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Increased circulating levels of FGF23: an adaptive response in primary hyperparathyroidism?

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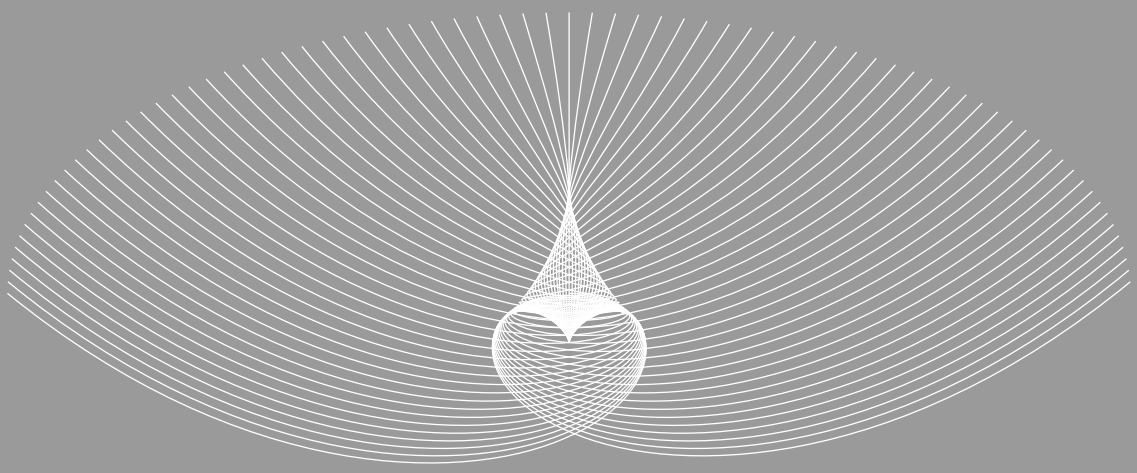

ABSTRACT

Introduction: Fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) are major players in the bone-parathyroid-kidney axis controlling phosphate homeostasis. In patients with primary hyperparathyroidism (PHPT) data on the relationship between PTH and FGF23 are scarce and not always concordant.

Objective: The aim of our study was to evaluate the relationship between PTH and FGF23 in patients with PHPT and in euparathyroid patients cured after successful parathyroidectomy (PTx).

Patients & Methods: Twenty-one patients with PHPT and 24 patients in long-term cure after successful PTx (EuPTH) were studied. All patients underwent biochemical evaluation of renal function, parathyroid status, vitamin D status, bone turnover markers, and serum intact FGF23 levels.

Results: Mean serum FGF23 concentration was significantly higher in PHPT than in EuPTH patients (50.8 ± 6.1 pg/mL vs. 33.1 ± 2.6 pg/mL, P=0.01). FGF23 levels significantly correlated with PTH levels (r=0.361, P=0.02), also after correction for $1,25(OH)_2D$ levels (r=0.419, P=0.01). FGF23 levels showed a significant negative correlation with $1,25(OH)_2D$, which was more pronounced in PHPT than in EuPTH patients (r= −0.674, P=0.001, vs. r= −0.509, P=0.01).

Conclusion: Our findings suggest that in PHPT, FGF23 levels are increased independent of $1,25(OH)_2D$ levels. The more pronounced negative relationship between FGF23 and $1,25(OH)_2D$ in the presence of high circulating PTH levels suggest that the increase in FGF23 levels may be an adaptive mechanism to counteract the PTH-induced increase in $1,25(OH)_2D$ levels, although not completely overriding it.

INTRODUCTION

Parathyroid hormone (PTH) and the active metabolite of vitamin D ($1,25(OH)_2D$) are prime regulators of calcium homeostasis but also have significant effects on phosphate homeostasis by respectively downregulating or upregulating the sodium phosphate co-transporters in the proximal tubules of the kidneys and in enterocytes of the intestinal tract (1-8). However, the major player of the bone-kidney axis controlling phosphate homeostasis has been shown to be fibroblast growth factor 23 (FGF23). FGF23 acts as a phosphaturic factor by the same mechanism of action as PTH, downregulating the cotransporters NaPi2a and NaPi2c in the kidney after binding to its receptor, FGFR-1, in the presence of Klotho (9-11). FGF23 also decreases $1,25(OH)_2D$ synthesis in the proximal tubules by direct inhibition of the 1α-hydroxylase enzyme (9,10,12).

FGF23 is predominantly produced and secreted by osteocytes in bone (9,10). This process is positively regulated by $1,25(OH)_2D$, via a vitamin D response element (VDRE) in the *fgf23* promoter (9,13-15). The process is also regulated by serum phosphate, although the exact mechanism by which this is achieved remains unclear. Extracellular phosphate does not appear to directly stimulate *FGF23* mRNA levels or *fgf23* promoter activity in osteoblastic cultures (9,14). Data on the effect of changes in phosphate intake on FGF23 concentrations are inconsistent, with different responses observed with short-term or long-term alterations in phosphate intake (16-20). It has also been shown that early and rapid changes in renal phosphate excretion occur following a high-phosphorus meal, independent of FGF23, PTH, secreted frizzled-related protein (sFRP-4), or $1,25(OH)_2D$, suggesting the presence of an intestinal "phosphate sensor", although its exact biochemical nature is not known (21-25).

The PTH/PTHrP receptor (PTHR1) is present on osteocytes (26) and constitutive activation of this receptor has been shown to upregulate *FGF23* mRNA expression *in vitro* (27,28). Administration of PTH (1-34) in mice and in healthy individuals is associated with an increase in $1,25(OH)_2D$ and in serum FGF23 levels and with a decrease in serum phosphate levels (13,28,29). In contrast, although intermittent administration of PTH to postmenopausal women

with osteoporosis induced an increase in $1,25(OH)_2D$ and in FGF23 levels, this was not associated with a decrease in serum phosphate levels (30). Taken together, these data suggest that PTH is a regulator of FGF23 synthesis and that this is likely to be independent of serum phosphate concentrations.

In patients with primary hyperparathyroidism (PHPT), data on the relationship between PTH and FGF23 are scarce and not always concordant. Compared to healthy controls, circulating FGF23 levels have been found to be elevated in patients with PHPT before parathyroidectomy (31,32) and to decrease immediately post-operatively (32), supporting the notion that PTH stimulates FGF23 secretion. However, this post-operative normalization of FGF23 levels was not observed in all studies (31,33), or was observed only transiently post-parathyroidectomy, with FGF23 levels returning to the originally high pre-operative values 7 days after surgery (32). The latter data suggest a possible alteration in FGF23 regulation, independent of PTH levels, in patients with PHPT. The aim of our study was to address the relationship between PTH and FGF23 in patients with primary hyperparathyroidism and in those with this disorder after cure following successful parathyroidectomy.

PATIENTS AND METHODS

Study population

Twenty-one consecutive patients with primary hyperparathyroidism, which was untreated, persistent or recurrent after PTx, and 24 consecutive euparathyroid patients who had a successful PTx for sporadic PHPT at the Leiden University Medical Center (LUMC) were invited and agreed to take part in the study of a 18 months period. All patients were under regular follow-up at the Outpatient Clinic of the Department of Endocrinology and Metabolic Diseases of the LUMC, with patients with persistent hyperparathyroidism being followed more closely than those cured after PTx, who were mostly seen at 1- or 2-year intervals.

The diagnosis of PHPT was established on the basis of a serum PTH concentration above the upper limit of the normal laboratory reference range (>8 pmol/L) in the presence of a high or inappropriately normal serum calcium

concentration (>2.55 mmol/L). Eight of these latter patients had PTH concentrations of 13.6 ± 2.2 pmol/L, (range 8.4-27.4 pmol/L) in the presence of a normal serum calcium (serum calcium 2.46 ± 0.02, range 2.38-2.52 mmol/L), in the absence of vitamin D deficiency ($25(OH)D_3$ 55.6 ± 7.2, range 35-93 nmol/L). Four of these eight patients had a genetically confirmed MEN-1 mutation, the other four patients had evidence for a parathyroid adenoma on localization studies and became hypercalcemic under vitamin D supplementation.

A diagnosis of cure was based on sustained normal serum calcium and PTH concentrations more than 6 months after PTx.

All patients and controls had to have a creatinine clearance >60 ml/min to be included in the study to preclude the confounding effect of renal impairment on FGF23 levels. All patients and controls had a 25(OH) vitamin D_3 level of >30 nmol/L except for 5 patients who had levels between 25 and 28 nmol/L. These five patients were, however, hypercalcaemic (2.72 ± 0.02, range 2.67-2.80 mmol/L) with increased PTH levels (serum PTH 23.5 ± 9.0, range 8.6-54.3 pmol/L) and high normal $1,25(OH)D_2$ levels (serum $1,25(OH)D_2$ 142 ± 20, range 87-205 pmol/L), which was the reason to withhold the vitamin D supplementation.

Serum Biochemistry

Serum concentrations of calcium (reference range 2.15-2.55 mmol/L), albumin (reference range 34-48 g/L), phosphate (reference range 0.90-1.50 mmol/L), and creatinine (reference range 44-80 μmol/l) were measured using semi-automated techniques. Creatinine clearance was calculated using Modification of Diet in Renal Disease (MDRD) formula. Serum alkaline phosphatase (ALP; reference range 40-120 U/L) was measured using a fully automated P800 modulator system (Roche BV). Serum P1NP (a marker of bone formation) and β-CTX (a marker of bone resorption) were determined using the E-170 system (Roche BV). Serum concentrations of intact PTH (reference range 1.5-8 pmol/L) were measured using the Immulite 2500 (Siemens diagnostics, Breda, Holland). Serum 25-hydroxycholecalciferol ($25(OH)D_3$; reference range 30-120 nmol/L) was measured using the LIAISON® 25-OH Vitamin D TOTAL assay (DiaSorin S.A./N.V., Bruxelles, Belgium) and $1,25(OH)_2$ vitamin D was measured using LIAISON®

1,25-OH2 Vitamin D TOTAL assay (DiaSorin S.A./N.V.). .Serum intact FGF23 (reference range 18-50 pg/mL (34)) was measured using an immunometric assay (Kainos Laboratories, Inc., Tokyo, Japan; intra-assay coefficient of variation (CV) 6% and inter-assay CV 10%).

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA). Results are expressed as mean ± S.E.M. unless otherwise stated. Chi-square test and Student's *t*-test were used as appropriate for categorical variables and continuous variables. Pearson correlation coefficients were calculated to assess correlations between FGF23, PTH, $1,25(OH)_2D$, creatinine clearance, phosphate and calcium. Serum PTH, FGF23, and $1,25(OH)_2D$ levels are shown in Table 1 in absolute values, but were log transformed before statistical correlation and regression analysis to correct for skewness. The relationship between several biochemical variables and FGF23 was investigated by backward regression analysis. A probability level of random difference of $P<0.05$ was considered significant.

The study was approved by the local ethics committee and informed consent was obtained from all patients prior to inclusion in the study.

RESULTS

Patients with PHPT did not differ significantly in age, gender, weight, body mass index (BMI) and renal function from those in long-term cure after successful PTx (EuPTH; Table 1).

Mean serum calcium and PTH concentrations were significantly higher and mean serum phosphate and 25(OH) vitamin D_3 concentrations were significantly lower in the PHPT group compared with the EuPTH group. However, serum $1,25(OH)_2D$ concentrations and the bone turnover markers, ALP, P1NP and CTX, were significantly increased in the PHPT group compared with the EuPTH group (Table 1).

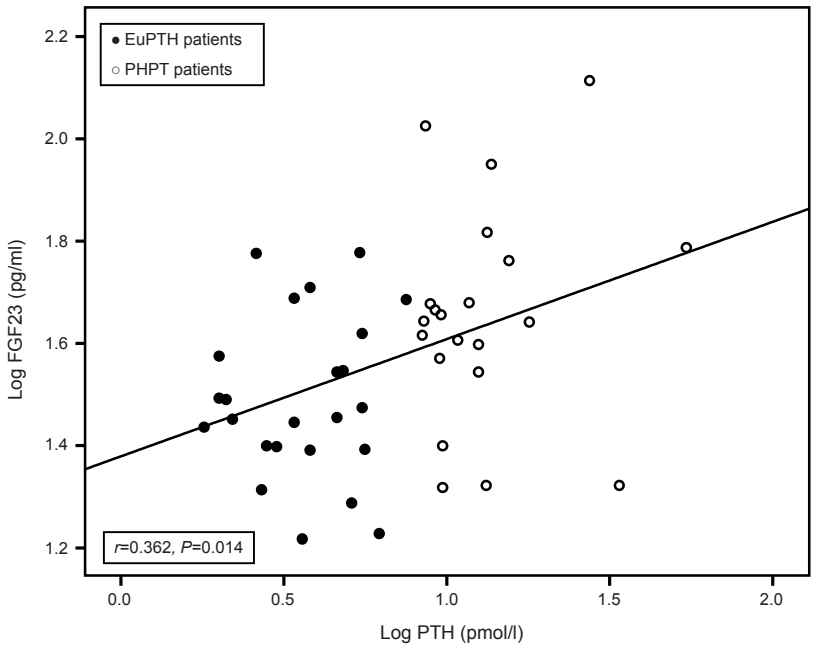

Figure 1: Relationship between serum FGF23 and PTH levels (Pearson's correlation). PTH and FGF23 levels were log transformed because of skewness.

Mean serum FGF23 concentration was significantly higher in patients with PHPT than in EuPTH patients (50.8 ± 6.1 pg/mL vs. 33.1 ± 2.6 pg/mL, P=0.01; Table 1). There was a significant positive relationship between PTH and FGF23 levels when PHPT and EuPTH were analyzed together (r=0.361, P=0.02; Figure 1), and this relationship was sustained and more pronounced after correction for 1,25$(OH)_2$D levels (r=0.419, P=0.01). There was no significant relationship between PTH and FGF23 when PHPT and EuPTH patients were analyzed separately (r=0.187, P=0.4, vs. r=0.114, P=0.6, respectively).

There was also no significant relationship between PTH and 1,25$(OH)_2$D levels in either PHPT patients (r= −0.269, P=0.3) or EuPTH patients (r=0.016, P=0.9) or when both groups were analyzed together (r=0.061, P=0.7).

In patients with PHPT, there was a significant negative correlation between FGF23 and 1,25$(OH)_2$D levels (r= −0.674, P=0.001; Figure 2). This relationship remained significant, albeit less marked, in EuPTH patients (r= −0.509, P=0.01; Figure 2). The negative relationship between FGF23 and 1,25$(OH)_2$D remained

significant when all patients were pooled together (r= −0.393, P<0.01). Using backward stepwise regression analysis, we also demonstrate that FGF23 levels exhibit significant and independent associations with PTH and 1,25$(OH)_2$D levels (β=0.372, P=0.015, and β= −0.429, P=0.003 respectively; Table 2).

Table 1. Demographic and laboratory data in 21 patients with PHPT and 24 patients in sustained cure after successful parathyroidectomy.

	PHPT (*n=21*)	EuPTH (*n=24*)	Ref. range	*P* value
Gender (men:women)	6:15	8:16		0.738
Age (years)	57 ± 3	63 ± 2		0.144
Height (cm)	172 ± 2	170 ± 1		0.279
Weight (kg)	79 ± 6	74 ± 2		0.425
BMI (kg/m^2)	27 ± 2	26 ± 1		0.664
Serum biochemistry				
MDRD (ml/min per 1.73 m^2)	90 ± 5	84 ± 3	>60	0.376
Corrected calcium (mmol/l)	2.59 ± 0.03	2.27 ± 0.02	2.15-2.55	0.000
Phosphate (mmol/l)	0.89 ± 0.04	1.10 ± 0.04	0.9-1.5	0.000
PTH (pmol/l)[a]	15.2 ± 2.4	3.9 ± 0.3	1.5-8.0	0.000
PTH (median (IQR)	11.7 (9.4-14.6)	3.7 (2.6-5.5)	1.5-8.0	0.000
25$(OH)D_3$ (nmol/L)	48 ± 4	60 ± 4	30-120	0.030
1.25$(OH)_2$D (pmol/l)[a]	163 ± 14	125 ± 7	40-140	0.020
1,25$(OH)_2$D (median (IQR))	150 (119-203)	125 (95-144)	40-140	0.020
FGF23 (pg/mL) [a]	50.8 ± 6.1	33.1 ± 2.6	18-50	0.012
FGF23 (median (IQR))	44.0 (36.1-59.6)	29.2 (24.8-40.6)	18-50	0.006
ALP (U/l)	93 ± 5	71 ± 4	40-120	0.002
P1NP (ng/ml)	41.4 ± 4.4	27.4 ± 2.4	16-80	0.010
β-CTX (ng/ml)	0.31 ± 0.04	0.12 ± 0.01	0.01-0.66	0.000

PHPT: primary hyperparathyroidism, EuPTH: euprathyroid controls, MDRD: glomerular filtration rate, IQR: interquartile ranger, [a] Log transformedbefore correlation analysis

There was no significant relationship between FGF23 concentrations and creatinine clearance or serum phosphate concentrations in either PHPT patients (r=0.085, P=0.7, and r=0.349, P=0.09, respectively) or EuPTH patients (r= −0.398, *P=0.06* and r= −0.247, P=0.3, respectively). Also using backward stepwise regression analysis, creatinine clearance and serum phosphate levels failed to emerge as significant modulating factors for FGF23 levels in this model (β= −0.033, P=0.811 and β= −0.068, P=0.642 respectively; Table 2).

There was also no significant relationship between FGF23 levels and all three markers of bone turnover, serum ALP activity, P1NP, or CTX concentrations, in either PHPT or EuPTH patients after correction for PTH and $1,25(OH)_2D$ levels.

Table 2. Result of multiple regression analysis, demonstrating a significant association between FGF23, PTH and $1,25(OH)_2D$

Predictor	*B*	S.E.M.	*β*	*t*	*P* value
PTH	0.895	0.353	0.372	2.534	0.015
$1.25(OH)_2D$	−0.192	0.061	−0.429	−3.124	0.003
Phosphate	−7.9595	16.996	−0.068	−0.468	0.642
MDRD	−0.039	0.160	−0.033	−0.241	0.811

DISCUSSION

Data from our study show that patients with primary hyperparathyroidism have higher levels of FGF23 than cured controls, and that this increase is independent of $1,25(OH)_2D$ levels. We further demonstrate a significant negative relationship between FGF23 and $1,25(OH)_2D$ levels, that is more pronounced in patients with PHPT, suggesting that FGF23 at least partially antagonizes the stimulatory effects of PTH on the 1α-hydroxylase enzyme, although not totally overriding it.

Data on FGF23 levels in PHPT and in the euparathyroid state following successful PTx are scarce and not always concordant. Two studies (31,33) demonstrated no significant difference in pre- and post-PTx FGF23 levels, but a further study (32) showed a return of FGF23 levels to high pre-operative levels several days after PTx. The authors of this latter paper (32) suggested that one of the reasons for these discrepant results may be the post-operative use of active vitamin D metabolites or analogues in their patients, which had not been taken into consideration in the interpretation of their results. To our knowledge, FGF23 levels have never been previously evaluated in long-term euparathyroid patients after successful PTx. Our findings from this study suggest that the increase in FGF23 levels observed in PHPT is reversible when the euparathyroid state is achieved by cure after successful PTx, providing that renal function is not impaired.

Although the cross-sectional design of our study does not allow the definitive determination of a causal relationship between PTH and FGF23, our data are in keeping with recently published data in parathyroidectomized rats, in which a direct relationship between PTH and FGF23 independent of $1,25(OH)_2D$ is demonstrated in the presence of high but not low levels of PTH (35).

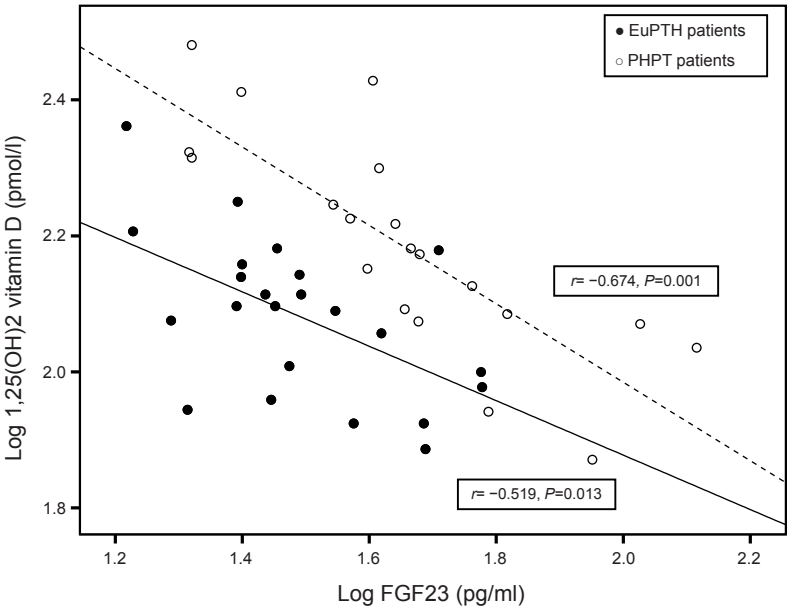

Figure 2: Relationship between serum FGF23 and $1,25(OH)_2D$ levels in 21 patients with primary hyperparathyroidism (PHPT: white dots) and 24 patients in long-term cure after parathyroidectomy for PHPT (EuPTH: black dots). FGF23 and $1,25(OH)_2D$ levels were log transformed because of skewness.

In the presence of high PTH and FGF23 levels in patients with PHPT, it is intruiging that a significant number of these patients do not develop hypophosphatemia despite chronic exposure to the two phosphaturic hormones, PTH and FGF23. In keeping with previous observations (13,30), indeed only 11 of our 22 patients with PHPT (50%) had phosphate levels below the lower limit of normal (<0.90 mmol/l). This suggests that in PHPT, factors other than PTH, FGF23 or their combined effect may play a role in phosphate homeostasis. A clear contender is $1,25(OH)_2D$. The net effect of $1,25(OH)_2D$ on gut, kidney, bone and parathyroids is to increase serum phosphate levels, by upregulating NaPi2b co-

transporter expression in the intestinal tract (1,7) and NaPi2 co-transporter (*NaPi3*) gene in the kidney, and by directly reducing PTH synthesis and secretion by the parathyroid (29).

In our study, patients with PHPT had significantly increased $1,25(OH)_2D$ levels compared with euparathyroid patients, but also demonstrated significantly increased FGF23 levels. A new hypothesis has been recently proposed to explain the need for two phosphaturic hormones, PTH and FGF23, with the former repressed and the latter induced by $1,25(OH)_2D$ (36). The suggested negative feedback loop includes FGF23-induced inhibition of $1,25(OH)_2D$ synthesis. It has been proposed that these counter-regulatory effects of FGF23 on the bone-kidney axis have the physiological task of securing the maintenance of serum phosphate levels, thus providing protection against the hyperphosphatemia-related soft tissue and vascular calcifications (37-40). A possible explanation for the antagonizing effect of FGF23 on 1α-hydroxylase enzyme may be the shorter half-life of PTH compared with longer half-life of FGF23 (41).

Our findings from this study extend our insight into the role of FGF23 in pathological states by showing that in primary hyperparathyroidism, FGF23 production is increased in the presence of high circulating PTH levels and that this increase is reversible after the euparathyroid state is achieved following successful PTx. The more pronounced negative relationship between FGF23 and $1,25(OH)_2$ vitamin D in patients with PHPT suggests that in these patients the increase in FGF23 levels may be an adaptive mechanism to counteract the PTH-induced $1,25(OH)_2D$ levels, although not completely overriding it.

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