

FGF23 and the parathyroid glands

Justin Silver · Tally Naveh-Many

Received: 3 March 2010 / Revised: 4 May 2010 / Accepted: 5 May 2010 / Published online: 5 June 2010
© IPNA 2010

Abstract Fibroblast growth factor 23 (FGF23) is a phosphatonin that is secreted by osteocytes and osteoblasts in response to hyperphosphatemia and 1,25-dihydroxyvitamin D (1,25D). It acts on its receptor complex, Klotho–FGFR1c (fibroblast growth factor receptor 1 c-splicing form), in the distal convoluted tubule to repress renal phosphorus reabsorption in the proximal tubule and suppress the renal synthesis of 1,25D. Klotho–FGFR1c is also expressed in the parathyroid glands. FGF23 acts on the receptor complex in the parathyroid glands to decrease parathyroid hormone (PTH) gene expression and PTH secretion through activation of the MAPK pathway. In chronic kidney disease (CKD), both FGF23 and PTH are increased, implying resistance of the parathyroid glands to FGF23. There is a decrease in the Klotho–FGFR1c complex in the parathyroid glands in both experimental CKD and in patients with end-stage renal disease. In addition, in advanced experimental CKD, FGF23 has a decreased ability to inhibit PTH expression.

Keywords Calcium · FGF23 · Klotho · Phosphate · PTH

Introduction

The world of phosphorus metabolism received a welcome boost with the discovery of fibroblast growth factor 23 (FGF23), a phosphatonin. Its source is the most unlikely of all endocrine organs, bone, where it is synthesized

predominantly by osteocytes [1, 2], cells that had been considered to be of limited functional significance apart from their response to mechanical stimuli, and to a lesser extent by osteoblasts. The osteocyte produces FGF23 in a regulated fashion [3]. These cells have myriads of interconnecting canaliculi that connect with the blood vessels of bone where they presumably secrete FGF23. FGF23 is a 30-kDa (251 amino acids) protein, and its cleavage at the RXXR motif generates biologically inactive – and C-terminal fragments of 18 and 12 kDa, respectively [4]. In autosomal dominant hypophosphatemic rickets (ADHR), mutations of the 176RXXR179 site (R176Q, R179W, and R179Q) prevent the cleavage and inactivation of FGF23 [5]. The metabolism of FGF23 in bone involves other proteins, such as dentin matrix acidic phosphoprotein 1 (DMP1) and matrix extracellular phosphoglycoprotein (MEPE). DMP1 and MEPE both have acidic, serine- and aspartic acid-rich motif (ASARM) peptides that are potential substrates for phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PheX) protein [6], a cell-surface endopeptidase also located predominately in osteoblasts and osteocytes. Mutations in genes in the XLH region often result in increased serum FGF23 levels. The substrate for PHEX has not been identified.

The stimuli for FGF23 synthesis and secretion are phosphorus and 1,25(OH)₂ vitamin D (1,25-dihydroxyvitamin D or 1,25D). The level of circulating FGF23 in patients with chronic kidney disease (CKD) is increased in both children and adults and is biologically active [7]. The levels of FGF23 in CKD are extremely high and can reach 100,000-fold normal levels, which is far more than the fold-increase or -decrease in other known parameters of mineral metabolism, such as parathyroid hormone (PTH) or serum inorganic phosphorus (Pi) [8, 9].

The receptor for FGF23 consists of the Klotho–FGFR1c (fibroblast growth factor receptor 1 c-splicing form)

J. Silver (✉) · T. Naveh-Many (✉)
Minerva Center for Calcium and Bone Metabolism, Nephrology
Services, Hadassah Hebrew University Medical Center,
Ein Karem,
Jerusalem 91120, Israel
e-mail: silver@huji.ac.il
e-mail: tally@cc.huji.ac.il

complex, which determines the site of action of FGF23 [10]. Mice with double deletion of FGF23 and Klotho genes are similar to FGF23 or Klotho knockout mice, suggesting that the effects of FGF23 are mediated by Klotho and that the principal function of Klotho is to allow FGF23 action [11]. Klotho was initially thought to be restricted to the kidney in general and to the distal convoluted cells in particular where it exerts its initial signaling [12]. Klotho–FGFR1c was subsequently shown to be expressed in the parathyroid glands, choroid plexus, and the sino-atrial node of the heart [13]. Klotho is also present in the plasma and urine. The major soluble form of Klotho originates from the shedding of the full-length protein. A smaller circulating form comes from RNA splicing at exon 3 in Klotho gene [14]. The physiological role of the circulating forms of Klotho remains to be established.

In the kidney, FGF23 acts on the distal tubule to activate the MAPK pathway and thereby exert its major physiological effect on the proximal tubule. Immunofluorescent analyses following FGF23 injection in mice revealed staining for phospho-ERK1/2, a marker of FGF23 bioactivity, only within the distal convoluted cells [12]. In the proximal tubule, FGF23 inhibits the activity of the Pi transporters, NaPi2a and NaPi2c, leading to a marked phosphaturia. In addition, FGF23 inhibits cytochrome P450 27B1 (CYP27B1), the 25(OH)-1 α hydroxylase that synthesizes 25-hydroxyvitamin D [1,25(OH)D] [15]. The mechanism of this inhibition is, at least in part, due to the effect of FGF23 on increasing the activity of the calcium channel, TRPV5, with the increased level of intracellular calcium inhibiting CYP27B1 [16].

FGF23 increases early in CKD and together with the decreased synthesis of 1,25D and increased serum PTH levels was thought to act in concert with PTH to cause phosphaturia [17, 18]. The phosphaturia would act to prevent any increase in the level of serum Pi as long as the kidneys could respond. There may actually be a trade-off for this rise in FGF23 because arterial calcification, left ventricular hypertrophy, and mortality have all been associated with the increased levels of FGF23 in CKD patients [19, 20]. It is therefore essential that we understand the mechanisms of these clinical observations and test these mechanisms in longitudinal studies with larger numbers of patients. Tools to specifically block FGF23 action are currently being developed.

FGF23 and the parathyroid glands

The tissue distribution of the FGF23 receptor Klotho has been demonstrated in transgenic mice using a reporter gene system (*kl geo*) [13]. In these transgenic mice, *klotho* expression was recognized exclusively in the kidney, the

sinoatrial node region of the heart, the parathyroid glands, and the choroid plexus. In our laboratory, we confirmed the expression of Klotho–FGFR1 in the parathyroid glands and determined its functionality [21]. Immunoblots with anti-Klotho antibody showed Klotho expression in rat microdissected parathyroid gland [21]. There was no expression of Klotho protein in the thyroid and liver. Quantitative reverse transcription (RT)-PCR for Klotho mRNA showed a high expression of the latter in the parathyroid glands and kidney, with negligible expression in the other tissues studied. Immunohistochemistry studies confirmed the localization of Klotho to the parathyroid glands and not to the surrounding thyroid tissue and also showed the presence of FGFR1 in the parathyroid tissue. These results show that the parathyroid gland expresses the FGFR–Klotho receptor complex and suggest that the parathyroid gland is a target organ for FGF23 [21].

Functional effect of FGF23 on PTH expression

Rats injected with FGF23 showed the expected decreases in serum 1,25D and serum phosphorus levels with no significant changes in serum calcium. Importantly, serum PTH and PTH mRNA levels were decreased after FGF23 injection. FGF23 acts on the Klotho–FGFR through the MAPK pathway in cells transfected with Klotho as well as in the kidney, as shown by an increased phosphorylation of ERK1/2 [10, 22]. The injection of FGF23 led to an increase in phospho-ERK1/2 in the parathyroid glands, indicating activation of the MAPK pathway in the FGF23-treated rats.

Short-term experiments have defined the FGF23 signal transduction in the parathyroid glands as well as its effect on PTH secretion. When FGF23 was given intravenously (iv), the serum PTH level was lower at 10 and 30 min post administration; when given intraperitoneally (ip), serum PTH levels were lower at 40 min and 24 h post administration. FGF23 decreased PTH mRNA levels at 40 min following administration, as shown by qRT-PCR. Based on these results, it can be concluded that FGF23 decreases PTH secretion and mRNA levels over the short term [21].

FGF23 activates MAPK in the parathyroid

To show that the MAPK pathway is required for the FGF23 effect on PTH secretion, we used the MAPK inhibitor, U0126 and devised a novel approach in which FGF23 was given iv and the inhibitor U0126 was added topically. Under these experimental conditions, FGF23 decreased serum PTH levels in the absence of the inhibitor. Importantly, U0126 prevented the FGF23-induced decrease

in serum PTH. We obtained similar results in in vitro studies using microdissected parathyroid glands. We can therefore conclude that FGF23 acts directly on the parathyroid glands to activate the MAPK pathway and decrease PTH secretion and gene expression both in vivo and in vitro [21].

FGF23 acts on bovine parathyroid cells to decrease PTH levels and increase 25(OH) vitamin D 1α hydroxylase expression

Krajisnik et al. [23] incubated bovine parathyroid cells in primary culture with FGF23 and found a decrease in PTH mRNA, indicating a direct effect of FGF23 on PTH expression. They also showed that FGF23 increased 25(OH) vitamin D 1α hydroxylase (CYP27B1) mRNA levels in the parathyroid cells and that the resultant increased levels of parathyroid 1,25D may then act in an autocrine fashion to decrease PTH gene transcription. The effect of FGF23 to increase CYP27B1 is in contrast to its inhibiting effect on this enzyme in the kidney.

FGF23 decreases serum PTH levels in transgenic mice expressing the human PTH gene

Lavi-Moshayoff et al. [24] generated transgenic mice with the human gene (hPTH) expressed in the mouse parathyroid, using a bacterial artificial chromosome (BAC) containing the human PTH (hPTH) gene within its 144-kb chromosomal region (hPTH Tg mice). The BAC construct maintains the native hPTH gene-surrounding sequences and isolates it from positional effects. The transgenic mice had normal levels of serum mouse PTH (mPTH) in addition to both intact and bioactive hPTH. The administration of recombinant FGF23 ip led to a decrease in serum mPTH in wild-type mice and in serum hPTH in the hPTH Tg mice, similar to the reported decrease in serum PTH in rats and mice after FGF23 administration [21, 25]. FGF23 signaling is conserved from mouse to man in the parathyroid glands.

The mechanism of resistance to FGF23 in the parathyroid glands

We have recently reported that a decrease in Klotho–FGFR1 expression and signal transduction may explain the resistance of the parathyroid gland to FGF23 in CKD [26]. Quantitative immunohistochemistry studies and qRT-PCR analyses using laser capture RNA retrieval revealed that Klotho and FGFR1 protein and mRNA levels were decreased in parathyroid sections of rats with dietary

adenine Pi-induced advanced CKD. Recombinant FGF23 also failed to decrease serum PTH or activate the MAPK pathway in parathyroid glands of rats with advanced CKD. In parathyroid organ culture, FGF23 decreased secreted PTH and PTH mRNA levels in parathyroid glands of control or early CKD rats but not in those of rats with advanced CKD. Therefore, in advanced experimental CKD, there is a decrease in parathyroid Klotho and FGFR1 mRNA and protein levels. This decrease corresponds with the resistance of the parathyroid glands to FGF23 in vivo, which is sustained in parathyroid organ culture in vitro. We propose that the increased levels of FGF23 fail to decrease PTH levels in established CKD because of a down-regulation of its receptor heterodimer complex Klotho–FGFR1c.

Fukugama’s group also showed a decrease in the expression of Klotho–FGFR1 in secondary hyperparathyroidism in human parathyroid tissue [27]. Komaba et al. examined the expression of Klotho and FGFR1 in surgically excised parathyroid glands of uremic patients [27] and found that, compared with normal tissue, the

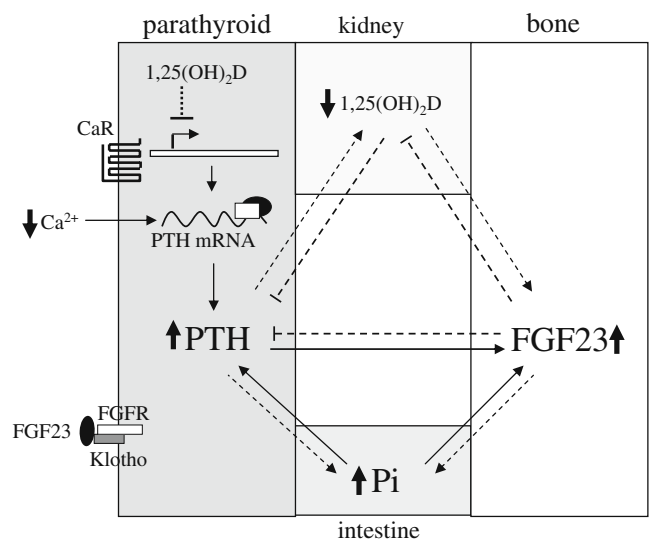


Fig. 1 Feedback loops in mineral metabolism. A low extracellular Ca²⁺ leads to relaxation of the calcium receptor (CaR) in the parathyroid glands, resulting in increased parathyroid hormone (PTH) secretion and gene expression. The increase in PTH gene expression is post-transcriptional and mediated by RNA binding proteins. 1,25-Dihydroxyvitamin D [1,25(OH)₂D] decreases PTH gene transcription. Fibroblast growth factor 23 (FGF23) binds to the Klotho–fibroblast growth factor receptor 1 c-splicing form (FGFR1c) complex, activates the MAPK pathway, and decreases PTH gene expression and serum levels. In chronic kidney disease (CKD) there is decreased urinary inorganic phosphorus (Pi) excretion and decreased 1,25D production, both of which stimulate PTH secretion. The Pi retention induces FGF23 synthesis and secretion. The high FGF23 and PTH levels would initially cause phosphaturia and correct the high serum Pi levels, but not as CKD progresses. In advanced CKD, the high FGF23 levels do not decrease serum PTH because of a down-regulation of the parathyroid Klotho–FGFR1 complex. Broken lines Pathways that are disrupted in CKD

expression of Klotho and FGFR1 decreased significantly in hyperplastic parathyroid glands, particularly in glands with nodular hyperplasia. This result suggests that the depressed expression of the Klotho–FGFR1c complex in hyperplastic glands may explain the resistance to extremely high FGF23 levels in uremic patients [27, 28]. Kumata et al. also recently reported a decreased expression of α -Klotho and FGFR1c in parallel with calcium receptor (CaR) expression in the parathyroid glands of patients with secondary hyperparathyroidism [29]. Lafage-Proust [30] has posed pertinent questions, such as: What are the mechanisms that lead to the decline of these receptors? Does hyperphosphatemia play a role? What is the relationship to the decrease in parathyroid vitamin D receptor (VDR) and CaR?. Together, these results demonstrate that the resistance of the parathyroid to FGF23 in experimental CKD is due to the down-regulation of the Klotho–FGFR1 receptor.

The mechanism of the increased FGF23 levels in CKD

The mechanism of the increased serum FGF23 levels in CKD is not clear. It may be an early response to Pi retention, subsequently acting on the kidney to enhance Pi clearance and prevent hyperphosphatemia [18]. In a cross-sectional study of 792 stable outpatients with a history of coronary artery disease, Ix et al. reported a significant upward change in the slope of FGF23, beginning at a glomerular filtration rate (GFR) of 90 ml/min/1.73 m², which precedes any reported decrease in 1,25D levels or increase in PTH in CKD [19]. 1,25D stimulates FGF23 production both in vivo and in vitro through vitamin D-response elements present in the FGF23 promoter [31]. The administration of 1,25D to patients undergoing dialysis results in increased serum FGF23 levels [32]. It is paradoxical that vitamin D therapy is beneficial to the survival of dialysis patients despite its effect to increase serum FGF23 levels, which itself is a predictor of mortality [8]. Treatment with a calcimimetic plus low-dose calcitriol analogs results in lower FGF23 levels compared with a treatment regimen using calcitriol analogs alone in end-stage renal disease (ESRD) [33], suggesting that decreasing serum PTH levels may in itself lead to a decrease in serum FGF23 levels.

In a mouse model of primary hyperparathyroidism, PTH–cyclin D1 transgenic mice had higher serum FGF23 concentrations than wild-type mice [4], with the serum FGF23 levels significantly and directly correlating with serum PTH and calcium levels and inversely correlating with phosphate levels. Following parathyroidectomy in the transgenic mice, both serum FGF23 and calcium levels decreased. In this model, therefore, PTH and/or calcium correlated with changes in serum FGF23 levels [34]. There

is also a clinical correlate that illustrates the complexity of the relationship between PTH action, calcium, and FGF23. In a patient with an activating mutation of the PTH/PTHrP (PTH-related protein) receptor, namely Jansen's metaphyseal chondrodysplasia, serum FGF23 concentrations were found to be markedly and persistently elevated despite hypophosphatemia and normal 1,25D levels [35]. This observation suggested that serum FGF23 could be governed by activation of the PTH/PTHrP receptor in bone. However, the patient also had a high serum calcium level, which itself increases serum FGF23 levels [36].

These observations point to a bone–parathyroid axis where the effect of FGF23 to suppress PTH expression represents one arm of a novel endocrinologic feedback loop [21]. The second arm of this loop is the effect of PTH to increase serum FGF23 levels (Fig. 1).

Conclusion

The Klotho–FGFR1 complex is expressed in the parathyroid glands and FGF23 binds to this receptor complex to activate the MAPK pathway and thereby decrease PTH expression. Patients with CKD have very high serum levels of both FGF23 and PTH. In CKD, there is a down-regulation of Klotho and FGFR1 in the parathyroid gland and a decreased ability of FGF23 to activate the parathyroid MAPK pathway both in vivo and in vitro. FGF23 decreases serum PTH levels, and PTH may increase serum FGF23 levels—a classic endocrine feedback loop (Fig. 1). In CKD, the effect of PTH on bone to increase FGF23 expression is maintained, but FGF23 is no longer able to suppress the synthesis and secretion of PTH.

Acknowledgments This work was supported in part by grants from the Israel Science Foundation and the Israel Ministry of Health.

References

1. Feng JQ, Ward LM, Liu S, Lu Y, Xie Y, Yuan B, Yu X, Rauch F, Davis SI, Zhang S, Rios H, Drezner MK, Quarles LD, Bonewald LF, White KE (2006) Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. *Nat Genet* 38:1310–1315
2. Pereira RC, Juppner H, Azucena-Serrano CE, Yadin O, Salusky IB, Wesseling-Perry K (2009) Patterns of FGF-23, DMP1, and MEPE expression in patients with chronic kidney disease. *Bone* 45:1161–1168
3. Feng JQ, Ye L, Schiavi S (2009) Do osteocytes contribute to phosphate homeostasis? *Curr Opin Nephrol Hypertens* 18:285–291
4. Shimada T, Muto T, Urakawa I, Yoneya T, Yamazaki Y, Okawa K, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T (2002) Mutant FGF-23 responsible for autosomal dominant hypophosphatemic rickets is resistant to proteolytic cleavage and causes hypophosphatemia in vivo. *Endocrinology* 143:3179–3182

5. White KE, Evans WE, O’Riordan JLH, Speer MC, Econs MJ, Lorenz-Depiereux B, Grabowski M, Meitinger T, Strom TM (2000) Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat Genet* 26:345–348
6. Quarles LD (2008) Endocrine functions of bone in mineral metabolism regulation. *J Clin Invest* 118:3820–3828
7. Shimada T, Urakawa I, Isakova T, Yamazaki Y, Epstein M, Wesseling-Perry K, Wolf M, Salusky IB, Juppner H (2010) Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. *J Clin Endocrinol Metab* 95:578–585
8. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Juppner H, Wolf M (2008) Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 359:584–592
9. Jean G, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, Chazot C (2009) High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. *Nephrol Dial Transplant* 24:2792–2796
10. Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, Baum MG, Schiavi S, Hu MC, Moe OW, Kuro-o M (2006) Regulation of fibroblast growth factor-23 signaling by klotho. *J Biol Chem* 281:6120–6123
11. Razzaque MS, Sitara D, Taguchi T, St Arnaud R, Lanske B (2006) Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D-mediated process. *FASEB J* 20:720–722
12. Farrow EG, Davis SI, Summers LJ, White KE (2009) Initial FGF23-mediated signaling occurs in the distal convoluted tubule. *J Am Soc Nephrol* 20:955–960
13. Takeshita K, Fujimori T, Kurotaki Y, Honjo H, Tsujikawa H, Yasui K, Lee JK, Kamiya K, Kitaichi K, Yamamoto K, Ito M, Kondo T, Iino S, Inden Y, Hirai M, Murohara T, Kodama I, Nabeshima Y (2004) Sinoatrial node dysfunction and early unexpected death of mice with a defect of klotho gene expression. *Circulation* 109:1776–1782
14. Imura A, Iwano A, Tohyama O, Tsuji Y, Nozaki K, Hashimoto N, Fujimori T, Nabeshima Y (2004) Secreted Klotho protein in sera and CSF: implication for post-translational cleavage in release of Klotho protein from cell membrane. *FEBS Lett* 565:143–147
15. Fukumoto S, Yamashita T (2002) Fibroblast growth factor-23 is the phosphaturic factor in tumor-induced osteomalacia and may be phosphatonin. *Curr Opin Nephrol Hypertens* 11:385–389
16. Alexander RT, Woudenberg-Vrenken TE, Buurman J, Dijkman H, van der Eerden BC, van Leeuwen JP, Bindels RJ, Hoenderog JG (2009) Klotho prevents renal calcium loss. *J Am Soc Nephrol* 20:2371–2379
17. Isakova T, Gutierrez O, Shah A, Castaldo L, Holmes J, Lee H, Wolf M (2008) Postprandial mineral metabolism and secondary hyperparathyroidism in early CKD. *J Am Soc Nephrol* 19:615–623
18. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collierone G, Juppner H, Wolf M (2005) Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol* 16:2205–2215
19. Ix JH, Shlipak MG, Wassel CL, Whooley MA (2010) Fibroblast growth factor-23 and early decrements in kidney function: the Heart and Soul Study. *Nephrol Dial Transplant* 25:993–997
20. Mirza MA, Hansen T, Johansson L, Ahlstrom H, Larsson A, Lind L, Larsson TE (2009) Relationship between circulating FGF23 and total body atherosclerosis in the community. *Nephrol Dial Transplant* 24:3125–3131
21. Ben Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro-o M, Mohammadi M, Sirkis R, Naveh-Manly T, Silver J (2007) The parathyroid is a target organ for FGF23 in rats. *J Clin Invest* 117:4003–4008
22. Yamashita T, Konishi M, Miyake A, Inui K, Itoh N (2002) Fibroblast growth factor (FGF)-23 inhibits renal phosphate reabsorption by activation of the mitogen-activated protein kinase pathway. *J Biol Chem* 277:28265–28270
23. Krajisnik T, Bjorklund P, Marsell R, Ljunggren O, Akerstrom G, Jonsson KB, Westin G, Larsson TE (2007) Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. *J Endocrinol* 195:125–131
24. Lavi-Moshayoff V, Silver J, Naveh-Manly T (2009) Human PTH gene regulation in vivo using transgenic mice. *Am J Physiol Renal Physiol* 297:F713–F719
25. Yamazaki Y, Tamada T, Kasai N, Urakawa I, Aono Y, Hasegawa H, Fujita T, Kuroki R, Yamashita T, Fukumoto S, Shimada T (2008) Anti-FGF23 neutralizing antibodies show the physiological role and structural features of FGF23. *J Bone Miner Res* 23:1509–1518
26. Galitzer H, Ben-Dov IZ, Silver J, Naveh-Manly T (2010) Resistance of the parathyroid to FGF23 in secondary hyperparathyroidism of chronic kidney disease. *Kidney Int* 77:211–218
27. Komaba H, Goto S, Fujii H, Hamada Y, Kobayashi A, Shibuya K, Tominaga Y, Otsuki N, Nibu KI, Nakagawa K, Tsugawa N, Okano T, Kitazawa R, Fukagawa M (2010) Depressed expression of Klotho and FGF receptor 1 in hyperplastic parathyroid glands from uremic patients. *Kidney Int* 77:232–238
28. Komaba H, Fukagawa M (2009) FGF23-parathyroid interaction: implications in chronic kidney disease. *Kidney Int* 77:292–298
29. Kumata C, Mizobuchi M, Ogata H, Koiwa F, Nakazawa A, Kondo F, Kadokura Y, Kinugasa E, Akizawa T (2010) Involvement of Alpha-Klotho and fibroblast growth factor receptor in the development of secondary hyperparathyroidism. *Am J Nephrol* 31:230–238
30. Lafage-Proust MH (2010) Does the downregulation of the FGF23 signaling pathway in hyperplastic parathyroid glands contribute to refractory secondary hyperparathyroidism in CKD patients? *Kidney Int* 77:390–392
31. Liu S, Tang W, Zhou J, Stubbs JR, Luo Q, Pi M, Quarles LD (2006) Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. *J Am Soc Nephrol* 17:1305–1315
32. Nishi H, Nii-Kono T, Nakanishi S, Yamazaki Y, Yamashita T, Fukumoto S, Ikeda K, Fujimori A, Fukagawa M (2005) Intravenous calcitriol therapy increases serum concentrations of fibroblast growth factor-23 in dialysis patients with secondary hyperparathyroidism. *Nephron Clin Pract* 101:c94–c99
33. Wetmore JB, Liu S, Krebill R, Menard R, Quarles LD (2010) Effects of cinacalcet and concurrent low-dose vitamin D on FGF23 levels in ESRD. *Clin J Am Soc Nephrol* 5:110–116
34. Kawata T, Imanishi Y, Kobayashi K, Miki T, Arnold A, Inaba M, Nishizawa Y (2007) Parathyroid hormone regulates fibroblast growth factor-23 in a mouse model of primary hyperparathyroidism. *J Am Soc Nephrol* 18:2683–2688
35. Brown WW, Juppner H, Langman CB, Price H, Farrow EG, White KE, McCormick KL (2009) Hypophosphatemia with elevations in serum FGF23 in a child with Jansen’s metaphyseal chondrodysplasia. *J Clin Endocrinol Metab* 94:17–20
36. Shimada T, Yamazaki Y, Takahashi M, Hasegawa H, Urakawa I, Oshima T, Ono K, Kakitani M, Tomizuka K, Fujita T, Fukumoto S, Yamashita T (2005) Vitamin D receptor-independent FGF23 actions in regulating phosphate and vitamin D metabolism. *Am J Physiol Renal Physiol* 289:F1088–F1095