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Seasonal variation of serum 25-hydroxyvitamin D and parameters of bone and mineral disorder in dialysis patients

Carola-Ellen Kleine[a,b], Yoshitsugu Obi[a,b], Elani Streja[a,b], Jui-Ting Hsiung[a,b], Christina Park[a,b], Michael F. Holick[c], Kamyar Kalantar-Zadeh[a,b,*]

[a] Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine, Orange, CA, USA
[b] Long Beach Veterans Affairs Healthcare System, Long Beach, CA, USA
[c] Division of Endocrinology, Metabolism and Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

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ABSTRACT

Background: Vitamin D deficiency is common among dialysis patients and may impact blood concentrations of calcium, phosphorus, intact parathyroid hormone (iPTH), and alkaline phosphatase (ALP). Seasonal variation of serum 25-hydroxyvitamin D [25(OH)D] concentrations has been well established for the general population; however, less is known about circannual variation in 25(OH)D as well as other parameters of mineral and bone disorder among dialysis patients.

Method: Based on 57,500 serum 25(OH)D measurements collected over two years from January 2009 to December 2010 among 25,025 dialysis patients, we evaluated the circannual variations in serum concentrations of 25(OH)D, calcium, phosphorus, iPTH, and ALP by a linear regression model with a cosinor function for the time period (month). We adjusted for potential confounders including case-mix variables, and ultraviolet index.

Results: Serum 25(OH)D concentrations showed significant circannual variation and mean serum 25(OH)D was 3.2 ng/mL higher in summer than in winter. Furthermore, 25(OH)D concentration increased steadily by 1.3 ng/mL per year. While serum calcium concentrations showed statistically significant but clinically negligible seasonal variation (0.02 mg/dL in peak-trough difference), serum phosphorus did not follow such a pattern. Serum iPTH concentrations also showed a modest seasonal variation with 9% higher values in winter than in summer. Concordantly, ALP concentrations in the winter were 2% higher than in the summer time. Seasonal variation of 25(OH)D was greater in male (vs. female), African-American (vs. non-African-American), and younger (vs. older) dialysis patients.

Conclusion: Serum 25(OH)D and iPTH concentrations show seasonal variation among dialysis patients while the variation in other parameters of mineral and bone disorder was clinically irrelevant, if any. Serum 25(OH)D also showed a gradual increase over time. Clinicians and researchers should be aware of these changes when interpreting laboratory results in dialysis patients.

1. Introduction

Vitamin D deficiency is highly prevalent among dialysis patients [1,2]. Risk factors for vitamin D deficiency include decreased sun exposure (ultraviolet [UV]-B radiation; 290–315 nm), use of medications that can enhance vitamin D catabolism and lower dietary intake of vitamin D, among others [3,4]. In the general population, vitamin D deficiency, as evaluated by a low serum total 25-hydroxyvitamin D [25(OH)D] level, results in a rise in parathyroid hormone (PTH) concentration as a compensatory response to maintain a normal serum calcium concentration. This secondary hyperparathyroidism stimulates bone resorption and the conversion of 25(OH)D to its active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], which in turn promotes calcium resorption from the bone, calcium absorption in the intestine and calcium reabsorption in the kidneys. Among patients with late stages of chronic kidney disease (CKD), however, the former adaptive response eventually leads to high turnover bone disease with uncoupling of bone formation and resorption. In addition, hyperphosphatemia ensues due to decreased urinary phosphate excretion. The adaptive response via increased 1α-hydroxylase by PTH is diminished among dialysis patients due to severely damaged kidneys, hyporesponsiveness to PTH and highly elevated fibroblast growth factor-23 (FGF23). Therefore,

* Corresponding author at: Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, 101 The City Drive South, City Tower, Suite 400 – ZOT: 4088, Orange, CA 92868, USA.
E-mail address: kkz@uci.edu (K. Kalantar-Zadeh).

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hypocalcemia is a common complication in late stages of CKD. Prior studies have indicated that those parameters of mineral and bone metabolism such as vitamin D, calcium, phosphorus, PTH, and alkaline phosphatase (ALP) are associated with clinical outcomes among patients with CKD including end-stage renal disease (ESRD) [1,2,5–24].

Interestingly, seasonal variation in serum 25(OH)D concentrations is well documented worldwide in the general population primarily according to the change in season. Kroll et al. examined 3.8 million blood samples obtained in the United States (US) and observed that the peak blood concentration of 25(OH)D occurred at the end of summer in early September, while nadir or trough concentrations were observed at the end of the winter in early March [25]. Blood concentrations of PTH followed a reciprocal pattern to 25(OH)D with the trough occurring in late September and a peak occurring in early April. The other mineral and bone parameters may be impacted similarly due to their interrelationship.

However, less is known about such circannual variations of mineral and bone parameters in dialysis patients. Although 25(OH)D is not effectively converted to $1,25(OH)_2D$ in the kidney among dialysis patients who have extremely high FGF23, they are still able to activate vitamin D to some extent via 1α-hydroxylase in monocytes and the parathyroid glands, which are not downregulated by FGF23 [26]. In addition, dialysis patients' secular trends in vitamin D as well as other mineral and bone markers, remain unclear despite the rapidly increasing usage of nutritional vitamin D supplements among pre-dialysis patients with CKD in recent years [27]. Therefore, we aimed to simultaneously examine seasonal variations and secular trends of 25(OH)D, calcium, phosphorus, intact PTH (iPTH), and ALP, over a two-year period in a large cohort of dialysis patients in the US.

2. Materials and methods

This study was approved by the institutional review committees of the University of California, Irvine. No written consent was obtained due to patient anonymity, large sample size and the noninvasive nature of the study.

2.1. Patients

This retrospective study population consisted of ESRD patients who started either hemodialysis or peritoneal dialysis in one of the outpatient dialysis facilities of a large dialysis organization (LDO) between 01/2007 and 12/2011. The observation period was restricted to January 2009 to December 2010 due to changes in laboratory assays for 25(OH)D, iPTH, ALP, calcium and phosphorus before and after that time period. Thus, in the final study population of 25,025 patients, we identified 57,500 25(OH)D measurements between January 2009 and December 2010. Analytical cohorts for iPTH, ALP, calcium and phosphorus were built upon the 25(OH)D study population; patients with missing iPTH, ALP, calcium, or phosphorus were excluded accordingly from the corresponding study cohort (Fig. S1). Patients who did not receive dialysis treatment between January 2009 and December 2010 and patients with unknown race/ethnicity were also excluded from the analytical cohorts.

2.2. Ultraviolet exposure ascertainment

The UV Index (UVI) is an accepted measurement of UV radiation as described elsewhere [28,29]. The National Oceanic and Atmospheric Administration publishes daily UV Indices for 58 major cities in the US, whereby each state is at least represented by one city [30]. For this study, the annual average of UVI was calculated for every state and then linked to each individual study participant using the geographic area of the dialysis facility where he or she received treatment. Furthermore, the standard deviation of the annual UVI was computed as a time-constant variable to account for seasonal variation in UV radiation.

2.3. Demographic, clinical and laboratory measures

The LDO's electronic records database was used to obtain data on baseline demographics including self-categorized race/ethnicity and geographic area of primary dialysis facility. Blood samples were drawn using standardized techniques in all dialysis clinics and were transported to a central laboratory within 24 h. Except for 25(OH)D measurement, all laboratory values were measured using automated and standardized methods. 25(OH)D was tested by chemiluminescent immunoassay (DiaSorin, LIAISON®). The within- and inter-assay precision has been reported to range between 8 and 13% and ≤15%, respectively [31]. A previous study examined within-subject variability of two 25(OH)D measurements within one year using the DiaSorin LIAISON® assay and reported highly consistent results in 25(OH)D measurements obtained from the same individual [32].

25(OH)D concentrations were stratified into vitamin D deficiency (20 to < 30 ng/mL), insufficiency (< 20 ng/mL), and sufficiency (≥30 ng/mL).

2.4. Statistical analyses

Patient characteristics for the primary cohort including demographic data and laboratory data from the first three months after dialysis initiation, were summarized using total numbers, proportions, means ± standard deviation (SD) and median (interquartile range [IQR]), where appropriate.

A cosinor model was used to evaluate seasonal variation in 25(OH)D, iPTH, ALP, calcium and phosphorus concentrations. First, to determine the phase shift needed to combine sine and cosine functions, for each dependent variable (i.e., 25(OH)D), time (i.e., months from 01/2009) was modelled as a radian (i.e., $2\pi \times 12 \times$ months) in both a sine and cosine function, where time itself and these two trigonometric functions were simultaneously put in a multivariable linear model with adjustment covariates and without interaction terms [33]. The following adjustment covariates were included based on a priori considerations: year, age, gender, race (i.e., African-American vs. non-African-American), serum albumin, body mass index (BMI), UVI, and yearly average of each month's SD of UVI (annual SD of monthly UVI). Based on the resultant coefficients from this model, the sine and cosine functions were then combined into one cosine function with a horizontal shift in time.

Next, a second regression model was run for each dependent variable, which then included interaction terms between the cosine function and the adjustment covariates (with the exception of year and UVI) to quantify their possible effect on the amplitude of seasonal variation. We standardized (with subtraction) each continuous variable of the adjustment covariates to clinically relevant cut-off values that were close to the continuous variable's median, i.e., 65 years for age, 30 kg/m^2 for BMI, 3.8 g/dL for serum albumin, and 3 for annual UVI. The determined cosine function for each dependent variable was then interpreted according to the following: The resulting coefficient for the cosine function represented the predicted amplitude of seasonal variation, where the peak-trough difference corresponds to twice the coefficient value. The coefficient for the raw time variable represented the mean annual change in a given dependent variable. Subgroup analysis was also performed according to age, gender, and race. Since iPTH and ALP were not normally distributed, values underwent natural logarithmic transformation in the regression model, and their predicted and actual values were subsequently exponentiated (exponential base e) to transform back to the original scale. Seasonal variation (difference between peak and trough level) for iPTH and ALP was calculated by multiplying the coefficient of log(cosine) by 2 and subsequently exponentiating 2xlog(cosine).

Data for UVI, BMI, and serum albumin, were missing for 18%, 27% and 16%, respectively, of the 25(OH)D cohort; 17%, 20%, 10%, respectively, of the iPTH cohort, and 17%, 19%, 9%, respectively, of the

Table 1
Cohort characteristics of 25,025 study participants of the primary cohort.

Variable	Primary cohort
N	25,025
Age (years)	61 ± 15
Female, % (n)	43.6 (10,920)
African-American, % (n)	26.2 (6543)
Insurance, % (n)	
Medicare	51.6 (12,908)
Medicaid	5.7 (1428)
Other	42.7 (10,689)
Region, % (n)	
Northeast	9.7 (2424)
Northwest	15.3 (3840)
South	37.6 (9405)
West	26.7 (6686)
Unknown/missing	10.7 (2,670)
Cause of end-stage renal disease, % (n)	
Diabetes mellitus	45.4 (11,372)
Hypertension	26.7 (6674)
Glomerulonephritis	11.2 (2790)
Cystic kidney disease	2.2 (559)
Other	24.5 (3630)
Prior kidney transplant, % (n)	1.7 (420)
Modality, % (n)	
Only in-center hemodialysis	75 (18,764)
Only peritoneal dialysis	6 (1516)
Other/switching modality	19 (4745)
Comorbidities, % (n)	
Atherosclerotic heart disease	17.8 (4446)
Congestive heart failure	40 (10,023)
Cerebrovascular disease	1.7 (433)
Hypertension	53.4 (13,374)
Dyslipidemia	37.7 (9427)
Diabetes mellitus	67.5 (16,891)
Sleep apnea	3 (762)
Chronic obstructive pulmonary disease	5 (1245)
Liver disease	1.5 (379)
Thyroid disorder	17.1 (4269)
History of cancer	2.5 (624)
HIV/AIDS	0.4 (102)
Substance abuse	0.2 (52)
Alcohol abuse	0.3 (70)
Dementia	1.2 (300)
Depression	2.8 (698)
Charlson comorbidity score	5 (4;7)
Laboratory measurements at dialysis start	
Albumin (g/dL)	3.6 ± 0.5
Alkaline phosphatase (U/L)	85 (67.3; 111.6)
Blood urea nitrogen (mg/dL)	49.4 ± 14.7
Calcium (mg/dL)	8.7 ± 0.6
Cholesterol (mg/dL)	154.9 ± 46.6
Creatinine (mg/dL)	5.9 ± 2.4
Ferritin (ng/mL)	269.7 (153.3; 463.5)
HbA1c (%)	6.4 ± 1.2
Hemoglobin (g/dL)	11.3 ± 1.2
Intact parathyroid hormone (pg/mL)	297.5 (187.3; 460.4)
Potassium (mmol/L)	4.4 ± 0.5
Sodium (mmol/L)	138.7 ± 0.3
White blood cell count (/μL)	7.8 ± 2.5
Body mass index (kg/m^2)	28.6 ± 7.4

Note: Results are expressed as mean ± SD, median (IQR) or total and percentage as appropriate.
Conversion factors for units: albumin and hemoglobin in g/dL to g/L, multiply by 10; alkaline phosphatase in U/L to μkat/L, multiply by 0.0167; blood urea nitrogen and cholesterol in mg/dL to mmol/L, multiply by 0.0259; creatinine in mg/dL to mmol/L, multiply by 88.4; calcium in mg/dL to mmol/L, multiply by 0.2495. No conversion is necessary for ferritin in ng/mL to mg/L, for intact parathyroid hormone in pg/mL to ng/L, for potassium and sodium in mmol/L to mEq/L; white blood cell count per μL to $\times 10^9$/μL, multiply by 0.001.

ALP, calcium, and phosphorus cohort. Missing values were handled by multiple imputation. We accounted for intra-individual correlation in regression analyses. All statistical analyses were performed with Stata, version 13.1 (Stata Corporation, College Station, Tex., USA), logarithmic values were exponentiated using Microsoft Excel 2016 (Microsoft, Redmond, WA) and figures were plotted using SigmaPlot Version 12.5 (systat Software, San Jose, CA).

3. Results

3.1. Patient characteristics of the primary cohort

In the 25,025 dialysis patients included in the 25(OH)D analysis, the mean age was 61 ± 15 years, approximately 44% of patients were female, 26% were self-reported African-Americans, 68% had diabetes and 40% had congestive heart failure (Table 1). Over the course of time on dialysis, 75% of our primary cohort were only on in-center hemodialysis, while 6% were only on peritoneal dialysis. 38% of patients resided in the southern part of the US, while 27% lived in the western regions. Mean BMI at dialysis start in this analytical cohort was 28.6 ± 7.4 kg/m^2.

3.2. Seasonal variation and secular trend in 25(OH)D, iPTH and ALP

Overall, 25(OH)D concentrations showed a significant seasonal variation ($p_{cosine} < .001$) with the peak and trough concentrations in summer and winter time, respectively (Table 2, Fig. 1A). The estimated peak-trough difference was 3.2 (coefficient$_{cosine}$ −1.6, 95% CI −1.9 to −1.2) ng/mL. In addition, mean monthly 25(OH)D concentrations showed an increasing trend by 1.3 (95% CI 1.0 to 1.5) ng/mL per year ($p < .001$) during our two-year observation period. In February 2009, approximately 77% of patients were considered vitamin D deficient/insufficient while in August 2009 only 36% had a 25(OH)D concentration < 20 ng/mL. Similarly, the prevalence of vitamin D concentration < 30 ng/mL decreased from 74% in February to 67% in August in 2010, respectively (Table 3).

Gender, race and serum albumin significantly modified the seasonal variation of 25(OH)D, where the amplitude of the cosine wave was attenuated with female gender, African-American race, and lower serum albumin ($p_{interaction} < .001$ for all, except female $p_{interaction} = .002$). Diabetes and the annual variation of monthly UVI (SD mean annual UVI) did not significantly modify the amplitude of the seasonal variation of 25(OH)D (Table 2).

Additionally, iPTH concentrations showed seasonal variation of 9% per year (coefficient$_{cosine}$ 1.04; 95% CI 1.03 to 1.05; $p < .001$) (Fig. 1B, Table 2), with the lowest estimated value occurring in the summer time. During the observation period, iPTH concentrations increased slightly by 4% per year (coefficient$_{year}$ 1.04, 95% CI 1.03 to 1.04; $p < .001$). In addition, ALP concentrations had a very small, but statistically significant seasonal variation of 2% per year (coefficient$_{cosine}$ 1.01, 95% CI 1.00 to 1.01; $p < .001$) (Fig. 1C, Table 2). Similar to iPTH, the lowest predicted ALP concentration was found in the summer time.

3.3. Other predictors of 25(OH)D, iPTH and ALP concentration

Females, African-American race, and diabetes were associated with lower 25(OH)D concentrations by −2.1 ng/mL (95% CI −2.5 to −1.8, $p < .001$), −0.7 ng/mL (95% CI −1.2 to −0.3, $p = .001$), and −2.0 ng/mL (95% CI −2.4 to −1.7, $p < .001$) compared to their counterparts, respectively. BMI ($p < .001$) and SD of annual UVI ($p = .02$) also showed negative correlations with 25(OH)D concentration. Serum albumin and older age were positively associated with 25(OH)D ($p < .001$ for both) (Table 2).

Compared to males and non-African-Americans, females and African-Americans had higher iPTH concentrations by 2% ($p = .02$) and 23% ($p < .001$), respectively. Serum albumin concentrations (19% per g/dL) and BMI (1% per 1 kg/m^2) correlated positively with iPTH concentrations ($p < .001$ for both). Every 10-year increase in age was associated with 6% lower iPTH concentrations ($p < .001$). Similarly, every unit increase of annual SD of monthly UVI was related to a 3%

Table 2
Multivariable linear regression analysis with 25(OH)D, iPTH and alkaline phosphatase as dependent variable.

		25(OH)D		iPTH		Alkaline Phosphatase	
		(n = 25,025)		(n = 24,979)		(n = 25,003)	
Variable	*Description*	Coef. (95%CI)	*P Value*	Coef.[a] (95%CI)	*P Value*	Coef.[a] (95%CI)	*P Value*
Cosine (2π*year [year])	*Amplitude of cosine wave*	-1.6 (-1.9;-1.2)	< .001	1.04 (1.03;1.05)	< .001	1.01 (1.00;1.01)	< .001
Year	*Annual trend*	1.3 (1.0;1.5)	< .001	1.04 (1.03;1.04)	< .001	1.03 (1.02;1.03)	< .001
Age (per 10 year, Ref. 65 years)		1.3 (1.2;1.4)	< .001	0.94 (0.93;0.94)	< .001	0.98 (0.98;0.99)	< .001
Female		-2.1 (-2.5;-1.8)	< .001	1.02 (1.00;1.03)	0.02	1.11 (1.10;1.12)	< .001
African-American		-0.7 (-1.2;-0.3)	0.001	1.23 (1.21;1.24)	< .001	0.98 (0.96;0.99)	< .001
Diabetes mellitus		-2.0 (-2.4;-1.7)	< .001	0.97 (0.96;0.99)	0.001	1.10 (1.08;1.11)	< .001
Serum albumin (per 1 g/dL, Ref. 3.8 g/dL)		3.0 (2.7;3.4)	< .001	1.19 (1.17;1.20)	< .001	0.85 (0.84;0.85)	< .001
BMI (per 1 kg/m^2, Ref. 30 kg/m^2)		-0.2 (-0.2;-0.1)	< .001	1.01 (1.00;1.01)	< .001	1.00 (1.00;1.00)	< .001
Mean annual UVI		-0.5 (-0.6;-0.4)	< .001	1.00 (1.00;1.01)	0.08	0.99 (0.99;1.00)	0.001
SD mean annual UVI (per 1, Ref. 3)		-0.9 (-1.7;-0.1)	0.02	0.97 (0.94;1.00)	0.03	0.98 (0.99;1.00)	0.1
Interaction terms with cosine (2π*year [year])							
Age (per 10 year, Ref. 65 years)	*Effect modifier*	0.2 (0.1;0.3)	< .001	1.00 (1.00;1.00)	0.7	1.00 (1.00;1.00)	0.1
Female	*Effect modifier*	0.4 (0.1;0.7)	0.002	1.00 (0.99;1.01)	0.5	1.00 (1.00;1.00)	0.8
African-American	*Effect modifier*	0.8 (0.5;1.2)	< .001	1.01 (1.00;1.02)	0.05	1.00 (1.00;1.01)	0.3
Diabetes mellitus	*Effect modifier*	0.2 (-0.1;0.5)	0.2	1.00 (0.99;1.01)	0.6	1.00 (1.00;1.01)	0.9
Serum albumin (per 1 g/dL, Ref. 3.8 g/dL)	*Effect modifier*	-0.9 (-1.3;-0.5)	< .001	1.01 (0.99;1.02)	0.3	1.01 (1.00;1.01)	0.02
BMI (per 1 kg/m2, Ref. 30 kg/m2)	*Effect modifier*	0.0 (0.0;0.1)	0.008	1.00 (1.00;1.00)	0.97	1.00 (1.00;1.00)	0.6
SD mean annual UVI (per 1, Ref. 3)	*Effect modifier*	-0.6 (-1.2;0.0)	0.07	1.00 (0.98;1.02)	0.9	1.00 (0.99;1.01)	0.7
Constant	*Mean value*	27.3 (25.9;28.6)	< .001	206.52 (197.01;216.48)	< .001	74.04 (71.40;76.78)	< .001

Abbreviations: Coef. – Coefficient, Ref. – reference value.
Note: Coefficient of cosine describes the amplitude of the cosine shaped wave, coefficient of year represents the annual trend, coefficients of the interaction terms are effect modifier of the amplitude or phase of the cosine wave, while the coefficient of the constant represents the mean value. Seasonal variation (difference between peak and trough level) for 25(OH)D was obtained by multiplying the coefficient of cosine by 2; for iPTH and ALP, the coefficient of log(cosine) was multiplied by 2 and subsequently exponentiated (exponential base e).
Note: Actual iPTH and ALP values underwent logarithmic transformation (natural logarithm) in the regression model, and their predicted values were subsequently exponentiated (exponential base e) to transform back to the original scale.
[a] Coefficient of log(iPTH) and log(ALP), respectively.

lower iPTH concentration ($p = .03$) (Table 2).

Female gender and diabetes were associated with higher ALP concentrations by 11% and 10% ($p < .001$ for both), while being African-American was related to lower ALP concentrations by 2% ($p < .001$) when compared to their counterparts (Table 2).

3.4. Examination of 25(OH)D, iPTH and ALP in pre-specified subgroups

Although seasonal variation of 25(OH)D was consistently observed across subgroups of dialysis patients ($p_{cosine} < .05$ for all), several factors modified its amplitude (Fig. 2). Male patients had a greater peak-trough concentration difference of 1.4 (coefficient$_{cosine}$ 0.7, 95% CI 0.1 to 0.9) ng/mL when compared to female patients who showed a peak-trough difference of 0.8 (coefficient$_{cosine}$ 0.4, 95% CI 0.1 to 0.6) ng/mL (data not shown), which was consistent with the signficant result for the interaction term between female and the cosine function presented in Table 2. African-American dialysis patients showed a greater peak-trough difference of 2.0 (coefficient$_{cosine}$ 1.0, 95% CI 0.6 to 1.3) ng/mL compared to non-African-American patients who had a peak-trough difference of 0.6 (coefficient$_{cosine}$ 0.3, 95% CI 0.1 to 0.5) ng/mL (data not shown). Dialysis patients younger than 65 years old had greater seasonal variation (coefficient$_{cosine}$ 0.7, 95% CI 0.5 to 0.9) than older patients (coefficient$_{cosine}$ 0.4, 95% CI 0.1 to 0.6). Additionally, annual increase in predicted 25(OH)D was greater in older patients ≥65 years old (1.6 ng/mL, 95% CI 1.2 to 1.9) than in younger patients (1.2 ng/mL, 95% CI 1.0 to 1.5) (data not shown).

IPTH concentrations showed seasonal variation across all subgroups ($p_{cosine} < .001$ for all) (Fig. S2). Female and male dialysis patients had a 10% and 9% peak-trough difference, respectively, while the peak-trough difference in African-Americans was 2% higher compared to non-African-Americans (data not shown). Even though patients ≥65 years old showed lower iPTH concentrations when compared to patients < 65 years, the peak-trough difference differed only by 1% across both subgroups (data not shown).

Similarly, as shown in Fig. S3, ALP concentrations followed seasonal variation across all subgroups of dialysis patients ($p_{cosine} < .001$ for all). However, with a peak-trough difference of as little as 2% and 3% in non African-Americans and African-Americans, respectively, the observed variation appears negligible (data not shown).

3.5. Seasonal variation and secular trend in calcium and phosphorus

Altogether, calcium concentrations showed statistical significant but clinically irrelevant seasonal variation with the estimated peak-trough difference of 0.02 mg/dL (coefficient$_{cosine}$ 0.01, 95% CI 0.00 to 0.02; $p = .01$) (Fig. S4A, Table S1). Calcium concentrations also showed a minimal increasing trend of 0.05 mg/dL/year (95% CI 0.04 to 0.05; $p < .001$) during the observation period. Higher albumin further mitigated the calcium seasonal variation ($p_{interaction} < .001$).

In contrast, phosphorus concentrations showed a negligible annual decrease by −0.02 mg/dL/year (95% CI −0.03 to −0.01; $p = .003$), and did not vary across seasons ($p_{cosine} = .08$; Fig. S4B, Table S1).

3.6. Other impact on calcium and phosphorus

Females and being African-American were positively associated (coefficient 0.09 and 0.05, respectively; $p < .001$ for both), while diabetes and greater annual variation in UVI were negatively associated with calcium concentrations (coefficient −0.07 and −0.05, respectively; $p < .001$ for both). Serum albumin (0.51 mg/dL per 1 g/dL) and higher age (0.01 mg/dL per 10 years) were also positively associated with calcium concentrations ($p < .001$ for both) (Table S1).

African-American race was associated with lower phosphorus concentrations (coefficient −0.14; $p < .001$) and higher annual SD of monthly UVI was also negatively associated with phosphorus concentrations (coefficient −0.17; $p < .001$, respectively) (Table S1).

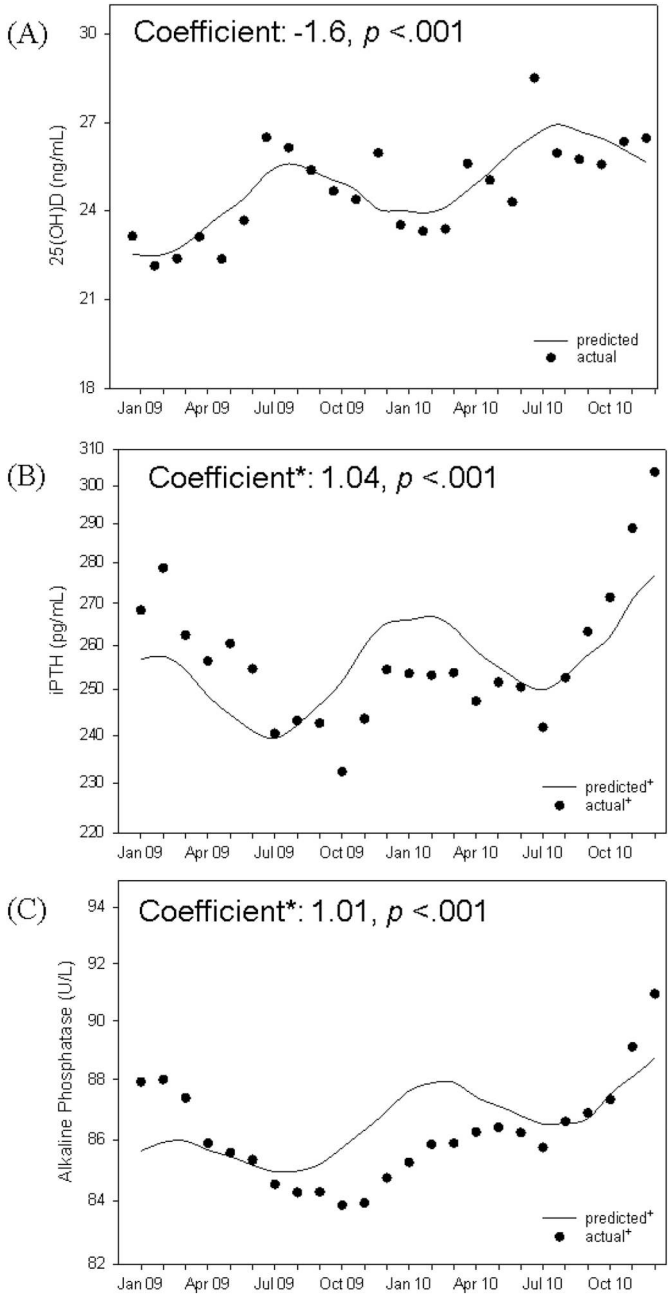

Fig. 1. Fitted cosinor model for predicted (A) 25(OH)D, (B) iPTH and (C) ALP status between January 2009 and December 2010. Superimposed are the actual (A) mean 25(OH)D, (B) iPTH and (C) ALP values.
Note: *coefficient of log(iPTH) and log(ALP), respectively. +Actual iPTH and ALP values underwent logarithmic transformation (natural logarithm) in the regression model, and their predicted values as well as logarithmic transformed actual values were subsequently exponentiated (exponential base e) to transform back to the original scale.

Table 3
Percentage of patients with deficient and insufficient 25(OH)D status in February (trough concentration) and August (peak concentration) in 2009 and 2010.

25(OH)D status	Feb-09	Aug-09	Feb-10	Aug-10
Insufficiency (< 20 ng/mL)	50%	36%	45%	36%
Deficiency (≥20–30 ng/mL)	27%	31%	29%	31%
Sufficiency (≥30 ng/mL)	23%	34%	26%	33%

Note: Numbers might not add up to 100% due to rounding.

3.7. Examination of calcium subgroups

The seasonal variation of calcium concentrations across all subgroups (p_{cosine} < .05 for all) were statistically significant, but small and accounted for 0.02 mg/dL/year variation (Fig. S5).

4. Discussion

In this longitudinal and national cohort of 25,025 adult dialysis patients, serum 25(OH)D concentration reached a peak in summer and trough in winter. Serum iPTH concentration varied reciprocally to 25(OH)D concentrations. These seasonal variations were consistent across pre-specified subgroups. Additionally, we observed a positive trend in serum 25(OH)D and iPTH concentrations between January 2009 and December 2010. In contrast, serum concentrations of calcium, phosphorus, and ALP did not show clinically relevant seasonal or secular variation, if any.

Our study is unique since we were able to simultaneously capture monthly averaged 25(OH)D iPTH, calcium, phosphorus and ALP concentrations over a two-year period and thus detect concurrent circannual variations in a large cohort. Yet, we are unable to account for vitamin D supplementation, which is a major limitation of this study. We might indirectly infer that vitamin D supplementation increased during the two year observation period, since we observed a positive trend in mean 25(OH)D concentration. Likewise, data from the Chronic Renal Insufficiency Cohort (CRIC) that recruited individuals with mild to moderate CKD, showed that during 2003 to 2011 the proportion of vitamin D supplementation increased which mirrored an increase in 25(OH)D concentration [27]. Of note, vitamin D supplementation might abolish seasonal variation in 25(OH)D concentrations and interfere with seasonality of other biomarkers of bone and mineral disorder such as iPTH [34,35]. Nevertheless, circannual variation of vitamin D status in CKD stage 5 or dialysis patients with higher concentrations in the summer than winter time has been previously described [36–39]. In our study, we did not see a modification of the amplitude of seasonal variation by the yearly average of each month's SD of UVI, which was unexpected since the association between UVB radiation and 25(OH)D concentrations has been well established [3,40–43]. However, vitamin D supplementation might mask the relationship between UVI and 25(OH)D concentration [34], or ESRD patients might be less physically active [44] and therefore have less exposure to UVB radiation. On the other hand, in our cohort we found that 74–77% of dialysis patients had a 25(OH)D concentrations as low as < 30 ng/mL in wintertime, compared to 67% in the summer time.

We were unable to identify reasons for seasonal variation of vitamin D in our cohort; however, previous studies may lend insight to underlying mechanisms. Broers et al. reported seasonal variation of body composition in HD patients, measured by bio-impedance spectroscopy, with higher fat mass in winter time [45]. While adipose tissue functions as 25(OH)D storage [46–48], seasonal variation in fat mass could contribute to the observed variation of 25(OH)D in dialysis patients. In addition, other factors such as lifestyle and dietary intake might be involved. Furthermore, evaluating the biological significance of the described seasonal variation may be challenging, given that serum 25(OH)D of an individual may fluctuate, which may complicate the detection of small changes throughout seasons. However, based on previous literature, it is possible that a seasonal variation as little as 3.2 ng/mL may impact clinical outcomes. Although the definition of vitamin D deficiency varies between studies, vitamin D deficiency has been associated with worse survival in CKD and dialysis patients [49–55] and was more prevalent during winter time in our cohort. Interestingly, all-cause, CV and infectious mortality also follow seasonal patterns with the highest incidence in the winter and lowest in the summer time for all three outcomes [56]. This observation may be ascribed to seasonal patterns in vitamin D status, but this point is speculative and needs to be investigated further.

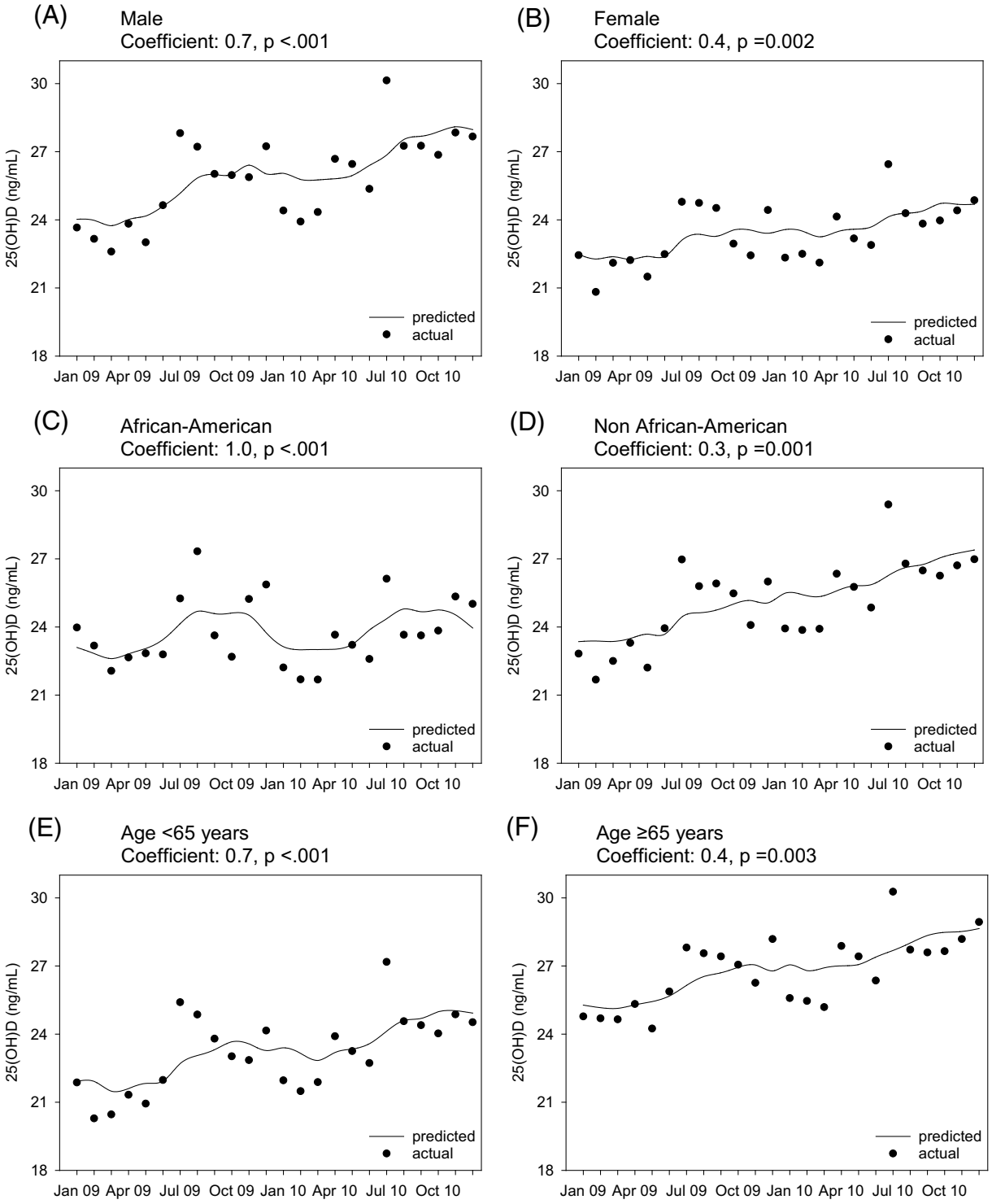

Fig. 2. Fitted cosinor model for predicted monthly mean 25(OH)D concentrations, superimposed on plotted actual mean 25(OH)D values between January 2009 and December 2010 for (A) male, (B) female, (C) African-American, (D) Non-African-American, (E) ESRD patients < 65 years old and (F) ESRD patients ≥65 years old.

Other studies have also described seasonal variation of PTH concentrations in dialysis patients with higher values in the winter than in the summer [57,58]. Moreover, in a cohort of chronic HD patients residing in mild Mediterranean climate, seasonal variation has been found for serum ALP concentrations, but with lower values in the colder months (March and December) [59]. In contrast, a study from Japan confirmed higher serum ALP concentrations in the winter than in the summer, which is consistent with our data [60]. Seasonal variation was not consistently observed for serum calcium and phosphorus across studies [59–61]. The conflicting data regarding seasonal variation of serum calcium and phosphorus concentrations and timing of peak and trough levels of phosphorus and ALP concentrations in different countries all located in the northern hemisphere are difficult to interpret. Differences in culture-specific nutritional and lifestyle factors (e.g. exposure to UV radiation [62], use of sunscreen or non-translucent clothing [63,64]) might contribute to differences in these findings. Besides, nutritional intake may also vary seasonally [65]. Similar factors may also contribute to the observed lesser seasonal variation of

25(OH)D concentration in non-African-American compared to African-American patients.

A strength of this study is the longitudinal approach with multiple measurements within individuals. Our cohort was diverse since it included different age groups. Additionally, we accounted for African-American race/ethnicity and we included patients from different geographic locations of the continental US. Several limitations should be mentioned: Due to the observational design, we cannot draw any causal conclusion regarding seasonal variation in 25(OH)D, iPTH, ALP, calcium and phosphorus and factors affecting these associations. Further, 25(OH)D concentrations were not measured using liquid chromatography-tandem mass spectrometry, which is considered to be the gold standard [66]. It should also be mentioned that intra- and inter-assay measurement variability might lead to fluctuation in 25(OH)D results, when tested repeatedly. However, Major et al. examined within-subject variability of two 25(OH)D measurements within one year using DiaSorin LIAISON® assay and reported highly consistent results in 25(OH)D measurements obtained from the same individual [32]. Conversely, since measurements were obtained at different times throughout the 2-year observation period, we cannot rule out that our results were affected by inter-assay variability, although all labs were shipped to and measured in the same central laboratory. Similarly, data on body composition was not available and using BMI as a proxy to estimate body shape may lead to some biases. We were also unable to identify sources of seasonal variation other than UV-B due to lack of information on medication, dietary intake or lifestyle changes that influence vitamin D, iPTH, ALP, calcium and phosphorus concentrations. Information was also unavailable for vitamin D binding protein, which binds the majority of circulating 25(OH)D in the blood [67]. However, previous published data suggest that vitamin D binding protein remains uninfluenced by seasons [68,69].

Additionally, we did not account for residual renal function or albuminuria, which can lead to decreased 25(OH)D concentrations [70]. Since we could not account for each patient's personal UV radiation exposure, we crudely estimated UV exposure dependent on the location of the dialysis unit. Moreover, forecasted clear sky UVI may not represent actual weather (i.e., cloudiness), and we lacked specific data to account for weather impact on these measurements.

In conclusion, we demonstrated seasonal variation of vitamin D and iPTH concentrations among ESRD patients during two consecutive years, while seasonal variations in ALP and calcium were clinically irrelevant. Clinicians and researchers should be aware of these changes when interpreting laboratory results in dialysis patients.

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MFH is on the speakers Bureau and has received honoraria from Shire, Sanofi-Adventis, HyperMarcus, Abbott Nutrition and an Academic Associate for Quest Diagnostics.

CEK, YO, ES, JTH and CP: Nothing to declare.

Author contributions

CEK contributed to the analysis and interpretation of data and drafting of the article. YO, ES and KKZ designed the study, contributed to analysis and interpretation of the data as well as drafting and critically revising the manuscript. CP and JTH contributed to analysis of the data and drafting the article. MFH revised the manuscript critically for intellectual content.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.03.003.

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