Compared with the included patients, the excluded patients more often had renal vascular disease, while diabetes mellitus and glomerulonephritis were less frequent causes primary kidney disease. Other baseline characteristics of these patients did not differ from the included patients. The proportion of patients who died during the study period was higher among the excluded patients compared with the included patients (48 vs 36%, $P = 0.007$).

Characteristics of the 1629 included patients 3 months after the start of dialysis are summarized in Table 1. When compared with HD patients, PD patients were significantly younger, differed in the causes of primary kidney disease, had a higher rGFR, higher plasma calcium concentrations and lower phosphorus and $Ca \times P$ concentrations. The proportion of HD patients with a moderate or high comorbidity score and with malnutrition were larger compared with PD patients.

Three months after the initiation of dialysis, the majority of patients had plasma calcium

Table 1. Patient characteristics 3 months after the start of dialysis treatment ($n = 1629$)

	PD ($n = 586$)	HD ($n = 1043$)
Age (years)*	52 (15)	63 (14)
Gender (% males)*	66	58
Primary kidney disease (%)*		
Diabetes mellitus	16	16
Glomerulonephritis	20	11
Renal vascular disease	12	21
Comorbidity (%)*		
Low	59	39
Moderate	34	50
High	7	11
rGFR (ml/min)*	4.28 (3.13)	3.46 (2.86)
Dialysis Kt/V_{urea} (per week)	1.51 (0.41)	2.79 (0.85)
Albumin (g/dl)	3.63 (0.54)	3.60 (0.52)
Nutritional status (% malnourished)*	18.1	33.3
BMI (kg/m^2)	24.7 (3.8)	24.7 (4.3)
Corrected calcium (mg/dl)*	10.0 (0.98)	9.64 (1.02)
IQR calcium (mg/dl)[a]	(9.36; 10.56)	(8.97; 10.14)
Phosphorus (mg/dl)*	5.37 (1.51)	5.79 (1.78)
IQR phosphorus (mg/dl)[a]	(4.25; 6.32)	(4.53; 6.79)
$Ca \times P$ product (mg^2/dl^2)*	53.7 (16.2)	55.6 (17.5)
IQR $Ca \times P$ product (mg^2/dl^2)[a]	(42.0; 63.6)	(43.1; 66.3)
iPTH (pg/ml)	208 (244)	220 (287)
IQR iPTH (pg/ml)[a]	(41; 269)	(56; 279)
Phosphate binders (% yes)	91	90

Mean values (SD) are presented for continuous variables. *$P < 0.05$, PD vs HD patients.
[a]IQR, Interquartile Range, lower (p25) and upper quartile (p75) of observations (p25; p75).
To convert plasma albumin in g/dl to g/l, multiply by 10; to convert calcium in mg/dl to mmol/l, multiply by 0.2495; to convert phosphorus in mg/dl to mmol/l, multiply by 0.3229.

concentrations exceeding the target range advised by K/DOQI. In PD patients, 29% had plasma calcium levels within the target range for calcium, while 40% of the HD patients met the guideline for calcium ($P < 0.001$). Conversely, 50% of the PD patients met the phosphorus-target, whereas only 39% of the HD patients ($P < 0.001$) had plasma phosphorus concentrations within the target range. In both patient groups, most of the remaining patients had higher plasma phosphorus levels than advised. The $Ca \times P$ target was reached by 58% of the PD and 54% of the HD patients. More than half of the patients had plasma iPTH concentrations below the proposed target range, and 22% of the PD and 21% of the HD patients met the iPTH target. Percentages of patients with plasma concentrations below, on or above the targets are depicted in Figure 1.

Hospital admissions

The maximal follow-up time was 7.8 years (1997–2005). The median follow-up time was 29 months (2.4 years) in the PD group and 28 months (2.3 years) in the HD group. During the study period, 272 PD and 609 HD patients were hospitalized at least once. Hospital admissions related to the start of dialysis were not included in this count. In Table 2, the

cardiovascular reasons for hospital admission in PD and HD patients are listed. CVD was the reason for hospitalization in 102 PD patients and in 271 HD patients. In total, 69 PD patients were hospitalized just one time due to a cardiovascular reason, 23 patients had two CVD-related hospitalizations and 33 PD patients had three or more hospitalizations. In HD patients, these numbers were 165, 69 and 37, respectively. The most frequent non-cardiovascular causes of hospitalization were shunt or catheter problems and infections. The median duration of the first CVD-related hospital admission was 8 days in PD patients and 7 days in HD patients.

The median time to first hospital admission with cardiovascular reason was 2.1 years in both the patient groups. In unadjusted analyses (data not shown), we found in PD patients with plasma calcium concentrations below the advised target an increased relative risk of CVD-related hospitalization [Hazard ratio (HR): 2.6, 95% confidence interval (CI): 1.1–6.4]. In HD patients, we found a 40% increased relative risk of CVD-related hospitalization (HR: 1.4, 95% CI: 1.1–1.8) for plasma calcium levels above the K/DOQI target range. Moreover, we observed in HD patients with suppressed plasma iPTH levels an increased HR of 1.3 (95% CI: 1.0–1.8).
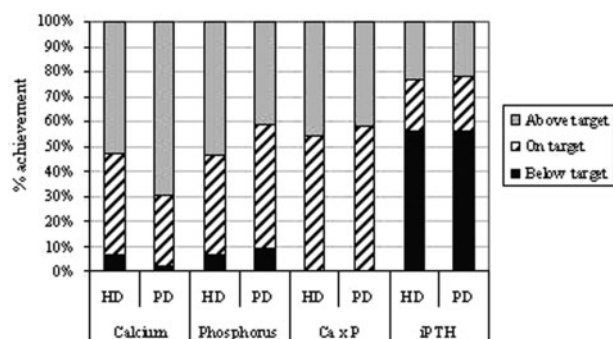
Fig. 1. Percentage achievement of the K/DOQI guideline for bone metabolism and disease in CKD, based on plasma concentrations at 3 months after the start of dialysis treatment.

In the adjusted analyses (Table 3), we found a significantly increased risk of CVD-related hospitalization of 4.3 (95% CI: 1.7–10.9) in PD patients with plasma calcium concentrations below the recommended target. In HD patients with elevated plasma calcium levels, we observed a significantly increased HR of 1.4. Plasma phosphorus, Ca × P and iPTH concentrations below or above the K/DOQI targets did not alter the cardiovascular morbidity risk.

Mortality

Two-year patient survival was 86% in PD and 74% in HD patients. In total, 146 PD and 444 HD patients died during the study period. The proportion that died from CVD was higher in the PD group (52%) than in the HD group (45%, $P = 0.07$). Other common causes of mortality were infections, malignant disease and refusal of further treatment by the patient or ceasing of the dialysis treatment for any other reason. The causes of death are listed in Table 4.

In the unadjusted analyses, we observed only a significantly increased cardiovascular mortality risk (1.4; 95% CI: 1.0–1.9) in PD patients with elevated plasma calcium concentrations. No effects of plasma phosphorus, Ca × P or iPTH concentrations outside the K/DOQI target ranges were found (data not shown).

After adjusting for predefined confounders, we observed a significantly increased cardiovascular mortality risk of 2.2 for phosphorus and of 2.4 for Ca × P concentrations above the K/DOQI thresholds in PD patients. Similarly, cardiovascular mortality in HD patients was increased for elevated plasma phosphorus (HR: 1.5) and for plasma Ca × P (HR: 1.5) concentrations. We did not observe any effect on cardiovascular mortality of plasma calcium or iPTH concentrations beyond the K/DOQI targets. HRs for cardiovascular mortality are shown in Tables 5 and 6. In addition, we analysed the relative risk of non-cardiovascular mortality (Tables 5 and 6).

Table 2. Reasons for CVD-related hospital admissions in PD and HD patients. In total, 881 patients (54%) were hospitalized during the study period

	PD ($n = 272$)		HD ($n = 609$)	
	N^a	Number of hospitalizations (%)	N^a	Number of hospitalizations (%)
Cardiovascular diagnoses	102	181 (100)	271	558 (100)
Coronary artery disease	25	40 (22)	81	174 (31)
Cardiac failure	9	12 (7)	47	64 (11)
Peripheral vascular disease	20	34 (19)	57	117 (21)
Myocardial infarction	16	21 (12)	23	30 (5)
Cerebro vascular accident	12	19 (10)	26	44 (8)
Hypertension	17	25 (14)	14	27 (5)
Other CVD	18	30 (17)	61	102 (18)

[a]N indicates the number of patients that were hospitalized. The numbers of hospitalized patients add up to more than the total number, because patients could have more than one CVD-related hospitalization during follow-up. The number of hospitalizations indicate the total number of hospital admissions for each diagnosis. Hospital admissions related to initiation of dialysis treatment were excluded.

Table 3. Time-dependent adjusted[a] HRs for CVD-related hospital admissions in PD and HD patients, based on plasma levels in categories of the K/DOQI guideline

	PD patients		HD patients	
	Adjusted HR	P-value	Adjusted HR	P-value
Calcium				
Below target	4.3 (1.7–10.9)	<0.01	1.2 (0.6–2.3)	0.59
On target	1.0		1.0	
Above target	1.3 (0.8–2.1)	0.35	1.4 (1.1–1.9)	0.01
Phosphorus				
Below target	0.9 (0.4–1.8)	0.71	0.8 (0.5–1.2)	0.26
On target	1.0		1.0	
Above target	1.2 (0.8–1.8)	0.41	1.0 (0.8–1.3)	0.92
Ca × P				
On target	1.0		1.0	
Above target	1.4 (0.9–2.0)	0.12	1.2 (0.9–1.5)	0.21
iPTH				
Below target	1.1 (0.7–1.7)	0.78	1.3 (1.0–1.8)	0.06
On target	1.0		1.0	
Above target	0.9 (0.5–1.6)	0.78	1.3 (0.9–1.9)	0.12

[a]Multivariate model contained: calcium, phosphorus, iPTH, age, comorbidity, primary kidney disease, nutritional status (SGA), albumin, Kt/V_{urea} per week and haemoglobin. K/DOQI guideline ranges: serum calcium 8.4–9.5 mg/dl, serum phosphorus 3.5–5.5 mg/dl, Ca × P < 55 mg²/dl², iPTH 150–300 pg/ml.

Table 4. Causes of death in PD and HD patients

Cause of death	PD ($n = 146$) (%)	HD ($n = 444$) (%)
Cardiovascular causes	52	45
Myocardial ischaemia and infarction	8	10
Hyperkalaemia	1	1
Cardiac failure	8	7
Cardiac arrest	12	9
Fluid overload	–	1
Cerebro vascular accident	6	5
Haemorrhage from ruptured aneurysm	–	1
Mesenteric infarction	1	2
Cause of death uncertain/not determined	16	9
Non-cardiovascular causes		
Infections[a]	13	13
Malignant disease[b]	10	8
Patient refused further treatment	9	13
Therapy ceased for any other reason	5	10
Other	11	11
Total	100	100

In total, 146 of 586 PD patients (25%) and 444 of 1043 HD patients (43%) died during the study period.
[a]Infections: septicaemia, pulmonary infections, peritonitis, pancreatitis and infections elsewhere.
[b]Malignant disease: includes malignant disease possibly induced by immunosuppressive therapy.

Table 5. Time-dependent adjusted[a] HRs for cardiovascular and non-cardiovascular mortality in PD patients, based on plasma levels in categories of the K/DOQI guideline

	Cardiovascular mortality		Non-cardiovascular mortality	
	Adjusted HR	P-value	Adjusted HR	P-value
Calcium				
Below target	2.8 (0.8–10.1)	0.13	0.6 (0.1–4.8)	0.63
On target	1.0		1.0	
Above target	1.0 (0.5–2.0)	0.98	0.8 (0.4–1.5)	0.47
Phosphorus				
Below target	1.1 (0.4–3.4)	0.84	0.6 (0.2–1.7)	0.33
On target	1.0		1.0	
Above target	2.4 (1.3–4.2)	<0.01	1.1 (0.6–2.0)	0.77
Ca × P				
On target	1.0		1.0	
Above target	2.2 (1.3–3.8)	<0.01	1.0 (0.6–1.8)	0.97
iPTH				
Below target	1.2 (0.6–2.4)	0.65	1.5 (0.7–3.4)	0.29
On target	1.0		1.0	
Above target	1.3 (0.6–2.9)	0.52	1.9 (0.8–4.6)	0.16

[a]Multivariate model contained: calcium, phosphorus, iPTH, age, comorbidity, primary kidney disease, nutritional status (SGA), albumin, Kt/V_{urea} per week and haemoglobin. K/DOQI guideline ranges: serum calcium 8.4–9.5 mg/dl, serum phosphorus 3.5–5.5 mg/dl, Ca × P < 55 mg²/dl², iPTH 150–300 pg/ml.

Table 6. Time-dependent adjusted[a] HRs for cardiovascular and non-cardiovascular mortality in HD patients, based on plasma levels in categories of the K/DOQI guideline

	Cardiovascular mortality		Non-cardiovascular mortality	
	Adjusted HR	P-value	Adjusted HR	P-value
Calcium				
Below target	1.5 (0.7–3.4)	0.32	1.1 (0.4–2.7)	0.87
On target	1.0		1.0	
Above target	1.0 (0.7–1.5)	0.94	1.1 (0.8–1.5)	0.69
Phosphorus				
Below target	0.7 (0.3–1.4)	0.27	0.8 (0.4–1.3)	0.34
On target	1.0		1.0	
Above target	1.5 (1.1–2.1)	0.02	1.3 (0.9–1.7)	0.13
Ca × P				
On target	1.0		1.0	
Above target	1.5 (1.1–2.1)	0.02	1.4 (1.0–1.9)	0.03
iPTH				
Below target	0.9 (0.6–1.3)	0.50	1.4 (0.9–2.1)	0.13
On target	1.0		1.0	
Above target	0.8 (0.5–1.3)	0.35	1.2 (0.8–2.1)	0.40

[a]Multivariate model contained: calcium, phosphorus, iPTH, age, comorbidity, primary kidney disease, nutritional status (SGA), albumin, Kt/V_{urea} per week and haemoglobin. K/DOQI guideline ranges: serum calcium 8.4–9.5 mg/dl, serum phosphorus 3.5–5.5 mg/dl, Ca × P < 55 mg²/dl², iPTH 150–300 pg/ml.

We found that HD patients with plasma Ca × P concentrations above the target had a 40% increased non-cardiovascular mortality risk. We did not find an association of non-cardiovascular mortality with plasma concentrations below or above the prescribed targets in PD patients.

In addition, we examined whether receiving phosphate binders was protective or not against cardiovascular mortality by adding the use of phosphate binders as a variable to our time-dependent model. This analysis did not alter the conclusions from the initial model.

As 19% of the patients switched from treatment modality during the study period, we also performed an analysis in which we censored the observation time of patients at the moment that they switched dialysis modality. This additional analysis did not affect our results in any way.

Discussion

In the current study, we showed that disordered mineral metabolism has a limited effect on the risk of hospital admission with a cardiovascular reason. Only in HD patients with plasma calcium concentrations above the K/DOQI target did we observe an increased relative risk of CVD-related hospitalization. Associations with cardiovascular mortality were more pronounced; plasma phosphorus and Ca × P concentrations above the K/DOQI thresholds significantly increase cardiovascular mortality in both PD and HD patients. No significant association of abnormal plasma iPTH concentration with cardiovascular morbidity or mortality was found. These findings indicate that the associations of plasma concentrations outside the target ranges advised in the K/DOQI guideline with cardiovascular mortality are similar in both patient groups.

Our study has some limitations. First, when the cause of death was uncertain or not determined, we classified it as cardiac arrest and thus as cardiovascular mortality because in these cases the patients died acutely. As a consequence, the proportion of cardiovascular causes of death may be slightly overestimated. However, this proportion is in concordance with the international literature [9], and when we performed an analysis in which an uncertain or undetermined cause of death was classified as non-cardiovascular, this had only a minor influence on our results. We may have underestimated the proportion of CVD-related hospital admissions, since we focused on primary diagnoses of hospitalizations and secondary diagnoses or events during hospitalization were not taken into account. Finally, data on the type of prescribed phosphate-binders and the use of vitamin D analogues were not available. About 90% of both PD and HD patients used phosphate binders at baseline. Over time, this proportion remained stable in the PD group and increased to a maximum of 97% in the fourth year after the start of dialysis in the HD group. The proportion of HD patients who used phosphate binders was over time somewhat higher than the proportion of PD patients, although this difference was only significant in the second year after the start of dialysis. During the greater part of the study period, non-calcium containing phosphate binders were not yet available in the Netherlands and we assume that the majority of patients were treated with calcium-acetate or calcium-carbonate. In addition, some patients, especially those with severe hyperphosphataemia, might have been treated with aluminium-containing phosphate binders. The elevated plasma calcium concentrations that we observed could have been caused by the use of calcium-based phosphate-binders and vitamin D analogues. As a result of the relatively high calcium levels, iPTH concentrations were probably suppressed and, in addition, PTH-release could be directly restrained by vitamin D analogues [15,16]. On the other hand, HD patients receiving some form of injectable active vitamin D have recently been shown to be at survival advantage compared with patients who did not, and this survival benefit was present at all levels of serum calcium, phosphorus or PTH [17].

A recent study has indicated that therapeutic interventions associated with excessive lowering of parathyroid activity like parathyroidectomy or a high calcium load favour low bone turnover and adynamic bone disease which could influence the development and progression of arterial calcifications [18]. We did not observe a relationship between iPTH and cardiovascular morbidity or mortality. Furthermore, only 67 patients (4.1%) underwent subtotal or total parathyroidectomy during the study period.

In a recent analysis of the USRDS cohort, Block et al. [2] observed that hyperphosphataemia and hyperparathyroidism were significantly associated with cardiovascular hospitalizations in prevalent HD patients. However, in our study we found that in incident HD patients, CVD-related hospital admissions were associated with elevated calcium concentrations and we could not detect any significant effects of elevated plasma phosphorus, Ca × P or iPTH levels. These discrepancies could be due to differences in methodology. The cross-sectional study in prevalent patients of Block et al. [2] used higher thresholds whereas the present study focused on target limits as recommended by K/DOQI and the sample size of this American study was substantially larger than of our study. So far, no one has studied these effects in PD patients.

In PD patients, we also observed a significant association of cardiovascular morbidity with plasma calcium concentrations below 8.4 mg/dl (2.10 mmol/l, HR: 4.3). We cannot explain this finding, but it should be kept in mind that only 48 out of 586 PD patients (8%) had at least once during follow-up, a plasma calcium concentration below the K/DOQI target range. A total of six CVD-related hospitalizations in four of these patients accounted for the observed association, which indicates that this association might be based on coincidence.

Several studies have been performed to determine the association between mineral metabolism and cardiovascular mortality [2–4,6]. In a cohort of 17 236 HD patients participating in the DOPPS study, Young et al. [4] found increased relative risks of cardiovascular death in HD patients with elevated serum concentrations of phosphorus, Ca × P and PTH. Similarly, Ganesh et al. [3] observed an increase of 41% of cardiovascular mortality risk in prevalent HD patients from the USRDS study who had serum phosphorus levels above 6.5 mg/dl (2.1 mmol/l)

compared with patients with serum levels between 2.4 and 6.5 mg/dl (0.8–2.1 mmol/l). The mortality risks that we observed in HD patients were similar to the findings in those previous studies. We are not aware of any previous studies in PD patients.

Associations of abnormal phosphorus and $Ca \times P$ concentrations with cardiovascular mortality were similar to those with non-cardiovascular mortality in HD patients. In PD patients, however, no associations with non-cardiovascular mortality could be detected. These results indicate that the association between disturbed mineral metabolism and cardiovascular mortality risk is similar for both treatment modalities, while the risk of non-cardiovascular mortality was only related to abnormalities in mineral metabolism in HD patients.

Several mechanisms may be involved in the increased cardiovascular morbidity and mortality associated with disordered mineral metabolism. Vascular and tissue calcification is increasingly recognized as a frequent complication in ESRD [18]. Moreover, cardiac valve calcification is a strong predictor for all-cause and cardiovascular mortality in long-term dialysis patients [19]. Growing evidence indicates that uraemic vascular calcification is an active and regulated cell-mediated process similar to osteogenesis in bone, rather than a passive precipitation of calcium and phosphorus. In this process, vascular smooth muscle cells (VSMCs) transform into osteoblasts-like cells which are capable of calcification *in vitro* [20]. Several stimuli such as oxidized low-density lipoprotein, high concentrations of PTH and vitamin D derivates have been shown to induce the transformation of VSMCs. In addition, increasing evidence implies that elevated plasma phosphorus and $Ca \times P$ concentrations could be important stimuli for excess vascular calcification in uraemic patients [21], which is confirmed by the findings of our current study. A lack of protective factors, such as the calcification-inhibiting glycoprotein fetuin-A (α2-Heremans–Schmid glycoprotein), may also contribute to the pathogenesis of uraemic vascular calcifications [22,23].

In conclusion, associations of disturbances in mineral metabolism with cardiovascular mortality are more pronounced than associations with CVD-related hospitalizations. Only in HD patients with plasma calcium concentrations above the K/DOQI threshold is the relative risk of CVD-related hospital admission increased. Cardiovascular mortality risk is increased in PD and in HD patients with elevated plasma phosphorus and $Ca \times P$ concentrations. Therefore, it seems appropriate to adopt the current guideline for PD patients.

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