HHS Public Access

Author manuscript

J Nephrol. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

J Nephrol. 2015 June ; 28(3): 351–359. doi:10.1007/s40620-014-0124-6.

Circadian variation of mineral and bone parameters in end-stage renal disease

Hariprasad Trivedi,
Divisions of Nephrology, Department of Medicine, Medical College of Wisconsin, 9200 W. Wisconsin Ave., CLCC 5220, Milwaukee, WI 53226, USA

Aniko Szabo,
Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI, USA

Shi Zhao,
Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI, USA

Tom Cantor, and
Scantibodies Laboratory, Inc., Santee, CA, USA

Hershel Raff
Division of Endocrinology, Metabolism and Clinical Nutrition, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

Endocrine Research Laboratory, Aurora St. Luke's Medical Center, Aurora Research Institute, Milwaukee, WI, USA

Hariprasad Trivedi: haritriv7@gmail.com

Abstract

Background—Mineral and bone parameters are actively managed in end-stage renal disease (ESRD). However, whether these undergo circadian variation is not known. We investigated the circadian variation of mineral and bone parameters in patients on long-term hemodialysis.

Methods—Seventeen ESRD patients on long-term hemodialysis and eight volunteers without kidney disease were enrolled. Subjects had all medications that affect calcium–phosphate–parathyroid hormone balance (phosphate binders, vitamin D analogues, and calcimimetics) discontinued. Thereafter, for a period of 5 days, subjects consumed a diet controlled in calcium (1,200 mg per day) and phosphorus (1,000 mg per day) content. On the sixth day (a non-dialysis day for the ESRD patients), enrollees underwent twelve 2-h blood draws for phosphate, ionized calcium, parathyroid hormone (PTH), total 25-hydroxy vitamin D (25OHD), and fibroblast growth factor-23 (FGF-23).

Correspondence to: Hariprasad Trivedi, haritriv7@gmail.com.

This work was presented at annual meeting of the American Society of Nephrology in Atlanta, Georgia in November 2013 and published in abstract form in the abstract edition of the *Journal of the American Society of Nephrology*.

Conflict of interests Aniko Szabo: None. Shi Zhao: None. Tom Cantor owns Scantibodies Laboratory, Inc. Hershel Raff: None.

Results—In the ESRD patients plasma phosphate demonstrated significant circadian variation (P < 0.00001). The peak occurred around 3:30 am and nadir occurred around 11:00 am. Ionized calcium (P = 0.0036), PTH (P = 0.0004) and 25OHD (P = 0.009) also varied significantly during the circadian period; for ionized calcium peak and nadir occurred around 12:15 pm and 8:00 pm, parathyroid hormone 5:45 pm and 10:15 am, and 25OHD 9:45 am and 4:00 pm respectively. FGF-23 did not show a significant circadian variation. Only phosphate (P < 0.0001) and PTH (P = 0.00008) demonstrated circadian variation in the control group.

Conclusions—Blood concentrations of phosphate, calcium, PTH and 25-hydroxy vitamin D, exhibit a circadian variation in patients with ESRD. Knowledge of these phenomena is pertinent for the interpretation of clinical testing.

Keywords

Phosphate; Calcium; Parathyroid hormone; Circadian variation; End-stage renal disease

Introduction

Management of mineral and bone disorder is one of the important facets of care of end-stage renal disease (ESRD) patients. Abnormalities in mineral and bone parameters are omnipresent in ESRD and along with serum calcium are actively managed with the aim of maintaining them within certain ranges [1]. Observational data have shown some of these, particularly high phosphate levels, are associated with increased mortality [2–4]. Abnormalities in calcium, phosphorus and parathyroid hormone lead to extra-osseous calcification involving vital organs including the lung, heart, and blood vessels [1]. Moreover, treatment of hyperphosphatemia has been associated with improved survival [5].

In order to control mineral and bone parameters these are routinely monitored during treatment of ESRD, typically once a month. While the importance of such monitoring is well appreciated, little is known about circadian variation of mineral and bone variables in ESRD. Particularly, there is a circadian rhythm of blood phosphate in the normal physiological state. The highest diurnal value is observed in the early morning hours, followed by a progressive decrease to the lowest value of the day, which been shown to occur around 11 am [6, 7]. Thereafter there is another increase, followed by a plateau, and then a gradual increase to the peak that typically occurs after midnight. Whether the circadian pattern is different in patients with ESRD is not known. Parathyroid hormone (PTH) also exhibits circadian variation under normal physiological conditions but there are no prior data in ESRD [8]. There are other mineral and bone parameters of interest in ESRD including 25-hydroxy vitamin D and fibroblast growth factor-23 (FGF-23) [9, 10]. No prior information exists whether they significantly vary throughout the day in this patient population.

We studied the circadian pattern of phosphate, ionized calcium, parathyroid hormone, total 25-hydroxy vitamin D and FGF-23 in ESRD.

Materials and methods

The study was approved by the Institutional Review Board of the Medical College of Wisconsin and Froedtert Hospital. Patients with ESRD on hemodialysis therapy for at least 30 days and controls with preserved renal function were enrolled after informed, written consent. Inclusion criteria were as follows: ESRD patients—age 18 years and older; controls—absence of known history of renal insufficiency; age 18 years and older; eGFR ≥70 mL/min/1.73 m^2 and serum creatinine <1.5 mg/dL in men, <1.3 g/dL in women.

Exclusion criteria were as follows: for ESRD patients—unwillingness to participate and adhere to the protocol requirements, including dietary regimen (included equivocal response with respect to dietary requirements of the protocol); pre-dialysis phosphate level less than 4 mg/dL or greater than 8 mg/dL, or calcium–phosphorus product greater than 70; pre-dialysis corrected calcium less than 8 mg/dL; pre-dialysis intact PTH less than 100 pg/mL or greater than 800 pg/mL; diabetes mellitus with a regimen of any anti-diabetic medications including insulin; known malabsorption disorders; acid-suppressant therapy for peptic ulcer disease (H2-blockers and proton pump inhibitors); use of bisphosphonates, diuretics, calcitonin, lithium, antacids or laxatives; pregnant women; use of oral corticosteroid preparations. For controls—unwillingness to participate and adhere to the protocol requirements, including dietary regimen (included equivocal response with respect to dietary requirements of the protocol); diabetes mellitus with a regimen of any anti-diabetic medications including insulin; known history of parathyroid disorders; known malabsorption disorders; acid-suppressant therapy for peptic ulcer disease (H2-blockers and proton pump inhibitors); abnormal parathyroid, phosphate, or corrected calcium values (confirmed by testing); use of bisphosphonates, diuretics, calcitonin, lithium, antacids, laxatives, calcium supplements or vitamin D (subjects taking calcium supplements were eligible if they were willing to stop for 7 days; subjects taking multivitamin or vitamin D 1,200 units or less per day were eligible if they were willing to stop these at the time of enrollment); pregnant women; use of oral corticosteroid preparations.

After confirmation of eligibility subjects met with the study dietician and a study diet was tailored for each subject. The study diet was similar to subject's usual diet based on food preferences and other requirements, if any, but was controlled to contain approximately 1,000 mg of phosphorus and 1,200 mg calcium per day. The following medications that affected calcium and phosphorus absorption from the GI tract were discontinued for 3 days prior to beginning the study diet: all phosphate binders, H2-blockers, and proton pump inhibitors. In addition, the following medications that affect calcium, phosphate, and/or PTH were discontinued prior to beginning the study diet for the following periods of time (corresponding to five half-lives of each agent): paricalcitol for 4 days, doxercalciferol for 8 days, calcitriol for 2 days, and cinacalcet for 9 days. After the required period of medication washout, subjects were provided the study diet prepared in the research kitchen, which they consumed for 5 days. The diet was provided in two batches (just prior to scheduled start of the diet) and on day 2, and subjects were asked to refrigerate food in-between. Subjects were asked to maintain a dietary log during partaking of the study diet. The study protocol was designed to achieve a steady state of calcium–phosphorus balance with no confounding factors.

After being on the study diet for 5 days, on the evening of day 5, subjects were admitted to the Adult Translational Research (TRU) unit. The timeline was designed such that day 6 was a non-dialysis day for the ESRD patients. On study day 6, enrollees had blood samples drawn beginning at 8 am (fasting sample) and every 2 h thereafter through 6 am the following day. The study diet was continued on day 6 in the TRU with breakfast provided at approximately 8 am, lunch approximately at noon (after the 12 pm blood draw), dinner at approximately 5 pm, and a late evening snack at approximately 8 pm. All study meals were delivered by bionutrition staff who recorded portions eaten. Dietary records showed excellent compliance with the study diet. The achieved average dietary calcium content of the ESRD patients was 1,200 ± 58 mg and of the controls was 1,243 ± 46 mg. The achieved average dietary phosphorus content of the ESRD patients was 1,027 ± 66 mg and of the controls was 1,056 ± 61 mg. During their stay in the research unit the study subjects were allowed to sleep by their normal rhythm and discharged after the 6 am blood draw on day 7.

Each blood sample was tested for phosphate, ionized calcium, intact PTH, total 25-hydroxy vitamin D and FGF-23. Plasma phosphate was measured by molybdate UV (Roche Cobas C701, Indianapolis, IN, USA); serum ionized calcium was measured by ion-selective electrode (Radiometer ABL 800 FLEX, Brønshøj, Denmark); plasma intact PTH was measured by immunoradiometric sandwich assay using the Duo PTH coated-bead technology kit (Scantibodies Laboratory, Inc., Santee, CA, USA); serum total 25-hydroxy vitamin D was measured by direct competitive chemiluminescence immunoassay (Liaison, Diasorin, Stillwater, MN, USA); serum intact FGF-23 was measured by ELISA (Millipore, St. Charles, MO, USA).

Statistical methods

A harmonic regression model with group-specific 24- and 12-h periodic components and random subject-specific intercept was fitted to log-transformed values. Harmonic regression is based on a mathematical result known as Fourier decomposition stating that any periodic function can be approximated by a sum of sine and cosine functions with periods equal to or dividing the period of the original function. The following equation shows the model fitted to each group: a linear combination of sine and cosine terms with 24- and 12-h periods. Smaller periods were not considered due to the limits of the sampling frequency and biological plausibility.

$$\log(Y_i(t)) = A + B_1\cos\left(\frac{2\pi t}{24}\right) + B_2\sin\left(\frac{2\pi t}{24}\right) + B_3\cos\left(\frac{2\pi t}{12}\right) + B_4\sin\left(\frac{2\pi t}{12}\right) + \alpha_i + \varepsilon_{it},$$

where $Y_i(t)$ is the measured value for subject i at time t, α_i is a normally distributed random subject-specific intercept, and $\varepsilon_i(t)$ is the normally distributed error term. The presence of a circadian rhythm was evaluated using a likelihood-ratio test comparing models with and without the harmonic terms. A linear term was not used because we assumed a circadian process that has a 24-h period and is stable on average over time.

The peak and nadir for each outcome were calculated based on the fitted regression models separately for each group: the average value of each parameter was estimated at 15 min

intervals, and the times corresponding to the lowest and highest values were used as the estimates of the times of peak and nadir. Since the models were fitted on a logarithmic scale, the absolute difference between the values at peak and nadir applies to the average subject, while the estimated relative difference is applicable to all subjects.

The modeling was performed using SAS 9.3 (SAS Institute, Cary, NC, USA). Unless specified otherwise, data are expressed as mean ± standard deviation.

Results

Seventeen subjects with ESRD on long-term hemodialysis and eight volunteers without history of kidney disease were studied. The etiology of ESRD was hypertension (n = 6), focal segmental glomerulosclerosis (n = 5), chronic interstitial nephritis (n = 2), chronic glomerulonephritis (n = 1), autosomal dominant polycystic kidney disease (n = 1), post-streptococcal glomerulonephritis (n = 1), and unknown (n = 1). All ESRD subjects except two were on phosphorus binders and all except one were on some form of active vitamin D or analogues. There was no statistical difference in the demographic characteristics of the two groups. Out of 1,500 samples (300 per analyte), results were not available for 34 samples due to technical issues, all in ESRD patients (phosphate = 6, ionized calcium = 6, PTH = 7, total 25-hydroxy vitamin D = 7, FGF-23 = 8). The majority of these (n = 23) were in one patient due to IV getting dislodged around 10 pm and inability to obtain another venous access. The conditions of testing were optimal based on the classical circadian pattern of concurrent cortisol measurements observed in the controls, which have been reported previously [11]. Table 1 depicts the baseline features of the study groups.

Plasma phosphate

Phosphate demonstrated a significant circadian variation in the control group ($P < 0.00001$) remarkably consistent with prior data showing a post-midnight peak and a midmorning nadir followed by another increase in the middle of the day [6, 7]. In the ESRD patients also the variation was highly significant ($P < 0.00001$) (Fig. 1). In the ESRD group the peak occurred around 3:30 am and the nadir occurred around 11:00 am. The mean difference between peak and nadir was 1.3 mg/dL, which was 29 % of the nadir value. In the control group the times of the peak and nadir were very similar (peak around 2:45 am, nadir around 10:15 am); the average difference between peak and nadir was 1.2 mg/dL (46 % of the nadir value).

Serum ionized calcium

Ionized calcium did not demonstrate a significant circadian variation in the control group ($P = 0.72$). However, in the ESRD group there was a significant circadian variation ($P = 0.0036$) (Fig. 2). The peak occurred around 12:15 pm and the nadir occurred around 8:00 pm. The average difference between peak and nadir was 0.05 mmol/L (4.5 % of the nadir value). In the control group the average difference between the peak and nadir was 0.02 mmol/L (1.7 % of the nadir).

Plasma intact parathyroid hormone (PTH)

PTH varied significantly during the circadian period in the ESRD patients (P = 0.0004) (Fig. 3a). Intact PTH demonstrated a significant circadian variation in the control group (P = 0.00008) (Fig. 3b). In ESRD patients the peak occurred around 5:45 pm and the nadir occurred around 10:15 am. The mean difference between peak and nadir was 62.2 pg/mL (about 17 % of the nadir). In the control group the times of peak and nadir were 2:45 am and 10:15 am respectively and the mean difference between the peak and nadir was 11.7 pg/mL (45 % of the nadir).

Serum total 25-hydroxy vitamin D

Total 25-hydroxy vitamin D did not demonstrate a significant circadian variation in the control group (P = 0.45). However, in the ESRD patients total 25-hydroxy vitamin D exhibited a significant circadian variation (P = 0.009) (Fig. 4). In ESRD subjects the peak level occurred around 9:45 am and the nadir occurred around 4:00 pm. The mean difference between peak and nadir was 2.1 ng/mL (11.1 % of the nadir value). In the control group the average difference between the peak and nadir was 1.5 ng/mL (6.7 % of the nadir).

Serum fibroblast growth factor-23

The circadian rhythm of FGF-23 could not be tested in the control group as the majority of values were below the lower limit of detection of the assay (<3.5 pg/mL). In the ESRD subjects there was no significant circadian variation in FGF-23 (P = 0.85). As depicted in Fig. 5, the values were quite stable over the 24-h period.

Discussion

Our results demonstrate that calcium, phosphate, parathyroid hormone and vitamin D levels exhibit a significant circadian variation in patients with end-stage renal disease on long-term dialysis. In volunteers with preserved renal function, only phosphate and parathyroid hormone exhibited a significant circadian rhythm.

The circadian variation in phosphate in the ESRD patients was very similar to the control group. Under normal physiologic conditions there is a circadian variation in urinary phosphate that correlates with blood levels and is related to dietary intake since it is attenuated in the fasting state [12, 13]. Tm of phosphorus is reached close to the normal physiologic range, after which excretion parallels filtration [14]. Therefore, in ESRD with decreased urinary phosphate loss one might expect an altered plasma circadian pattern but the findings are contrary. These data suggest the mechanism of circadian variation of plasma phosphate in ESRD is not related to urinary excretion and merits further investigation.

Ionized calcium also had a significant circadian variation in the ESRD patients. The curves of circadian calcium rhythm did not show a pattern inverse to that of phosphate. Particularly the nadir at around 8:00 pm was not close to the phosphate peak. There is an inverse relationship between ionized calcium and phosphate, as phosphate increases calcium–phosphate binding leads to lower ionized calcium levels [1]. Our findings suggest that other factors are involved in the circadian calcium pattern. Parathyroid hormone also

demonstrated a significant circadian rhythm in the ESRD group. There appears to be an inverse relationship between the ionized calcium and PTH curves. Ionized calcium levels peaked during the late morning to noon hours when PTH was at the nadir and troughed towards the late afternoon hours when PTH levels rose. Low calcium levels stimulate PTH levels and vice versa. It is noteworthy that these variations could impact clinical decision making. For instance, calcium and PTH testing done in the late morning, when calcium levels are at their highest and PTH at the nadir, could lead to reduction in vitamin D analogue therapy used to treat secondary hyperparathyroidism in ESRD. However if the same patient underwent hemodialysis during a late afternoon shift, or were a nocturnal hemodialysis patient who typically begins hemodialysis in the evening hours, the patient's PTH levels would be higher and ionized calcium lower. Based on these results, clinical decision making could potentially involve increasing dosage of vitamin D analogue therapy.

In recent years, there has been interest in vitamin D levels in chronic kidney disease with a significant body of data showing low levels of 25-hydroxy vitamin D in ESRD, leading to investigations on the impact of supplementation on outcomes [15, 16]. We tested the circadian rhythm of total 25-hydroxy vitamin D in the ESRD patients and found a statistically significant variation. The values peaked during the morning hours that could potentially coincide with blood draw times for many patients. However the average amplitude was only 2.1 ng/dL, about 11 % of the nadir value. It remains to be seen whether this degree of variation is of clinical significance. FGF-23 also has been studied extensively in chronic kidney disease with a body of data suggesting that high levels are related to poorer outcomes [10, 17]. Of interest, among the studied analytes FGF-23 was the only bone mineral parameter that did not undergo a significant circadian variation in ESRD.

There are established guidelines for management of bone mineral parameters in ESRD [1]. Our results suggest that random testing of bone mineral parameters in ESRD, and treatment decisions based on such results, should consider the circadian pattern particularly when values are close to the boundaries of the desired range. Further, the guidelines need to consider circadian changes in the recommendations. It remains a challenge whether to regard the peak or the nadir in treatment recommendations. Furthermore, most of the data relating to outcomes associated with abnormal bone and mineral parameters in chronic kidney disease are based on observational data that consist of randomly tested results of these parameters [2, 4]. The interpretation of such results warrant caution, and at the very least the data merit sensitivity analyses that consider the circadian variability. Moreover, these results suggest interpretation of single values of mineral and bone parameters in patients with ESRD is fraught with pitfalls. Besides circadian variation depicted here, Seiler et al. [18] showed significant day-to-day variations in mineral and bone parameters in ESRD patients on hemodialysis therapy.

It is pertinent to reflect on the clinical impact of the observed circadian variation of mineral and bone parameters in ESRD. We are particularly intrigued by the phosphate variation that depicts a pattern and amplitude very similar to the control subjects. It must be borne in mind that plasma inorganic phosphate is but a small component of blood phosphorus, which also exists extra-cellularly bound to organic molecules, and intra-cellularly in both organic and inorganic forms [14]. Since there is negligible urinary excretion in ESRD, given the

observed findings, it is tempting to speculate that the phosphorus that would have undergone urinary excretion in normal circumstances is transferred to a non-inorganic component. If indeed that were the case, there could be a high intracellular phosphorus burden in ESRD and higher concentration of phosphorylated compounds, such as phosphorylated lipids. Further investigations are necessary to study such a possibility including measurements of transcellular phosphorus flux and phosphorus concentration in various blood components in the ESRD state.

There are limitations of the present study. Firstly, patients with diabetes mellitus were not included and hence the results cannot be necessarily extrapolated to this population. In diabetic patients plasma phosphate can be affected by insulin administration, or stimulation of insulin secretion by secretagogues, due to insulin-mediated formation of glucose-phosphate esters [19, 20]. Assessment of the circadian phosphate rhythm in diabetics merits a separate study that accounts for the effect of changes in insulin levels. Patients on peritoneal dialysis were also not included. Besides changes in glucose load, related to dextrose-based dialysate prescription and the timing thereof, phosphate clearance via peritoneal dialysis could affect the results [21]. Similar to diabetic subjects a dedicated study would be merited in this group of patients that considers these factors.

In conclusion, plasma phosphate, ionized calcium, parathyroid hormone and total 25-hydroxy vitamin D levels undergo significant circadian variation in patients with end-stage renal disease. Knowledge of these phenomena is pertinent for the interpretation of clinical testing.

Acknowledgments

The authors thank Mary F. Hannan, ACNP for her assistance in gathering baseline study data. We also greatly thank all the staff of the Adult Translational Research Unit for their excellent work. Supported in part by Grant 8UL1TR000055 from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health; supported in part by an investigator-initiated Grant from Genzyme Corporation; and supported in part by Lemann Clinical Scientist Endowment Fund.

Hariprasad Trivedi: Advisory Board, Abbott Laboratories (monies received); recipient of investigator-initiated research grant, Genzyme Corporation; speaker, Medical Education Partners Program, Sanofi Renal Medical Affairs (monies received).

References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003; 42(Suppl 3):S1–S202. [PubMed: 14520607]
2. Block GA, Klassen PS, Lazarun JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004; 15:2208–2218. [PubMed: 15284307]
3. Floege J, Kim J, Ireland E, Chazot C, Drueke T, de Francisco A, Kronenberg F, Marcelli D, Passlick-Deetjen J, Schernthaner G, Fouqueray B, Wheeler DC. ARO Investigators. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. Nephrol Dial Transpl. 2011; 26:1948–1955.
4. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int. 2006; 70:771–780. [PubMed: 16820797]

5. Isakova T, Gutierrez OM, Chang Y, Shah A, Tamez H, Smith K, Thadhani R, Wolf M. Phosphorus binders and survival on hemodialysis. J Am Soc Nephrol. 2009; 20:388–396. [PubMed: 19092121]
6. Portale AA, Halloran BP, Morris RC. Dietary intake of phosphate modulates the circadian rhythm in serum concentration of phosphorus. Implication for the renal production of 1,25-dihydroxyvitamin D. J Clin Invest. 1987; 80:1147–1154. [PubMed: 3654974]
7. Kemp GJ, Blumsohn A, Morris BW. Circadian changes in plasma phosphate concentration, urinary phosphate excretion, and cellular phosphate shifts. Clin Chem. 1992; 38:400–402. [PubMed: 1547558]
8. Fuleihan GE, Klerman EB, Brown EN, Choe Y, Brown EM, Czeisler CA. The parathyroid hormone circadian rhythm is truly endogenous—a general clinical research study. J Clin Endocrinol Metab. 1997; 82:281–286. [PubMed: 8989274]
9. Nigwekar SU, Bhan I, Thadhani R. Ergocalciferol and cholecalciferol in CKD. Am J Kidney Dis. 2012; 60:139–156. [PubMed: 22560832]
10. Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008; 359:584–592. [PubMed: 18687639]
11. Raff H, Trivedi H. Circadian rhythm of salivary cortisol, plasma cortisol, and plasma ACTH in end-stage renal disease. Endocr Connect. 2013; 2(1):23–31. doi:10.1530/EC-12-0058. [PubMed: 23781315]
12. Carruthers BM, Copp DH, McKintosh HW. Diurnal variation in urinary excretion of calcium and phosphate and its relation to blood levels. J Clin Lab Med. 1964; 63:959–968.
13. Fraser WD, Logue FC, Christie JP, Cameron DA, O'Reilly DS, Beastall GH. Alterations of the circadian rhythm of intact parathyroid hormone following a 96-hour fast. Clin Endocrinol. 1994; 40:523–528.
14. Agrawal, R.; Knochel, JP. Hypophosphatemia and hyperphosphatemia. In: Brenner, BM., editor. The kidney. 6th edn. Philadelphia: WB Saunders; 2000. p. 1071-1128.
15. Porter A, Gilmartin C, Srisakul U, Arruda J, Akkina S. Prevalence of 25-OH vitamin D deficiency in a population of hemodialysis patients and efficacy of an oral ergocalciferol supplementation regimen. Am J Nephrol. 2013; 37:568–574. [PubMed: 23735861]
16. Jean G, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, Chazot C. Daily oral 25-hydroxycholecalciferol supplementation for vitamin D deficiency in haemodialysis patients: effects on mineral metabolism and bone markers. Nephrol Dial Transpl. 2008; 23:3670–3676.
17. Jean G, Terrat J-C, Vanel T, Hurot J-M, Lorriaux C, Mayor B, Chazot C. High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. Nephrol Dial Transpl. 2009; 24:2792–2796.
18. Seiler S, Lucisano G, Ege P, Fell LH, Rogacev KS, Lerner-Gräber A, Klingele M, Ziegler M, Fliser D, Heine GH. Single FGF-23 measurement and time-averaged plasma phosphate levels in hemodialysis patients. Clin J Am Soc Nephrol. 2013; 8:1764–1772. [PubMed: 23846463]
19. Stadie WC. The relation of insulin to phosphate metabolism. Yale J Biol Med. 1994; 16(5):539–559. [PubMed: 21434171]
20. Riley MS, Schade DS, Eaton RP. Effects of insulin infusion on plasma phosphate in diabetic patients. Metabolism. 1979; 28:191–194. [PubMed: 105228]
21. Schmitt C, Borzych D, Nau B, Wühl E, Zurowska A, Schaefer F. Dialytic phosphate removal: a modifiable measure of dialysis efficacy in automated peritoneal dialysis. Perit Dial Int. 2009; 29:465–471. [PubMed: 19602613]

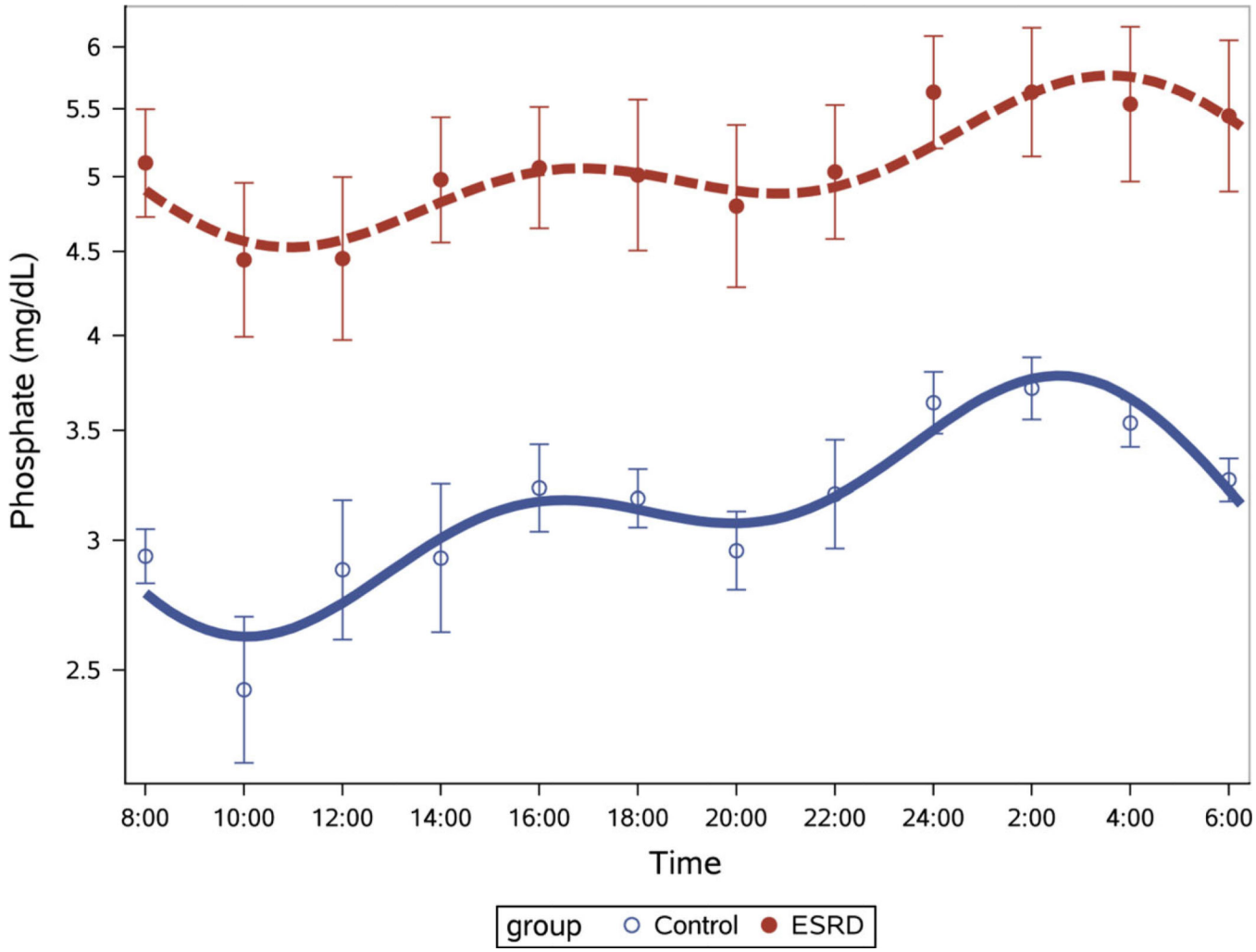

Fig. 1.

Circadian variation of plasma phosphate in ESRD patients ($P < 0.00001$) and controls ($P < 0.00001$) (*circles* represent means and *vertical bars* standard error of the mean)

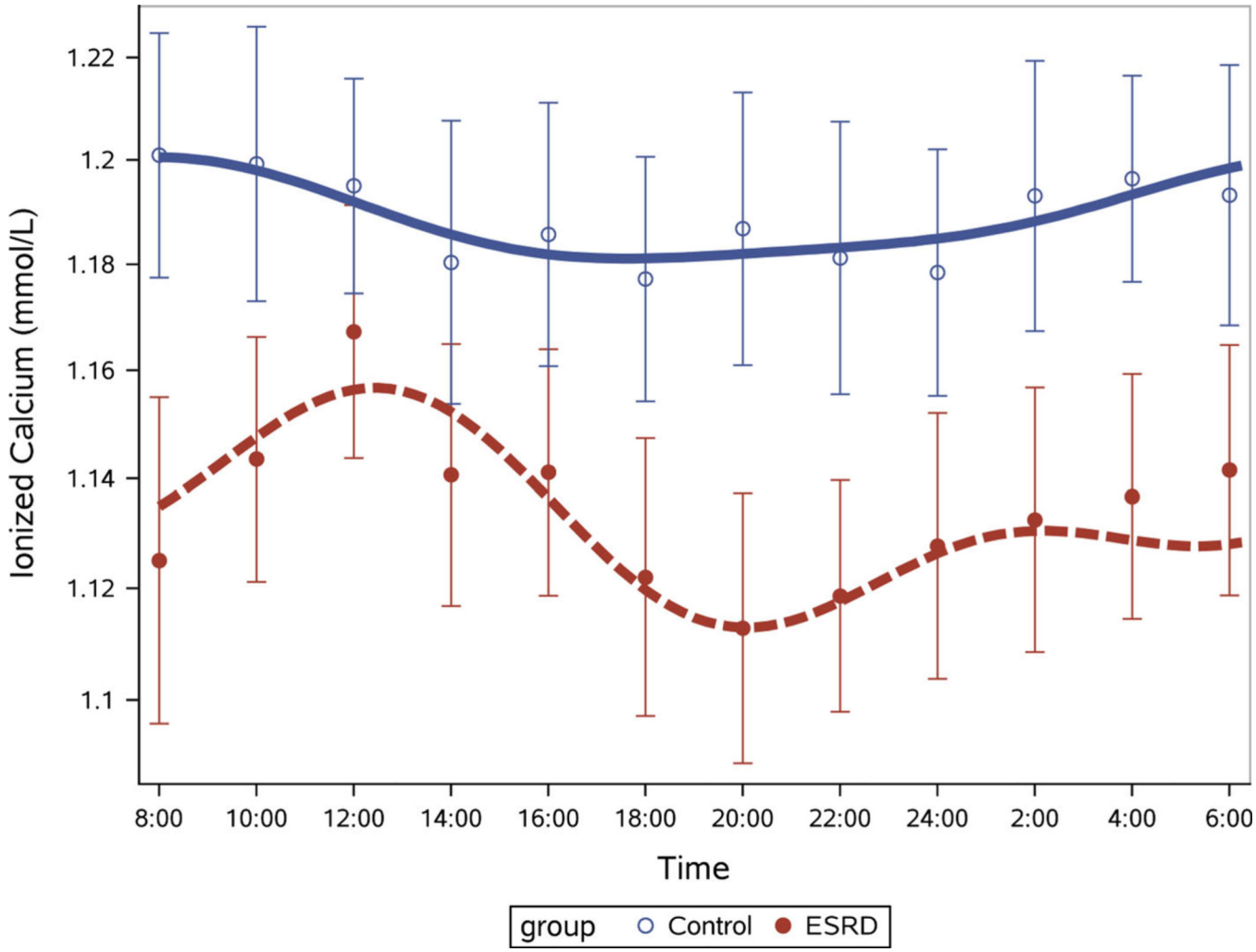

Fig. 2.

Circadian variation of ionized calcium in ESRD patients (P = 0.0036) and controls (P = 0.0036) (*circles* represent means and *vertical bars* standard error of the mean)

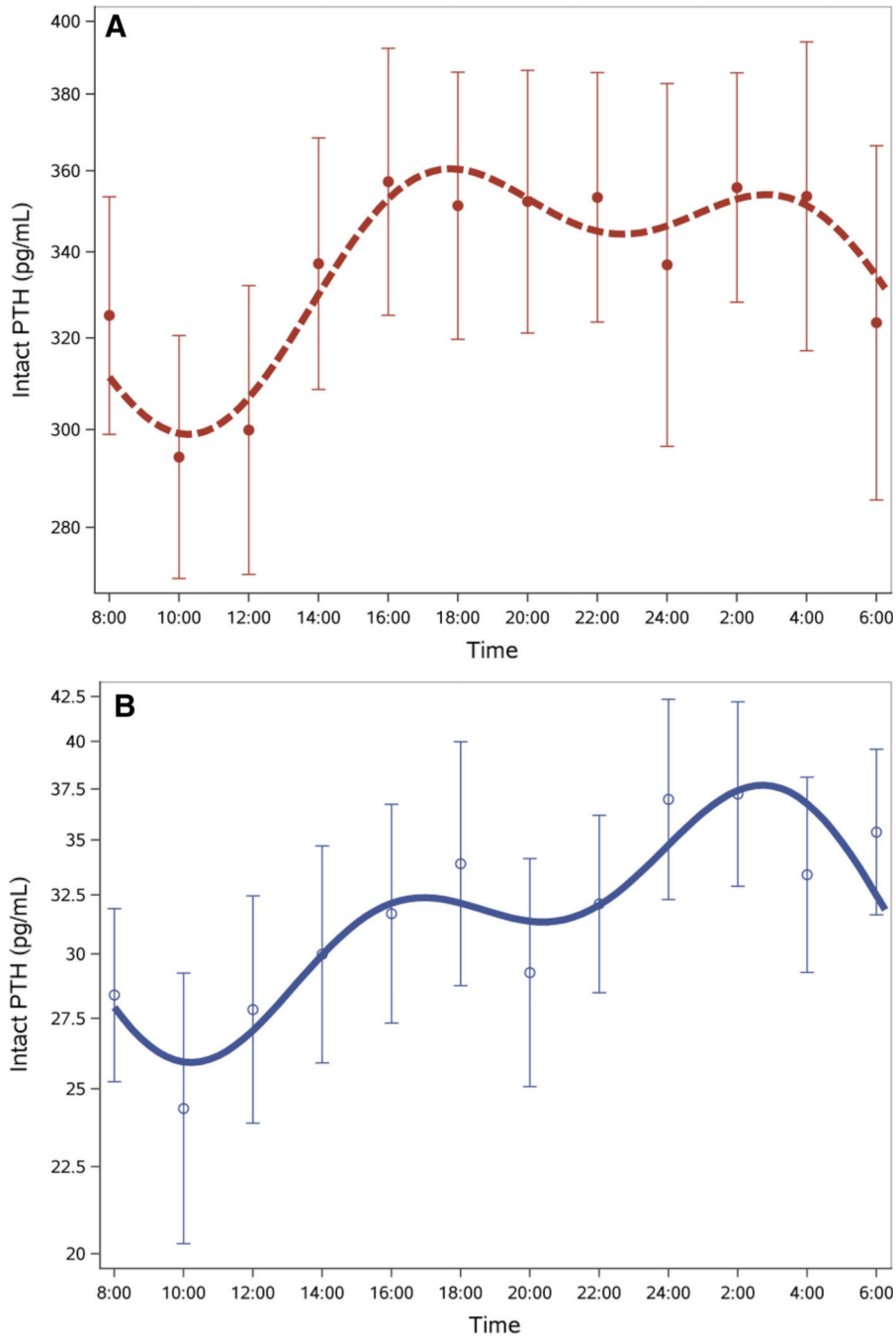

Fig. 3.

a Circadian variation of parathyroid hormone in ESRD patients (P = 0.0004) (*circles* represent means and *vertical bars* standard error of the mean). **b** Circadian variation of parathyroid hormone in controls with preserved renal function (P = 0.00008) (*circles* represent means and *vertical bars* standard error of the mean)

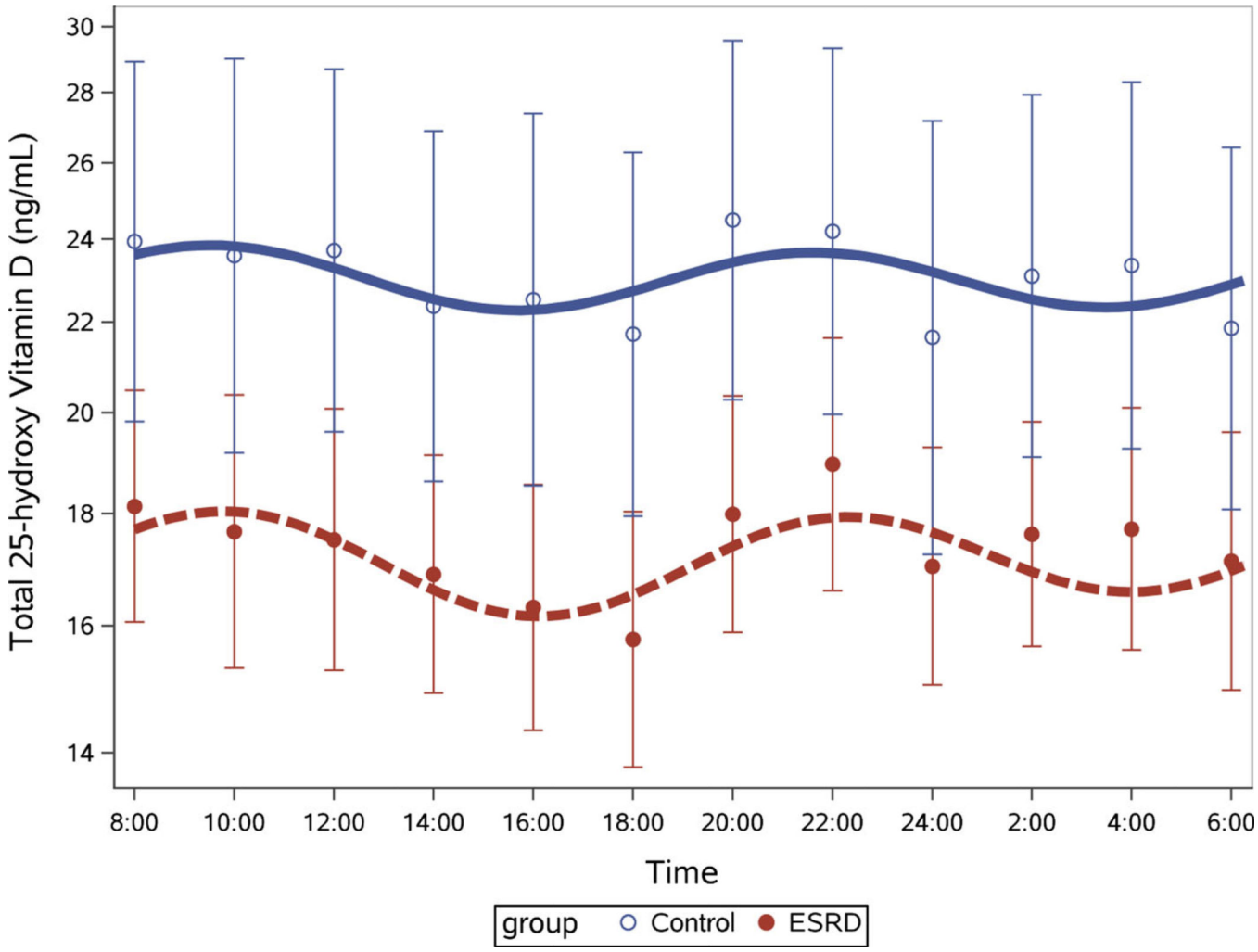

Fig. 4.

Circadian variation of total 25 hydroxy vitamin D in ESRD patients (P = 0.009) and controls (P = 0.45) (*circles* represent means and *vertical bars* standard error of the mean)

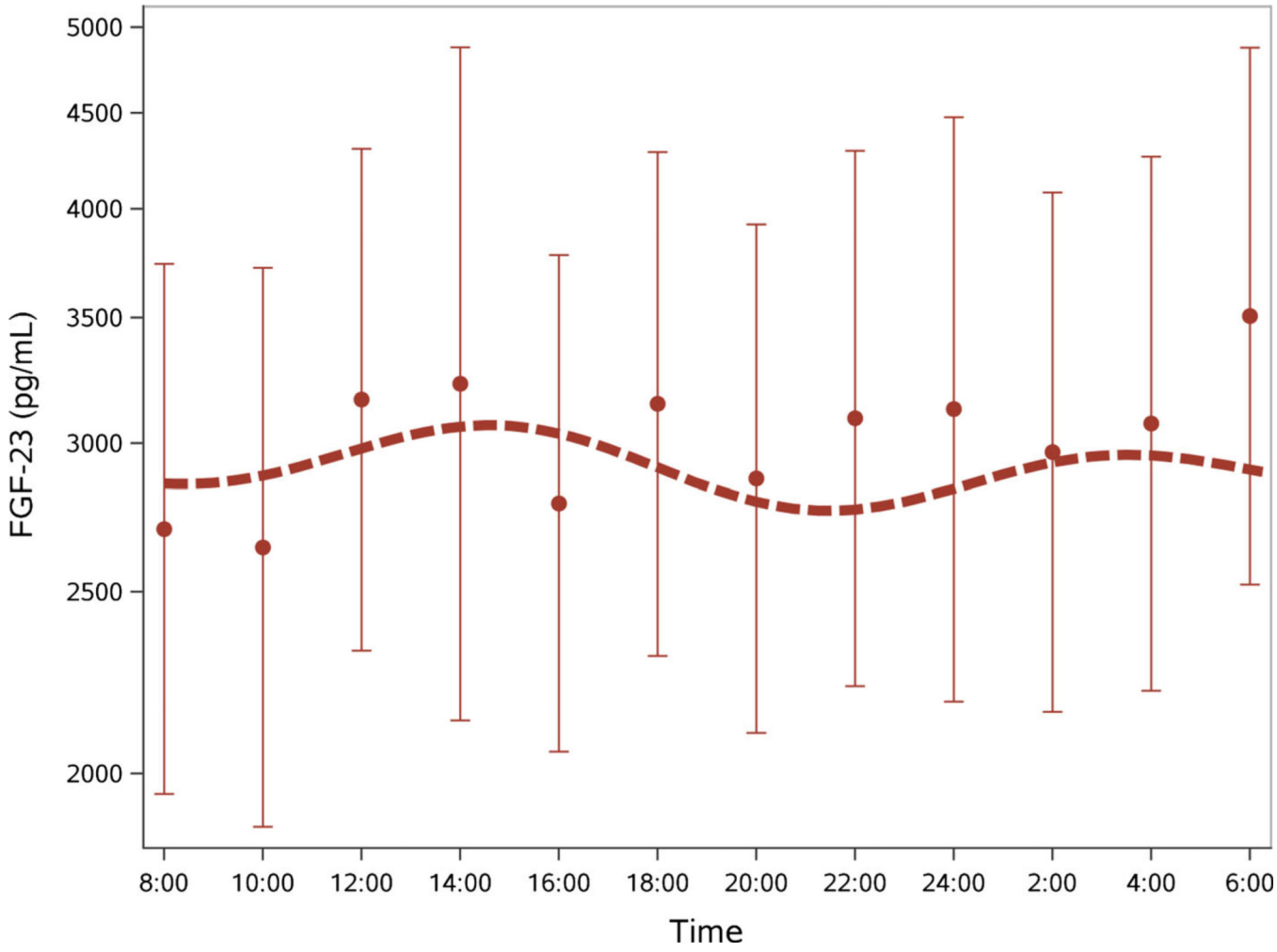

Fig. 5.

Circadian variation of FGF-23 in ESRD patients (P = 0.85) (*circles* represent means and *vertical bars* standard error of the mean)

Table 1

Subject characteristics

	End-stage renal disease subjects (N = 17)	**Controls (N = 8)**
Age (years)	45.4 ± 12.2	55.4 ± 4.9
Sex (male; %)	88	75
Race (Caucasian/African Americans; %)	41/59	50/50
Baseline phosphate (mg/dL)	5.3 ± 0.9	3.1 ± 0.1 mg/dL
Baseline parathyroid hormone (pg/mL)	342.6 ± 168.5	40.1 ± 4.9
Baseline corrected calcium (mg/dL)	9.6 ± 0.7	9.1 ± 0.1
Baseline total 25-hydroxy vitamin D (ng/mL)[a]	20.5 ± 11.8	26.8 ± 11.9
Baseline FGF-23 (pg/mL)[a]	5,988.5 ± 8,027.2	Undetectable in majority
Average 6 days' calcium intake (mg)	1,200 ± 58	1,243 ± 46
Average 6 days' phosphorus intake (mg)	1,027 ± 66	1,056 ± 61
Mean serum creatinine (mg/dL)	–	0.89 ± 0.12
Average eGFR (mL/min/1.73 m^2)	–	93.8 ± 21.2
Average duration of hemodialysis (months)	48.3 ± 56.6	–
Mean urea reduction ratio (%)	75.6 ± 5.8	–
Phosphate binder therapy	Sevelamer HCL or carbonate (n = 9; mean dose 9,777 ± 4,729 mg)	–
	Calcium acetate (n = 8; mean dose 4,585 ± 1,531 mg)	
	Lanthanum carbonate (n = 2; mean dose 643 mg)	
Active treatment for secondary hyperparathyroidism	Paricalcitol (n = 13; mean dose 5.4 ± 3.4 mcg)	–
	Doxercalciferol (n = 2; mean dose 4 mcg)	
	Calcitriol (n = 1; dose 2 mcg)	
	Cinacalcet (n = 5; 78 ± 58 mg)	

[a] 8 am sample mean