Bone Reports 18 (2023) 101659

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Clinical performance of a new intact FGF23 immunoassay in healthy individuals and patients with chronic hypophosphatemia

Hajime Kato [a,b], Hiromi Miyazaki [c], Takehide Kimura [c], Yoshitomo Hoshino [a,b], Naoko Hidaka [a,b], Minae Koga [a,b], Masaomi Nangaku [a], Noriko Makita [a,b], Nobuaki Ito [a,b,*]

[a] Division of Nephrology and Endocrinology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[b] Osteoporosis Center, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[c] Minaris Medical Co., Ltd., 600-1, Minami-ishiki, Nagaizumi-cho, Sunto-gun, Shizuoka 411-0932, Japan

ARTICLE INFO

Keywords:
Fibroblast growth factor 23
Immunoassay
Hypophosphatemia
X-linked hypophosphatemic rickets/osteomalacia
Tumor-induced osteomalacia

ABSTRACT

While the positive association between automated intact fibroblast growth factor (FGF) 23 measurement kit (Determinar CL FGF23 [CL]) and the former assay (Kainos [KI]), and clinical utility of CL was well established, the clinical performance of Medfrontier FGF23 (MED), which was the manual intact FGF23 measurement kit with same antibody set as CL, has not yet been validated. Therefore, this study aims to compare MED FGF23 levels to KI FGF23 levels. A total of 380 samples were collected from healthy individuals, and 200 samples were collected from 20 patients with chronic hypophosphatemia. The intact FGF23 level of each sample was measured by KI and MED. Among the healthy individuals, the reference range of MED FGF23 levels was 18.6–59.8 pg/mL when calculated as the average ± 2 standard deviations. When compared with KI FGF23 levels, MED FGF23 levels were lower than KI levels both among samples from healthy individuals (KI FGF23, 40.9 [interquartile (IQR), 31.1–50.6]; MED FGF23, 38.0 [IQR, 31.5–45.7]; p value = 0.02) and among samples from patients with chronic hypophosphatemia (KI FGF23, 172.5 [IQR, 115.8–290.7]; MED FGF23, 130.2 [IQR, 93.6–247.0]; p value = 0.003). The linear regression analysis showed that the correlation between KI FGF23 and MED FGF23 was interpreted as a slope of 0.83 with a y-intercept of 0.53, revealing good linearity (R^2 = 0.99). This study showed that the discrepancy between KI and MED was very similar to the previously reported data between KI and CL.

1. Introduction

Fibroblast growth factor (FGF) 23 is secreted by mature osteocytes and is one of the major regulators of serum phosphate levels. FGF23 consists of 251 amino acids constituting a 32 kDa protein with N-terminal homology to other FGFs (Yamashita et al., 2000). Before secretion, FGF23 is susceptible to proteolysis by the subtilisin-like proprotein convertase FURIN. Proteolysis of FGF23 results in inactivated forms of C-terminal and N-terminal FGF23, while intact FGF23 has biological functions (Shimada et al., 2002; Tagliabracci et al., 2014). In the proximal tubule, FGF23 suppresses the expression of the sodium-phosphate cotransporter, which results in decreased phosphate absorption in the kidney. Additionally, FGF23 has a suppressive effect on the expression of 1α-hydroxylase and increases the expression of 24-hydroxylase in the proximal tubule, which results in low levels of 1,25-dihydroxy vitamin D ($1,25OH_2D$) (Shimada et al., 2004). Synergistically, oversecretion of FGF23 decreased serum phosphate levels, leading to the development of chronic hypophosphatemic rickets/osteomalacia.

The most prevalent inherited form of FGF23-related hypophosphatemic rickets/osteomalacia (FGF23rHR) is X-linked hypophosphatemic rickets (XLH), and there are autosomal dominant and recessive forms of FGF23rHR (Carpenter et al., 2011; Kinoshita and Fukumoto, 2018). Raine syndrome, osteoglophonic dysplasia, Jansen syndrome, parts of neurofibromatosis 1, biliary atresia, McCune-Albright syndrome, and epidermal nevus syndrome were also reported to cause FGF23rHR (Kinoshita et al., 2014; Kinoshita and Fukumoto, 2018; Sahoo et al., 2019). Tumor-induced osteomalacia (TIO) is the one of the differential diagnoses for acquired forms of FGF23rHR. Some injection forms of iron preparation were reported to develop FGF23rHR (David et al., 2016; Schouten et al., 2009; Shimizu et al., 2009). Recently, alcohol-induced FGF23rHR was introduced from our laboratory and is supposed to occur rarely in a particular population (Hidaka

* Corresponding author at: Division of Nephrology and Endocrinology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail address: nobitotky@gmail.com (N. Ito).

https://doi.org/10.1016/j.bonr.2023.101659
Received 23 October 2022; Received in revised form 30 January 2023; Accepted 1 February 2023
Available online 2 February 2023

et al., 2021). FGF23rHR can be treated with more radical or effective methods, such as resection of FGF23-producing tumors, cessation of the drug or alcohol, and anti-FGF23 antibody burosumab, than the traditional therapy for hypophosphatamic rickets/osteomalacia with active vitamin D and phosphate preparation (Briot et al., 2021; Imanishi et al., 2021; Insogna et al., 2019; Insogna et al., 2018; Jan de Beur et al., 2021; Portale et al., 2019). Thus, the differential diagnosis between FGF23rHR and other chronic hypophosphatemic rickets/osteomalacia, including Fanconi syndrome and vitamin D deficient or dependent rickets/osteomalacia, by measuring blood intact FGF23 levels is of clinical importance and incorporated into the guidelines in some countries, including Japan and Belgium (Fukumoto et al., 2015; Laurent et al., 2021). Measurement of blood intact FGF23 is also beneficial to precisely diagnose the etiology of familial tumoral calcinosis with massive ectopic calcifications around large joints, the majority of which are caused by chronic hyperphosphatemia due to the decreased action of FGF23, although the prevalence of this condition with an autosomal recessive form is extremely rare (Ito and Fukumoto, 2021).

There are two types of FGF23 measurement kits. The former is an N-terminal or C-terminal FGF23 assay kit setting the epitopes on the same sides to the physiological cleavage point, measuring the N-terminal or C-terminal fragment in addition to full-length FGF23. The latter is a full-length FGF23 assay with the epitopes on the opposite sides to the breaking point, which only measures full-length FGF23. As mentioned above, N-terminal and C-terminal fragments are inactive forms; therefore, the N-terminal and C-terminal FGF23 assay kits reflect the transcriptional state of *FGF23* mRNA, which is subject not only to serum phosphate levels but also to inflammation, iron status, parathyroid hormone, and the use of erythropoiesis stimulating agents (David et al., 2016; Farrow et al., 2011; Flamme et al., 2017; Hanudel et al., 2019; Imel et al., 2011; Ito et al., 2021a, 2015). In contrast, the measurements by the full-length FGF23 assay are supposed to genuinely reflect the activity of FGF23, rendering it the most ideal tool for the differential diagnosis of chronic hypophosphatemic rickets/osteomalacia.

To date, several full-length FGF23 measurement kits have been introduced by reagent companies worldwide, including Human FGF-23 (Intact) ELISA (Quidel, San Diego, CA, USA) and LIAISON FGF23 TEST (DiaSorin, Saluggia, Italy) (Jonsson et al., 2003; Souberbielle et al., 2017). In 2002, we developed the KAINOS-FGF-23 ELISA Kit (KI) (KAINOS, Tokyo, Japan) and, in 2019, completed the new development of the automated chemiluminescent enzyme immunoassay (CLEIA); Determinar CL FGF23 (CL) (Minaris Medical corporation, Tokyo, Japan) independently (Ito et al., 2021b, 2005; Kato et al., 2021; Yamazaki et al., 2002).

To date, we have reported the usefulness of KI in differentiating FGF23-related hypophosphatemia from other causes of hypophosphatemia, including Fanconi syndrome, vitamin D deficiency, and renal tubular acidosis. Furthermore, the cutoff value of serum intact FGF23 for the diagnosis of FGF23-related hypophosphatemia was reported to be equal to or >30.0 pg/mL with concomitant chronic hypophosphatemia using KI (Endo et al., 2015, 2008). We have recently introduced the novel automated analyzer of intact FGF23 (CL) invented by Minaris Medical Corporation and its clinical performance of diagnosis on FGF23-related hypophosphatemia (Ito et al., 2021b; Kato et al., 2021). CL got approval from the Ministry of Health, Labour, and Welfare in Japan and is covered by the national health insurance. However, in countries other than Japan, CL was not available and a 96-well plate-based Medfrontier intact FGF23 assay kit (MED) with the antibodies same as CL, was supplied. Table 1 shows the difference between KI, CL, and MED. CL and MED adopted automated and manual assay systems respectively with identical antibody sets. The main aim of this study was, therefore, to confirm whether the clinical performance of MED FGF23 was similar to CL FGF23 using the same samples in the previous research (Kato et al., 2021).

2. Methods

2.1. Measurement of intact FGF23 levels

Intact FGF23 measurement was performed using MED as previously reported. Briefly, MED uses two monoclonal antibodies that detect only intact FGF23, assayed by CLEIA. Intact FGF23 was also measured among the same sample sets by KI as previously reported (Shimizu et al., 2012). When intact FGF23 levels of samples were lower than the limit of detection (LOD) of KI (3.0 pg/mL) and MED (10.0 pg/mL), values were replaced with LOD/2 (1.5 pg/mL for KI and 5.0 pg/mL for MED). Diluted samples were remeasured when intact FGF23 levels were above the detection range of both assays (800.0 pg/mL for KI and 3000.0 pg/mL for MED).

2.2. Sample and clinical data collection from healthy controls

Healthy controls were recruited following the exclusion criteria: self-reported comorbidities, including hypophosphatemic rickets/osteomalacia, chronic kidney disease, metabolic bone diseases, malignant neoplasms, infectious diseases, and autoimmune diseases. The inclusion criteria were serum phosphate and creatinine levels within the reference range (serum phosphate: 2.5–4.5 mg/dL, serum creatinine: 0.61–1.04 mg/dL [men], 0.47–0.79 mg/dL [women]). After enrollment, serum phosphate and creatinine levels were measured again, and participants with serum phosphate and creatinine levels that were above or below the reference range were excluded. A total of 425 adults were enrolled at first, and 45 participants were excluded. Finally, 380 healthy individuals were included in the present study. These 380 healthy individuals were also included in the previous study (Kato et al., 2021). Serum phosphate and creatinine levels of healthy individuals were measured by a 7170S clinical analyzer (Hitachi High-Tech Corporation, Tokyo, Japan) using the manufacturer's standard reagents. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine levels based on a previously reported equation for Japanese individuals (Matsuo et al., 2009).

Table 1
Characteristics of the previously reported KAINOS FGF-23 ELISA kit (KI), Determinar CL FGF23 (CL), and Medfrontier intact FGF23 assay (MED).

Name	Modality of assay	Antibody 1	Antibody 2	Procedure	Reference
KAINOS FGF-23 ELISA kit	ELISA	Biotin-conjugated mouse monoclonal anti-FGF23 antibody	Peroxidase-conjugated mouse monoclonal anti-FGF23 antibody	Manual	Yamazaki et al., 2002
Determinar CL FGF23	CLEIA	Same as KAINOS FGF-23 ELISA kit	Alkaline phosphatase-labeled mouse monoclonal anti-FGF23 antibody (using the same mouse monoclonal anti-FGF23 antibody as antibody 2 in KAINOS FGF-23 ELISA kit)	Automated	Ito et al., 2021b Kato et al., 2021
Medfrontier intact FGF23 assay	CLEIA	Same as KAINOS FGF-23 ELISA kit	Same as Determinar CL FGF23	Manual	

FGF, fibroblast growth factor; ELISA, enzyme-linked immunosorbent assay; CLEIA, chemiluminescent enzyme immunoassay.

2.3. Sample and clinical data collection from patients with chronic hypophosphatemia

A total of 22 patients with chronic hypophosphatemia with TIO, XLH, or vitamin D-dependent rickets (VDDR) were included in this study. Patients with chronic hypophosphatemia enrolled in the present study were same as the subjects in the previous study (Kato et al., 2021). Because samples were collected several times from patients with tumor-induced osteomalacia (TIO) at systemic FGF23 venous sampling and before and after the resection of the responsible tumors, a total of 200 samples were collected from patients with chronic hypophosphatemia. Age, sex, clinical diagnosis, and laboratory data, including serum phosphate, calcium, albumin, creatinine, alkaline phosphatase (ALP), and eGFR of patients with chronic hypophosphatemia were retrospectively collected from electronic health records in the hospital. Blood chemistry tests, including serum phosphate, calcium, albumin, creatinine, and ALP, were analyzed with a LABOSPECT008 (Hitachi High-Tech Corporation, Tokyo, Japan).

All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki, and procedures for healthy individuals and patients with chronic hypophosphatemia were approved by the institutional ethical board of Minaris Medical Co. Ltd. (Ref. 2016/2#1 and 2016/2#4) and the University of Tokyo Hospital (Ref. 2879 and 2945), respectively. Informed consent was obtained from all individual participants included in the study.

2.4. Statistical analysis

For the precision analysis, mean values, inter- and intra-assay variance (standard deviation [SD]), and coefficients of variation (CVs) were calculated for each control level. For the linearity analysis of serially diluted samples, the linearity relationship between the mean and the target value was evaluated.

For the comparison between KI and MED, the Mann–Whitney *U* test was chosen. To assess the correlation between KI and MED, linear regression analysis was used. A p value < 0.05 was considered significant. All analyses were performed using GraphPad Prism version 6.05 for Windows (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Assay performance

Three or five replicates of three levels of quality control samples were assayed over three days to evaluate the intra-assay and interassay imprecision of MED. The intra-assay SDs were 0.5, 11.5, and 108.1, and the intra-assay CVs (%) of CL were 2.1, 1.9, and 3.5 for mean intact FGF23 levels of 22.8, 548.5, and 3104.3 pg/mL, respectively. The corresponding interassay SDs were 1.0, 36.5, and 9.3, and the corresponding interassay CVs (%) were 4.5, 6.4, and 0.3 Triplicate measurements of seven samples were diluted fractionally to assess the linearity of MED. Serially diluted samples with intact FGF23 levels demonstrated almost complete linearity up to 268.1 pg/mL in MED FGF23 (Fig. 1).

3.2. Intact FGF23 levels among healthy controls

Table 2A shows the age, sex, and biochemical data of 380 healthy controls. The median MED FGF23 level among healthy individuals was 40.9 pg/mL. The reference range of MED FGF23 levels among healthy controls was 18.6–59.8 pg/mL when calculated as the average ± 2 standard deviations (SDs). A significant difference in MED FGF23 was observed between males and females (female, 36.3 [IQR, 30.1–43.7]; male, 38.8 [IQR, 33.7–46.7]; p value = 0.001) but not between age categories per 10 years old (p value = 0.76). When comparing intact FGF23 levels assayed by KI and MED, there was a significant difference

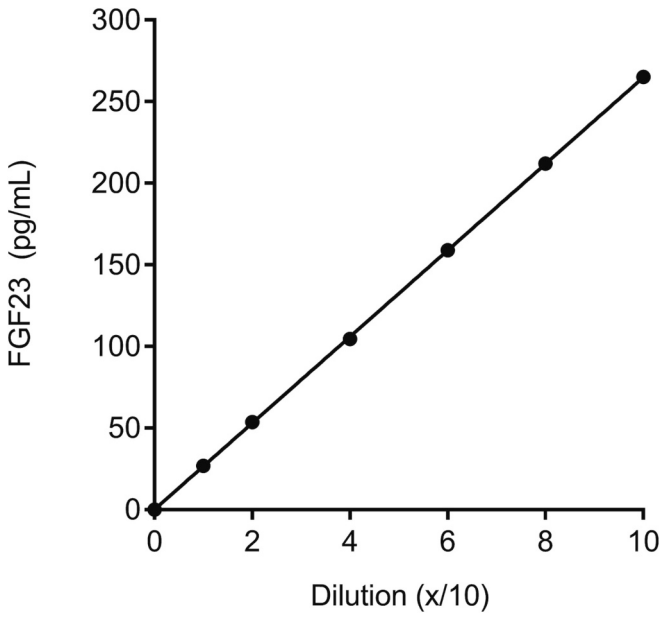

Fig. 1. Serial dilution samples measured with MED.
MED showed almost complete linearity up to 268.1 pg/mL.

Table 2
Clinical data of healthy controls and patients with chronic hypophosphatemia.

(A) Healthy controls	RI, adult	Total (n = 380)
Sex, female (%)		182 (48)
Age, years		54 (37–67)
Serum phosphate (mg/dL)	2.5–4.5	3.4 (3.1–3.7)
eGFR (mL/min/1.73 m^2)	>60	83.9 (75.4–97.0)

(B) Patients with chronic hypophosphatemia	RI, adults	Total (n = 22)
Sex, female (%)		8 (36)
Age, years		52 (14–82)
Disease category		
TIO, n (%)		18 (82)
XLH, n (%)		3 (13)
VDDR, n (%)		1 (5)
Treatment		
Inorganic phosphate or active vitamin D, n (%)		21 (95)
Calcium lactate hydrate, n (%)		1 (5)
Serum albumin-adjusted Ca (mg/dL)	8.8–10.1	8.7 (8.1–9.9)
Serum phosphate (mg/dL)	2.5–4.5	2.0 (1.0–3.2)
eGFR (mL/min/1.73 m^2)	>60	97 (29–193)
ALP (IU/L)	38–113	177 (76–782)

RI, reference interval; eGFR, estimated glomerular filtration rate; TIO, tumor-induced osteomalacia; XLH. X-linked hypophosphatemia; VDDR, vitamin D-dependent rickets; Ca, calcium; ALP, alkaline phosphatase.
Values are described as the median (range).

(KI FGF23, 40.9 [IQR, 31.1–50.6]; MED FGF23, 38.0 [IQR, 31.5–45.7]; p value = 0.02). The correlation between KI FGF23 (x) and MED FGF23 (y) was interpreted as a slope of 0.55 with a y-intercept of 16.4 with moderate linearity ($R^2 = 0.59$) (Fig. 2A).

3.3. Intact FGF23 levels among patients with chronic hypophosphatemia

A total of 200 samples were collected from 22 patients with chronic hypophosphatemia, which consisted of 18 patients with TIO, three patients with X-linked hypophosphatemic rickets (XLH), and one patient with Fanconi syndrome. A total of 186 preoperative samples and 10 postoperative samples were included in the total of 196 samples collected from a patient with TIO. The description of the clinical data of

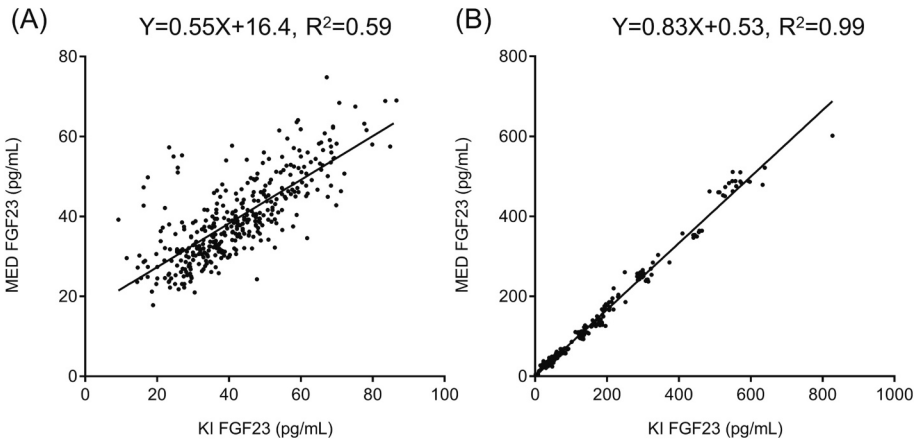

Fig. 2. Correlation between KI FGF23 and MED FGF23 among healthy controls (A) and patients with chronic hypophosphatemia (B).

each patient is listed in Table 2B. Similar to the measurement of intact FGF23 levels among healthy controls, intact FGF23 levels among patients with chronic hypophosphatemia showed higher intact FGF23 levels with KI than with MED (KI FGF23, 172.5 [IQR, 115.8–290.7]; MED FGF23, 130.2 [IQR, 93.6–247.0]; p value = 0.003). The linear regression analysis showed that the correlation between KI FGF23 and MED FGF23 was interpreted as a slope of 0.83 with a y-intercept of 0.53, which showed good linearity ($R^2 = 0.99$) (Fig. 2B).

3.4. Evaluation of diagnostic criteria of MED FGF23 level

The diagnostic criteria for FGF23-related hypophosphatemia were reported to be 30.0 pg/mL when measured by KI (Endo et al., 2008). Regarding the correlations between KI FGF23 and MED FGF23 among patients with chronic hypophosphatemia, the diagnostic criteria of 30.0 pg/mL in KI FGF23 were interpreted as 25.5 pg/mL in MED FGF23. The specificity and the sensitivity of the newly calculated criteria in MED FGF23 were 100 % (Fig. 3).

4. Discussion

In the present study, using the novel CLEIA FGF23 kit (MED), assay performance and clinical performance were analyzed. When we compared the two different measurement kits for intact FGF23, KI, and MED; significantly lower levels of MED FGF23 relative to KI FGF23 were observed.

Since the measurement of intact FGF23 was first introduced and is now available by the KI kit for research use (Shimada et al., 2002), other types of measurement kits have become available, including MED and CL, both of which adopted the same antibody set. In a previous report, the reference range of CL among healthy controls was reported to be 16.1–49.3 pg/mL, which was similar to that of MED (18.6–59.8 pg/mL) calculated in the current study (Kato et al., 2021). On the other hand, KI was reported to yield higher levels of intact FGF23 than CL (Kato et al., 2021), which was compatible with the present study showing the significant difference between the intact FGF23 values measured by KI and MED. In the linear regression analysis using samples from patients with chronic hypophosphatemia, MED showed an approximately 20 % reduced value of intact FGF23 when compared to KI. This correlation was reminiscent of a previous study showing that CL FGF23 was approximately 25 % lower than KL FGF23 (Kato et al., 2021). Considering the previous and present data, the discrepancy between KI FGF23 and MED FGF23 was similar to the difference between KI FGF23 and CL FGF23.

The intact FGF23 measurement was reported to be useful among patients with chronic hypophosphatemia (Endo et al., 2015, 2008; Fukumoto et al., 2015; Laurent et al., 2021). Previous studies with KI suggested that intact FGF23 levels of 30.0 pg/mL and more could discriminate patients with FGF23-rHR from other causes of chronic hypophosphatemia, such as VDDR and Fanconi syndrome (Endo et al., 2008). Because these previous studies adopted KI for intact FGF23 measurement, diagnostic criteria should be shifted when MED FGF23

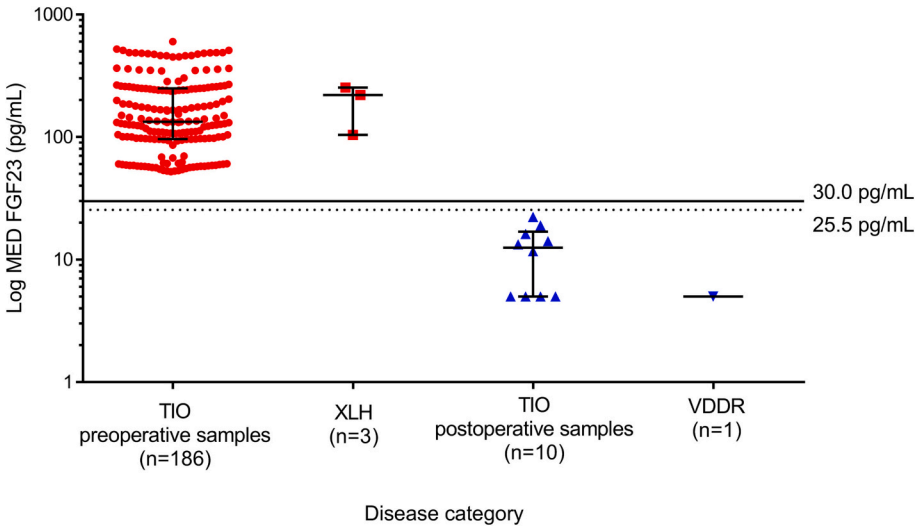

Fig. 3. Comparison of previously reported cutoff values and newly calculated values to differentiate FGF23-related hypophosphatemia (preoperative TIO and XLH) from non-FGF23-related hypophosphatemia (postoperative TIO and vitamin D-deficient rickets). Both the specificity and sensitivity of MED FGF23 were at 100 % when the cutoff level was set to either 30.0 pg/mL (previously reported cutoff value, solid line) or 25.5 pg/mL (newly calculated cutoff value, dotted line).

was used for the differential diagnosis of chronic hypophosphatemic rickets/osteomalacia. However, our data revealed that MED yielded 100 % sensitivity and specificity for the diagnosis of FGF23-rHR regardless of the cutoff values set at a previously reported value (30.0 pg/mL) or the newly calculated value (25.5 pg/mL), suggesting that it might not be necessary to change the diagnostic criteria for MED FGF23 as we reported in the previous study with CL (Kato et al., 2021).

Furthermore, measurement of intact FGF23 was also reported to be useful to predict mortality among patients with chronic kidney disease (Gutiérrez et al., 2008; Isakova et al., 2018, 2011; Mehta et al., 2016). Because intact FGF23 levels among patients with chronic kidney diseases were sometimes extremely high (>1000.0 pg/mL), sample dilution was regularly needed. Considering that the upper detection limit of MED (3000.0 pg/mL) was higher than that of KI (800.0 pg/mL), MED would be more convenient for researchers interested in the association of intact FGF23 and mortality or other clinical outcomes in patients with chronic kidney disease.

There are several limitations to our study. First, because most samples were obtained from patients with TIO preoperatively and postoperatively, we might not accurately assess the cutoff value for differentiating causes of chronic hypophosphatemia: FGF23- or non-FGF23-related. However, the correlation between KI and MED should be fully evaluated because samples collected from patients with chronic hypophosphatemia ranged from 5.0 to 601.6 pg/mL. Second, enrollment of healthy controls with several criteria could not completely exclude patients with conditions in which intact FGF23 was elevated because the one adopted in the exclusion criteria was “self-reported hypophosphatemic rickets/osteomalcia.”

In conclusion, the present study revealed the clinical performance of MED, such as the reference value, the diagnostic ability for FGF23-related hypophosphatemia, and the deviation from the former assay (KI), was almost equal to that of CL. As the clinical utility of CL has already been established, MED could be used in a clinical setting with sufficient reliability.

Disclosure summary

This study was funded by Minaris Medical Co., Ltd.

CRediT authorship contribution statement

Hajime Kato: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Hiromi Miyazaki:** Writing – review & editing. **Takehide Kimura:** Conceptualization, Data curation, Writing – review & editing. **Yoshitomo Hoshino:** Writing – review & editing. **Naoko Hidaka:** Writing – review & editing. **Minae Koga:** Writing – review & editing. **Masaomi Nangaku:** Writing – review & editing. **Noriko Makita:** Writing – review & editing. **Nobuaki Ito:** Conceptualization, Supervision, Writing – review & editing.

Conflict of interest

HM and TK are full-time employees of Minaris Medical Co., Ltd. However, the authors had full control of the findings, and the results were presented without supervision or interference from the sponsor of the work. HK, YH, NH, MK, MN, NM and NI have no conflicts of interest.

Data availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

Briot, K., et al., 2021. Burosumab treatment in adults with X-linked hypophosphataemia: 96-week patient-reported outcomes and ambulatory function from a randomised phase 3 trial and open-label extension. RMD Open. https://doi.org/10.1136/RMDOPEN-2021-001714.

Carpenter, T.O., et al., 2011. A clinician’s guide to X-linked hypophosphatemia. J. Bone Miner. Res. https://doi.org/10.1002/jbmr.340.

David, V., et al., 2016. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. Kidney Int. 89, 135–146. https://doi.org/10.1038/ki.2015.290.

Endo, I., et al., 2015. Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment. Endocr. J. 62, 811–816. https://doi.org/10.1507/endocrj.EJ15-0275.

Endo, I., et al., 2008. Clinical usefulness of measurement of fibroblast growth factor 23 (FGF23) in hypophosphatemic patients. Proposal of diagnostic criteria using FGF23 measurement. Bone 42, 1235–1239. https://doi.org/10.1016/j.bone.2008.02.014.

Farrow, E.G., et al., 2011. Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice. Proc. Natl. Acad. Sci. U. S. A. 108, E1146–E1155. https://doi.org/10.1073/pnas.1110905108.

Flamme, I., et al., 2017. FGF23 expression in rodents is directly induced via erythropoietin after inhibition of hypoxia inducible factor proline hydroxylase. PloS one 12. https://doi.org/10.1371/JOURNAL.PONE.0186979.

Fukumoto, S., et al., 2015. Pathogenesis and diagnostic criteria for rickets and osteomalacia–proposal by an expert panel supported by the Ministry of Health, Labour and Welfare, Japan, the japanese Society for Bone and Mineral Research, and the Japan Endocrine Society. J. Bone Miner. Metab. 33, 467–473. https://doi.org/10.1007/S00774-015-0698-7.

Gutiérrez, O.M., et al., 2008. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N. Engl. J. Med. 359, 584–592. https://doi.org/10.1056/NEJMOA0706130.

Hanudel, M.R., et al., 2019. Effects of erythropoietin on fibroblast growth factor 23 in mice and humans. Nephrol. Dial. Transplant. 34, 2057–2065. https://doi.org/10.1093/NDT/GFY189.

Hidaka, N., et al., 2021. Induction of FGF23-related hypophosphatemic osteomalacia by alcohol consumption. Bone Rep. https://doi.org/10.1016/J.BONR.2021.101144.

Imanishi, Y., et al., 2021. Interim analysis of a phase 2 open-label trial assessing burosumab efficacy and safety in patients with tumor-induced osteomalacia. J. Bone Miner. Res. 36, 262–270. https://doi.org/10.1002/jbmr.4184.

Imel, E.A., et al., 2011. Iron modifies plasma FGF23 differently in autosomal dominant hypophosphatemic rickets and healthy humans. J. Clin. Endocrinol. Metab. 96, 3541–3549. https://doi.org/10.1210/jc.2011-1239.

Insogna, K.L., 2019. Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase 3, single-arm, international trial. J. Bone Miner. Res. 34, 2183–2191. https://doi.org/10.1002/JBMR.3843.

Insogna, K.L., et al., 2018. A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. J. Bone Miner. Res. 33, 1383–1393. https://doi.org/10.1002/jbmr.3475.

Isakova, T., et al., 2018. Longitudinal FGF23 trajectories and mortality in patients with CKD. J. Am. Soc. Nephrol. 29, 579–590. https://doi.org/10.1681/ASN.2017070772.

Isakova, T., et al., 2011. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA 305, 2432–2439. https://doi.org/10.1001/JAMA.2011.826.

Ito, N., et al., 2021a. Sclerostin directly stimulates osteocyte synthesis of fibroblast growth Factor-23. Calcif. Tissue Int. 109, 66–76. https://doi.org/10.1007/S00223-021-00823-6.

Ito, N., et al., 2021b. Clinical performance of a novel chemiluminescent enzyme immunoassay for FGF23. J. Bone Miner. Metab. https://doi.org/10.1007/s00774-021-01250-1.

Ito, N., et al., 2015. Regulation of FGF23 expression in IDG-SW3 osteocytes and human bone by pro-inflammatory stimuli. Mol. Cell. Endocrinol. 399, 208–218. https://doi.org/10.1016/J.MCE.2014.10.007.

Ito, N., et al., 2005. Comparison of two assays for fibroblast growth factor (FGF)-23. J. Bone Miner. Metab. 23, 435–440. https://doi.org/10.1007/s00774-005-0625-4.

Ito, N., Fukumoto, S., 2021. Congenital hyperphosphatemic conditions caused by the deficient activity of FGF23. Calcif. Tissue Int. 108, 104–115. https://doi.org/10.1007/S00223-020-00659-6.

Jan de Beur, S.M., et al., 2021. Burosumab for the treatment of tumor-induced osteomalacia. J. Bone Miner. Res. 36, 627–635. https://doi.org/10.1002/jbmr.4233.

Jonsson, K.B., et al., 2003. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N. Engl. J. Med. 348, 1656–1663. https://doi.org/10.1056/NEJMOA020881.

Kato, H., et al., 2021. Performance evaluation of the new chemiluminescent intact FGF23 assay relative to the existing assay system. J. Bone Miner. Metab. https://doi.org/10.1007/s00774-021-01258-7.

Kinoshita, Y., et al., 2014. Functional analysis of mutant FAM20C in Raine syndrome with FGF23-related hypophosphatemia. Bone 67, 145–151. https://doi.org/10.1016/j.bone.2014.07.009.

Kinoshita, Y., Fukumoto, S., 2018. X-linked hypophosphatemia and FGF23-related hypophosphatemic diseases: Prospect for new treatment. Endocr. Rev. 39, 274–291. https://doi.org/10.1210/er.2017-00220.

Laurent, M.R., et al., 2021. Consensus recommendations for the diagnosis and management of X-linked hypophosphatemia in Belgium. Front. Endocrinol. (Lausanne) 12. https://doi.org/10.3389/FENDO.2021.641543.

Matsuo, S., et al., 2009. Revised equations for estimated GFR from serum creatinine in Japan. Am. J. Kidney Dis. 53, 982–992. https://doi.org/10.1053/j.ajkd.2008.12.034.

Mehta, R., et al., 2016. Association of fibroblast growth factor 23 with atrial fibrillation in chronic kidney disease, from the chronic renal insufficiency cohort study. JAMA Cardiol. 1, 548–556. https://doi.org/10.1001/JAMACARDIO.2016.1445.

Portale, A.A., et al., 2019. Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. Calcif. Tissue Int. 105, 271–284. https://doi.org/10.1007/S00223-019-00568-3.

Sahoo, S.K., et al., 2019. Elevated FGF23 in a patient with hypophosphatemic osteomalacia associated with neurofibromatosis type 1. Bone 129. https://doi.org/10.1016/J.BONE.2019.115055.

Schouten, B.J., et al., 2009. FGF23 elevation and hypophosphatemia after intravenous iron polymaltose: a prospective study. J. Clin. Endocrinol. Metab. 94, 2332–2337. https://doi.org/10.1210/jc.2008-2396.

Shimada, T., et al., 2004. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J. Bone Miner. Res. 19, 429–435. https://doi.org/10.1359/JBMR.0301264.

Shimada, T., et al., 2002. Mutant FGF-23 responsible for autosomal dominant hypophosphatemic rickets is resistant to proteolytic cleavage and causes hypophosphatemia in vivo. Endocrinology 143, 3179–3182. https://doi.org/10.1210/endo.143.8.8795.

Shimizu, Y., et al., 2012. Evaluation of a new automated chemiluminescence immunoassay for FGF23. J. Bone Miner. Metab. 30, 217–221. https://doi.org/10.1007/s00774-011-0306-4.

Shimizu, Y., et al., 2009. Hypophosphatemia induced by intravenous administration of saccharated ferric oxide. Bone 45, 814–816. https://doi.org/10.1016/j.bone.2009.06.017.

Souberbielle, J.C., et al., 2017. Evaluation of a new fully automated assay for plasma intact FGF23. Calcif. Tissue Int. 101, 510–518. https://doi.org/10.1007/S00223-017-0307-Y.

Tagliabracci, V.S., et al., 2014. Dynamic regulation of FGF23 by Fam20C phosphorylation, GalNAc-T3 glycosylation, and furin proteolysis. Proc. Natl. Acad. Sci. U. S. A. 111, 5520–5525. https://doi.org/10.1073/pnas.1402218111.

Yamashita, T., et al., 2000. Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. Biochem. Biophys. Res. Commun. 277, 494–498. https://doi.org/10.1006/BBRC.2000.3696.

Yamazaki, Y., et al., 2002. Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia. J. Clin. Endocrinol. Metab. 87, 4957–4960. https://doi.org/10.1210/jc.2002-021105.