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2013

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citation for published version (APA)

van den Beukel, T. O. (2013). *Ethnic differences in survival on dialysis in Europe: The role of demographic, clinical and psychosocial factors*. [PhD-Thesis – Research external, graduation internal, Vrije Universiteit Amsterdam].

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Ethnic differences in the association of bone mineral metabolism disorders with mortality in incident chronic dialysis patients in the United Kingdom

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ABSTRACT

Background Evidence suggests that the regulation of mineral metabolism differs between ethnic groups. It is currently unknown whether optimal levels of calcium, phosphate, and PTH vary between ethnic groups on dialysis. We investigated whether calcium, phosphate, and PTH levels after the start of dialysis treatment are associated differently with mortality in whites, blacks, and South Asians.

Methods We analyzed 30,021 white, 1,740 black, and 2,878 South Asian incident dialysis patients in the UK (1997-2008). Cox proportional hazards analysis was used to calculate Hazard Ratios (HRs) for mortality per ethnic group and per calcium, phosphate, and PTH category, with patients on target as reference group (target levels: calcium 8.4-9.5 mg/dL; phosphate 3.5-5.5 mg/dL; PTH 150-300 pg/mL). HRs were adjusted for the effects of socio-demographic and clinical characteristics.

Results Calcium and phosphate were highest in whites and lowest in blacks; PTH was highest in blacks and lowest in whites. In all ethnic groups, calcium above target was associated with increased mortality. Calcium below target was associated with increased mortality among whites, while it was not associated with mortality among South Asians and blacks. Phosphate levels above and below target were associated with increased mortality among whites, but not among South Asians and blacks. PTH above target tended to be associated with increased mortality among whites, but among blacks extremely elevated PTH concentrations seemed to exhibit the opposite trend. PTH below target was not associated with mortality.

Conclusion We showed ethnic differences in associations of mineral metabolism disorders after the start of dialysis with mortality. Randomized clinical trials are required to elucidate whether ethnic specific targets for mineral metabolism control in dialysis patients are needed.

INTRODUCTION

In patients with end-stage renal disease (ESRD), disturbances in mineral metabolism occur frequently and have been associated with several adverse outcomes, such as arterial calcification, bone disease, poor cardiovascular outcomes, and increased mortality.¹⁻⁴ Hence, several treatment guidelines for control of mineral metabolism have been published over the last decade recommending tight control of calcium, phosphate, and parathyroid hormone (PTH) in ESRD patients.⁵⁻⁸

Guidelines for control of mineral metabolism in ESRD patients do not take data on ethnicity into consideration. However, ethnic differences in the regulation of mineral metabolism have been found. In the general population, blacks have lower levels of calcidiol, higher PTH levels, larger parathyroid glands, increased synthesis of calcitriol, enhanced renal reabsorption of calcium, and reduced renal calcium excretion compared with whites.⁹⁻¹¹ Lower levels of calcidiol and higher levels of PTH and calcitriol have also been demonstrated in Asians compared with whites.^{12;13} Besides, ethnic differences in mineral metabolism have been seen in patients with early chronic kidney disease¹⁴ and in patients with ESRD on dialysis.¹⁵

Ethnic disparities in the regulation of mineral metabolism might imply that optimal levels of calcium, phosphate, and PTH in ESRD patients vary between ethnic groups.^{16;17} Supporting evidence for this hypothesis is found by Sawaya et al. showing that bone responses to PTH differ between black and white dialysis patients¹⁸ and by Moore et al. demonstrating that black dialysis patients have higher PTH levels than expected in relation to bone histology.¹⁹ Furthermore, a recent study among hemodialysis (HD) patients from the United States showed distinct survival associations for African Americans and non African-Americans with different ranges of calcium, phosphate, and PTH.²⁰

It is important to further explore whether optimal levels of calcium, phosphate, and PTH in ESRD patients vary between ethnic groups, to enable appropriate treatment for the control of mineral metabolism in non-white dialysis patients. Therefore, we aim to investigate whether calcium, phosphate, and PTH levels shortly after the start of dialysis treatment are associated differently with mortality in white, black, and South Asian incident dialysis patients in the United Kingdom (UK).

MATERIALS AND METHODS

Study design

We used data of the UK Renal Registry (UKRR). Details regarding the UKRR have been described previously.²¹ In brief, the UKRR provides independent audit and analysis of renal replacement therapy (RRT) in the UK. Demographic, clinical, and outcome data are extracted electronically from renal centers at quarterly intervals. Suspicious data are identified using algorithms, verified, and if necessary corrected by contacting renal centers. In the present study, we included incident patients who started their first RRT in England or Wales between 1 January 1997 and 31 December 2008, had either HD or peritoneal dialysis (PD) as first RRT, continued dialysis treatment for at least 90 days, were ≥ 18 years of age at initiation of dialysis treatment, and had data on ethnicity available. Baseline was set at 3 months after the initiation of dialysis treatment.

Biochemical values

Biochemical values were measured nearest to the end of the calendar quarter following the quarter of dialysis initiation. Measurements took place at local dialysis centers using standard laboratory techniques. Because of U-shaped associations of calcium, phosphate, and PTH with mortality, mineral metabolism variables were divided into categories, based on the Kidney Disease Outcome Quality Initiative (KDOQI) guideline for Bone Metabolism and Disease.⁵ We observed calcium levels on target as >8.4 and ≤ 9.5 mg/dL (>2.10 and ≤ 2.37 mmol/L); phosphate levels on target as >3.5 and ≤ 5.5 mg/dL (>1.13 and ≤ 1.78 mmol/L); and PTH levels on target as >150 and ≤ 300 pg/mL (>15.8 and ≤ 31.5 pmol/L). Levels above target were further divided in levels intermediate above target and in levels high above target (high above target: calcium ≥ 10.2 mg/dL (≥ 2.54 mmol/L), phosphate ≥ 7.0 mg/dL (≥ 2.26 mmol/L), and PTH ≥ 600 pg/mL (≥ 63 pmol/L)).

Ethnicity

Ethnicity data were recorded either by uploading the ethnicity coding from the hospital patient administration systems which is based on self-reported ethnicity, or by renal unit ascription. Patients were grouped into whites, blacks, South Asians, and others.²² Whites were observed as individuals originating from Europe. Blacks were observed as black Caribbeans, black Africans, blacks other, and blacks mixed. South Asians were people originating from India, Pakistan, Bangladesh, or other countries of the Indian subcontinent, East African Asians, and Asians other non-mixed. All other patients, including Chinese and

North African Arabs, were included in the group other. If renal units did not submit ethnicity data to the UKRR, patients were recorded as white if they lived in a UK Census 2001 ward with $\geq 97.5\%$ white ethnicity, otherwise data on ethnicity were observed as missing.²³

Socio-demographic and clinical characteristics

Socio-demographic and clinical characteristics were determined at the start of dialysis treatment, except for dialysis modality which was defined as the modality in use at day 90 or the initial treatment when a patient had changed dialysis modality between day 0 and 90 without continuation for at least 90 days. Townsend deprivation score is considered as proxy for social economic status and is based on the percentage of unemployed individuals and the percentage of households that had no car, were overcrowded, and were not owner-occupied. The Townsend deprivation score is derived from patient's postcode of residence, which was matched to the 2001 UK Census output area information. Five ordered deprivation groups were formed, with higher groups indicating higher levels of deprivation.²⁴ The estimated Glomerular Filtration Rate (eGFR) was calculated using the abbreviated 4-variable MDRD study equation²⁵ and based on creatinine data obtained within 14 days before the start of dialysis treatment. Primary kidney disease was based on the ERA-EDTA coding system for primary renal diagnosis.²² Smoking was defined as current smoker or a history of smoking within the last year.

Statistical analysis

Descriptive statistics are presented as mean with standard deviation or in case of a skewed distribution as median with interquartile range. ANOVA F and Kruskal-Wallis tests were used to compare continuous variables and Pearson's chi-square test was used to compare categorical variables between the 3 ethnic groups. Survival time was defined as the time between the start of dialysis treatment and the date of death or censoring. Patients were treated as censored when they had a recovery of renal function, underwent a renal transplantation, were lost to follow-up, or reached the end of the study period at December 31, 2008. Cox proportional hazards analysis was used to calculate crude Hazard Ratios (HRs) for mortality per ethnic group and per calcium, phosphate, and PTH category, with white patients on target as reference group. In addition, adjustments were made for the effects of socio-demographic and clinical characteristics. We did not adjust for biochemical variables, since these variables may be observed as intermediates in the causal pathway of the associations under study. Plots of $\log[-\log(\text{survival rate})]$ against $\log(\text{survival time})$ were used to test proportional hazards assumptions. To quantify observed ethnic differences in the

association of mineral metabolism disorders with mortality, we explored multiplicative effect modification. Effect modification is the phenomenon whereby the effect of a risk factor on outcome varies across different groups.²⁶ Effect modification was explored by adding interaction terms to our Cox regression models (ethnicity and calcium, phosphate, and PTH). Because of U-shaped associations of calcium, phosphate, and PTH levels with mortality, this was analyzed separately for patients with levels below target and above target.

Calcium, phosphate, and PTH was missing from 13%, 19%, and 46% of patients, respectively. Other variables used in the Cox regression models with missing values were Townsend deprivation score (3%), primary kidney disease (5%), and eGFR (40%). In order to create complete datasets for multivariate Cox analyses, missing values were imputed with standard multiple imputation techniques in SPSS (using 10 repetitions).²⁷ The imputation model was built on characteristics described in table 1, plus ethnicity, log of days of follow-up, mortality data, and biochemical values measured nearest to the end of the first and third calendar quarter. Ferritin, PTH, and days of pre-dialysis care were square root transformed before entering the multiple imputation model since these variables had skewed distributions. The Cox regression models were fitted to each of the imputed datasets and results were averaged by using Rubin's rules.²⁸ The comorbidity variables, smoking status, and days of pre-dialysis care were used in the imputation model but not included in the Cox regression models because these variables had more than 50% missing values (53%, 54%, and 58%, respectively).²⁹ Analyses other than the Cox proportional hazards analyses were based on the original dataset. Analyses were carried out with SPSS 18.0 for Windows statistical software.

Sensitivity analyses

To test the robustness of our data various sensitivity analyses were performed. We calculated adjusted HRs for mortality per ethnic group and per calcium, phosphate, and PTH category (1) by following patients after renal transplantation (i.e. no censoring at transplantation), (2) with additional adjustment for the presence of diabetes, ischemic heart disease, peripheral vascular disease, and malignancy (in the subgroup of patients with available data), and (3) with additional adjustment for calcium, phosphate, and PTH, hemoglobin, ferritin, and albumin (except for the variable under study).

RESULTS

In total 43,884 incident ESRD patients of ≥ 18 years of age started dialysis treatment in England or Wales between 1 January 1997 and 31 December 2008. For this particular study 8,439 patients were excluded because they died within the first 90 days of RRT ($n=3,681$) or were censored ($n=1,890$) within the first 90 days, or had no information available on ethnicity ($n=2,868$). Of the remaining patients, 30,021 were white, 1,740 black, 2,878 South Asian, and 806 patients were grouped as other ethnicity. Patients with other ethnicity were excluded from the analyses.

Baseline characteristics for the 3 ethnic groups are demonstrated in Table 1. At start of RRT, whites were older than black and South Asian patients, were more often male, and were more often treated with PD. Whites had lower deprivation scores and a higher prevalence of smoking compared with blacks and South Asians. Blacks and South Asians, however, had higher proportions with diabetic nephropathy. Both calcium and phosphate levels were the highest in whites, followed by South Asians and blacks. PTH levels, however, were the highest in blacks, followed by South Asian and whites.

Table 1. Socio-demographic, clinical, and biochemical characteristics of white, black, and South Asian dialysis patients.

Characteristic *	Whites (n=30021)		Blacks (n=1740)		South Asians (n=2878)	
Socio-demographic						
Age years	62	16	54	16	56	15
Sex % men	63		56		60	
Deprivation group % ≥4	40		82		71	
Year of start dialysis treatment % ≥ 2003	67		78		75	
Clinical						
Pre-dialysis treatment months	16.5	2.8 – 46.4	18.8	4.1 – 47.2	19.6	4.5 – 46.2
Treatment modality % HD	69		77		75	
Estimated GFR ml/min/1.73m ²	8.3	3.3	8.4	3.3	8.0	3.3
Smoking	17		6		6	
Primary kidney disease %						
Diabetic nephropathy	19		32		38	
Glomerulonephritis	11		10		9	
Renal vascular disease	14		19		7	
Other	57		39		46	
Comorbidity %						
Diabetes Mellitus †	8		5		9	
Ischemic heart disease ‡	24		11		25	
Peripheral vascular disease §	13		5		9	
Malignancy	12		6		3	
Biochemical variables 						
Calcium mg/dL ¶	9.6	0.8	9.2	0.8	9.4	0.9
Phosphate mg/dL	5.1	1.6	4.7	1.5	4.9	1.6
PTH pg/ml	171	77 – 323	322	161 – 590	209	88 – 401
Hemoglobin g/dL	11.2	1.7	10.9	1.9	11.2	1.8
Ferritin µg/L	277	155 – 459	309	179 – 496	313	175 – 514
Albumin g/dL	3.5	0.6	3.6	0.6	3.6	0.6

Values are presented as mean (standard deviation) or median (interquartile range) or percentage.

All *p* values ≤ 0.001, except for pre-dialysis treatment (*p* = 0.002).

* Characteristics represent data determined at the start of dialysis treatment, except for treatment modality (determined 90 days after the start of dialysis treatment) and biochemical variables (determined at the end of the calendar quarter following the quarter of dialysis initiation).

† Diabetes not listed as primary kidney disease.

‡ Angina pectoris, and/or myocardial infarction, and/or coronary artery bypass graft, and/or coronary angioplasty.

§ Intermittent claudication, and/or ischemic or neuropathic ulcer, and/or non-coronary angioplasty, and/or vascular graft, and/or aneurysm, and/or amputation for peripheral vascular disease. Malignancy: any malignancy, excluding basal cell carcinoma.

|| Conversion factors of metric units to SI units: calcium mg/dL x 0.2495 = mmol/L; phosphate mg/dL x 0.323 = mmol/L; PTH pg/mL x 0.105 = pmol/L; hemoglobin g/dL x 0.621 = mmol/L; ferritin µg/L x 2.247 = pmol/L; albumin g/dL x 10 = g/L.

¶ Albumin corrected.

Figure 1 shows percentages achievement of calcium, phosphate, and PTH targets per ethnic group, based on concentrations in the calendar quarter following the quarter of dialysis initiation. In white patients, 51% had calcium levels above the target range, whereas only 35% of the black patients and 38% of the South Asian patients had calcium concentrations above the target range. Furthermore, whites achieved more often phosphate levels above the target range compared with blacks and South Asians (35%, 26%, and 31%, respectively). Conversely, 53% of the black patients had PTH levels above the target range, while only 27% of the whites and 36% of the South Asians had PTH levels exceeding the target range.

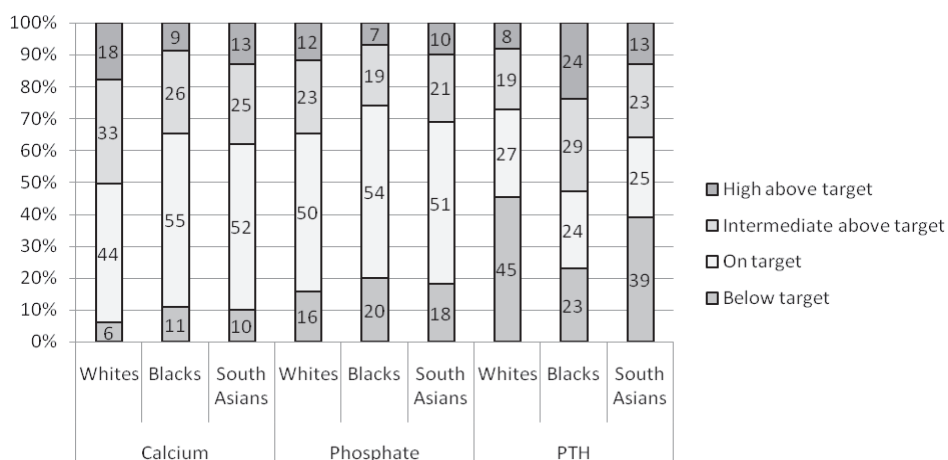


Figure 1. Percentages achievement of calcium, phosphate, and PTH targets per ethnic group, based on concentrations in the calendar quarter following the quarter of dialysis initiation.

The duration of follow-up and incidence rates for different outcomes are listed in Table 2. When compared with blacks and South-Asians, whites were more likely to die on dialysis (crude death rates 68, 93, and 166 per 1000 person-years for blacks, South Asians, and whites, respectively) and more likely to receive a renal transplant (incidence rates for renal transplantation 58, 65, and 73 per 1000 person-years for blacks, South Asians, and whites, respectively).

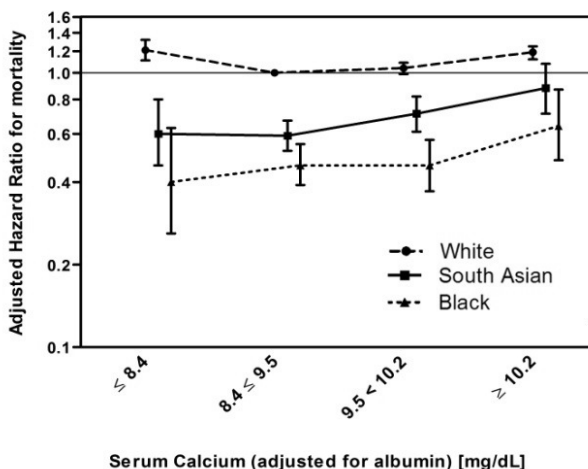
Table 2. Median follow-up time and outcomes by ethnic group.

	Whites (n=30021)	Blacks (n=1740)	South Asians (n=2878)
Follow-up years; <i>median (IQR)</i> *	1.9 (1.0 – 3.5)	2.4 (1.1 – 4.0)	2.2 (1.1 – 3.8)
<i>Outcomes incidence rates; per 1000 person-years</i>			
Death	166 (n=12297)	68 (n=335)	93 (n=728)
Transplanted	73 (n=5382)	58 (n=285)	65 (n=507)
Recovery of renal function	5 (n=398)	5 (n=25)	3 (n=22)
Lost to follow-up	4 (n=289)	7 (n=35)	6 (n=46)

* Time from end-stage renal disease onset to first noted event (death or censoring); IQR = interquartile range.

Figures 2-4 show adjusted HRs for mortality per ethnic group across four increments of calcium, phosphate, and PTH concentrations, with white patients on target as reference group. Figure 2 demonstrates that calcium levels high above target were associated with increased mortality in all ethnic groups. Calcium below target was associated with increased mortality risk among whites, while among blacks and South Asians there was no association with mortality. The corresponding interaction term of calcium and ethnicity was statistically significant in blacks and whites with calcium levels below target ($p=0.05$), indicating that the association between calcium below target with mortality was different in blacks and whites. Figure 3 shows that among whites phosphate levels above and below target were associated with increased mortality risk. In blacks, these phosphate levels were not associated with mortality, although interaction analyses showed no indications that the effect of phosphate on mortality varied across blacks and whites. In South Asians, phosphate levels above and below target were not associated with mortality, but HRs for mortality revealed similar patterns of associations compared with whites. Figure 4 illustrates that PTH concentrations high above target tended to be associated with somewhat increased mortality among whites. In blacks and South Asians, there was no association of PTH high above target with mortality. In blacks, extremely elevated PTH concentrations seemed to even exhibit the opposite trend in association with mortality compared with whites. The interaction term of PTH and ethnicity tended towards being statistically significant in blacks and whites with PTH levels above target ($p=0.09$). In all ethnic groups, PTH levels below target were not associated with mortality. Repeating the analyses presented in Figures 2-4 excluding patients with imputed values for the mineral metabolism variable under study, did not reveal materially different patterns of associations.

Figure 2. Adjusted Hazard Ratios for mortality per ethnic group across four increments of serum calcium (adjusted for albumin), with white patients on target as reference group.



Serum Calcium		Below target (≤ 8.4 mg/dL)	On target ($8.4 \le 9.5$ mg/dL)	Intermediate above target ($9.5 < 10.2$ mg/dL)	High above target (≥ 10.2 mg/dL)
Crude mortality rate per 1000 py	Whites	173	152	152	164
	South Asians	81	85	91	104
	Blacks	56	66	71	101
Crude HR (95% CI)	Whites	1.16 (1.07 - 1.27)	Reference	0.99 (0.94 - 1.03)	1.12 (1.06 - 1.18)
	South Asians †	0.52 (0.40 - 0.68)	0.54 (0.48 - 0.61)	0.57 (0.49 - 0.66)	0.68 (0.56 - 0.83)
	Blacks ‡	0.33 (0.21 - 0.52)	0.40 (0.34 - 0.47)	0.41 (0.33 - 0.51)	0.58 (0.43 - 0.79)
Adjusted HR (95% CI) *	Whites	1.21 (1.11 - 1.32)	Reference	1.04 (0.99 - 1.09)	1.19 (1.12 - 1.25)
	South Asians §	0.60 (0.46 - 0.80)	0.59 (0.52 - 0.67)	0.71 (0.61 - 0.82)	0.88 (0.71 - 1.08)
	Blacks	0.40 (0.26 - 0.63)	0.46 (0.39 - 0.55)	0.46 (0.37 - 0.57)	0.64 (0.48 - 0.87)

py = person-years; HR = hazard ratio; CI = confidence interval.

* Adjusted for age, sex, deprivation score, primary kidney disease, estimated glomerular filtration rate, treatment modality, year of start dialysis treatment.

Interaction term for the combined effect of calcium and ethnicity on mortality (continuous calcium value):

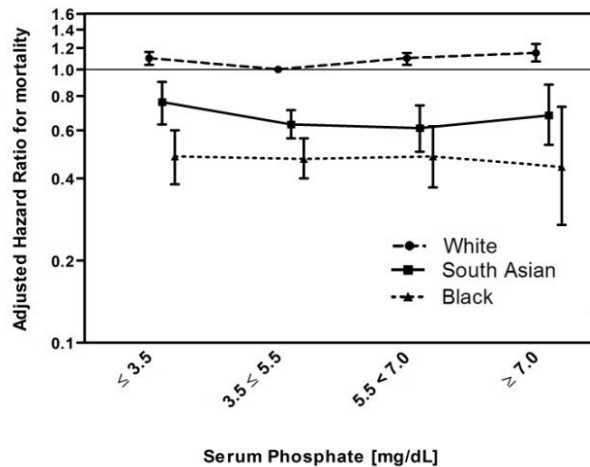
† Calcium \le target: $p=0.31$; Calcium \ge target: $p=0.74$.

‡ Calcium \le target: $p=0.02$; Calcium \ge target: $p=0.11$.

§ Calcium \le target: $p=0.27$; Calcium \ge target: $p=0.19$.

|| Calcium \le target: $p=0.05$; Calcium \ge target: $p=0.40$.

Figure 3. Adjusted Hazard Ratios for mortality per ethnic group across four increments of serum phosphate, with white patients on target as reference group.



Serum Phosphate		Below target (≤3.5 mg/dL)	On target (3.5 ≤ 5.5 mg/dL)	Intermediate above target (5.5 < 7.0 mg/dL)	High above target (≥ 7.0 mg/dL)
Crude mortality rate per 1000 py	Whites	178	151	144	145
	South Asians	115	86	74	79
	Blacks	82	67	68	50
Crude HR (95% CI)	Whites	1.20 (1.13 - 1.27)	Reference	0.97 (0.92 - 1.01)	0.93 (0.87 - 0.99)
	South Asians †	0.72 (0.60 - 0.86)	0.55 (0.49 - 0.62)	0.49 (0.40 - 0.58)	0.49 (0.38 - 0.63)
	Blacks ‡	0.48 (0.38 - 0.60)	0.40 (0.34 - 0.47)	0.40 (0.31 - 0.52)	0.29 (0.17 - 0.49)
Adjusted HR (95% CI) *	Whites	1.10 (1.04 - 1.16)	Reference	1.10 (1.04 - 1.15)	1.15 (1.07 - 1.24)
	South Asians §	0.76 (0.63 - 0.90)	0.63 (0.56 - 0.71)	0.61 (0.50 - 0.74)	0.68 (0.53 - 0.88)
	Blacks	0.48 (0.38 - 0.60)	0.47 (0.40 - 0.56)	0.48 (0.37 - 0.62)	0.44 (0.27 - 0.73)

py = person-years; HR = hazard ratio; CI = confidence interval.

* Adjusted for age, sex, deprivation score, primary kidney disease, estimated glomerular filtration rate, treatment modality, year of start dialysis treatment.

Interaction term for the combined effect of phosphate and ethnicity on mortality (continuous phosphate value):

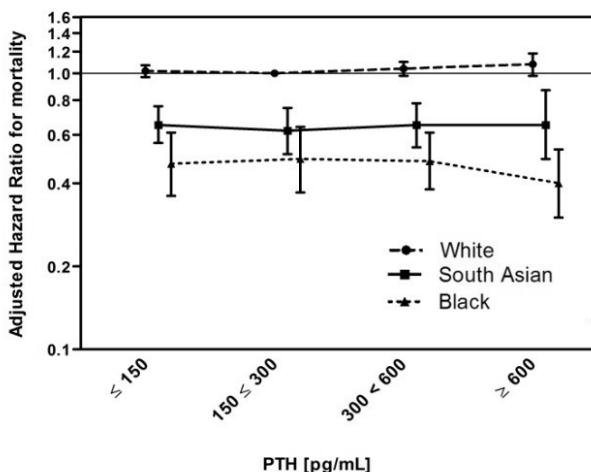
† Phosphate ≤ target: p=0.82; Phosphate ≥ target: p=0.60.

‡ Phosphate ≤ target: p=0.86; Phosphate ≥ target: p=0.49.

§ Phosphate ≤ target: p=0.79; Phosphate ≥ target: p=0.38.

|| Phosphate ≤ target: p=0.99; Phosphate ≥ target: p=0.41.

Figure 4. Adjusted Hazard Ratios for mortality per ethnic group across four increments of parathyroid hormone (PTH), with white patients on target as reference group.



PTH		Below target (≤ 150 pg/mL)	On target (150 ≤ 300 pg/mL)	Intermediate above target (300 < 600 pg/mL)	High above target (≥ 600 pg/mL)
Crude mortality rate per 1000 py	Whites	161	149	147	141
	South Asians	82	79	82	77
	Blacks	79	66	63	43
Crude HR (95% CI)	Whites	1.04 (0.99 - 1.09)	Reference	0.99 (0.93 - 1.04)	0.93 (0.85 - 1.02)
	South Asians †	0.58 (0.50 - 0.67)	0.55 (0.46 - 0.66)	0.57 (0.48 - 0.68)	0.49 (0.37 - 0.64)
	Blacks ‡	0.46 (0.36 - 0.59)	0.41 (0.32 - 0.54)	0.42 (0.33 - 0.53)	0.33 (0.25 - 0.44)
Adjusted HR (95% CI) *	Whites	1.02 (0.97 - 1.07)	Reference	1.04 (0.98 - 1.10)	1.08 (0.98 - 1.18)
	South Asians §	0.65 (0.56 - 0.76)	0.62 (0.51 - 0.75)	0.65 (0.54 - 0.78)	0.65 (0.49 - 0.87)
	Blacks	0.47 (0.36 - 0.61)	0.49 (0.37 - 0.64)	0.48 (0.38 - 0.61)	0.40 (0.30 - 0.53)

py = person-years; HR = hazard ratio; CI = confidence interval.

* Adjusted for age, sex, deprivation score, primary kidney disease, estimated glomerular filtration rate, treatment modality, year of start dialysis treatment.

Interaction term for the combined effect of PTH and ethnicity on mortality (continuous PTH value):

† PTH ≤ target: p=0.93; PTH ≥ target: p=0.54.

‡ PTH ≤ target: p=0.60; PTH ≥ target: p=0.19.

§ PTH ≤ target: p=0.82; PTH ≥ target: p=0.74.

|| PTH ≤ target: p=0.91; PTH ≥ target: p=0.09.

Several sensitivity analyses were performed. First, we investigated the potential role of censoring for renal transplantation by repeating the analyses following patients after renal transplantation (i.e. no censoring at transplantation). Results were essentially similar to the main analyses, albeit the interaction term of calcium and ethnicity in blacks and whites with calcium levels below target lost significance ($p = 0.06$). Second, we performed sensitivity analyses in a subgroup of patients with data available on comorbidity, hence we excluded 53% whites, 50% blacks, 49% South Asians. Repeating the analyses in this subgroup of patients yielded comparable patterns of associations to the main analyses, although confidence intervals were wider because of smaller sample size and the interaction term of calcium and ethnicity in blacks and whites with calcium below target was no longer significant ($p=0.42$). Additional adjustment for comorbidity did not materially change the patterns of associations. Third, we additionally adjusted for biochemical variables. This did not alter the patterns of associations, except for phosphate levels below target which were no longer associated with a higher mortality in whites. The interaction term of calcium and ethnicity in blacks and whites with calcium levels below target was no longer significant ($p=0.19$).

DISCUSSION

Our data confirm previously reported differences in calcium, phosphate, and PTH levels between white, black, and South Asian incident dialysis patients. Our data also indicate ethnic differences in the association of calcium below target, phosphate above and below target, and PTH above target with mortality. These differences persisted in several sensitivity analyses. In line with others³⁰⁻³⁵, we found that whites were more likely to die on dialysis compared with blacks and South Asians.

There are several factors, which need to be considered in interpreting our results. First, data on medication use and nutritional status were either unavailable or insufficient. This prevents us from identifying the role of these factors in our observations. Second, our data provide observational evidence of different patterns of associations between mineral metabolism and mortality in ethnic groups. Because of the observational nature of this study, associations found in the present study should not be interpreted as causal associations. Accordingly, ethnic specific recommendations for the treatment of abnormal mineral metabolism in dialysis patients remain speculative at this time.³⁶ Third, a number of

patients had missing data on calcium, phosphate, or PTH in the calendar quarter following the quarter of dialysis initiation. Nevertheless, we consider it unlikely that this has influenced the results substantially. We accounted for missing data by using multiple imputation techniques (in the imputation model biochemical values measured in the first and third calendar quarter were taken into account). Moreover, repeating the analyses including only cases with non-imputed values yielded comparable results. Fourth, data on laboratory assays and mathematical albumin correction for calcium were not accessible, since laboratory measurements and mathematical corrections took place at local dialysis centers. This may yield variation in the laboratory measurements, in particular in calcium and PTH measurements. However, we do not have indications that a particular assay or mathematical correction was predominantly used in a specific ethnic group. This means that the misclassification, if any, is non-differential and might therefore result in dilution of the effects of calcium and PTH-related outcomes, implying that the real effect could be even stronger.^{37;38} Finally, the loss of significance for interaction terms in sensitivity analyses might partly be due to a power effect, since most sensitivity analyses were based on subgroups.

Our data are consistent with previous studies showing that black and Asian dialysis patients have higher levels of PTH^{15;18;33;35;39-41} and slightly lower levels of calcium^{15;18;33;35;39-41} and phosphate^{18;33;39;40} compared with whites, albeit not statistically significant in all studies. However, there are also conflicting reports in the literature as to equal or higher calcium⁴² and phosphate levels^{35;41;42} among non-white dialysis patients when compared with whites. The cause of ethnic disparities in calcium, phosphate, and PTH levels on dialysis is likely to be multifactorial. Ethnic differences in medication use, e.g. phosphate binders, calcimimetics, and activated vitamin D^{43;44}, and in nutritional status⁴⁵ may play a role. Furthermore, differences in the physiology of mineral metabolism between ethnic groups are likely to underlie ethnic disparities in calcium, phosphate, and PTH levels on dialysis. In individuals without overt kidney disease, non-white individuals have reduced cutaneous synthesis of vitamin D as a consequence of skin pigmentation⁴⁶, a lower threshold level of calcidiol that is associated with a rise of PTH⁴⁷, higher circulating PTH levels⁴⁸, and increased circulating calcitriol levels.⁹ It has been suggested that differences in the physiology of mineral metabolism between ethnic groups exaggerate with the development of renal failure.^{15;23}

To our knowledge this is the first study exploring differences in the association between mineral metabolism and survival in whites, blacks, and South Asians. A recent study from the United States found differences in mortality predictabilities of different ranges of calcium,

phosphate, and PTH between African-American and non-African American HD patients.²⁰ However, our findings of distinct survival associations between calcium below target, phosphate below and above target, and PTH above target with mortality in white and black dialysis patients were not confirmed by this study. This might be explained by different compositions of ethnic groups (in the US study all non-black patients were combined), the use of time-dependent analyses, and censoring for transfer to PD treatment in the US study.

Different possible explanations for ethnic differences in the association of mineral metabolism disorders with mortality could be postulated. First, ethnic groups might have different evolutionary developed steady states for mineral metabolism, e.g. due to differences in cutaneous synthesis of vitamin D⁴⁶ and in body composition.⁴⁹ Consequently, similar levels of calcium, phosphate, and PTH across ethnic groups might have distinct causal effects on outcome. We found that blacks had lower levels of calcium and higher levels of PTH than whites and showed that these levels indeed exhibit opposite associations with mortality for blacks and whites. It may be that black dialysis patients are protected against the detrimental effects of low calcium and high PTH. However, to provide evidence for distinct causal effects randomized controlled trials (RCTs) are required. A second explanation for ethnic differences in the association of mineral metabolism disorders with mortality could be related to medication use and dialysis regimen. To achieve similar levels of calcium, phosphate, and PTH, different treatment regimens might be needed in the different ethnic groups. These variations in treatment, for example differences in treatment with activated vitamin D, could lead to ethnic differences in outcome, independent of direct effects of calcium, phosphate, and PTH levels. Finally, ethnic differences in the association of mineral metabolism with mortality might be due to additional, unknown factors.

In line with several others, we found lower death rates for black and South-Asian dialysis patients compared with whites.³⁰⁻³⁵ This has been extensively studied before. Although explanations are not completely elucidated, growing evidence suggests that therapy with activated vitamin D is a potential explanation for ethnic survival disparities on dialysis.^{20;41} Wolf et al. found that survival advantages of black dialysis patients appeared restricted to those receiving activated vitamin D and that the survival advantage for black dialysis patients was lost after adjustment for vitamin D dosage.⁴¹ Therefore, higher levels of PTH among non-white patients may be an underlying cause of ethnic differences in survival on dialysis since mainly PTH levels are used to indicate and modify treatment with activated vitamin D⁵⁻⁸ and treatment using activated vitamin D has been associated with improved survival

among dialysis patients.^{44;50} Unfortunately, in the UKRR treatment with activated vitamin D therapy is not monitored and the role of this therapy could therefore not be addressed in the present study.

CONCLUSION

We found ethnic differences in calcium, phosphate, and PTH levels, as well as different patterns of associations between disordered mineral metabolism and mortality in ethnic groups. Additional studies, in particular randomized controlled trials (RCTs), are urgently required to verify the causality of these associations and to elucidate whether ethnic specific targets in the control of mineral metabolism in dialysis patients are needed. Therefore, we call for the inclusion of data on ethnicity in the design of RCTs that aim to identify optimal targets for calcium, phosphate, and PTH in patients with ESRD and for adequate power of these RCTs to detect effect modification by ethnicity.

ACKNOWLEDGEMENTS

The authors thank the clinicians and patients in the renal units who contributed data to the UK Renal Registry, and the staff of the UK Renal Registry for their valuable contributions. T.O.vdB. is grateful to the European Renal Association-European Dialysis and Transplant Association for the support with a research fellowship (53-2009).

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