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Fibroblast Growth Factor-23 Relationship to Dietary Phosphate and Renal Phosphate Handling in Healthy Young Men

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The renal handling of inorganic phosphate (Pi) is controlled not only by PTH, but also by hitherto undetermined mechanisms dependent on phosphate intake. Recently, fibroblast growth factor (FGF)-23 was identified as a novel phosphaturic factor in tumor-induced osteomalacia and autosomal-dominant hypophosphatemic rickets. We hypothesized that phosphate intake could influence FGF-23 concomitantly to the changes in renal Pi handling. Twenty-nine healthy males were subjected to a 5-d low-phosphate diet and a phosphate binder, followed by a high-phosphate diet including supplements. Concomitant modifications in calcium intake allowed minimizing PTH changes in response to dietary phosphate. Serum FGF-23 levels significantly decreased on the low-phosphate diet, then increased with the oral phosphate load. Changes in FGF-23 were positively correlated with changes in 24-h urinary Pi excretion and negatively correlated with changes in the maximal tubular reabsorption of Pi and $1,25(OH)_2D_3$ (calcitriol), whereas PTH was not. In multivariate analysis, changes in FGF-23 remained the most significantly correlated to changes in $1,25(OH)_2D_3$ and maximal tubular reabsorption of Pi. Moreover, FGF-23 was positively correlated to serum osteocalcin, a marker of osteoblastic activity.

In summary, FGF-23 was inversely related to renal Pi transport and serum calcitriol levels in healthy young men. These data suggest that FGF-23 may be implicated in the physiological regulation of Pi homeostasis in response to dietary phosphate changes, independent of PTH. (*J Clin Endocrinol Metab* 90: 1519–1524, 2005)

INORGANIC PHOSPHATE (Pi) homeostasis is tightly controlled at the level of tubular Pi reabsorption [maximal tubular reabsorption of Pi (TmPi/GFR)] in the kidney and at the level of intestinal Pi absorption. These two processes are primarily regulated by PTH and $1,25(OH)_2D_3$ (calcitriol), respectively (1–3). Although dietary phosphate has a major influence on PTH synthesis and secretion in both normal and uremic animals and humans (4), there are clear suggestions that circulating factors other than PTH are implicated in the regulation of renal Pi handling in response to dietary phosphate changes (2). In thyro-parathyroidectomized rodents for instance, a low-phosphate diet results in a dramatic increase of the tubular reabsorption of Pi, independent of PTH (5). Moreover, normal mice parabiosed to X-linked hypophosphatemic (XLH) mice have a persisting renal Pi wasting after parathyroidectomy (6). Among the other factors possibly implicated in this regulation, IGF-I directly stimulates renal Pi reabsorption (7, 8). However, experiments in hypophysectomized rats suggest that the GH-IGF-I axis does not play a major role in the renal adaptive response to phosphate restriction (9).

Over the past 10 yr, much progress has been made in understanding the mechanisms and regulation of renal and intestinal Pi handling, first through the identification of distinct Pi transporters (10). Among them, the sodium-dependent Pi cotransporter NaPi-2 is the most abundantly expressed in mouse proximal tubular cells (11, 12), and a low-phosphate diet increases, whereas PTH decreases the abundance of NaPi-2 transporters in opossum kidney cells (13, 14). Another major area of discovery in this field has been the identification of so-called phosphatonins (15, 16). Among them, fibroblast growth factor (FGF)-23 has recently been identified as a novel phosphaturic agent in a number of pathological conditions in humans and mice (10). Hence, missense mutations in FGF-23 that likely prevent its cleavage and inactivation by the appropriate enzyme are the cause of autosomal-dominant hypophosphatemic rickets (ADHR) (17), a disorder characterized by hypophosphatemia, renal phosphate wasting, and inappropriately low serum calcitriol levels. Naked DNA injection of an ADHR mutant form of FGF-23 (hFGF-23R179Q) in mice inhibited NaPi-2 cotransport activities in both the kidney and small intestine (18). In these mice, $1,25(OH)_2D_3$ was also suppressed, whereas PTH remained unaffected. Most interestingly, liver expression (after naked DNA injection) of hFGF-23R179Q in rats that were fed a low-phosphate diet prevented the increase in the level of NaPi-2 cotransporters, suggesting that low-FGF-23 activity may be necessary for the adaptation of renal Pi transport to decreased phosphate intake (19).

FGF-23 is also one of the factors responsible for tumor-induced osteomalacia, as shown in rodents implanted with FGF-23-secreting tumors or given injections with human recombinant FGF-23, which present with renal Pi wasting and hypophosphatemia (20). The recent development of a serum

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Abbreviations: ADHR, Autosomal-dominant hypophosphatemic rickets; FGF, fibroblast growth factor; Pi, inorganic phosphate; RU, reference units; TmPi/GFR, maximal tubular reabsorption of Pi; TRCaI, tubular reabsorption of calcium index; XLH, X-linked hypophosphatemic.

assay for FGF-23 in humans indicates that in most patients with tumor-induced osteomalacia, FGF-23 levels are elevated, but levels decrease dramatically after tumor removal (21). Elevated circulating FGF-23 levels have also been found in some, but not all, patients with XLH (21–23) and the McCune Albright syndrome, fibrous dysplasia of bone (24). In XLH patients, FGF-23 levels were inversely correlated to serum Pi levels, whereas PTH was not, suggesting that serum FGF-23 is the most important determinant of serum Pi in XLH (23). In these studies, FGF-23 was also detectable in the circulation of normal individuals. Yet, the role of FGF-23 in the physiological regulation of Pi homeostasis in humans remains unclear (16).

Because PTH stimulates the tubular reabsorption of calcium, whereas it decreases that of Pi, it is obvious that PTH alone cannot simultaneously ensure both calcium and Pi homeostasis when the availability of both minerals from the environment varies in the same direction. Thus, it has been experimentally demonstrated that decreasing both dietary phosphate and calcium can be followed by an increase in plasma PTH levels and in the excretion of nephrogenic cAMP, a marker of PTH activity, whereas the tubular capacity to reabsorb Pi is adequately enhanced (25). These observations led us to investigate the effects of phosphate intake on circulating FGF-23 levels concomitant to changes in renal phosphate handling. Our results in 29 healthy male volunteers, investigated over 2 wk, indicate that serum FGF-23 is regulated by dietary phosphate. In turn, FGF-23 negatively correlates with both renal Pi reabsorption and calcitriol levels, supporting the notion of a physiological role for this phosphaturic agent on Pi homeostasis.

Subjects and Methods

Twenty-nine healthy male volunteers were recruited among 105 men aged 20.7–38.6 yr, students from the University of Geneva (26). Exclusion factors were: 1) known acute or chronic disease; and 2) medications known to affect intestinal absorption, kidney function, or bone turnover. The study, in keeping with appropriate treatment of human subjects, was approved by the Ethics Committee of the Geneva University Hospital, and written informed consent to participate in the study was obtained from each subject.

Dietary intervention and compliance

Dietary intervention was performed on an ambulatory basis under the guidance of a trained dietitian. The study occurred over a 2-d run-in period, during which subjects were allowed to eat their regular diet, followed by 5 d of phosphate restriction, 2-d reequilibration on their regular diet, and, eventually, 5 d of an oral phosphate load. During the restriction period, subjects received a magnesium- and aluminum-containing phosphate binder (Alucol, Novartis, Basel, Switzerland), 1 g before each meal; whereas during the supplementation period, they received 1000 mg phosphorus element per day (potassium-phosphorus syrup). To minimize directional changes in serum PTH due to phosphate, calcium intake was also decreased during phosphate restriction and increased during phosphate supplementation, respectively, which was mostly achieved through counseled modifications of dairy food intake.

During the study, subjects weighed all of their food; and dietary calcium and phosphate intake were evaluated by a dietitian, using a quantitative daily food record (26). Compliance with the assigned regimen was additionally ascertained by 24 urinary measurements of calcium and Pi excretion on the first and last day of each dietary intervention period. Measurements were corrected for daily creatinine excretion to adjust for potentially incomplete collection of urine.

Biochemical determinations

Fasting blood and urine samples were collected at steady state, *i.e.* on the second day of the run-in and equilibration period and on the last day of the restriction and supplementation period. Calcium and Pi were measured using standard methods, and the thresholds for renal tubular reabsorption of phosphate (TmPi/GFR) and calcium [tubular reabsorption of calcium index (TRCaI)] were calculated using published nomograms (27, 28). Vitamin D metabolites [25-OH-D_3 and 1,25$(OH)_2D_3$] were determined by RIA and protein binding assays, respectively (INCSTAR Corp., Stillwater, MN); intact PTH was measured using the Immulite assay (Diagnostic Products, Los Angeles, CA); and serum IGF-I was measured by RIA (Nichols Institute, San Juan Capistrano, CA), after separation from binding proteins by acid-ethanol extraction and cryoprecipitation. FGF-23 was measured by a sandwich ELISA that was developed by Immunotopics Inc. (San Clemente, CA). This assay uses two affinity-purified goat polyclonal antibodies to detect epitopes in the carboxy-terminal (amino acid 180-251) portion of FGF-23. Hence, FGF-23 levels, as evaluated by this assay, represent the sum of intact FGF-23 and FGF-23 C-terminal fragments. According to the manufacturer's notice, the lower limit of detection for FGF-23 is 3 reference units (RU)/ml, with a linear range (at 450 nm) up to 680 RU/ml, and the interassay coefficient of variation in human serum ranges from 5–7.3%. For this measurement, each sample was tested in duplicate and averaged.

Serum osteocalcin was measured by RIA (CIS-Bio International, Gif-sur-Yvette, France), and total urinary deoxypyridinoline excretion was measured by fluorescence emission after acid hydrolysis. Urinary cAMP was measured by ELISA from Immunotech (Marseille, France).

Statistics

The measurement error of the C-term FGF-23 assay was estimated by calculating the SD of repeated measurements, using paired samples collected during the phosphate supplementation period (29). Differences in calcium and phosphate intake and biochemical measurements between dietary period groups were analyzed by ANOVA. To account for multiple comparisons between partly correlated measurements, a P value ≤ 0.005 was considered statistically significant. For *post hoc* comparisons between specific dietary groups, we used Fisher's projected least significant difference statistics, with $P < 0.01$ as the minimal level of significance. Dietary-induced changes in the various biochemical measurements were calculated as Δ_1 = restriction minus baseline and Δ_2 = supplementation minus reequilibration values. Pearson's correlation coefficients between Δs for FGF-23 and other variables were then evaluated using simple linear and multiple regression analyses.

Results

Calcium and phosphate intake and biochemical indices of mineral metabolism at the end of the four dietary periods are shown in Table 1. The assigned regimen induced marked changes in dietary phosphate and calcium intake, as assessed by daily food records. Consistent with these changes and the administration of phosphate binders or supplements, 24-h urinary Pi excretion, a reflection of the amount of mineral absorbed in the intestine at steady state, decreased 50% during phosphate restriction, then increased 80% during the supplementation period, respectively, compared with baseline. Some changes in 24-h urinary calcium excretion were also observed, reflecting dietary modifications in the absence of binders or supplements for this mineral. These dietary modifications were accompanied by significant changes in the tubular reabsorption of Pi (TmPi/GFR), FGF-23, and, to a lesser extent, serum Pi levels (Table 1). Thus, during phosphate restriction, serum Pi levels declined significantly ($P = 0.006$), whereas TmPi/GFR rose slightly ($P = 0.08$) compared with baseline. Conversely, the oral phosphate load caused a significant decrease in TmPi/GFR ($P = 0.0003$) (Fig. 1A), whereas serum Pi remained stable. Serum calcitriol levels did

TABLE 1. Biochemical indices of mineral metabolism in relation to dietary phosphate intake

	Dietary period				*P*	Reference interval
	Baseline	Restriction[a]	Equilibration	Supplement[a]		
Dietary intake						
Phosphate (g/d)	1.40 ± 0.10	0.54 ± 0.04[b]	1.43 ± 0.10	2.86 ± 0.11[c]	**<0.0001**	
Calcium (g/d)	1.26 ± 0.15	0.59 ± 0.10[b]	1.22 ± 0.13	1.66 ± 0.15[c]	**<0.0001**	
24-h Urinary excretion						
Pi (mg/d)	945 ± 33	455 ± 39[b]	885 ± 51	1690 ± 74[c]	**<0.0001**	400–1300
Calcium (mg/d)	188 ± 13	133 ± 10[b]	196 ± 16	170 ± 17	0.012	100–350
Tubular reabsorption						
TmPi/GFR (mg/liter)	3.57 ± 0.09	3.74 ± 0.11	3.65 ± 0.09	2.99 ± 0.08[c]	**<0.0001**	2.4–4.2
TRCaI/GFR (mg/liter)	10.7 ± 0.12	10.7 ± 0.08	10.7 ± 0.12	10.8 ± 0.08	0.95	9.6–11.6
Serum levels						
Pi (mg/dl)	3.90 ± 0.09	3.53 ± 0.09[b]	4.03 ± 0.09	3.81 ± 0.09	**0.003**	2.5–4.1
iCa (mg/dl)	4.80 ± 0.02	4.80 ± 0.03	4.80 ± 0.03	4.80 ± 0.03	0.93	4.5–5.3
PTH (pg/ml)	26 ± 2.1	30 ± 2.3	27 ± 2.3	34 ± 2.6	0.12	9.4–57.0
$1,25(OH)_2D_3$ (pg/ml)	37.5 ± 1.0	39.5 ± 1.6	36.3 ± 1.1	35.6 ± 1.4	0.24	17–55
IGF-I (ng/ml)	286.9 ± 13.1	271.3 ± 12.8	258.6 ± 12.0	263.9 ± 12.7	0.41	133–498
FGF-23 (RU/ml)	48.3 ± 4.6	34.0 ± 3.6[b]	43.3 ± 3.1	53.9 ± 4.4[c]	**0.005**	ND

Mean ± SEM in 29 subjects. ND, not determined; Ca, calcium; iCa, ionized Ca. Multiplication factors to convert metric units to Systeme International units are as follows: Pi and TmPi, × 0.323; 24-hr urinary Pi, × 0.032; iCa and TRCaI, × 0.25; 24-hr urinary Ca, × 0.025; PTH, × 0.11; and $1,25\text{-}(OH)_2D_3$, × 2.4.

[a] Including Pi binder (1 g before each meal) during restriction and Pi supplements (1000 mg/d) during supplementation.

Significant *P* values for the overall comparison between the four dietary periods (by ANOVA, adjusted for multiple comparisons) are in *bold*, with [b] $P < 0.01$ for differences between restriction and baseline and [c] $P < 0.01$ for differences between supplementation and restriction (by *post hoc* Fisher's projected least significant difference).

not vary significantly overall, but decreased slightly between the low- and high-Pi intake ($P = 0.08$) (Table 1). In contrast, none of the measured indices of calcium metabolism, including TRCaI, serum calcium, and PTH levels, varied significantly between dietary periods (Table 1), although PTH levels were the highest during phosphate supplementation ($P = 0.04$ compared with baseline).

Mean serum FGF-23 levels in the 29 subjects participating

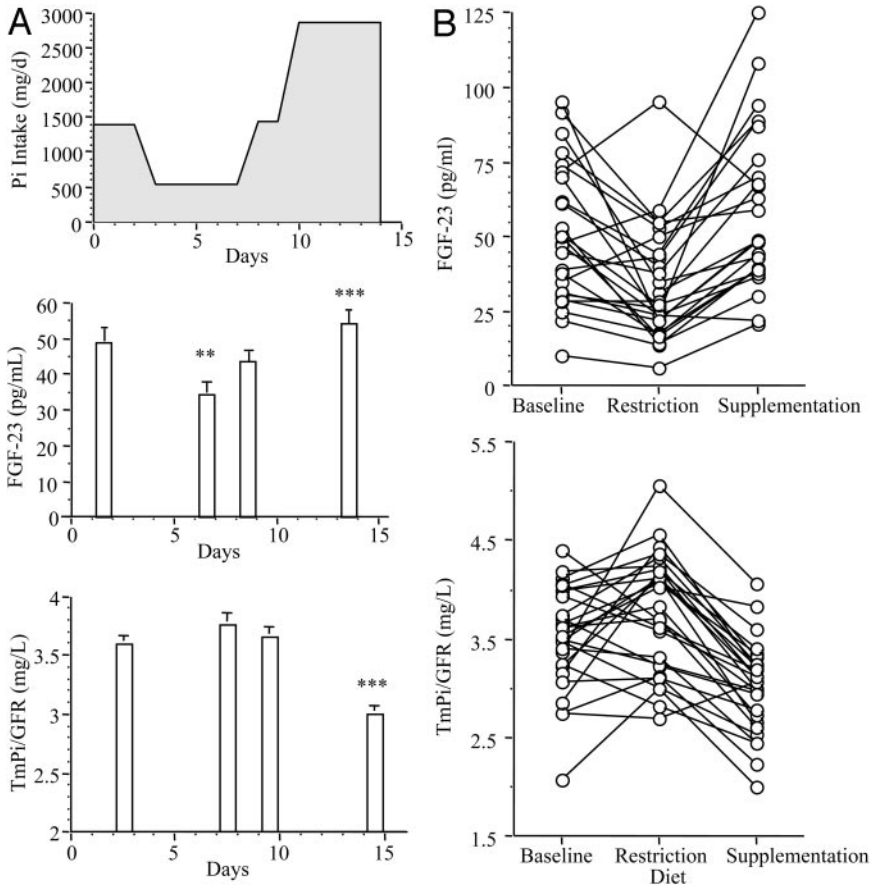

FIG. 1. Renal Pi handling and serum FGF-23 levels in relation to dietary phosphate intake. A, The average phosphate intake was evaluated by quantitative food records. Mean serum FGF-23 and tubular threshold for Pi reabsorption (TmPi/GFR) were determined at baseline (d 2), during phosphate restriction (d 7), reequilibration (d 9), and phosphate supplementation (d 14) in all subjects (n = 29). **, $P \leq 0.01$ *vs.* baseline; and ***, $P < 0.001$ compared with restriction. B, Individual changes in serum FGF-23 levels and TmPi/GFR in 26 subjects compliant with the ascribed diet are shown. Multiplication factor to convert metric units to Systeme International units for TmPi is × 0.323.

in the study decreased significantly during phosphate restriction, then increased during the reequilibration and supplementation periods (Fig. 1A). Because three subjects failed to lower their 24-h urinary Pi excretion during Pi restriction, possibly indicating a poor compliance with the assigned regimen, the mean percentage change in FGF-23 was additionally calculated in the remaining 26 subjects. In those, FGF-23 declined 29.1 ± 6.5% during restriction compared with baseline and increased 31.1 ± 9.5% during supplementation compared with reequilibration. Despite these clear differences in the mean percentage change of FGF-23 between phosphate restriction and load ($P < 0.0001$), individual changes in FGF-23 levels and TmPi/GFR showed that all but two FGF-23 values during these periods fell within the range of values observed at baseline (10–95 RU/ml) (Fig. 1B). This led us to consider the measurement error of the C-term FGF-23 assay. For this purpose, FGF-23 was remeasured in all subjects on samples collected on the second consecutive day during the oral phosphate load. In these conditions, the SD of replicated FGF-23 measurements on the same subject was 11.1 RU/ml. This is less than the variability observed between subjects in Fig. 1B (SD 16.3–23.9 RU/ml depending on the dietary period) and represents about half the difference in FGF-23 levels between Pi restriction and supplementation (Table 1). Thus, a large proportion of the changes in FGF-23 values observed in this study can be ascribed to the interindividual variability, rather than measurement error, of FGF-23 under the influence of dietary phosphate intake.

To additionally evaluate the contribution of FGF-23 to Pi homeostasis, changes in FGF-23 levels were correlated with changes in other variables that occurred in response to dietary modifications in all subjects (n = 29) (Fig. 2). Consistent with the higher levels of serum FGF-23 during the oral Pi load, changes in FGF-23 were positively and specifically correlated to the changes in 24-h urinary Pi excretion (R = 0.484; $P = 0.0003$), but not urinary calcium excretion (R = 0.024; not significant; data not shown). In turn, changes in FGF-23 were negatively correlated with changes in the tubular reabsorption of Pi (TmPi/GFR; R = 0.538; $P < 0.0001$) and serum calcitriol levels (R = 0.360; $P = 0.009$) (Fig. 2). In contrast, changes in FGF-23 were apparently not correlated with changes in serum Pi levels (R = 0.017; not significant), as expected after reaching steady state.

Multiple regression analysis, including FGF-23, as well as known regulators of phosphate homeostasis, such as PTH and IGF-I, confirmed that changes in FGF-23 were the only significant determinant of changes in both TmPi/GFR and serum calcitriol (Table 2). Noteworthy, in these experimental conditions, PTH was not significantly correlated to any parameter of phosphate metabolism, but was weakly correlated to 24-h urinary calcium excretion (R = 0.21; $P = 0.023$) and tubular reabsorption of calcium (TRCaI; R = 0.19; $P = 0.042$). Moreover, PTH was significantly correlated to urinary cAMP excretion (R = 0.30; $P = 0.0015$), whereas FGF-23 was not (data not shown).

FGF-23 is produced by bone cells, and it has recently been correlated with bone turnover markers in patients with fibrous dysplasia of bone (24). We therefore investigated FGF-23 in relation to serum osteocalcin, a marker of osteoblastic activity, urinary deoxypyridinoline, and hydroxyproline, two markers of osteoclastic activity, in our normal subjects. FGF-23 was positively correlated to osteocalcin (R = 0.292; $P = 0.0020$) but not with the bone resorption markers. In multiple regression analysis, including major regulators of bone turnover, namely PTH, calcitriol, and IGF-I, FGF-23 remained the factor most significantly correlated with osteocalcin levels (Table 2).

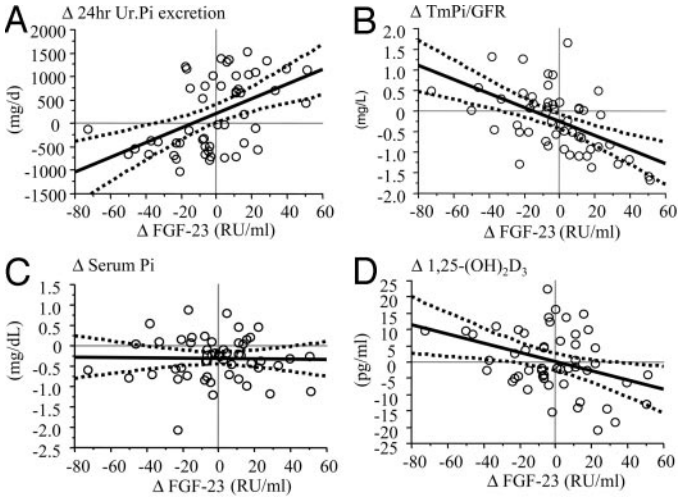

FIG. 2. Relationship between FGF-23 and indices of Pi metabolism. Simple linear regression of changes in serum FGF-23 with changes in 24-h urinary Pi excretion (A), TmPi/GFR (B), serum Pi (C), and $1,25(OH)_2D_3$ (D) were based on differences (Δ) in these biochemical measurements between restriction and baseline and between supplementation and reequilibration periods in all subjects (n = 29). *Dotted lines* represent 95% confidence interval of the mean. Pearson's correlation coefficient, R values, and *P* values are provided in the text. Multiplication factors to convert metric units to Systeme International units are as follows: Pi and TmPi, × 0.323; 24-h urinary Pi, × 0.032; and $1,25(OH)_2D_3$, × 2.4. Ur, Urinary.

Discussion

By investigating the FGF-23 response to phosphate intake and its correlation with biochemical indices of bone and mineral metabolism in ambulatory healthy humans, we made two major findings. First, an oral phosphate load increases circulating FGF-23 levels. Second, dietary-induced changes in serum FGF-23 are inversely correlated with the tubular reabsorption of Pi and with plasma calcitriol levels. Taken together with recent evidence that injection of recombinant FGF-23 in normal and thyro-parathyroidectomized rats results in a reduction of serum phosphate, $1,25(OH)_2D_3$ levels, and the renal expression of NaPi-2 cotransporter (30), our results additionally suggest that FGF-23 may be implicated in the regulation of phosphate homeostasis, independent of PTH.

Although increased FGF-23 levels and the concomitant decline of TmPi/GFR are likely to explain the absence of increased serum Pi during the oral phosphate load, decreased FGF-23 levels failed to completely prevent a decrease in serum Pi during phosphate restriction. One possible explanation for this observation may be the design of our study, in which phosphate supplementation always followed phosphate restriction (with a short reequilibration period in between), thereby allowing for a large increase in phosphate

TABLE 2. Regression coefficients of FGF-23 with other biochemical variables

Independent variable (X)	Dependent variable (Y)					
	TmPi/GFR		$1,25(OH)_2D_3$		Osteocalcin	
	β	P	β	P	β	P
FGF-23	−0.016	**0.0001**	−0.141	**0.011**	+0.162	**0.002**
PTH	−0.011	0.17	−0.016	0.88	+0.136	0.107
$1,25(OH)_2D_3$	NI		NI		+0.076	0.61
IGF-I	−0.004	0.18	NI		+0.029	0.082
sPi	NI		−1.48	0.54	NI	NI

The regression coefficient, β, and P values for potential determinants (X) of TmPi/GFR and $1,25(OH)_2D_3$ changes in response to diet, as well as for serum osteocalcin levels, a marker of osteoblastic activity, were calculated by multiple regression analysis in 29 subjects. NI, Variable not included in the model; sPi, serum inorganic phosphate. Significant P values are shown in *bold*.

intake over a rather short period of time. Alternatively, these results suggest that changes in FGF-23 levels are most efficient to maintain serum Pi homeostasis when stimulated by an oral phosphate load, which is consistent with the notion that FGF-23 is primarily a phosphaturic agent (20, 23). In addition, the small but significant decline of serum calcitriol levels on the high- compared with low-Pi diet, and its inverse correlation to serum FGF-23, additionally indicate that FGF-23 primarily functions to prevent Pi overload in the extracellular milieu. In contrast, serum $1,25(OH)_2D_3$ levels did not markedly increase during the restriction compared with baseline diet. Therefore, it is probable that larger decreases in dietary phosphate intake are required to detect meaningful changes in circulating $1,25(OH)_2D_3$, as reported by Portale *et al.* (31), and that some of these changes are directly mediated by serum Pi.

Our results somewhat differ from those of Larsson *et al.* (32) who did not detect significant changes in serum FGF-23 levels in six healthy males during 2 d of phosphate restriction followed by 3 d of supplementation. Although we used a similar assay for C-terminal FGF-23, the two studies differ in some regards. First, we decreased and increased calcium intake concomitantly to phosphate restriction and supplementation, respectively; whereas in the other study, subjects apparently received a standardized diet throughout the study. The latter regimen resulted in a nonsignificant decline of PTH in most subjects after 2 d of phosphate restriction, which may have offset changes in FGF-23 that would otherwise be required for adaptation of renal Pi transport. Second, we investigated a larger number of volunteers over a longer period of time. As explained by Larsson *et al.* (32), high levels of FGF-23 were found in four of six volunteers on the high-phosphate intake, suggesting that FGF-23 could respond to more sustained changes in dietary phosphate. By fulfilling these conditions, we found FGF-23 levels to increase 60% between the low- and high-phosphate diet. Yet, such changes are clearly less than the 3- to 4-fold mean increase in FGF-23 observed in patients with XLH and other phosphaturic conditions (21, 23). However, they compare favorably to the 40–75% increase in serum PTH in response to chronic dietary calcium restriction in healthy humans (33). Hormone variations of this magnitude therefore appear sufficient to maintain mineral homeostasis under physiological conditions. Nevertheless, it should be noted that the FGF-23 assay used in this study detects both intact and C-terminal fragments of the molecule. It is likely that the development of novel FGF-23 assays for the intact, bioactive form of the molecule (22) may allow a better discrimination of FGF-23 levels in both physiological and pathological conditions.

Several phosphatonins capable of causing phosphaturia and hypophosphatemia by cAMP-independent pathways have now been identified, including FGF-23, secreted frizzle-related protein 4, and matrix extracellular phosphoglycoprotein (20, 34, 35). Mutations in FGF-23 that prevent proper cleavage of the molecule cause ADHR (17). Some patients with XLH (21–23) and the McCune Albright fibrous bone dysplasia, who also present renal phosphate wasting (24), have elevated FGF-23 levels. In these patients, FGF-23 levels are inversely correlated to serum Pi levels, whereas in our healthy subjects, there was no apparent correlation between these two factors. These findings, however, are not contradictory if the physiological function of FGF-23 is to maintain serum Pi homeostasis (at steady state) by directly regulating renal Pi handling and indirectly (through calcitriol) regulating intestinal Pi absorption. To additionally elucidate the mechanisms regulating serum Pi homeostasis, it will be crucial to determine whether a Pi sensor exists and where regulation of FGF-23 production, in response to phosphate, actually takes place. The positive correlation between FGF-23 levels and osteocalcin, a marker of osteoblastic activity, observed in our healthy subjects, taken together with the evidence that FGF-23 levels correlate with osteoblastic activity in patients with fibrous bone dysplasia (24), suggest that bone could be involved in this regulation.

In conclusion, circulating FGF-23 was inversely related to renal Pi transport and serum calcitriol levels in healthy young men. These data strongly suggest that FGF-23 is implicated in the physiological regulation of Pi homeostasis independent of PTH, particularly in response to a dietary phosphate load.

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