Chapter 8

Effects of dietary phosphate and calcium intake on Fibroblast growth Factor-23

Marc G Vervloet, Frans J van Ittersum, Rahel M Büttler, Annemieke Heijboer, Marinus A Blankenstein, Piet M ter Wee

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Abstract

Background and objectives: Little is known about the influence of dietary phosphate intake on fibroblast growth factor 23 (FGF23), and its subsequent effects on vitamin D levels. The present study addresses changes in both iFGF23 and cFGF23, phosphaturia and levels of vitamin D on high and low phosphate and calcium intake.

Design, setting, participants & measurements: Ten healthy subjects adhered to a diet either low or high in phosphate and calcium content for 36 hours each, with a one week interval during which subjects used their usual diet. Serum phosphate, calcium, vitamin D metabolites, PTH and FGF-23 levels (cFGF23 and iFGF23) were measured several times a day.

Results: Serum phosphate levels and urinary phosphate increased during high dietary phosphate intake (from 1.11 to 1.32 mmol/l, p<0.0001 and 21.6 to 28.8 mmol/day, p=0.0005 respectively). FGF-23 serum levels increased during high dietary phosphate/calcium intake (cFGF23 from 60 to 72 RU/ml, p<0.001; iFGF23 from 33 to 37 ng/L, p=0.003), while PTH declined. 1,25-Dihydroxy vitamin D showed an inverse relation with FGF-23.

Conclusion: Variation in dietary phosphate and calcium intake induces changes in FGF-23 (on top of a circadian rhythm) and 1,25-dihydroxy vitamin D blood levels as well as urinary phosphate excretion. These changes are detectable the day following the change in phosphate content of meals. Higher FGF-23 levels are associated with phosphaturia and a decline in 1,25D levels.
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Introduction
Phosphorus is an important constituent of nucleotides and essential for bone mineralization, muscle function, cellular signal transduction and energy storage. The kidney has a major role in phosphorous homeostasis that is regulated by several hormones such as parathyroid hormone (PTH), 1,25-dihydroxy vitamin D (1,25D), and the more recently identified fibroblast growth factor 23 (FGF-23). FGF-23, produced by osteocytes, induces phosphaturia and is considered to prevent the occurrence of elevated phosphate levels. In patients with chronic kidney disease, it is independently associated with mortality. However, changes in FGF-23 levels following a dietary phosphate load are not completely understood.

Previous studies on FGF-23 response on phosphate loading have revealed conflicting results due to differences in timing of sample collection, follow-up and different assays used to determine FGF23 levels.3-5

One study demonstrated a rise in cFGF23 on phosphate loading, but measured FGF23 only after 5 days, thereby precluding any conclusion on the time-window prior to that. Several other studies did not find effects of phosphate intake on FGF23, but these were short-termed (up to 6-16 hours).2,7,8 However, these studies found an early increase in phosphate excretion, probably due to an early rise in PTH. One study did find an increase of FGF23, but not before 8 hours following the highest phosphate dose.9 Phosphaturia preceded the rise in FGF23 in the latter study.

Therefore, we studied the effects of dietary phosphorus and calcium intake on FGF-23 levels, using frequent sampling and adequate duration of follow up. Assays for both C-terminal (cFGF23) and intact FGF23 (iFGF23) were used simultaneously.

Materials and methods
Study subjects
Ten healthy subjects where recruited among medical students of the VU University Medical Centre in Amsterdam. They all had unremarkable medical history and were non-smokers. All subjects had a creatinine clearance above 100 ml/min using a 24 hours urine collection. This study was approved by the local Medical Ethical Committee and all participants gave informed consent to the study.
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Study protocol

This study was conducted as an open-label cross-over study. There were two separate study periods of three days each, with a one week interval. The first study period consisted of a low phosphate and calcium diet, whereas subjects adhered to a phosphate and calcium enriched rich diet during the second study period. The reason for giving simultaneously high or low calcium and phosphate in the diet was to prevent a phosphate induced rise in PTH, because that would have made expected rise in phosphaturia due to FGF23 more difficult to interpret, and because this would reflect more real life, since most foods rich in phosphate are also rich in calcium. The days prior to the two study periods and on day one until last blood drawing at 16\textsuperscript{th} h, subjects adhered to their regular diet. After that, the dietary intervention, prescribed by a dietician, started until the end of that study period. dietary intervention meals of each study period were prescribed by a dietician. On the first day of each study period, baseline fasting measurements of serum phosphate, calcium, urea, creatinin, albumin, PTH and FGF-23 levels were performed at fixed time points (at 8\textsuperscript{th} h fasting, and at 12\textsuperscript{th} h and, before lunch and dinner respectively). 25-Hydroxy vitamin D (25D) and 1,25D levels were measured once a day, at 16\textsuperscript{th} h. Urine was collected for two consecutive 24 hours during each study period, for measurement of total calcium and phosphate excretion. On the second day of each study period blood samples and 24-hour-urine collection were taken as described for day 1. On the third day of each study period a single morning blood sample was taken.

Study meals

In the first study period of low phosphate (and low calcium) diet, the daily intake was restricted to 850 mg phosphate and 280 mg calcium. This is well below the amount in a typical western diet, containing 1500 mg\textsuperscript{10-13}. During the second study period dietary phosphate and calcium intake were high, 2.880 mg and 1.700 mg respectively\textsuperscript{14}. The total energy intake was about the same in both study periods 2.000 kcal/day and 2.360 kcal/day respectively. In healthy U.S. citizens aged 20 to 39 years dietary phosphate intake is average 1.400 mg and calcium intake 900 mg\textsuperscript{15}. In this study phosphate and calcium intake during the first and second study period were respectively at the lowest and upper edge of normal phosphate and calcium intake.
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**Biochemical analyses**

Plasma phosphate (ref range 0.7-1.4 mmol/l), calcium (ref. range 2.2-2.6 mmol/l), albumin (ref. range 35-52 g/l), urea (ref. range 3-7.5 mmol/l) and creatinine (ref. range 60-110 μmol/l) as well as urinary phosphate, calcium and creatinine, were analysed using modular system of Roche Diagnostics (Mannheim, Germany). Corrected serum calcium levels were calculated using the formula (corrected calcium = measured calcium -0.025*albumin + 1) to correct for serum albumin levels.

Intact PTH (ref. range 2-11 pmol/l) was analysed in EDTA-plasma using an immunometric luminescence assay (Architect, Abbott Laboratories, Diagnostics Division, Abbott Park, Illinois USA). The intra- and interassay CV’s are both 5%. 25-Hydroxy vitamin D (ref. range 25-150 nmol/l) was analysed using a radio immunoassay (Diasorin, Stillwater, Minnesota, USA). The intra- and interassay CV’s are 7-9% and 10% respectively. 1,25-dihydroxyvitamin D (ref. range 50-160 pmol/l) was analysed in serum using a radio immunoassay (IDS, Tyne and Wear, UK). The intra- and interassay CV’s are 8-9% and 11% respectively.

FGF-23 was analysed with two assays. The cFGF23 was assessed in EDTA-plasma using a sandwich enzyme-linked immunosorbent assay (ELISA) (Immutopics, San Clemente, CA, USA) according to the manufacturer’s instructions. The intra- and interassay CV’s are <5% and <16%, respectively The iFGF23 was determined in serum using a sandwich ELISA, (Kainos Laboratories, Tokio, Japan), The intra- and interassay CV’s are <10% and <14%, respectively.

All laboratory measurements were performed in the VU University Medical Centre clinical chemistry department.

**Study endpoints**

The primary study endpoint was the change in FGF-23 serum levels with dietary phosphate and calcium restriction and high dietary phosphate and calcium intake. Secondary endpoints were the correlation between cFGF23 and iFGF23, changes in serum phosphate, calcium, PTH, 1,25-dihydroxy vitamin D and urinary phosphate and calcium excretion as well as correlations between above-mentioned parameters.

**Statistical analyses**
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Statistical analysis was performed for both cFGF23 and iFGF23. Data were analysed with the longitudinal data analysis technique generalized estimating equations (GEE) using Stata 11 for Windows. This method is suitable for longitudinal data analysis between a continuous variable and several time dependent and time independent co-variates16. Both iFGF23 and cFGF23 were analyzed as dependent variables, using diet (low, normal and high phosphate content) time point of day, as independent variables. If appropriate, adjustments were made for differences in baseline values, PTH levels, and creatinine clearance. In case of skewed data, analyses were performed after log-transformation. P-values < 0.05 were considered statistically significant.

Results

Study subjects

Eight women and two men were included. Their mean age was 23.5 ± 1.6 years. They all adhered to the complete study protocol, and there were no missing data.

Biochemical changes induced by diet

The table shows numerical results for phosphate, calcium, PTH, vitamin D metabolites, urea, albumin and creatinine serum levels. Creatinine clearance decreased from 125 (±27) ml/min on baseline to 114 (±20) ml/min during phosphate/calcium-restriction and increased to 131 (±22) ml/min during phosphate/calcium-enriched meals. Mean fasting serum phosphate levels during the baseline periods were 1.10 ± 0.09 mmol/L. Serum phosphate levels did not change during dietary phosphate/calcium restriction compared to baseline (p= 0.22), but increased during high dietary phosphate/calcium intake to a maximum of 1.32 mmol/l (P<0.0001). Serum phosphate levels did not change significantly in the course of the day (Figure 1). The two dietary interventions led to significant changes in 24 hour urinary urea content (p=0.003 for change from regular to P-restricted diet, and p=0.0006 form regular
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<table>
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<tr>
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<th>Baseline 1</th>
<th>P-restricted</th>
<th>Baseline 2</th>
<th>P-enriched</th>
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<td><strong>Phosphate (mmol/L)</strong></td>
<td>1.09 (0.12)</td>
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<td><strong>Calcium (mmol/L)</strong></td>
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<td><strong>Albumin (g/L)</strong></td>
<td>43 (3)</td>
<td>43 (3)</td>
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<td><strong>BUN (mmol/L)</strong></td>
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<td>3.5 (0.8)</td>
<td>3.8 (0.6)</td>
<td>4.8 (0.7)</td>
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<tr>
<td><strong>Creatinine (μmol/L)</strong></td>
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<td>72 (9)</td>
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<td><strong>PTH (pmol/L)</strong></td>
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<td><strong>25OH-D3 (nmol/L)</strong></td>
<td>101.9 (34.27)</td>
<td>100.2 (34.12)</td>
<td>96.9 (32.9)</td>
<td>95.7 (35.30)</td>
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<tr>
<td><strong>1,25(OH)2-D3 (pmol/L)</strong></td>
<td>147.7 (47.2)</td>
<td>156.3 (43.7)</td>
<td>143.1 (47.8)</td>
<td>118.2 (27.6)</td>
</tr>
</tbody>
</table>

*Table 1: Values of laboratory results during the two study periods. Data are shown as mean (SD)*

*Figure 1: Change in serum phosphate levels during the two study periods. All measurements on day 1 were done while on regular diet, followed by dietary intervention. Depicted are means ± standard errors. The mean of day 1 (regular diet) did not change on day 2 while on P/Ca restricted diet (open circles). Following P/Ca enriched diet (closed circles) these means changed from 1.11 mmol/l to 1.25 mmol/l (p<0.0001)*
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Figure 2: Change in 24 hours urinary urea appearance. Values on day one were taken following 24 hours on regular diet, values on day two were taken during 24 hour on either phosphate-enriched or restricted diet. Depicted are means ± standard deviations. Both the decline following P/Ca-restriction ($p=0.003$) and the rise on P/Ca-enriched meals ($p=0.0006$) were highly significant.

Figure 3: Change in 24 hour phosphate excretion comparing P excretion while on regular diet (day 1) or on either P-enriched or restricted meals. Depicted are means ± standard deviation. Phosphaturia declined non-significantly on P/Ca-restriction ($p=0.09$), and rose while on P/Ca enriched meals ($p=0.005$).
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to P-enriched diet) indicating reasonable separated levels of protein-intake (Figure 2). The tight correlation between protein intake and phosphorous intake is well established\textsuperscript{17}. Urinary phosphate excretion tended to decrease (p=0.09) during phosphate/calcium restriction and increased from 21.6 ± 4.4 mmol/24 h to 28.8 ± 4.4 mmol/24 h (p=0.005) during high dietary phosphate/calcium intake (Figure 3).

\textit{Changes in FGF-23 levels}

During the two days, while subjects used their regular meals, cFGF23 increased from 45±27 RU/l to 68±45 RU/l (p=0.002), while iFGF23 declined during daytime from 36±6 to 31±5 ng/l (p<0.001) (Figures 4 and 5). To correct for this apparently circadian rhythm, we added time point of day into our GEE-model to dissect the influence of dietary intervention from daytime fluctuations of FGF23 in subsequent analysis. To compare subsequent days, values for each day are expressed as means for day 1 and day 2 respectively. As compared with regular meals, phosphate/calcium restriction led to a small decline in cFGF23 from 50.0 to 42.0 RU/l (p=0.038), while phosphate/calcium-enriched meals led to an increase of cFGF23 from 60 to 72 RU/l (p<0.001) (Figure 4). Intact FGF23 (Figure 5) did not change significantly on phosphate/calcium restricted diet (from 33 to 32 ng/l) but increased from 33 to 37 ng/l on phosphate/calcium enriched diet (p=0.003). Despite the fact that the entire range of serum phosphate levels was quite small, the univariate analysis showed a statistically significant, positive association between phosphate levels and both cFGF23 and iFGF23 (p=0.001 and 0.005 respectively). Adding the phosphate-content in meals to a multivariate model, the association between serum phosphate and FGF23 disappeared, whereas the effect of meal on FGF23 remained highly significant, probably indicating that serum phosphate is a poor marker for phosphate burden in the meals.
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**Figure 4 and 5:** Changes in c-terminal FGF23 (upper panel) and intact FGF23 (lower panel) while on regular diet (all values on day 1) followed by dietary intervention of either P-enriched or restricted diet. Depicted are means ± standard errors. See text for the comparison of the different timepoints on day 1 and the comparison between the subsequent days.
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Changes induced in PTH

Following P/Ca-restricted meals PTH was unchanged: mean of 5.7 ±2.6 pmol/l during the day while on regular diet, followed by 5.4 ±2.2 pmol/l (NS) on the subsequent day while on P/Ca-restricted diet. However, P/Ca enriched meals led to a decline of PTH from 5.2 ±2.8 to 4.3 ±1.6 pmol (p=0.008 after correcting for calcium and phosphate (Figure 6).

![Graph](image)

**Figure 6:** Effects on PTH following dietary intervention. Only P/Ca loading led to a significant change (p=0.008) from 5.2 to 4.3 pmol/l (means of days 1 and 2 respectively)

Phosphate excretion as a function of cFGF23 levels:

Phosphate excretion during regular diet was 21.8 mmol/24 hours and declined to 18.9 mmol/24 hours (NS). However, during phosphate/calcium enriched meals, phosphate excretion increased from 21.6 to 28.8 mmol/24 hours (p<0.001). As expected, the phosphate/calcium and protein enriched diet led to a significant increase in creatinine clearance, of 114, 125 and 131 ml/min for low-P diet, regular diet and high-P diet respectively (p=0.002). A significant 16% of variance of phosphaturia could be attributed to increased creatinine clearance (p<0.0001), the remainder 84% being due to diminished tubular reabsorption of phosphate (TRP). Both PTH and FGF23 are known to influence TRP. However, we found a significant inverse correlation between PTH an P-content of meals (p=0.006). Multivariate analysis, including time point of the day, PTH, meal used, and
baseline values, demonstrated a significant increase in phosphaturia and cFGF23 and iFGF23 levels (p=0.024 and p=0.017 respectively).

**Changes in vitamin D metabolites due to FGF23**

During the entire experiments there were no changes in the levels of 25 hydroxyvitamin D3 (25D). There was a highly significant negative association between both cFGF23 (p<0.0001) and iFGF23 (p<0.0001) and 1,25D. Although, as mentioned above, PTH levels declined along with a rise in FGF23, and this lower PTH could have caused the decline in activation of vitamin D, correcting for change in PTH did not at all affect the level of significance between FGF23 and 1,25D. Remarkably, our analysis revealed a significant and independent effect of phosphate/calcium-enriched meals on the levels of 1,25D, even after correcting for PTH and FGF23, demonstrating lower 1,25D levels with phosphate/calcium-enriched meals.

**Discussion**

Our results reveal a circadian rhythm of both iFGF23 and cFGF23. Intact FGF23 peaks and the morning and declines during the day. This pattern might reflect the circadian rhythm of bone-metabolism that during nighttime unloads, and loads during daytime, possibly driven by the endogenous circadian rhythm of PTH\(^1\). Opposed to iFGF23, cFGF23 rises during daytime. Due to the fact that the assay for cFGF not only detects full-length FGF23, but also c-terminal fragments, this suggests that these fragments accumulate during the day.

On top of the above-mentioned rhythm an effect of phosphate-content in meals was observed. Both cFGF23 and iFGF23 rose within a day after dietary phosphate and calcium loading. Phosphate and calcium restriction led to a decline in FGF23, albeit non-significant for iFGF23,. The positive association we found between FGF23 and phosphaturia, independently from PTH, supports the assumption that FGF23 is of importance for phosphate homeostasis, at least in the period starting 16 hours after high phosphate (and calcium) intake. Finally we found a negative association between FGF23 level and 1,25D, which is in line with previous studies that showed a FGF23 induced downregulation of the \(1\alpha\)-hydroxylase, the enzyme that converts 25D to 1,25D.

Integrating our results with previous studies mentioned in the introduction, suggests that on phosphate loading, there is a prompt response of PTH, causing very early phosphaturia\(^2,19,20\).
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However, within a time frame of 8-16 hours on continuing high phosphate intake, FGF23 rises and takes over phosphaturic effects of PTH. From a homeostatic point of view it seems advantageous for phosphate homeostasis not to be dependent on PTH solely, because that would also increase phosphate levels by activation of vitamin D. Indeed, in early CKD it has been suggested that postprandial hypocalcemia, probably induced by a transient rise in GFR, leads to elevating PTH, thus adding another potential mechanism to early secondary hyperparathyroidism of CKD\textsuperscript{21}. In our study we found a decline of PTH during phosphate-enriched meals, probably due to simultaneous increase in calcium intake, and therefore PTH cannot explain the change in phosphaturia. The clinical meaning of phosphate-induced rises in FGF23, leading to increased phosphaturia, appears to be a two-edged sword. Besides its protective effect against a rising phosphate level, both animal\textsuperscript{22} studies and human studies\textsuperscript{23-25} suggest that it might have detrimental effects. The small increase in phosphate levels we demonstrated on our phosphate/calcium enriched meals could be meaningful in terms of cardiovascular risk, giving the epidemiological data correlating phosphate level, even in the normal range in non-CKD patients to subsequent cardiovascular risk\textsuperscript{26}, as it does in hemodialysis patients\textsuperscript{27}.

A clinical important finding of our study is that, although the changes in serum phosphate were rather small and remained within the so-called normal range, they led to important increases in both cFGF23 and iFGF23. Therefore, serum phosphate levels seem to be a poor marker of phosphate load. Especially when kidney function is preserved, phosphate levels appear to remain rather stable on phosphate loading, but at the expense of a higher level of FGF23. This higher level of FGF23 is associated with reduced calcitriol level, as has been established in CKD\textsuperscript{28}, and is confirmed for healthy adults in our study. The stable levels of serum phosphate seen in the present study are in contrast with the situation in CKD, where the phosphaturic effects of FGF23 are limited due to a decrease in number of functioning nephrons. The subsequent hyperphosphatemia leads to continuous stimulation for FGF23 release. Our data suggest biological effects of such rises in FGF23, since an association exists between these levels and phosphaturia. Phosphate excretion is accomplished by ultrafiltration and subsequently regulated phosphate reabsorption by PTH and FGF23 at the proximal tubules by the sodium-phosphate exchanger\textsuperscript{29}. Therefore, when examining phosphaturia, data have to be corrected for changes in GFR. Increases in GFR are induced by higher protein or amino acid intake\textsuperscript{30}. In the present study, it was noticed that a phosphate-
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(and thus protein) enriched diet led to increases in creatinine clearance. However, in the multivariate analysis, of the 7.2 mmol increase in phosphate excretion, only 1 mmol could be explained by the increase in GFR. The remaining 6.2 mmol was due to reduced tubular reabsorption.

Another well-described biological effect of FGF23 is its inhibition of 1 alpha hydroxylation of 25 hydroxyvitamin D, leading to decreased levels of 1,25D31. Our data demonstrate for the first time that this phenomenon is also present in healthy subjects, already on the first day after the initiation of a phosphate/calcium enriched diet. Although we found a decrease in PTH, which may have caused the decline in 1,25D level, FGF23 remained an independent negative regulator of active vitamin D levels in multivariable analysis. Remarkable is that, even after correcting for the lower PTH and higher FGF23 following P/Ca-enriched meals, these meals in itself caused a decline in 1,25D levels. Phosphate itself32-34, calcium35 or some other constituent in protein enriched diets might inhibit 1α-hydroxylase directly, not mediated through PTH or FGF23. However, adding both phosphate and albumin-corrected calcium to the model (data not shown), did not change the 1,25D lowering effects of phosphate-enriched meals. Another possibility is that in our study design we missed an earlier more pronounced decline in PTH. This seems unlikely however, because previous studies all described an early rise in PTH, and not a decline, on phosphate loading.

Different from several other studies36 examining the physiological responses to phosphate loading, we found a decrease in PTH as already mentioned. This is most likely explained by the high calcium content of our P/Ca-enriched diet, or could be the consequence of the concomitant rise in FGF2337. It is also possible that we have missed an initial rise in PTH following phosphate loading as a consequence of our sampling times. However, the aforementioned studies that did measure PTH showed that at 16 hours after phosphate loading PTH was still above baseline levels, whereas we found levels below baseline.

The present study shows that the kinetics of C-terminal fragments are different from full-length FGF23. This conclusion is based on the assumption that the C-terminal assay detects both the c-terminal fragment and the full-length (intact) FGF23, whereas iFGF23 detects only full length FGF2338. We showed that over the day cFGF23 increased, while iFGF23 declined, which suggests accumulation of FGF23 fragments. Some have shown agonizing effects of FGF23 fragments39 while other found that fragments have competitive inhibitory effects on
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the Klotho-FGFR1 complex\textsuperscript{40} and the FGF23-receptor\textsuperscript{41}. The reason for the discordant kinetics of iFGF23 and cFGF23 is unclear, but we speculate that there is a circadian rhythm of FGF23 production, being highest early in the day, as reflected by the iFGF23 curve, with a delayed clearance of fragments formed during the day.

Our study faces some limitations. First of all, we examined only young healthy volunteers, which limits the validity of our findings to other individuals, especially those with CKD. However, the assumed major difference would be a much higher FGF23 in the latter, due to higher serum phosphate levels. Second, we did not test the early response after the initiation of the several dietary interventions, so we cannot be sure that observations made from time point 16 hours on, were the consequence of what happened in that time frame, especially changes in PTH. As mentioned, those studies that did test up to 16 hours after dietary intervention showed that changes in PTH had not been extinguished yet. Furthermore, the effects of PTH on phosphaturia are instantaneous, different from FGF23\textsuperscript{32} so changes in phosphaturia we found, were not likely the effects of unnoticed changes in PTH. Finally, we did not collect urine samples on several occasions each day, precluding to draw any conclusions on changes in fractional phosphate excretion during the day.

Conclusion.

FGF23 shows a circadian rhythm, which is different for iFGF23 and cFGF23. The former peaks in the morning, the latter peaks late in the afternoon. On top of that, phosphate (and calcium) loading rises FGF23. This rise is associated with increased phosphaturia and a reduction in levels of 1,25D.
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Statement of competing financial interest:
None
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