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Quantifying exposure to calcium and phosphate in ESRD; predictive of atherosclerosis on top of arteriosclerosis?

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ABSTRACT

Background: Long-term exposure to hypercalcaemia and hyperphosphataemia leads to media calcification and predicts mortality in patients with end-stage renal disease (ESRD). It is debatable whether this exposure is only a risk factor for arteriosclerosis, or also for superimposed atherosclerosis. Calcium-phosphate exposure is difficult to quantify, because it is variable in time and exerts its deleterious effects only after prolonged presence.

Methods: In 90 dialysis patients, calcium and phosphate values from the complete dialysis period were collected. From three-month averages, measures for calcium-phosphate exposure were derived after exclusion of transplant periods. Calcium-phosphate exposure was then related to intima-media thickness (IMT) and to ankle-brachial index (ABI) as markers of early atherosclerosis.

Results: Calcium-phosphate exposure was quantified in three ways using 1670 patient-quarters (i.e. three-months periods) covering 93% of the time on dialysis: averaged calcium-phosphate exposure, percentage of time with above-reference values, and burden of hypercalcaemia/hyperphosphataemia represented by this percentage multiplied by months on dialysis. No association was found with IMT. Patients with increased, not decreased, ABI had higher calcium-phosphate exposure throughout dialysis treatment: hyperphosphataemia burden was 31 (19 to 43) months for patients with ABI between 0.90 and 1.40 and 79 (58 to 100) months for patients with ABI >1.40 or incompressible ankle arteries (p<0.001).

Conclusion: These findings do not support the hypothesis that calcium-phosphate exposure leads to atherosclerotic changes on top of arteriosclerosis in ESRD, and confirm its role in causing arteriosclerotic damage leading to increased arterial stiffness and incompressible ankle arteries. The used tool for quantifying calcium-phosphate exposure is easy to apply and can properly weigh the complete exposure during ESRD.

KEYWORDS

Atherosclerosis, calcium, haemodialysis, phosphate, quantification

INTRODUCTION

Cardiovascular disease is the leading cause of mortality in patients with end-stage renal disease (ESRD). Long-term exposure to increased concentrations of calcium and phosphate is an important predictor of mortality in these patients, and is progressively seen as the main focus of therapy.[1-6] This exposure is difficult to quantify because it is variable in time and exerts its deleterious effects only after prolonged presence.

There is an ongoing debate about the predominance of atherosclerotic versus arteriosclerotic abnormalities in ESRD.[7-9] Atherosclerosis is characterised by plaque-forming degenerative intima changes of the aorta and of large elastic arteries resulting in vessel obstruction, whereas in arteriosclerosis there is concentric media

thickening of muscular arteries primarily leading to vascular stiffening. Both processes can be accompanied with calcification, but with a distinct pattern.[7,9] Intima calcification is characterised by patchy calcification of the intima around lipid deposits as present in plaque calcification, considered as classical atherosclerosis, and ascribed to hyperlipidaemia and age-related degeneration.[8,9] Media calcification is characterised by absence of lipid deposits, but by metabolite-induced vascular changes that lead to upregulation of osteogenic differentiation of vascular smooth muscle cells;[8,9] it is primarily attributed to increased calcium-phosphate levels. This process is typical for ESRD, as it can be induced in animal models of chronic kidney disease and already occurs in young adults with ESRD.[1,9,10] Even with advanced imaging techniques, the distinction between intimal and medial calcification is difficult.[4,9] Still, because in ESRD the pathophysiology, prognosis and treatment differ for atherosclerosis and arteriosclerosis, it may be important to distinguish these processes when possible.[7,9,11]

We had a population of patients with ESRD, for whom detailed calcium-phosphate exposure and markers of early atherosclerosis could be measured. Literature data show a convincing association between calcium-phosphate exposure and measures of arteriosclerosis, in casu decreased carotid compliance and increased aortic pulse wave velocity, in ESRD.[12,13] With this study we test the hypothesis that calcium-phosphate exposure is also associated with measures of atherosclerosis. Confirmation of this hypothesis would support the opinion that calcium-phosphate exposure leads to combined arteriosclerotic and atherosclerotic changes, not only to arteriosclerosis. The markers of early atherosclerosis tested were intima-media thickness (IMT) and ankle-brachial pressure index (ABI). We collected all available calcium and phosphate values from patients' complete period of dialysis treatment. To obtain true calcium-phosphate exposure over time, various time-averaged calcium-phosphate parameters were derived and these were related to IMT and ABI.

MATERIALS AND METHODS

Study design and research population

The present study is a prospective cohort study of all haemodialysis and peritoneal dialysis patients who participated in the Second Manifestations of ARTerial disease (SMART) study. SMART is an ongoing prospective study of patients with manifestations of or risk factors for vascular disease.[14] Entry criteria for the present study were: treatment with chronic outpatient peritoneal dialysis or haemodialysis, age between 18 and 80 years and absence of a terminal malignancy. All patients underwent IMT and ABI measurements according to the study protocol. The study was approved by the ethics committee of the University Medical Center Utrecht and written informed consent was obtained from all participants.

Data collection and calcium-phosphate monitoring

Data regarding patient demographics, medical history and laboratory examinations including risk factors for atherosclerosis were collected from self-report questionnaires and chart reviews, at the time of the IMT and ABI measurements.

During the years of dialysis treatment, phosphate binder prescription was aimed at a phosphate <1.7 mmol/l and a calcium <2.60 mmol/l, with the use of various phosphate binders including calcium carbonate and calcium acetate, aluminium hydroxide in early years and sevelamer in recent years.

Calcium-phosphate exposure was assessed by collecting all available calcium and phosphate values, generally measured twice a month, from the start of renal replacement therapy until the IMT/ABI measurements. If a patient had had a functioning renal transplant between the start of renal replacement therapy and the IMT/ABI measurements, values from the transplant period were excluded. All available calcium and phosphate values were averaged for every three months (quarter) of dialysis of a given patient; the calcium-phosphate product (Ca*P) was also averaged per quarter. From these quarterly averages, the following three measures for calcium-phosphate exposure were derived:

A. Averaged values for calcium, phosphate and Ca*P for the complete dialysis period;

B. Percentage of time on dialysis with above-reference levels, i.e. the number of dialysis-quarters a patient had with mean calcium >2.60 mmol/l, phosphate >1.70 mmol/l or Ca*P >4.50 $mmol^2/l^2$, divided by the total number of quarters this patient was treated with dialysis, multiplied by 100%.

C. Cumulative burden of hypercalcaemia and hyperphosphataemia, i.e. the percentage of dialysis time a patient had calcium >2.60 mmol/l, phosphate >1.70 mmol/l or Ca*P >4.50 $mmol^2/l^2$, multiplied by the total duration of dialysis in months of this patient; this burden represents the absolute number of months on dialysis a patient had above-reference levels of calcium and phosphate.

Carotid artery intima-media thickness and ankle-brachial index

Left and right common carotid arteries were examined in the anterolateral, posterolateral, and mediolateral directions with an ATL Ultramark 9 (Advanced Technology Laboratories) equipped with a 10-MHz linear-array transducer, as described previously.[14] The mean IMT of six measurements in each patient was calculated, and categorised in tertiles. Plaques and stenosis of the common

and internal carotid arteries at both sides were measured with colour Doppler-assisted Duplex scanning.

The ABI was obtained by computing the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm. In haemodialysis patients, blood pressure was obtained from the arm without fistula or graft. For the analyses, we used the values of both legs, and categorised these as ≤0.90, >0.90 and ≤1.40, or >1.40. In case of discrepancy in category between the legs, the patient was categorised according to the most abnormal leg. After leg amputation, ABI was categorised as ≤0.90; when arterial compression was not possible due to arterial rigidity, ABI was categorised as >1.40.

Statistical analysis

ANOVA with generalised linear models were used to compare unadjusted and adjusted means of the calcium-phosphate parameters for each category of IMT and ABI. Averaged values for calcium and phosphate were adjusted for age, sex and duration of dialysis treatment. The analyses of the other two measures of calcium-phosphate exposure were only adjusted for age and sex, in order to do justice to the long-standing exposure to calcium and phosphate.

Statistical analyses were performed using SAS (vs. 8.2, SAS institute Inc, Cary, North Carolina, United States) and SPSS software (vs. 15.0; SPSS Inc. Headquarters, Chicago, Illinois, United States).

RESULTS

The SMART study included 90 patients with ESRD; characteristics are listed in *table 1*. Seventy-six patients were on haemodialysis and 14 on peritoneal dialysis at the time of the IMT/ABI studies. Median duration of renal replacement therapy was 39 months (interquartile range (IQR) 16 to 104). Twenty-three patients had had a temporarily functioning kidney transplant for 43 months (IQR 24 to 74).

In *table 2*, the calcium and phosphate exposure during the complete period of dialysis treatment is presented. There were no differences in exposure between patients treated with haemodialysis compared with patients treated with peritoneal dialysis. Averaged calcium concentration was 2.46±0.15 mmol/l, averaged phosphate 1.83±0.38 mmol/l and averaged Ca*P was 4.50±0.90 mmol^2/l^2. In total, 1670 quarters with calcium-phosphate data were collected, covering 93% of the time patients were treated with a form of dialysis.

Carotid intima-media thickness

Mean IMT was 0.86±0.37 mm in 89 patients. In two patients a stenosis of one of the carotid arteries was found of ≥50%. The patients in the highest IMT tertile were older than those in the lowest tertile (59.9±9.9 *vs* 43.3±12.0 years), more often had diabetes mellitus (33 *vs* 11%), had a longer duration of dialysis (median 54 *vs* 30 months), a higher systolic blood pressure (146±26 *vs* 131±16 mmHg) and more often a history of cardiovascular disease. Values

Table 1. *Baseline characteristics*

	ESRD (n=90)
Demographics	
Age at baseline (years)#	51.6±12.8
Men	72%
Diabetes mellitus	22%
Ever smoking	77%
Duration of dialysis (months)*	39 (16, 104)
Renal transplant in past	26%
Localisation of cardiovascular disease	
Cerebrovascular disease in past	2%
Coronary arterial disease in past	13%
Aortic aneurysm in past	2%
Peripheral arterial disease in past	7%
Modifiable risk factors	
Body mass index (kg/m^2)#	23.8±3.7
Waist-hip ratio#	0.90±0.09
Systolic blood pressure (mmHg)#	139±21
Diastolic pressure (mmHg)#	80±11
Pulse pressure (mmHg)#	59±18
Serum measurements	
Total cholesterol (mmol/l)#	4.5±1.1
Fasting triglycerides (mmol/l)#	2.2±1.6
HDL cholesterol (mmol/l)#	1.2±0.4
LDL cholesterol (mmol/l)#	2.3±0.9
C-reactive protein (mg/)#	10.9±14.1
Albumin (g/l)#	39.9±2.8
Parathyroid hormone (pmol/l)#	30.4±31.4

***median (IQR 25%, 75%) # = mean ± SD**

Table 2. *Parameters of calcium-phosphate exposure during the complete period of dialysis treatment*

	ESRD (n=90)
Averaged serum calcium (mmol/l)	2.46±0.15
Averaged serum phosphate (mmol/l)	1.83±0.38
Averaged Ca-P product (mmol^2/l^2)	4.50±0.90
Percentage time on dialysis with calcium ≥2.60 mmol/l (%)†	29±28
Percentage time on dialysis with phosphate ≥1.70 mmol/l (%)†	61±32
Percentage time on dialysis with Ca-P product ≥4.50 mmol^2/l^2 (%)†	52±33
Hypercalcaemia burden# (months)	29±55
Hyperphosphataemia burden# (months)	46±56
Hypercalcaemia/hyperphosphataemia burden# (months)	39±51

†percentage of time on dialysis with above-reference values, i.e. the number of dialysis-quarters (3-month periods) a patient had with mean calcium, phosphate or Ca*P above the given value, divided by the total number of quarters this patient was treated with dialysis, multiplied by 100%

#cumulative burden of hypercalcaemia and hyperphosphataemia, i.e. the percentage of dialysis time a patient had with calcium >2.60 mmol/l, phosphate >1.70 mmol/l or Ca*P >4.50 mmol^2/l^2, multiplied by the total duration of dialysis in months for this patient. All results in above table are presented by mean ± SD.

of cholesterol, C-reactive protein (CRP), albumin and parathyroid hormone (PTH) were comparable between the IMT groups.

Table 3 provides the data concerning calcium and phosphate exposure for patients in the different IMT tertiles. For A: averaged values, B: percentage of time with above-reference values, and C: burden of hypercalcaemia/hyperphosphataemia, no differences were found between the IMT groups in the unadjusted analyses, nor were differences present after adjustment for age, sex and duration of dialysis, where applicable.

Ankle-brachial index

Mean ABI was 1.22±0.21 in 86 patients. Six patients had an ABI of less than 0.90, including one with an amputation. Of the 19 patients in the category ABI >1.40, eight had non-compressible ankle arteries, resulting in an infinitely high ABI. The patients in the lowest ABI category were excluded from further study on calcium-phosphate exposure because the small number of patients precluded valid analyses. The patients from the remaining two groups (ABI 0.90 to 1.40 and ABI >1.40) had comparable age (50.9±13.9 *vs* 50.9±10.2 years respectively), diabetes incidence (20 *vs* 21%), systolic blood pressure (142±16 *vs* 134±26 mmHg) and history of cardiovascular disease. The percentage of men was somewhat lower in the middle ABI group compared with the high ABI group (69 *vs* 84%), as was duration of dialysis (median 21 *vs* 75 months). Values of cholesterol, CRP, albumin and PTH were comparable between the groups.

In *table 4,* the calcium-phosphate exposure for both groups of patients is presented:

A. Although the averaged values of calcium, phosphate and Ca*P were consequently higher in the high ABI group, the differences were not statistically significant, also not after adjustment for age, sex and duration of dialysis treatment.

B. Percentage of time with above-reference values was not different between the two groups, whether or not adjustment was done.

C. Regarding burden of hypercalcaemia/hyperphosphataemia, patients from the high ABI group experienced the highest exposure of hypercalcaemia and hyperphosphataemia, also after adjustment. Exploring this further, we found that this difference persisted even after additional

Table 3. *Calcium and phosphate parameters for different categories of IMT*

	IMT lowest tertile	IMT intermediate tertile	IMT highest tertile	P
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Averaged serum calcium (mmol/l)				
• Unadjusted	2.49 (2.43-2.55)	2.44 (2.39-2.50)	2.47 (2.41-2.52)	0.48
• Adjusted*	2.51 (2.45-2.58)	2.45 (2.40-2.50)	2.45 (2.39-2.50)	0.25
Averaged serum phosphate (mmol/l)				
• Unadjusted	1.85 (1.71-2.00)	1.86 (1.73-2.00)	1.78 (1.64-1.91)	0.63
• Adjusted*	1.83 (1.67-2.00)	1.86 (1.72-2.00)	1.80 (1.64-1.95)	0.83
Averaged Ca-P product ($mmol^2/l^2$)				
• Unadjusted	4.59 (4.24-4.94)	4.52 (4.20-4.84)	4.39 (4.06-4.72)	0.71
• Adjusted*	4.58 (4.19-4.97)	4.52 (4.20-4.85)	4.40 (4.03-4.77)	0.81
Percentage time on dialysis with calcium ≥2.60 mmol/l (%)†				
• Unadjusted	31 (20-42)	27 (17-37)	30 (20-40)	0.85
• Adjusted**	33 (21-45)	27 (17-37)	28 (17-39)	0.76
Percentage time on dialysis with phosphate ≥1.70 mmol/l (%)†				
• Unadjusted	66 (53-78)	61 (49-72)	58 (46-70)	0.67
• Adjusted**	64 (51-78)	61 (49-72)	59 (46-72)	0.86
Percentage time on dialysis with Ca-P product ≥4.50 $mmol^2/l^2$ (%)†				
• Unadjusted	53 (40-65)	51 (40-63)	51 (39-63)	0.98
• Adjusted**	53 (39-68)	51 (40-63)	50 (37-63)	0.95
Hypercalcaemia burden (months)#				
• Unadjusted	30 (9-51)	22 (3-42)	35 (15-55)	0.68
• Adjusted**	31 (7-54)	22 (3-42)	34 (12-56)	0.70
Hyperphosphataemia burden (months)#				
• Unadjusted	39 (18-61)	45 (25-65)	52 (32-72)	0.69
• Adjusted**	33 (10-57)	44 (25-64)	58 (36-80)	0.38
Hypercalcaemia/hyperphosphataemia burden (months)#				
• Unadjusted	34 (15-54)	38 (20-56)	44 (26-63)	0.76
• Adjusted**	31 (10-53)	37 (19-55)	48 (27-68)	0.59

***adjusted for age, sex and duration of dialysis treatment; **adjusted for age and sex; †percentage of time on dialysis with above-reference values, i.e. the number of dialysis quarters (3-month periods) a patient had with mean calcium, phosphate or Ca*P above the given value, divided by the total number of quarters this patient was treated with dialysis, multiplied by 100%; #cumulative burden of hypercalcaemia and hyperphosphataemia, i.e. the percentage of dialysis time a patient had with calcium >2.60 mmol/l, phosphate >1.70 mmol/l or Ca*P >4.50 $mmol^2/l^2$, multiplied by the total duration of dialysis in months of this patient.**

Table 4. *Calcium and phosphate parameters for different categories of ABI*

	ABI >0.90 and ≤1.40 n=61	ABI >1.40 n=19	
	Mean (95% CI)	Mean (95% CI)	P
Averaged serum calcium (mmol/l)			
• Unadjusted	2.46 (2.42-2.50)	2.51 (2.44-2.58)	0.19
• Adjusted*	2.46 (2.42-2.50)	2.51 (2.44-2.58)	0.24
Averaged serum phosphate (mmol/l)			
• Unadjusted	1.83 (1.73-1.92)	1.91 (1.75-2.08)	0.36
• Adjusted*	1.82 (1.72-1.91)	1.94 (1.76-2.11)	0.26
Averaged Ca-P product ($mmol^2/l^2$)			
• Unadjusted	4.48 (4.26-4.70)	4.76 (4.37-5.15)	0.22
• Adjusted*	4.46 (4.24-4.69)	4.81 (4.39-5.23)	0.16
Percentage time on dialysis with calcium ≥2.60 mmol/l (%)*			
• Unadjusted	28 (20-35)	36 (23-49)	0.26
• Adjusted**	27 (20-34)	37 (24-50)	0.18
Percentage time on dialysis with phosphate ≥1.70 mmol/l (%)*			
• Unadjusted	63 (55-71)	62 (48-77)	0.96
• Adjusted**	63 (54-71)	63 (48-78)	0.99
Percentage time on dialysis with Ca-P product ≥4.50 $mmol^2/l^2$ (%)†			
• Unadjusted	52 (44-61)	54 (39-69)	0.82
• Adjusted**	52 (43-60)	55 (40-70)	0.72
Hypercalcaemia burden (months)#			
• Unadjusted	19 (7-31)	50 (28-72)	0.02
• Adjusted**	19 (7-31)	51 (28-73)	0.02
Hyperphosphataemia burden (months)#			
• Unadjusted	30 (19-42)	80 (59-101)	<0.0001
• Adjusted**	31 (19-43)	79 (58-100)	0.0002
Hypercalcaemia/hyperphosphataemia burden (months)#			
• Unadjusted	25 (14-35)	71 (52-90)	<0.0001
• Adjusted**	25 (15-36)	70 (51-89)	0.0001

***adjusted for age, sex and duration of dialysis treatment; **adjusted for age and sex; †percentage of time on dialysis with above-reference values, i.e. the number of dialysis quarters (3-month periods) a patient had with mean calcium, phosphate or Ca*P above the given value, divided by the total number of quarters this patient was treated with dialysis, multiplied by 100%; #cumulative burden of hypercalcaemia and hyperphosphataemia, i.e. the percentage of dialysis time a patient had with calcium >2.60 mmol/l, phosphate >1.70 mmol/l or Ca*P >4.50 $mmol^2/l^2$, multiplied by the total duration of dialysis in months for this patient.**

adjustment for time on dialysis, but only for hyperphosphataemia and combined hypercalcaemia/hyperphosphataemia: adjusted hypercalcaemia burden was 27 months (95% CI 20 to 33) for the middle ABI and 26 months (95% CI 14 to 39) for the high ABI group (p=0.97), adjusted hyperphosphataemia burden was 38 (95% CI 31 to 44) *vs* 56 months (95% CI 44 to 68, p=0.01) and combined hypercalcaemia/hyperphosphataemia burden was 32 (95% CI 26 to 37) *vs* 49 months (95% CI 39 to 60) for the respective groups (p=0.006).

DISCUSSION

After longitudinally collecting all calcium and phosphate values from the patients' complete periods of dialysis, the associations between several parameters of calcium and phosphate exposure and the early markers of atherosclerosis IMT and ABI were examined. We found that calcium-phosphate exposure was not correlated with IMT, irrespective of which parameter of exposure was chosen. Regarding ABI, high calcium-phosphate exposure did not predict a decreased ABI, the established marker of atherosclerosis, but was instead predictive of increased ABI.

Intima-media thickness is a generally applied marker of atherosclerosis. An increased IMT was not mediated by calcium-phosphate exposure, and no trend was present suggesting any relation between calcium-phosphate exposure and IMT. Literature data show conflicting results on this issue. Phosphate, but not calcium, was found to be associated with increased IMT in haemodialysis patients.[15] In studies of IMT and carotid plaque formation, calcium was associated with plaque formation but not with IMT,[16] and plaque formation but not IMT, was associated with cardiovascular events.[17] Furthermore, it seems that in dialysis patients IMT values are difficult to interpret, because the homogeneity of the carotid intima-media is disturbed.[18] However, in all of these studies either once-measured calcium and phosphate,[16,17] or values from three to six months of dialysis[15,18] were used, whereas the present study used the exposure during the complete dialysis period. To cope with the skewed distribution of IMT and the difficulty in distinguishing patients with

high IMT from patients with early plaque formation, we chose to divide the patients in tertiles of IMT. Hence the patients with very high IMT and/or carotid plaques were included in the high IMT group. Nevertheless, when the analyses were done with IMT as continuous variable, or after exclusion of patients with IMT values above 1.20, the results were virtually the same. We conclude that although increased IMT is an established risk factor for mortality in general, it is not influenced by calcium-phosphate exposure in our patients. This part of the data therefore rejects the hypothesis that calcium-phosphate exposure contributes to early atherosclerosis in ESRD. This result is supported by Bui *et al*. who recently found no relation between severity of kidney dysfunction and carotid IMT, also suggesting that classical atherosclerosis plays a minor role in the increased cardiovascular risk in renal disease.[19]

How to interpret the association between calcium-phosphate exposure and not decreased, but increased ABI? ABI, the other marker for atherosclerosis in this study, is also a known risk factor for mortality in patients with ESRD. Remarkably, a decreased as well as an increased ABI were reported to predict increased mortality rates.[20-26] It is presumed that low ABI reflects generalised atherosclerosis, whereas high ABI reflects media calcification and stiffened vessels.[22,24,26] Surprisingly, very few patients appeared to have a decreased ABI in our study despite high calcium-phosphate exposure; this could be the result of inclusion bias, or reflect a low rate of obstructed peripheral arteries by classical atherosclerosis. There was a clear association between calcium-phosphate exposure and increased ABI, in particular for cumulative burden of hypercalcaemia and hyperphosphataemia (*table 4*). Literature data on this issue are scarce. A small study on the relation between left ventricular mass and ABI found a reverse correlation between ABI and once-measured calcium and phosphate.[27] More convincing data from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort showed a strong association between quartiles of phosphate concentrations and high ABI, but again phosphate was measured only once at the time of the ABI study.[28] Our study confirms and extends the latter study in finding the same results while using complete calcium-phosphate exposure. It was specifically the total burden of hyperphosphataemia and combined hyperphosphataemia/hypercalcaemia, i.e. the absolute time period a patient had the above-reference levels, which predicted a high ABI. This is the first study finding a relation between high ABI and time-averaged measures of calcium-phosphate exposure. It fits in with the hypothesis that the calcification process only takes place in periods when calcium and phosphate exceed their solubility product, possibly in combination with shortage of calcification inhibitor proteins.[29] It also underscores the findings of the group of London *et al*. of increased arterial stiffening after longstanding dialysis,[11,13] and again hypothesises that atherosclerosis probably plays a minor role. To prove that not the duration of dialysis per se could explain the results, the additional adjustment for time on dialysis was done, after which not hypercalcaemia burden, but still the burden of high phosphate and high calcium-phosphate product remained significant.

In this study, a new method to quantify exposure to high calcium and phosphate levels is presented. Most studies so far report on calcium and phosphate measured at one moment in time, or sometimes use averaged values for three to six months of dialysis.[28,30-33] However, in many patients treated with dialysis, there are prolonged periods with either low or high exposure. As hypercalcaemia and hyperphosphataemia are such important risk factors for morbidity and mortality in ESRD, and are frequently monitored in clinical practice, it is rather unsatisfying to use so little of the available calcium and phosphate information for risk stratification. Furthermore, hypercalcaemia and hyperphosphataemia exert their unfavourable influence only after prolonged periods of time. A method to determine the presence of these risk factors in an objective and reproducible way is therefore essential.

Calculation of quarterly averages of serum calcium and phosphate enabled inclusion of all measurements, and periods with frequent measurements could be equally weighed as periods with scarce measurements. Calcium-phosphate data from >90% of dialysis time of the patients were collected, covering more than 400 patient-years. These quarterly averages enabled subsequent calculation of the three measures of calcium-phosphate exposure, representing (A) overall exposure, (B) the percentage of time on dialysis in which calcium and phosphate were not well controlled, and (C) the absolute length of time with above-reference values. By using these measures, short periods of time with high exposure in a patient can be identified, even if average levels are not increased.

The choice of the reference values is arbitrary. Most of the data used for this study result from a period before the strict Kidney Disease Outcomes Quality Initiative (KDOQI) Guideline for Bone Metabolism and Disease was applied. Calcium was targeted below 2.60 mmol/l in this period, and phosphate below 1.70 mmol/l, which is why these values were chosen as cut-off levels. The phosphate concentration averaged over the complete duration of dialysis was of the same order as other cross-sectional[3] or time-averaged data.[33,34] However, averaged calcium was slightly higher, reflecting the liberal use of calcium containing phosphate binders in this period, and possibly due to development of a dynamic bone disease. Still, this tool can be refined by using variable cut-off levels.

The present study design has some limitations. Retrospective collection of calcium and phosphate data

during the complete period of dialysis is prone to survival bias: only patients alive at the time of IMT/ABI studies were included in the analyses. This is inherent to the present design, but it does not alter the finding of high calcium-phosphate exposure in patients with increased ABI. Secondly, stronger results could possibly have been found if calcium concentrations had been corrected for serum albumin levels. Theoretically, calcium load could have been higher than described, because patients on dialysis can have a low albumin due to their chronic inflammatory state. However, in this patient group albumin concentration was fairly normal, so we assume that correcting for albumin would not have significantly influenced the final results. For future studies, using calcium concentrations corrected for albumin would be wise. Thirdly, we did not collect the traditional risk factors for atherosclerosis in these patients longitudinally. However, because of the reverse associations between e.g. weight, hyperlipidaemia and blood pressure and mortality known in ESRD patients and lack of positive intervention studies, one can at least question the role of traditional risk factors in the atherosclerotic process in ESRD. Finally, of course, data on hyperparathyroidism would have been interesting. During such long dialysis periods many variables such as treatment with vitamin D analogues and parathyroid surgery play a role which are difficult to score objectively.

All in all, we showed that long-term calcium-phosphate exposure in patients with ESRD, assessed by a standardised method, is not associated with IMT and not with decreased ABI, both early markers of atherosclerosis. We thus found no arguments to state that the vascular changes in ESRD are caused by atherosclerosis on top of arteriosclerosis. This possibly explains why intervention studies with statins fail to show any benefit in this population.[35,36] That calcium-phosphate exposure, measured during long-term dialysis, predicts increased ABI or incompressible ankle arteries gives further support to the opinion that it is mainly arteriosclerosis with media calcification and increased vascular stiffness that is responsible for the increased risk of vascular disease. Using our standardised tool to calculate true calcium-phosphate exposure will help to specify individual risks for patients in predialysis and dialysis periods.

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