FGF23 and hypophosphatemic rickets/osteomalacia

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Abstract

Purpose of review

X-linked hypophosphatemia and tumor-induced osteomalacia are diseases characterized by hypophosphatemia with impaired proximal tubular phosphate reabsorption. Complete resection of responsible tumors is the first line therapy for patients with tumor-induced osteomalacia. In contrast, phosphate and active vitamin D have been used for patients with X-linked hypophosphatemia and inoperable ones with tumor-induced osteomalacia. The purpose of this review is to summarize the pathogenesis of these diseases and discuss about the new treatment.

Recent findings

Excessive FGF23 production has been shown to underline several kinds of hypophosphatemic rickets/osteomalacia including X-linked hypophosphatemia and tumor-induced osteomalacia. Burosumab, an anti-FGF23 monoclonal antibody, was approved for clinical use while the indications of burosumab are different depending on countries.

Summary

The inhibition of excessive FGF23 activity has been approved as a new therapy for several kinds of hypophosphatemic diseases. Further studies are necessary to clarify the long-term effects and safety of burosumab.

Key words: hypophosphatemia, osteomalacia, rickets, FGF23, burosumab

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Introduction

Rickets and osteomalacia are diseases characterized by impaired mineralization of growth

plate and bone, respectively [1]. These diseases are caused by common etiologies. While there are

many causes for rickets/osteomalacia, chronic hypophosphatemia is an important one. Patients with

rickets show growth retardation and bone deformities. Bone pain and muscle weakness are main

symptoms in patients with osteomalacia. Privational rickets usually associated with vitamin D

deficiency had been a big clinical problem. Patients with vitamin D deficient rickets/osteomalacia

can be cured by native vitamin D. In contrast, the wording of vitamin D-resistant

rickets/osteomalacia has been used for diseases that cannot be cured by native vitamin D. Vitamin D-

resistant rickets/osteomalacia has sometimes been used as a synonym for X-linked

hypophosphatemia (XLH) [2]. However, there are other causes for vitamin D-resistant

rickets/osteomalacia. The studies in the past 20 years revealed that most cases with vitamin D-

resistant rickets are caused by excessive production of FGF23. In addition, a new therapy to inhibit

the excessive actions of FGF23 has recently become available for these diseases. We summarize the

new development concerning FGF23-related hypophosphatemic rickets/osteomalacia and present

our private experience for the new treatment.

Actions of FGF23

*FGF23* was identified as a causative gene for autosomal dominant hypophosphatemic

rickets (ADHR) and by homology to *Fgf15* [3, 4]. FGF23 was also identified as a causative factor

for tumor-induced osteomalacia (TIO) [5]. There results indicated that FGF23 is involved in

phosphate metabolism. Human *FGF23* gene encodes a protein with 251 amino acids. The N-

terminal 24 amino acids form a signal peptide. A part of FGF23 protein is proteolytically cleaved

between 179Arg and 180Ser before secretion [5]. This cleavage inactivates FGF23 activity as

discussed below [6].

FGF23 is produced by osteoblasts/osteocytes and binds to KLOTHO-FGF receptor 1 (FGFR1) complex in target organs [7, 8]. FGF23 suppresses the expression of type 2a and 2c sodium-phosphate cotransporters in the brush border membrane of renal proximal tubules, thus inhibits proximal tubular phosphate reabsorption [9]. In addition, FGF23 suppresses the expression of *CYP27B1* which encodes an enzyme converting 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. FGF23 also enhances the expression of *CYP24A1* whose product works to reduce 1,25(OH)$_2$D level [9]. 1,25(OH)$_2$D is a hormone that stimulates intestinal phosphate absorption. Therefore, FGF23 reduces serum phosphate by directly inhibiting proximal tubular phosphate reabsorption and indirectly suppressing intestinal phosphate absorption through lowering 1,25(OH)$_2$D (Figure).

FGF23 and hypophosphatemic rickets/osteomalacia

After the cloning of FGF23, several kinds of enzyme-linked immunosorbent assay for FGF23 were developed [10, 11]. Using these assays, FGF23 levels in patients with chronic hypophosphatemia were evaluated. FGF23 levels were shown to be suppressed in patient with chronic hypophosphatemia from vitamin D deficiency and Fanconi syndrome [12]. These results suggested that chronic hypophosphatemia or other associated metabolic changes suppresses FGF23 production. In contrast, FGF23 levels were elevated in hypophosphatemic patients with ADHR and TIO indicating that excessive or inappropriate production and secretion of FGF23 cause hypophosphatemia in these patients [10-13]. Therefore, elevated FGF23 level or FGF23 in inappropriately high normal range in patients with chronic hypophosphatemia indicates that this hypophosphatemia is caused by excessive actions of FGF23.

XLH is the most prevalent cause of genetic hypophosphatemic rickets with the incidence

of about 1 in 20,000 [14]. FGF23 levels in patients with XLH were shown to be elevated [10, 11].

XLH is caused by inactivating mutations in *phosphate-regulating gene with homologies to*

*endopeptidases on the X chromosome* (*PHEX*) [15]. *Hyp* mouse is a model of XLH and shows

hypophosphatemia with high FGF23. A deletion in the 3' region of *Phex* is present in *Hyp* mice [16].

Conditional deletion of *Phex* in osteoblasts/osteocytes using osteocalcin-Cre resulted in

hypophosphatemia, enhanced expression of *Fgf23* in bone and high FGF23 [17]. These results

indicate that inactivating mutations in *PHEX* somehow enhance FGF23 production in bone resulting

in hypophosphatemia. However, it is not understood how deficient actions of PHEX cause excessive

FGF23 production.

In addition to ADHR, TIO and XLH, several kinds of hypophosphatemic

rickets/osteomalacia have been shown to be caused by excessive actions of FGF23 [18] (Table 1).

While the responsible genes for genetic hypophosphatemic rickets have been identified, it is largely

unknown how mutations in these genes cause overproduction of FGF23. TIO is one of

paraneoplastic syndromes. The most responsible tumors of TIO are pathologically classified as

phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT) [19]. *Fibronectin*

(*FN1*)-*FGFR1* or *FN1-FGF1* fusion genes have been reported in some tumors causing TIO [20, 21].

It is proposed that FGFR1 is activated and is involved in the overproduction of FGF23 in the tumors

with these fusion genes. It is also reported that some tumors without these fusion genes express

*KLOTHO* suggesting that FGF23 can activate KLOTHO-FGFR1 complex in these tumors causing

TIO [22]. Activation of FGFR1 was shown to enhance FGF23 production by preventing the

proteolytic processing of FGF23 protein in bone suggesting the similar mechanism is working in

tumors responsible for TIO [23].

Some intravenous iron preparations such as iron polymaltose, ferric carboxymaltose and

saccharated ferric oxide cause hypophosphatemic rickets/osteomalacia with high FGF23 levels in

patients with iron deficiency anemia [24-26]. It is proposed that iron deficiency enhances both

*FGF23* transcription and the cleavage between 179Arg and 180Ser resulting in normal FGF23 and

phosphate levels [26]. Some intravenous iron preparations prevent the processing of FGF23 protein

causing high FGF23 and hypophosphatemia in patients with iron deficiency anemia. However, it is

not clearly shown how some iron preparations affect the processing of FGF23 protein.


Conventional treatment for patients with FGF23-related hypophosphatemic rickets/osteomalacia

Hypophosphatemia improves after stopping intravenous iron preparations. Patients with

XLH have been treated with phosphate salt and active vitamin D. These medications ameliorate

rickets and osteomalacia in some degree [27, 28]. Complete surgical removal of responsible tumors

is the first line treatment for patients with TIO. However, it is not always possible to find the

responsible tumors because the causative tumors are often small and present everywhere in the body.

In addition, even when the tumors are found, it is not always possible to completely remove them

because of various reasons. For inoperable patients with TIO, the same phosphate salt and active

vitamin D have been used. However, these medications can be associated with several adverse

events such as hypercalciuria, nephrolithiasis, secondary-tertiary hyperparathyroidism, diarrhea and

so on [29]. Therefore, careful monitoring of the effects and adverse events are necessary for patients

treated with these drugs. In addition, phosphate salt needs to be administered three times or more per

day because absorbed phosphate is rapidly excreted into urine. This frequently causes drug non-

compliance. While phosphate salt and active vitamin D are effective in patients with FGF23-related

hypophosphatemic rickets/osteomalacia, there also have been several limitations for these drugs.


New treatments for patients with FGF23-related hypophosphatemic rickets/osteomalacia –

Preclinical data

After the cloning of *FGF23*, several hypophosphatemic diseases have been shown to be caused by excessive actions of FGF23 as mentioned above. This led to the hypothesis that the inhibition of FGF23 activity can be new treatments for patients with FGF23-related hypophosphatemic diseases. There are several ways to inhibit FGF23 actions. FGF23 binds to KLOTHO-FGFR1 complex and activate intracellular signaling pathways including extracellular signal-regulated kinase (ERK). *In vitro* study showed that the processed C-terminal fragment of FGF23 can inhibit the actions of FGF23 probably by competing with full-length FGF23 for the binding to KLOTHO-FGFR1 complex [30]. Purified C-terminal fragment and C-tail Fc fusion protein were shown to increase serum phosphate of *Hyp* mice [30, 31]. Similarly, inhibitors of FGFR and ERK pathway were also reported to increase serum phosphate in model mice of FGF23-related hypophosphatemic diseases [32, 33]. Furthermore, anti-FGF23 antibodies also increased serum phosphate in *Hyp* mice [34]. These antibodies also enhanced renal tubular phosphate reabsorption and corrected impaired mineralization of bone [34]. Of these several methods, anti-FGF23 antibody advanced to clinical trials.

New treatments for patients with FGF23-related hypophosphatemic rickets/osteomalacia – Clinical data

Based on preclinical results of anti-FGF23 antibodies, human monoclonal anti-FGF23 antibody, burosumab, was developed. Burosumab is a IgG1 monoclonal antibody that recognizes N-terminal portion of FGF23. Subcutaneous or intravenous single administration of burosumab to 29 adult patients with XLH increased serum phosphate, tubular maximum transport of phosphate per glomerular filtration rate (TmP/GFR) and $1,25(OH)_2D$ in a dose-dependent manner in a phase 1 clinical trial [35]. Subcutaneous administration produced more prolonged increase of serum phosphate compared to that by intravenous route. Therefore, subcutaneous administration was used

in all the subsequent clinical studies. Subsequent phase 1/2 study examined effects of repeated administration of burosumab both in a dose escalation and an extension study [36]. Subcutaneous administration of burosumab every 4 weeks increased serum phosphate, TmP/GFR and $1,25(OH)_2D$ in all 28 adult patients with XLH for more than 1 year. Serum phosphate plateaued one or two weeks after the administration and then decreased. Most patients received 0.6 or 1 mg/kg burosumab in the extension study.

Phase 2 study compared the effect of every 2 weeks and every 4 weeks dosing of burosumab in 52 child patients with XLH aged 5 to 12 years [37]. The dose of burosumab was adjusted by fasting serum phosphate level 2 weeks after administration. The mean doses of burosumab at 40 weeks were 0.98 mg/kg and 1.50 mg/kg for every 2 weeks and 4 weeks groups, respectively. While burosumab increased serum phosphate, TmP/GFR and $1,25(OH)_2D$ in both groups, every 2 weeks dosing caused more stable increase of these parameters. In addition, burosumab decreased alkaline phosphatase, improved radiographic findings of rickets and increased standing-height z score in these patients. The increase of standing-height z score was more prominent in every 2 weeks group compared to that in every 4 weeks. Another phase 2 study in 13 child patients with XLH aged 1 to 4 years confirmed effects of burosumab to increase serum phosphate and $1,25(OH)_2D$, decrease alkaline phosphatase, and improve rickets [38]. Patients received 0.8 mg/kg or 1.2 mg/kg of burosumab every 2 weeks in this study.

Phase 3 study examined effects of burosumab and conventional therapy with phosphate salt and active vitamin D in 61 child patients with XLH aged 1 to 12 years [39]. All patients had been treated with conventional therapy. In a burosumab group, 0.8 mg/kg or 1.2 mg/kg dose was administered every 2 weeks. Burosumab significantly improved radiographic findings of rickets, increased serum phosphate, TmP/GFR, $1,25(OH)_2D$, and decreased alkaline phosphatase compared to conventional therapy. Burosumab also significantly increased recumbent length and standing

height z score. Another double-blind, placebo-controlled phase 3 trial examined effects of

burosumab in 134 adult patients with XLH who were symptomatic with pain [40]. Most of these

patients had been treated with conventional therapy. Burosumab group received 1 mg/kg burosumab

every 4 weeks. Burosumab increased serum phosphate, TmP/GFR and $1,25(OH)_2D$. Burosumab also

significantly reduced the Western Ontario and the McMaster Universities Osteoarthritis Index

(WOMAC) stiffness score and promoted fracture healing compared to placebo at 24 weeks. The

biochemical improvement was maintained up to 48 weeks [41]. Significant reduction of WOMAC

stiffness and physical function impairment scores, and Brief Pain Inventory (BPI) worst pain were

observed at 48 weeks. Burosumab also significantly improved total distance walked in 6 minutes at

48 weeks. In another phase 3 trial, paired bone biopsy was conducted in 11 adult patients with XLH

who had not been treated for at least 2 years both before and after burosumab therapy of 1 mg/kg

every 4 weeks [42]. At 48 weeks, burosumab was shown to improve histomorphometric measures of

osteomalacia.

Effects of burosumab were also examined in two single arm phase 2 trials in patients with

TIO and cutaneous skeletal hypophosphatemia syndrome [43, 44]. In both studies, the initial dose of

burosumab was 0.3 mg/kg and then the dose was adjusted according to phosphate level. The mean

stable dose was around 1.0 mg/kg every 4 weeks. Burosumab increased serum phosphate, TmP/GFR

and $1,25(OH)_2D$, and decreased alkaline phosphatase in both studies. Burosumab also promoted

healing of fractures/pseudofractures and decreased osteoid thickness and mineralization lag time.

Safety issues have been investigated in the clinical trials mentioned above. While many

adverse events such as injection site reaction, nasopharyngitis, arthralgia, and eczema were reported,

burosumab was generally well tolerated. No treatment-emergent adverse event of grade 3 or more

has been reported in these studies except for one case of restless leg syndrome [36].

Future direction

Burosumab has been approved for patients with XLH, TIO and other FGF23-related hypophosphatemic diseases depending on countries. For example, burosumab is approved for patients with radiographic evidence of bone disease in children 1 year of age and older, and adolescent and adult XLH patients in Europe. Burosumab is used for adult and pediatric XLH patients 6 months of age and older, and TIO patients whose tumors cannot be resected or localized in adult and pediatric patients 2 years of age and older. In Japan, burosumab is approved for all patients with FGF23-related hypophosphatemic rickets/osteomalacia. In addition, the effects of burosumab in hypophosphatemic patients induced by intravenous iron and fibrous dysplasia were reported [45, 46]. While burosumab is theoretically considered to be effective in other FGF23-related hypophosphatemic diseases such as ADHR and autosomal recessive hypophosphatemic rickets, the efficacy has not been reported in these patients. In addition, adult patients with XLH can have several clinical problems such as enthesopathy, ossification of paraspinal ligaments, dental abscess and hearing impairment. It is not known whether burosumab affect the development of these problems. Furthermore, while burosumab was shown to increase height compared to conventional therapy, it is not evident whether burosumab can normalize height of patients with XLH. Long-term safety of burosumab also needs to be assessed. Further studies are necessary to clarify these issues.

Conclusion

FGF23 is a hormone produced by bone and lowers serum phosphate level. Excessive actions of FGF23 underlie several hypophosphatemic diseases such as XLH and TIO. Burosumab is a promising new drug for patients with FGF23-related hypophosphatemic diseases.

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Figure. Actions of FGF23.

FGF23 is physiologically produced by osteoblasts/osteocytes and binds to Klotho/FGF receptor 1(FGFR1) complex. FGF23 suppresses the expression of type 2a and 2c sodium-phosphate cotransporters in the brush border membrane of renal proximal tubule. In addition, FGF23 suppresses the expression of *CYP27B1* which encodes an enzyme converting 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. FGF23 also enhances the expression of *CYP24A1* whose product works to reduce 1,25$(OH)_2$D level. FGF23 reduces serum phosphate by directly inhibiting proximal tubular phosphate reabsorption and indirectly suppressing intestinal phosphate absorption through lowering 1,25$(OH)_2$D.

Table 1. FGF23-related hypophosphatemic rickets/osteomalacia

X-linked hypophosphatemia (OMIM #307800)

Autosomal dominant hypophosphatemic rickets (OMIM #193100)

Autosomal recessive hypophosphatemi2 rickets 1 (OMIM #241520)

Autosomal recessive hypophosphatemic rickets 2 (OMIM #613312)

Hypophosphatemic rickets with dental anomalies and ectopic calcification (OMIM #259775)

McCune-Albright syndrome/Fibrous dysplasia of bone (OMIM #174800)

Jansen-type metaphyseal chondrodysplasia (OMIM #156400)

Osteoglophonic dysplasia (OMIM #166250)

Neurofibromatosis, type I (OMIM #613113)

Cutaneous-skeletal hypophosphatemia syndrome (OMIM #163200)

Tumor-induced osteomalacia

Intravenous iron preparations for patients with iron-deficiency anemia

Biliary atresia