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Race, Mineral Homeostasis and Mortality in Patients with End-Stage Renal Disease on Dialysis

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Abstract

Background—Abnormalities in mineral homeostasis are ubiquitous in patients on dialysis, and influenced by race. We determine the race-specific relationship between mineral parameters and mortality in patients initiating hemodialysis.

Methods—We measured fibroblast growth factor 23 (FGF23) and 25-hydroxyvitamin D (25D) in 184 African American and 327 non-African American hemodialysis patients who enrolled between 1995–1998 in the Choices for Healthy Outcomes in Caring for ESRD Study. Serum calcium, phosphorus, parathyroid hormone (PTH) and total alkaline phosphatase were averaged from clinical measurements during the first 4.5 months of dialysis. We evaluated the associated prospective risk of mortality using multivariable Cox proportional hazards models stratified by race.

Results—PTH and total alkaline phosphatase were higher, whereas calcium, phosphorus, FGF23 and 25D were lower in African Americans compared to non-African Americans. Higher serum

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phosphorus and FGF23 were associated with greater mortality risk overall, however phosphorus was only associated among African Americans (HR 5.38; 95% CI 2.14–13.55 for quartile 4 vs 1), but not among non-African Americans (p-interaction=0.04). FGF23 was associated with mortality in both groups, but more strongly in African Americans (HR 3.91; 95% CI 1.74–8.82 for quartiles 4 vs 1; p-interaction=0.09). Serum calcium, PTH, and 25D were not consistently associated with mortality. The lowest and highest quartiles of total alkaline phosphatase associated with higher mortality risk, but this did not differ by race (p-interaction= 0.97).

Conclusions—Aberrant phosphorus homeostasis, reflected by higher phosphorus and FGF23, may be a risk factor for mortality in patients recently initiating hemodialysis, particularly African Americans.

Keywords

Dialysis; end-stage renal disease; epidemiology; fibroblast growth factor 23; phosphorus; vitamin D

Introduction

Abnormalities of mineral homeostasis are among the most potent risk factors for adverse outcomes in the ESRD population and are potentially modifiable(1, 2). Elevation of serum phosphorus due to inadequate renal and dialytic clearance, contributes to rising phosphorus regulatory hormones, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). Elevated FGF23 inhibits 1-α hydroxylase that converts 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D, inducing 1,25-dihydroxyvitamin D deficiency and contributing to further elevation of PTH, impaired calcium absorption and abnormal bone turnover(3). The resulting abnormalities in mineral and bone homeostasis may contribute to the pathogenesis of cardiovascular disease in patients with ESRD by promoting vascular calcification(4), left ventricular hypertrophy and fibrosis(5, 6), and sudden cardiac death(7, 8).

Levels of these mineral and bone parameters differ between African Americans and non-African Americans(9), with higher PTH and phosphorus and lower FGF23 and 25-hydroxyvitamin D commonly observed in African Americans on dialysis(1, 10). The consequences of abnormalities in mineral homeostasis may also differ by race as highlighted by a recent study among a racially diverse population of young adults in which deficiency of 25-hydroxyvitamin D was associated with coronary heart disease in Caucasians, but not African Americans (11). Findings such as these suggest that race-specific targets for mineral and bone parameters may be needed.

Our group previously reported that elevated levels of serum calcium, phosphorus and PTH were each associated with an increased risk of mortality in incident dialysis patients enrolled in the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study (12). In the current study, we extend these findings to include measurements of FGF23, total alkaline phosphatase and 25-hydroxyvitamin D and test the hypothesis that the association of mineral homeostasis with mortality differs by race.

Subjects and Methods

Study Population

All participants included in this study were recruited as part of the CHOICE Study between 1995 and 1998 from dialysis clinics affiliated with Dialysis Clinic, Inc. (DCI, Nashville, TN). Inclusion criteria for CHOICE included the initiation of chronic outpatient dialysis within the past 6 months, ability to provide informed consent for participation, age older than 17 years, and ability to speak English or Spanish. Samples were drawn in hemodialysis patients prior to dialysis treatments, immediately processed and stored at −80C. This analysis includes the 184 African American and 327 non-African American participants with samples available in the specimen bank. Although the initial CHOICE cohort included both peritoneal and hemodialysis patients only patients on hemodialysis contributed to the specimen bank. The Johns Hopkins University School of Medicine Institutional Review Board and the review boards for each clinical center approved the study protocol and all patients gave written informed consent.

Exposure

The primary exposures for this study are serum calcium, phosphorus, parathyroid hormone (PTH), and total alkaline phosphatase, and plasma fibroblast growth factor 23 (FGF23) and 25-hydroxyvitamin D. Serum calcium, phosphorus, PTH and total alkaline phosphatase were calculated as the average of all clinical measurements performed during routine dialysis care up to 4.5 months after enrollment to correspond to the time when FGF23 and 25-hydroxyvitamin D were measured. The majority of participants had at least 5 measurements of calcium (95%), phosphorus (95%) and total alkaline phosphatase (85%), and 1–2 measurements of PTH (77%; 10.4% had >2 measurements of PTH) in the time interval. PTH was measured using the Diasorin intact assay (Diasorin, Inc., Stillwater, MN, USA). Serum calcium levels were not corrected for albumin in primary analyses due to the adjustment for serum albumin in multivariate models, and because the use of albumin-adjusted calcium did not qualitatively change the findings (data not shown). C-terminal FGF23 (Immutopics, San Clemente, CA, USA) and 25-hydroxyvitamin D (Immunodiagnostic Systems, Scottsdale, AZ, USA) were measured at a single timepoint in stored plasma samples drawn within 6 months of enrollment (median of 90 days).

Covariates

Demographics and medical history were ascertained by a combination of self-report and chart review. Race was classified as either African American (n=184; 36%) or non-African American (n=327; 64%), which included Caucasian (n=295) and other races (n=32). Baseline atherosclerotic cardiovascular disease was defined as a history of coronary artery disease, myocardial infarction, cerebrovascular disease, peripheral vascular disease or transient ischemic attack prior to dialysis initiation. The presence and severity of comorbidity were assessed using the Index of Coexistent Disease (ICED), an instrument that has been validated in dialysis populations (13, 14). Body mass index (BMI) was calculated based on the height and weight reported on Centers for Medicare & Medicaid Services Form 2728 that is completed by providers at dialysis initiation. Laboratory covariates include serum albumin and hemoglobin measured as the average of all clinical measurements up to

4.5 months after enrollment. High-sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6) were measured as previously reported(15).

Outcomes

The primary outcome is all-cause mortality ascertained through December 31, 2008 using direct contact with dialysis clinics and through data linkage to the United States Renal Data System (USRDS), the national registry of patients with ESRD in the United States. Date of death is directly ascertained in the USRDS through mandated reporting. The secondary outcome is atherosclerotic cardiovascular death, defined as a death with an immediate or underlying cause attributed to coronary artery disease, cerebrovascular disease, peripheral vascular disease, and abdominal aortic aneurysm or ischemia. Causes of death were ascertained through linkage to the National Death Index and adjudication by trained physicians, as previously described(15), and were available through December 31, 2004. Both outcomes were censored at the time of kidney transplantation and secondary analyses were censored for death due to non-cardiovascular causes.

Statistical Analysis

Descriptive statistics were used to compare the characteristics of CHOICE participants that were included in our study population versus not, and characteristics by African American versus non-African American race. Levels of mineral parameters were classified in quartiles. FGF23 and PTH were log transformed for continuous analyses.

We evaluated cumulative incidence of death by levels of each mineral parameter and race using the Kaplan Meier method and the log rank test. Due to measurement of exposure in stored specimens collected after dialysis initiation, participants were left censored to the time of measurement. We modeled hazard of death using Cox proportional hazards models adjusted for age, sex, race, education (less than high school, high school graduate, college graduate or declined to answer), smoking, body mass index, ICED, diabetes mellitus, history of atherosclerotic cardiovascular disease, serum albumin and hemoglobin, accounting for correlation within dialysis clinic clusters using stratification. Missing data were handled by model-wise deletion. Nine percent of participants were missing a covariate and therefore were not included in fully adjusted models. These participants did not differ from those included in fully adjusted models in terms of age, sex, comorbidity index or history of diabetes mellitus or cardiovascular disease (data not shown), but were more likely to be African American (p=0.02).

We stratified models by race and tested interactions by race in models including mineral parameters as continuous variables. In these interaction models, PTH and total alkaline phosphatase were modeled using restricted cubic splines with knots at the 10^{th}, 50^{th} and 90^{th} percentiles due to evidence of a non-linear association with mortality in this and other studies(16). In secondary analyses, we conducted similar analyses with risk of cardiovascular mortality.

In sensitivity analyses, we additionally adjusted primary models for the inflammatory markers, CRP and IL-6, and repeated analyses using race specific quartiles of each mineral parameter. We accounted for the impact of missed dialysis treatments, as a measure of poor

adherence to treatment, on both mineral parameters and outcomes with analyses restricted to the subset of the population who missed ≤3% of scheduled dialysis treatments over a median of 3.6 years (interquartile range 2.1–4.9 years). Finally, we accounted for differing levels of residual renal function by performing analyses restricted to participants who reported ≥250 cc of urine per day at study enrollment (n=392). Statistical analyses were performed using Stata (Special Edition, version 11.1; Stata Corporation, College Station, TX, USA). Two-sided p-values ≤ 0.05 were considered significant, except for tests of interaction for which p ≤ 0.10 was considered significant due to reduced power in these comparisons.

Results

The study population includes 511 participants on hemodialysis from CHOICE with samples available for measurement of FGF23 and 25-hydroxyvitamin D. Participants had lower educational attainment, higher serum albumin, calcium and phosphorus, lower hemoglobin, and were more likely to have diabetes and higher index of coexistent disease compared to those without samples available (n=530; Supplemental Table 1). Participants enrolled in CHOICE a median of 51 days after dialysis initiation [interquartile range (IQR) 31 to 79 days] and began to accrue follow up in this study a median of 145 days (IQR 113 to 184) after dialysis initiation, at the time blood samples were obtained. Mean age was 58 ± 15 years. 57% of the study population had diabetes and 56% had atherosclerotic cardiovascular disease. Among those with medication information available, only 12% were using intravenous calcitriol at enrollment and use did not differ by race (p=0.39). African American participants were younger, less likely to have cardiovascular disease and had lower ICED compared to non-African Americans, among other differences (Table 1).

Baseline serum calcium in the study population was 9.3 ± 0.6 mg/dl, with 6% of participants above 10.2 and 7% below 8.5 mg/dl. Baseline serum phosphorus was 5.4 ± 1.3 mg/dl and 44% of the population was >5.5 mg/dl. Median FGF23 was 1577 RU/mL (IQR 818, 4946), median PTH was 148 pg/ml (IQR 70, 286), median 25-hydroxyvitamin D was 13.0 ng/ml (IQR 9.7, 17.2) and median total alkaline phosphatase was 89 IU/L (IQR 68.8, 113.5). African Americans had higher levels of PTH and total alkaline phosphatase, but lower levels of calcium, phosphorus, FGF23 and 25-hydroxyvitamin D than non-African Americans (Supplemental Figure 1).

Over a median of 3.4 years of follow up (IQR 1.8 to 5.9), 361 participants died from any cause (incidence rate 196 per 1000 person-years). Cause-specific mortality was ascertained over a shorter interval (median 3 years), during which 159 participants died from cardiovascular causes (incidence rate 88 per 1000 person-years). Cumulative survival was higher among African Americans compared to non-African Americans (p<0.001). Cumulative survival according to each mineral parameter and race is depicted in Figure 1.

Association of serum calcium with mortality

Higher serum calcium was not associated with risk of mortality after demographic adjustment (p=0.10). The risk of mortality was higher in the second quartile of serum calcium (8.9 to 9.2 mg/dl) after full adjustment (HR 2.10; 95% CI 1.45–3.05), but not in demographic adjusted models (p=0.16), and there was no linear relationship in continuous

analyses (p=0.72). When stratified by race, this overall pattern was observed among non-African Americans, but not African Americans, although the interaction was not statistically significant (Table 2; p=0.20).

Association of serum phosphorus with mortality

Similar to prior studies(17), higher quartiles of serum phosphorus were not associated with higher mortality in univariate analyses, but a significant association emerged after demographic adjustment (HR1.46, 95% CI 1.01–2.09 for highest compared with lowest; HR 1.14 per 1 mg/dl higher phosphate in continuous analyses, 95% CI 1.03–1.26) and persisted with full adjustment (Table 2). The associations were stronger among African Americans (p-interaction=0.04) with an over 5-fold higher risk among African Americans in the highest quartile compared to the lowest (HR 5.38, 95% CI 2.14–13.55; Table 2).

Association of FGF23 with mortality

Higher FGF23 was associated with greater mortality in continuous models that were demographic-adjusted (p=0.01) and fully adjusted (Table 2; p=0.004). A graded relationship between higher FGF23 was evident among African Americans (p=0.001; HR 3.91, 95% CI 1.74–8.82 for the highest versus lowest quartile). Quartiles 2 and 4 were associated with higher risk compared to quartile 1 in non-African Americans, but there was no relationship between log-transformed FGF23 and mortality in continuous analyses (p=0.23; p-interaction=0.09).

Association of PTH, 25-hydroxyvitamin D and total alkaline phosphatase with mortality

PTH and 25-hydroxyvitamin D were not associated with outcomes in any models. The highest and lowest quartiles of total alkaline phosphatase were associated with higher mortality overall, but there was no interaction by race (Table 2).

Secondary and Sensitivity Analyses

Results from models of cardiovascular mortality revealed similar estimates, although power was limited to test interaction (Table 3). In sensitivity analyses, additional adjustment for inflammatory markers or use of race-specific quartiles in lieu of overall quartiles did not meaningfully modify the results (data not shown). Analyses restricted to participants who missed fewer than 3% of their hemodialysis sessions (Supplemental Figure 2) and those with ≥250 cc/day of urine output were similar to primary analyses (Supplemental Figure 3).

Discussion

We report increased relative risk of all-cause and cardiovascular mortality associated with aberrant phosphorus metabolism, as indicated by higher serum phosphorus and FGF23, in patients recently initiating hemodialysis. The relative risks associated with higher phosphorus were evident only among African Americans whereas the risk associated with FGF23 were evident in both groups, but greater in African Americans compared to non-African Americans. Both higher and lower levels of total alkaline phosphatase were associated with mortality overall and there was no interaction by race. Prior studies in incident ESRD patients also found greater risk associated with elevated FGF23 in African

Americans compared to non-African Americans(1). Our study extends these findings over a long follow-up period and by including multiple mineral parameters and their association with overall and cardiovascular mortality.

Our results differ from a previous report in a large cohort of prevalent hemodialysis patients(18). In this study, there was no meaningful modification in the relationship between calcium, phosphorus, PTH and alkaline phosphatase by race. FGF23 was not measured and unlike our study, the majority of participants were using active vitamin D sterols, which may provide a survival benefit despite raising serum phosphorus(19). In addition, it is possible that the use of prevalent, as opposed to incident dialysis patients that were studied here, may have contributed to the disparate findings(1, 18).

The differences in mean levels of mineral parameters by race in this study mirror prior findings with higher levels of PTH among African Americans(20, 21), despite lower FGF23 and phosphorus(18, 22–24). This constellation of abnormalities could be consistent with more severe 1,25-dihydroxyvitamin D deficiency in African Americans, but we were not able to measure these levels to confirm this. We only had information available on use of intravenous calcitriol and not other vitamin D analogues that may have been in use during the follow-up period. The overall limited use of calcitriol at baseline in this cohort may have the advantage of revealing associations without confounding by treatment status or dose, but findings could differ in a more contemporary, treated cohort, particularly in light of changing PTH treatment guidelines over this time(25). We also did not have information available on the use of phosphorus binders; however, we do have data on achieved serum phosphorus, which has been commonly associated with outcomes in other cohorts(2).

25-hydroxyvitamin D levels, which were low in most of the participants, were not associated with mortality in either African Americans or non-African Americans in this study. Similarly, no relationship between 25-hydroxyvitamin D and death or ESRD events was found in a recent study of African Americans with pre-dialysis CKD(16). It is important to note that our study was initiated in 1995–1998 when nutritional vitamin D supplementation was not widespread which may explain the universally low levels. Our results confirm findings of another recently reported cohort of patients with advanced CKD and ESRD, in which 1-25-hydroxyvitamin D, but not 25-hydroxyvitamin D, was associated with death (23), reflecting risk that could be attributable to impaired 1-α hydroxylation due to FGF23 elevation. This group of results differs from the general population and other studies of CKD and ESRD populations in which low 25-hydroxyvitamin D was associated with higher mortality(26–32). In the prior studies of incident hemodialysis patients, only severe deficiency was associated with increased mortality(28), or risk was evaluated only for early dialysis mortality, within 90 days, in which low 25-hydroxyvitamin D may have reflected already declining health status (27).

It is unclear whether the differences in risk associated with aberrant phosphorus metabolism by race represent true heterogeneity in the biological impact of mineral homeostasis in African Americans on dialysis or are the result of differences in other characteristics of African Americans compared to non-African Americans with ESRD. African Americans on dialysis tend to be younger and have fewer comorbid diseases compared to non-African

Americans(33), differences that may be attributable to a higher prevalence of major risk alleles for kidney disease(34, 35). Despite higher risk for ESRD(36, 37), African Americans on dialysis have better survival compared with non-African Americans in most age groups(38, 39). As the result of major genetic contributions to ESRD in African Americans, it is possible that African Americans with ESRD have more organ-limited disease at dialysis initiation(40). A lower burden of systemic disease in African Americans and longer survival may result in less competing causes of death that are not attributable to dialysis-specific risk factors. As a result dialysis-specific risk factors may be more easily detected in African American populations. In fact, our group recently reported heterogeneity of the risk association between biomarkers of vascular calcification and mortality according to diabetic status with greater risk evident only among non-diabetics(41) and more linear association between blood pressure and outcomes in low-risk groups(42). Each of these results suggest that targeting dialysis-specific risk factors may be most useful in those with lower overall mortality risk.

Alternatively, it may be that the higher risk of adverse outcomes associated with aberrant phosphorus metabolism in African Americans is not merely due to competing risks, but instead attributable to biological differences. True differences in bone and mineral homeostasis by race are suggested by different rates of osteoporosis, vascular calcification, greater peripheral resistance to the actions of PTH(43–45) and genetic differences in the binding and handling of vitamin D (9, 22, 44, 46–49). A recent study suggests that APOL1, a major risk allele for ESRD in African Americans, may also promote cardiovascular disease (50), underscoring the possibility that genetic differences between African Americans and non-African Americans could result in differing implications of bone and mineral abnormalities and their possible role in cardiovascular disease pathogenesis.

Our study has several limitations including being an observational study where causality cannot be established. Although our data collection in this prospective cohort study was thorough, we may still be missing information on potential confounders that may affect the associations we found including data on control of comorbid illnesses. However, our study has several strengths as well. We were able to control for multiple known risk factors which were collected in a standardized fashion. We had multiple measurements for several mineral metabolism analytes to allow for more comprehensive characterization and physician adjudication of causes of death.

In summary, African Americans have a higher mortality risk with elevated serum phosphate and FGF23 levels compared to non-African Americans. Our findings provide impetus for research examining race-specific treatment targets for bone and mineral parameters and particularly for aberrant phosphorus metabolism. Such studies designed to test interventions of bone and mineral homeostasis should be powered adequately to evaluate possible differences in treatment effects by race.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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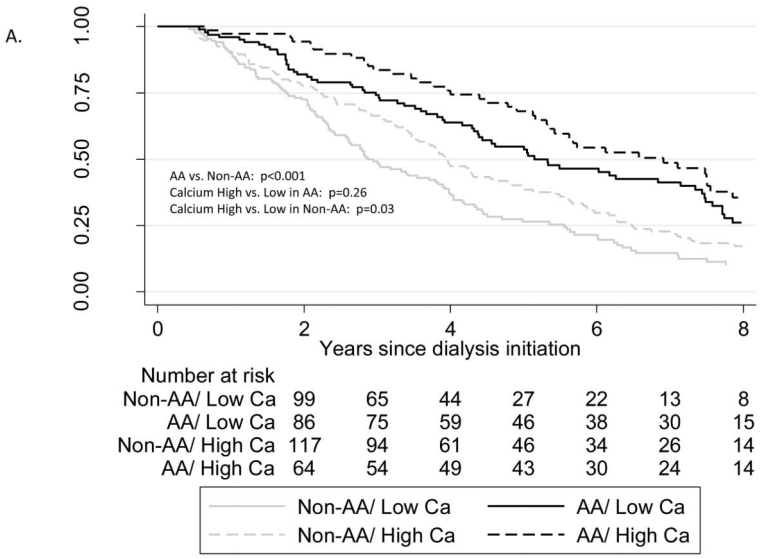
References

1. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis. N Engl J Med. 2008; 359(6): 584–92. [PubMed: 18687639]
2. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: A national study. Am J Kidney Dis. 1998; 31(4):607–17. [PubMed: 9531176]
3. Silver J, Naveh-Many T. FGF-23 and secondary hyperparathyroidism in chronic kidney disease. Nat Rev Nephrol. 2013; 9(11):641–9. [PubMed: 23877588]
4. Jono S, McKee M, Murry C, Shioi A, Nishizawa Y, Mori K, et al. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000; 87:e10–e7. [PubMed: 11009570]
5. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011; 121(11):4393–408. [PubMed: 21985788]
6. Amann K, Tornig J, Kugel B, Gross M, Tyralla K, El-Shakmak A, et al. Hyperphosphatemia aggrevates cardiac fibrosis and microvascular disease in experimental uremia. Kidney Int. 2003; 63:1296–301. [PubMed: 12631346]
7. Lam D, Kao W, Sozio S, Meoni L, Shafi T, Jaar B, et al. Interdialytic ionized calcium is associated with a pro-arrhythmic phenotype in incident dialysis patients: the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) Study [Abstract]. J Am Soc Nephrol. 2011; 22:487A.
8. Pun P, Horton J, Middleton J. Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. Clin J Am Soc Nephrol. 2013; 8(5):797–803. [PubMed: 23371957]
9. Bell N, Greene A, Epstein S, Oexmann M, Shaw S, Shary J. Evidence for alteration of the vitamin D-endocrine system in blacks. J Clin Invest. 1985; 76:470–3. [PubMed: 3839801]
10. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. J Am Soc Nephrol. 2011; 22(10):1913–22. [PubMed: 21903574]
11. Robinson-Cohen C, Hoofnagle A, Ix J, Sachs M, Tracy R, Siscovick D, et al. Racial differences in the association of serum 25-hydroxyvitamin D concentration with coronary heart disease events. JAMA. 2013; 310(2):179–88. [PubMed: 23839752]
12. Melamed M, Eustace J, Plantinga L, Jaar B, Fink N, Coresh J, et al. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. Kidney Int. 2006; 70(2):351–7. [PubMed: 16738536]
13. Miskulin DC, Martin AA, Brown R, Fink NE, Coresh J, Powe NR, et al. Predicting 1 year mortality in an outpatient haemodialysis population: a comparison of comorbidity instruments. Nephrol Dial Transplant. 2004; 19(2):413–20. [PubMed: 14736967]
14. Athienites NV, Miskulin DC, Fernandez G, Bunnapradist S, Simon G, Landa M, et al. Comorbidity assessment in hemodialysis and peritoneal dialysis using the index of coexistent disease. Semin Dial. 2000; 13(5):320–6. [PubMed: 11014695]
15. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, et al. Association Between Cholesterol Level and Mortality in Dialysis Patients: Role of Inflammation and Malnutrition. JAMA. 2004; 291(4):451–9. [PubMed: 14747502]

16. Scialla J, Astor B, Isakova T, Xie H, Appel L, Wolf M. Mineral metabolites and chronic kidney disease progression in African Americans. J Am Soc Nephrol. 2012; 24(1):125–35. [PubMed: 23243213]
17. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. Journal of the American Society of Nephrology. 2004; 15(8):2208–18. [PubMed: 15284307]
18. Kalantar-Zadeh K, Miller J, Kovesdy C, Mehrotra R, Lukowsky L, Streja E, et al. Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. J Bone Miner Res. 2010; 25(12):2724–34. [PubMed: 20614473]
19. Wolf M, Betancourt J, Chang Y, Shah A, Teng M, Tamez H, et al. Impact of activated vitamin D and race on survival among hemodialysis patients. J Am Soc Nephrol. 2008; 19(7):1379–88. [PubMed: 18400938]
20. Ennis J, Worcester E, Coe F. Contribution of calcium, phosphorus and 25-hydroxyvitamin D to the excessive severity of secondary hyperparathyroidism in African-Americans with CKD. Nephrol Dial Transplant. 2012; 27(7):2847–53. [PubMed: 22505656]
21. Gupta A, Kallenback L, Zasuwa G, Divine G. Race is a major determinant of secondary hyperparathyroidism in uremic patients. J Am Soc Nephrol. 2000; 11:330–4. [PubMed: 10665940]
22. de Boer IH, Gorodetskaya I, Young B, Hsu C-y, Chertow GM. The Severity of Secondary Hyperparathyroidism in Chronic Renal Insufficiency is GFR-Dependent, Race-Dependent, and Associated with Cardiovascular Disease. J Am Soc Nephrol. 2002; 13(11):2762–9. [PubMed: 12397047]
23. Kendrick J, Cheung A, Kaufman J, Greene T, Roberts W, Smits G, et al. Associations of plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations with death and progression to maintenance dialysis in patients with advanced kidney disease. Am J Kidney Dis. 2012; 60(4): 567–75. [PubMed: 22621970]
24. Jovanovich A, Chonchol M, Cheung A, Kaufman J, Greene T, Roberts W, et al. Racial differences in markers of mineral metabolism in advanced chronic kidney disease. Clin J Am Soc Nephrol. 2012; 7:640–7. [PubMed: 22383748]
25. KDIGO CKD-MBD Working 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(Suppl 113):S1–S130.
26. Melamed M, Michos E, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med. 2008; 168(15):1629–37. [PubMed: 18695076]
27. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, et al. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007; 72(8):1004–13. [PubMed: 17687259]
28. Dreschsler C, Verduijn M, Pilz S, Dekker F, Krediet R, Ritz E, et al. Vitamin D status and clinical outcomes in incident dialysis patients: results from the NECOSAD study. Nephrol Dial Transplant. 2011; 26(3):1024–32. [PubMed: 20947538]
29. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. Arch Intern Med. 2008; 168(12):1340–9. [PubMed: 18574092]
30. Navaneethan S, Schold J, Arrigain S, Jolly S, Jain A, Schreiber M, et al. Low 25-hydroxyvitamin D levels and mortality in non-dialysis dependent CKD. Am J Kidney Dis. 2011; 58(4):536–43. [PubMed: 21816525]
31. Pilz S, Tomaschitz A, Friedl C, Amrein K, Drechsler C, Ritz E, et al. Vitamin D status and mortality in chronic kidney disease. Nephrol Dial Transplant. 2011; 26(11):3603–9. [PubMed: 21378153]
32. Zittermann A, Iodice S, Pilz S, Grant W, Banardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analytis of prospective cohort studies. Am J Clin Nutr. 2012; 95(1):91–100. [PubMed: 22170374]
33. Kucirka L, Grams M, Lessler J, Hall E, James N, Massie A, et al. Association of race and age with survival among patients undergoing dialysis. JAMA. 2011; 306(6):620–6. [PubMed: 21828325]

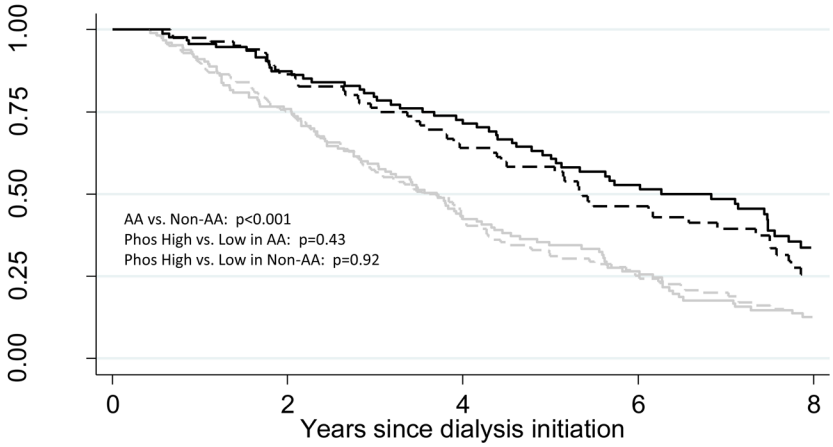
34. Foster M, Coresh J, Fronage M, Astor B, Grams M, Franceschini N, et al. APOL1 variants associate with increased risk of CKD among African Americans. J Am Soc Nephrol. 2013; 24(9): 1484–91. [PubMed: 23766536]
35. Parsa A, Kao W, Xie D, Astor B, Li M, Hsu C, et al. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013; 369(23):2183–96. [PubMed: 24206458]
36. Grams M, Chow E, Segev D, Coresh J. Lifetime incidence of CKD stages 3–5 in the United States. Am J Kidney Dis. 2013; 62(2):245–52. [PubMed: 23566637]
37. Kiberd B, Clase C. Cumulative risk for developing end-stage renal disease in the US population. J Am Soc Nephrol. 2002; 13:1635–44. [PubMed: 12039993]
38. Crews D, Sozio S, Liu Y, Coresh J, Powe N. Inflammation and the paradox of racial differences in dialysis survival. J Am Soc Nephrol. 2011; 22(12):2279–86. [PubMed: 22021717]
39. Yan G, Norris K, Yu A, Ma J, Greene T, Yu W, et al. The relationship of age, race and ethnicity with survival in dialysis patients. Clin J Am Soc Nephrol. 2013; 8(6):953–61. [PubMed: 23539227]
40. Buckalew VJ, Freedman B. Reappraisal of the impact of race on survival in patients on dialysis. Am J Kidney Dis. 2010; 55:1102–10. [PubMed: 20137840]
41. Scialla J, Kao W, Crainiceanu C, Sozio S, Oberai P, Shafi T, et al. Biomarkers of vascular calcification and mortality in patients with ESRD. Clin J Am Soc Nephrol. 2014; 9(4):745–55. [PubMed: 24458076]
42. Shafi T, Zager P, Sozio S, Grams M, Jaar B, Christenson R, et al. Troponin I and NT-proBNP and the association of systolic blood pressure with outcomes in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study. Am J Kidney Dis. 2014 Epub ahead of print.
43. Wassel C, Pankow J, Peralta C, Choudhry S, Seldin M, Arnett D. Genetic ancestry is associated with subclinical cardiovascular disease in African-Americans and Hispanics from the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Genet. 2009; 2:629–36. [PubMed: 20031644]
44. Bild D, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2005; 111(10): 1313–20. [PubMed: 15769774]
45. Weinstein R, Bell N. Diminished rates of bone formation in normal black adults. N Engl J Med. 1988; 319:1698–701. [PubMed: 3205266]
46. Powe C, Evans M, Wenger J, Zonderman A, Berg A, Nalls M, et al. Vitamin D-binding protein and vitamin D status of black americans and white americans. N Engl J Med. 2013; 369:1991–2000. [PubMed: 24256378]
47. Bhan I, Powe C, Berg A, Ankers E, Wenger J, Karumanchi S, et al. Bioavailable vitamin D is more tightly linked to mineral metabolism than total vitamin D in incident hemodialysis patients. Kidney Int. 2012; 82:84–9. [PubMed: 22398410]
48. Cosman F, Morgan D, Nieves J, Shen V, Luckey M, Dempster D, et al. Resistance to bone resorbing effects of PTH in black women. J Bone Miner Res. 1997; 12:958–66. [PubMed: 9169356]
49. Levin G, Robinson-Cohen C, de Boer I. Genetic variants and associations of 25-hydroxyvitamin D concentrations with major clinical outcomes. JAMA. 2012; 308:1898–905. [PubMed: 23150009]
50. Ito K, Bick A, Flannick J, Friedman D, Genovese G, Parfenov M, et al. Increased burden of cardiovascular disease in carriers of APOL1 genetic variants. Circ Res. 2014; 114(5):845–50. [PubMed: 24379297]

A.



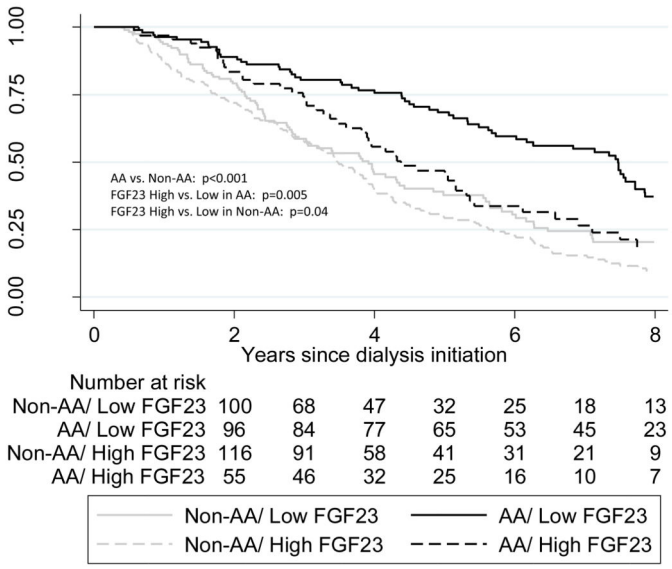
Number at risk							
Non-AA/ Low Ca	99	65	44	27	22	13	8
AA/ Low Ca	86	75	59	46	38	30	15
Non-AA/ High Ca	117	94	61	46	34	26	14
AA/ High Ca	64	54	49	43	30	24	14

B.



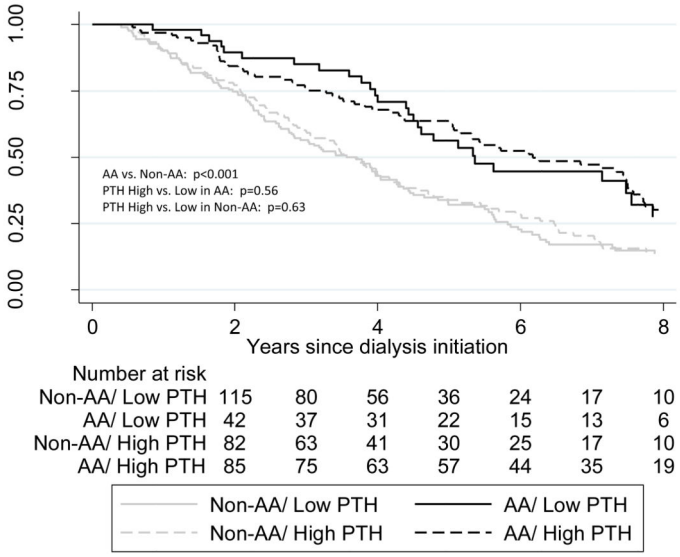
Number at risk							
Non-AA/ Low Phos	103	76	53	36	27	18	11
AA/ Low Phos	81	70	62	50	39	32	19
Non-AA/ High Phos	113	83	52	37	29	21	11
AA/ High Phos	69	59	46	39	29	22	10

C.



Number at risk							
Non-AA/ Low FGF23	100	68	47	32	25	18	13
AA/ Low FGF23	96	84	77	65	53	45	23
Non-AA/ High FGF23	116	91	58	41	31	21	9
AA/ High FGF23	55	46	32	25	16	10	7

D.



Number at risk							
Non-AA/ Low PTH	115	80	56	36	24	17	10
AA/ Low PTH	42	37	31	22	15	13	6
Non-AA/ High PTH	82	63	41	30	25	17	10
AA/ High PTH	85	75	63	57	44	35	19

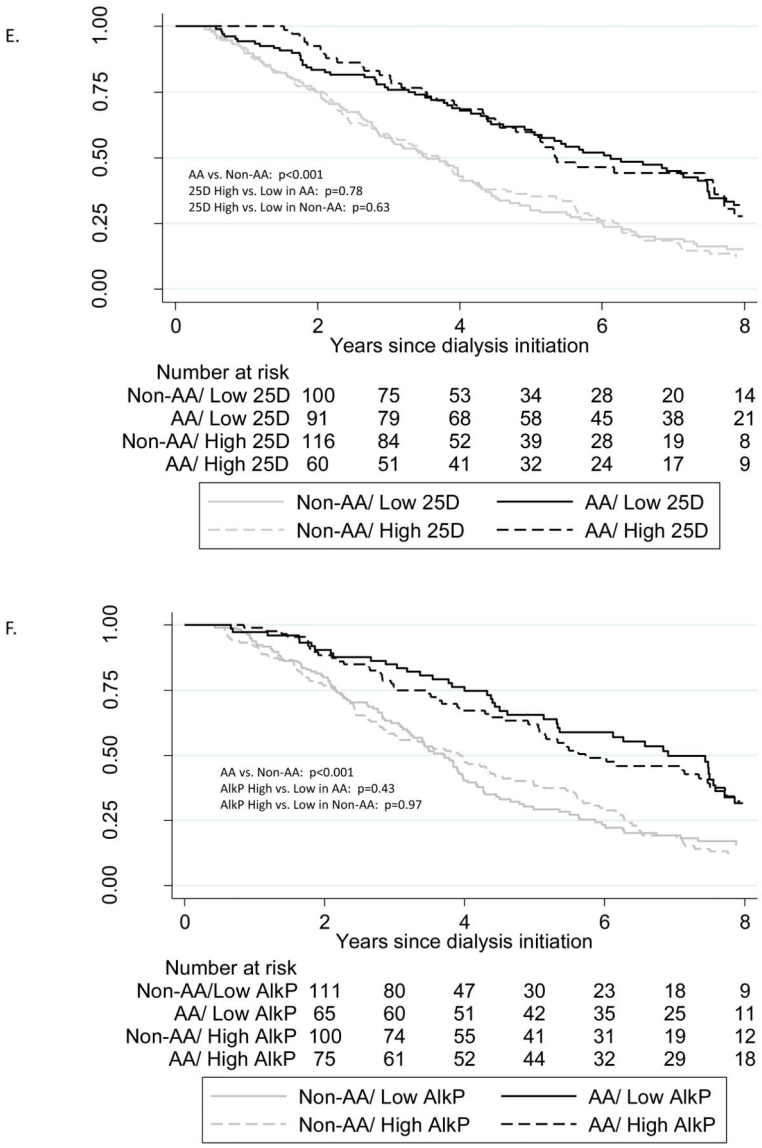


Figure 1.

Cumulative survival stratified by levels of mineral parameters and race. Race is defined as African American (AA) versus non-African American (Non-AA). Levels of mineral parameters are divided at the median: serum calcium ≤9.2 (Low Ca) versus >9.2 (High Ca); serum phosphorus ≤5.2 (Low Phos) versus >5.2 (High Phos); fibroblast growth factor 23 <1590 (Low FGF) versus ≥1590 (High FGF); parathyroid hormone <150 (Low PTH) versus ≥ 150; 25-hydroxyvitamin D <13.0 (Low 25D) versus ≥ 13.0 (High 25D); and total alkaline phosphatase ≤89.0 (Low AlkP) versus >89.0 (High AlkP). P-values are derived using the log-rank test.

(A)Serum calcium

(B) Serum phosphorus

(C) Fibroblast growth factor 23

(D)Parathyroid hormone

(E) 25-hydroxyvitamin D

(F) Total alkaline phosphatase

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Table 1

Baseline characteristics of study population by race

Mean ± SD, or n (%)	All patients (N=511)	African American (N=184)	Non-African American (N= 327)	P-value‡
Sociodemographics				
Age (years)	57.9 ± 14.8	54.6 ± 14.2	59.8 ± 14.8	<0.001
Female sex	231 (45%)	96 (52%)	135 (41%)	0.02
High school graduate	331 (65%)	98 (53%)	233 (71%)	<0.001
Clinical				
Late referral to nephrology (<4 months)	132 (26%)	57 (31%)	75 (23%)	0.03
Ever smoked	294 (58%)	106 (58%)	188 (57%)	0.99
Body mass index (kg/m^2)	27.4 ± 7.3	28.0 ± 7.7	27.1 ± 7.1	0.18
Diabetes mellitus	292 (57%)	110 (60%)	182 (56%)	0.39
Atherosclerotic cardiovascular disease	284 (56%)	86 (47%)	198 (61%)	0.002
Index of co-existent disease				0.03
0–1 (low)	150 (29%)	66 (36%)	84 (26%)	
2 (moderate)	206 (40%)	72 (39%)	134 (41%)	
3 (severe)	154 (30%)	46 (25%)	108 (33%)	
Reported urine output at enrollment				0.04
<250 cc/day	94 (18.4%)	44 (23.9%)	50 (15.3%)	
≥250 cc/day	392 (76.7%)	131 (71.2%)	261 (79.8%)	
Laboratory				
Albumin (g/dl)	3.72 ± 0.31	3.70 ± 0.30	3.72 ± 0.32	0.51
Hemoglobin (g/dl)	10.9 ± 1.0	10.6 ± 1.1	11.0 ± 0.9	<0.001
Calcium (mg/dl)	9.3 ± 0.6	9.1 ± 0.5	9.3 ± 0.6	<0.001
Phosphorus (mg/dl)	5.4 ± 1.3	5.2 ± 1.2	5.6 ± 1.3	<0.001
Intact parathyroid hormone (pg/ml)†	148 (70, 286)	206 (108, 361)	115 (61, 252)	<0.001
Fibroblast growth factor 23 (RU/ml)†	1577 (818, 4946)	1280 (603, 3546)	2133 (1004, 6089)	<0.001
25-hydroxyvitamin D (ng/ml)†	13.0 (9.7, 17.2)	11.9 (9.2, 14.6)	13.9 (10.0, 18.8)	<0.001
Total alkaline phosphatase (IU/L)†	89.0 (68.8, 113.5)	92.3 (70.2, 125.5)	87.1 (67.5, 107)	0.03
C-reactive protein (mg/l)†	4.3 (1.7, 11.1)	3.9 (1.4, 9.8)	4.4 (2.2, 12.4)	0.04

Mean ± SD, or n (%)	All patients (N=511)	African American (N=184)	Non-African American (N= 327)	P-value‡
Interleukin-6 (pg/ml)	4.3 (2.6, 7.6)	3.8 (2.5, 6.7)	4.7 (2.8, 9.0)	0.02

†Data presented as median (IQR). Abbreviations: SD: standard deviation, IQR: interquartile range

‡P-values for comparison between races by chi-square, one-way ANOVA or the Kruskal-Wallis test

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Table 2

Adjusted[†] hazard ratio (95% confidence interval) of mortality by mineral parameters and stratified by race

	Overall n=466 332 deaths	**African Americans n=160 109 deaths**	**Non-African Americans n=306 223 deaths**	**p-interaction[‡]**
Serum calcium (mg/dl)				
≤8.8	1.0	1.0	1.0	0.20
8.9–9.2	2.10 (1.45–3.05)	1.20 (0.59–2.42)	2.90 (1.76–4.80)	
9.3–9.6	1.30 (0.89–1.91)	0.77 (0.35–1.70)	1.51 (0.92–2.50)	
≥9.7	1.29 (0.86–1.92)	1.61 (0.70–3.70)	1.33 (0.79–2.25)	
Continuous (per 1 mg/dl)	1.04 (0.83–1.32)	1.32 (0.77–2.26)	0.97 (0.72–1.30)	
Serum phosphorus (mg/dl)				
≤4.5	1.0	1.0	1.0	0.04
4.6–5.2	1.03 (0.71–1.51)	1.16 (0.52–2.57)	0.83 (0.52–1.34)	
5.3–6.2	1.59 (1.07–2.37)	3.82 (1.68–8.69)	1.13 (0.68–1.88)	
≥6.3	1.68 (1.11–2.54)	5.38 (2.14–13.55)	1.08 (0.64–1.83)	
Continuous (per 1 mg/dl)	1.20 (1.07–1.34)	1.56 (1.23–1.97)	1.08 (0.94–1.25)	
Fibroblast growth factor 23 (RU/ml)				
≤818	1.0	1.0	1.0	0.09
819–1589	1.74 (1.18–2.57)	1.65 (0.79–3.45)	1.78 (1.05–2.99)	
1590–5000	1.95 (1.32–2.88)	3.80 (1.61–8.95)	1.61 (0.96–2.70)	
>5000	2.04 (1.38–3.01)	3.91 (1.74–8.82)	1.76 (1.04–2.96)	
Continuous (per LnFGF23)	1.17 (1.05–1.31)	1.49 (1.17–1.89)	1.09 (0.95–1.25)	
Parathyroid hormone (pg/ml)[§]				
≤70	0.96 (0.65–1.42)	1.51 (0.51–4.45)	0.85 (0.54–1.34)	0.29
71–149	1.0	1.0	1.0	
150–286	0.91 (0.62–1.34)	1.80 (0.70–4.61)	0.70 (0.43–1.15)	
≥287	1.05 (0.70–1.57)	2.42 (0.95–6.16)	0.88 (0.54–1.45)	
Continuous (per LnPTH)[*]	1.00 (0.89–1.14)	1.18 (0.89–1.57)	0.96 (0.83–1.12)	
25-hydroxyvitamin D (ng/ml)				
<9.7	0.92 (0.61–1.40)	0.75 (0.26–2.19)	0.87 (0.52–1.46)	0.44
9.7–12.9	0.91 (0.62–1.32)	0.86 (0.31–2.41)	0.75 (0.46–1.20)	

	Overall n=466 332 deaths	African Americans n=160 109 deaths	Non-African Americans n=306 223 deaths	p-interaction‡
13.0–17.2	0.93 (0.65–1.34)	0.78 (0.27–2.22)	0.99 (0.65–1.52)	
≥17.3	1.0	1.0	1.0	
Continuous (per ng/ml)	1.00 (0.98–1.02)	1.03 (0.96–1.10)	1.01 (0.98–1.04)	
Total alkaline phosphatase (IU/L)‖				
<68.8	1.57 (1.05–2.35)	1.64 (0.66–4.12)	1.54 (0.94–2.55)	0.97
68.8–89.0	1.39 (0.95–2.02)	1.35 (0.59–3.10)	1.36 (0.86–2.16)	
89.1–113.5	1.0	1.0	1.0	
≥113.6	1.66 (1.15–2.39)	1.23 (0.57–2.65)	1.76 (1.10–2.80)	
Continuous (per 10 IU/L)*	1.02 (1.00–1.04)	1.02 (0.98–1.07)	1.03 (0.99–1.06)	

† Adjusted for age, sex, education, smoking, body mass index, baseline index of coexistent disease (ICED), baseline diabetes mellitus, baseline cardiovascular disease, serum albumin and hemoglobin

‡ P-interaction from fully adjusted model in which mineral parameter was modeled as a continuous variable. Due to some evidence of non-linearity in quartile models, continuous parathyroid hormone and total alkaline phosphatase were modeled using restricted cubic splines for interaction testing

§ n=409 with available parathyroid hormone; Quartile 2 is used as reference quartile due to possible non-linear relationship with outcomes

‖ n=466 with available total alkaline phosphatase. Quartile 3 is used as the reference quartile due to prior reports of non-linear relationships with outcomes.

* Continuous model tests linear relation between PTH or total alkaline phosphatase and outcome

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Table 3

Adjusted[†] hazard ratio (95% confidence interval) of cardiovascular mortality by selected mineral parameters and stratified by race

	Overall n=466 146 events	**African Americans n=160 39 events**	**Non-African Americans n=306 107 events**
Serum phosphorus (mg/dl)			
≤4.5	1.0	1.0	1.0
4.6–5.2	0.88 (0.49–1.57)	0.60 (0.13–2.80)	0.71 (0.36–1.43)
5.3–6.2	1.49 (0.83–2.67)	3.53 (0.87–14.4)	1.16 (0.55–2.42)
≥6.3	1.90 (1.05–3.43)	6.95 (1.50–32.15)	1.28 (0.61–2.71)
Continuous (per 1 mg/dl)	1.27 (1.08–1.49)	1.65 (1.11–2.46)	1.20 (0.97–1.49)
Fibroblast growth factor 23 (RU/ml)			
≤818	1.0	1.0	1.0
819–1589	1.25 (0.69–2.25)	1.02 (0.27–3.85)	1.30 (0.60–2.79)
1590–5000	1.38 (0.76–2.50)	3.69 (0.88–15.5)	1.13 (0.53–2.40)
>5000	2.27 (1.28–4.00)	3.71 (0.97–14.2)	2.14 (1.04–4.41)
Continuous (per LnFGF23)	1.23 (1.05–1.45)	1.49 (1.00–2.24)	1.20 (0.98–1.47)
Parathyroid hormone (pg/ml)[‡]			
≤70	1.09 (0.62–1.91)	0.65 (0.11–3.82)	1.07 (0.56–2.03)
71–149	1.0	1.0	1.0
150–286	1.24 (0.72–2.14)	0.93 (0.21–4.03)	1.18 (0.60–2.33)
≥287	1.00 (0.54–1.86)	1.51 (0.37–6.10)	0.75 (0.35–1.63)
Continuous (per LnPTH)[§]	0.98 (0.82–1.17)	1.23 (0.80–1.88)	0.92 (0.74–1.13)

[†]Adjusted for age, sex, education, smoking, body mass index, baseline index of coexistent disease (ICED), baseline diabetes mellitus, baseline cardiovascular disease, serum albumin and hemoglobin

[‡]n=409 for parathyroid hormone due to missing data; Quartile 2 is used as reference quartile due to possible non-linear relationship with outcomes

[§]Continuous model tests linear relation between PTH and outcome