Nephrol Dial Transplant, 2023, **38**, 2589–2597
https://doi.org/10.1093/ndt/gfad122
Advance access publication date: 22 June 2023

Mineral and bone metabolism markers and mortality in diabetic patients on haemodialysis

Beatriz Martín-Carro[1], Juan F. Navarro-González[2,3,4,5], Alberto Ortiz[6,7,8], Carmine Zoccali[9,10,11], Jürgen Floege[12], Manuel A. Ferreira[13,14], José L. Gorriz-Teruel[15,16], Natalia Carrillo-López[1], Sara Panizo[1], Francesco Locatelli[17], Markus Ketteler[18], Gerard M. London[19], Manuel Naves-Díaz[1,20], Cristina Alonso-Montes[1,†], Jorge B. Cannata-Andía[1,20,21,†] and José L. Fernández-Martín[1,20,†]

[1]Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Bone and Mineral Research Unit, REDinREN and RICORS2040 del ISCIII, Oviedo, Spain
[2]Unidad de Investigación y Servicio de Nefrología, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain
[3]RICORS2040 (RD21/0005/0013), Instituto de Salud Carlos III, Madrid, Spain
[4]GEENDIAB, Sociedad Española de Nefrología, Santander, Spain
[5]Instituto de Tecnologías Biomédicas, Universidad de La Laguna, Santa Cruz de Tenerife, Spain
[6]Department of Nephrology and Hypertension, IIS-Fundación Jimenez Diaz UAM, Madrid, Spain
[7]RICORS2040, Madrid, Spain
[8]Departamento de Medicina, Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain
[9]Renal Research Institute, New York, USA
[10]Institute of Molecular Biology and Genetics (Biogem), Ariano Irpino, Italy
[11]Associazione Ipertensione Nefrologia Trapianto Renal (IPNET), c/o Nefrología, Grande Ospedale Metropolitano, Reggio Calabria, Italy
[12]RWTH Aachen University, Div. Nephrology, Aachen, Germany
[13]Nova Medical School-Vice Dean, Lisboa, Portugal
[14]Centro Hospitalar Universitário de Lisboa Central – Hospital Curry Cabral, Nephrology Department, Lisboa, Portugal
[15]Department of Nephrology, Hospital Clínico Universitario, Valencia, Spain
[16]Department of Medicine, Health Research Institute INCLIVA, University of Valencia, Valencia, Spain
[17]Department of Nephrology, Alessandro Manzoni Hospital (past director), Lecco, Italy
[18]Department of General Internal Medicine and Nephrology, Robert-Bosch-Krankenhaus GmbH, Stuttgart, Germany
[19]Department of Nephrology, Centre Hospitalier FH, Manhes, France
[20]Hospital Universitario Central de Asturias, Bone and Mineral Research Unit, REDinREN and RICORS2040 del ISCIII, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain
[21]Department of Medicine, Universidad de Oviedo, Oviedo, Spain
Correspondence to: Jorge B. Cannata-Andía; E-mail: cannata@hca.es, jorge.cannata@gmail.com, Manuel Naves-Díaz; E-mail: mnaves.huca@gmail.com
[†]Equal contribution as senior authors.

ABSTRACT

Background. Diabetic patients on haemodialysis have a higher risk of mortality than non-diabetic patients. The aim of this COSMOS (Current management of secondary hyperparathyroidism: a multicentre observational study) analysis was to assess whether bone and mineral laboratory values [calcium, phosphorus and parathyroid hormone (PTH)] contribute to this risk.

Methods. COSMOS is a multicentre, open-cohort, 3-year prospective study, which includes 6797 patients from 227 randomly selected dialysis centres in 20 European countries. The association between mortality and calcium, phosphate or PTH was assessed using Cox proportional hazard regression models using both penalized splines smoothing and categorization according to KDIGO guidelines. The effect modification of the association between the relative risk of mortality and serum calcium, phosphate or PTH by diabetes was assessed.

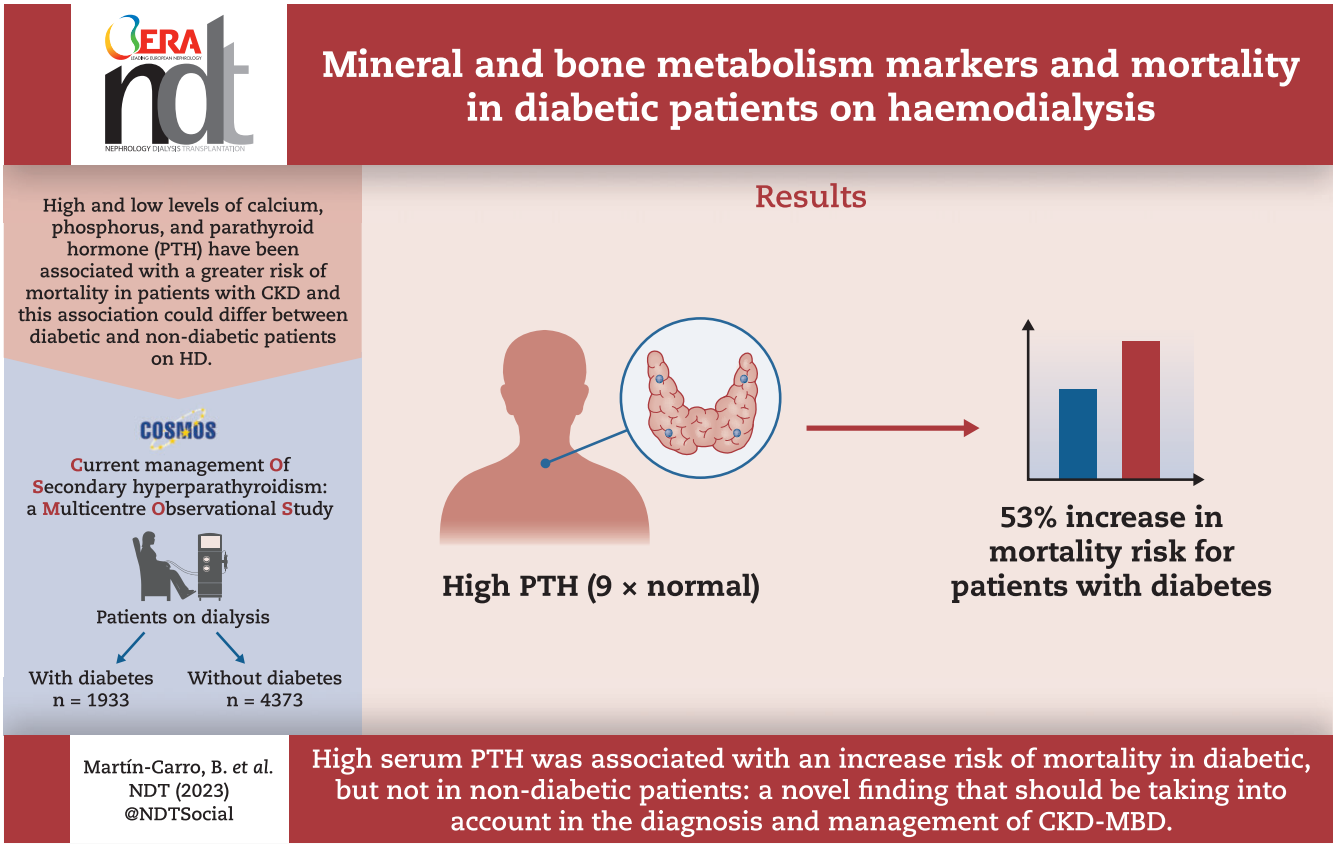
Results. There was a statistically significant effect modification of the association between the relative risk of mortality and serum PTH by diabetes ($P = .011$). The slope of the curve of the association between increasing values of PTH and relative risk of mortality was steeper for diabetic compared with non-diabetic patients, mainly for high levels of PTH. In addition, high serum PTH (>9 times the normal values) was significantly associated with a higher relative risk of mortality in diabetic patients but not in non-diabetic patients [1.53 (95% confidence interval 1.07–2.19) and 1.17 (95% confidence interval 0.91–1.52)]. No significant effect modification of the association between the relative risk of mortality and serum calcium or phosphate by diabetes was found ($P = .2$ and $P = .059$, respectively).

Conclusion. The results show a different association of PTH with the relative risk of mortality in diabetic and non-diabetic patients. These findings could have relevant implications for the diagnosis and treatment of chronic kidney disease–mineral and bone disorders.

Keywords: chronic kidney disease–mineral and bone disorders (CKD-MBD), diabetes, haemodialysis, mortality, PTH

Received: February 14, 2023; Editorial decision: April 17, 2023

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Diabetic patients on haemodialysis are at a higher risk of mortality than non-diabetic patients.
- High and low levels of calcium, phosphorus and parathyroid hormone (PTH) have been associated with a greater risk of mortality in patients with chronic kidney disease.
- To our knowledge, the association between these bone metabolism markers and mortality has not been analysed separately in diabetic and non-diabetic patients.

This study adds:

- The present analysis of COSMOS shows, for the first time, a significant different association between serum PTH and the relative risk of mortality between diabetic and non-diabetic patients on haemodialysis.
- In diabetic patients with high serum PTH, the relative risk of mortality was greater compared with non-diabetic patients.

Potential impact:

- The findings of the present study suggest that the targets for serum PTH should be different in diabetic and non-diabetic patients.
- According to the present results, the control of hyperparathyroidism should be stricter in diabetic patients on haemodialysis.

INTRODUCTION

Diabetes is the most common cause of chronic kidney disease (CKD) that needs renal replacement therapy [1], accounting for close to 50% of such patients in recent international studies [2, 3].

CKD–mineral and bone disorders (CKD-MBD) are non-traditional cardiovascular risk factors [4] defined as a systemic disorders characterized by laboratory abnormalities [calcium, phosphate, parathyroid hormone (PTH) or vitamin D], bone and/or vascular alterations or other soft tissue calcification [5, 6]. Many studies have shown that both high and low levels of serum calcium, phosphate and PTH are associated with an increased risk of mortality [7–14]. In CKD patients, the abnormalities of these laboratory values have been implicated in increasing vascular calcification [15, 16].

Diabetes is considered a traditional risk factor for cardiovascular events and mortality in dialysis patients [4]; in fact, diabetic patients on haemodialysis have double the relative risk of all-cause and cardiovascular mortality versus non-diabetic patients [17]. In addition, diabetes is associated with a higher prevalence of vascular calcification [18, 19], especially in peripheral arteries [20, 21], regardless of mineral and bone metabolism abnormalities and time on dialysis [21]. Diabetic patients also have other risk factors that negatively impacting morbidity and mortality, such as an increased inflammation [21] and inadequate glycaemic control [22].

Diabetic patients have lower PTH [23] than non-diabetic patients, however the association of this abnormality, and others disturbances in classical laboratory values of CKD-MBD, such as calcium, phosphate and the relative risk of mortality, have not been studied in large-scale epidemiological studies.

The objective of this analysis of COSMOS (Current management of secondary hyperparathyroidism: a multicentre observational study) was to evaluate the association of serum calcium, phosphate and PTH with the relative risk of mortality in diabetic and non-diabetic patients on haemodialysis.

MATERIALS AND METHODS

Study design

COSMOS is a multicentre, open-cohort, 3-year prospective study which includes 6797 patients from 227 randomly selected dialysis centres in 20 European countries, which aimed to survey CKD-MBD in haemodialysis. Detailed description of the study has been previously reported [14, 24–27]. The study was designed to represent the European haemodialysis population. Both, dialysis centres and 20 adult patients by centre with no previous kidney transplant were randomly selected within each participating country. The number of patients by country was proportional to the haemodialysis population of each country [24]; 4500 patients were randomly recruited for the study. In addition, 2297 patients new on haemodialysis (<1 year), were also recruited to replace those that were lost to follow-up for any reason, achieving a total number of 6797 patients.

At baseline, each centre completed a web form with 27 questions and 185 items, including demographics, comorbidities (diabetes and others), treatments and laboratory values for the previous 6 months (serum PTH, phosphate, calcium, albumin and haemoglobin) [26]. Every 6 months, outcomes, treatments and laboratory values for the previous 6 months were collected. At baseline and every 6 months, mean values of the monthly laboratory values were calculated.

The serum PTH values (N = 31700) were corrected by the PTH assay used [28]. The number of PTH values by PTH assays were: Elecsys PTH Roche (8934, 28.2%), Immulite 2000-intact PTH (4522, 14.2%), ELISA-PTH (3072, 9.7%), PTH IRMA Immunotech (1446, 4.6%), PTH AdviaCentaur Bayer (1510, 4.8%), Total-intact PTH IRMA (1377, 4.3%), Intact PTH advantage (1008, 3.2%), Allegro-intact PTH (986, 3.1%), LIAISON N-tact PTH (691, 2.2%), TOSOH AIA-PACK Intact PTH (344, 1.1%), N-tact PTH IRMA (355, 1.1%), PTH-ACS 180 Bayer (310, 1.0%) and BioIntact PTH advantage (151, 0.5%). The serum PTH values were converted to the most frequently assay used, the Elecsys PTH. In those centres not reporting the exact PTH assay but reporting that they used Biointact PTH, the serum PTH was multiplied by 1.95 (1401, 4.4%). The remaining serum PTH values were not corrected and used as reported by the centres (5600, 17.7%).

The Ethics Committee of the University Hospital Doctor Peset approved the study (approval number 05/054, Valencia, Spain), and the research was conducted according to principles of the Declaration of Helsinki. All patients provided their informed consent for participation in the study.

Statistical analysis

Data were described using mean [standard deviation (SD)] and median [interquartile range (IQR)] for normally and non-normally distributed variables and percentages for categorical variables. Diabetic and non-diabetic patients were compared by using Student's t-test, Mann–Whitney U-test (numeric variables) or Chi-squared test (categorical variables) as appropriate.

The outcome was all-cause mortality and the exposure serum levels of calcium, phosphate or PTH. Cox proportional hazard regression models with penalized splines smoothing was used to analyse the association between the relative risk of death and serum calcium, phosphate and PTH. The use of this method allows modelling of non-linear relationships without categorization of serum values of calcium, phosphate and PTH. Akaike information criterion was used for the selection of smoothing laboratory values in penalized splines models. Three different progressive multivariate models were used to adjust hazard ratios including the following variables. Model 1: age, sex, body mass index (BMI), smoking habit, time on haemodialysis, aetiology of CKD, diabetes, cardiovascular disease, parathyroidectomy and calcification (valvular, vascular or calciphylaxis). Model 2: variables from Model 1 plus calcium concentration in the dialysate, hours of haemodialysis per week, prescription of erythropoiesis-stimulating agents (ESAs), vitamin D metabolites/analogues (calcitriol, alfacalcidol or paricalcitol), native vitamin D or calcidiol, calcimimetics and phosphate binding agents (PBAs: calcium-containing PBAs, sevelamer, aluminium-containing PBAs, lanthanum carbonate or other PBAs). Model 3: variables from Model 2 plus haemoglobin, albumin, serum calcium, phosphate and PTH. Serum calcium, phosphate and PTH were considered as time-dependent variables as well as parathyroidectomy in Model 1; likewise all treatments in Model 2 and laboratory values in Model 3. In multivariate models, the facility for stratification was used.

The effect modification of the association between the relative risk of mortality and serum calcium, phosphate or PTH by diabetes was assessed. Additionally, serum PTH levels were categorized according to the ranges recommended by the KDIGO guidelines of 2009 as follows: <130, 130–585 and >585 pg/mL. Cox regression was used to analyse the association between serum PTH and mortality, using as reference the intermediate category 130–585 pg/mL of serum PTH. Progressive multivariate models were used as detailed above. R software for statistical computing and graphics (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analysis.

RESULTS

The present analysis includes 6306 patients (92.7% of the whole COSMOS cohort), 4373 non-diabetic and 1933 diabetic patients, for whom follow-up data and accurate information on their diabetic status were confirmed. Mean time of follow-up was 23.5 months (median 24), 23.8 in non-diabetic and 22.8 in diabetic patients; 1642 patients died (652 diabetic patients), 642 were transplanted (111 diabetic patients), 239 were referred to other haemodialysis units (68 diabetic patients), 23 switched to peritoneal dialysis (8 diabetic patients) and 52 left the study for other reasons (11 diabetic patients). Overall, the mortality rate was 13.3 deaths per 100 patient-years, which was higher in diabetic compared with non-diabetic patients: 17.8 vs 11.4. The global cardiovascular mortality rate was 5.9 deaths per 100 patient-years, also higher in diabetic than non-diabetic patients (9.0 vs 4.6).

The main baseline patient characteristics are detailed in Table 1. At baseline, diabetic patients were 30.7% of the whole cohort, they were older, with fewer smokers, higher BMI, more frequent history of cardiovascular disease and lower frequency of parathyroidectomies. The hours of haemodialysis per week was

Table 1: Main baseline characteristics of patients included in the study.

	Overall	Non-diabetics	Diabetics	P-value
N	6306	4373	1933	
Sex = male [*n* (%)]	3831 (60.8)	2635 (60.3)	1196 (61.9)	.236
Age (years) [mean (SD)]	64.0 (14.4)	62.8 (15.3)	66.7 (11.7)	<.001
BMI (kg/m²) [mean (SD)]	25.3 (5.1)	24.5 (4.5)	27.3 (5.6)	<.001
Current smokers = yes [*n* (%)]	878 (13.9)	641 (14.7)	237 (12.3)	.012
CVD history = yes [*n* (%)]	4540 (72.1)	2934 (67.2)	1606 (83.1)	<.001
Parathyroidectomy = yes [*n* (%)]	308 (4.9)	278 (6.4)	30 (1.6)	<.001
Months on HD [mean (SD)]	38.9 (49.5)	44.2 (55.0)	26.9 (30.8)	<.001
Hours of dialysis per week [mean (SD)]	12.0 (2.1)	12.0 (2.1)	12.1 (2.1)	.049
Type of dialysis [*n* (%)]				.433
Low-flux	3409 (54.1)	2380 (54.5)	1029 (53.2)	
High-flux	2340 (37.1)	1600 (36.6)	740 (38.3)	
Others	554 (8.8)	390 (8.9)	164 (8.5)	
Calcium concentration in dialysate [*n* (%)]				.158
2.5 mEq/L	1676 (29.7)	1163 (30.0)	513 (29.2)	
3.0 mEq/L	2863 (50.8)	1940 (50.0)	923 (52.5)	
3.5 mEq/L	1098 (19.5)	777 (20.0)	321 (18.3)	
Patients prescribed PBAs = yes [*n* (%)]	5360 (85.1)	3771 (86.4)	1589 (82.3)	<.001
Patients prescribed VDRAs = yes [*n* (%)]	2993 (47.5)	2117 (48.5)	876 (45.4)	.025
Patients prescribed calcimimetics = yes [*n* (%)]	388 (6.2)	299 (6.9)	89 (4.6)	.001
Patients prescribed ESAs = yes [*n* (%)]	5595 (90.6)	3872 (90.4)	1723 (90.9)	.586
Phosphorus (mg/dL) [mean (SD)]	5.4 (1.4)	5.4 (1.5)	5.3 (1.3)	.281
Calcium (mg/dL) [mean (SD)]	9.1 (0.7)	9.1 (0.8)	9.0 (0.7)	<.001
PTH (pg/mL) [median (IQR)]	208.3 (107.5, 378.0)	213.7 (109.8, 403.4)	195.2 (105.4, 333.6)	.001
Albumin (g/dL) [mean (SD)]	3.8 (0.5)	3.8 (0.5)	3.7 (0.5)	<.001
Haemoglobin (g/dL) [mean (SD)]	11.4 (1.4)	11.4 (1.4)	11.4 (1.3)	.501

HD: hemodialysis; CVD: cardiovascular disease.

slightly but significantly higher. The percentage of patients who were prescribed drugs to correct bone and mineral abnormalities, such as PBAs, vitamin D receptor activators (VDRAs) and calcimimetics, was lower in diabetic patients. There were no significant differences in serum phosphate or haemoglobin levels, but diabetic patients showed significantly lower serum levels of calcium, PTH and albumin.

A statistically significant effect modification of the association between the relative risk of mortality and serum PTH by diabetes was found (Fig. 1, $P = .011$). The slope of the curve of the association between increasing PTH values and the relative risk of mortality was steeper for diabetic compared with non-diabetic patients, mainly for high levels of PTH (>400 pg/mL). By contrast, there were no significant differences in the effect modification of the association between the relative risk of mortality and serum calcium or phosphate by diabetes (Supplementary data, Figs S1 and S2).

The association between serum PTH and mortality categorized according to KDIGO-recommended targets is shown in Table 2. In all patients, the fully adjusted model (Model 3) showed that both low (<130 pg/mL) and high (>585 pg/mL) PTH levels were associated with an increased relative risk of all-cause mortality (16% and 23%, respectively) (Table 2A), compared with serum PTH levels of 130–585 pg/mL. High serum PTH (>585 pg/mL) remained significantly associated with all-cause mortality in diabetic patients [1.53 (95% confidence interval 1.07–2.19), Table 2B] but this was not the case for non-diabetic patients [1.17 (95% confidence interval 0.91–1.52), Table 2C].

DISCUSSION

The present study showed differences in the association between serum PTH and the relative risk of mortality among diabetic and non-diabetic patients. In diabetic patients, it was observed that the higher the serum PTH, the greater the mortality risk. By contrast, no association was observed between serum calcium and phosphate and the relative risk of mortality. The effect modification by diabetes using penalized splines smoothing showed that the slopes of the association between serum PTH and mortality risk were different in diabetic and non-diabetic patients. Furthermore, the serum PTH range in which the minimum relative risk of mortality was observed was narrower in diabetic patients compared with non-diabetic subjects. These findings were consistent after categorizing the serum PTH according to the recommended targets of the KDIGO clinical guidelines.

In CKD, diabetes has been associated with low serum PTH levels [29], poor glycaemic control and high HbA1c, which negatively correlated with serum PTH [29, 30]. Also, autonomic nervous system dysfunction and low and high magnesium has been shown to be involved in the low serum PTH levels observed in diabetic patients [31–34]. In the present analysis of COSMOS, median serum PTH levels were lower in diabetic than in non-diabetic patients, although differences did not seem clinically relevant (195.2 vs 213.7 pg/mL). The differences in serum PTH could have been greater if the number of parathyroidectomized patients had been similar in both groups. Instead, 278 parathyroidectomies were performed in non-diabetic patients, and only 30 (9-fold fewer) in diabetic patients. In addition to the significantly lower need for surgical parathyroid surgery, fewer drugs were needed to control serum PTH in diabetic patients, including PBAs, VDRAs and calcimimetics (Table 1).

Multiple reasons may explain the greater mortality in diabetic patients on haemodialysis, which in our study was 56% higher than in non-diabetic patients. Inflammation is a relevant factor in the pathogenesis of diabetes and could worsen the prognosis

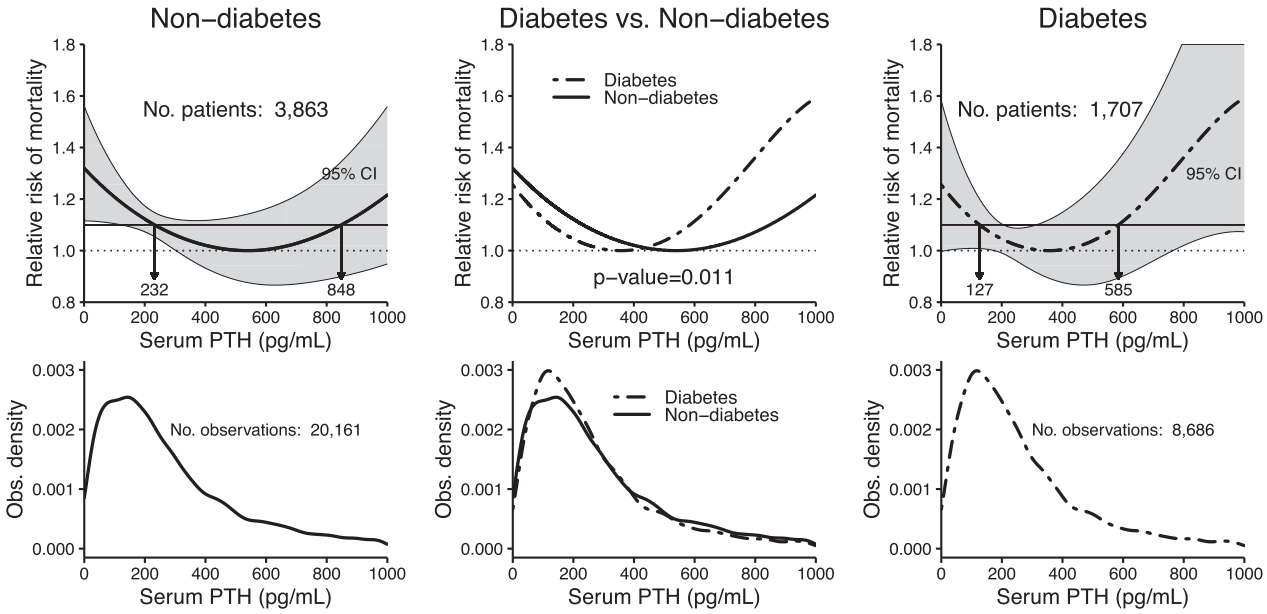


Figure 1: Association between serum PTH and relative risk of mortality using penalized splines smoothing in diabetic and non-diabetic patients. The left panels show the relative risk of mortality (top) and the observations density (bottom) in non-diabetic patients. The right panels show the relative risk of mortality (top) and the observations density (bottom) in diabetic patients. The middle panels show the comparison between diabetic and non-diabetic patients. The relative risk of mortality was adjusted by age, sex, BMI, smoking habit, time on HD, aetiology of CKD, diabetes, cardiovascular disease, parathyroidectomy, HD type, calcium in the dialysate, hours of HD per week, ESAs, VDRAs, native vitamin D or calcidiol, PBAs, calcimimetics, haemoglobin, albumin, serum calcium and serum phosphate. Shaded area represents the 95% confidence interval. The reference [hazard ratio (HR) = 1] was the serum PTH with the minimum log(HR) in diabetics and non-diabetics, respectively. Arrows shows the range of serum PTH with the minimum mortality risk. HD: haemodialysis.

Table 2: Multivariate analysis of the association between serum PTH categorized according to KDIGO recommended targets and mortality; the intermediate category (130–585 pg/mL) was used as reference (HR = 1.00).

			Serum PTH (pg/mL)		
Model	Number of patients	Number of deaths	<130 HR (95% CI)	130–585 Reference	>585 HR (95% CI)
(A) All patients					
Unadjusted	6220	1614	1.53 (1.37–1.70)	1.00	0.92 (0.78–1.08)
Model 1	6209	1613	1.40 (1.24–1.57)	1.00	1.13 (0.94–1.34)
Model 2	5950	1536	1.32 (1.16–1.49)	1.00	1.28 (1.06–1.54)
Model 3	5570	1409	1.16 (1.01–1.32)	1.00	1.23 (1.01–1.49)
(B) Diabetics					
Unadjusted	1919	645	1.46 (1.23–1.72)	1.00	1.13 (0.87–1.46)
Model 1	1918	644	1.37 (1.13–1.67)	1.00	1.38 (1.02–1.88)
Model 2	1836	619	1.38 (1.12–1.71)	1.00	1.57 (1.13–2.17)
Model 3	1707	568	1.21 (0.96–1.52)	1.00	1.53 (1.07–2.19)
(C) Non-diabetics					
Unadjusted	4301	969	1.57 (1.37–1.80)	1.00	0.87 (0.71–1.07)
Model 1	4291	969	1.44 (1.24–1.69)	1.00	1.09 (0.87–1.58)
Model 2	4114	917	1.31 (1.11–1.56)	1.00	1.25 (0.98–1.58)
Model 3	3863	841	1.19 (0.99–1.44)	1.00	1.17 (0.91–1.52)

Multivariate adjustments; Model 1: age, sex, BMI, aetiology of chronic kidney disease, time on haemodialysis, smoking habit, diabetes, cardiovascular disease history, bone fracture history in the previous 12 months, vascular or valvular calcification and parathyroidectomy. Model 2: Model 1 plus dialysis type, calcium concentration in the dialysate, hours of haemodialysis per week, treatment with ESAs, prescription of vitamin D metabolites/analogues, native vitamin D or calcidiol, PBAs. Model 3: Model 2 plus haemoglobin, albumin, PTH and calcium.
HR: hazard ratio.

of diabetic patients [35]. Also, among CKD-MBD laboratory values, low or high serum PTH levels have been extensively identified as drivers of bone fragility fractures [36, 37], vascular and valvular calcification [38–42], and myocardial dysfunction [41–43], resulting in lower survival [11, 14, 44, 45]. However, to the best of our knowledge, there are no studies specifically analysing these differences between diabetic and non-diabetic patients on haemodialysis.

In the present study, the association between serum PTH and mortality differed in both groups of patients. The slope of the curve of the association between serum PTH and mortality was steeper in diabetic patients with high serum PTH,

indicating a higher risk of mortality compared with non-diabetic subjects. The results remained consistent after categorizing serum PTH according to the KDIGO recommended targets (2–9 times the normal values); in fact, a serum PTH >585 pg/mL (9 times the normal values) was associated with a significantly higher relative risk of mortality in diabetic but not in non-diabetic patients.

The effect modification of the association between the relative risk of mortality and serum phosphate by diabetes was not statistically significant ($P = .059$). It can be said the association was marginal, if any; the main difference between diabetic and non-diabetic patients was found for low serum phosphate (Supplementary data, Fig. S2), a finding that could be more related to malnutrition—associated with the lower phosphate—rather than to the serum phosphate itself.

So far, the management of secondary hyperparathyroidism in haemodialysis patients is mainly done considering the serum calcium, phosphate and PTH targets, regardless of the diabetic status. The results of our analysis suggest that the impact of the CKD-MBD could be different in non-diabetic and diabetic patients and strongly indicated that high PTH exerts a more negative effect in diabetic patients, suggesting that the control of serum PTH should be stricter in these patients. In fact, the range of minimum mortality risk, considering a hazard ratio <1.1 (a <10% increase in the relative risk of mortality [13, 14, 46], Fig. 1), was 21% narrower (458 vs 616 pg/mL) in the diabetic patients (127–585 pg/mL) than in the non-diabetic patients (232–848 pg/mL), respectively.

The mechanisms by which high PTH levels might be more detrimental to diabetic patients are unknown. Both, diabetes and high PTH have been associated with a greater prevalence of vascular calcifications [22, 47], which in turn could be partly responsible for the higher mortality. In addition, a very recent study has shown that PTH is able to induce dysfunction of valvular endothelial cells, triggering the transformation of valvular interstitial cells to an osteogenic phenotype [40]. Thus, we could also speculate that high PTH levels could further exacerbate the risk of vascular calcifications in diabetic patients.

On the other hand, inflammation is a relevant factor in this scenario, where diabetic patients on haemodialysis are a critical risk group, since diabetes plus end-stage renal disease have additive impacts on the development and progression of atherosclerosis [48]. Elevated inflammatory markers in these subjects have been independently associated with all-cause and cardiovascular mortality [49]. Finally, a potential role of fibroblast growth factor 23 (FGF23) cannot be ruled out. In haemodialysis patients, high levels of FGF23 have been independently associated with increased mortality [50]. Diverse studies have shown that FGF23 concentrations are elevated in patients with type 2 diabetes [51, 52] while inflammation directly stimulates the production of FGF23 [53]. Finally, it has been also shown that high levels of PTH directly and indirectly stimulate FGF23 production [54]. However, the causal role of FGF23 in mortality remains debated and has not been shown to be greater in diabetic than in non-diabetic patients on haemodialysis.

In this analysis of COSMOS, the differences found between diabetic and non-diabetic haemodialysis patients are novel and carry practical messages for the CKD-MBD management of the diabetic patients on haemodialysis. However, the study has also limitations, mainly due to its observational nature, which does not allow causality to be established, and the fact the data were collected >12 years ago. The main strength of COSMOS is its large sample size and the prospective randomized selection of centres and patients that truly represents the European haemodialysis population.

In summary, the study revealed that diabetic patients with high serum PTH could be at a higher risk of mortality compared with non-diabetic patients, a finding which has important implications in the diagnosis and treatment of secondary hyperparathyroidism in these patients. At present, the serum PTH target recommended by KDIGO is 2–9 times the maximum normal value regardless of the diabetes status. The results of the present study suggest that the serum PTH target should be different for non-diabetic and diabetic patients, possibly lower and narrower for the latter. They also suggest the control of secondary hyperparathyroidism should be stricter in diabetic patients. Further research in this area is needed to confirm and complement the results of the present study.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

We acknowledge the COSMOS participating centres, the Biostatistics and Epidemiology Platform of the Instituto de Investigación Sanitaria del Principado de Asturias (ISPA) and the Asociación para la Lucha Contra las Enfermedades Renales of the Principality of Asturias (ALCER).

For COSMOS participating centres: see Supplementary Appendix.

FUNDING

COSMOS is sponsored by the Bone and Mineral Research Unit (Hospital Universitario Central de Asturias), SAFIM (Sociedad Asturiana Fomento Investigaciones Óseas), the European Renal Association. This study has been funded by Instituto de Salud Carlos III (ISCIII), the ISCIII Retic REDinREN (RD06/0016/1013, RD12/0021/0023 and RD16/0009/0017), the ISCIII Red de Investigación Cooperativa Orientada a Resultados en Salud RICORS2040 (RD21/0005/0001, RD21/0005/0013 and RD21/0005/0019, Next Generation EU; Recovery, Transformation and Resilience Plan), the ISCIII (ICI14/00107, PI17/00384 and PI20/00633, co-funded by the European Union), Plan Estatal de I + D + I 2013–2016, Plan de Ciencia, Tecnología e Innovación 2013–2017 y 2018–2022 del Principado de Asturias (GRUPIN14-028, IDI-2018-000152, IDI/2021/000080), Fundación Renal Íñigo Álvarez de Toledo (FRIAT) and the Spanish Society of Nephrology (Estudio Estratégico de la SEN). Logistics (meetings, secretarial help, printing of materials, development of Web site for data entry, etc.) have been financially supported by AMGEN Europe and Fundación Renal Íñigo Álvarez de Toledo (FRIAT). The authors are not aware of any additional relationships, funding or financial holdings that might be perceived as affecting the objectivity of this study. B.M.-C. was supported by a graduate fellowship from the Gobierno del Principado de Asturias ('Severo Ochoa' program).

AUTHORS' CONTRIBUTIONS

Conception and study design: C.Z., J.F., M.A.F., J.L.G.-T., F.L., M.K., G.L., J.B.C.-A., J.L.F.-M. Analysis design: B.M.-C., C.Z., J.F., M.A.F., J.L.G.-T., F.L., M.K., G.L., M.N.-D., C.A.-M., J.B.C.-A., J.L.F.-M. Statistical analysis: B.M.-C., N.C.-L., S.P., M.N.-D., C.A.-M., J.B.C.-A., J.L.F.-M. Interpretation of results: B.M.-C., J.F.N.-G., A.O., C.Z., J.F., F.L.,

M.N.-D., C.A.-M., J.B.C.-A., J.L.F.-M. Draft writing: B.M.-C., N.C.-L., S.P., J.B.C.A., J.L.F.-M. Manuscript revision: all authors. Acquisition of funding: C.A.-M., J.B.C.-A., J.L.F.-M.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

A.O. has received grants from Sanofi and consultancy or speaker fees or travel support from Adviccene, Alexion, Astellas, AstraZeneca, Amicus, Amgen, Boehringer Ingelheim, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Mundipharma, Kyowa Kirin, Lilly, Freeline, Idorsia, Chiesi, Otsuka, Novo-Nordisk, Sysmex and Vifor Fresenius Medical Care Renal Pharma, and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra Astrazeneca-UAM of chronic kidney disease and electrolytes. He has stock in Telara Farma. J.L.G.-T. has been an advisor on scientific boards for AstraZeneca, Bayer and Novo Nordisk, lectures for AstraZeneca, Boehringer Ingelheim, Esteve, Bayer, Eli Lilly and Company, Bayer, Astellas and Novo Nordisk, and research activities for AstraZeneca. J.F.N.-G. has served as a consultant and has received speaker fees or travel support from AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Esteve, Eli Lilly, GSK, MSD, Mundipharma, Novartis, NovoNordisk, Sanofi-Genzyme, Servier, Shire and Vifor Pharma. J.F.N.-G. is Academic Editor for the *Journal of Clinical Medicine* and Associate Editor for *Frontiers in Medicine*. J.F.N.-G. is member of the Scientific Advisory Board of the European Renal Association. F.L. is or was a member of an advisory board of Amgen, Astellas, Baxter, Otsuka, GSK, Travere and Vifor Pharma, and speaker at meetings supported by unrestricted grants from Amrn, Astellas and Vifor Pharma. J.C. has been consultant, member of advisory boards and received research grants from Amgen, Vifor Pharma, Abbvie, Kyowa Kirim, Fresenius Medical Care and FAES. J.B.C.-A. has received grants or consultancy, speaker fees and travel support from Amgen, Kyowa Kirin and Vifor Fresenius Medical Care Renal Pharma. The remaining authors declare no conflict of interest in relation to the work.

REFERENCES

1. Webster AC, Nagler EV, Morton RL *et al.* Chronic kidney disease. *Lancet North Am Ed* 2017;**389**:1238–52. https://doi.org/10.1016/S0140-6736(16)32064-5
2. Tabibzadeh N, Karaboyas A, Robinson BM *et al.* The risk of medically uncontrolled secondary hyperparathyroidism depends on parathyroid hormone levels at haemodialysis initiation. *Nephrol Dial Transplant* 2021;**36**:160–9. https://doi.org/10.1093/ndt/gfaa195
3. Ficociello LH, Zhou M, Mullon C *et al.* Effect of citrate-acidified dialysate on intact parathyroid hormone in prevalent hemodialysis patients: a matched retrospective cohort study. *Int J Nephrol Renovasc Dis* 2021;**14**:475–86. https://doi.org/10.2147/IJNRD.S340028
4. Jegatheesan D, Yang W, Krishnasamy R *et al.* Cardiovascular disease in dialysis patients. In: Karkar A (ed.), *Aspects in Dialysis*. IntechOpen, 2017, 59–90. http://dx.doi.org/10.5772/intechopen.70362
5. Moe S, Drueke T, Cunningham J *et al.* Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;**69**:1945–53. https://doi.org/10.1038/sj.ki.5000414
6. Cannata-Andia JB, Martin-Carro B, Martin-Virgala J *et al.* Chronic kidney disease-mineral and bone disorders: pathogenesis and management. *Calcif Tissue Int* 2021;**108**:410–22. https://doi.org/10.1007/s00223-020-00777-1
7. Block GA, Klassen PS, Lazarus JM *et al.* Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004;**15**:2208–18. https://doi.org/10.1097/01.ASN.0000133041.27682.A2
8. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006;**70**:771–80. https://doi.org/10.1038/sj.ki.5001514
9. Tentori F, Blayney MJ, Albert JM *et al.* Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2008;**52**:519–30. https://doi.org/10.1053/j.ajkd.2008.03.020
10. Wald R, Sarnak MJ, Tighiouart H *et al.* Disordered mineral metabolism in hemodialysis patients: an analysis of cumulative effects in the Hemodialysis (HEMO) Study. *Am J Kidney Dis* 2008;**52**:531–40. https://doi.org/10.1053/j.ajkd.2008.05.020
11. Naves-Diaz M, Passlick-Deetjen J, Guinsburg A *et al.* Calcium, phosphorus, PTH and death rates in a large sample of dialysis patients from Latin America. The CORES Study. *Nephrol Dial Transplant* 2011;**26**:1938–47. https://doi.org/10.1093/ndt/gfq304
12. Floege J, Kim J, Ireland E *et al.* Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant* 2011;**26**:1948–55. https://doi.org/10.1093/ndt/gfq219
13. Fouque D, Roth H, Pelletier S *et al.* Control of mineral metabolism and bone disease in haemodialysis patients: which optimal targets? *Nephrol Dial Transplant* 2013;**28**:360–7. https://doi.org/10.1093/ndt/gfs404
14. Fernandez-Martin JL, Martinez-Camblor P, Dionisi MP *et al.* Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. *Nephrol Dial Transplant* 2015;**30**:1542–51. https://doi.org/10.1093/ndt/gfv099
15. Shanahan CM, Crouthamel MH, Kapustin A *et al.* Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. *Circ Res* 2011;**109**:697–711. https://doi.org/10.1161/CIRCRESAHA.110.234914
16. Byon CH, Chen Y. Molecular mechanisms of vascular calcification in chronic kidney disease: the link between bone and the vasculature. *Curr Osteoporos Rep* 2015;**13**:206–15. https://doi.org/10.1007/s11914-015-0270-3
17. Ma L, Zhao S. Risk factors for mortality in patients undergoing hemodialysis: a systematic review and meta-analysis. *Int J Cardiol* 2017;**238**:151–8. https://doi.org/10.1016/j.ijcard.2017.02.095
18. Taniwaki H, Ishimura E, Tabata T *et al.* Aortic calcification in haemodialysis patients with diabetes mellitus. *Nephrol Dial Transplant* 2005;**20**:2472–8. https://doi.org/10.1093/ndt/gfi039
19. Merjanian R, Budoff M, Adler S *et al.* Coronary artery, aortic wall, and valvular calcification in nondialyzed individuals with

type 2 diabetes and renal disease. *Kidney Int* 2003;**64**:263–71. https://doi.org/10.1046/j.1523-1755.2003.00068.x
20. Porter CJ, Stavroulopoulos A, Roe SD *et al.* Detection of coronary and peripheral artery calcification in patients with chronic kidney disease stages 3 and 4, with and without diabetes. *Nephrol Dial Transplant* 2007;**22**:3208–13. https://doi.org/10.1093/ndt/gfm377
21. Sutandar W. Vascular calcification of the aortic arch and peripheral artery in haemodialysis patients with and without diabetes mellitus. *Acta Med Indones* 2008;**40**:181–6.
22. Ishimura E, Okuno S, Kitatani K *et al.* Different risk factors for peripheral vascular calcification between diabetic and non-diabetic haemodialysis patients—importance of glycaemic control. *Diabetologia* 2002;**45**:1446–8.
23. Vincenti F, Hattner R, Amend WJ, Jr *et al.* Decreased secondary hyperparathyroidism in diabetic patients receiving hemodialysis. *JAMA* 1981;**245**:930–3. https://doi.org/10.1001/jama.1981.03310340020020
24. Cannata-Andia JB, Fernandez-Martin JL, Zoccali C *et al.* Current management of secondary hyperparathyroidism: a multicenter observational study (COSMOS). *J Nephrol* 2008;**21**:290–8.
25. Cannata-Andia JB, Fernandez-Martin JL, Locatelli F *et al.* Use of phosphate-binding agents is associated with a lower risk of mortality. *Kidney Int* 2013;**84**:998–1008. https://doi.org/10.1038/ki.2013.185
26. Fernandez-Martin JL, Carrero JJ, Benedik M *et al.* COSMOS: the dialysis scenario of CKD-MBD in Europe. *Nephrol Dial Transplant* 2013;**28**:1922–35. https://doi.org/10.1093/ndt/gfs418
27. Fernandez-Martin JL, Dusso A, Martinez-Camblor P *et al.* Serum phosphate optimal timing and range associated with patients survival in haemodialysis: the COSMOS study. *Nephrol Dial Transplant* 2019;**34**:673–81. https://doi.org/10.1093/ndt/gfy093
28. Souberbielle JC, Boutten A, Carlier MC *et al.* Inter-method variability in PTH measurement: implication for the care of CKD patients. *Kidney Int* 2006;**70**:345–50. https://doi.org/10.1038/sj.ki.5001606
29. Murakami R, Murakami S, Tsushima R *et al.* Glycaemic control and serum intact parathyroid hormone levels in diabetic patients on haemodialysis therapy. *Nephrol Dial Transplant* 2008;**23**:315–20. https://doi.org/10.1093/ndt/gfm639
30. Dan S, Aditya P, Samanta M *et al.* Effect of glycemic control on intact parathyroid hormone level in end stage renal disease patients on maintenance hemodialysis. *Diabetes Res Clin Pract* 2014;**105**:352–5. https://doi.org/10.1016/j.diabres.2014.04.002
31. Pabico RC, Rivero AJ, McKenna BA *et al.* Parathyroid hormone in patients with diabetes mellitus and end-stage renal disease on chronic haemodialysis. *Proc Eur Dial Transplant Assoc* 1983;**19**:221–6.
32. Massry SG, Coburn JW, Kleeman CR. Evidence for suppression of parathyroid gland activity by hypermagnesemia. *J Clin Invest* 1970;**49**:1619–29. https://doi.org/10.1172/JCI106379
33. Slatopolsky E, Mercado A, Morrison A *et al.* Inhibitory effects of hypermagnesemia on the renal action of parathyroid hormone. *J Clin Invest* 1976;**58**:1273–9. https://doi.org/10.1172/JCI108582
34. Fisher RS, Lipshutz W, Cohen S. The hormonal regulation of pyloric sphincter function. *J Clin Invest* 1973;**52**:1289–96. https://doi.org/10.1172/JCI107297
35. Pérez-Morales RE, Del Pino MD, Valdivielso JM *et al.* Inflammation in diabetic kidney disease. *Nephron* 2019;**143**:12–6. https://doi.org/10.1159/000493278
36. Danese MD, Kim J, Doan QV *et al.* PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. *Am J Kidney Dis* 2006;**47**:149–56. https://doi.org/10.1053/j.ajkd.2005.09.024
37. Jadoul M, Albert JM, Akiba T *et al.* Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2006;**70**:1358–66. https://doi.org/10.1038/sj.ki.5001754
38. Kaur R, Singh R. Mechanistic insights into CKD-MBD-related vascular calcification and its clinical implications. *Life Sci* 2022;**311**:121148. https://doi.org/10.1016/j.lfs.2022.121148
39. Salam S, Gallagher O, Gossiel F *et al.* Vascular calcification relationship to vascular biomarkers and bone metabolism in advanced chronic kidney disease. *Bone* 2021;**143**:115699. https://doi.org/10.1016/j.bone.2020.115699
40. Vadana M, Cecoltan S, Ciortan L *et al.* Parathyroid hormone induces human valvular endothelial cells dysfunction that impacts the osteogenic phenotype of valvular interstitial cells. *Int J Mol Sci* 2022;**23**:3776. https://doi.org/10.3390/ijms23073776
41. Purra S, Lone AA, Bhat MH *et al.* Cardiac structural and functional abnormalities in primary hyperparathyroidism. *J Endocrinol Invest* 2022;**45**:327–35. https://doi.org/10.1007/s40618-021-01645-x
42. Brown SJ, Ruppe MD, Tabatabai LS. The parathyroid gland and heart disease. *Methodist Debakey Cardiovasc J* 2017;**13**:49–54. https://doi.org/10.14797/mdcj-13-2-49
43. Carrasco-Ruiz MF, Ruiz-Rivera A, Soriano-Ursua MA *et al.* Global longitudinal strain is superior to ejection fraction for detecting myocardial dysfunction in end-stage renal disease with hyperparathyroidism. *World J Cardiol* 2022;**14**:239–49. https://doi.org/10.4330/wjc.v14.i4.239
44. Lamina C, Kronenberg F, Stenvinkel P *et al.* Association of changes in bone mineral parameters with mortality in haemodialysis patients: insights from the ARO cohort. *Nephrol Dial Transplant* 2020;**35**:478–87. https://doi.org/10.1093/ndt/gfz060
45. Al Salmi I, Bieber B, Al Rukhaimi M *et al.* Parathyroid hormone serum levels and mortality among hemodialysis patients in the Gulf Cooperation Council countries: results from the DOPPS (2012-2018). *Kidney360* 2020;**1**:1083–90. https://doi.org/10.34067/KID.0000772020
46. Molina P, Molina MD, Pallardo LM *et al.* Disorders in bone-mineral parameters and the risk of death in persons with chronic kidney disease stages 4 and 5: the PECERA study. *J Nephrol* 2021;**34**:1189–99. https://doi.org/10.1007/s40620-020-00916-9
47. Coen G, Manni M, Mantella D *et al.* Are PTH serum levels predictive of coronary calcifications in haemodialysis patients? *Nephrol Dial Transplant* 2007;**22**:3262–7. https://doi.org/10.1093/ndt/gfm370
48. Shoji T, Kawagishi T, Emoto M *et al.* Additive impacts of diabetes and renal failure on carotid atherosclerosis. *Atherosclerosis* 2000;**153**:257–8. https://doi.org/10.1016/S0021-9150(00)00529-3
49. Zimmermann J, Herrlinger S, Pruy A *et al.* Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999;**55**:648–58. https://doi.org/10.1046/j.1523-1755.1999.00273.x
50. Gutierrez OM, Mannstadt M, Isakova T *et al.* Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008;**359**:584–92. https://doi.org/10.1056/NEJMoa0706130

51. Hu X, Ma X, Luo Y *et al.* Elevation in fibroblast growth factor 23 and its value for identifying subclinical atherosclerosis in first-degree relatives of patients with diabetes. *Sci Rep* 2016;**6**:34696. https://doi.org/10.1038/srep34696
52. Bar L, Feger M, Fajol A *et al.* Insulin suppresses the production of fibroblast growth factor 23 (FGF23). *Proc Natl Acad Sci USA* 2018;**115**:5804–9. https://doi.org/10.1073/pnas.1800160115
53. David V, Martin A, Isakova T *et al.* Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. *Kidney Int* 2016;**89**:135–46. https://doi.org/10.1038/ki.2015.290
54. Lopez I, Rodriguez-Ortiz ME, Almaden Y. *et al.* Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 in vivo. *Kidney Int* 2011;**80**:475–82. https://doi.org/10.1038/ki.2011.107

Received: February 14, 2023; Editorial decision: April 17, 2023