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Role of FGF23 in Vitamin D and Phosphate Metabolism: Implications in Chronic Kidney Disease

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Abstract

FGF23 is a bone-derived hormone that regulates systemic phosphate homeostasis, vitamin D metabolism and α-klotho expression through a novel bone-kidney axis. FGF23 inhibits renal tubular reabsorption of phosphate through mechanisms independent of PTH as well as reduces circulating 1, 25$(OH)_2$D through its dual effects to suppress Cyp27b1 production and to stimulate Cyp24 catabolism of 1,25$(OH)_2$D. 1,25$(OH)_2$D and other factors regulating bone remodeling/mineralization are the major physiological regulators of FGF23 expression. FGF23 also suppresses the gene transcription of α-klotho by the kidney, which exists as a membrane and soluble protein. Membrane Klotho acts as a coreceptor for and dictates organ specificity of FGF23, whereas soluble Klotho act as an endocrine factor that regulates activity of cell surface glycoproteins and receptors in multiple tissues. Elevated FGF23 levels are responsible for several hereditary and acquired hypophosphatemic rickets disorders. FGF23 and Klotho deficiency have similar phenotypes characterized by hyperphosphatemia, elevated 1,25$(OH)_2$D and tumoral calcinosis. FGF23 levels progressively increase during chronic kidney disease (CKD). FGF23 has been proposed to be the initial adaptive response leading to reductions in 1,25$(OH)_2$D and secondary hyperparathyroidism (HPT) in CKD. The overall biological effect of this initial step may be to orchestrate a coordinated adaptation to protect the organism from the adverse effects of excess phosphate retention. The second step involves the effects of PTH on bone remodeling that further stimulates FGF23 production through both direct and indirect mechanisms related to alterations in extracellular matrix factors. PTH further amplifies FGF23 expression in later stages of CKD to compensate for the increased phosphate efflux from bone caused by excessive bone turnover. While many aspects of the regulation and functions of FGF23 remain to be established, the idea that FGF23 hormone is the initial adaptive hormonal response in CKD that suppresses 1,25$(OH)_2$D, reduces gastrointestinal calcium and phosphate absorption and leads to a secondary HPT represents a paradigm shift in the conceptualization of the pathogenesis of secondary hyperparathyroidism. In addition, the prevalent thought that CKD is a functional “vitamin D deficient state” requiring therapy with 1,25$(OH)_2$D analogues is challenged by effects of FGF23 to potentially lower both 25(OH)D and 1,25(OH)D by induction of Cyp24-mediated degradation. Finally, increments in FGF23 are associated with increased cardiovascular mortality in CKD. Whether these effects represent direct effects of FGF23 or represent a marker of other abnormalities in CKD remain to be determined.

Keywords

1,25(OH)2D; bone; kidney; calcium; osteoblasts; osteocytes; cyp27b1; cyp24; klotho

Overview of FGF23

FGF23 is a ~32 kDa secreted protein, predominately expressed in osteoblasts and osteocytes (45, 51, 84, 103), that principally targets receptor complexes consisting of FGFR 1,3 or 4 and the transmembrane β glucuoronidase, α-Kl (37, 43, 92, 105) in the kidney to inhibit renal phosphate reabsorption by decreasing Na-dependent co-transporters and to suppress circulating $1,25(OH)_2D$ levels by inhibiting Cyp27b1 (which converts 25(OH)D to $1,25(OH)_2D$) and by stimulating the catabolism of $1,25(OH)_2D$ by activating the 24-hydroxylase (Cyp24) (3, 23, 77–78, 80, 90, 101). Elevated FGF23 causes several hereditary (including, XLH, ADHR, and ARHR) and acquired (*e.g.,* MAS and TIO) hypophosphatemic disorders. In contrast, reductions in FGF23 lead to tumoral calcinosis, characterized by hyperphosphatemia, increased $1,25(OH)_2D$ and soft tissue calcifications (62) (46, 62–63)]. FGF23 is markedly elevated in chronic kidney disease (CKD)(54), where FGF23 regulation and function remain to be fully characterized.

Physiological regulation FGF23

FGF23 is regulated by both systemic and local factors. FGF23 acts as a counter regulatory factor for $1,25(OH)_2D$ (49) and participates in a bone-kidney feedback loop, consisting of $1,25(OH)_2D$ stimulation of FGF23 production in bone and FGF23 suppression of $1,25(OH)_2D$ production by the kidney (49). A less well characterized feedback loop exists that involves stimulation of FGF23 expression in bone when FGF23 signaling in the kidney is blocked either through ablation of FGFR or α-Kl (50, 92). PTH regulation of FGF23 is controversial. FGF23 is elevated by activating PTH/PTHrp receptor and GNAS mutations (8). In addition, FGF23 is elevated in mice overexpressing a constitutively active PTH receptor in osteocytes (Dmp1-caPTHR1) and a PTH directly stimulates FGF23 expression in UMR 106 osteoblasts (41, 67–68). FGF23 is also increased in some animal models of excess PTH (29, 41, 76). The ability of PTH to stimulate FGF23, however, is context dependent. For example, PTH failed to directly stimulate FGF23 production or FGF23 promoter activity in Ros17/2.8 osteoblasts *in vitro* (49), or in calvarial cultures ex vivo (73). In other circumstances PTH had no effect on FGF23 expression (73, 75). The mechanism underlying the variable effects of PTH on FGF23 gene expression is not known.

There is also emerging evidence linking bone metabolism with FGF23 regulation. FGF23 appears to coordinate renal phosphate handling to match bone mineralization/remodeling (12, 47, 51, 71), which impact upon the influx and efflux of calcium and phosphate from bone (64, 76, 94) (i.e., increased bone avidity for phosphate→ decreased FGF23, and decreased phosphate uptake or increased efflux due to increased bone remodeling→increased FGF23) (17, 62) (8). There are numerous examples of single gene mutations leading to alterations in bone remodeling leading to increased FGF23 (33, 49, 63). Dmp1, Phex and ENPP1 mutations which block bone mineralization also lead to increased FGF23 production by osteocytes (27, 48), whereas nutritional osteomalacia is associated with decreased FGF23 that paradoxically increases after healing of bone (93). OPG- or alendronate-mediated inhibition of bone turnover that limit phosphate influx to bone also increase FGF23 (75). Bone remodeling/mineralization may be linked to FGF23 through multiple pathways, including both canonical FGFR and integrative nuclear FGF receptor 1 signaling and Wnt signaling (62). Leptin, estrogens and glucocorticoids also coordinately regulate FGF23 and bone remodeling (91). Although FGF23 is a phosphate regulating

hormone, tight coupling between changes in serum phosphate and FGF23 are not present (49, 52). Some studies have failed to observe changes in FGF23 in healthy individuals in response to either low or high phosphate diets (40, 57). In contrast, other studies have shown that alterations in dietary phosphate lead to differences in FGF23, albeit after a lag time of up to 1 week (1, 9, 13, 55, 60, 96). The effects of phosphate on FGF23 are also be modulated by the vitamin D status, since increasing dietary phosphorus does not increase FGF23 in the absence of the VDR (80). Phosphate may indirectly regulate FGF23 by affecting bone mineralization (49, 52).

Physiological functions of FGF23

Excess FGF23 causes hypophosphatemia, suppression of $1,25(OH)_2D$, and rickets/osteomalacia (2, 15, 39, 78, 80). Loss of Fgf23 function results in hyperphosphatemia, excess $1,25(OH)_2D$, and soft tissue calcifications (6, 28, 38, 51, 77, 82–83). FGF23 regulation of cellular function in target tissues is mediated by binding to FGF receptor/Klotho complexes. α-Klotho is an obligate co-receptor for FGF23 and the tissue restricted actions of FGF23 are dictated by the sites of the transmembrane, full-length form of α-Klotho. These physiological effects of FGF23 and the localization of α-Klotho in the kidney, suggest that FGF23 principally targets the kidney. In the kidney, FGF23 inhibits renal phosphate reabsorption by decreasing Npt2 co-transporters and suppresses $1,25(OH)_2D$ levels by inhibiting Cyp27b1 and stimulating Cyp24 (3, 23, 77–78, 80, 90, 101). FGFR 1, 3 and 4 appear to be targets for FGF23 in the kidney, the FGFR 3 and 4 playing a greater role in regulation of vitamin D metabolism and FGFR1 in the regulation of phosphate reabsorption (42). Klotho is known to be present in the distal tubule and its expression in the proximal tubule, sites of phosphate reabsorption and vitamin D metabolism, remains uncertain. Consequently, a distal to proximal feedback loop has been postulated to explain the proximal tubular actions of FGF23.

Low expression of α-klotho is also reported in the pituitary gland, placenta, skeletal muscle, urinary bladder, aorta, pancreas, testis, ovary and colon (4, 36), where the function of FGF23 is not certain. Knock-in of the lacZ gene downstream of the translational initiation codon of α-klotho also shows expression of α-klotho in the parathyroid gland (5), and sinoatrial cells of the heart (79, 87). In addition, Klotho, itself is released into the circulation by ectodomain shedding of the membrane Klotho or by secretion of an alternatively spliced form of Klotho that lacks the transmembrane domain. Secreted Klotho inhibits insulin- and IGF-1-induced autophosphorylation of insulin receptor and IGF-1 receptor in vitro and Klotho-deficient mice exhibit hypoglycemic, hypoinsulinemic, and increased insulin sensitivity, as well as other abnormities leading to decreased survival (35). Klotho production is markedly decreased in CKD (32). Thus, FGF23 may affect other organs indirectly through its affects on circulating Klotho levels, analogous to its effects on serum $1,25(OH)_2D$ concentrations. It has also been suggested that Klotho regulates phosphate absorption independently of FGF23. Secreted Klotho is filtered by the glomerulus and taken up by the proximal tubule where it has been shown to decrease the cell surface expression of the sodium-phosphate transporter (24). However, since FGF23 decreases the Klotho gene transcription; the phosphaturic actions of FGF23 are associated with decreased Klotho expression and attenuation of its direct phosphaturic actions, which is physiologically incongruous. Increased circulating levels of FGF23 are associated with increased mortality in patients with CKD (19) (14) and may be a cardiovascular disease risk factor in the general population(53). These observations and the finding of membrane Klotho in other tissues as well as the endocrine functions of secreted Klotho, suggest that FGF23 may have both direct and indirect actions on other biological processes other than regulation of phosphate and vitamin D metabolism. Thus, FGF23 effects on cardiovascular mortality could potentially represent a direct effect of FGF23 on cardiac tissues. Further studies are needed to elucidate

the potential direct and indirect mechanisms that might explain the association between FGF23 and mortality.

FGF23 effects on the parathyroid gland (PTG) are controversial (36, 44). FGF23 directly suppresses PTH mRNA expression *in vitro* and decreases serum PTH *in vivo* (4), however, FGF23 does prevent the development of hyperparathyroidism (HPT) in any clinical circumstance and there is a strong association between elevated FGF23 levels and the severity of HPT in CKD and other disorders (92), suggesting FGF23 may promote the development of HPT (36, 44, 92). Recent studies indicate resistance to FGF23 develops in uremic PTGs due to down-regulation of Kl and FGFR expression (16, 34), which may explain this paradox. The mechanism of this down-regulation is not known, but FGF23 is known to decrease Klotho expression in the kidney. Alternatively, there is some indirect data that FGF23 may stimulate PTG proliferation leading to hyperplasia and refractory HPT(100).

Role of FGF23 in CKD-Mineral Bone Disorder (CKD-MBD)?

The pathogenesis of CKD is traditionally viewed from the perspective of the PTH-Vitamin D axis, and current treatments focus on suppressing PTH with active vitamin D analogues (99), which can raise serum calcium and phosphate concentrations (89) and further stimulate FGF23 (7, 19, 65, 104). Cross-sectional studies in humans show early FGF23 elevations in CKD in proportion to reduced GFR (18) and is associated with reductions of $1,25(OH)_2D$ and increments in Cyp24 (20). FGF23 is markedly elevated in ESRD (18, 25, 97), where levels correlate with the degree of hyperphosphatemia (25, 97), predict refractory HPT in some studies (34) and is associated with increased mortality (86). There are many important questions about FGF23 in CKD that remain to be answered (102).

What comes first, FGF23 and PTH?

Cross sectional studies in CKD have found that increased FGF23 concentration is an early marker of CKD (14, 18, 95). FGF23 is positively correlated with parathyroid hormone and phosphate concentrations and negatively correlated with $1,25(OH)_2D$, estimated glomerular filtration rate, and tubular phosphate reabsorption. Several longitudinal studies in animal models of CKD show a near simultaneous increase in FGF23 and PTH and efforts to establish which comes first gives opposite conclusions. This has led to two competing hypotheses.

There is compelling data to support the scenario that FGF23 is the initial event in CKD leading to reductions in $1,25(OH)_2D$ and secondary increments in PTH. Analysis of the expression of enzymes that regulate vitamin D metabolism, Cyp27b1 and Cyp24, suggest a pattern most consistent with an effect of FGF23 in CKD (21). In a rat model of anti-GBM nephritis treatment with a neutralizing anti-FGF23 antibody (20) increased serum $1,25(OH)_2D$ and Cyp27b1 and reduced Cyp24 as well as suppressed PTH. Ttreatment with paracalcitol further elevates FGF23 and suppresses PTH in ESRD (85).

On the other hand, there is equally compelling evidence for a PTG-bone feedback loop, where, FGF23 directly suppresses PTH mRNA expression *in vitro* and decreases serum PTH *in vivo* (4) and PTH stimulates FGF23 expression in bone in CKD (29, 31, 66, 76). The most compelling are studies reported by Lavi-Moshayoff et al, which found that PTH increases FGF23 gene expression and mediates the high-FGF23 levels of in a 0.75% adenine 1.5% high-phosphorus diet-induced CKD model in rats (41). In these studies early PTX prevented the increase in FGF23 observed in rats with adenine-induced renal failure without PTX. These investigators also found that continuous PTH administration at high doses (50 ug/kg/day) stimulated FGF23 production in both mice and PTH also stimulated FGF23

expression in UMR-106 osteoblasts cultures. However, FGF23 does prevent the development of HPT in any clinical circumstance and there is a strong association between elevated FGF23 levels and the severity of HPT in CKD and other disorders (36, 44, 92). To reconcile these discrepancies this hypothesis proposes that resistance to FGF23-mediated suppression of PTH develops in CKD, permitting elevations in PTH in spite of concurrent increments in FGF23 (4, 16, 34),

Several observations fail to support the hypothesis that PTH directly regulates FGF23 hypothesis. First, there are important limitations to the high dietary phosphate-adenine model of "CKD", including its rapid onset, early hypocalcemia (likely induced by high phosphate diet), and the failure to observe reductions of $1,25(OH)_2D$ (whereas reduction in $1,25(OH)_2D$ is the hallmark of CKD in humans. These conflicting findings highlight the importance other factors, such as calcium, dietary phosphate intake, bone turnover, vitamin D status, which can confound establishing cause-and-effect relationships. Second, PTH does not directly stimulate FGF23 production or FGF23 promoter activity in osteoblasts *in vitro* (49), or in calvarial cultures ex vivo (73), and PTH administration has been shown to suppress FGF23 in normal mice (75). FGF23 is also not elevated in patients with primary HPT (88). Second, in studies showing a relationship between PTH and FGF23, the increase in FGF23 could be indirectly due to the effects of PTH to stimulate $1,25(OH)_2D$ (21, 29, 74). Nevertheless, the finding of PTH regulation of FGF23 suggests a modified traditional hypothesis where increased PTH levels (in response to hypocalcemia, phosphate retention or calcitriol deficiency (11)) secondarily stimulates FGF23.

Do alterations in bone remodeling/mineralization explain the variable effects of PTH on FGF23?

Another possibility is that PTH induction of high bone turnover (*osteitis fibrosa*) might lead to increased production of FGF23 in peritrabecular osteoblasts, similar to McCune-Albright syndrome (MAS), caused by activating mutations of Gαs (30, 69, 81). The pattern of FGF23 expression in bone of Col4a3 null mice resembles MAS (69) (see Preliminary studies). Excessive bone resorption in excess of bone formation, as occurs with continuous PTH administration, resulted in increased FGF23, whereas the administration of intermittent PTH that leads to a net increase in bone formation and increased bone mass resulted in reductions in FGF23(75). Targeted disruption of Kif3a in osteoblasts using OC-Cre leads to a 3-fold increase in FGF23 in association with low turnover osteopenia from disruption of the Ihh pathway (which is linked to PTHrp and PTHR1 (22)). PTH-stimulated FGF23 expression was also inhibited by disruption of Wnt-signaling with sclerostin, consistent with an indirect paracrine rather than direct regulation of FGF23 by PTH (41).

Does bone metabolism account for the variable effects of phosphate in regulating FGF23?

Serum phosphate levels positively correlate with elevations in FGF23 levels in ESRD (97), but phosphate restriction failed to lower elevated FGF23 levels in patients with CKD (26). A study in CKD patients with elevated FGF23 randomized to either sevelamer or calcium carbonate found that urinary phosphorus excretion and PTH decreased in both treatment groups, but FGF23 only decreased in the sevelamer arm, a binder known to provide an acidic load which may alter bone phosphate flux (59). A small reduction in FGF23 (84 vs 61 pg/ml) has been reported in a low phosphate vegetarian diet in CKD (55). In an adenine induced CKD rat model, sevelamer prevented the increase in PTH and FGF23, but the effects were delayed, requiring 2-weeks to achieve reductions in FGF23, whereas correction in hyperphosphatemia occurred rapidly (56). A high phosphorus diet was shown to enhance, and a low phosphorus diet to inhibit, the elevation of serum FGF23 levels in 5/6 nephrectomized rats, but this result was obtained after 4 weeks of dietary treatment (72). Phosphate effects on bone mineralization could account for the delayed effects of phosphate

on FGF23 expression, involving pathways similar to those affected by Phex, Dmp1, ENPP1 mutations (*vide supra*).

Integrated Hypothesis of FGF23 Regulation and Function in CKD (Fig 1)

A two-step hypothesis may reconcile the conflicting data regarding the respective roles of FGF23 and PTH in the pathogenesis of abnormal mineral metabolism in CKD. The first part of the hypothesis integrates current knowledge of the FGF23 -Vitamin D endocrine loop, whereas the later proposition incorporates emerging knowledge regarding the role of intrinsic bone matrix-derived factors in the regulation of FGF23. There is evidence to support that that increased FGF23 (due to impair renal phosphate clearance, reduced GFR or some other signal from kidney to bone feedback loop) is the initial adaptive response in CKD. FGF23 leads to a decrease in both 25(OH)D and $1,25(OH)_2D$ due Cyp24-mediated catabolism and the resulting reduction of $1,25(OH)_2D$ leads to secondary increments in PTH, due to impaired calcium absorption by the intestines and loss of direct effects of $1,25(OH)_2D$ on PTG and bone (i.e., a FGF23-mediated functional vitamin D deficiency). The next step involves PTH actions to restore calcium balance by stimulating bone remodeling, leading to both increased bone calcium and phosphate efflux, and by actions on the kidney to increase Cyp27b1 and reduce renal calcium excretion. PTH-mediated effects on mineralization/bone remodeling leads to local alterations in the bone matrix that further amplify FGF23 expression. The additional FGF23 facilitates the renal excretion of phosphate released from bone. In addition, FGF23, through reductions in $1,25(OH)_2D$ and soluble secreted Klotho, may have additional indirect effects on multiple other organ systems to explain the associations between elevated FGF23 and adverse cardiovascular outcomes and mortality.

Clinical Implications in CKD-MBD and Areas of Further Study

Revising the “vitamin D deficient” hypothesis of CKD-MBD pathogenesis

Contradictory and competing hypotheses and uncertainties about the cause-and-effect relationship between FGF23, PTH and $1,25(OH)_2D$ are confounding the understanding of the pathogenesis and treatment of CKD-MBD. It makes a big difference whether FGF23 is the initial event leading to increased PTH or is secondary to increments in PTH. If the two step hypothesis is correct, it may be possible to separately focus interventions on different mechanisms leading to increased FGF23 at different stages of CKD. In this conceptual framework, early CKD does not represent a true “vitamin D deficient” state; rather FGF23-mediated suppression of circulating $1,25(OH)_2D$ levels is an adaptive response, which protects against hyperphosphatemia through reduction of $1,25(OH)_2D$’s effects on gastrointestinal phosphate absorption and by increasing PTH, which acts in concert with FGF23 to stimulate phosphaturia. On the other hand, late stages of CKD and in ESRD, the dominant stimulus for FGF23 elevations may be bone remodeling, leading to treatments that alter the local factors stimulating

Novel and more rational treatments of CKD-MBD

If this hypothesis is correct, FGF23 may be an early bi-omarker for earlier interventions. In addition, treatment approaches to prevent the elevations of FGF23 may become the initial therapeutic focus, but may differ depending on the stage of CKD. Since calcitriol increases FGF23 (a vicious cycle), calcitriol sparing therapies may be warranted, such as combined low dose paracalcitol and calcimimetics, which lowers FGF23 levels in ESRD patients (98–99). Moreover, if the reductions in $1,25(OH)_2D$ is due to increased Cyp24 rather than decreased Cyp27b1, approaches to either inhibit Cyp24 selectively or block FGFR3 and 4 selectively may be devised, which correct the FGF23-mediated abnormal vitamin D metabolism without affecting the phosphaturic actions of FGF23. Increased catabolism of

25(OH)D by Cyp24 would also explain the unexpected high prevalence of low 25(OH)D levels and the relative refractoriness of patients with CKD to ergocalciferol and cholecalciferol treatment. There is an emerging paradox that treatment with active vitamin D analogues is associated with improved survival, yet vitamin D analogues also increase serum phosphate and FGF23 levels, which may contribute to accelerated calcifications and increased mortality (58). Since most patients with ESRD receive therapy with active vitamin D analogues and there have been no prospective clinical trials comparing treatment paradigms that do not use calcitriol analogues, it is not known whether the current standard of care is optimal. Knowledge that treatment with active vitamin D analogues further increases FGF23, which is independently associated with increased mortality, may result in treatment strategies that reduce FGF23, which may include normalization of bone remodeling/mineralization.

Redefining the implications of vitamin D levels below the normal range

CKD is more prevalent in elderly adults than is detected by serum creatinine. If FGF23 elevations due to CKD are contributing to the low levels of 25(OH)D in elderly patients, future translational may need to distinguish FGF23-mediated reductions from true nutritional deficiencies. This may require assessing FGF23 and/or $24,25(OH)_2D$ levels to interpret low 25(OH)D levels (e.g., true deficiency or increased catabolism secondary to increased FGF23 in subclinical CKD). This would add a new perspective to the existing uncertainties regarding the definition of vitamin D insufficiency and effects of vitamin D supplementation (70).

Summary and Conclusions

The discovery of FGF23 expression by osteoblasts/osteocytes has revealed the “endocrine functions” of bone in the regulation of phosphate and vitamin D metabolism. In addition, bone may have other endocrine functions to regulate insulin secretion and glucose metabolism that are mediated by the release of decarboxylated osteocalcin (Ocn) by bone resorption. Ocn is proposed to target receptors, such as GPRC6A, located in β-cells and peripheral tissues to regulate insulin secretion and insulin sensitivity (10, 61). Thus, the skeleton may play an important role in the integrative physiology of vitamin D, phosphate and “energy metabolism”. Assessment of the circulating levels of bone derived hormones may prove to have diagnostic utility and knowledge of the regulator factors controlling their secretion may provide new therapeutic opportunities, particular if systemic abnormalities associated with metabolic bone diseases, such as vascular calcifications and cardiovascular diseases, are mediated by these bone-derived hormones. Maintenance of normal bone remodeling and mineralization may not only be important to skeletal strength but to the bodies overall health.

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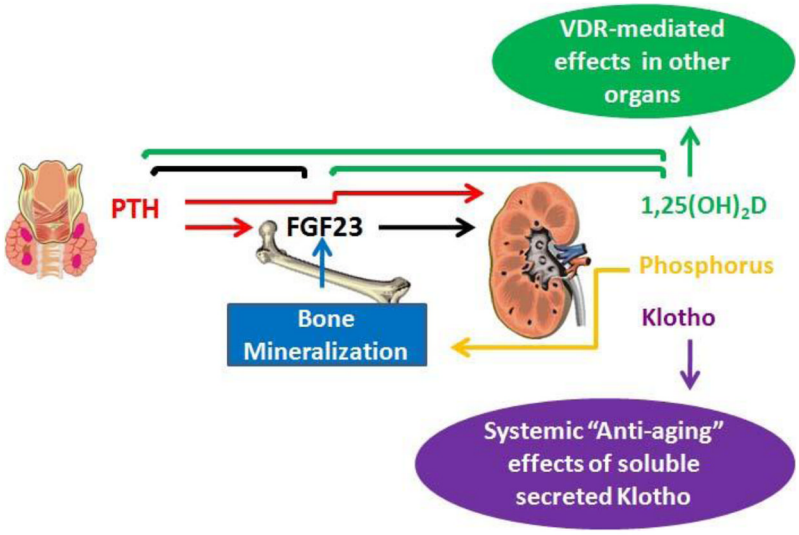

Figure 1.

Integrative physiology of FGF23. FGF23 can exert multiple direct and indirect effects on a wide range of biological functions and is involved in complex endocrine networks involving $1,25(OH)_2D$, Klotho, and PTH endocrine factors. FGF23 participates in a bone-kidney axis to regulate $1,25(OH)_2$ D production and renal phosphate handling. FGF23 is regulated by $1,25(OH)_2D$, which creates an endocrine loop between FGF23 and $1,25(OH)_2D$. In addition, FGF23 regulates gene expression of Klotho, a transmembrane co-receptor for FGF23. Klotho is secreted by ectodomain shedding and by alternatively splicing and acts as a circulating hormone that regulates ion channels and function of receptors in multiple tissues. FGF23 expression in bone is also regulated by local intrinsic bone-derived factors that link FGF23 to bone mineralization and bone turnover, thereby linking bone phosphate buffering capacity with the renal handling of phosphate. PTH also stimulates FGF23 in a context dependent fashion that is modulated by the vitamin D status, and experimental data suggest that FGF23 may also suppress PTH, although most states of FGF23 excess are associated with increased PTH levels.