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Calcium, phosphorus, PTH and death rates in a large sample of dialysis patients from Latin America. The CORES Study

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Abstract

Background. Mineral metabolism parameters may play a role in the survival of patients with chronic kidney disease (CKD).

Methods. In the CORES Study, we analysed the association between calcium, phosphorus and PTH and mortality (all-cause and cardiovascular) in 16 173 haemodialysis (HD) patients over 18 years from six Latin American countries, who underwent haemodialysis up to 54 months. Unadjusted, case-mix-adjusted and time-dependent multivariable-adjusted hazard ratio (HR) of death were calculated for categories of serum albumin-corrected calcium (Ca_{Alb}), phosphorus and PTH using as 'reference values' the range in which the lowest death rate was observed. Age, gender, vitamin D treatment, diabetes, vintage, vascular access, weight, blood pressure and laboratory variables (serum albumin, haemoglobin, creatinine, ferritin and Kt/V) were used as confounding variables.

Results. Low (<9.5 mg/dL) and high (>10.5 mg/dL) Ca_{Alb} increased the HR for all-cause mortality. Low (<9.0 mg/dL) Ca_{Alb} increased the HR for cardiovascular mortality. High phosphorus (>5.5 mg/dL) increased the HR for both all-cause and cardiovascular mortality. Low phosphorus (<4.0 and <3.0 mg/dL) increased the HR for both all-cause and cardiovascular mortality. Furthermore, low (<150 pg/mL) and high (>500 and >300 pg/mL) PTH increased the HR for both all-cause and cardiovascular mortality. In addition, only phosphorus >6.0 mg/dL increased the HR for cardiovascular hospitalizations. No effect was observed with Ca_{Alb} or PTH.

Conclusions. In summary, in 16 173 HD patients, elevated and reduced serum levels of albumin-corrected calcium, phosphorus and PTH levels were associated with increments in all-cause mortality. Similar results were obtained when only cardiovascular mortality was analysed.

Keywords: CORES Study; haemodialysis; mineral metabolism; mortality risk

Introduction

Patients on haemodialysis (HD) have chronic kidney disease–mineral and bone disorder (CKD–MBD) [1,2]. Several studies have shown an association between high calcium, phosphorus and PTH and all-cause mortality [3–7]. However, these studies have examined associations between baseline serum mineral values and subsequent survival without taking into account any changes in the concentrations of these measures and other covariates over time. In fact, recent studies using time-dependent models, not restricted to fixed baseline data but including changes over time, seem to show more realistic clinical scenarios [8,9].

In addition, most studies, except the DOPPS carried out in Europe and Asia [9,10], have been carried out in HD patients from North America. So far, there is not a single large population-based study carried out in Latin America. Thus, in the CORES Study, a large observational study from Latin America, a likely different clinical management of bone metabolism markers may contribute to different outcomes.

On the other hand, although the K/DOQI guidelines have assumed ranges of serum mineral parameters as 'normality' [11], the recently published K/DIGO guidelines [12] take a different approach, opening a new scenario.

This study analysed, using time-dependent Cox models, the risk for all-cause mortality and the risk for cardiovascular mortality according to serum calcium, phosphorus and PTH levels in a large cohort of 16 173 haemodialysis patients from six Latin American countries who were followed up from January 2000 to June 2004.

Materials and methods

A historical cohort of chronic haemodialysis patients from six Latin American countries (Argentina, Brazil, Colombia, Chile, Mexico and Venezuela) who underwent haemodialysis three times a week (98.8%) and twice a week (1.2%) in 183 different dialysis facilities associated or operated by

Fresenius Medical Care comprises the CORES Study. The entire CORES population (n = 22 230) consisted of patients older than 18 years who either initiated haemodialysis (incident patients, 72.4% of the cohort) or were already in haemodialysis (prevalent patients, 27.6% of the cohort) after 1 January 2000. Patients were followed up for a maximum period of time of 54 months (median 16 months) until 30 June 2004 or until they were lost to follow-up.

In addition, 6057 (27.2%) patients who remained <90 days on chronic haemodialysis were excluded from the analysis due to the greater instability in the bone and mineral markers in addition to a higher mortality rate, factors that may bias the results. The different reasons for the exclusions were: beginning of haemodialysis after April 2004 (41.8%), death (29.3%), switch to peritoneal dialysis (11.5%), recovery of renal function (7.1%), voluntary withdrawal from therapy (4.7%), unknown circumstances (3.3%) and renal transplantation (2.3%). Therefore, the sample of the study consisted of 16 173 renal patients (over 18 years) undergoing chronic haemodialysis.

During the study period and once the patient was admitted to the haemodialysis centre, demographic, clinical, laboratory and other general data were collected prospectively and entered into a central database updated by medical personnel and stored by Fresenius Medical Care (FME Register®). From this database, the following data were analysed: age, gender, weight, country, date of first dialysis, systolic and diastolic pressure, vascular access, primary cause of renal failure, dose of dialysis, medications administered in each haemodialysis session (name, date, dose and route of administration), and laboratory tests. Two active vitamin D analogues were used; calcitriol was used in the 99.6% of the patients, and only 0.4% of the patients used alphacalcidol. The main route of administration of active vitamin D was the oral route (97.7% of patients).

Dialysis vintage was defined as the duration of time between the first day of maintenance dialysis treatment and the last day that the patient was in the study. All missed haemodialysis treatments (e.g. because of hospitalization or non-compliance) and all permanent discharges (e.g. transplantation, voluntary withdrawal from therapy, transfer to a non-Fresenius dialysis unit, change to peritoneal dialysis or loss to follow-up) were also gathered. All patient hospitalizations were recorded in the database as a type of permanent discharge by each different centre, including the date and cause of hospitalization. The different causes of hospitalization and death were classified according to the International Classification of Diseases (ICD-10). Co-morbidities were grouped into vascular, neoplastic, infectious, respiratory, neurological or diabetes according to Table 1. Death causes were grouped as vascular, infectious, neoplastic, neurological, respiratory or unknown. All dialysis facilities underwent a centralized and uniform administrative control. Thus, all the collected data were checked to ensure their accuracy and completeness. The study met the privacy standards implemented by Fresenius with a waiver for informed consent.

For each patient, values of the different parameters studied (calcium, phosphorus and PTH measured by the Nichols Advantage chemiluminescence assay) were updated every month (time-dependent). Serum calcium was corrected for serum albumin using a formula already validated for haemodialysis patients: corrected calcium=measured calcium+[0.0176 × (34 − serum albumin in gram per decilitre)] [13]. Serum albumin-corrected calcium, phosphorus and PTH were stratified into categories from <8.5 to >11.0 mg/dL, <3.0 to >7.5 mg/dL and <50 to >800 pg/mL, respectively. The analysis examined only patients who survived for at least 90 days after initiating chronic haemodialysis.

The analyses of hospitalization as outcome included only the cardiovascular hospitalization, which previous studies suggested is a good surrogate marker of mortality in HD patients.

Table 1. International Classification of Diseases and Related Health Problems (10th revision)

Vascular
Diseases of the circulatory system
- I05-I09 Chronic rheumatic fever
- I10-I15 Hypertensive diseases
- I20-I25 Ischaemic heart diseases
- I26-I28 Pulmonary heart disease and disease of pulmonary circulation
- I30-I52 Other forms of heart disease
- I60-I69 Cerebrovascular diseases
- I70-I79 Diseases of arteries, arterioles and capillaries

Infectious
Certain infectious and parasitic diseases
- A00-A09 Intestinal infectious diseases
- A15-A19 Tuberculosis
- A30-A49 Other bacterial diseases
- A50-A64 Infectious with a predominantly sexual mode of transmission
- A65-A69 Other spirochaetal diseases
- A70-A74 Other diseases caused by chlamydiae
- A75-A79 Rickettsioses
- A80-A89 Viral infections of the central nervous system
- A90-A99 Arthropod-borne viral fevers and viral haemorrhagic lesions
- B00-B09 Viral infectious characterized by skin and mucous membrane lesions
- B15-B19 Viral hepatitis
- B20-B24 Human immunodeficiency virus (HIV) disease
- B25-B34 Other viral diseases
- B35-B49 Mycoses
- B50-B64 Protozoal diseases
- B65-B83 Helminthiases
- B90-B94 Sequelae of infectious and parasitic diseases

Diseases of the respiratory system
- J00-J06 Acute upper respiratory infections
- J09-J18 Influenza and pneumonia
- J20-J22 Other acute lower respiratory infectious

Diseases of the skin and subcutaneous tissue
- L00-L08 Infectious of the skin and subcutaneous tissue

Diseases of the musculoskeletal system and connective tissue
- M00-M03 Infectious arthropathies

Diseases of the genitourinary system
- N70-N77 Inflammatory diseases of female pelvic organs

Neoplastic
Neoplams
- C00-C75 Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue
- C76-C80 Malignant neoplasms of ill-defined, secondary and unspecified sites
- C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue
- D00-D09 *In situ* neoplasms
- D10-D36 Benign neoplasms
- D37-D48 Neoplasms of uncertain or unknown behaviour

Neurological
Diseases of the nervous system
- G00-G09; G20-G26; G30-G32; G35-G37; G40-G47; G60-G64; G80-G83; G90-G99

Respiratory
Diseases of the respiratory system
- J30-J39; J40-J47; J60-J70; J80-J84; J90-J94; J95-J99

Diabetes
Endocrine, nutritional and metabolic diseases
- E10-E14 Diabetes mellitus

Statistical analyses

Standard univariate analyses (chi-square and ANOVA tests) for the different categories of the three variables analysed (serum albumin-corrected calcium, phosphorus and PTH) were performed. Values were reported as mean or median for continuous variables and as proportions for categorical variables.

Cox proportional hazards regression was used to estimate all-cause and cardiovascular mortality hazard ratio according to the serum albumin-corrected calcium, phosphorus and PTH. Similar to that described by Tentori *et al.* [9] and opposed to previous studies published in this field [10,14,15], in our study, for the three variables analysed (albumin-corrected calcium, phosphorus and PTH), we selected as reference value the serum range of calcium, phosphorus and PTH in which the mortality rate was lower. Patients contributed person-time until they died, underwent kidney transplantation, voluntarily withdrew from chronic haemodialysis

Table 2. Patient characteristics by serum albumin-corrected calcium category

mg/dL (*n*)	<8.5 (451)	8.5–9.0 (1529)	9.0–9.5 (3433)	9.5–10.5 (6605)	10.5–11.0 (1296)	>11.0 (811)	P-value
Age (years)	55.7	56.1	55.7	54.4	54.1	53.6	<0.001
Gender (% female)	39.2	39.9	42.1	40.6	45.2	44.3	0.010
Diabetes (%)	33.7	35.4	28.6	24.3	18.8	19.2	<0.001
Vintage (years) (median)	1.00	1.48	1.90	2.28	2.55	1.95	<0.001
AV fistula (%)	43.0	46.6	50.9	50.8	50.3	45.3	<0.001
Mortality rate (%)	30.4	25.0	19.5	16.5	19.2	22.9	<0.001
Weight (kg)	64.3	64.6	63.9	64.4	63.9	62.4	0.004
Vitamin D treatment (%)	38.8	46.6	50.8	52.2	51.4	43.9	<0.001
Phosphorus (mg/dL)	4.96	5.04	5.01	5.00	5.07	5.20	<0.001
PTH (pg/mL)	368	330	294	276	264	293	<0.001
Albumin (g/dL)	3.48	3.61	3.73	3.82	3.90	3.80	<0.001
Kt/V	1.27	1.31	1.36	1.35	1.39	1.33	<0.001
Creatinine (mg/dL)	7.76	7.68	7.96	8.38	8.74	8.55	<0.001
Haemoglobin (g/dL)	9.09	9.46	9.78	10.01	10.09	9.92	<0.001
Cholesterol (mg/dL)	173	174	180	183	187	185	<0.001
Ferritin (μg/L) (median)	333	363	372	394	456	429	<0.001
Systolic pressure	138.4	139.3	139.0	139.4	138.1	138.9	0.352
Diastolic pressure	77.77	78.45	78.44	78.94	78.80	78.95	0.082
Phosphate binders (%)	64.8	83.6	81.5	76.9	65.8	53.2	<0.001

P-value represents the chi-square in case of a categorical variable or one-way ANOVA among groups in case of a continuous variable.

or reached the end of the follow-up period, whichever occurred first. Cox proportional hazards models were used to calculate hazard ratios for mortality associated with serum albumin-corrected calcium, phosphorus and PTH in models in which laboratory measures were updated every month (time-dependent), or every 6 months (time-dependent) in the case of serum PTH. For each analysis, three types of models were examined based on the level of multivariate adjustment: (i) unadjusted models including serum albumin-corrected calcium, phosphorus and PTH as the predicting variable, and mortality as the outcome variable; (ii) case-mix-adjusted models including additional fixed baseline covariates: age, gender, country, diabetes mellitus, vintage and vascular access; and (iii) case-mix and the following clinical and laboratory time-varying variables (monthly changing) with known associations with survival in haemodialysis patients, such as weight, albumin, ferritin, haemoglobin, creatinine, systolic and diastolic blood pressure, active vitamin D treatment, and Kt/V (delivered dose of dialysis). Kt/V was calculated using the following formula: delivered Kt/V = $-\ln(R - 0.008 \times t) + (4 - 3.5\,R) \times \mathrm{UF}/\mathrm{W}$, where R=post-dialysis/pre-dialysis blood urea nitrogen, t=dialysis hours, UF=pre-dialysis–post-dialysis weight change and W=post-dialysis weight. Serum albumin-corrected calcium, phosphorus and PTH were also included as additional time-varying variables.

Since it was impossible to obtain a standardized mortality rate in all countries, in order to reduce the country effect on the mortality rate, all the analyses were carried out after adjusting by country. Similarly, a Cox proportional hazards regression to estimate cardiovascular hospitalization hazard ratio according to the serum albumin-corrected calcium, phosphorus and PTH was carried out. The Cox model included a time-dependent multivariable adjustment which included the same covariates used in the survival analyses.

Results

Tables 2–4 summarize the potential association between the different demographic, laboratory, clinical and treatment variables used in the multivariable adjustment, and

Table 3. Patient characteristics by serum phosphorus category

mg/dL (*n*)	<3.0 (496)	3.0–4.0 (2466)	4.0–5.0 (4925)	5.0–5.5 (2287)	5.5–6.5 (2907)	6.5–7.5 (1167)	>7.5 (490)	P-value
Age (years)	61.0	58.6	56.9	53.9	51.8	48.6	45.8	<0.001
Gender (% female)	44.4	41.4	42.6	44.6	40.4	37.6	29.0	<0.001
Diabetes (%)	25.6	26.4	28.3	25.4	24.0	21.6	16.7	<0.001
Vintage (years) (median)	1.64	1.77	1.88	2.04	2.16	2.32	2.49	<0.001
AV fistula (%)	36.7	45.0	49.8	50.7	52.2	51.9	46.1	<0.001
Mortality rate (%)	27.8	22.2	20.0	16.3	17.0	17.1	16.9	<0.001
Weight (kg)	58.0	60.0	63.3	64.7	66.8	68.1	70.9	<0.001
Vitamin D treatment (%)	39.1	48.2	49.5	51.7	52.5	44.7	30.8	<0.001
albumin-corrected calcium (mg/dL)	9.72	9.74	9.74	9.76	9.76	9.81	9.85	0.032
PTH (pg/mL)	162	193	239	300	364	468	531	<0.001
Albumin (g/dL)	3.57	3.69	3.76	3.80	3.82	3.85	3.89	<0.001
Kt/V	1.38	1.35	1.34	1.36	1.35	1.32	1.27	<0.001
Creatinine (mg/dL)	6.84	7.13	7.77	8.44	9.05	9.95	10.76	<0.001
Haemoglobin (g/dL)	9.34	9.72	9.88	9.90	9.84	9.97	9.67	<0.001
Cholesterol (mg/dL)	168	177	180	186	186	178	175	<0.001
Ferritin (μg/L) (median)	430	408	379	383	403	384	386	<0.001
Systolic pressure	138.6	137.9	138.2	138.7	140.2	140.8	144.2	<0.001
Diastolic pressure	78.07	78.38	78.19	78.28	79.57	80.49	82.48	<0.001
Phosphate binders (%)	49.2	66.6	75.0	79.6	79.8	72.0	50.2	<0.001

P-value represents the chi-square in case of a categorical variable or one-way ANOVA between groups in case of a continuous variable.

Table 4. Patient characteristics by serum PTH category

mg/dL (*n*)	<50 (1663)	50–150 (3446)	150–300 (3125)	300–500 (1862)	500–800 (1003)	>800 (822)	P-value
Age (years)	55.7	56.0	55.9	54.5	51.5	49.6	<0.001
Gender (% female)	40.4	38.5	41.0	42.0	45.5	50.7	<0.001
Diabetes (%)	28.3	27.6	27.8	23.4	17.5	11.2	<0.001
Vintage (years) (median)	1.73	2.01	2.16	2.31	2.73	3.68	<0.001
AV fistula (%)	42.8	51.7	55.6	56.0	56.3	57.3	<0.001
Mortality rate (%)	22.5	19.2	15.2	17.8	16.2	17.4	<0.001
Weight (kg)	60.7	63.3	65.3	67.0	66.2	65.8	<0.001
Vitamin D treatment (%)	38.6	38.1	59.8	72.2	71.3	71.0	<0.001
albumin-corrected calcium (mg/dL)	10.06	9.80	9.67	9.64	9.67	9.79	<0.001
phosphorus (mg/dL)	4.67	4.80	4.97	5.23	5.53	5.86	<0.001
Albumin (g/dL)	3.75	3.76	3.78	3.82	3.82	3.87	<0.001
Kt/V	1.37	1.35	1.36	1.35	1.36	1.37	0.519
Creatinine (mg/dL)	7.68	7.97	8.25	8.72	8.98	9.26	<0.001
Haemoglobin (g/dL)	9.90	9.97	10.05	9.98	9.99	9.90	0.009
Cholesterol (mg/dL)	186	182	182	180	180	176	<0.001
Ferritin (μg/L) (median)	423	398	384	382	387	417	<0.001
Systolic pressure	140.7	139.1	138.2	137.0	136.9	137.8	0.023
Diastolic pressure	78.88	78.57	78.23	77.86	77.93	78.69	0.002
Phosphate binders (%)	39.4	77.2	80.2	83.6	80.4	82.0	<0.001

P-value represents the chi-square in case of a categorical variable or one-way ANOVA among groups in case of a continuous variable.

the category values of each parameter (serum albumin-corrected calcium, phosphorus and PTH) analysed at the time of recruitment for 16 173 HD patients from 183 facilities. Mean follow-up was 1.65 ± 1.14 years (median, 1.35 years).

Age was inversely correlated with serum albumin-corrected calcium ($r=-0.063$), serum phosphorus ($r=-0.223$) and serum PTH ($r=-0.114$). Diabetes also inversely correlated with the three variables: $r=-0.121$, $r=-0.046$ and $r=-0.107$, for serum albumin-corrected calcium, phosphorus and PTH, respectively. Conversely, serum creatinine and vintage directly correlated with serum albumin-corrected calcium ($r=0.128$ and $r=0.131$), P ($r=0.377$ and $r=0.081$) and PTH ($r=0.160$ and $r=0.207$).

The proportion of patients taking active vitamin D were 45.5%. Meanwhile, fistula was the vascular access most used (46% of patients), and catheter was used in 21.4% of patients. Unfortunately, data of vascular access were not available in 27% of patients. A total of 3151 (19.5%) patients died during the follow-up period (January 2000–June 2004). From the total amount of deaths, 1211 (38.4%) were attributable to a cardiovascular cause.

Serum albumin-corrected calcium

Figure 1 shows the unadjusted, case-mix-adjusted and time-dependent multivariable-adjusted hazard risk (HR) of all-cause and cardiovascular mortality, and 95% confidence intervals (CI) associated with serum albumin-corrected calcium, considering 9.5–10.0 and 10.0–10.5 mg/dL as the reference range because it showed the lowest mortality. The time-dependent multivariable-adjusted all-cause mortality results (Figure 1) showed a bimodal relationship (U-shaped curve), with a significant increase in the HR associated with serum calcium concentrations >10.5 mg/dL [10.5–11.0 mg/dL: HR (95% CI): 1.25 (1.02–1.53) and >11 mg/dL: HR (95% CI): 1.78 (1.40–2.26)] and <9.5 mg/dL [9.0–9.5 mg/dL: HR (95% CI): 1.25 (1.09–1.44); 8.5–9.00: HR (95% CI): 1.61 (1.34–1.92) and <8.5 mg/dL: HR (95% CI): 3.92 (2.95–5.21)]. In contrast, only serum calcium concentrations <9.0 were associated with cardiovascular mortality [<8.5 mg/dL: HR (95% CI): 3.30 (2.02–5.38) and 8.5–9.0 mg/dL: HR (95% CI): 1.59 (1.21–2.09)] (Figure 1).

According to the results observed in Table 2 (the lowest categories for serum albumin-corrected calcium were associated with the lowest frequencies of vitamin D use) and in order to exclude any interaction between serum albumin-corrected calcium and vitamin D, an additional analysis stratifying the cohort between vitamin D users and non-users was performed. Both vitamin D users and non-users showed similar results for all-cause mortality [<8.5 mg/dL: HR (95% CI): 3.88 (3.06–4.90) and HR (95% CI): 3.95 (2.86–5.47) vs >11 mg/dL: HR (95% CI): 2.20 (1.77–2.74) and HR (95% CI): 2.11 (1.61–2.77), respectively].

Serum phosphorus

Figure 2 shows the unadjusted, case-mix-adjusted and time-dependent multivariable adjusted HR of all-cause and cardiovascular mortality, and 95% CI associated with serum phosphorus, considering the serum phosphorus concentrations of 5.0–5.5 mg/dL, where the mortality was lowest, as the reference range. The time-dependent multivariable-adjusted all-cause mortality results showed a significant increase in HR associated with serum phosphorus concentrations <4.0 mg/dL. Significant increases in HR for all-cause and cardiovascular mortalities were observed with serum phosphorus concentrations >5.5 mg/dL, particularly when the serum phosphorus concentration was >7.5 mg/dL [HR (95% CI): 2.24 (1.50–3.34) and HR (95% CI): 2.51 (1.34–4.72) for all-cause and cardiovascular mortalities, respectively].

Serum PTH

Figure 3 shows the unadjusted, case-mix-adjusted and time-dependent multivariable-adjusted HR of all-cause

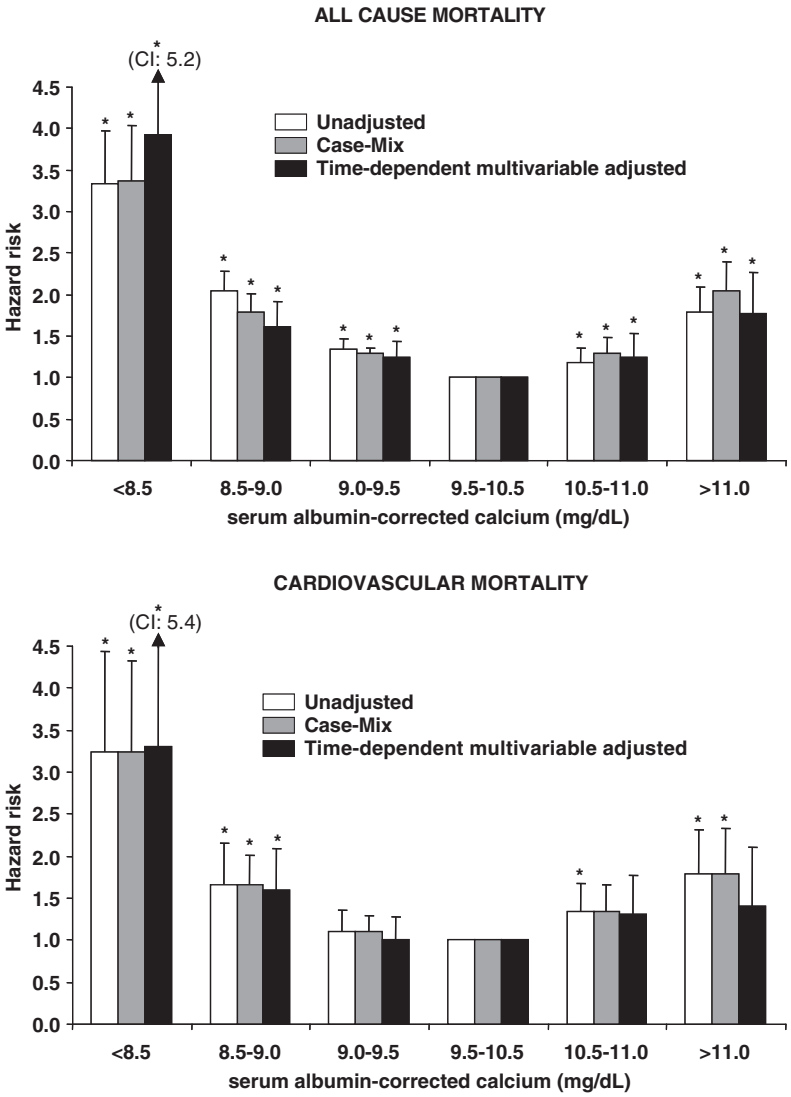

Fig. 1. Association between the time-varying serum albumin-corrected calcium values (reference range 9.50–10.50 mg/dL) in 16 173 haemodialysis (HD) patients followed up from January 2000 to June 2004 using unadjusted, case-mix-adjusted and time-dependent Cox models with time-varying repeated measures. *P<0.05 compared with the reference group.

and cardiovascular mortality, and 95% CI associated with categories of serum PTH, considering serum PTH concentrations 150–300 pg/mL as the reference range. Both all-cause and cardiovascular mortality showed a significant increase in the HR associated with serum PTH concentrations <150 pg/mL [<50 pg/mL: HR (95% CI): 2.42 (1.93–3.03) and HR (95% CI): 3.06 (2.13–4.39), respectively; and 50–150 pg/mL: HR (95% CI): 1.27 (1.06–1.53) and HR (95% CI): 1.52 (1.12–2.06), respectively] and >500 pg/mL [500–800 pg/mL: HR (95% CI): 1.33 (1.07–1.66) and HR (95% CI): 1.61 (1.11–2.33), respectively; and >800 pg/mL: HR (95% CI): 1.57 (1.23–1.99) and HR (95% CI): 2.02 (1.37–2.98), respectively]. In addition, cardiovascular mortality was also significantly associated with serum PTH concentrations between 300 and 500 pg/mL [HR (95% CI): 1.42 (1.06–1.91)].

Similar results for all parameters analysed (serum albumin-corrected calcium, phosphorus and PTH) were obtained when incident patients (72.4% of the patients) and prevalent patients were analysed. The results were as follows: for incident patients, <8.5 mg/dL: HR (95% CI): 4.14 (2.97–5.77) and >11 mg/dL: HR (95% CI): 1.84 (1.37–2.52) for serum albumin-corrected calcium; <3.0 mg/dL: HR (95% CI): 1.75 (1.17–2.59) and >7.5 mg/dL: HR (95% CI): 2.17 (1.31–3.60) for serum phosphorus; and <50 pg/mL: HR (95% CI): 2.24 (1.72–2.92) and >800 pg/mL: HR (95% CI): 1.67 (1.20–2.33) for serum PTH; and for prevalent patients, <8.5 mg/dL: HR (95% CI): 3.72 (2.14–6.48) and >11 mg/dL: HR (95% CI): 1.61 (1.09–2.36) for serum albumin-corrected calcium; <3.0 mg/dL: HR (95% CI): 2.01 (1.11–3.62) and >7.5 mg/dL: HR (95% CI): 2.62 (1.36–5.05) for serum phosphorus; and <50 pg/mL: HR (95% CI): 2.93 (1.89–4.53) and >800 pg/mL: HR (95% CI): 1.44 (1.00–2.09) for serum PTH. In addition, the stratification by phosphate binders showed identical results for all parameters of mineral metabolism (data not shown).

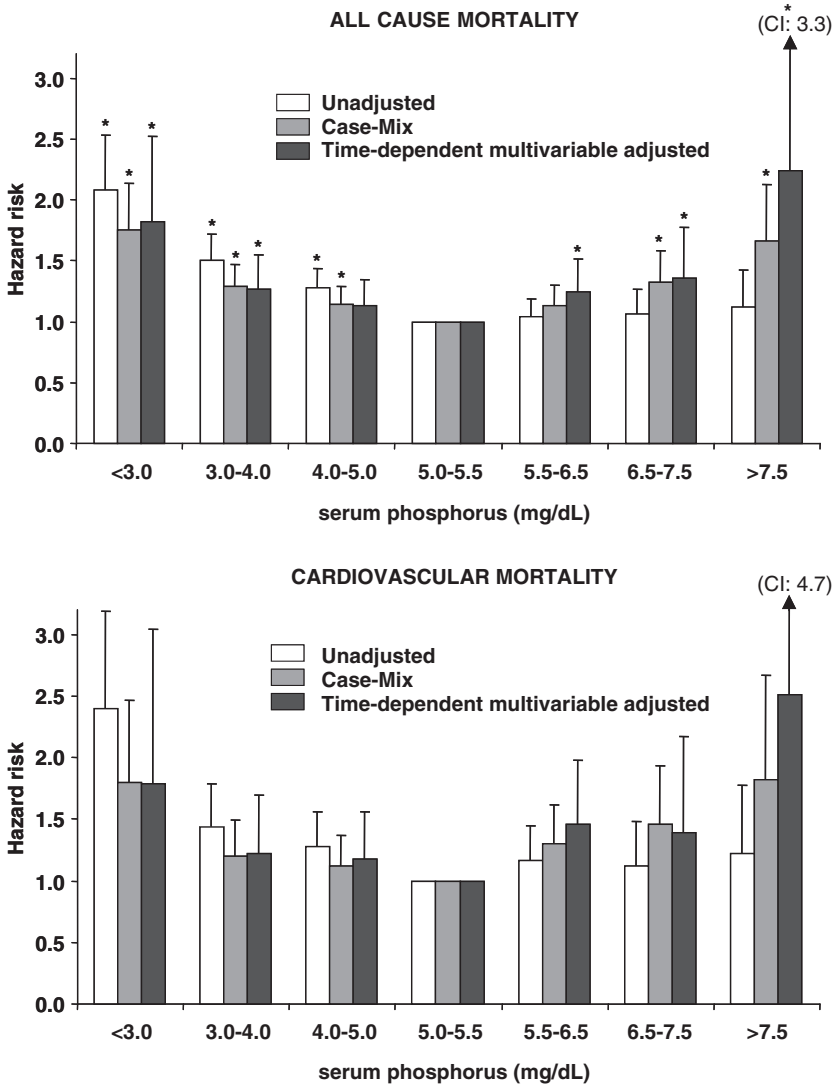

Fig. 2. Association between the time-varying serum phosphorus values (reference range 9.50–10.50 mg/dL) in 16 173 haemodialysis (HD) patients followed up from January 2000 to June 2004 using unadjusted, case-mix-adjusted and time-dependent Cox models with time-varying repeated measures. *P<0.05 compared with the reference group.

Cardiovascular hospitalization

There were 1787 cardiovascular hospitalizations recorded. Significant increases in the HR for cardiovascular hospitalizations were observed with serum phosphorus concentrations >6.0 mg/dL [6.0–7.0 mg/dL: HR (95% CI): 2.51 (1.06–5.94) and >7.0 mg/dL: HR (95% CI): 3.96 (1.17–13.38), respectively]. No associations were found with low phosphorus. There was no association between serum calcium and PTH and the risk of cardiovascular hospitalization.

Discussion

This retrospective observational study performed on 16 173 HD patients from Latin America from January 2000 to June 2004 sought to examine the relationship between different parameters of mineral metabolism and the risk of all-cause and cardiovascular mortality. In the last years, several studies have shown an increase in the risk of death of CKD patients on HD likely favoured by serum calcium, phosphorus and PTH disturbances [3–6,8,10]. However, less attention has been paid to cardiovascular mortality. Moreover, previously published studies have been performed on North American, Japanese and European populations, and there were no data available from the Latin American CKD population [10,14,16–18].

As we explained in the Materials and methods section, one of the main strengths of our approach was not to analyse the data based on the K/DOQI ranges, which is the comparison with the assumed 'normality' [19]. We were interested in knowing within which ranges of this cohort, with all their intrinsic characteristics, we observe the lowest death rates; then we assumed that range was the safest, and we used it as the 'reference range'. This different approach has been described previously by others [9], and

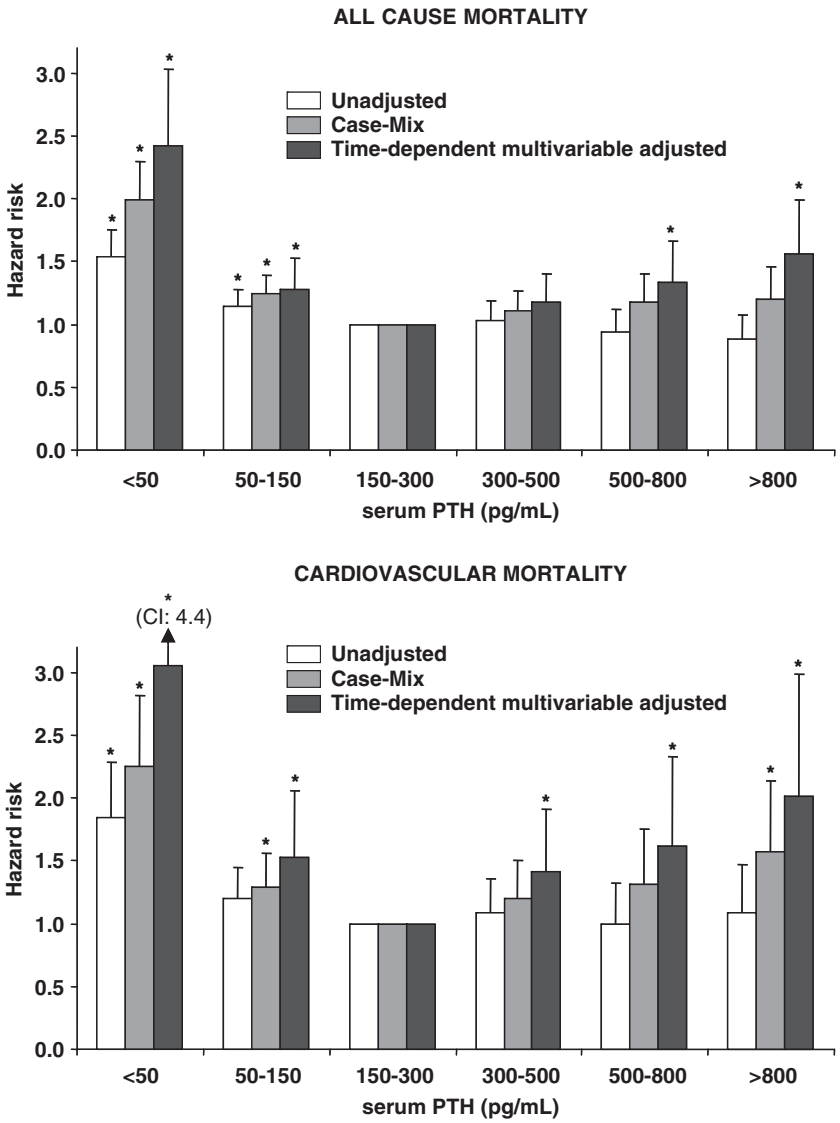

Fig. 3. Association between the time-varying serum PTH values (reference range 9.50–10.50 mg/dL) in 16 173 haemodialysis (HD) patients followed up from January 2000 to June 2004 using unadjusted, case-mix-adjusted and time-dependent Cox models with time-varying repeated measures. *P< 0.05 compared with the reference group.

our results confirmed previous data in different cohorts [3,8]. For serum calcium and phosphorus, we found that our reference range (lowest range of mortality) was different to the serum calcium and phosphorus K/DOQI target ranges. In contrast, in the serum PTH, the lowest range of mortality coincides with the serum PTH K/DOQI target range.

Another advantage of the CORES Study is that it also investigates the cardiovascular mortality in a multiracial cohort of dialysis patients never studied before, an important aspect not addressed by many previous studies [9,14].

Serum albumin-corrected calcium

Serum albumin-corrected calcium >10.5 mg/dL significantly increased the HR of mortality after adjusting for several confounding variables (time-dependent multivariable adjustment) [13]. Additionally, serum albumin-corrected calcium <9.0 mg/dL also increased the HR of mortality in the time-dependent multivariable-adjusted analyses. When we compared these figures with previous studies, it seemed clear that, in our study, the reference range of serum albumin-corrected calcium, which is the lowest range of mortality, is higher than most previously recommended values. Some characteristics of the Latin America cohort, with HD practice patterns similar to those used in Europe and USA before, might explain the reasons for finding higher serum calcium levels in this cohort. In fact, the mean dialysate calcium concentration used in this cohort was very high (3.07±0.51 mEq/L); 69% of the patients were dialysed with >3 mEq/L of calcium, and a high percentage of patients (74%) received calcium acetate or calcium carbonate as phosphate binders. These practice patterns are not the ones recommended by K/DIGO which propose a calcium dialysate between 2.5 and 3.0 mEq/L and to restrict the dose of calcium-based phosphate binder

[12]. However, these facts do not explain why we have observed the lowest death range at serum calcium levels slightly higher than previous published studies [4,8,9].

The negative effect of high serum calcium levels on the cardiovascular system and on mortality has already been demonstrated in several studies, and it seems that there is evidence to support several deleterious effects of high serum calcium [4,8,10]. Nevertheless, the results are less homogeneous in the range of low serum calcium levels, for which the association with mortality has been contradictory. While Block *et al*. [4] and Young *et al*. [10] found a protective effect of low serum calcium levels on all-cause mortality, Kalantar-Zadeh *et al*. [8], Tentori *et al*. [9] and others [20,21] have found, like us, an increased risk of mortality associated to low serum calcium levels.

It seems clear that this is still an issue open for discussion. Physiologically, there is no reason to justify a better survival due to low serum calcium levels, especially in the very low ranges. Quite the contrary, it is easier to relate low levels of serum calcium to higher morbidity and mortality mainly due to factors such as its association with secondary hyperparathyroidism, osteoporotic bone fractures, neurological sequelae and myocardial dysfunction due to abnormal cardiac contractility [22–25].

Serum phosphorus

In epidemiologic [3,4,8–10] and experimental studies [26,27], high serum phosphorus levels have been consistently associated with aortic calcifications and other poor cardiovascular outcomes. Our study also showed that high serum phosphorus was associated with a higher risk of mortality. These results are not surprising since high serum phosphorus levels have been consistently related to all-cause and cardiovascular mortality. In fact, reducing serum phosphorus with phosphate binders has shown a better survival, even in the normal ranges of serum phosphorus [28]. Furthermore, recent studies have proven that several cardiovascular advantages are obtained after an adequate serum phosphorus control in CKD 5 patients [29], and experimental studies have also demonstrated that phosphorus inversely correlated with survival [30].

Regarding low serum phosphorus, our results, like those in previously published studies, demonstrated an increase in the risk of all-cause and cardiovascular mortality, particularly with serum phosphorus levels <3 mg/dL [4,8,10], likely due to undernutrition [31,32].

Serum PTH

One of the more controversial issues is the association of serum PTH levels with morbidity and mortality. The normal K/DOQI ranges were selected as such based mainly on the correlation between serum PTH and bone histological parameters. The main objective was to have a useful surrogate bone marker to separate high and low bone turnover. Because of the relationship between bone turnover, calcium and phosphorus uptake and release from bone and their possible implications in hard outcomes, the so-called 'normal' PTH ranges also began to be used in the analysis of morbidity and mortality.

Serum PTH values <150 pg/mL showed higher HR values and, consequently, a higher risk of mortality than PTH values >300 pg/mL. In fact, the highest HR values (2.4 and 3.1 for all-cause and cardiovascular mortality, respectively) were found with serum PTH values <50 pg/mL, whereas in the highest serum PTH values (>500 pg/mL), mortality risk increased up to 1.6 and 2.0 for all-cause and cardiovascular mortality, respectively. The importance of low serum PTH values has already been stressed, showing that patients who start dialysis with very low PTH levels were more likely to die [33,34].

Previous studies using the same ranges showed similar trends, but the results cannot be fully compared as the authors used different cut-off values, and also, the adjustments were not exactly the same [4,8,10]. As an example, despite active vitamin D treatment being involved in changes in survival [35,36], Block *et al*. [4] did not mention any active vitamin D treatment adjustment, whereas other authors did [4,8,10]. Tsuchihashi *et al*. [37] found that HD patients with serum PTH levels <60 pg/mL experienced greater cardiovascular complications than patients with PTH values between 60 and 200 pg/mL. However, the number of patients was small (48), and the results were not calcium-adjusted. The NECOSAD Study showed no effect of either high or low PTH levels on cardiovascular mortality [14]. The DOPPS showed no relationship between low PTH and cardiovascular mortality [9]; yet, as they were not able to control the different PTH assays used, the results are difficult to interpret. In our study, we found a clear relationship between cardiovascular mortality and extreme PTH serum values, both high and low, particularly in the latter. The strength of our study resides not only in the sample size but in the fact that all centres used the same PTH assay. This fact minimizes any variability related to the assay, which has proven to be a relevant factor [38]. Interestingly, our findings agree with those from the ARO CKD Research Initiative Study (authors' unpublished data) that showed reduced and elevated iPTH (<150 and >500 pg/mL, respectively), albumin-corrected calcium, and phosphorus levels were all associated with an increase in all-cause mortality using time-dependent analysis.

To conclude, a few words on cardiovascular outcomes: similarly to previous results [4,16], high serum phosphorus was associated with an increased relative risk of death and cardiovascular hospitalization. On the other hand, there was no association between serum calcium and PTH and the risk of cardiovascular hospitalization.

Limitations of the study

One of the limitations of our study is its retrospective and observational nature. However, the fact that it was conducted in a large database of 16 173 patients minimizes any probable selection bias.

Since only HD patients were included in the analysis, no extrapolation is possible to patients on peritoneal dialysis or renal patients with less advanced CKD stages 3–5. In addition, unmeasured confounding variables could increase or decrease the HR for mortalities and/or hospitalization. A recent prospective study has showed an association between

vitamin D deficiency and increased cardiovascular mortality in haemodialysis patients [39]. Physiological doses of active vitamin D have shown protective cardiovascular effects reducing the inflammatory response to cardiovascular injury, the myocardial cell hypertrophy and proliferation, and the renin–angiotensin system activation [40]. Although Latin America has an adequate sunshine availability, the vitamin D deficiency/insufficiency in Latin America is as endemic as in the northwestern hemisphere [41,42], probably due the low intake of vitamin D-supplemented foods. Since levels of 25(OH)D and $1.25(OH)_2$ were not available in our population, the main effect of serum PTH (both low and high) on the risk of death could only be adjusted according to the presence or absence of an active vitamin D treatment. Finally, a major limitation of the study is the lack of information of outcomes across countries.

To sum up, the CORES Study consists in a large database of patients from six Latin American countries followed up for up to 54 months. We have found in the CORES Study that elevated and reduced serum levels of albumin-corrected calcium, phosphorus and PTH were associated with increments in both all-cause and cardiovascular mortalities. Moreover, we found a significantly higher cardiovascular hospitalization rate in patients with elevated serum phosphorus.

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(See related article by Cunningham *et al.* CKD–MBD: comfort in the trough of the U. *Nephrol Dial Transplant* 2011; 26: 1764–1766)

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