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Chapter 5 |

Compliance with KDOQI and KDIGO guidelines for serum phosphorus and serum calcium in relation to disease progression in pre-dialysis patients

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Submitted

Abstract

Background

Mineral metabolism disorders are associated with poor outcome in (pre-)dialysis patients. This study assessed whether non-compliance with the KDOQI and KDIGO guidelines for serum phosphorus and serum calcium at the start of pre-dialysis care is associated with shorter dialysis-free survival and accelerated decline of kidney function. It was also studied whether these associations differed between patients aged < or ≥65 years.

Methods

Incident pre-dialysis patients (N=500, 68% male, age 65±14 years, phosphorus 1.42±0.32 mmol/L, calcium 2.32±0.15 mmol/L) from the PREPARE-2 cohort were included. Associations with the start of dialysis were studied using Cox regression models, while decline of kidney function was studied using linear mixed models. The analyses were adjusted for age, sex, and primary kidney disease. Furthermore, analyses were stratified for age < or ≥65 years.

Results

Phosphorus levels above the KDOQI (HR 1.9 [95 %CI 1.4;2.6]) and KDIGO (2.6 [95% CI 1.9;3.5]) target ranges were associated with shorter dialysis-free survival. For calcium levels, these risks were 1.3 (95% CI 0.8;2.3) and 1.4 (95% CI 0.9;2.1), respectively. Furthermore, each 0.1 mmol/L increase in phosphorus (HR 1.2 [95% CI 1.2;1.3]), but not calcium (1.0 [95% CI 0.9;1.1]), was associated with shorter dialysis-free survival. No association between guideline compliance and decline of kidney function was found. However, each 0.1 mmol/L increase in phosphorus (-0.9 mL/min/1.73m^2 [95% CI -1.1;-0.8]), but not calcium (-0.2 [95% CI 0.7;0.2]), was associated with a faster decline of kidney function. All results were similar in patients aged <65 *versus* ≥65 years.

Conclusions

High phosphorus levels are associated with a shorter dialysis-free survival and a faster decline of kidney function. No associations between calcium levels and dialysis-free survival and decline of kidney function were found. Results were similar for patients aged <65 *versus* ≥65 years.

Introduction

Disturbances of the mineral metabolism including hyperphosphatemia and hypocalcemia are highly prevalent in patients with chronic kidney disease (CKD).[1;2] In dialysis patients it has been shown that these disturbances are associated with a higher prevalence of muscle and skin problems[3] and an increased all-cause mortality risk.[4-7] Furthermore, in pre-dialysis patients hyperphosphatemia is associated with both a faster decline in kidney function and an increased all-cause mortality risk.[7]

The observed associations between mineral metabolism disorders and poor outcome in CKD patients led to the introduction of two treatment guidelines. First, the American National Kidney Foundation-Kidney Disease Outcome Quality Initiative (KDOQI) guideline was introduced in 2003.[1] More recently, in 2009, the Kidney Disease: Improving Global Outcomes: Chronic Kidney Disease-Mineral and Bone Disorder (KDIGO CKD-MBD) guideline has been established.[2] Differences between both guidelines include the definition of renal osteodystrophy, which has been changed to describe the bone pathology associated with CKD, and the target ranges for serum phosphorus and serum calcium concentrations.

The KDOQI target ranges for phosphorus are specific for different stages of CKD. In CKD stages 3-4 phosphorus concentrations should be maintained between 0.87 and 1.49 mmol/L, while in CKD stage 5 the concentrations should be maintained between 1.13 and 1.78 mmol/L. For calcium the KDOQI guideline established a target range between 2.10 and 2.54 mmol/L in CKD stages 3-4, while the concentrations should be within the normal range, but preferably toward the lower end (between 2.10 and 2.37 mmol/L) in CKD stage 5.[1] According to the KDIGO guideline, patients with CKD stages 3-5 should have phosphorus and calcium concentrations within the normal range, which is between 0.81 and 1.45 mmol/L and between 2.1 and 2.5 or 2.6 mmol/L, respectively.[2]

Several studies have shown that only 50-89% of the patients with CKD stage 4 and 29- 72% of the patients with CKD stage 5 have phosphorus concentrations within the target ranges as recommended by the KDOQI guideline.[6-9] To our knowledge there are not yet studies which focus on compliance with the KDIGO guideline. The aim of the present study was to examine the compliance with the KDOQI and KDIGO guidelines for phosphorus and calcium at the start of pre-dialysis care. Furthermore, it was studied whether compliance is associated with the risk of dialysis within two years after the start of pre-dialysis care and decline of kidney function during pre-dialysis care. Finally, in light of the growing ageing population, it was investigated whether the associations were different for patients aged <65 *versus* ≥65 years.

Methods

Study design

The PREdialysis PAtients REcords (PREPARE-2) Study is an ongoing, prospective study of incident pre-dialysis patients treated in one of 25 nephrology outpatient clinics in the Netherlands. Patients were included between July 2004 and June 2011, at the start of pre-dialysis care. They were treated by their nephrologists in their regular scheme according to the

treatment guideline of the Dutch Federation of Nephrology[10], a Dutch guideline analogous to the KDOQI and KDIGO guidelines.[1;2] At study inclusion and in subsequent six month intervals clinical data were collected. Patients were followed-up till the start of dialysis, death, or censoring. Censoring was defined as: receiving a kidney transplant, move to an outpatient clinic not participating in the PREPARE-2 Study, recovery of kidney function, refusal of further study participation, or September 1, 2011, whichever came first. For the present analysis follow-up was restricted to the first two years of pre-dialysis care. The study was approved by the medical ethics committees or institutional review board of all participating centers.

Patients

To be eligible for inclusion in the PREPARE-2 Study, patients had to be at least eighteen years of age and they should have been referred to a specialized pre-dialysis outpatient clinic for pre-dialysis care. In practice, this refers to patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m^2, in whom the need for renal replacement therapy was expected within one year. Patients with a failing kidney transplant were also included in the study if the transplantation was at least one year ago. All participants gave their written informed consent prior to study inclusion.

Data collection

Data on demography, biometry, primary kidney disease, comorbidities, and medication use were collected at study inclusion and/or during follow-up. Laboratory data were extracted from the electronic hospital information systems or medical records. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association into four categories (diabetes mellitus, glomerulonephritis, renal vascular disease, and other).[11]

Determinants

The glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease formula.[12] Phosphorus, calcium, albumin, and creatinine (uncalibrated) concentrations were measured using routine laboratory techniques at each outpatient clinic. Calcium concentrations were corrected for albumin concentrations to better reflect the free calcium.[13] For the present analyses, patients were classified based on the achievement of the target ranges for phosphorus and calcium as recommended by the KDOQI and KDIGO guidelines (below, within, and above the KDOQI or KDIGO target ranges).[1;2] The KDOQI target ranges for phosphorus were specific for different stages of CKD: 0.87 to 1.49 mmol/L for CKD stages 3-4 (i.e. eGFR between 15 and 60 mL/min/1.73m^2) or 1.13 to 1.78 mmol/L for CKD stage 5 (i.e. eGFR below 15 mL/min/1.73m^2). For calcium the KDOQI target ranges were 2.10 to 2.54 mmol/L for CKD stages 3-4 or within the normal range, but preferably toward the lower end; 2.10 to 2.37 mmol/L for CKD stage 5.[1] According to the KDIGO guideline the target range for phosphorus is between 0.81 and 1.45 mmol/L and for calcium between 2.1 and 2.5 or 2.6

mmol/L, irrespective of CKD stage.[2] For the current analysis we used 2.5 mmol/L as the upper limit of the calcium target range. To convert phosphorus in mmol/L to mg/dL, multiply by 0.3229. To convert calcium in mmol/L to mg/dL, multiply by 0.2495.

Statistical analyses

Continuous variables were expressed as mean±standard deviation and categorical variables as percentages. The following baseline parameters were available for a subset of patients: albumin in 370 patients, calcium in 368 patients, phosphorus in 389 patients, parathyroid hormone in 271 patients, eGFR in 403 patients, systolic bloodpressure in 496 patients, diastolic bloodpressure in 496 patients, body mass index in 489 patients. To enhance power, missing values were imputed using multiple imputation techniques. Multiple imputation is a recommended technique whereby missing data for each subject are imputed using a predicted value that is based on the subject's other known characteristics.[14;15] For the current analyses we used age, sex, primary kidney disease, albumin, creatinine, calcium, phosphorus, parathyroid hormone, bloodpressure (both systolic and diastolic), body mass index (all at baseline), eGFR at every study visit, follow-up time, and reason for end of study to impute the missing data. Multiple imputation was performed ten times using standard multiple imputation methods in SPSS. Incidence rates for the association between compliance with KDOQI and KDIGO guidelines for phosphorus and calcium and the start of dialysis within two years of pre-dialysis care were calculated. In addition, we used Cox proportional hazards models to estimate hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) for the risk of starting dialysis within this period. These analyses were additionally adjusted for the possible confounding effects of age, sex, and primary kidney disease. Furthermore, linear mixed effects models were used to analyze whether the yearly rate of decline of kidney function was different for patients with phosphorus and calcium concentrations below, within, and above the target ranges. These analyses were also adjusted for age, sex, and primary kidney disease. Under the assumption that the decline of kidney function in a relatively short period is almost linear,[16] we restricted follow-up time for this analysis to the first year of pre-dialysis care. Finally, it was examined whether the associations studied differed between elderly patients and younger patients. To that end, analyses were stratified for patient age at inclusion (<65 *versus* ≥65 years). All analyses were performed with SPSS (version 17.0; SPSS, Chicago, IL).

Results

Study population

Between July 2004 and June 2011, 500 patients were included in the PREPARE-2 Study, of whom 216 (43.2%) were aged <65 years and 284 (56.8%) ≥65 years. Baseline patient characteristics are listed in Table 1. At baseline 234 (46.8%) patients were using one or more phosphate-binding drugs, including calcium carbonate (n=184), sevelamer (n=101), calcium acetate (n=8), and aluminium hydroxide (n=1).

Achievement of guidelines

The majority of the patients (>56%) complied with the KDOQI and KDIGO guidelines for phosphorus and calcium at the start of pre-dialysis care. Up to 43% of the patients had phosphorus and/or calcium concentrations above the target ranges and at most 8% below the target ranges (Figure 1). Results were similar for patients aged <65 *versus* ≥65 years (Figure 2).

Table 1. Patient characteristics (N=500) at start of pre-dialysis care.

	All patients (N=500)
Age *year*	64.9 (14.3)
Sex *% male*	68.0
Primary kidney disease *%*	
Renal vascular disease	30.4
Diabetes mellitus	14.4
Glomerulonephritis	13.2
Other	42.0
Comorbidities *%*	
Diabetes mellitus, type I	3.4
Diabetes mellitus, type II	22.3
Cardiovascular disease*	41.2
Systolic bloodpressure *mmHg*	142.5 (22.2)
Diastolic bloodpressure *mmHg*	77.9 (11.6)
Body mass index kg/m^2	26.8 (5.2)
eGFR $mL/min/1.73m^2$	16.8 (6.1)
Chronic kidney disease *%*	
Stage 3 (30-59 mL/min/1.73m^2)	2.4
Stage 4 (15-29 mL/min/1.73m^2)	53.8
Stage 5 (<15 mL/min/1.73m^2)	43.8
Serum albumin *g/L*	40.6 (4.5)
Corrected serum calcium *mmol/L*	2.32 (0.15)
Serum phosphorus *mmol/L*	1.42 (0.32)
Parathyroid hormone *pmol/L*	25.2 (20.9)

Values are mean (standard deviation) or percentage as appropriate; eGFR, estimated glomerular filtration rate; *cerebrovascular accident, peripheral vascular disease, angina pectoris, myocardial infarction, congestive heart failure.

Follow-up

Median (inter-quartile range) follow-up from the start of pre-dialysis care until censoring was 1.16 (0.56; 2.00) years. During follow-up, 215 (43%) patients started with dialysis, while 110 (22%) patients were censored for different reasons, i.e. refusal of further study participation (n=33), transplantation (n=31), mortality (n=29), recovery of kidney function (n=8), treatment was continued in another outpatient clinic not participating in PREPARE-2 (n=8), and other reasons (n=1). The remaining 175 (35.0%) patients were censored because of reaching the end of the observation period (two years of follow-up or September 1, 2011).

Figure 1. Compliance with the KDOQI and KDIGO guidelines for serum phosphorus and serum calcium at the start of pre-dialysis care (N=500).

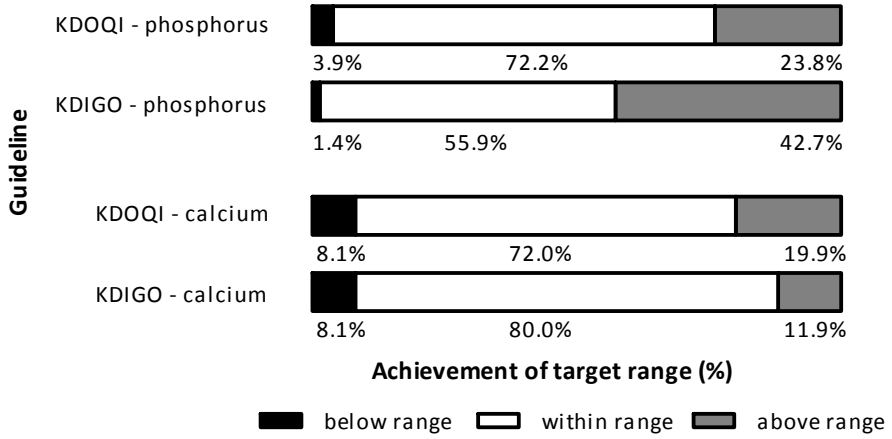


Figure 2. Compliance with the KDOQI and KDIGO guidelines for serum phosphorus and serum calcium at the start of pre-dialysis care in patients aged <65 (n=216) and patients aged ≥65 years (n=284).

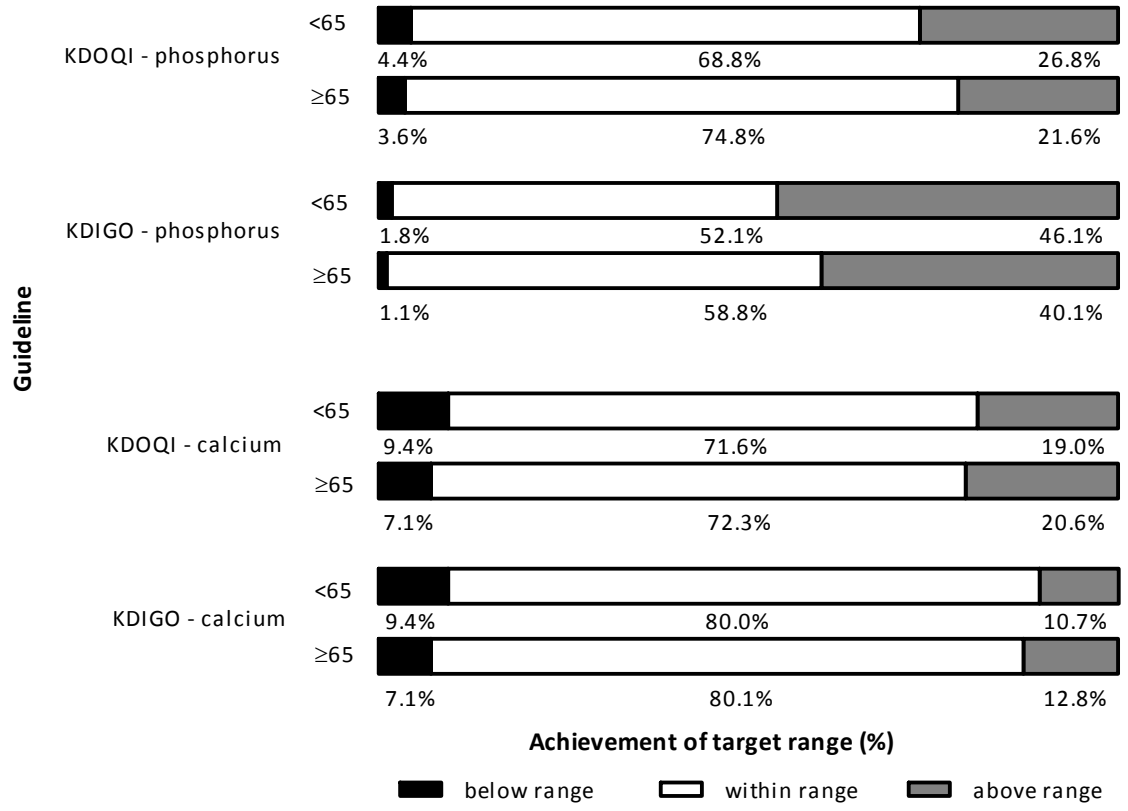
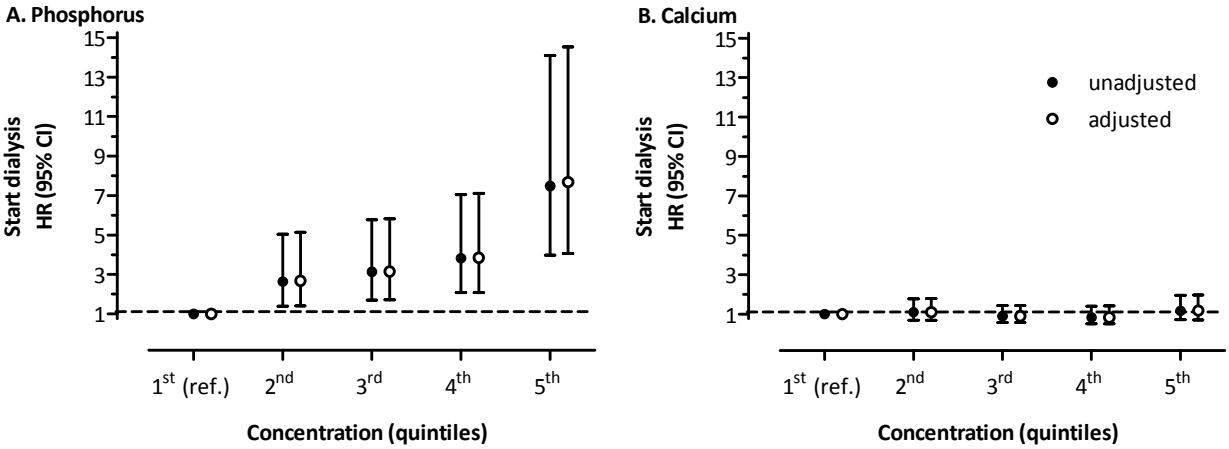


Figure 3. Association between serum phosphorus and serum calcium levels (quintiles) and the risk for the start of dialysis within the first two years of pre-dialysis care (n=500). In this figure, the quintile limits for phosphorus are: 1.15, 1.30, 1.47, and 1.63 mmol/L and the quintile limits for calcium are: 2.19, 2.27, 2.35, and 2.45 mmol/L.



Dashed line indicates hazard ratio, hazard ratio (HR)=1, i.e. no association; *adjusted for age, sex, and primary kidney disease.

Start of dialysis

Of the 215 patients who started with dialysis therapy, 131 (60.9%) patients started with hemodialysis and 84 (39.1%) patients with peritoneal dialysis. Based on the results of quintile-analyses (Figure 3), linear relationships between phosphorus and calcium concentrations and the risk for the start of dialysis therapy within two years of pre-dialysis care were assumed. A linear analysis showed that for each 0.1 mmol/L increase in phosphorus concentration, the unadjusted HR for the start of dialysis was 1.22 (95% CI 1.16 to 1.27), which was 1.22 (95% CI 1.17 to 1.28) after adjustment for age, sex, and primary kidney disease. Each 0.1 mmol/L increase in calcium concentration was associated with an unadjusted HR of 1.02 (95% CI 0.91 to 1.14) for the start of dialysis, which was 1.02 (95% CI 0.90 to 1.15) after adjustment. The incidence rates for the start of dialysis associated with phosphorus and calcium concentrations below the KDOQI and KDIGO target ranges were slightly lower, and these for above the target ranges were slightly higher as compared to the incidence rates for concentrations within the target ranges (Table 2). The corresponding crude and adjusted hazard ratios showed a similar pattern. In patients aged <65 *versus* patients aged ≥65 years, the associations between phosphorus and calcium levels and the start of dialysis were similar (Table 3).

Decline of kidney function

The mean rate of decline of kidney function in the first year of pre-dialysis care was -2.16 mL/min/1.73m^2/year (95% CI -3.20 to -1.12). Furthermore, within this period, for each 0.1 mmol/L increase in phosphorus concentration the mean decline of renal function changed with -0.95 mL/min/1.73m^2/year (95% CI -1.13 to -0.77), which was -0.94 (95%CI -1.12 to -0.76) after adjustment for age, sex, and primary kidney disease.

Table 2. Association between compliance with KDOQI and KDIGO guidelines for serum phosphorus and serum calcium and the start of dialysis (incidence rates per 100 person-years [py] and hazard ratios together with 95% confidence interval [CI]) within the first two years of pre-dialysis care.

		KDOQI			KDIGO		
		Rate/100py (95% CI)	Hazard ratio (95% CI)		Rate/100py (95% CI)	Hazard ratio (95% CI)	
			Crude	Adjusted		Crude	Adjusted
Phosphorus	Below	16 (6; 41)	0.49 (0.15; 1.59)	0.47 (0.14; 1.56)	6 (1; 72)	n.a.	n.a.
	Within	32 (26; 37)	1.00 (ref.)	1.00 (ref.)	24 (19; 29)	1.00 (ref.)	1.00 (ref.)
	Above	58 (44; 72)	1.86 (1.37; 2.54)	1.85 (1.36; 2.54)	60 (49; 70)	2.59 (1.91; 3.51)	2.59 (1.91; 3.50)
Calcium	Below	33 (20; 53)	1.02 (0.57; 1.83)	0.99 (0.54; 1.81)	33 (20; 54)	0.93 (0.51; 1.67)	0.91 (0.50; 1.67)
	Within	32 (27; 38)	1.00 (ref.)	1.00 (ref.)	35 (30; 41)	1.00 (ref.)	1.00 (ref.)
	Above	54 (39; 68)	1.67 (1.13; 2.45)	1.69 (1.14; 2.51)	42 (29; 61)	1.20 (0.77; 1.86)	1.21 (0.77; 1.91)

*Adjusted for: age, sex, and primary kidney disease; ref.: reference category; n.a.: not applicable (too few events).

Each 0.1 mmol/L increase in calcium concentration was associated with a change of the mean decline of renal function of -0.27 mL/min/1.73m^2/year (-0.71 to 0.18), which was -0.24 (-0.69 to 0.21) after adjustment. No association between compliance with the guidelines and the rate of decline of kidney function was found (Table 4). Similarly, in patients <65 and in patients ≥65 years no associations between phosphorus and calcium levels and decline of kidney function were found.

Table 3. Association between compliance with KDOQI and KDIGO guidelines for serum phosphorus and serum calcium and the start of dialysis hazard ratios adjusted for age, sex, and primary kidney disease, together with 95% confidence interval [CI]) within the first two years of pre-dialysis care.

Phosphate		KDOQI		KDIGO	
		<65 years	≥65 years	<65 years	≥65 years
	Below	0.70 (0.19; 2.62)	n.a.	n.a.	n.a.
	Within	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Above	2.03 (1.26; 3.27)	1.70 (1.07; 2.70)	2.85 (1.82; 4.48)	2.39 (1.59; 3.59)
Calcium		KDOQI		KDIGO	
		<65 years	>65 years	<65 years	>65 years
	Below	0.72 (0.29; 1.78)	1.47 (0.68; 3.17)	0.66 (0.27; 1.66)	1.34 (0.62; 2.90)
	Within	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Above	1.76 (1.04; 2.97)	1.57 (0.90; 2.68)	1.31 (0.65; 2.64)	1.07 (0.54; 2.14)

Table 4. Association between compliance with KDOQI and KDIGO guidelines for serum phosphorus and serum calcium and the rate of decline of kidney function (eGFR, mL/min/1.73m^2/year) with 95% confidence interval (CI) within the first year of pre-dialysis care.

Guideline	Parameter	Model	Difference in rate of decline of eGFR (95% CI)		
			Below	Within	Above
KDOQI	Phosphorus	Crude	0.2 (-6.9 to 7.2)	0.0 (ref.)	-0.7 (-3.5 to 2.1)
		Adjusted*	0.1 (-6.9 to 7.2)	0.0 (ref.)	-2.5 (-8.8 to 3.8)
	Calcium	Crude	1.1 (-2.7 to 4.8)	0.0 (ref.)	2.0 (-1.3 to 5.2)
		Adjusted*	1.1 (-2.6 to 4.8)	0.0 (ref.)	2.0 (-1.2 to 5.2)
KDIGO	Phosphorus	Crude	-5.2 (-26.1 to 15.8)	0.0 (ref.)	0.4 (-2.0 to 2.8)
		Adjusted*	-5.4 (-26.4 to 15.7)	0.0 (ref.)	0.4 (-1.9 to 2.8)
	Calcium	Crude	0.8 (-2.8 to 4.5)	0.0 (ref.)	1.8 (-2.6 to 6.2)
		Adjusted*	0.9 (-2.8 to 4.5)	0.0 (ref.)	1.8 (-2.5 to 6.2)

Positive values indicate a slower, whereas negative values indicate a faster rate of decline of kidney function as compared to the reference category; *adjusted for: age, sex, and primary kidney disease; ref.: reference category.

Discussion

The current study, including 500 incident Dutch pre-dialysis patients, showed that at start of pre-dialysis care at least 56% of the patients comply with the KDOQI and KDIGO guidelines for phosphorus and calcium. More than 43% of the patients have concentrations above the target

ranges, while at most 8% of the patients have concentrations below the target ranges. In addition, it was shown that patients with phosphorus concentrations above the target ranges at start of pre-dialysis care have a shorter dialysis-free survival. A similar association was found with respect to guidelines for calcium, although less pronounced. Non-compliance with the guidelines for phosphorus and calcium was not associated with a faster rate of decline of kidney function. Nevertheless, each 0.1 mmol/L increase in phosphorus concentration was associated with both a faster rate of decline of kidney function and a shorter dialysis-free survival. Together, these results underline the importance of adequate management of phosphorus and calcium concentrations right from the start of pre-dialysis care.

This study shows that higher phosphate concentrations are associated with a higher risk for the start of dialysis within two years after the start of pre-dialysis care. Associations between disturbances of the mineral metabolism and poor outcome have been shown frequently. For example, in healthy young adults, elevation of serum phosphorus concentrations is associated with coronary atherosclerosis.[17] Besides, in patients with CKD or end-stage renal disease, associations between phosphorus levels and cardiovascular morbidity and mortality have been observed.[18-22] Disorders of the mineral metabolism are shown to develop early in the course of CKD and worsen with progressive loss of kidney function.[20] Moreover, in pre-dialysis patients elevated phosphorus concentrations are associated with a faster rate of decline of kidney function[7], which was confirmed by the analysis in which we estimated the risk associated with each 0.1 mmol/L increase in phosphate level. To adequately manage phosphorus and calcium concentrations in patients with CKD, guidelines have been introduced, which include specified target ranges for phosphorus and calcium. Achievement of the KDOQI guidelines for mineral metabolism has been studied occasionally in patients with CKD stage 3-5 (not on dialysis),[7-9] though studies on the achievement of KDIGO guidelines in these patients are, to our knowledge, lacking. The present study investigated the compliance with the KDOQI and KDIGO guidelines in patients at start of pre-dialysis care.

From an epidemiologic point of view, we have to discuss different factors that might have influenced our observations. First, due to the strong interplay between different parameters of the mineral metabolism, it is difficult to unravel separate effects of phosphorus or concentrations on disease progression in CKD. Multivariate adjustment might help to overcome this problem, but should be used with caution to avoid adjustment for intermediate factors. For example, adjustment for the presence of proteinuria might (partly) remove the observed association between baseline phosphorus level and decline of kidney function, since proteinuria might have developed as a(n indirect) consequence of the baseline phosphorus level. For that reason, we only adjusted our analyses for the effects of age, sex, and primary kidney diseases. Second, associations might have been obscured by (changes in) the multiple (pharmacological) interventions that are given to restore the disordered mineral metabolism. To limit the possible effects of changes in lifestyle and medication use, we only studied short-term effects within the first year or the first two years of pre-dialysis care. In addition, even when the decline of kidney function was analyzed only within the first six months of pre-dialysis care, results were

comparable with the results of the original analyses (not shown). Third, patients were classified in three categories based on whether the KDOQI or KDIGO target ranges were achieved. The majority of the patients had phosphorus and calcium concentrations within the target ranges, while a minority had concentrations below and the remainder above the target ranges. Consequently, the power for the different analyses using the classification in three categories was relatively low. This can also be seen by the wide 95% confidence intervals in several analyses. Despite the wide confidence intervals, trends were visible especially for the categories above the target ranges, which was confirmed in the analyses with phosphorus expressed in mmol/L. Fourth, in the analyses using the classification of phosphorus in three categories only slightly increased risks for the start of dialysis therapy within two years of pre-dialysis care were observed, while the analyses using phosphorus levels as a continuous parameter, showed much larger associations. How can this be explained? In the analysis using the categorization of patients into three categories, patients with extremely low and these with levels just below the target range were all categorized into one category. Similarly, patients with extremely high levels were categorized in the same category as patients with only slightly increased levels. Therefore, there is less contrast between the groups and associations are weaker. Fifth, calcium levels above the target ranges as proposed by the KDOQI guideline, but not the KDIGO guideline, were associated with an increased risk for the start of dialysis within the first two years of pre-dialysis care. This can be explained as follows: the KDOQI guideline has different target ranges for patients with CKD stages 3-4 *versus* these with stage 5, with a smaller target range for the latter patient group. The target range proposed by the KDIGO guideline however, applies to all patients, irrespective of their CKD stage. Consequently, a subset of the patients with CKD stage 5 has calcium levels that are above the KDOQI target range, but within the KDIGO target range. Therefore, there is more contrast between the 'within' and 'above' categories of the KDOQI guideline as compared to the KDIGO guideline. Furthermore, no association was found between each unit increase in calcium level and the risk to start with dialysis, despite that there was an association between calcium levels above the KDOQI target range and the start of dialysis. This indicates that in general there is no association between calcium levels and the start of dialysis, only for (extremely) high levels of calcium. Finally, recently it has been observed that compliance with guidelines for mineral metabolism in dialysis patients was influenced by several unmodifiable patient factors, including dialysis vintage and age.[23] In light of this observation and the worldwide growing elderly population, we did additional analyses to examine whether the association between compliance with guidelines, the start of dialysis, and the decline of kidney function is different for elderly pre-dialysis patients (≥65 years) and pre-dialysis patients aged <65 years. These analyses showed that there were no differences in effect between the two age groups.

The present analysis showed that the majority of the patients complied with the guidelines for phosphorus and calcium at the start of pre-dialysis care. This may be explained by a good balance of the mineral metabolism in these patients, but also may merely reflect the (compliance to) therapy which has been initiated previously. Irrespective of the cause of achievement,

though, we were able to assess whether compliance with the guidelines was associated with the risk to start dialysis therapy within two years after the start of pre-dialysis care. Within this analysis a small trend was observed that patients with phosphorus or calcium concentrations below the target ranges had a longer dialysis-free survival as compared to patients with concentrations within the target ranges. This might be explained by a better general health condition of these patients, or by a better compliance to previously started treatment. It was also shown that patients with phosphorus (and to a lesser extent calcium, i.e. only when referring to the KDOQI guideline) concentrations above the target ranges had a shorter dialysis-free survival time as compared to patients with concentrations within the recommended ranges. This might be explained as follows: CKD patients have a tendency towards hyperphosphatemia due to the reduced phosphorus filtering capacity of the kidney.[20] Hyperphosphatemia is one of the main factors in causing secondary hyperparathyroidism, which is an important factor in causing uremic complications. The presence of uremic complications may be one of the reasons to start dialysis therapy.[24]

Our data have clinical implications. The present analysis showed that phosphorus concentrations - and to a lesser extent calcium concentrations - above the target ranges as recommended by the KDOQI and KDIGO guidelines are associated with a shorter dialysis-free survival. Furthermore, each unit increase in phosphorus concentration is associated with a faster decline of kidney function within the first year of pre-dialysis care. A better preserved kidney function not only postpones the time to the start of dialysis, but once started with dialysis a better preserved kidney function is also associated with improved quality of life and a better survival.[25] Thus, compliance to the KDOQI or KDIGO guidelines for phosphorus and calcium, might have consequences even after the start of dialysis.

Disclosure

The authors have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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