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Clinical Vignette

Cinacalcet in the Management of Tumor-Induced Osteomalacia

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ABSTRACT: Both FGF-23 and PTH inhibit renal phosphate reabsorption. We treated two patients with TIO and FGF-23–mediated hypophosphatemia with cinacalcet to test the hypothesis that medicinally induced hypoparathyroidism would decrease renal phosphate wasting. Cinacalcet treatment resulted in increased renal phosphate reabsorption, allowed for a decrease in phosphate supplementation, and showed evidence of bone healing in one of the two patients.

Introduction: Tumor-induced osteomalacia (TIO) is a rare, acquired disease of renal phosphate wasting, which results in hypophosphatemia and osteomalacia. It is caused by mesenchymal tumors that produce the phosphate and vitamin D–regulating hormone, fibroblast growth factor (FGF)-23. Removal of the tumor is curative, but the tumors are often difficult to locate. Medical treatment involves high doses of oral phosphate and calcitriol, but the phosphate is often poorly tolerated and leads to diarrhea. Because PTH also promotes phosphaturia, and patients with hypoparathyroidism are hyperphosphatemic in the setting of elevated serum FGF-23, we postulated that the calcium-sensing receptor agonist, cinacalcet, which can induce hypoparathyroidism, would be an effective adjuvant in the treatment of TIO.
Materials and Methods: Two subjects with presumed TIO in whom the tumor was not located after extensive testing and who did not tolerate medical therapy with phosphorus and calcitriol were treated with cinacalcet.
Results: Neither treatment with phosphorus nor combined treatment with phosphorus and calcitriol had an effect on serum FGF-23 levels. Treatment with cinacalcet resulted in increased renal phosphate reabsorption and serum phosphorus and allowed for a decrease in phosphate supplementation to a dose that was tolerated. On this regimen, one patient showed significant bone healing as shown by resolution of activity on bone scan and lack of osteomalacia as assessed by histomorphometry.
Conclusions: These data show that medically induced hypoparathyroidism with cinacalcet is a therapeutic option for disorders of FGF-23–mediated hypophosphatemia and that, in the absence of PTH, the phosphaturic effect of FGF-23 is decreased.
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Key words: hypophosphatemia, fibroblast growth factor-23, phosphatonin, hypoparathyroidism, phosphate, oncogenic osteomalacia

INTRODUCTION

Fibroblast growth factor-23 (FGF-23) is a peptide hormone with an important role in phosphate and vitamin D homeostasis.[1] Synthesized by osteogenic cells,[2–4] FGF-23 acts in the proximal renal tubule to decrease renal phosphate reabsorption by inhibition of the expression of the type 2 sodium-phosphate co-transporter (NaPi2) and inhibition of the expression of the mitochondrial CYP 27B1-hydroxylase, which is responsible for conversion of 25-hydroxyvitamin D_3 to its active metabolite, 1,25-dihydroxyvitamin D_3.[5,6]

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome caused by high serum levels of FGF-23 secreted by benign mesenchymal neoplasms.[7,8] TIO typically presents in adulthood with proximal muscle weakness, bone pain, and pathological fractures. Biochemical findings typically include hyperphosphaturia, hypophosphatemia, inappropriately normal (or frankly low) serum 1,25-dihydroxyvitamin D_3, and markedly elevated serum FGF-23.[9] Although the definitive treatment of TIO is removal of the causative neoplasm, such tumors are notorious for evading the most rigorous anatomic and functional investi-

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TABLE 1. BASELINE VALUES FOR KEY VARIABLES AT INITIAL EVALUATION OF SUBJECTS WITH TIO

Subject	*Age (years)*	*Serum phosphate*	*Urine TmP/GFR*	*Serum 1,25-D*	*Serum FGF-23*	*Serum 25-D*	*Serum PTH*	*Creatinine clearance*
1	52	1.5	1.1	5	1604	19	36.7	88
2	61	1.6	1.3	12	156	29	51.9	109
Normal range		2.5–4.8 mg/dl	2.8–4.2 mg/dl	22–67 pg/ml	10–100 RU/ml	10–68 ng/ml	6–40 pg/ml	90–125

TmP/GFR, tubular maximum reabsorption of phosphate per glomerular filtration rate (assessed by the method of Bijvoet et al.[26]; 1,25-D, 1,25-dihydroxyvitamin D; FGF-23, fibroblast growth factor-23; 25-D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

gative studies currently available. Consequently, there may be several years from the time of diagnosis until tumor localization. Medical treatment includes high doses of supplemental phosphate and 1,25-dihydroxyvitamin D_3.[8] The high doses of supplemental phosphate that are needed to maintain euphosphatemia are often poorly tolerated because of gastrointestinal upset, including diarrhea. In addition, secondary and tertiary hyperparathyroidism frequently develop, possibly as a consequence of the underlying perturbations of the phosphorus/vitamin D/calcium axis and exacerbated by high-dose phosphate supplementation.[8] Moreover, although such therapy may transiently normalize the serum phosphate, it fails to address the underlying problem of renal phosphate loss. Furthermore, both oral phosphate loading and 1,25-dihydroxyvitamin D_3 administration have been shown to increase serum FGF-23,[10–12] raising the question of whether this medical regimen could stimulate further elevation in serum FGF-23.

We have recently shown that patients with hypoparathyroidism maintain high serum phosphate, even with concurrently elevated levels of serum FGF-23, suggesting that the phosphaturic effect of FGF-23 may in part require the presence of PTH.[11,12] The development of allosteric modulators of the calcium-sensing receptor that are able to decrease serum PTH afforded the opportunity to test the hypothesis that induction of relative hypoparathyroidism could be a useful adjuvant in the treatment of FGF-23–mediated renal phosphate wasting disorders such as TIO. In preclinical studies, treatment with the type II calcimimetic, NPS R-568, resulted in a sustained increase in serum phosphate while decreasing serum PTH and calcium.[13] Thus, we hypothesized that the calcimimetic, cinacalcet (Sensipar; Amgen, Thousand Oaks, CA, USA) might be efficacious in the treatment of TIO.

MATERIALS AND METHODS

Subjects

Two adult white men, 51 and 60 yr of age (subject 1 and subject 2, respectively) presented with an acquired syndrome characterized by diffuse muscle weakness, pathological fractures, hypophosphatemia with concomitant renal phosphate wasting, low serum 1,25-dihydroxyvitamin D_3, normal serum PTH, and elevated serum FGF-23 (Table 1). Because the definitive diagnosis of TIO requires tumor localization and cure after removal, the diagnosis of TIO in these subjects was presumptive. After giving informed consent, they were enrolled in an Institutional Review Board (IRB)-approved protocol. Despite exhaustive diagnostic studies, including total body X-rays, CT, MRI, Octreoscan, fluorodeoxyglucose-positron emission tomography (FDG-PET), technetium methylene diphosphonate (^{99}Tc-MDP), and sestamibi scanning, as well as two courses of total body venous sampling, the source of FGF-23 remained elusive in both subjects.

Treatment

Phosphate and calcitriol: After a 14-day washout period during which phosphate and calcitriol were withheld, both subjects were started on a standardized regimen of oral phosphate supplementation (K-phos neutral; Beach Pharmaceuticals, Tampa, FL, USA) and 1,25-dihydroxyvitamin D_3 administration (calcitriol, Rocaltrol; Hoffmann-La Roche, Nutley, NJ, USA). Phosphorus supplementation was started on day 2 at a dose of 250 mg elemental phosphorus every 6 hours. The dose was escalated as tolerated to raise serum phosphorus into the normal range. Calcitriol was added on day 5 at a dose of 0.5 μg every 12 h and the dose escalated (Fig. 1).

Cinacalcet treatment: Neither subject tolerated the dose of phosphate supplementation needed to maintain euphosphatemia. Subject 1 was started on treatment with cinacalcet (Sensipar; Amgen) at 30 mg/d. After cinacalcet showed efficacy in subject 1, the acute effects of cinacalcet were studied in subject 2. After a 14-day washout period off all medications, a single 30-mg dose of cinacalcet was given to subject 2, and the effects on PTH, tubular reabsorption of phosphate (TRP), serum phosphorus, and serum FGF-23 were assessed over 48 h (Fig. 2). Long-term effects of cinacalcet are shown in Table 2. Oral phosphate and calcitriol were added to the medical regimen of cinacalcet, and the doses adjusted to the minimum dose necessary to maintain a normal serum phosphate and PTH (Table 2). Throughout the treatment period, serum and urine testing were performed at ~8:00 a.m. after an overnight fast. Subjects 1 and 2 developed hypercalciuria at 3 and 4 wk of treatment with cinacalcet, respectively, necessitating the addition of hydrochlorothiazide (25 mg daily in divided doses) to the treatment regimen.

Skeletal healing: To assess for skeletal healing and to be assured that healing could take place in the induced hypoparathyroid state, after 9 mo on cinacalcet therapy, both subjects underwent bone scans and an iliac crest bone biopsy for histomorphometric assessment of osteomalacia.

Histology and histomorphometry: Iliac crest bone biopsies were fixed in 4% neutral buffered formaldehyde, washed in phosphate buffer, and embedded undecalcified

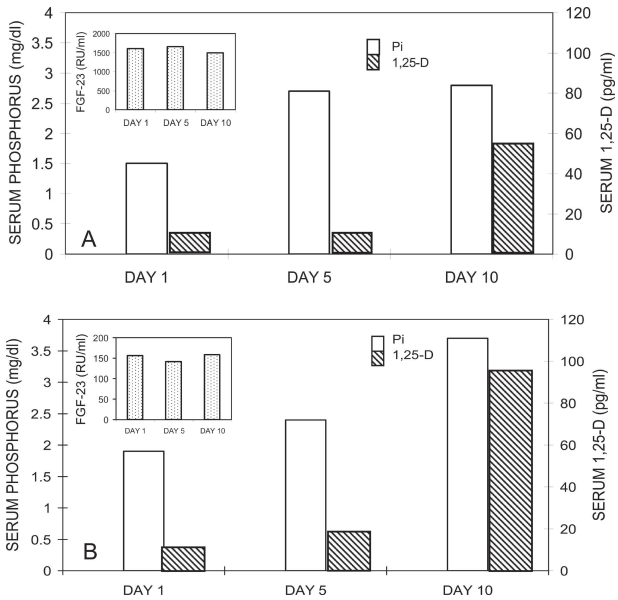

FIG. 1. Effect of phosphorus and calcitriol supplementation on serum FGF-23 in TIO. (A) Subject 1. (B) Subject 2. Subjects were on no medications on day 1, phosphorus supplementation was started on day 2 at a dose of 250 mg elemental phosphorus every 6 h. In both subjects 1 and 2, the dose was escalated to 750 mg every 6 h to raise serum phosphorus into the normal range. Calcitriol was added on day 5 at a dose of 0.5 μg every 12 h, and the dose escalated to 0.75 and 1.25 μg every 12 h in subjects 1 and 2, respectively. FGF-23 was measured by a C terminus assay. Serum phosphorus is indicated by open columns, serum 1,25-dihydroxyvitamin D levels by cross-hatched columns, and serum FGF-23 levels are in the inset panel. Neither phosphate treatment nor phosphate and calcitriol treatment had an effect on serum FGF-23 levels.

in methyl-methacrylate. Five-micron-thick sections were cut and stained with either Goldner or von Kossa stain. For histomorphometric analysis, a semiautomatic image analyzer (IAS 2000; Delta System, Rome, Italy) was used. The values of osteoid surface/bone surface and osteoid thickness were measured on either Goldner- and von Kossa–stained sections and compared with published data for age-matched normal subjects.[14] Unfortunately, both subjects had been started on medical therapy before referral, and pretreatment biopsies were not available for comparison.

Assays: Initially, FGF-23 was measured using a C terminus assay (Immutopics, San Clemente, CA, USA). When it became available, an assay that measured intact FGF-23 was used (Kainos, Tokyo, Japan). The intra- and interassay CVs for the C terminus assay are ≤5% and ≤7%, respectively,[15] and for the intact assay are ≤3% and ≤4%, respectively. Results of the C terminus FGF-23 assay are reported in relative units (RU) per microliter, and the intact assay in picograms per milliliter. All other assays reported were standard, commercially available assays.

RESULTS

Subject 1

Neither treatment with phosphate alone nor in combination with calcitriol had an effect on serum FGF-23 levels (Fig. 1A). The long-term effects of treatment with cinacalcet are shown in Table 2. The initiation of cinacalcet (30 mg/d) was accompanied by the expected decrease in serum PTH and a sustained increase in TRP. This allowed for a 75% decrease in the dose of phosphorus needed to maintain euphosphatemia (Table 2). Thus, the phosphaturic effect of FGF-23 seemed to be inhibited by the decrease in serum PTH. Over 270 days of treatment, there was an increase in serum FGF-23.

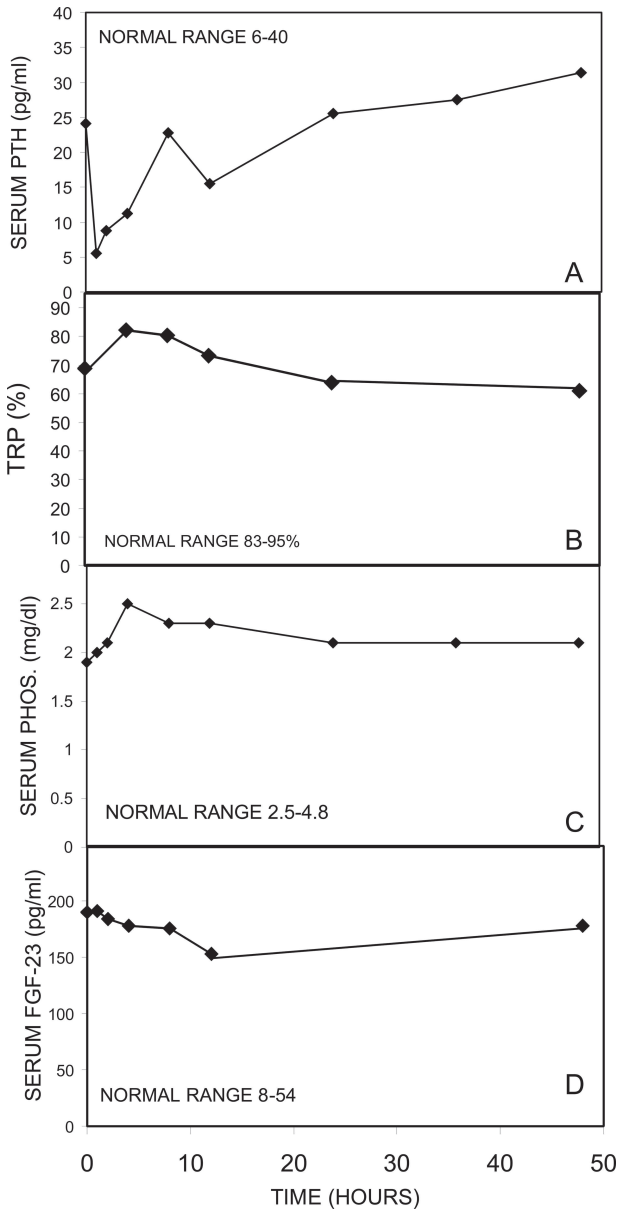

FIG. 2. Effect of the first dose of cinacalcet on serum and urine phosphorus metabolism parameters in a subject with TIO. The first dose of cinacalcet was given at 8:00 a.m. while off phosphorus and calcitriol supplementation. (A) The anticipated decrease in serum PTH was observed, and was accompanied by (B) a significant increase in the tubular reabsorption of phosphorus (TRP%) and (C) increase in serum phosphorus at a time of day when TRP and serum phosphorus normally decrease.[16] (D) There was little effect on serum FGF-23. Normal ranges are indicated in each panel.

TABLE 2. LONG-TERM EFFECTS OF CINACALCET THERAPY IN SUBJECTS WITH TIO

		Days on cinacalcet				
		0	30	60	120	270
Biochemistry						
Serum Pi (2.5–4.8 mg/dl)	Subject 1	2.8	3.0	3.3	2.7	3.7
	Subject 2	2.8	2.3	2.8	3.6	3.4
Percent TRP (85–95%)	Subject 1	49	73	57	70	81
	Subject 2	48	87	86	68	65
Serum FGF-23 (10–50 pg/ml)	Subject 1	3625	3323	ND	3984	5140
	Subject 2	152	172	163	285	240
Serum PTH (10–65 pg/ml)	Subject 1	19.5	<10	ND	ND	4.1
	Subject 2	24.1	12	ND	4	7
Serum Ca (8.5–10.2 mg/dl)	Subject 1	8.6	8.1	8.4	9.6	9.2
	Subject 2	9.1	8.8	8.4	8.8	8.0
Serum Cr (0.9–1.4 mg/dl)	Subject 1	1.4	1.6	1.6	1.6	1.8
	Subject 2	1.0	1.1	1.1	1.3	1.1
Urine Ca–24 h (40–350 mg/24 h)	Subject 1	250	412	128	376	268
	Subject 2	383	506	445	247	243
Therapy						
K-phos (mg/d)	Subject 1	3000	750	750	750	750
	Subject 2	2250	750	750	750	750
Calcitriol (μg/d)	Subject 1	1.5	1.0	1.0	1.0	1.0
	Subject 2	2.5	1.0	1.0	1.0	1.0
HCTZ (mg/d)	Subject 1	0	0	25	25	25
	Subject 2	0	0	25	50	50

The dose of cinacalcet was 30 mg/d throughout.

Pi, phosphate;'TRP, tubular reabsorption of phosphate; Ca, calcium; Cr, creatinine; K-phos, K-Phos neutral; HCTZ, hydrochlorothiazide; ND, not determined.

Within 60 days of treatment with cinacalcet, subject 1 developed significant hypercalciuria (Table 2). To decrease hypercalciuria, which together with hyperphosphaturia would contribute to the risk of nephrocalcinosis or nephrolithiasis, hydrochlorothiazide was added to the medical regimen. This intervention was effective in normalizing urinary calcium.

To assess for evidence of bone healing on this regimen while hypoparathyroid, pre- and post-treatment bone scans were compared (Figs. 3A and 3B), and nondecalcified iliac crest biopsy specimens were analyzed for evidence of osteomalacia (Figs. 4A and 4B; Table 3). Pretreatment scans showed intense activity at the costochondral junctions, as well as tracer uptake consistent with pathologic fractures (Figs. 3A and 3B). After 9 mo of therapy with cinacalcet, during which time he was euphosphatemic, subject 1 showed stable disease activity on bone scan. Histological evaluation (Figs. 4A and 4B) and histomorphometric analysis (Table 3) mirrored the findings on bone scintigraphy, showing evidence of persistent osteomalacia.

Subject 2

As in subject 1, neither treatment with phosphate alone nor in combination with calcitriol had an effect on serum FGF-23 levels in subject 2 (Fig. 1B). The acute effects over 48 h of the first dose of cinacalcet were assessed in subject 2. The first dose of cinacalcet (30 mg) was given at 8:00 a.m. Four hours later, there was an anticipated decrease in serum PTH from 24.1 to 8.8 pg/ml (63%; Fig. 2A) and an increase in TRP from 69% to 82% (19%; Fig. 2B). Serum phosphorus increased from 1.9 to 2.5 mg/dl (32%) from 8:00 a.m. to 12:00 noon, during a time of day when TRP and serum phosphorus normally decrease (Fig. 2C).[16] During this interval, there was little change in serum FGF-23—190 to 178 pg/ml (6%; Fig. 2D).

The long-term effects of cinacalcet (30 mg/d) in subject 2 showed the expected sustained decrease in serum PTH and a sustained increase in TRP (Table 2). This allowed for a 67% decrease in the dose of phosphorus needed to maintain euphosphatemia. As in subject 1, over 270 days of treatment, there was an increase in serum FGF-23. Both subjects reported a decrease in pain with cinacalcet treatment.

Subject 2 showed a marked reduction in tracer uptake at costochondral junctions and resolution of pathological fractures on bone scan (Figs. 3C and 3D). Histologically, there was no evidence of thickened osteoid seams (Figs. 4C and 4D), and histomorphometric analysis confirmed the absence of osteomalacia (Table 3). Taken together, these data suggested that, on this medical regimen, there was bone healing despite markedly elevated and increasing serum FGF-23 levels.

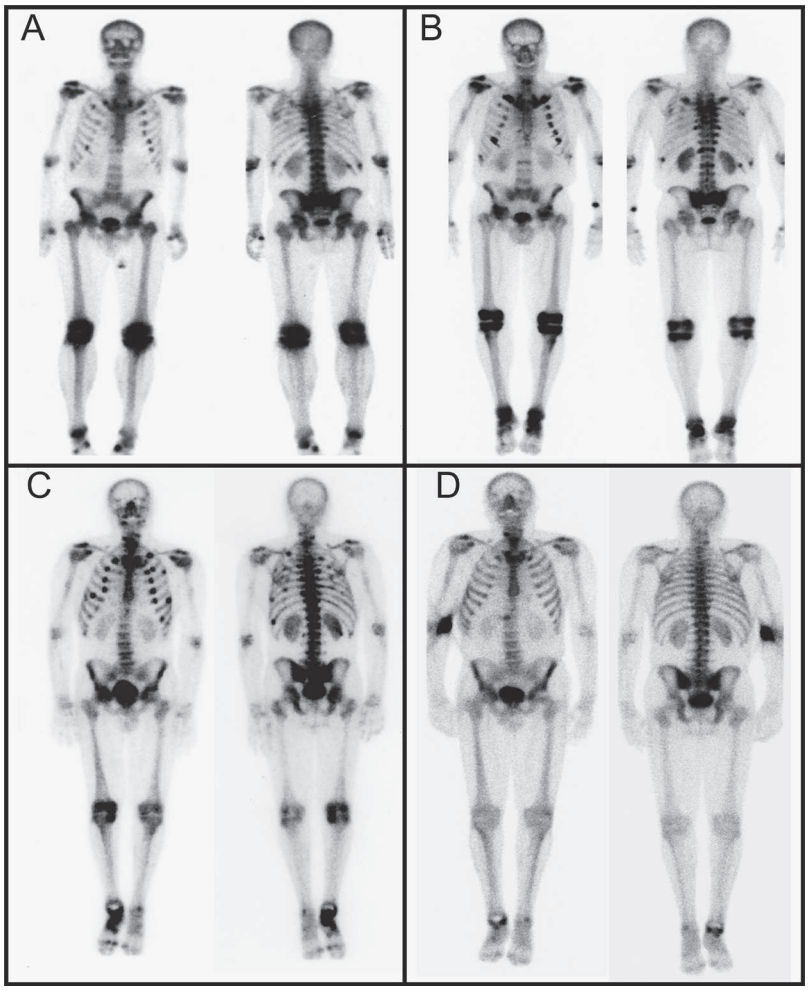

FIG. 3. Pre- and post-treatment ^{99}Tc-MDP bone scans of two subjects with TIO. Pretreatment bone scans for (A) subject 1 and (C) subject 2 show evidence of active metabolic bone disease with marked activity at (i) most costochondral junctions, (ii) the cartilage/bone interface of the knees and ankles, and (iii) pathological fracture sites. After 9 months of treatment with cinacalcet, (D) subject 2, but not in (B) subject 1, had significantly less uptake of ^{99}Tc-MDP, suggesting bone healing.

DISCUSSION

In these two subjects with FGF-23–mediated renal phosphate wasting, the induction of relative hypoparathyroidism with cinacalcet was associated with improved phosphorous economy. These data support the hypothesis that the phosphaturic effect of FGF-23 is at least in part PTH dependent.

These data are consistent with recently presented preliminary data in children with the FGF-23–mediated renal phosphate wasting syndrome of X-linked hypophosphatemia who were treated with cinacalcet.[17] The fact that tubular reabsorption of phosphate was normal, or near normal, in the setting of extremely elevated serum FGF-23 suggests that there must be cross-talk between the FGF-23 and PTH/cAMP signaling pathways at the proximal renal tubule cell in terms of regulation of phosphate reabsorption. Phosphate reabsorption in the proximal renal tubule is primarily accomplished through the type 2a sodium-phosphate cotransporter (NPT2a) expressed on the luminal (brush border) aspect of the proximal renal tubule cell.[18] Both PTH and FGF-23 decrease renal reabsorption of phosphate through decreasing brush border expression of the NPT2a. How PTH and FGF-23, which have the same effect on brush border NPT2a levels, interact or cross-talk remains to be determined. The molecular mechanism by which PTH regulates NPT2a levels is through the cAMP/protein kinase A and C pathway(s). FGF-23 seems to bring about its biological effects through a Klotho protein–dependent binding of FGF-23 to FGF receptor(s) with subsequent activation of FGF receptor–related tyrosine kinases.[19,20] However, there is also evidence that the FGF-23 effects on renal phosphate handling may be mediated through the mitogen-activated protein kinase pathway.[21] The model suggested by these data is that FGF-23–mediated regulation of NPT2a is downstream, or at least modulated by, PTH/cAMP/protein kinase A (PKA) signaling.

These data also suggest that paraneoplastic production of FGF-23 by phosphaturic tumors is not influenced by changes in serum phosphate or 1,25-dihydroxyvitamin D_3 levels, at least in the short term (Fig. 1). This stands in contrast to what has been observed under physiologic conditions in animals and humans. In rodents[22,23] and humans,[10,11,24,25] serum FGF-23 levels are altered by changes in serum phosphate level. In addition, in both rodents[22,26] and humans,[12] serum FGF-23 levels are regulated by the serum 1,25-dihydroxyvitamin D_3 concentration. However, serum FGF-23 did increase in the long term

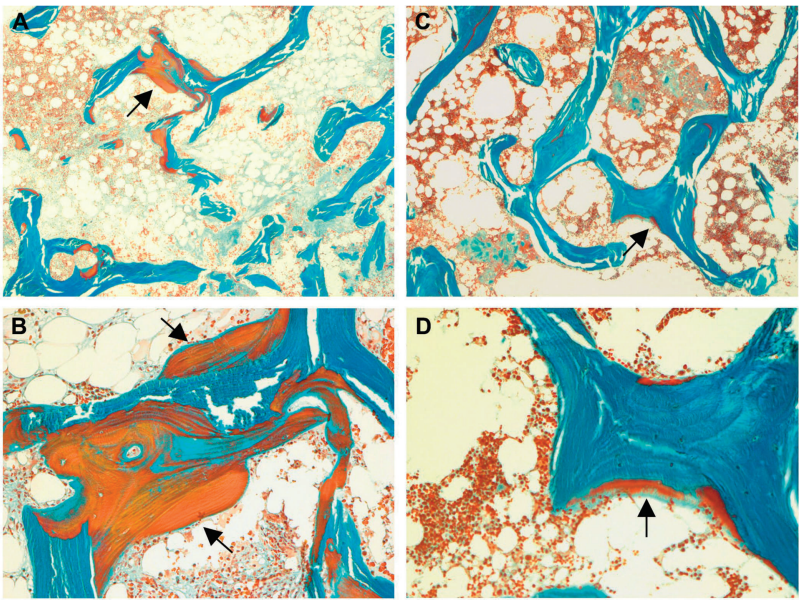

FIG. 4. Post-treatment histological findings in subjects with TIO. Goldner stain of bone samples showing calcified (green) and uncalcified (red) matrix. (A and B) Larger amount of uncalcified bone matrix were detected in samples from subject 1. (C and D) Sparse and thin layers of osteoid were observed on trabecular borders in subject 2 (arrows point to osteoid).

TABLE 3. POST-TREATMENT HISTOMORPHOMETRY IN TWO SUBJECTS WITH TIO

Subject	*Bone volume (BV/TV%)*	*Osteoid thickness (μm)*	*Osteoid surface (OS/BS)*
1	26.32	26.15	22.01
(nl. range)*	19.9 ± 2.0	9.13 ± 0.90	14.2 ± 2.3
2	35.8	8.55	14.14
(nl. range)*	20.1 ± 0.9	10.03 ± 2.17	10.4 ± 2.6

*Normal range.[14]

BV/TV%, percent of bone volume per trabecular volume; OS/BS, osteoid surface per bone surface.

(by day 120 in subject 1 and day 270 in subject 2). This could either represent a long-term response to treatment or disease progression.

Although pretreatment biopsies were not available for comparison with those performed while on cinacalcet, the post-treatment histological findings and bone scintigraphy findings in subject 2 suggest that bone healing can take place in TIO while in the hypoparathyroid state. Why subject 1 did not show bone healing may simply be because of the greater severity of his disease. His serum FGF-23 was in excess of 5000 pg/ml, and his TRP and serum phosphorus tended to be lower than that of subject 2.

During treatment with cinacalcet, both subjects developed significant hypercalciuria that necessitated the addition of hydrochlorothiazide (12.5 mg twice daily). Patients treated in this manner need to be monitored for the development of potentially hazardous hypercalciuria and treated as indicated. On treatment, subject 1 had an increase in serum creatinine from 1.4 to 1.8 mg/dl (Table 2). Evaluation did not reveal nephrocalcinosis by CT scan, and it was proposed that this may be caused by use of nonsteroidal anti-inflammatory drugs, but it is possible this was a direct effect of cinacalcet treatment, and this too needs to be monitored.

Medically induced hypoparathyroidism by the calcium-sensing agonist, cinacalcet, reduces FGF-23–mediated renal phosphate wasting. These observations suggest that cinacalcet may be a useful adjuvant in the treatment of FGF-23–mediated phosphate wasting disorders and that the maximal phosphaturic effect of FGF-23 is at least in part PTH dependent.

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