REVIEW

FGF23-related hypophosphatemic rickets/ osteomalacia: diagnosis and new treatment

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Abstract

FGF23 is a phosphaturic hormone produced by bone. FGF23 reduces serum phosphate by suppressing proximal tubular phosphate reabsorption and intestinal phosphate absorption. After the identification of FGF23, several kinds of hypophosphatemic rickets/osteomalacia such as X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO) have been shown to be caused by excessive actions of FGF23. Circulatory FGF23 is high in patients with these hypophosphatemic diseases while FGF23 is rather low in those with chronic hypophosphatemia from other causes such as vitamin D deficiency. These results indicate that FGF23 measurement is useful for the differential diagnosis of hypophosphatemia. Chemiluminescent enzyme immunoassay for FGF23 has been approved for clinical use in Japan. The first choice treatment for patients with TIO is complete removal of responsible tumors. However, it is not always possible to find and completely remove responsible tumors. Phosphate and active vitamin D have been used for patients with hypophosphatemic diseases caused by excessive actions of FGF23 including TIO patients with unresectable tumors. However, these medications have limited effects and several adverse events. The inhibition of excessive FGF23 actions has been considered to be a novel therapy for these hypophosphatemic diseases. Human MAB for FGF23, burosumab, has been shown to improve biochemical abnormalities, roentgenological signs of rickets, growth, fracture healing and impaired mineralization in patients with XLH. Burosumab has been approved in several countries including Europe, North America and Japan. Long-term effects of burosumab need to be addressed in future studies.

Key Words

- ▶ antibody
- ▶ FGF receptor
- ▶ Klotho
- ▶ mineralization
- ▶ phosphate

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Introduction

FGF23 was cloned as a responsible gene for autosomal dominant hypophosphatemic rickets (ADHR) (ADHR Consortium 2000). FGF23 was also identified as a responsible humoral factor for tumor-induced osteomalacia (TIO), a rare paraneoplastic syndrome characterized by hypophosphatemia (Shimada *et al.* 2001). Since then it has been shown that FGF23 works as a hormone regulating phosphate and

vitamin D metabolism. In addition, several other kinds of hypophosphatemic rickets/osteomalacia have been shown to be caused by excessive actions of FGF23 (Fukumoto & Martin 2009). Recently, a new treatment for these hypophosphatemic diseases has become available in several countries. I will summarize recent findings concerning FGF23-related hypophosphatemic diseases.

Function of FGF23

After the cloning of *FGF23*, the function of FGF23 was examined using recombinant FGF23. Results indicated that FGF23 suppresses the expression of type 2a and 2c sodium-phosphate cotransporters in the brush border membrane of renal proximal tubules and inhibits proximal tubular phosphate reabsorption (Shimada *et al.* 2004). About 80–90% of phosphate filtered from glomeruli is reabsorbed in proximal tubules through these sodium-phosphate cotransporters. In addition, FGF23 suppresses the expression of *CYP27B1* which encodes an enzyme that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$) (Shimada *et al.* 2004). FGF23 also enhances *CYP24A1* expression coding, an enzyme that works to reduce circulatory level of $1,25(\text{OH})_2\text{D}$ (Shimada *et al.* 2004). From these changes of the expression of vitamin D-metabolizing enzymes, FGF23 reduces serum $1,25(\text{OH})_2\text{D}$ level. $1,25(\text{OH})_2\text{D}$ enhances the expression of type 2b sodium-phosphate cotransporter in the brush border membrane of intestinal cells and stimulates intestinal phosphate absorption (Xu *et al.* 2002). Therefore, FGF23 reduces serum phosphate level by inhibiting both proximal tubular phosphate reabsorption and intestinal phosphate absorption through reducing $1,25(\text{OH})_2\text{D}$ level (Fig. 1).

Physiological sources of FGF23 are believed to be bone, osteoblasts and osteocytes (Liu *et al.* 2003). On the other hand, FGF23 works in kidney indicating that there is a specific receptor for FGF23 in kidney. FGF23 belongs to FGF family. There are 22 FGF family members in mouse and human. Human *FGF19* is an ortholog of murine *Fgf15*. FGF family members have been shown to bind to FGF receptors (FGFRs). There are four *FGFR* genes and alternative splicing form genes producing many FGFR subtypes (Itoh & Ornitz 2004). However, the expression of these FGFR subtypes is basically tissue non-specific. Investigation of binding proteins to FGF23 in kidney identified Klotho (Urakawa *et al.* 2006). Subsequent studies indicated that FGF23 binds to Klotho-FGFR1 complex for its action (Kurosaki *et al.* 2006, Urakawa *et al.* 2006) (Fig. 1).

FGF23 activates several signal transduction pathways in the downstream of FGFR1 including extracellular signal-regulated kinase (ERK), AKT and phospholipase C γ (Goetz & Mohammadi 2013). It is likely that the renal actions of FGF23 are mainly mediated by ERK pathway (Zhang *et al.* 2012) (Fig. 1).

Posttranslational modification of FGF23

FGF23 encodes a protein with 251 amino acids (Shimada *et al.* 2001). The N-terminal 24 amino acids compose a

Figure 1

Actions of FGF23. FGF23 is produced by osteoblasts/osteocytes. FGF23 binds to Klotho/FGF receptor 1 complex and activates several intracellular signaling pathways including extracellular signal-regulated kinase (ERK). FGF23 suppresses proximal tubular phosphate reabsorption by reducing expression levels of type 2a and 2c sodium-phosphate cotransporters. FGF23 also decreases $1,25(\text{OH})_2\text{D}$ by modifying the expression of vitamin D-metabolizing enzyme. From these effects, FGF23 reduces serum phosphate.

signal peptide. A part of FGF23 protein is proteolytically cleaved between 179Arg and 180Ser before secretion (Shimada *et al.* 2001). This processing is mediated by enzymes that recognize R-X-X-R motif of FGF23 protein. While full length FGF23 has biological activities as shown above, the processed N-terminal and C-terminal fragments are inactive (Shimada *et al.* 2002) (Fig. 2). Posttranslational modification of FGF23 has been reported to affect this processing of FGF23. The attachment of mucin-type O-linked glycan to 178Thr prevents the processing between 179Arg and 180Ser (Kato *et al.* 2006, Frishberg *et al.* 2007). This glycation is initiated by an enzyme called polypeptide N-acetylgalactosaminyltransferase 3 encoded by *GALNT3*. On the other hand, phosphorylation of 180Ser by family with sequence similarity 20, member C (FAM20C) works to enhance the processing of FGF23 protein (Tagliabracci *et al.* 2014). Therefore, FGF23 concentration and activities can be regulated not only by *FGF23* transcription and translation but also by the posttranslational modification of FGF23 protein.

Regulation of FGF23 production

The regulatory mechanisms of FGF23 production and serum FGF23 level have not been completely understood. Because FGF23 regulates serum phosphate level, it seemed likely that changes in serum phosphate affect FGF23 production and FGF23 level. While high phosphate diet

Figure 2

Splicing of FGF23. FGF23 gene produces a peptide with 251 amino acids. After the cleavage of signal peptide with 24 amino acids, full-length FGF23 is secreted into circulation. A part of FGF23 protein is cleaved into inactive fragments by enzymes that recognize R-X-X-R motif.

increased FGF23 levels in both mouse and human (Ferrari *et al.* 2005, Perwad *et al.* 2005, Antonucci *et al.* 2006), i.v. infusion of phosphate and subsequent increase of serum phosphate for several hours did not change FGF23 concentration in healthy volunteers (Ito *et al.* 2007). In the regulation of serum calcium level, the increase of serum calcium inhibits PTH secretion within several minutes through calcium-sensing receptor on the surface of parathyroid cells (Brown *et al.* 1993). However, there seems to be no such rapid regulation of FGF23 level in the regulation of serum phosphate (Takashi *et al.* 2019). Recent study revealed the importance of posttranslational modification of FGF23 protein in response to phosphate. High phosphate diet for 2 weeks increased serum phosphate and FGF23 in mice as expected. However, the expression of *Fgf23* in femur did not change by this diet. On the other hand, high phosphate diet increased the expression of *Galnt3* in bone suggesting that high phosphate diet increased serum FGF23 by preventing the proteolytic processing of FGF23 protein. Further *in vivo* and *in vitro* analysis showed that phosphate enhances *Galnt3* expression through FGFR1–FGF receptor substrate 2a–ERK pathway (Takashi *et al.* 2019). These results indicate that FGFR1 works at least as one component of phosphate-sensing mechanism in the regulation of FGF23 level in response to phosphate.

In addition to phosphate, 1,25(OH)₂D and PTH have been reported to enhance FGF23 production (Saito *et al.* 2005, Rhee *et al.* 2011). FGF23 reduces 1,25(OH)₂D level as mentioned previously and was reported to inhibit PTH synthesis and secretion (Ben-Dov *et al.* 2007).

These results indicate that there are multiple negative feedback loops involving FGF23, phosphate, 1,25(OH)₂D and PTH regulating phosphate metabolism.

On the other hand, FGF23 production has been shown to be affected by several other factors. Inflammatory cytokines such as tumor necrosis factor- α and interleukin-1 β , iron deficiency and erythropoietin have been shown to enhance FGF23 production (Farrow *et al.* 2011, Ito *et al.* 2015, Daryadel *et al.* 2018). These factors are considered to be potential mediators for high FGF23 in patients with chronic kidney disease. In addition, a recent study identified lysophosphatidic acid as an inducer of FGF23 production in acute kidney injury (Simic *et al.* 2020). Furthermore, studies using genetically modified murine models indicated the involvement of membrane Klotho and some G protein-coupled receptor coupled with extra large as in the enhanced FGF23 production (He *et al.* 2019, Xiao *et al.* 2019). It has been also reported that insulin and energy deprivation reduce FGF23 production (Bar *et al.* 2018, Vidal *et al.* 2020). These factors activate quite different intracellular signaling pathways including JAK-STAT, hypoxia inducible factor 1 α , ERK, phosphatidylinositol-3 kinase, and AMP-activated protein kinase. It is currently unknown how these different factors are involved in the physiological regulation of FGF23 production for the maintenance of phosphate and vitamin D metabolism.

FGF23-related hypophosphatemic rickets/osteomalacia

After the identification of FGF23, several kinds of hypophosphatemic rickets/osteomalacia other than ADHR and TIO have been shown to be caused by excessive actions of FGF23 (Table 1). Of these, X-linked hypophosphatemic rickets (XLHR) in children is by far the most prevalent cause of genetic hypophosphatemic rickets (Fukumoto & Martin 2009). The responsible gene for X-linked hypophosphatemia (XLH) in adults and children XLHR has been cloned by positional cloning and named *PHEX* (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) (The HYP Consortium 1995). *PHEX* is a type 2 membrane protein with a short N-terminal intracellular region. *PHEX* is mainly expressed in bone and teeth (Beck *et al.* 1997). *Hyp* mouse is a murine model of XLH and has a deletion in the 3' region of *Phex* gene (Beck *et al.* 1997). FGF23 was shown to be overexpressed in bone of *Hyp* mice while the detailed mechanism of this FGF23 overexpression is not clear (Liu *et al.* 2003). Similarly, in other genetic

Table 1 Examples of FGF23-related hypophosphatemic diseases.

Disease	Responsible gene
X-linked hypophosphatemic rickets (XLHR)	<i>Phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX)</i>
X-linked hypophosphatemia (XLH)	
Autosomal dominant hypophosphatemic rickets (ADHR)	<i>Fibroblast growth factor 23 (FGF23)</i>
Autosomal recessive hypophosphatemic rickets 1 (ARHR1)	<i>Dentin matrix protein 1 (DMP1)</i>
Autosomal recessive hypophosphatemic rickets 2 (ARHR2)	<i>Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)</i>
Hypophosphatemic rickets with dental anomalies and ectopic calcification	<i>Family with sequence similarity 20, member C (FAM20C)</i>
McCune-Albright syndrome/Fibrous dysplasia of bone	<i>Guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1 (GNAS1)</i>
Jansen-type metaphyseal chondrodysplasia	<i>Parathyroid hormone 1 receptor (PTH1R)</i>
Cutaneous-skeletal hypophosphatemia syndrome	<i>HRAS, KRAS, NRAS</i>
Tumor-induced osteomalacia (TIO)	<i>Fibronectin 1(FN1)-FGF receptor 1(FGFR1) fusion gene, FN1-FGF1 fusion gene*</i>
Some i.v. iron preparations	

*These fusion genes have been reported in some tumors causing TIO. These fusion genes may be involved in the overproduction of FGF23 in these tumors.

hypophosphatemic rickets such as autosomal recessive hypophosphatemic rickets 1 and 2 (ARHR 1, 2) (Feng *et al.* 2006, Lorenz-Depiereux *et al.* 2006, 2010, Levy-Litan *et al.* 2010), FGF23 is considered to be overexpressed in bone. However, it is largely unknown how the mutations in the responsible genes cause enhanced expression of FGF23.

Mutations in patients with ADHR change either 176Arg or 179Arg of FGF23 to other amino acids (ADHR Consortium 2000). These changes make the mutant protein resistant for the processing between 179Arg and 180Ser (White *et al.* 2001, Shimada *et al.* 2002). This resistance to the processing seems to contribute to increase serum FGF23 level. However, this resistance to the cleavage alone cannot explain high FGF23 and hypophosphatemia in patients with ADHR. FGF23 production is regulated by several factors as mentioned previously. Therefore, the physiological regulatory mechanism of FGF23 production should prevent the overproduction of FGF23 even when the patients have one mutant allele of *FGF23*. In patients with ADHR, other environmental factors seem to be necessary for the development of hypophosphatemia. Actually, it is known that the biochemical abnormalities and disease phenotype wax and wane in patients with ADHR (Imel *et al.* 2007). Especially, iron deficiency is considered to be one of these factors (Imel *et al.* 2011). Iron deficiency enhances both *FGF23* transcription and the cleavage between 179Arg and 180Ser resulting in normal FGF23 and phosphate level in subjects without mutations in *FGF23* (Wolf *et al.* 2013). However, in patients with ADHR, FGF23 increases because of the resistance of the mutant FGF23 protein for the processing. Theoretically, other non-physiological environmental factors that

enhance *FGF23* transcription can induce high FGF23 and hypophosphatemia in patients with ADHR.

TIO is a rare paraneoplastic syndrome. The most frequent causes are bone and soft tissue tumors whose pathological diagnosis is phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT) (Folpe *et al.* 2004). These tumors overproduce FGF23. However, the mechanism of this overproduction of FGF23 is not clear. Some tumors causing TIO have been shown to have *fibronectin (FN)-FGFR1* or *FN-FGF1* fusion gene (Lee *et al.* 2015, 2016). In addition, Klotho was shown to be expressed in some tumors causing TIO (Kinoshita *et al.* 2019, Lee *et al.* 2020). It is possible that these fusion genes and signals from Klotho/FGFR1 complex are involved in the overproduction of FGF23. Some i.v. iron preparations have also been reported to cause FGF23-related hypophosphatemic diseases (Schouten *et al.* 2009a,b, Shimizu *et al.* 2009). It is proposed that i.v. iron administration prevents the processing of FGF23 protein in patients with iron deficiency anemia in whom iron deficiency has already enhanced *FGF23* transcription and the processing (Wolf *et al.* 2013).

Diagnosis of FGF23-related hypophosphatemic diseases

The characteristic biochemical features of patients with FGF23-related hypophosphatemic diseases are chronic hypophosphatemia, low tubular maxim transport of phosphate per glomerular filtration rate (TmP/GFR), low to low normal 1,25(OH)₂D and high or high normal FGF23 levels. After the cloning of FGF23, several kinds of ELISA for FGF23 have been developed (Yamazaki

et al. 2002, Jonsson *et al.* 2003). The intact assay uses two monoclonal antibodies that detect N-terminal and C-terminal portion of the processing site of FGF23 (Fig. 3). This assay measures only biologically active FGF23 (Yamazaki *et al.* 2002). On the other hand, the C-terminal assay uses two kinds of antibodies against the C-terminal portion (Fig. 3). This assay detects both the intact and the processed C-terminal fragment of FGF23 (Jonsson *et al.* 2003). FGF23 level measured by C-terminal assay is considered to reflect the amount of FGF23 transcription or translation. FGF23 values by the intact and C-terminal assays usually correlate well (Ito *et al.* 2005). Both intact and C-terminal assay may be useful in clinical medicine. However, these values can be quite discrepant when the processing of FGF23 protein is accelerated (Fukumoto & Martin 2009). As shown below, intact assay has been approved for clinical use in Japan.

In contrast to patients with FGF23-related hypophosphatemic diseases, intact FGF23 levels were shown to be low in patients with chronic hypophosphatemia from other causes (Endo *et al.* 2008). In addition, FGF23 rapidly decreases after complete removal of responsible tumors in patients with TIO with a half-life of about 20–60 min and becomes undetectable in some patients (Takeuchi *et al.* 2004, Khosravi *et al.* 2007, Fukumoto 2014, Hana *et al.* 2017). These results indicate that chronic hypophosphatemia and/or other associated metabolic changes suppress FGF23 production. Therefore, FGF23 levels seem to be useful for the diagnosis of FGF23-related hypophosphatemic diseases. We are proposing that intact FGF23 levels of more than 30 pg/mL by Kainos assay in patients with chronic hypophosphatemia indicate the presence of FGF23-related hypophosphatemic diseases (Endo *et al.* 2008). An automated chemiluminescent enzyme immunoassay (CLEIA) for full-length FGF23 has been approved in 2019 and is now covered by public health insurance in Japan for the diagnosis and follow-up of patients with FGF23-related hypophosphatemic diseases (Shimizu *et al.* 2012). FGF23 measurement for hypophosphatemic patients is not clinically approved in other countries.

Vitamin D deficiency is an important cause for rickets/osteomalacia. Both patients with vitamin D deficient rickets and XLHR can present hypophosphatemia and high or slightly elevated PTH. While measurement of 25-hydroxyvitamin D [25(OH)D] has a pivotal role in the diagnosis of vitamin D deficient rickets, there was a considerable overlap of 25(OH)D levels in patients with vitamin D deficient rickets and XLHR (Kubota *et al.* 2014). In addition, there are also overlaps in serum calcium and

Figure 3

Schematic basis of intact and C-terminal assays of FGF23. Intact assay uses two kinds of antibodies for the N-terminal and C-terminal portions of the processing site of FGF23. On the other hand, C-terminal assay uses antibodies against the C-terminal portion of FGF23. Intact assay detects only full-length FGF23 while C-terminal assay measures both full-length and the processed C-terminal fragment of FGF23. The figure does not indicate the precise positions of the epitopes.

PTH in these two diseases (Kubota *et al.* 2014). On the other hand, FGF23 levels completely discriminated these two diseases (Kubota *et al.* 2014).

Treatment of FGF23-related hypophosphatemic diseases

The first choice for the treatment of patients with TIO is complete removal of responsible tumors. This can correct all the biochemical abnormalities and cure osteomalacia. However, the responsible tumors for TIO can be present anywhere in the body and are often difficult to detect. In addition, even if the tumors can be found, they may not be always resectable because of the localization of the tumors or health problems of the patients. For patients with FGF23-related hypophosphatemic diseases including TIO patients with unresectable tumors, phosphate and active vitamin D have been administered (Carpenter *et al.* 2011). These medications have shown to improve impaired mineralization of both children and adult patients with XLH and ameliorate symptoms of patients with TIO (Glorieux *et al.* 1980, Sullivan *et al.* 1992). However, the height of the treated XLHR patients with these medications is shorter than that of healthy control (Zivicnjak *et al.* 2011). In addition, these medications can induce several adverse events such as secondary–tertiary hyperparathyroidism, hypercalciuria, nephrocalcinosis, nephrolithiasis, diarrhea and so on (Carpenter *et al.* 2011).

Table 2 Region/country and indications of burosumab approval as of July 2020.

Region/country	Indications
European Union	X-linked hypophosphatemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeleton
United States of America	X-linked hypophosphatemia in adult and pediatric patients 6 months of age and older FGF23-related hypophosphatemia in tumor induced osteomalacia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older
Canada	X-linked hypophosphatemia in adult and pediatric patients 6 months of age and older
United Arab Emirates	X-linked hypophosphatemia in adult and pediatric patients 1 year of age and older
Brazil	X-linked hypophosphatemia in adult and pediatric patients 1 year of age and older
Japan	FGF23-related hypophosphatemic rickets/osteomalacia
Switzerland	X-linked hypophosphatemia in adult and pediatric patients 1 year of age and older
Israel	X-linked hypophosphatemia in adult and pediatric patients 1 year of age and older
Oman	X-linked hypophosphatemia in adult and pediatric patients 1 year of age and older
Bahrain	X-linked hypophosphatemia in adult and pediatric patients 1 year of age and older

Furthermore, phosphate needs to be administered several times per day frequently which causes a compliance problem. For these reasons, better treatment for these diseases has been wanted (Carpenter *et al.* 2011).

Because excessive actions of FGF23 are causing FGF23-related hypophosphatemic diseases such as XLH and TIO, the inhibition of FGF23 activities was considered to be a new candidate for the treatment of these diseases. FGF23 binds to Klotho/FGFR1 complex and activates intracellular signaling pathways including ERK. Therefore, the inhibition of FGF23 for the binding to Klotho/FGFR1 complex and inhibitors of FGFR or ERK pathway have been shown to suppress FGF23 actions and ameliorate hypophosphatemia in *Hyp* mice (Goetz *et al.* 2010, Zhang *et al.* 2012, Wöhrle *et al.* 2013). In addition, antibodies to FGF23 were shown to improve hypophosphatemia, rickets and impaired mineralization of bone and increase grip power in *Hyp* mice (Aono *et al.* 2009, 2011). Based on these preclinical results, human MAB to FGF23, burosumab, has been developed as a new therapeutic agent for FGF23-related hypophosphatemic diseases.

In a phase 1 clinical trial, single injection or infusion of burosumab increased serum phosphate and $1,25(\text{OH})_2\text{D}$ in a dose-dependent manner in 38 adult patients with XLH (Carpenter *et al.* 2014). Subsequent phase 1/2 study indicated that s.c. injections of burosumab every 4 weeks induced prolonged increase in serum phosphate and $1,25(\text{OH})_2\text{D}$ for more than 1 year in adult patients with XLH (Imel *et al.* 2015). Safety profiles were favorable and the most common drug-related adverse event was the injection site reaction. Phase 2 study in children with XLHR indicated that burosumab increased serum phosphate and $1,25(\text{OH})_2\text{D}$ and induced radiographic improvement of rickets (Carpenter *et al.* 2018). This study

showed that every 2 weeks injections were more effective than every 4 weeks dosings in child patients (Carpenter *et al.* 2018). Phase 3 study in child patients indicated that burosumab was more effective than conventional therapy with phosphate and active vitamin D in increasing serum phosphate, TmP/GFR and $1,25(\text{OH})_2\text{D}$, decreasing alkaline phosphatase, improving radiographic findings of rickets, and increasing recumbent length and standing height Z score (Imel *et al.* 2019). Phase 3 trial in adult patients with XLH indicated that burosumab improved bone mineralization, WOMAC physical function and stiffness scores, and induced fracture healing more effectively than placebo (Insogna *et al.* 2018, 2019). Burosumab was also shown to increase serum phosphate and $1,25(\text{OH})_2\text{D}$ and improve osteomalacia in patients with TIO (<https://ir.ultragenyx.com/news-releases/news-release-details/ultragenyx-and-kyowa-kirin-announce-us-fda-approval-crysvitar>). From these results, burosumab was approved for patients with XLH or XLHR since 2018 in several countries including Europe and USA. The approval of burosumab is now expanding to other countries in Asia, South America and Middle East (Table 2). The indication of burosumab is different depending on countries. In addition to XLH or XLHR, burosumab is approved for patients with TIO in several countries and for patients with FGF23-related hypophosphatemic diseases in Japan.

However, it is not currently known whether burosumab can normalize height of patients with XLHR. It is not clear either whether burosumab affects other associated conditions such as enthesopathy, dental problems and hearing disturbance in patients with XLH. Long-term safety of burosumab on several parameters such as renal function and ectopic calcification needs to be established in the future studies.

Conclusion

The cloning of *FGF23* indicated that bone works as an endocrine organ. In addition, several kinds of hypophosphatemic rickets/osteomalacia previously classified as metabolic bone diseases are now considered to be caused by overproduction of FGF23. FGF23 measurement is useful for the diagnosis of FGF23-related hypophosphatemic diseases. While long-term effects of burosumab need to be addressed in future studies and the assay for FGF23 is not clinically available in most countries, it is desirable that such progress results in more efficient management of patients with hypophosphatemic diseases.

Declaration of interest

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