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Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment

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Abstract. A nationwide epidemiologic survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases was conducted in 2010 to clarify the prevalence and the clinical presentations of the disorders. A questionnaire inquiring the experience of patients with these diseases was sent to randomly selected hospitals throughout Japan. The estimated annual incidence of the diseases was 117 cases (95% CI 75 - 160), 55 males (95% CI 30 - 81) and 62 females (95% CI 40 - 84). Tumor-induced osteomalacia (TIO) and X-linked hypophosphatemic rickets (XLH) were the most prevalent causes of acquired and genetic FGF23-related hypophosphatemic diseases, respectively. The estimated incidence of XLH was about 1 in 20,000. We have also collected clinical data of the patients by a secondary survey. These patients showed FGF23 levels of above 30 pg/mL by intact assay in the presence of hypophosphatemia. While complete resection of responsible tumors improved biochemical abnormalities in patients with TIO, treatment with phosphate and/or active vitamin D₃ did not normalize serum phosphate and tubular maximum transport of phosphate in patients with XLH. Our results suggest that there is no racial difference in the incidence of XLH. While FGF23 measurement is useful for the diagnosis of FGF23-related hypophosphatemic diseases, the better management is necessary especially for patients with genetic hypophosphatemic rickets caused by excessive actions of FGF23.

Key words: Hypophosphatemia, Rickets, Osteomalacia, FGF23

FIBROBLAST GROWTH FACTOR 23 (FGF23) is a hormone produced by bone and reduces serum phosphate by inhibiting proximal tubular phosphate reabsorption and intestinal phosphate absorption through decreasing serum 1,25-dihydroxyvitamin D [1]. It has been shown that excessive actions of FGF23 cause several kinds of FGF23-related hypophosphatemic

diseases such as X-linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR) 1 and 2, tumor-induced osteomalacia (TIO), hypophosphatemic disease associated with McCune-Albright syndrome/fibrous dysplasia and hypophosphatemia caused by intravenous administration of saccharated ferric oxide [2]. However, there have been no epidemiological studies concerning these FGF23-related hypophosphatemic diseases. In addition, the clinical presentations of and the treatment methods for these diseases are not sufficiently

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Table 1 Diseases caused by excess actions of FGF23

Diseases	Responsible gene
X-linked hypophosphatemic rickets	<i>PHEX</i>
Autosomal dominant hypophosphatemic rickets	<i>FGF23</i>
Autosomal recessive hypophosphatemic rickets 1, 2	<i>DMP1, ENPP1</i>
Hypophosphatemic disease associated with McCune-Albright syndrome/fibrous dysplasia	<i>GNAS</i>
Tumor-induced rickets/osteomalacia	
Hypophosphatemic disease caused by intravenous administration of saccharated ferric oxide	
Linear nevus sebaceous syndrome	

PHEX, phosphate-regulating gene with homologies to endopeptidases on the X chromosome; *FGF23*, fibroblast growth factor 23; *DMP1*, dentine matrix protein 1; *ENPP1*, ectonucleotide pyrophosphatase/phosphodiesterase 1; *GNAS*, guanine nucleotide binding protein alpha-stimulating

described mainly because these are rare diseases. In contrast, these epidemiological and clinical data are essential for establishing correct diagnostic criteria and appropriate treatment. Therefore, The Hormone Receptor Abnormality Research Committee and The Epidemiological Study Group of Specified Rare and Intractable Diseases supported by Ministry of Health, Labour and Welfare of Japan conducted a nationwide survey of FGF23-related hypophosphatemic diseases in Japan in 2010.

Patients and Methods

This study was approved by the ethics committee of Tokushima University. The primary and the secondary surveys were conducted. The purpose of the primary survey was to estimate the number of patients with hypophosphatemic diseases caused by excess actions of FGF23. In addition, the secondary survey was done to clarify the clinical features and course of these patients. A nationwide primary mail survey was conducted in 2010. Patients who visited hospitals because of suspected FGF23-related hypophosphatemic diseases in 2009 were the targets of the primary survey. According to the Nationwide Epidemiologic Survey Manual issued by The Epidemiological Study Group of Specified Rare and Intractable Diseases, we selected three medical departments of internal medicine (including endocrinology), orthopedics and pediatrics as candidates for the survey. Study hospitals were selected randomly from the list of all hospitals in Japan. The selection rate was decided according to the stratification classified by the number of beds in the hospitals; the more beds a hospital has, the higher the probability to be selected. The selection rate was 100% for hospitals with more than or equal to 500 beds and medical university hospitals, whereas only 5% of

hospitals with less than 100 beds were selected at random. After the selection of the study hospitals, we sent questionnaires to the three departments of the selected hospitals with a list of diseases known to be caused by excess actions of FGF23 at that time (Table 1). The questionnaires asked the number of new patients with these FGF23-related hypophosphatemic diseases in 2009 and the total number of patients between 2005 and 2009. When some department with the hypophosphatemic diseases responded, the second mail survey questionnaire asking detailed clinical features including the diagnosis, biochemical data and treatment for each patient was sent to that department. All blood and urine sample were taken at fasting. We also offered to measure FGF23 in hypophosphatemic patients if FGF23 levels were unknown to confirm the diagnosis of FGF23-related hypophosphatemic diseases.

Considering the selection rate and the response rate to the survey, we estimated the total numbers of patients with FGF23-related hypophosphatemic diseases as follows.

The formula for the estimation of the patient number in each stratum is;

The estimated number of patients

= reported number of patients / (selection rate x response rate)

And the numbers of patients for each stratum were summed up. Ninety-five percent confidence intervals were calculated with an assumption of multinomial hypergeometric distribution [3].

Results

From 14,100 departments of internal medicine, orthopedics and pediatrics all over Japan, 2895 (20.5%) study departments were selected at random for the primary survey. Replies were obtained from 1149

Table 2 Results of the secondary survey of FGF23-related hypophosphatemic diseases in Japan

Diagnosis	Number		Ages at diagnosis
TIO	male	19	27 - 64
	female	16	16 - 79
	total	35	
Genetic hypophosphatemic diseases (XLH, ADHR, ARHR1, 2)	male	15	0 - 7
	female	26	0 - 7
	total	41	
Saccharated ferric oxide induced	male	3	58 - 87
	female	3	43 - 54
	total	6	
Linear nevus sebaceous syndrome	male	0	
	female	2	1 - 5
	total	2	
	total	84	

TIO, tumor-induced osteomalacia; XLH, X-linked hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets, ADHR, autosomal dominant hypophosphatemic rickets

Table 3 Results of biochemical parameters in the secondary survey

Diagnosis	Serum P (mg/dL)	TmP/GFR (mg/dL)	FGF23 (range; pg/mL)
TIO	1.74 ± 0.35	1.31 ± 0.37	1304.1 ± 3660.3 (44.0 – 18286.4)
Genetic hypophosphatemic diseases	2.47 ± 0.58	2.17 ± 0.71	325.2 ± 1086.3 (40.3 – 4540.0)
Saccharated ferric oxide	1.12 ± 0.18	0.82 ± 0.68	277.5 ± 242.7 (30.2 – 654.0)
Linear nevus sebaceous syndrome	2.03 ± 0.31	1.82 ± 0.48	92.6

TmP/GFR, tubular maximum transport of phosphate per glomerular filtration rate; FGF23, fibroblast growth factor 23; TIO, tumor-induced osteomalacia

(39.7%) departments and 95 departments reported the presence of patients with FGF23-related hypophosphatemic diseases. Total number of the patients was 311 per 5 years and the number of new patients in 2009 was 63. The annual incidence of FGF23-related hypophosphatemic diseases in Japan was estimated to be 55 in males (95% confidence interval 30 – 81) and 62 in females (40 – 84) resulting in 117 (75 – 160) by summing up the estimated number of patients in each stratum according to the hospital size.

On the second survey, 36 departments (37.9%) replied and clinical data of 84 patients were collected. The demographic information of these patients is shown in Table 2. There were 35 patients with TIO and the diagnosis was confirmed by resection of the responsible tumors in all of these patients. The numbers of male and female patients with TIO were almost the same. The ages at the time of diagnosis were quite variable. There were 41 patients with genetic hypophosphatemic rickets, 36 patients with XLH, 3 patients with ARHR1, 1 patient each with ARHR2 and ADHR. The number of female patients was larger than that of male patients. All the patients with genetic hypophosphatemic rickets were diagnosed at seven years old or younger. Of

these, the diagnosis was confirmed by genetic analysis in 15 patients. In addition, there were 6 hypophosphatemic patients by intravenous administration of saccharated ferric oxide. Serum phosphate increased in all of these patients after the cessation of the causative drug. There were 2 hypophosphatemic female patients caused by linear nevus sebaceous syndrome.

Table 3 shows baseline biochemical data by the secondary survey. The mean phosphate level and standard deviation in patients with TIO was 1.74 ± 0.35 mg/dL, and TmP/GFR (tubular maximum transport of phosphate per glomerular filtration rate) was 1.31 ± 0.37 mg/dL. Serum phosphate in patients with genetic hypophosphatemic diseases was 2.47 ± 0.58 mg/dL and at the lower limit of the reference range for adults. However, this value was considered to be low because more than half of the patients in this group were children. Serum phosphate and TmP/GFR were 1.12 ± 0.18 and 0.82 ± 0.68 mg/dL, respectively, in hypophosphatemic patients caused by saccharated ferric oxide. FGF23 concentrations measured by full-length assay were above 30 pg/mL in all the patients [4]. However, FGF23 levels were quite variable as shown in Table 3. At baseline, no patients had renal disorder or elevation

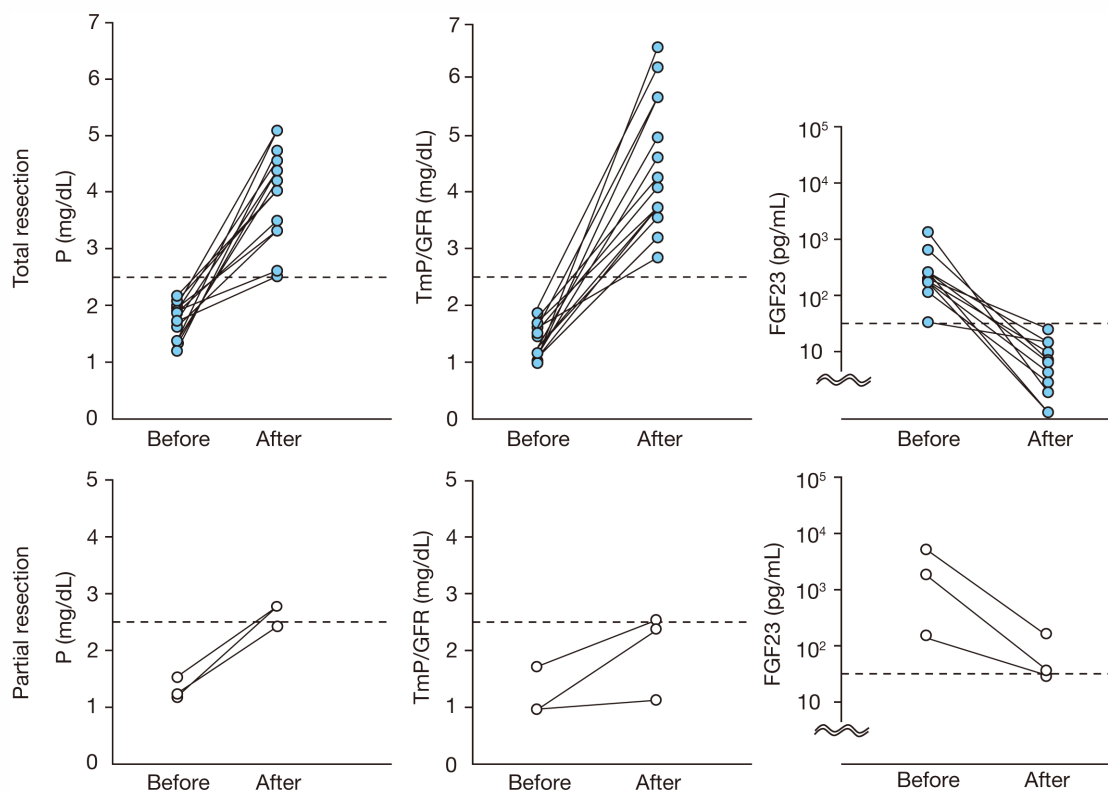


Fig. 1 Serum phosphate, TmP/GFR and FGF23 levels before and after resection of responsible tumors in patients with tumor-induced osteomalacia. The closed circles indicate patients cured by the surgery with complete resection of responsible tumors (14 patients) and the open ones show patients whose responsible tumors could not be completely resected (3 patients). The broken lines indicate the lower limit of the reference range of serum phosphate and TmP/GFR, and the upper limit of the reference range of FGF23. TmP/GFR: tubular maximum transport of phosphate per glomerular filtration rate.

of serum creatinine.

We also obtained the biochemical data of 17 patients with TIO both before and after the resection of responsible tumors. Of these, the responsible tumors were completely removed in 14 patients and the results were shown in the upper panel of Fig. 1. Serum phosphate, TmP/GFR and FGF23 normalized in all of the 14 patients. On the other hand, TmP/GFR did not normalize and FGF23 remained high or in the high normal range in 3 patients whose tumors could not be completely removed.

We collected biochemical data of 7 children and 4 infants with XLH both before and after the initiation of treatment with phosphate and/or active vitamin D₃. As shown in Fig. 2, serum phosphate and TmP/GFR did not normalize despite the initiation of the treatment with oral phosphate and/or active vitamin D₃. We also obtained the biochemical data of 7 adults, 4 children and 1 infant who already had been treated with active vitamin D₃ and/or phosphate at baseline. Their treat-

ment period was at least 2 years and the serum phosphate levels were under the lower limit of the reference range at baseline while on treatment.

Finally, we assessed the clinical course of hypophosphatemic disease caused by intravenous administration of saccharated ferric oxide. As shown in Fig. 3, the mean serum phosphate and TmP/GFR during the administration of saccharated ferric oxide were quite low. However, after the cessation of the responsible drug, serum phosphate and TmP/GFR increased to the reference range and FGF23 decreased.

Discussion

The results of this nationwide survey indicate that estimated annual incidence was about 100 patients with FGF23-related hypophosphatemic diseases in Japan. Of these, TIO and XLH were the most prevalent causes of acquired and genetic FGF23-related hypophosphatemic diseases, respectively. The num-

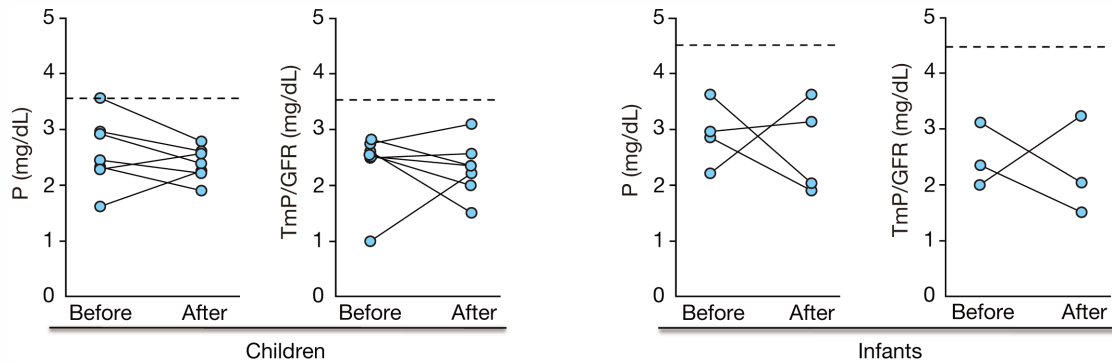


Fig. 2 Serum phosphate and TmP/GFR in patients with XLH before and after the treatment with phosphate and/or active vitamin D₃. The broken lines indicate the lower limit of the reference range of serum phosphate and TmP/GFR. TmP/GFR: tubular maximum transport of phosphate per glomerular filtration rate.

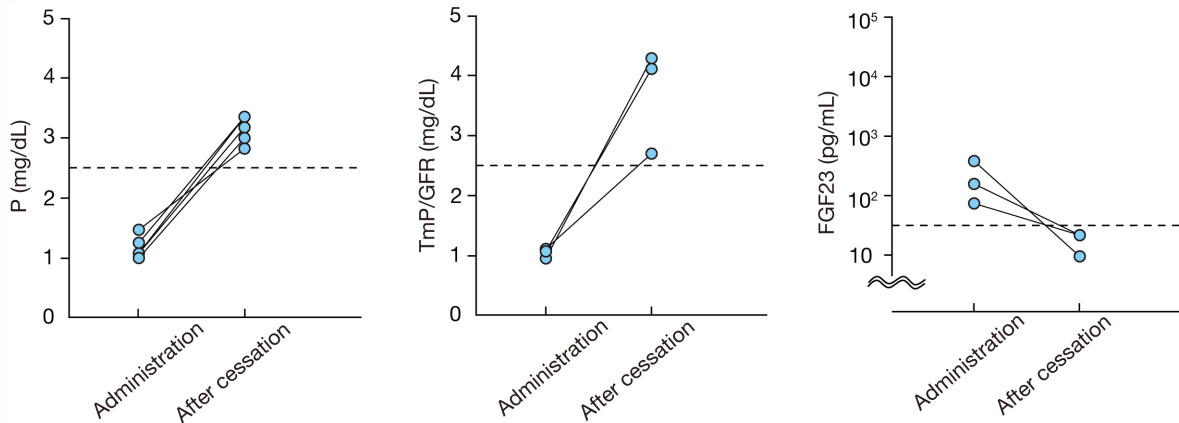


Fig. 3 Serum phosphate, TmP/GFR and FGF23 levels during administration and after cessation of saccharated ferric oxide in hypophosphatemic patients. The broken lines indicate the lower limit of the reference range of serum phosphate and TmP/GFR, and the upper limit of the reference range of FGF23. TmP/GFR: tubular maximum transport of phosphate per glomerular filtration rate.

bers of patients with TIO and XLH were similar indicating that there are about 50 new patients with XLH in Japan. Considering that the number of live births is almost 1,000,000 per year in Japan, the incidence of XLH is estimated to be about 1 in 20,000. This number is exactly the same as that reported in North America suggesting that there is no big racial difference in the incidence of XLH [5].

Previously, we have proposed that FGF23 levels above 30 pg/mL by intact FGF23 assay in the presence of hypophosphatemia indicate the diseases caused by excessive actions of FGF23 such as TIO and XLH [6]. In this secondary survey, all the patients showed serum FGF23 above 30 pg/mL while serum phosphate was low or low normal range. Therefore, the validity of the previous proposal was confirmed by this survey.

TIO occurs mainly in adults with a mean age of 45 ± 16 years [7] and men and women appear to be equally

affected [8]. Our data indicate almost the same epidemiological results. In the present study, all TIO patients with successful resection of responsible tumors showed improvement in serum phosphate, TmP/GFR and FGF23. However, serum phosphate and/or TmP/GFR did not normalize in patients with remaining tumors. These results indicate that complete resection of responsible tumors is necessary to cure patients with TIO.

We obtained biochemical parameters both before and after the treatment from 11 patients with XLH and also corrected serum phosphate data from 12 XLH patients who already had been treated with active vitamin D₃ and/or phosphate. These data indicate that the treatment with oral phosphorus and/or active vitamin D₃ did not normalize serum phosphate and TmP/GFR as these drugs do not enhance proximal tubular phosphate reabsorption. Therefore, novel therapeutic approach to inhibit FGF23 actions is necessary for

patients with FGF23-related hypophosphatemic diseases including XLH. A clinical trial using anti-FGF23 antibody has already demonstrated that the inhibition of FGF23 activity results in increased serum phosphate and enhanced renal tubular phosphate reabsorption in adult patients with XLH [9].

Serum phosphate was quite low and around 1 mg/dL in patients treated with saccharated ferric oxide. However, high FGF23 and hypophosphatemia improved after the cessation of the responsible drug. Saccharated ferric oxide is widely used for iron deficiency anemia in Japan and there are several reports of hypophosphatemic osteomalacia by this drug [10]. It is likely that long-lasting hypophosphatemia causes symptomatic osteomalacia. Therefore, it would be prudent to monitor serum phosphate in patients treated with saccharated ferric oxide even if they are asymptomatic.

The major drawback of the study was the low response rate even in the secondary survey. There seem to be a couple of reasons for the low reply rate. First, the importance of FGF23 in the development of hypophosphatemic diseases may not have yet been well recognized. In addition, while we offered to measure FGF23 levels in hypophosphatemic patients if necessary, it is possible that doctors could not easily evaluate serum FGF23 in clinical practice. Notwithstanding

this limitation, the survey produced the same estimated incidence of XLH as the previous report [5].

In conclusion, this is the first epidemiological survey concerning FGF23-related hypophosphatemic diseases. Our results suggest that the incidence of XLH is similar in Japan to that in North America. While FGF23 measurement is useful for the diagnosis of FGF23-related hypophosphatemic diseases, the better management is necessary especially for patients with genetic hypophosphatemic rickets caused by excessive actions of FGF23.

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Disclosure

The authors declare no conflicts of interest.

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