Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population

Jürgen Floege[1], Joseph Kim[2], Elizabeth Ireland[2], Charles Chazot[3], Tilman Drueke[4], Angel de Francisco[5], Florian Kronenberg[6], Daniele Marcelli[7], Jutta Passlick-Deetjen[7], Guntram Schernthaner[8], Bruno Fouqueray[9], David C. Wheeler[10] on behalf of the ARO Investigators

[1]RWTH University of Aachen, Aachen, Germany, [2]Amgen Ltd, Uxbridge, UK, [3]Nephrocare Tassin, France, [4]Hopital Necker, Paris, France, [5]Hospital Universitario Valdecilla, Santander, Spain, [6]Innsbruck Medical University, Division of Genetic Epidemiology, Innsbruck, Austria, [7]Fresenius Medical Care, Bad Homburg, Germany, [8]Rudolfstiftung Hospital-Vienna, Vienna, Austria, [9]Amgen (Europe) GmbH, Zug, Switzerland and [10]University College London, UK

Correspondence and offprint requests to: Jürgen Floege, Div. Nephrology, RWTH University of Aachen, Germany;
E-mail: juergen.floege@rwth-aachen.de

Abstract

Background. A number of US observational studies reported an increased mortality risk with higher intact parathyroid hormone (iPTH), calcium and/or phosphate. The existence of such a link in a European haemodialysis population was explored as part of the Analysing Data, Recognising Excellence and Optimising Outcomes (ARO) Chronic Kidney Disease (CKD) Research Initiative.
Methods. The association between the markers of mineral and bone disease and clinical outcomes was examined in 7970 patients treated in European Fresenius Medical Care facilities over a median of 21 months. Baseline and time-dependent (TD) Cox regression were performed using Kidney Disease Outcomes Quality Initiative (KDOQI) target ranges as reference categories, adjusting for demographics, medical history, dialysis parameters, inflammation, medications and laboratory parameters. Fractional polynomial (FP) models were also used.
Results. Hazard ratio (HR) estimates from baseline analysis for iPTH were U-shaped [>600 pg/mL, HR = 2.10, 95% confidence interval (CI) 1.62–2.73; <75 pg/mL, HR = 1.46, 95% CI 1.17–1.83]. TD analysis confirmed the results for iPTH. Baseline analysis showed that calcium >2.75 mmol/L increased risk of death (HR = 1.70, 95% CI 1.19–2.42). TD analysis showed that both low (HR = 1.19, 95% CI 1.04–1.37) and high calcium (HR = 1.74, 95% CI 1.30–2.34) increased risk of death. Baseline analysis for phosphate showed a U-shaped pattern (<1.13 mmol/L, HR = 1.18, 95% CI 1.01–1.37; >1.78 mmol/L, HR = 1.32, 95% CI 1.13–1.55). TD analysis confirmed the results for phosphate <1.13 mmol/L. HR estimates were higher in patients with diabetes *versus* those without diabetes for baseline analysis only (P-value = 0.014). FP analysis confirmed the results of baseline and TD analyses.

Conclusion. Patients with iPTH, calcium and phosphate levels within the KDOQI target ranges have the lowest risk of mortality compared with those outside the target ranges.

Keywords: calcium; KDOQI; mineral bone disorders; parathyroid hormone; phosphate

Introduction

Over the past decade, a number of large observational studies have evaluated whether markers of chronic kidney disease–mineral and bone disorder (CKD–MBD) determine long-term mortality in haemodialysis (HD) patients [1–6]. These studies, mainly from the USA, generally found higher levels of intact parathyroid hormone (iPTH), calcium and/or phosphate to be associated with an increased risk of mortality.

Based on these findings and supplemented by expert opinion, the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI™) published clinical practice guidelines in 2003. The guidelines provided recommended target ranges for various markers of MBD, such as iPTH, total serum calcium and serum phosphate [7]. The KDOQI guidelines were widely adopted throughout Europe despite possible differences in patient characteristics and practice patterns between Europe and the USA [8–10]. Furthermore, it is unclear whether achieved target levels of soluble markers of MBD effect outcomes in the European HD population as had been previously shown for the US HD population.

The Analysing Data, Recognising Excellence and Optimising Outcomes (ARO) CKD Research Initiative began in 2007 in an effort to better understand the practice of

care and improve patient outcomes in European HD patients. A unique strength of the ARO CKD Research Initiative is the inclusion of Eastern European populations who have largely been excluded in previous studies (authors' unpublished data). The aim of the present analysis was to examine the relation between levels of soluble markers of MBD (iPTH, total serum calcium and serum phosphate) and long-term mortality in this population.

Materials and methods

Study population

This study was carried out in accordance with the ethical standards of the relevant committees on human experimentation in the individual institutes and countries involved, and also with the Declaration of Helsinki 1975, as revised in 2000. Details of the rationale and methods of the study are described elsewhere (de Francisco *et al.*, submitted for publication). Briefly, the investigated population ($n = 11\,153$) consisted of randomly selected patients who underwent HD therapy between 1 January 2005 and 31 December 2006 at a participating European Fresenius Medical Care (EU-FME) dialysis facility from 11 countries: Czech Republic, France, Hungary, Italy, Poland, Portugal, Slovakia, Slovenia, Spain, Turkey and the UK. Patients were classified as incident if they were on HD therapy for <6 months at the time of enrolment; patients were otherwise classified as prevalent.

We excluded 1352 patients from centres which had missing data on key dialysis parameters, 90% of which had missing baseline Kt/V or actual blood flow. UK patients were excluded because information was missing on all medications ($n = 838$). Patients with a history of parathyroidectomy ($n = 173$), those who underwent parathyroidectomy during the course of follow-up ($n = 44$) and patients who had a history of cinacalcet use ($n = 247$) were excluded to remove possible confounding effects. Incident patients who remained in the study for <3 months ($n = 529$) were excluded as their risk profile for mortality could differ from that of patients who had survived the initial phase of dialysis treatment. A total of 7970 patients were included in the present analysis.

CKD–MBD parameters

Individual measures for iPTH, calcium and phosphate were averaged over the first quarter of follow-up and were then divided into clinically relevant categories. The KDOQI target ranges for each MBD marker were used as the reference category: iPTH [150–300 pg/mL (15.9–31.8 pmol/L)], total serum calcium (2.10–2.37 mmol/L) and serum phosphate (1.13–1.78 mmol/L). Although second-generation assays were used for iPTH measurements, a standard assay was not used across all ARO facilities. Approximately 75% of iPTH measures captured in ARO were assayed with the Elecsys® System (Roche Diagnostics, Indianapolis, IN, USA) or with an Immulite Assay (Diagnostic Products Corporation, Los Angeles, CA, USA).

Covariates of interest

Patient demographic characteristics available for this study included age, gender, country of origin, smoking history and body mass index (BMI). Information on medical history included aetiology of CKD, history of cardiovascular disease (CVD) (defined as peripheral vascular disease, congestive heart failure, coronary artery disease, myocardial infarction, angina, cerebrovascular accident or transient ischaemic attack), history of diabetes (defined as a recorded history of diabetes, diagnosis of diabetic nephropathy or history of diabetic medications use at baseline) and history of cancer.

Detailed information was available on dialysis vintage (incident/prevalent), dialysis access [arteriovenous (AV) fistula, AV graft, temporary venous catheter and permanent venous catheter], actual blood flow and dialysis adequacy (Kt/V). All dialysers were of the single-use variety. Information on dialyser type was not available.

Data on medications included phosphate binders, oral vitamin D sterols, anti-aggregants, antihypertensives [including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)] and oral anticoagulants. Information on intravenous vitamin D was not available. Laboratory data included markers of inflammation [C-reactive protein (CRP) and albumin], haemoglobin, ferritin, total cholesterol and blood leucocyte count.

Study outcomes

All-cause mortality was the primary outcome of interest in this study. CVD-related mortality was considered as a secondary outcome of interest. Patients were considered to be lost to follow-up if they left a dialysis facility for any reason and did not return to the same facility within 45 days.

Statistical analysis

Variables, which followed a normal distribution, were described using mean and standard deviation; median and interquartile range (IQR) were otherwise reported. The association between categories of iPTH and patient characteristics was assessed using a linear model for continuous variables and a chi-square test for trend for categorical variables.

Crude and adjusted hazard ratios (HR) for mortality were determined using baseline (i.e. fixed-covariate) Cox regression models. The assumption of proportional hazards was checked graphically using a log-minus-log Kaplan–Meier plot. The multivariable Cox analysis adjusted for demographic characteristics (age, gender, country, BMI, smoking status), medical history (CKD aetiology, diabetes, CVD, cancer), dialysis vintage, dialysis parameters (vascular access type, Kt/V, blood flow), markers of inflammation (serum albumin, CRP), CVD-related medications (ACE inhibitors, ARBs, other antihypertensive drugs, oral anticoagulants, anti-aggregants), MBD-related medications (oral vitamin D, phosphate binders) and laboratory parameters (iPTH, calcium, phosphate, haemoglobin, ferritin, cholesterol, blood leucocyte counts). Quantitative variables (i.e. laboratory parameters and dialysis prescription) were averaged over the first quarter of study follow-up and categorized into clinically meaningful intervals or into quartiles. The adjustment also included hospitalization or change in vascular access type that may have occurred during the first quarter of follow-up.

Time-dependent Cox analysis was performed to evaluate any potential effects of updating exposure and selected covariates over time. The analysis included all of the covariates adjusted for in the baseline analysis except for serum albumin, CRP, oral vitamin D use, phosphate binder use, ferritin, hospitalization and change in vascular access type which were included in the Cox model as time-dependent covariates. Missing data in the time-dependent models were handled using last observation carried forward (LOCF). To evaluate the presence of a possible non-linear relation between markers of MBD and mortality, we repeated both the baseline Cox analysis and the time-dependent Cox analysis using fractional polynomial (FP) analysis [11,12]. Casewise deletion was applied in all analyses involving FP. We carried out a formal test of interaction to evaluate whether history of diabetes modifies the relation between MBD markers and mortality.

All statistical analyses were performed using Stata SE (version 10, College Station, TX, USA) and were reproduced independently by a second statistician. A P-value of <0.05 was considered to be statistically significant.

Results

Consequent to the open-cohort study design, incident patients had a shorter duration of follow-up (median 12.6 months, IQR 7.6–20.0 months) than prevalent patients (median 23.9 months, IQR 13.5–23.9 months). Of the 7970 patients selected for analysis, 1477 (19%) died, 399 (5%) underwent a successful renal transplant, 884 (11%) were lost to follow-up and 5210 (65%) completed the study. Overall, patients were followed up for a median of 20.9 months (IQR 9.8–23.9 months) and contributed a total of 11 304 patient-years.

Table 1. Patient characteristics by baseline iPTH category (*n* = 7970)

Patient characteristics	<75 pg/mL (*n* = 670)	75–<150 pg/mL (*n* = 833)	150–300 pg/mL (*n* = 1092)	>300–600 pg/mL (*n* = 890)	>600 pg/mL (*n* = 461)	Missing (*n* = 4024)	P-value*
Age (years)	66.6 ± 14.4	65.8 ± 14.1	65.7 ± 14.0	63.2 ± 15.0	61.2 ± 15.0	61.4 ± 15.1	<0.01
Gender							
Female	314 (46.9)	325 (39.0)	403 (36.9)	381 (42.8)	222 (48.2)	1711 (42.5)	0.56
Male	356 (53.1)	508 (61.0)	689 (63.1)	509 (57.2)	239 (51.8)	2313 (57.5)	
Dialysis vintage							
Prevalent	471 (70.3)	562 (67.5)	692 (63.4)	584 (65.6)	337 (73.1)	2536 (63.0)	0.92
Incident	199 (29.7)	271 (32.5)	400 (36.6)	306 (34.4)	124 (26.9)	1488 (37.0)	
Calcium (mmol/L)	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.3	2.2 ± 0.2	<0.01
Phosphate (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	1.6 ± 0.4	1.7 ± 0.4	1.5 ± 0.4	<0.01
History of diabetes	201 (30.0)	237 (28.5)	292 (26.7)	209 (23.5)	79 (17.1)	1048 (26.0)	<0.01
History of CVD	562 (83.9)	667 (80.1)	854 (78.2)	686 (77.1)	352 (76.4)	2785 (69.2)	<0.01
History of cancer	63 (9.4)	63 (7.6)	66 (6.0)	58 (6.5)	29 (6.3)	193 (4.8)	0.02
CKD aetiology							
Hypertension/vascular	101 (15.1)	129 (15.5)	148 (13.6)	137 (15.4)	59 (12.8)	489 (12.2)	0.40
Glomerulonephritis	98 (14.6)	128 (15.4)	158 (14.5)	119 (13.4)	82 (17.8)	719 (17.9)	0.65
Diabetic nephropathy	109 (16.3)	129 (15.5)	188 (17.2)	127 (14.3)	51 (11.1)	521 (12.9)	0.03
Tubulointerstitial	87 (13.0)	119 (14.3)	141 (12.9)	109 (12.2)	71 (15.4)	582 (14.5)	0.82
Polycystic kidney disease	32 (4.8)	46 (5.5)	64 (5.9)	55 (6.2)	36 (7.8)	202 (5.0)	0.04
Miscellaneous	24 (3.6)	19 (2.3)	42 (3.8)	41 (4.6)	22 (4.8)	162 (4.0)	0.04
Unknown	219 (32.7)	263 (31.6)	351 (32.1)	302 (33.9)	140 (30.4)	1349 (33.5)	0.95
Vascular access							
Fistula	461 (68.8)	619 (74.3)	787 (72.1)	646 (72.6)	318 (69.0)	2544 (63.2)	0.99
Graft	30 (4.5)	28 (3.4)	47 (4.3)	39 (4.4)	33 (7.2)	42 (1.0)	0.04
Temporary catheter	80 (11.9)	79 (9.5)	110 (10.1)	86 (9.7)	43 (9.3)	411 (10.2)	0.20
Permanent catheter	64 (9.6)	59 (7.1)	71 (6.5)	71 (8.0)	41 (8.9)	286 (7.1)	0.77
Other/missing	35 (5.2)	48 (5.8)	77 (7.1)	48 (5.4)	26 (5.6)	741 (18.4)	0.85
Haemoglobin (g/dL)	11.3 ± 1.6	11.3 ± 1.5	11.5 ± 1.5	11.5 ± 1.5	11.4 ± 1.5	10.8 ± 1.5	0.04
Ferritin (ug/L)	407 (224, 746)	390 (204, 677)	362 (185, 617)	322 (145, 549)	334 (166, 540)	531 (227, 943)	<0.01
Total cholesterol (mmol/L)	4.4 ± 1.1	4.3 ± 1.1	4.4 ± 1.1	4.4 ± 1.1	4.4 ± 1.0	4.5 ± 1.1	0.47
C-reactive protein (mg/L)	10 (4,22)	8 (3, 18)	7 (3, 15)	7 (3, 16)	7 (3, 15)	9 (4, 19)	<0.01
Albumin (g/L)	38 ± 5	39 ± 6	40 ± 6	39 ± 6	41 ± 7	38 ± 5	<0.01
Antihypertensive drugs	165 (24.6)	241 (28.9)	324 (29.7)	263 (29.6)	122 (26.5)	933 (23.2)	0.28
ACE inhibitors	106 (15.8)	173 (20.8)	219 (20.1)	179 (20.1)	87 (18.9)	590 (14.7)	0.22
Anti-aggregants	126 (18.8)	191 (22.9)	233 (21.3)	195 (21.9)	95 (20.6)	562 (14.0)	0.56
Oral vitamin D sterols	117 (17.5)	152 (18.2)	261 (23.9)	260 (29.2)	94 (20.4)	586 (14.6)	<0.01
Phosphate binders							
None	385 (57.5)	491 (58.9)	610 (55.9)	476 (53.5)	248 (53.8)	2742 (68.1)	0.03
Calcium-containing only	211 (31.5)	232 (27.9)	297 (27.2)	207 (23.3)	89 (19.3)	961 (23.9)	<0.01
Other type	74 (11.0)	110 (13.2)	185 (16.9)	207 (23.3)	124 (26.9)	321 (8.0)	<0.01
Hospitalization	118 (17.6)	126 (15.1)	150 (13.7)	110 (12.4)	64 (13.9)	526 (13.1)	<0.01
Vascular access type change	94 (14.0)	118 (14.2)	147 (13.5)	124 (13.9)	50 (10.8)	685 (17.0)	0.22

*P-value indicates test for linear trend for continuous variables and chi-square test for trend for nominal variables. The missing category was excluded in the tests for trend. Mean ± standard deviation are reported if the variable is normally distributed; median (interquartile range) are reported otherwise. Categorical variables are reported using *n* (%). Incident dialysis was defined as <6 months of dialysis treatment.
ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; CVD, cardiovascular disease.

In our study population (Table 1), patients with lower levels of iPTH were more likely to be older and have a history of diabetes, CVD or cancer compared to those with higher levels of iPTH. They were also more likely to have higher serum calcium levels but lower phosphate levels during the first quarter of follow-up. Patients with lower iPTH had higher ferritin and CRP levels as well as lower albumin levels, consistent with an activated inflammatory response. They were also more likely to have been hospitalized during the first quarter of follow-up.

iPTH and the risk of mortality

In the adjusted baseline Cox analysis, the relative risk estimates for mortality by iPTH category showed a U-shaped relation (Table 2), where patients with iPTH levels outside the KDOQI target range (150–300 pg/mL) had a greater risk of death compared to those who were within target range. Patients in the highest iPTH category (>600 pg/mL) experienced a 2-fold increase in risk [HR 2.10; 95% confidence interval (CI) 1.62–2.73, P < 0.001] compared to patients who were within target range, whereas those in the lowest iPTH category (<75 pg/mL) had almost a 50% greater risk of death (HR 1.46; 95% CI 1.17–1.83, P = 0.001). The overall U-shaped pattern was preserved in the adjusted time-dependent analysis.

We found evidence of an interaction between history of diabetes, iPTH and mortality in the baseline Cox model, in which the relative risk estimates were higher among patients with diabetes than those without diabetes (P = 0.014). Patients with diabetes in the highest iPTH category had nearly a 3-fold increase in risk of death compared to

Table 2. Results of baseline and time-dependent Cox regression for all-cause mortality in the ARO population (n = 7970)

MBD marker	Baseline analysis		Time-dependent analysis	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
iPTH (pg/mL)				
<75	2.02 (1.63–2.51)	1.46 (1.17–1.83)	2.10 (1.79–2.45)	1.46 (1.24–1.71)
≥75–<150	1.46 (1.18–1.82)	1.31 (1.05–1.64)	1.45 (1.22–1.71)	1.18 (1.00–1.40)
≥150–≤300	1.00	1.00	1.00	1.00
>300–≤600	1.20 (0.96–1.50)	1.43 (1.14–1.79)	1.08 (0.90–1.31)	1.28 (1.06–1.55)
>600	1.51 (1.17–1.94)	2.10 (1.62–2.73)	1.21 (0.97–1.52)	1.53 (1.22–1.92)
Total calcium (mmol/L)				
<2.10	1.11 (0.95–1.31)	0.98 (0.83–1.16)	1.37 (1.20–1.58)	1.19 (1.04–1.37)
≥2.10–≤2.37	1.00	1.00	1.00	1.00
>2.37–≤2.75	1.03 (0.89–1.19)	1.05 (0.90–1.22)	0.96 (0.84–1.09)	1.06 (0.93–1.21)
>2.75	1.51 (1.08–2.12)	1.70 (1.19–2.42)	1.51 (1.13–2.00)	1.74 (1.30–2.34)
Phosphate (mmol/L)				
<1.13	1.45 (1.25–1.68)	1.18 (1.01–1.37)	1.83 (1.62–2.06)	1.31 (1.15–1.48)
≥1.13–≤1.78	1.00	1.00	1.00	1.00
>1.78	0.99 (0.85–1.16)	1.32 (1.13–1.55)	0.83 (0.71–0.95)	1.05 (0.91–1.22)

Adjusted for demographics (age, gender, country, BMI, smoking status), medical history (CKD aetiology, history of diabetes, history of CVD, history of Cancer), dialysis parameters (vintage, vascular access type, Kt/V, blood flow), markers of inflammation (serum albumin, CRP), CVD medications (antihypertensive drugs, ACE inhibitors, oral anticoagulants, anti-aggregants), BMD medications (vitamin D, phosphate binders) and other lab parameters (PTH, calcium, phosphate, Hb, ferritin, cholesterol, blood leucocytes) and miscellaneous (hospitalization, change in vascular access type). Serum albumin, CRP, oral vitamin D use, phosphate binder use, ferritin, hospitalization and change in vascular access type were updated over time in the time-dependent models.

patients who were within the target range (HR 2.89, 95% CI 1.73–4.82, P < 0.001). Conversely, for patients without diabetes, the increase in risk of death was <2-fold (HR 1.85, 95% CI 1.36–2.52, P < 0.001). Moreover, patients with diabetes in the lowest iPTH category had almost a 2-fold increase in the risk of mortality (HR 1.89, 95% CI 1.27–2.81, P = 0.002) than patients without diabetes, whose relative risk estimates were attenuated (HR 1.29, 95% CI 0.98–1.70, P = 0.070). In contrast to the baseline analysis, the test for interaction between diabetes, iPTH and mortality in the time-dependent analysis was not statistically significant (P = 0.233). Results of the Cox regression models based on FP analysis confirmed the overall trends in the relative risk estimates for iPTH (Figures 1a and 2). The FP analysis also showed an attenuation of effect in the time-dependent analysis with higher values of iPTH.

Serum calcium and the risk of mortality

With regard to the adjusted baseline analysis for total serum calcium, we found that patients with high serum calcium levels (>2.75 mmol/L) had a higher risk of death than those who were within target range (2.10–2.37 mmol/L) (HR 1.70, 95% CI 1.19–2.42, P = 0.003). The results for high calcium levels in the adjusted time-dependent analysis were consistent with those found in the baseline analysis (HR 1.74, 95% CI 1.30–2.34, P < 0.001). Although the adjusted baseline analysis for low serum calcium levels (<2.10 mmol/L) showed no effect on the risk of death (HR 0.98, 95% CI 0.83–1.16, P = 0.808), the time-dependent analysis showed that patients with low calcium levels had a slightly higher risk of death than those who were within target range (HR 1.19, 95% CI 1.04–1.37, P = 0.015). The test for interaction between history of

diabetes, mortality and total serum calcium was not significant in the baseline analysis (P-value = 0.604) as well in the time-dependent analysis (P-value = 0.908). The time-dependent analysis for total serum calcium appeared to be more accentuated in the regions outside the KDOQI target range. The FP analysis confirmed the overall trends in the relative risk estimates for total calcium (Figure 1b).

Serum phosphate and the risk of mortality

The overall pattern of results for serum phosphate was similar to that for iPTH showing a U-shaped pattern in the adjusted relative risk estimates. In the baseline Cox analysis, patients with low serum phosphate as well as those with high serum phosphate had an increased risk of death compared to those who were within target range (1.13–1.78 mmol/L) (HR 1.18, 95% CI 1.01–1.37, P = 0.033 and HR 1.32, 95% CI 1.13–1.55, P = 0.001, respectively) after covariate adjustment. The adjusted time-dependent analysis was consistent with the baseline-adjusted analysis for low phosphate (HR 1.31, 95% CI 1.15–1.48, P < 0.001), but not for high phosphate levels (HR 1.05, 95% CI 0.91–1.22, P = 0.495). The test for interaction between history of diabetes, mortality and serum phosphate was marginally significant in the baseline analysis (P-value = 0.044), but not in the time-dependent analysis (P-value = 0.831). The results of the FP model confirmed the U-shaped association between serum phosphate and mortality in the baseline Cox model (Figure 1c).

Discussion

Given that most previous epidemiological studies in large CKD patient cohorts have been performed in the USA,

our findings help to clarify associations between MBD markers and mortality in the wider European HD community, including patients from Western Europe and the more rarely studied patients from Eastern Europe. For the three MBD markers considered, the overall findings from this study show that the lowest risk of mortality was among patients whose MBD markers were within the KDOQI target range.

Our results should be considered in the context of other controversial studies [2,4–6]. Results from previous studies evaluating the effect of serum calcium on mortality using

baseline Cox analysis have been inconsistent (Table 3). In contrast, nearly all studies based on time-dependent analysis have shown that low calcium levels increase the risk of mortality. Thus, a high calcium level seems to have strong prognostic value for long-term mortality (as evidenced by our baseline analysis), whereas a low calcium level has little prognostic value despite its positive association with mortality, when all values of calcium are updated over time.

The evidence for serum phosphate seems to suggest that either a low or a high level is a risk factor for mortality (Table 3). With respect to low phosphate levels, this seems clinically plausible since a low serum phosphate is a marker for malnutrition, a known predictor of mortality [13]. However, we found that the relation persisted even after adjustment for serum albumin [14], which suggests the possibility that the effect of serum phosphate on mortality is acting through another biological mechanism besides nutritional status. Nevertheless, our findings for serum phosphate support the current KDOQI target range (1.13–1.78 mmol/L) as patients who were within the target range had the lowest risk of mortality compared to those with phosphate levels outside the range.

Perhaps the most notable finding of this study was the U-shaped association between iPTH and mortality. In contrast to most previous studies which have reported that high iPTH (but not low iPTH) increases the risk of mortality (Table 3), our data suggest that low iPTH levels (<75 pg/mL) are a potential risk factor for mortality. This has been previously reported by Kalantar-Zadeh and colleagues [4], although the result was significant only in their time-dependent Cox model and not in their baseline model. Another, albeit much smaller, study ($n = 345$) published by Avram and colleagues showed that patients with iPTH <65 pg/mL ($n = 67$) had a higher risk of death than
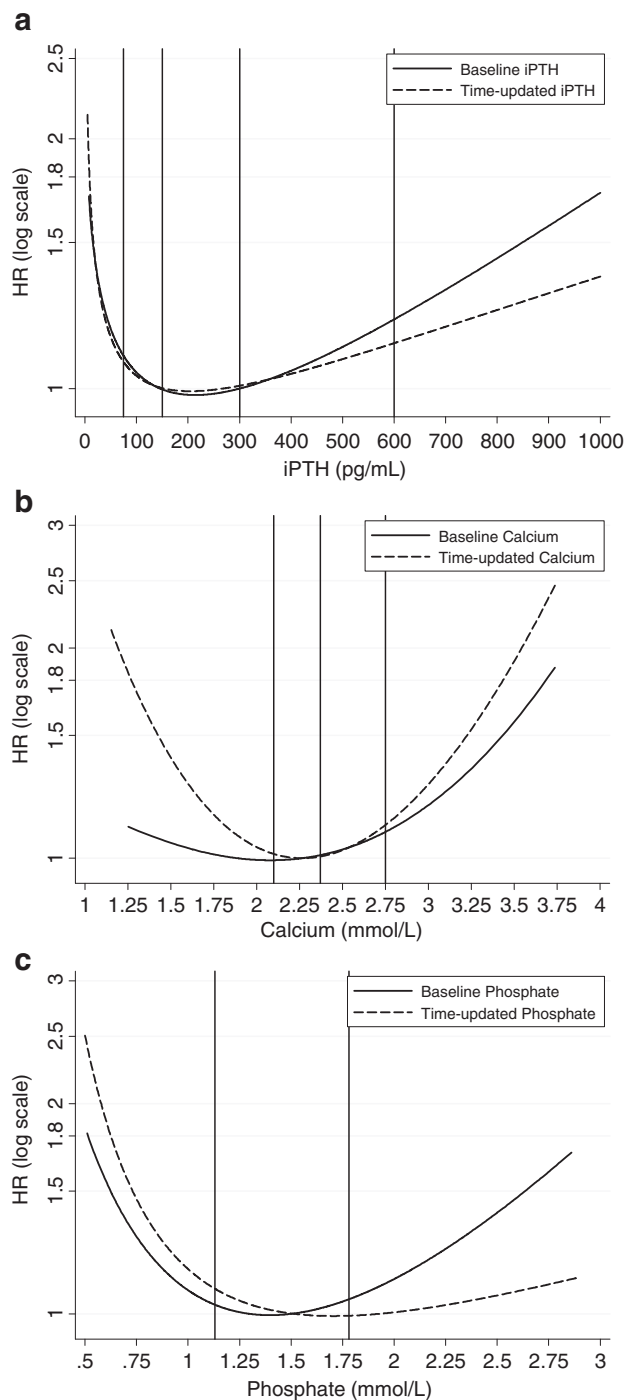
Fig. 1. (a) Relative risk of all-cause mortality for iPTH comparing baseline *versus* time-dependent Cox regression using fractional polynomials. Values <0.5% percentile and >99.5% percentile were removed from both models (baseline model = 29 observations removed and time-dependent model = 838 observations removed). iPTH values >1000 pg/mL not shown. Baseline model: log (HR) = $-0.28 \text{iPTH}^{0.5} + 0.04 \text{iPTH}^{0.5} \log \text{iPTH} + \beta_k \times_k$ (P = 0.001); time-dependent model: log (HR) = $-0.38 \log \text{iPTH} + 0.05 \text{iPTH}^{0.5} + \beta_k \times_k$ (P < 0.001). (b) Relative risk of all-cause mortality for total serum calcium comparing baseline *versus* time-dependent Cox regression using fractional polynomials. Calcium values <1.15 mmol/L and >3.74 mmol/L not shown. Baseline model: log (HR) = $-0.23 \text{ calcium}^2 + 0.19 \text{ calcium}^2 \log \text{ calcium} + \beta_k \times_k$ (P = 0.82); time-dependent model: log (HR) = $-4.10 \text{ calcium}^1 + 2.26 \text{ calcium}^1 \log \text{ calcium} + \beta_k \times_k$ (P = 0.015). (c) Relative risk of all-cause mortality for serum phosphate comparing baseline *versus* time-dependent Cox regression using fractional polynomials. Baseline model: log (HR) = $-6.48 \text{ phosphate}^{0.5} + 2.78 \text{ phosphate}^{0.5} \log \text{ phosphate} + \beta_k \times_k$ (P = 0.027); time-dependent model: log (HR) = $5.18 \text{ phosphate}^{-0.5} + 1.98 \log \text{ phosphate} + \beta_k \times_k$ (P < 0.001). (a–c) Adjusted for demographics (age, gender, country, body mass index, smoking status), medical history (chronic kidney disease aetiology, history of diabetes, history of CVD and history of cancer), dialysis parameters [dialysis vintage, vascular access type, dialysis adequacy (Kt/V) and blood flow], markers of inflammation (serum albumin and CRP), CVD medications (antihypertensives, angiotensin-converting enzyme inhibitors, oral anticoagulants and anti-aggregants), mineral and bone disorder medications (oral vitamin D and phosphate binders), calcium, phosphate, iPTH, haemoglobin, ferritin, cholesterol, blood leucocytes, hospitalization, and change in vascular access type. In the time-dependent model, serum albumin, CRP, vitamin D, phosphate binders, hospitalization and change in vascular access were treated as time-dependent covariates.
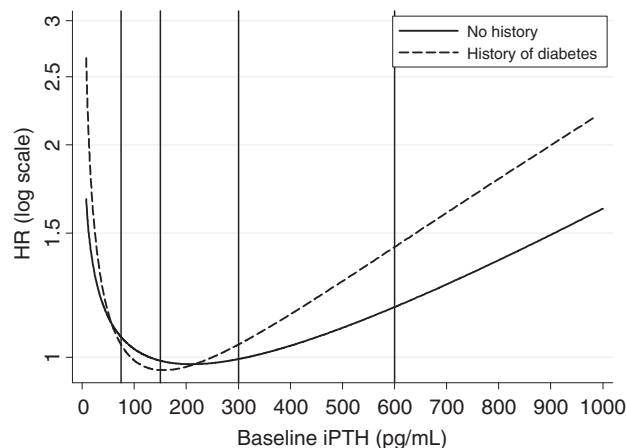
Fig. 2. Relative risk of all-cause mortality for iPTH baseline Cox regression using fractional polynomials in patients with diabetes and without diabetes. Values <0.5% percentile and >99.5% percentile were removed from both models (no history of diabetes model = 22 observations removed; history of diabetes model = 7 observations removed). Number of observations used: no history of diabetes model = 2906; history of diabetes model = 1011. iPTH values >1000 pg/mL not shown. No history of diabetes: $\log(HR) = -0.23 \log iPTH + 0.001 iPTH^1 + \beta_k \times_k$ (P = 0.03); history of diabetes model: $\log(HR) = -0.70 \log iPTH + 0.11 iPTH^{0.5} + \beta_k \times_k$ (P = 0.03). Adjusted for demographics (age, gender, country, body mass index, smoking status), medical history (chronic kidney disease aetiology, history of diabetes, history of CVD and history of cancer), dialysis parameters [dialysis vintage, vascular access type, dialysis adequacy (Kt/V) and blood flow], markers of inflammation (serum albumin and C-reactive protein), CVD medications (antihypertensives, angiotensin-converting enzyme inhibitors, oral anticoagulants and anti-aggregants), mineral and bone disorder medications (oral vitamin D and phosphate binders), calcium, phosphate, haemoglobin, ferritin, cholesterol, blood leucocytes, hospitalization, and change in vascular access type.

patients with iPTH levels >200 pg/mL [15]. Furthermore, Stevens and colleagues showed patients with iPTH levels <257 pg/mL in association with high serum calcium and phosphate had a lower chance of survival compared with patients with iPTH levels >257 pg/mL and well-controlled serum calcium and phosphate levels [16]. Interestingly, our findings agree with those from the CORES study (Prof. Cannata, personal communication) that showed reduced and elevated iPTH (<150 pg/mL and >500 pg/ml, respectively), as well as albumin-corrected calcium and phosphorus levels were associated with an increase in all-cause mortality based on the results of time-dependent analysis.

The findings of our FP analysis confirmed those of the categorical analysis, showing that low iPTH is an important risk factor for mortality. Furthermore, the analysis suggests that this is not entirely explained by the use of arbitrary cutoff points in the categorical analysis. Overall, the trends in the adjusted relative risk estimates for CVD-related mortality were consistent with those for all-cause mortality (data not shown).

The lack of consistency between this study and other studies with respect to the association between very low iPTH levels and mortality may be due, in part, to the covariates adjusted for in the multivariable analysis [2,4,6]. For instance, Block and colleagues [2] did not include smoking status, history of CVD, history of cancer, vascular access type or CRP as covariates in their multivariable analysis. Another reason for the discrepancy may have been the

potential differences in patient characteristics and practice patterns between the USA and Europe. It is unlikely, however, to be a result of variation inherent in the assay [17] since variability in patients with a low iPTH was minimal.

Results from previous studies that have evaluated the association between iPTH and bone histology have indicated that an iPTH level <79.7 pg/mL or as low as 57 pg/mL [median 142 pg/mL (95% CI 57–570 pg/mL)] is indicative of low bone turnover or adynamic bone disease [18,19]. Some recent studies have suggested that adynamic bone disease is the most common type of bone disorder in HD patients [20,21]. Adynamic bone disease, in turn, often results in hypercalcaemia, given the impaired capacity of the bone to buffer calcium loads [22]. This impaired calcium-buffering capacity has been associated with accelerated cardiovascular calcification in a cross-sectional study [19] as well as in a recent prospective clinical trial reported by Ok *et al.* at the American Society of Nephrology Renal Week 2008 (Abstract LB-005 available at: http://www.abstracts2view.com/asn/). Given that any cardiovascular calcification in dialysis patients is a potent predictor of mortality [23–25], our study further strengthens the assumption that over-suppression of iPTH is associated with low turnover bone disease, cardiovascular calcification and mortality. Excessively high iPTH levels, in contrast, may stimulate excessive calcium release from bone and thereby initiate a similar cascade of accelerated calcification and mortality [26,27].

Our baseline Cox analysis of iPTH suggests a possible link between glucose metabolism, bone metabolism and long-term mortality in HD patients. We found that the risk of mortality associated with low iPTH levels was particularly pronounced among patients with diabetes, who had nearly twice the risk of death compared to those without diabetes. Previous studies have reported an interaction between bone and diabetic nephropathy as a potential cause of lower bone turnover [28]. In addition, there is clinical evidence that glycosylated haemoglobin levels >6.5% predispose to very low serum iPTH levels in patients with diabetes [29]. Finally, in dialysis patients who switch from a calcium-containing to a calcium-free phosphate binder, iPTH levels increase to a significantly greater extent in individuals without diabetes compared with those with diabetes [30]. Previous studies have reported an interaction between bone as well as parathyroid glands and diabetes as a potential cause of lower bone turnover [31]. These observations imply that patients with diabetes, in particular those with suboptimal glycemic control, are predisposed to low turnover bone disease. Interestingly, transgenic mouse models also show that low serum osteocalcin levels, as observed in adynamic bone disease, are a cause of glucose intolerance and insulin resistance, highlighting the possibility that adynamic bone disease may exacerbate diabetes [32].

A key strength of this study is that serum calcium, serum phosphate and iPTH were analysed as a continuous variable using the method of FP [11]. This has several advantages over analyses carried out using categories of exposure: the cutoff points used in categorical data analysis are chosen arbitrarily, which also assumes that all values within the cat-

Table 3. Qualitative overview of published studies on MBD and mortality in various large HD populations

	HD population	Risk of mortality in HD patients with serum levels above or below study reference category					
		Low calcium	High calcium	Low phosphate	High phosphate	Low iPTH	High iPTH
Baseline analysis							
Block *et al.* 2004 [2]*	USA (n = 40 538)	↓	↑	=	↑	=	↑
Kalantar-Zadeh *et al.* 2006 [4]†	USA (n = 58 058)	↓	↑	↑	↑	=	↑
Wald *et al.* 2008 [5]‡	USA (n = 1846)	=	=	=	↑	=	=
Tentori *et al.* 2008 [6]§	Worldwide (n = 25 529)	↑	↑	↑	↑	=	↑
ARO**	Europe (n = 7970)	=	↑	↑	↑	↑	↑
Time-dependent analysis							
Kalantar-Zadeh *et al.* 2006 [4]†	USA (n = 58 058)	↑	↑	↑	↑	↑	↑
Wald *et al.* 2008 [5]‡	USA (n = 1846)	↑	↑	=	↑	=	=
ARO**	Europe (n = 7970)	↑	↑	↑	=	↑	↑

Time-dependent analysis was not carried out in Block *et al.* [2] or in Tentori *et al.* [6]. Reference categories differ slightly across studies. Kalantar-Zadeh *et al.* [4] reported corrected serum calcium; all others reported total serum calcium. =, no difference in any of the estimates above or below the reference category; ↓, decreased relative risk (RR) in at least one RR; ↑, increased RR in at least one RR.
*Multivariable analysis adjusted for age, gender, race or ethnicity, diabetes, dialysis vintage, body weight, urea reduction ratio, serum albumin, creatinine, pre-dialysis blood urea nitrogen, bicarbonate, cholesterol, haemoglobin, ferritin and aluminium.
†Multivariable analysis adjusted for indicators of osteodystrophy (calcium, phosphate, Ca × P, iPTH or alkaline phosphatase) as the predicting variable, entry quarter as the covariate and mortality as the outcome variable, age, gender, race and ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marriage status, and standardized mortality ratio of the dialysis clinic during entry quarter, continuous values of Kt/V dialysate calcium concentration, and administered doses of each vitamin D analogue within each calendar quarter, and 11 indicators of nutritional status and inflammation (including time-varying BMI), averaged dose of recombinant human erythropoietin in each calendar quarter, serum albumin, normalized protein nitrogen appearance or normalized protein catabolic rate, serum total iron-binding capacity, serum creatinine, serum bicarbonate, serum ferritin, blood haemoglobin, peripheral white blood cell count, and lymphocyte percentage.
‡Multivariable analysis adjusted for age, sex, race (African American *vs* non-African American), time on dialysis therapy at time of randomization (evaluated as > or < the median value of 3.7 years), presence of diabetes, co-morbidity measured using the Index of Co-existent Diseases (excluding diabetes), baseline albumin level and an interaction term between baseline albumin level and time from randomization. Data were also adjusted for presence of any residual kidney function at the time of randomization (defined as urea clearance >0), dose intervention group, and flux intervention group, because of the potential for these variables to affect serum mineral markers and the outcomes of interest.
§Multivariable analysis adjusted for age, sex, race, years with end-stage renal disease, BMI, diabetes mellitus, coronary artery disease, congestive heart failure, other CVD, hypertension diagnosis, cerebrovascular disease, peripheral arterial disease, lung disease, cancer (other than skin), gastrointestinal bleeding, neurological disease, psychiatric disorder, prior parathyroidectomy, recurrent cellulitis.
**Multivariable analysis adjusted for demographic characteristics (age, gender, country, BMI, smoking status), medical history (chronic kidney disease aetiology, diabetes, CVD, cancer), dialysis vintage, dialysis parameters (vascular access type, Kt/V, blood flow), markers of inflammation (serum albumin, C-reactive protein), CVD-related medications (antihypertensive drugs, angiotensin-converting enzyme inhibitors, oral anticoagulants, anti-aggregants), MBD-related medications (vitamin D, phosphate binders), and laboratory parameters (iPTH, calcium, phosphate, haemoglobin, ferritin, cholesterol, blood leucocyte counts). Adjustment for iPTH, calcium and phosphate was omitted where these markers were the main exposure variables of interest. The adjustment also included hospitalization or change in vascular access type that may have occurred during the at-risk period.
iPTH, intact parathyroid hormone.

egory are homogeneous with respect to the magnitude of effect on the outcome. Furthermore, the FP analysis uses all available information by representing the exposure as a continuous variable and maximizing the power to detect any differences in effect. It also allows the variable to take on a non-linear form and does not therefore restrict the exposure–disease association to a linear relation. However, the method of FP should be used with caution, especially in areas in which data are sparse, since the functional form of the model can be influential to outliers.

A limitation of this study is that the analyses were based on observational data, and therefore, no causal inference can be made from the study results. Missing data were common among all the MBD markers considered, as were some potentially important confounding factors such as dialysate calcium concentration and intravenous administration of active vitamin D therapy derivatives. We attempted to adjust for any potential effects of missing data by including a separate indicator variable as part of the multivariable analysis. Another limitation was that the results could not be stratified by dialysis vintage (incident *versus* prevalent) due to the relatively small sample size of the incident subgroup. We could not adjust for serum 25(OH) vitamin D because this information was not captured in the ARO database.

In conclusion, patients whose serum iPTH, serum total calcium and serum phosphate values were within the KDOQI recommended targets experienced the lowest risk of mortality compared to those who were outside the respective target ranges. The data presented here are consistent with the more recent Kidney Disease: Improving Global Outcomes (KDIGO) recommendations on CKD–MBD target parameters [33], although some patients could be at increased risk of mortality compared to those treated to within the KDOQI target range. Our findings also suggest that very low or high values of iPTH and phosphate, as well as high values of calcium, should be avoided.

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

References

1. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31: 607–617

2. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004; 15: 2208–2218

3. Young EW, Albert JM, Satayathum S *et al*. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2005; 67: 1179–1187

4. 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: 771–780

5. 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: 531–540

6. 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: 519–530

7. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42: S1–S201

8. Goodkin DA, Young EW, Kurokawa K, Prütz KG, Levin NW. Mortality among hemodialysis patients in Europe, Japan, and the United States: case-mix effects. *Am J Kidney Dis* 2004; 44: 16–21

9. Goodkin DA, Bragg-Gresham JL, Koenig KG *et al*. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; 14: 3270–3277

10. Lacson E Jr, Wang W, Hakim RM, Teng M, Lazarus JM. Associates of mortality and hospitalization in hemodialysis: potentially actionable laboratory variables and vascular access. *Am J Kidney Dis* 2009; 53: 79–90

11. Royston P, Sauerbrei W. Building multivariable regression models with continuous covariates in clinical epidemiology—with an emphasis on fractional polynomials. *Methods Inf Med* 2005; 44: 561–571

12. Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. *Stat Med* 2007; 26: 5512–5528

13. Qureshi AR, Alvestrand A, Divino-Filho JC *et al*. Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. *J Am Soc Nephrol* 2002; 13: S28–S36

14. de Mutsert R, Grootendorst DC, Indemans F, Boeschoten EW, Krediet RT, Dekker FW. Association between serum albumin and mortality in dialysis patients is partly explained by inflammation, and not by malnutrition. *J Ren Nutr* 2009; 19: 127–135

15. Avram MM, Mittman N, Myint MM, Fein P *et al*. Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. *Am J Kidney Dis* 2001; 38: 1351–1357

16. Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. *J Am Soc Nephrol* 2004; 15: 770–779

17. Souberbielle J-C, Boutten A, Carlier M-C *et al*. Inter-method variability in PTH measurement: implication for the care of CKD patients. *Kidney Int* 2006; 70: 345–350

18. Coen G, Ballanti P, Bonucci E *et al*. Bone markers in the diagnosis of low turnover osteodystrophy in haemodialysis patients. *Nephrol Dial Transplant* 1998; 13: 2294–2302

19. London GM, Marchais SJ, Guérin AP, Boutouyrie P, Métivier F, de Vernejoul MC. Association of bone activity, calcium load, aortic stiffness and calcifications in ESRD. *J Am Soc Nephrol* 2008; 19: 1827–1835

20. Malluche HH, Mawad H, Monier-Faugere MC. The importance of bone health in end-stage renal disease: out of the frying pan, into the fire? *Nephrol Dial Transplant* 2004; 19: i9–i13

21. Adragao T, Herberth J, Monier-Faugere MC *et al*. Low bone volume—a risk factor for coronary calcifications in hemodialysis patients. *Clin J Am Soc Nephrol* 2009; 4: 450–455

22. Kurz P, Monier-Faugere MC, Bognar B *et al*. Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. *Kidney Int* 1994; 46: 855–861

23. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007; 71: 438–441

24. Schlieper G, Kruger T, Djuric Z *et al*. Vascular access calcification predicts mortality in hemodialysis patients. *Kidney Int* 2008; 74: 1582–1587

25. Wang AY, Wang M, Woo J *et al*. Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: a prospective study. *J Am Soc Nephrol* 2003; 14: 159–168

26. Moe SM. Vascular calcification and renal osteodystrophy relationship in chronic kidney disease. *Eur J Clin Invest* 2006; 36: 51–62

27. Bover J, Canal C, Marco H, Fernandez-Llama P, Bosch RJ, Ballarín J. Diagnostic procedures and rationale for specific therapies in chronic kidney disease-mineral and bone disorder. *Contrib Nephrol* 2008; 161: 222–233

28. Takahashi N, Kojima T, Ogawa H, Ishiguro N. Correlation between parathyroid hormone, bone alkaline phosphatase and N-telopeptide of type 1 collagen in diabetic and non-diabetic haemodialysis patients. *Nephrology (Carlton)* 2007; 12: 539–545

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: 315–320

30. Iwata Y, Wada T, Yokoyama H *et al*. Effect of sevelamer hydrochloride on markers of bone turnover in Japanese dialysis patients with low biointact PTH levels. *Intern Med* 2007; 46: 447–452

31. Sugimoto T, Ritter C, Morrissey J *et al*. Effects of high concentrations of glucose on PTH secretion in parathyroid cells. *Kidney Int* 1990; 37: 1522–7

32. Lee NK, Sowa H, Hinoi E *et al*. Endocrine regulation of energy metabolism by the skeleton. *Cell* 2007; 130: 456–469

33. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int* 2009; 76: S1–S130