Oncogenic osteomalacia illustrating the effect of fibroblast growth factor 23 on phosphate homeostasis

Per-Anton Westerberg¹, Torbjörn Linde³, Dirk Vanderschueren²,³, Jaak Billen²,³, Ivo Jans²,³ and Osten Ljunggren¹

¹Department of Medical Sciences, Uppsala University, Uppsala, Sweden, ²Laboratory of diagnostic medicine, Katholieke Universiteit Leuven, Leuven, Belgium and ³Laboratory of experimental medicine and endocrinology, Katholieke Universiteit Leuven, Leuven, Belgium

Correspondence and offprint requests to: Per-Anton Westerberg; E-mail: per-anton.westerberg@medsci.uu.se

Abstract

In oncogenic osteomalacia (OOM), fibroblast growth factor 23 (FGF23) induces renal phosphate wasting and inhibits the appropriate increase of calcitriol. A patient suffering from OOM is described. Serum calcium, phosphate, biointact parathyroid hormone and intact FGF23 as well as the calcitriol and 24,25-vitamin D levels were measured before and after tumour removal. The clinical approach to a patient with hypophosphataemia is discussed and the changes in mineral metabolism after removal of a FGF23-producing tumour are described.

Keywords: FGF23; mineral metabolism; osteomalacia; phosphate

Background

Phosphate homeostasis is maintained by a complex interaction between vitamin D, parathyroid hormone (PTH) and bone-derived fibroblast growth factor 23 (FGF23). Phosphate depletion increases the rate of synthesis of calcitriol, while phosphate loading has the opposite effect [1, 2]. FGF23 decreases tubular phosphate reabsorption by internalization of the sodium–phosphate co-transporters NaPi-IIa and -IIc. It increases tubular phosphate reabsorption by internalization of the sodium–phosphate co-transporters NaPi-IIa and -IIc. It decreases the rate of synthesis of calcitriol. While phosphate loading has the opposite effect [1, 2]. FGF23 decreases tubular phosphate reabsorption by internalization of the sodium–phosphate co-transporters NaPi-IIa and -IIc. It decreases the rate of synthesis of calcitriol. While phosphate loading has the opposite effect. FGF23 decreases tubular phosphate reabsorption by internalization of the sodium–phosphate co-transporters NaPi-IIa and -IIc. It decreases the rate of synthesis of calcitriol. While phosphate loading has the opposite effect [1, 2]. FGF23 decreases tubular phosphate reabsorption by internalization of the sodium–phosphate co-transporters NaPi-IIa and -IIc. It decreases the rate of synthesis of calcitriol. While phosphate loading has the opposite effect.

Case report

A 73-year-old woman, without any skeletal disease in the family or rickets in her childhood, developed spontaneous fractures, muscle weakness and severe pain. She had a history of oestrogen receptor-positive endometrial adenocarcinoma 13 years earlier, which was cured by hysterectomy, bilateral oophorectomy and treatment with the progestagen megestrol for 11 years. The last 3 years, she developed progressive skeletal pain, muscle weakness and low energy fractures of the right hip. Tibias and vertebrae. She received treatment by calcium carbonate and cholecalciferol 800 IU/day. Biochemical analyses (see Table 1) revealed hypophosphataemia and increased fractional excretion (FE) of phosphate in the urine, calculated as (serum phosphate × urine creatinine)/(urine phosphate × serum creatinine) × 100. The maximal phosphate reabsorption per glomerular filtration rate (TmP/GFR) according to the nomogram of Bivojet was 0.6 mmol/L (1.9 mg/dL) [normal range >0.85 mmol/L (>2.63 mg/dL)]. Alendronate treatment was started and treatment with phosphate capsules 1500 mg thrice daily and 1-alfa-calcidol (Etalpha) 1.5 μg daily was initiated 6 months before diagnostic work-up. The calcium level was normal and the PTH level became slightly elevated after start of phosphate substitution. Her calcidiol level was sufficient: 88 nmol/L (35.2 ng/mL). Her creatinine clearance was 91 mL/min/1.73 m². Urinary excretion of albumin was 24 mg/24 h. There was no glucosuria on dipstick testing. The serum bicarbonate level was 27 mEq/L and the urinary pH was 6. There was no monoclonal immunoglobulin in serum or urine. The FGF23 level was increased to 100 pg/mL. The level of alkaline phosphatase was increased to 3.7 μkat/L (reference range 0.6–1.8). Bone density measured by dual X-ray absorption was 0.603 g/cm² (T-score −3.3) at the left hip and 0.884 g/cm² (T-score −2.5) at lumbar spine. For differential diagnoses of hypophosphaturic hypophosphataemia and their relation to FGF23 level see Table 2.

In conclusion, the patient suffered from an acquired form of hypophosphataemic osteomalacia due to excess FGF23, which makes OOM the most likely diagnosis. The challenge in such cases is to localize a small tumour that can be located anywhere in the body.

Radiological and nuclear examinations, including venous sampling for a venous gradient of FGF23 and fluorodeoxyglucose positron emission tomography, lead to the localization of a small subcutaneous tumour in the sole of the right forefoot. The 1-alfa-calcidol treatment was stopped 3 days before surgery and the phosphate supplementation was gradually tapered from the day after surgery.

Immunoblot assay for FGF23 was used for analyses of bioactive 1-84 PTH (Scantibodies) and intact FGF23 (Kainos;
On histopathological examination, the 11-mm nodular tumour had the features of a mesenchymal tumour with abundant matrix with small spindle-shaped cells and granular calcifications and a cell-rich component of irregular cells with foci of multinucleated osteoclast-like cell in accordance with a phosphaturic mesenchymal tumour of the mixed connective tissue type [7].

### Table 1. Laboratory parameters before and after tumour removal

| Time (hour:minute) | Phosphate (mmol/L) | Calcium (mmol/L) | BiPTH (pg/mL) | FGF23 (pg/mL) | 1,25-vitD (pg/mL) | 24,25-vitD (ng/mL) | FE-Pi % | FE-Ca % |
|-------------------|--------------------|-----------------|---------------|---------------|-----------------|-----------------|--------|--------|
| 0                 | 0.87               | 2.32            | 46.4          | 71.3          | 88.5            | 5.6             | 32     | 0.59   |
| 0:35              | ND                 | ND              | 27.3          | 38.9          | 74.8            | 4.3             |        |        |
| 1:45              | 0.72               | 2.30            | 30            | 34.8          | 80.8            | 5.2             |        |        |
| 3:05              | 0.79               | 2.29            | ND            | 31.7          | 76.2            | 5.2             |        |        |
| 4:05              | ND                 | ND              | ND            | 31            | 74.6            | 5               |        |        |
| 5:20              | ND                 | ND              | 35.5          | 29            | 90.2            | 6.2             |        |        |
| 6:15              | 0.75               | 2.21            | ND            | 28            | 75.2            | 5.2             |        |        |
| 10:15             | ND                 | ND              | 40.9          | 28            | 95.2            | 4.5             |        |        |
| 14:20             | 0.79               | 2.37            | ND            | 28            | 122.2           | 5.5             |        |        |
| 18:20             | ND                 | ND              | ND            | 28            | 134             | 5               |        |        |
| 22:20             | 0.81               | 2.37            | ND            | 29            | 162.3           | 3.9             |        |        |
| 48                | 0.80               | ND              | 56.4          | ND            | ND              | 16              | 0.69   |        |
| 1 week            | 1.36               | 2.37            | 21.8          | 28            | 267             | 3.1             |        |        |
| 2 weeks           | 1.36               | 2.34            | 38.2          | 28            | 211.4           | 2.8             |        |        |
| 6 months          | 1.34               | 2.68            | 10.9          | 27            | 159.1           | 5.5             |        |        |

### Table 2. Hyperphosphaturic hypophosphataemic disorders

| Diagnosis or clinical manifestation (OMIM number) | Defective protein (gene) | Tissue | Serum FGF23 |
|--------------------------------------------------|--------------------------|--------|-------------|
| XLH (307800)                                     | Phosphate-regulating gene with homology to endopeptidases on the X chromosome (PHEX) | Bone   |             |
| ADHR (193100)                                    | Fibroblast growth factor 23 (FGF23) | Osteocytes |             |
| ARHR-1 (241520)                                  | Dentin matrix protein 1 (DMP1) | Bone   |             |
| ARHR-2 (613312)                                  | Ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1) | Bone   |             |
| Hyperphosphaturia, osteoporosis, kidney stones    | NaPi co-transporter IIa (SLC34A1) | Proximal tubules | =, ↓ |
| HHRH (241530)                                    | NaPi co-transporter IIc (SLC34A3) | Proximal tubules | =, ↓ |
| Oncogenic osteomalacia                           | Acquired, unregulated FGF23 production | Mesenchymal tumour | ↑, ↑ |
| Fanconi syndrome                                 | Genetic or acquired       | Proximal tubules | =, ↓ |

### Discussion

This case illustrates the clinical picture of a hypophosphataemic syndrome due to excess FGF23 and the time-related changes in the parameters of mineral metabolism as FGF23 is normalized.

Other causes of chronic hypophosphataemia could be excluded by clinical history: there were no congenital or inherited skeletal problems, no malnutrition, malabsorption nor exposure to tubular toxins; and the calcium level was normal. For an up-to-date discussion of the approach to the hypophosphataemic patient, see [8].

Increased FGF23 may be due to a mutation in the FGF23 gene, making it resistant against enzymatic degradation as in autosomal dominant hypophosphataemic rickets [9]. Mutations in the PHEX, DMP1 or ENPP1 genes, respectively, induce a defect in the normal regulation of FGF23 synthesis in osteocytes by unknown mechanisms. These mutations all give rise to hereditary rickets, see Table 2 and [10]. The recessive disorder hereditary hypophosphataemic rickets with hypercalcemia.
condition is associated with increased calcitriol and hypercalciuria and a decrease in serum FGF23. Mutations in SLC34A1 resulting in a decrease in NaPi-IIa cause nephro lithiasis, osteoporosis and mild hypophosphataemia [12] (see Figure 2). Acquired chronic hypophosphataemia may be due to general or selective proximal tubular damage or Fanconi syndrome, caused by light chains associated with monoclonal gammopathies or other tubular toxins. FGF23 is normal or decreased in chronic hypophosphataemic disorders not caused by FGF23 excess [13]. The patient in this case had an acquired form of phosphate wasting, the FGF23 level was increased and there were no other features of general tubular dysfunction.

After surgery, the phosphate level normalized within 1 week, and the phosphate FE % had decreased already 2 days after surgery (Table 1).

PTH gradually increased to above pre-operative levels the first day after extirpation after a short decrease immediately after surgery. The finding is unexpected as FGF23 inhibits PTH secretion in vitro and in animal experiments [14]. Though, in chronic kidney disease and other situations with increased FGF23, there is development of hyperparathyroidism. In OOM as well as in other states with phosphate wasting due to FGF23 as X-linked hypophosphataemia (XLH), treatment with high doses of phosphate and active vitamin D induces an increase in FGF23 and PTH [15]. Also, in experiments with FGF23-neutralizing antibodies in the hyp mice, an animal homologue of XLH, there was actually an immediate decrease in PTH [16]. The regulation of PTH in hypophosphataemic disorders is incompletely understood. Vitamin D deficiency and calcium malabsorption, aggravated by large phosphate intake, may induce hyperparathyroidism. The fast post-operative decrease in PTH is difficult to explain. It may have been induced by the drop in phosphate level, increasing the free calcium fraction or increasing intracellular pre-PTH degradation in the parathyroid gland.

Serum calcitriol level started to increase after ~10 h mirrored by a decline in 24,25-vitamin D starting after ~20 h. CYP27B1 is the rate-limiting enzyme in calcitriol synthesis, while CYP24 inactivates calcitriol and its precursor 25-hydroxy vitamin D. CYP24 is stimulated by calcitriol, an effect attenuated by PTH [17]. FGF23 stimulates CYP24 activity in the kidney. Increased CYP24 activity, rather than decreased CYP27b1 activity, seems to be the cause of calcitriol deficiency in uroemic rat [18]. Treatment with FGF23 antibodies in hyp mice increases CYP27B1 expression and decreases the CYP24 activity [16].

FGF23 induced hypophosphataemia due to decreased phosphate reabsorption and prevented an appropriate increase of calcitriol. When FGF23 normalized, phosphate reabsorption increased the activity of CYP27B1 and CYP24 reacted adequately to the low serum phosphate. The calcitriol remained elevated after 6 months, when PTH and FGF23 were in reference range, reflecting an intrinsic regulation of calcitriol production stimulated by a positive phosphate balance due to continuing mineralization of the skeleton and need for increased phosphate reabsorption to maintain homeostasis.
In conclusion, this case verifies the known effects of FGF23, illustrates the utility of FGF23 determination when encountering a patient with hypophosphatemia and points to one of the unsolved questions concerning FGF23, namely its direct versus indirect effects on the parathyroid glands.

Acknowledgements. This clinical project was funded by Uppsala University.

Conflict of interest statement. None declared.

References

1. Portale AA, Halloran BP, Murphy MM et al. Oral intake of phosphorus can determine the serum concentration of 1,25-dihydroxyvitamin D by determining its production rate in humans. J Clin Invest 1986; 77: 7–12
2. Portale AA, Booth BE, Halloran BP et al. Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. J Clin Invest 1984; 73: 1580–1589
3. Jonsson KB, Zahradnik R, Larsson T et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med 2003; 348: 1656–1663
4. Yamazaki Y, Okazaki R, Shibata M et al. Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia. J Clin Endocrinol Metab 2002; 87: 4957–4960
5. Chong WH, Molinolo AA, Chen CC et al. Tumor-induced osteomalacia. Endocr Relat Cancer 2011; 18: R53–R77
6. Casetta B, Jans I, Billen J et al. Development of a method for the quantification of 1alpha, 25(OH)2-vitamin D3 in serum by liquid chromatography tandem mass spectrometry without derivatization. Eur J Mass Spectrom (Chichester, Engl) 2010; 16: 81–89
7. Folpe AL, Fanburg-Smith JC, Billings SD et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. Am J Surg Pathol 2004; 28: 1–30
8. Bacchetta J, Salusky IB. Evaluation of hypophosphatemia: lessons from patients with genetic disorders. Am J Kidney Dis 2012; 59: 152–159
9. ADHR consortium. Autosomal dominant hypophosphatemic rickets is associated with mutations in FGF23. Nat Genet 2000; 26: 345–348
10. Carpenter TO. The expanding family of hypophosphatemic syndromes. J Bone Miner Metab 2012; 30: 1–9
11. Bergwitz C, Roslin NM, Tieder M et al. Development of a method for the quantification of biologically active full-length FGF-23 in patients with moderate renal insufficiency. J Bone Miner Res 2009; 24: 1235–1239
12. Magen D, Berger L, Coady MJ et al. A loss-of-function mutation in NaPi-IIa and renal Fanconi’s syndrome. N Engl J Med 2010; 362: 1102–1109
13. Endo I, Fukumoto S, Ozono K et al. Clinical usefulness of measurement of fibroblast growth factor 23 (FGF23) in hypophosphatemic patients: proposal of diagnostic criteria using FGF23 measurement. Bone 2008; 42: 1235–1239
14. Gallitzer H, Ben-Dov I, Lavi-Moshayoff V et al. Fibroblast growth factor 23 acts on the parathyroid to decrease parathyroid hormone secretion. Curr Opin Nephrol Hypertens 2008; 17: 363–367
15. Imel EA, DiMeglio LA, Hui SL et al. Treatment of X-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations. J Clin Endocrinol Metab 2010; 95: 1846–1850
16. Aono Y, Yamazaki Y, Yasutake J et al. Therapeutic effects of anti-FGF23 antibodies in hypophosphatemic rickets/osteomalacia. J Bone Miner Res 2009; 24: 1879–1888
17. Petkovich M, Jones G. CYP24A1 and kidney disease. Curr Opin Nephrol Hypertens 2011; 20: 337–344
18. Helvig CF, Cuerrier D, Hosfield CM et al. Dysregulation of renal vitamin D metabolism in the uremic rat. Kidney Int 2010; 76: 463–472

Received for publication: 27.11.11; Accepted in revised form: 24.2.12