Daily Variability in Mineral Metabolites in CKD and Effects of Dietary Calcium and Calcitriol

Tamara Isakova,* Huiliang Xie,† Allison Barchi-Chung,* Kelsey Smith,* Nicole Sowden,* Michael Epstein,* Gina Collerone,‡ Leigh Keating,§ Harald Jüppner,* and Myles Wolf*

Overview

Introduction
Abnormalities in mineral metabolism, including disordered phosphate and calcium homeostasis, secondary hyperparathyroidism, vitamin D deficiency, and fibroblast growth factor 23 (FGF23) excess, are frequent complications in CKD patients (1,2). Although initial changes in parathyroid hormone (PTH) and FGF23 are adaptive in the setting of declining kidney function, elevations often progress to levels that are difficult to treat or may have off-target systemic effects, leading to increased risks of bone disease and cardiovascular morbidity and mortality (3–5). These trends have led to a growing interest among nephrologists in developing therapeutic strategies that might attenuate mineral metabolism abnormalities early in the course of CKD in the hopes of improving patient-related outcomes. Thus, factors controlling the early pathophysiology of mineral metabolism and the effects of available interventions on mineral metabolites when instituted early in the course of the disease are of major importance.

We previously reported that patients with CKD stages 3 and 4 who had normal fasting calcium and PTH levels developed subtle postprandial hypocalcemia and subsequent elevations in PTH after an increase in postprandial calcitriuria (6). This observation suggested that excessive urinary calcium losses in CKD patients, who are prone to tenuous calcium balance because of relative calcitriol deficiency, may promote intermittent reductions in serum calcium with resulting spikes in PTH, which eventually manifest clinically as secondary hyperparathyroidism. This hypothesis is supported by studies in the general population and CKD that showed that excessive calciuria driven by loop diuretics was associated with elevated PTH (7–11).

In the current study, we evaluated daily fluctuations in mineral metabolites in stages 3 and 4 CKD patients before and after calcitriol treatment and investigated the effects of a single meal with augmented dietary calcium content on postprandial calcium handling and PTH secretion. We hypothesized that, compared with controls, CKD patients would show a blunted daily variability in mineral metabolites at baseline that would be restored by treatment with calcitriol. Furthermore, we...
tested the hypothesis that dietary calcium and calcitriol supplementation would blunt postprandial hypocalcemia and increase PTH levels, and thereby, they would normalize the calcemic and parathyroid responses to breakfast meals in CKD participants.

Materials and Methods

Study Population

Twelve CKD patients were recruited from nephrology clinics at the Massachusetts General Hospital. Twelve age-, sex-, and race-matched controls were recruited through email advertisements. The study was approved by the Institutional Review Board, and written informed consent was obtained from each subject.

Eligible CKD patients were included if they were aged 18 years or older and had an estimated GFR of 15–59 ml/min per 1.73 m², normocalcemia, normophosphatemia, and 25-hydroxyvitamin D (25D) levels ≥30 ng/ml. Controls were included if they had normal kidney function, urinalysis, and 25D levels. All participants with screening 25D levels ≤30 ng/ml were repleted with ergocalciferol 1–2 months before enrollment.

CKD patients were excluded if they had rapidly advancing CKD, current treatment with phosphate binders or active vitamin D, anemia, hospitalization within the previous 4 weeks, history of primary hypoparathyroidism, or previous subtotal parathyroidectomy or if they were pregnant or breastfeeding mothers. Because loop diuretics increase and thiazides decrease urinary calcium excretion and loop diuretics are associated with higher PTH levels in CKD (11), we excluded CKD patients who had a change in dose of these diuretics within 4 weeks before enrollment.

Procedures

After a screening and run-in period, CKD subjects returned to the General Clinical Research Center for two 30-hour admissions, during which time we evaluated hourly changes in blood and urinary mineral metabolites (Figure 1A). Throughout the admissions, standardized meals were consumed with free access to water. On the
first morning of admission, we studied the postprandial calcemic and parathyroid responses to a standardized breakfast meal containing 250 mg calcium (meal 1) (Figure 1B). On the second morning, we again studied these parameters in response to a standardized meal containing 500 mg calcium (meal 2) (Figure 1B). The two inpatient visits were separated by 1 week, between which time CKD patients were treated with calcitriol and consumed ad lib diets. Controls completed one inpatient assessment and were not treated with calcitriol. The timeline of the inpatient visits is shown in Figure 1B. Details of the interventions and measurements are provided in Supplemental Appendix.

**Statistical Analyses**

We estimated that 12 CKD patients would provide 90% power, allowing for a 5% α, to detect a 15% difference in change in PTH in the postprandial period after the 250-mg calcium meal before and after calcitriol supplementation and after the 500-mg calcium meal before and after calcitriol supplementation.

We used unpaired t and Wilcoxon rank sum tests for comparisons of baseline characteristics between CKD subjects and controls. Pre- and post-calcitriol comparisons within CKD subjects were performed with use of paired t or Wilcoxon sign rank tests. To test our hypotheses, we used linear mixed effects models, in which group and time represented the fixed effect terms and individual participants were coded as random effects terms. Between-group differences were assessed by the significance of the group by time interaction terms. If there was no significant group by time interaction, then a model without the interaction term was fitted to determine the significance of the main effects of group and time. For the comparison of daily pattern of change in mineral metabolites in CKD patients at the baseline visit versus controls, study group was a fixed effect term. This term was replaced by visit day in the models that tested the effect of calcitriol on daily variability in mineral metabolites in CKD patients.

To determine the effects of dietary calcium and calcitriol on the postprandial calcemic and parathyroid responses in CKD, we evaluated fasting and postprandial levels of mineral metabolites before and 5 hours after the 250-mg calcium breakfast meal and after three interventions: (1) the 500-mg calcium breakfast meal, (2) 1 week of calcitriol treatment and the 250-mg calcium breakfast meal, and (3) the combination of the 500-mg calcium breakfast meal and 1 week of calcitriol. In these models, intervention was the group fixed effects term. To test the hypothesis that the postprandial response in CKD patients after calcium and calcitriol supplementation approximated the postprandial response in controls, we employed linear mixed effects models, with study group representing the group fixed effects term. Natural log transformations were used for analyses of non-normally distributed variables. Analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). All statistical tests were two-sided, and P values <0.05 were considered significant.

**Results**

**Baseline Characteristics**

Baseline characteristics of the CKD patients and controls are shown in Table 1. Per the matched study design, demographic characteristics were balanced in the study groups. CKD patients had significantly lower 24-hour urinary calcium, higher fasting fractional excretion of phosphate (FePi),

### Table 1. Demographic, clinical, and laboratory characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Patients with CKD (n=12)</th>
<th>Controls (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60±7</td>
<td>55±9</td>
<td>0.25</td>
</tr>
<tr>
<td>Women (n/total N)</td>
<td>3/12</td>
<td>3/12</td>
<td>—</td>
</tr>
<tr>
<td>Black (n/total N)</td>
<td>4/12</td>
<td>4/12</td>
<td>—</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.6±6.4</td>
<td>29.8±5.5</td>
<td>0.70</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>40.4±8.0</td>
<td>83.6±18.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.9±0.5</td>
<td>1.1±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.4±0.2</td>
<td>9.4±0.3</td>
<td>0.80</td>
</tr>
<tr>
<td>FeCa (%)</td>
<td>0.4 (0.2–0.9)</td>
<td>0.6 (0.4–0.8)</td>
<td>0.40</td>
</tr>
<tr>
<td>24-Hour urine calcium (mg/d)</td>
<td>50 (26–73)</td>
<td>181 (126–220)</td>
<td>0.001</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>3.3±0.5</td>
<td>3.0±0.4</td>
<td>0.15</td>
</tr>
<tr>
<td>FePi (%)</td>
<td>24.8±8.6</td>
<td>13.9±4.7</td>
<td>0.002</td>
</tr>
<tr>
<td>24-Hour urine phosphate (mg/d)</td>
<td>629 (590–772)</td>
<td>776 (691–1107)</td>
<td>0.05</td>
</tr>
<tr>
<td>25D (ng/ml)</td>
<td>44 (35–57)</td>
<td>39 (35–53)</td>
<td>0.50</td>
</tr>
<tr>
<td>1,25D (pg/ml)</td>
<td>39 (27–47)</td>
<td>39 (35–53)</td>
<td>0.20</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>50.8 (39.7–60.5)</td>
<td>32.0 (28.2–47.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>FGF23 (RU/ml)a</td>
<td>119.7 (107.5–222.2)</td>
<td>57.9 (45.5–76.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dietary calcium intake (mg/d)</td>
<td>921 (657–1040)</td>
<td>1138 (791–1266)</td>
<td>0.10</td>
</tr>
<tr>
<td>Dietary phosphate intake (mg/d)</td>
<td>1218 (1108–1568)</td>
<td>1710 (1467–1824)</td>
<td>0.05</td>
</tr>
<tr>
<td>Caloric intake (kcal/d)</td>
<td>2071 (1663–2734)</td>
<td>2384 (1939–2786)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Values are means ± SD or medians (interquartile range). P values are from t or Wilcoxon rank sum tests. eGFR, estimated GFR; FeCa, fractional excretion of calcium; FePi, fractional excretion of phosphate; 25D, 25-hydroxyvitamin D; 1,25D, 1,25-hydroxyvitamin D; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23, RU, reference units.

*aFGF23 levels were available in 11 of 12 participants with CKD.
PTH, and FGF23 levels compared with controls. There were no significant differences in fasting fractional excretion of calcium (FeCa), serum calcium, phosphate, and vitamin D levels.

**Diurnal Variation in Mineral Metabolites in CKD**

Mean (SE) hourly values for FeCa, serum calcium, PTH, FePi, serum phosphate, and FGF23 are shown in Figure 2. There were no significant between-group differences over time for any parameter (for group X time interactions for all, *P* > 0.05). Consistent with prior reports, there was an almost immediate increase in FeCa in both groups after breakfast (for main effect of time, *P* < 0.001), which was followed by additional peaks after lunch and dinner in the controls, but additional increases were absent in the CKD group (for main effect of study group, *P* = 0.002). Serum calcium levels trended to lower nadirs in CKD patients (for main effect of study group, *P* = 0.06) compared with controls, although levels decreased to the end of the day in both groups (for main effect of time, *P* < 0.001). PTH levels dipped transiently in the morning, with a nadir at 10:00 AM (for main effect of time, *P* = 0.03) that was then

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**Figure 2.** Daily variation in mineral metabolites in healthy and CKD patients. Fasting and postprandial measurements of (A) fractional excretion of calcium, (B) serum calcium, (C) parathyroid hormone, (D) fractional excretion of phosphate, (E) serum phosphate, and (F) fibroblast growth factor 23 on visit day 7 in healthy volunteers (green squares) and CKD subjects (blue triangles). Fasting measurements were obtained at 8:00 AM relative clock time. Results are reported as mean ± SE. Rectangles indicate timing of meals.
followed by a rise in both groups but a higher peak in the CKD group (for main effect of study group, \( P=0.02 \)).

Similar to the pattern of urinary calcium excretion, FePi increased in both study groups almost immediately after meal consumption (for main effect of time, \( P<0.001 \)), except for the absence of a third peak in FePi after dinner in CKD (for main effect of study group, \( P=0.002 \)). Serum phosphate levels dipped in the morning and peaked in the afternoon between 16:00 and 17:00 PM (for main effect of time, \( P<0.001 \)), with the daily patterns nearly superimposable between CKD participants and controls (for main effect of study group, \( P=0.43 \)). FGF23 levels were significantly higher in the CKD group (for main effect of study group, \( P=0.001 \)) but were relatively stable in both groups throughout the 16-hour observation period without large diurnal or postprandial fluctuations.

**Effects of Calcitriol on Diurnal Variation in Mineral Metabolites in CKD**

Fasting levels of mineral metabolites before and after 1 week of calcitriol treatment are shown in Table 2. Serum creatinine levels were unchanged by the intervention. The only significant changes were in PTH and FGF23. In contrast, calcitriol seemed to modestly affect the hourly variation in all mineral metabolites (for main effect of visit day, \( P<0.05 \) for all; data not shown) in CKD, with the overall pattern in variability more closely approximating the pattern of controls. For example, compared with patterns observed in CKD at the baseline visit, serum calcium levels were higher, and PTH levels were lower throughout the day after calcitriol supplementation, with the curves for these two analytes becoming more comparable with those curves observed in controls. Notably, serum phosphate levels rose after calcitriol, with the afternoon peak reaching 3.8 versus 3.4 mg/dl at baseline (for main effect of visit day, \( P<0.001 \)).

**Effects of Interventions on Calcemic and Parathyroid Postprandial Responses**

The postprandial responses in CKD participants before and after the interventions are displayed in Figure 3. Whereas use of 500 mg dietary calcium and calcitriol alone trended with slightly higher postprandial serum calcium and FeCa and lower PTH levels, calcitriol in combination with 500 mg dietary calcium resulted in the lowest postprandial PTH levels and the highest postprandial serum calcium and FeCa (Figure 3, A–E) (for main effect of intervention, \( P<0.001 \) for all). The lowest postprandial FePi was observed after the combined intervention (Figure 3D) (for main effect of intervention, \( P<0.001 \)). The patterns after 500 mg dietary calcium and calcitriol supplementation closely resembled the postprandial responses observed in controls after consumption of the 250 mg calcium breakfast meal (for main effect of group, \( P=0.05 \) for all) (Figure 3, F–J).

**Heterogeneous Effect of Calcitriol on FGF23**

Although calcitriol treatment increased FGF23 levels significantly by a mean of 28±24\% (\( P=0.01 \)) (Table 2), the response was highly variable; FGF23 nearly doubled in some participants, whereas others manifested no change (Figure 4). Although the dose of calcitriol was increased on day 5 of the 7-day intervention period in six participants, the change in dose did not seem to influence the FGF23 response to treatment (mean change in FGF23 of 25±32\% versus 31±4\%, \( P=0.80 \)), although the sample size for this comparison was small. In contrast, calcitriol resulted in a nearly universal decrease in PTH levels in all but two participants, and there was no significant correlation between change in FGF23 and change in PTH (\( r=-0.24, P=0.48 \)). However, change in serum phosphate levels (\( r=0.69, P=0.02 \)) and change in FeCa (\( r=0.78, P=0.01 \)) in response to calcitriol significantly correlated with change in FGF23.

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**Table 2. Laboratory data of patients with CKD before and after calcitriol supplementation**

<table>
<thead>
<tr>
<th></th>
<th>Pre-calcitriol (n=12)</th>
<th>Post-calcitriol (n=12)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Medians (Interquartile Range)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.9±0.5</td>
<td>1.8 (1.6–2.0)</td>
<td>1.9±0.5</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.4±0.2</td>
<td>9.4 (9.3–9.5)</td>
<td>9.5±0.3</td>
</tr>
<tr>
<td>FeCa (%)</td>
<td>0.5±0.4</td>
<td>0.4 (0.2–0.9)</td>
<td>0.5±0.4</td>
</tr>
<tr>
<td>24-Hour urine calcium (mg/d)</td>
<td>65±58</td>
<td>50 (26–73)</td>
<td>65±50</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>3.3±0.5</td>
<td>3.4 (2.9–3.6)</td>
<td>3.4±0.7</td>
</tr>
<tr>
<td>FePi (%)</td>
<td>24.8±8.6</td>
<td>26.0 (18.1–29.7)</td>
<td>23.5±9.8</td>
</tr>
<tr>
<td>24-Hour urine phosphate (mg/d)</td>
<td>749±331</td>
<td>629 (590–772)</td>
<td>732±264</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>58.7±34.9</td>
<td>50.8 (39.7–60.5)</td>
<td>42.8±21.6</td>
</tr>
<tr>
<td>FGF23 (RU/ml)(^a)</td>
<td>199.1±200.8</td>
<td>119.7 (107.5–222.2)</td>
<td>270.1±294.0</td>
</tr>
</tbody>
</table>

\( P \) values are from paired \( t \) or Wilcoxon sign rank tests. FeCa, fractional excretion of calcium; FePi, fractional excretion of phosphate; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23, RU, reference units.

\(^a\)FGF23 levels were available in 11 of 12 participants with CKD.
Figure 3. Calcemic and parathyroid responses to study interventions. Fasting and postprandial measurements of (A) serum calcium, (B) serum phosphate, (C) fractional excretion of calcium, (D) fractional excretion of phosphate, (E) parathyroid hormone, and in CKD participants after the 250-mg calcium breakfast meal (dashed black line), the 500-mg calcium breakfast meal (circle), calcitriol (x), and the 500-mg calcium breakfast meal and calcitriol (*). In F–J, the postprandial responses in CKD patients after the 500-mg calcium breakfast meal and calcitriol supplementation (*) are represented along with the responses to the 250-mg calcium breakfast meal in healthy volunteers (dashed blue line). Fasting measurements were obtained at 8:00 AM relative clock time. Results are reported as means.
Discussion

Initiating mechanisms for disordered mineral metabolism in CKD continue to be under intense investigation. Although hyperphosphatemia and hypocalcemia are well established factors that promote secondary PTH elevation in advanced CKD (12), these manifestations are typically absent in stages 3 and 4 (1,2). We have previously reported that normocalcemic patients with intermediate CKD, low 1,25D, and normal fasting PTH levels developed subtle but significant reductions in serum calcium levels in the postprandial state (6). The relative hypocalcemia followed an increase in calcium and was associated with a subsequent increase in postprandial PTH levels (6). We speculated that this dynamic hypocalcemia could have resulted from a combination of insufficient dietary calcium intake, inefficient intestinal calcium absorption because of calcitriol deficiency, and excessive calciuria. In support of the latter, in a cohort of patients with stages 2–4 CKD, we found that use of loop diuretics was associated with greater urinary calcium excretion and higher PTH levels (11). Here, we extend our original physiologic observations by studying CKD patients over a longer period of time in the context of repeated meals and before and after calcium and calcitriol supplementation. Although our sample size was small, we again found that urinary calcium excretion increased in the immediate postprandial period, with peak levels occurring at 11:00 AM in both the CKD and healthy groups. Postprandial urinary phosphate excretion also rose in both study groups, consistent with previously described urinary excretion patterns after meals (6,13,14). PTH levels dipped transiently at 10:00 AM in both groups, which would be expected from prior observations of the diurnal variation in PTH (14,15), but began to rise soon thereafter, with peak levels at 1:00 PM. Notwithstanding the short duration of our intervention and normal baseline 1,25D levels, the rise in PTH was blunted in the CKD group by dietary calcium and calcitriol, with the combination resulting in normalization of the postprandial PTH response. Thus, our findings further support the hypothesis that tenuous calcium balance in patients with intermediate CKD predisposes them to PTH elevation in settings of increased urinary calcium losses and that interventions known to augment dietary calcium absorption offset this risk.

The apparent beneficial effects of dietary calcium intake and calcitriol observed in our study need to be interpreted with caution given the short duration and low dose of the interventions. Calcium balance in CKD is negative when dietary intake is 800 mg/d, but it becomes neutral to positive at 2000 mg/d (16,17). However, the median daily intake in a cohort of CKD stages 2–4 patients was estimated to be 615 mg/d (1) and was 921 mg/d in the current study. This difference suggests that low-dose calcium and calcitriol supplementation in CKD may enhance dietary calcium absorption and provide protection against dynamic hypocalcemia and resultant PTH elevation. However, increased calcium intake combined with active vitamin D over a long period of time may be harmful because of PTH oversuppression, positive calcium balance, hypercalcemia, and extrasosseous calcium deposition (18). Taken together, the net consequences of our approach and its potential ability to safely prevent secondary hyperparathyroidism will likely depend on underlying calcium balance, calcitriol sufficiency, dietary calcium intake, and dose and duration of calcemic interventions.

FGF23 elevation in CKD is another important etiologic factor in the pathogenesis of disordered mineral metabolism. FGF23 decreases 1,25D levels by inhibiting 1-α hydroxylase and stimulating the 24-hydroxylase (19), and human and animal studies have established FGF23 excess as a primary cause for 1,25D deficiency in CKD, which in turn, leads to secondary hyperparathyroidism (20,21). FGF23 levels are increased in states of dietary phosphate loading (22), calcitriol supplementation (23), and decreased kidney function (1), although the exact stimuli for FGF23 secretion in early CKD remain unknown. Consistent with our prior observations (6), we found that FGF23 levels were significantly higher in CKD patients compared with controls. However, in this study, unlike the previous study (6), baseline 1,25D levels were not suppressed, but fasting PTH levels were already higher in the CKD group compared with controls. Possible explanations for these discrepancies include the known imprecision of the 1,25D assay (24) that could have obscured small but physiologically relevant differences and the PTH stimulatory effect on 1,25D production that may have offset the FGF23-mediated 1-α hydroxylase inhibition.

We detected no large daily fluctuations in FGF23 levels in either study group. This finding was in contrast to the marked variability in all other mineral metabolites in both healthy and CKD groups. The finding of relatively constant daily FGF23 levels in both groups in our study is in agreement with two studies that also found no diurnal variability in FGF23 levels throughout the day (25,26). We previously reported no postprandial changes in FGF23 (6), which were confirmed here. In contrast, a single study of 10 healthy volunteers, in whom FGF23 levels were measured three times during the day, found that there was some circadian variability in FGF23 levels, with a rise in mean (±SE) cFGF23 levels from 45±27 to 68±45 reference units/ml at the end of the day (27). Taken together, the findings to date seem to indicate that, if circadian variability in FGF23 levels does exist, it is likely of very low amplitude.

Figure 4. | Fibroblast growth factor 23 response to calcitriol is heterogeneous. Change from baseline in fibroblast growth factor 23 levels after 1 week of calcitriol treatment. Data are displayed for each individual CKD participant, with a total of 11 responses (fibroblast growth factor 23 levels were not available for one CKD participant). The response is shown for the participants who required an increase in calcitriol dose (blue dashed lines) and those participants in whom the dose of calcitriol was kept constant (magenta straight lines).
Calcitriol increased FGF23 levels, but the response seemed to be heterogeneous. This novel finding provides a potential explanation for seemingly conflicting findings from previous studies. Calcitriol has been associated with improved survival among patients with CKD (28). However, calcitriol raises FGF23 levels (23), and elevated FGF23 is an independent risk factor for death (4). Our finding of the variable FGF23 response to calcitriol suggests the existence of undefined factors that may modulate this response and as a result, may lead to differential risks in hard clinical outcomes. Early candidate determinants from our preliminary evaluation seem to be change in serum phosphate and FeCa in response to calcitriol, but future studies are needed to confirm these findings and determine whether the magnitude of change in FGF23 associates with risk of mortality.

The emerging emphasis on prevention of disorders of mineral metabolism in CKD necessitates knowledge of the initiating factors and an ability to identify their presence early in the course of the pathogenic process so that interventions can be implemented prior to establishment of full-blown disease. The preservation of diurnal variability in mineral metabolites that we found in stages 3 and 4 CKD patients may be of great clinical and research importance. The observed difference in fasting, post-breakfast, and afternoon serum phosphate levels, for example, implies that, depending on time of day, serum phosphate measurements may yield values that differ by at least 0.4 mg/dl. Similarly, assessments of PTH levels may vary based on time of day and fasting status. In contrast, FGF23 levels exhibit relative stability during the day, with little circadian or postprandial variation. This finding implies that, whereas PTH and serum phosphate measurements should be standardized to the time of day, FGF23 measurements will provide similar results within an individual throughout the day. This characteristic of FGF23 adds to its ability to perform as an early marker of disordered mineral metabolism and should be leveraged in future studies.

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Disclosures
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References


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