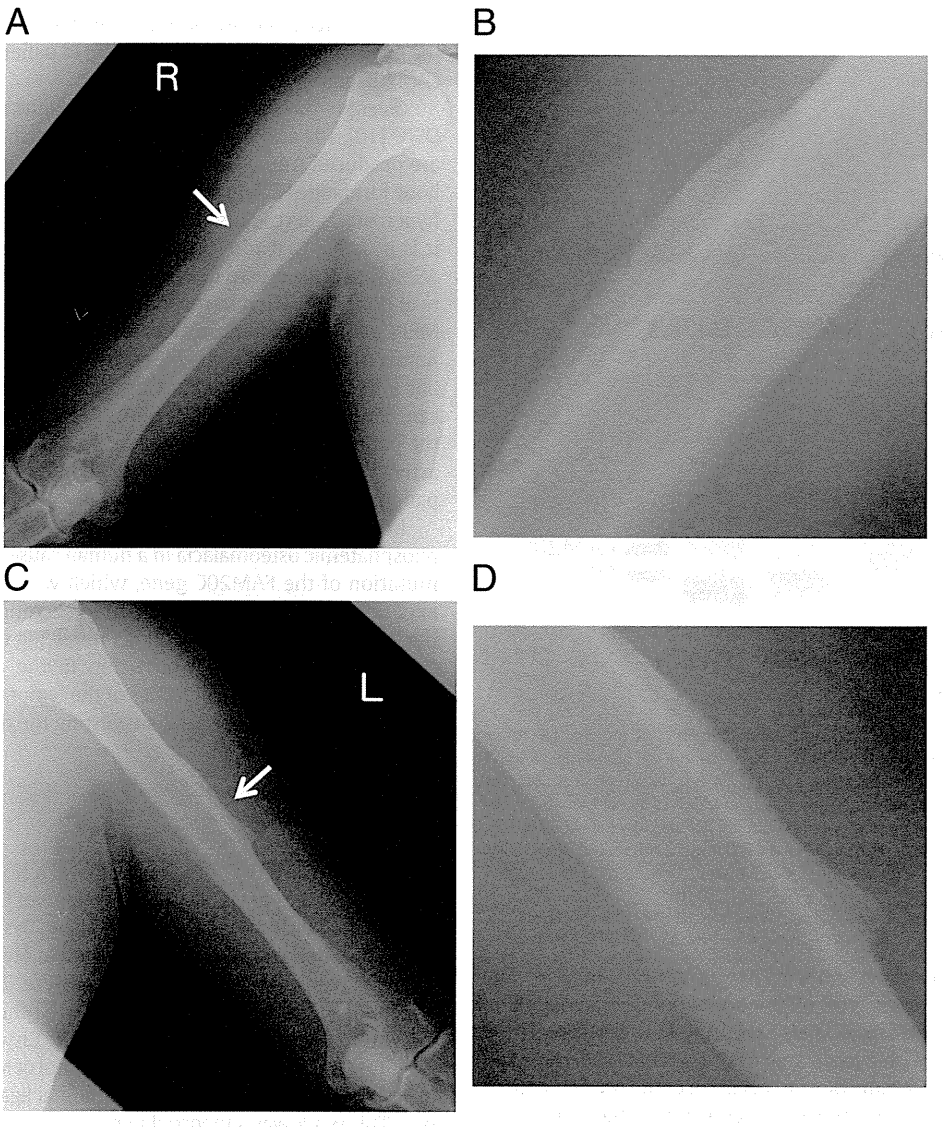

Fig. 5. Radiographs of the (A and B) right and (C and D) left humerus at the age of 61 years. The arrows indicate periosteal hyperostosis. (B and D) A close-up view of periosteal hyperostosis.

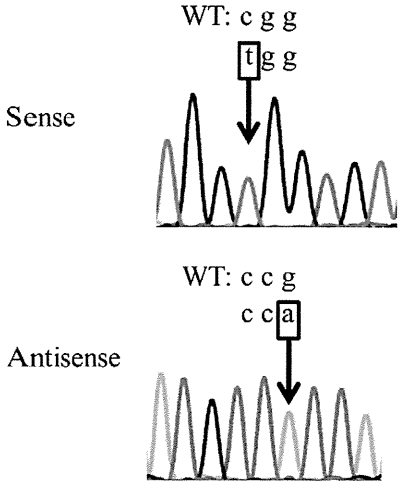

Fig. 6. Mutational analysis of *FAM20C*. The novel homozygous missense mutation c.1222C>T, R408W in exon 6 of the FAM20C gene is shown.

neck and lumbar vertebrae remains unknown. However, osteomalacia of our patient can be explained by the increased serum FGF23 levels. Increased serum FGF23 levels have recently been reported in FAM20C gene KO mice [8]. Markedly increased serum FGF23 levels (309 pg/mL; normal range: 10–50) were observed in our patient after stopping the medication of alfacalcidol (1 μg) for 10 days, being similar to reports on XLH patients [22]. The serum FGF23 level under therapy was 386 pg/mL (normal range: 10–50), being thought to be increased by the therapy [23].

Therefore, it is likely that serum FGF23 levels play an important role in hypophosphatemic rickets in humans with *FAM20C* mutations. Another possibility is the abnormal differentiation of osteoblasts due to impaired FAM20C functions. This mechanism was supported by

Table 2
FAM20C mutations in non-lethal Raine syndrome.

Protein	Phenotype	Hypophosphatemia	Reference
D451N	Raine	+	[6]
P328S	Raine	+	[27]
T268M + Y305X	Hypophosphatemia	+	[7]
R408W	Raine	+	

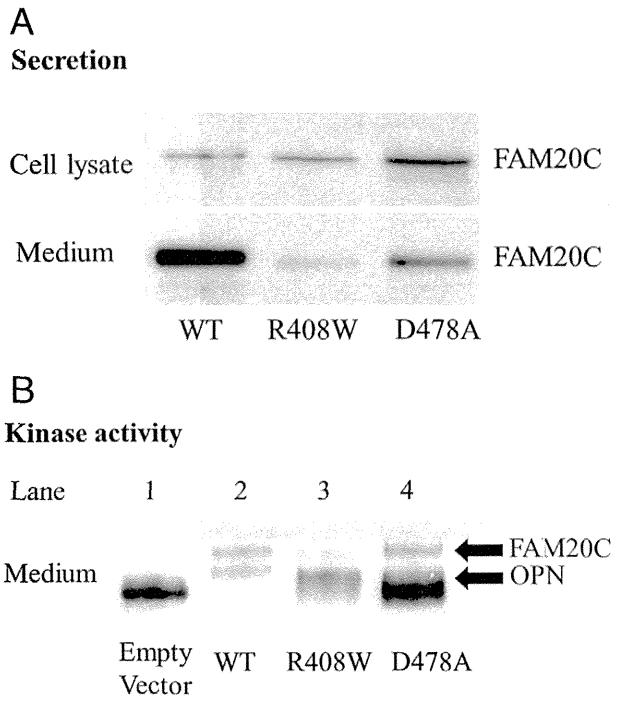

Fig. 7. Secretion and kinase activity of wild-type and mutant FAM20C proteins. (A) While the medium contained more wild-type FAM20C protein than the cell lysate, most R408W mutant FAM20C was present in the cell lysate. (B) When wild-type FAM20C was co-expressed with OPN (Lane 2), the molecular weight of OPN was higher than that without FAM20C expression (Lane 1). Kinase-dead D478A did not alter the molecular weight of OPN (Lane 4), whereas R408W slightly increased it (Lane 3). WT, wild-type; R408W, our patient; D478A, previously reported kinase-dead mutant; OPN, osteopontin.

histological findings in the long bones of FAM20C gene KO mice [8]. The impaired maturation of osteocytes with a wider periosteocytic region and loss of osteocyte processes was also reported in these mice. These findings are consistent with a large area of osteomalacia surrounding osteocytes in the iliac crest bone biopsy specimen of the present patient (Fig. 3). Moreover, they showed the down-regulation of the DMP1 gene in the calvaria of *FAM20C*-deficient mice. These lines of evidence support the hypothesis that the impaired maturation of osteoblasts and osteocytes due to *FAM20C* mutations causes osteomalacia. However, whether or not the mechanism of osteomalacia associated with *FAM20C* mutations is shared in humans and mice has not yet been confirmed.

The patient was complicated by ossification of the posterior longitudinal ligament, an advanced form of enthesopathy [24], characterized by mineral deposition near the tendon at the spine and lower extremities. Enthesopathies have been reported in patients with XLH, ARHR2 [25], and possibly ADHR [26], in which serum FGF23 levels are elevated.

Our patient has the novel homozygous missense mutation c.1222C>T, R408W in the FAM20C gene. Other non-lethal mutations in the FAM20C gene that cause hypophosphatemia have been reported: D451N [6], P328S [27], and compound heterozygous mutations of T268M and Y305X [7] (Table 2). The number of cases is too small to explain what mutation causes hypophosphatemia. We speculate that all non-lethal mutations in the FAM20C gene cause hypophosphatemia.

In our patient, we showed a homozygous missense mutation of R408W in the FAM20C gene and detected the impaired kinase activity and secretion of the mutated FAM20C protein using an assay for the phosphorylation of osteopontin. However, we have no clear explanation for the reduced amount of osteopontin in lanes 2 and 3 (Fig. 7B), but it is possible that the phosphorylation of osteopontin affects the stability of this protein, although we did not confirm the result using antibodies against FAM20C and osteopontin. Further studies are required to clarify the genotype–phenotype relationship in patients with mutations of the FAM20C gene.

Osteopontin is one of the SIBLING proteins, such as MEPE, DMP1, and DSPP [10]. The acidic serine- and aspirate-rich motif (ASARM) peptides are produced from SIBLING proteins and have been shown to inhibit bone formation [27]. In addition, osteopontin KO mice exhibited cortical hyperostosis in response to PTH [28]. Based on these two observations, it is possible that the impaired function of the osteopontin-derived ASARM peptide due to inactivated mutations in *FAM20C* increased cortical bone formation in response to PTH. The reduced function of the MEPE-derived ASARM peptide, for example, may also explain the phenomena of increased bone mineral density in the femoral neck and lumbar vertebrae of the patient because of the increased mass of the cancellous bone in *MEPE* KO mice [29]. Another hypothesis to explain the patient's high bone mineral density is the long-term treatment by active vitamin D metabolite and phosphate, which were shown in XLH patients [19,30].

In conclusion, we herein describe the first reported case of hypophosphatemic osteomalacia in a human caused by a novel homozygous mutation of the FAM20C gene, which was R408W. The transfection experiments suggested the impaired secretion and kinase activity of the R408W mutant FAM20C. It is interesting that osteomalacia and increased periosteal bone formation in the upper extremities with increased bone mineral densities of the femoral neck and lumbar vertebrae coexisted in our patient, suggesting the dual functions of FAM20C in bone.

Acknowledgments

We thank Drs. Yoshiki Seino at Osaka Kosei Nenkin Hospital and Yoshiki Nisizawa at Osaka City University of Graduate School of Medicine for their useful suggestions. We thank Drs. Hiroyuki Tanaka at Okayama Saiseikai Hospital and Kosei Yoh at Hyogo College of Medicine Sasayama Hospital for helping us analyze PHEX genes and prepare bone biopsy specimens for bone histomorphometry, respectively. We also thank Yasunori Okamoto at Minoh City Hospital and Masafumi Kashii at Osaka University Graduate School of Medicine for the diagnosis of ossification of the posterior longitudinal ligament and surgical therapies. This work was supported in part by Grants-in-Aid from the Ministry of Health, Labour, and Welfare of Japan (to SF: H23-Nanti-007 and 11KJB530007KO: H24-Nanti-040).

References

[1] Raine J, Winter RM, Davey A, Tucker SM. Unknown syndrome: microcephaly, hypoplastic nose, exophthalmos, gum hyperplasia, cleft palate, low set ears, and osteosclerosis. *J Med Genet* 1989;26:786–8.
[2] Mahafza T, El-Shanti H, Omari H. Raine syndrome: report of a case with hand and foot anomalies. Clin Dysmorphol 2001;10:227–9.
[3] Simpson MA, Hsu R, Keir LS, Hao J, Sivapalan G, Ernst LM, et al. Mutations in FAM20C are associated with lethal osteosclerotic bone dysplasia (Raine syndrome), highlighting a crucial molecule in bone development. Am J Hum Genet 2007;81:906–12.
[4] Fradin M, Stoetzel C, Muller J, Koob M, Christmann D, Debry C, et al. Osteosclerotic bone dysplasia in siblings with a Fam20C mutation. Clin Genet 2011;80:177–83.
[5] Ababneh FK, AlSwaid A, Youssef T, Al Azzawi M, Crosby A, AlBalwi MA. Hereditary deletion of the entire FAM20C gene in a patient with Raine syndrome. Am J Med Genet A 2013;161A:3155–60.
[6] Simpson MA, Scheuerle A, Hurst J, Patton MA, Stewart H, Crosby AH. Mutations in FAM20C also identified in non-lethal osteosclerotic bone dysplasia. Clin Genet 2009;75:271–6.
[7] Rafaelsen SH, Raeder H, Fagerheim AK, Knappskog P, Carpenter TO, Johansson S, et al. Exome sequencing reveals FAM20c mutations associated with fibroblast growth factor 23-related hypophosphatemia, dental anomalies, and ectopic calcification. J Bone Miner Res 2013;28:1378–85.
[8] Wang X, Wang S, Li C, Gao T, Liu Y, Rangiani A, et al. Inactivation of a novel FGF23 regulator, FAM20C, leads to hypophosphatemic rickets in mice. PLoS Genet 2012;8:e1002708.
[9] Tagliabracci VS, Engel JL, Wen J, Wiley SE, Worby CA, Kinch LN, et al. Secreted kinase phosphorylates extracellular proteins that regulate biomineralization. Science 2012;336:1150–3.

[10] Ishikawa HO, Xu A, Ogura E, Manning G, Irvine KD. The Raine syndrome protein FAM20C is a Golgi kinase that phosphorylates bio-mineralization proteins. PLoS One 2012;7:e42988.
[11] Addison WN, Masica DL, Gray JJ, McKee MD. Phosphorylation-dependent inhibition of mineralization by osteopontin ASARM peptides is regulated by PHEX cleavage. J Bone Miner Res 2010;25:695–705.
[12] Gattineni J, Baum M. Genetic disorders of phosphate regulation. Pediatr Nephrol 2012;27:1477–87.
[13] Walton RJ, Bijvoet OL. Nomogram for derivation of renal threshold phosphate concentration. Lancet 1975;2:309–10.
[14] Marie PJ, Glorieux FH. Relation between hypomineralized periosteocytic lesions and bone mineralization in vitamin D-resistant rickets. Calcif Tissue Int 1983;35:443–8.
[15] Jiang B, Cao Z, Lu Y, Janik C, Lauziere S, Xie Y, et al. DMP1 C-terminal mutant mice recapture the human ARHR tooth phenotype. J Bone Miner Res 2010;25:2155–64.
[16] Koshida R, Yamaguchi H, Yamasaki K, Tsuchimochi W, Yonekawa T, Nakazato M. A novel nonsense mutation in the DMP1 gene in a Japanese family with autosomal recessive hypophosphatemic rickets. J Bone Miner Metab 2010;28:585–90.
[17] Wang X, Wang S, Lu Y, Gibson MP, Liu Y, Yuan B, et al. FAM20C plays an essential role in the formation of murine teeth. J Biol Chem 2012;287:35934–42.
[18] Vogel P, Hansen GM, Read RW, Vance RB, Thiel M, Liu J, et al. Amelogenesis imperfecta and other biomineralization defects in Fam20a and Fam20c null mice. Vet Pathol 2012;49:998–1017.
[19] Cheung M, Roschger P, Klaushofer K, Veilleux LN, Roughley P, Glorieux FH, et al. Cortical and trabecular bone density in x-linked hypophosphatemic rickets. J Clin Endocrinol Metab 2013;98:E954–61.
[20] de Oliveira JR, de Oliveira MF. Familial idiopathic basal ganglia calcification: rediscovering an old challenge in organic psychiatric disorders. Rev Bras Psiquiatr 2013;35:219–20.
[21] Manyam BV. What is and what is not 'Fahr's disease'. Parkinsonism Relat Disord 2005;11:73–80.
[22] Endo I, Fukumoto S, Ozono K, Namba N, Tanaka H, Inoue D, et al. Clinical usefulness of measurement of fibroblast growth factor 23 (FGF23) in hypophosphatemic patients: proposal of diagnostic criteria using FGF23 measurement. Bone 2008;42:1235–9.
[23] Fukumoto S. Phosphate metabolism and vitamin D. Bonekey Rep 2014;3:497.
[24] Chen J, Song D, Wang X, Shen X, Li Y, Yuan W. Is ossification of posterior longitudinal ligament an enthesopathy? Int Orthop 2011;35:1511–6.
[25] Saito T, Shimizu Y, Hori M, Taguchi M, Igarashi T, Fukumoto S, et al. A patient with hypophosphatemic rickets and ossification of posterior longitudinal ligament caused by a novel homozygous mutation in ENPP1 gene. Bone 2011;49:913–6.
[26] Karaplis AC, Bai X, Falet JP, Macica CM. Mineralizing enthesopathy is a common feature of renal phosphate-wasting disorders attributed to FGF23 and is exacerbated by standard therapy in hyp mice. Endocrinology 2012;153:5906–17.
[27] Rowe PS. Regulation of bone-renal mineral and energy metabolism: the PHEX, FGF23, DMP1, MEPE ASARM pathway. Crit Rev Eukaryot Gene Expr 2012;22:61–86.
[28] Kitahara K, Ishijima M, Rittling SR, Tsuji K, Kurosawa H, Nifuji A, et al. Osteopontin deficiency induces parathyroid hormone enhancement of cortical bone formation. Endocrinology 2003;144:2132–40.
[29] Gowen LC, Petersen DN, Mansolf AL, Qi H, Stock JL, Tkalcevic GT, et al. Targeted disruption of the osteoblast/osteocyte factor 45 gene (OF45) results in increased bone formation and bone mass. J Biol Chem 2003;278:1998–2007.
[30] Beck-Nielsen SS, Brixen K, Gram J, Mølgaard C. High bone mineral apparent density in children with X-linked hypophosphatemia. Osteoporos Int 2013;24:2215–21.

J Bone Miner Metab (2014) 32:337–350
DOI 10.1007/s00774-014-0586-6

SPECIAL REPORT

Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update

Yasuo Suzuki · Hajime Nawata · Satoshi Soen · Saeko Fujiwara · Hisanori Nakayama · Ikuko Tanaka · Keiichi Ozono · Akira Sagawa · Ryoichi Takayanagi · Hiroyuki Tanaka · Takami Miki · Naomi Masunari · Yoshiya Tanaka

Received: 13 February 2014 / Accepted: 3 March 2014 / Published online: 13 May 2014

Keywords Glucocorticoid · Osteoporosis · Management · Guideline · Update

Introduction

Glucocorticoids (GCs) are widely used to treat various inflammatory, immunologic, and allergic disorders that cause rheumatic, respiratory, bowel, hepatic, neurological, renal, and skin diseases. Osteoporosis is the most common and important adverse effect of GC therapy, and fractures occur in 30–50 % of adult patients receiving long-term GC therapy [1, 2]. Glucocorticoid-induced osteoporosis (GIO) is the most common type of secondary osteoporosis, and it occurs in patients of all ages, from children to the elderly.

An early rapid decrease of bone mineral density (8–12 %) occurs within several months of starting GC therapy, although bone mineral density decreases more slowly thereafter, with the annual loss being approximately 2–4 % [3]. In addition, it is known that there is a significant increase in the risk of vertebral and hip fractures before marked bone loss occurs [4]. Therefore, it is important to prevent early bone loss and to decrease in fracture risk as early as possible after the start of GC therapy.

Based on the concept of early prevention and treatment, the American College of Rheumatology (ACR) developed recommendations for the prevention and treatment of GIO

Y. Suzuki · H. Nawata · S. Soen · S. Fujiwara · H. Nakayama · I. Tanaka · K. Ozono · A. Sagawa · R. Takayanagi · H. Tanaka · T. Miki · Y. Tanaka
Committee for the Revision of Guidelines on the Management and Treatment of Glucocorticoid-Induced Osteoporosis of the Japanese Society for Bone and Mineral Research, Kobe, Japan

Y. Suzuki · S. Soen · S. Fujiwara · H. Nakayama · I. Tanaka · N. Masunari · Y. Tanaka
Working Group for the Revision of Guidelines on the Management and Treatment of Glucocorticoid-Induced Osteoporosis of the Japanese Society for Bone and Mineral Research, Kobe, Japan

Y. Suzuki (✉)
Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
e-mail: y3suzuki@is.icc.u-tokai.ac.jp

H. Nawata
Department of Medicine, Seiwakai Muta Hospital, Fukuoka, Japan

S. Soen
Department of Orthopaedic Surgery and Rheumatology, Nara Hospital, Kinki University School of Medicine, Ikoma, Japan

S. Fujiwara
Health Management and Promotion Center, Hiroshima Atomic Bomb Casualty Council, Hiroshima, Japan

H. Nakayama
Soshigayaokura Clinic, Tokyo, Japan

I. Tanaka
Nagoya Rheumatology Clinic, Nagoya, Japan

K. Ozono
Department of Pediatrics, Osaka University Graduate School of Medicine, Suita, Japan

A. Sagawa
Sagawa-Akira Rheumatology Clinic, Sapporo, Japan

in 1996 [5]. As the beneficial effects of bisphosphonates on GIO were reported from 1997 to 1999, guidelines for the management of GIO were also published in the United Kingdom, Canada, and Australia [6–8]. In Japan, the Japanese Society for Bone and Mineral Research (JSBMR) released guidelines on the management and treatment of GIO in 2004 [9].

An approach to determining the pharmacological intervention threshold based on assessment of the absolute risk of fractures was initiated in the mid-2000s, and FRAX®, a computer-based fracture risk assessment tool supported by the World Health Organization (WHO), was published in 2007 [10]. FRAX® can be used to calculate the 10-year probability of a major osteoporotic fracture and the 10-year probability of hip fracture with or without bone mineral density (BMD) measurement, and it includes GC therapy as an independent risk factor for fracture.

Regarding pharmacological intervention, the efficacy of teriparatide for the treatment of GIO was reported in 2007 and 2009 [11, 12].

Based on such new evidence regarding GIO, the ACR recommendations were updated to incorporate FRAX® as an assessment tool for fracture risk in the 2010 revision [13]. The Joint GIO Guidelines Working Group of the International Osteoporosis Foundation and the European Calcified Tissue Society have also published a framework for the development of guidelines for the management of GIO [14].

In response to these international changes related to GIO, the Japanese Society for Bone and Mineral Research (JSBMR) set up a Committee for the Revision of Guidelines on the Management and Treatment of Glucocorticoid-Induced Osteoporosis.

R. Takayanagi
Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

H. Tanaka
Department of Pediatrics, Okayama Saiseikai General Hospital, Okayama, Japan

T. Miki
Department of Geriatrics and Neurology, Osaka City University Graduate School of Medicine, Osaka, Japan

N. Masunari
Department of Liberal Arts and Basic Science, The Japanese Red Cross Kyushu International College of Nursing, Munakata, Japan

Y. Tanaka
The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Policies guiding the update

In order to update the guidelines, the committee has performed revisions based on the following policies.

(a) Although several guidelines for the management of GIO have been published during the last decade, it has been reported that the adherence to these guidelines is low, and a study performed in Japan demonstrated that the level of adherence to guidelines in clinical practice was only 23.3 % [15, 16]. The following problems have been pointed out: (1) lack of understanding about the importance of prevention and treatment of GIO among both doctors and patients; and (2) a low rate of BMD measurement for screening and monitoring. Because GCs are used in various medical fields and most doctors prescribing GCs are not specialists in the treatment of osteoporosis, the updated guidelines should make management decisions easier for physicians in clinical practice, even without fracture risk assessment by measurement of BMD.

(b) Because of the following limitations, the committee decided not to incorporate FRAX® into the revised guideline as a fracture risks assessment tool for GIO.

1. FRAX® cannot be used in premenopausal women or men under 40 years old.
2. The dose and duration of GC therapy are not incorporated into the algorithm, so fracture risk is likely to be underestimated in patients on high-dose GC therapy. In addition, FRAX® includes both past and current GC use as an independent risk factor.
3. FRAX® is mainly useful for predicting for non-vertebral fractures and clinical vertebral fractures, whereas morphometric vertebral fractures are a major problem in patients taking GCs [17].

(c) The committee collected data on several Japanese GIO cohorts and performed analyses to identify specific risk factors for fractures in Japan and their relative weights for calculation of scores in individuals, which could be employed by physicians to determine the pharmacological threshold for stating drug therapy. A working group was organized by the committee to study fracture risk factors and intervention threshold by analyzing the Japanese GIO cohorts.

(d) Pharmacological interventions recommended by the updated guidelines are limited to agents approved for the treatment of osteoporosis in Japan. The committee systematically reviewed data from randomized or controlled clinical trials. Each recommendation for

Table 1 Patients cohorts: demographic and disease characteristics

	Populations studied to determine the cut off score for intervention ($N = 903$ [117[a]])			Populations studied to verify the cut off score for intervention ($N = 144$ [1[a]])	
	Cohort A	Cohort B	Cohort C	Cohort D	Cohort E
Number of subjects	108 [18[a]]	617 [64[a]]	178 [35[a]]	108 [1[a]]	36 [0[a]]
Age (years)	54.4 ± 14.6	59.7 ± 11.1	50.1 ± 14.9	48.1 ± 15.6	49.3 ± 15.9
GC dose (mg/day)[b]	11.5 ± 13.6	5.7 ± 4.6	11.1 ± 13.6	45.7 ± 13.4	41.7 ± 26.4
Duration of GC therapy (years)	7.9 ± 8.8	4.8 ± 6.1	Data not available	0	0.07 ± 0.19
Lumbar BMD (%YAM)	88.2 ± 16.9	80.0 ± 15.6	78.7	95.9 ± 15.6	91.4 ± 16.5
Prior fragility fracture	17 (15.7%)	146 (23.7 %)	48 (27.0 %)	6 (6 %)	4 (11.1 %)
New fracture	8 (7.4 %)	96 (15.6%)	52 (29.2 %)	10 (11.4 %)	6 (16.7 %)
Underlying disease					
RA	26 (24.1 %)	467 (75.7 %)	83 (46.6 %)	1 (0.9 %)	3 (8.3 %)
SLE	36 (33.3 %)	36 (5.8 %)	44 (24.7 %)	37 (34.3 %)	11 (30.6 %)
PM/DM	12 (11.1 %)	12 (1.9 %)	13 (7.3 %)	30 (27.8 %)	7 (19.4 %)
Vasculitis syndrome	4 (3.7 %)	4 (0.6 %)	0	13 (12.0 %)	4 (11.1 %)
PMR	2 (1.9 %)	12 (1.9 %)	1 (0.6 %)	0	1 (2.8 %)
Miscellaneous	23 (21.3 %)	41 (6.6 %)	37 (20.8 %)	23 (21.3 %)	8 (22.2 %)
Overlap syndrome					
RA + SLE	0	0	0	0	2
RA + PM/DM	1	0	0	0	0
RA + miscellaneous	1	36	0	0	0
SLE + PM/DM	1	0	0	1	0
SLE + miscellaneous	2	6	0	0	0
PM/DM + miscellaneous	0	2	0	0	0
RA + PM/DM + miscellaneous	0	1	0	0	0

RA rheumatoid arthritis, *SLE* systemic lupus erythematosus, *PM/DM* polymyositis/dermatomyositis, *PMR* polymyalgia rheumatica

[a] Number of male patients

[b] Prednisolone equivalent mg/day. In patients receiving methylprednisolone pulse therapy, 50 mg/day (1 mg/kg body weight) was set as the usual dose following pulse therapy for convenience

pharmacological interventions was based on comprehensive assessment of the beneficial effects on BMD and fractures.

Subjects and methods

Subjects

In order to determine risk factors for fractures, the committee requested data on the following Japanese GIO cohorts: patients in a Japanese multicenter randomized controlled trial (RCT) on the primary and secondary prevention of GIO with alendronate plus alfacalcidol: The GOJAS study (cohort E and A), the longitudinal GIO cohort of the National Hospital Organization National Sagamihara Hospital (cohort B), the longitudinal GIO cohort of Fujita Health University Hospital (cohort C), and patients in an RCT of the University of Occupational and Environmental Health investigating primary prevention of GIO (cohort D).

The items investigated were the date of starting each study, age, sex, menopausal status, underlying diseases, GC dose at study start (prednisolone equivalent), duration of GC therapy, history of methylprednisolone pulse therapy, medications for osteoporosis, basal lumbar BMD (expressed as % YAM), prior fragility fractures, and new fractures during the study period (which varied from 2 to 4 years for these cohorts).

A total of 1,047 patients were recruited from these five Japanese cohorts. The demographic profile and disease characteristics of the patients are shown in Table 1.

Cohorts A, D, and E were in randomized controlled studies, while cohorts B and C were in longitudinal studies. With regard to underlying diseases, rheumatoid arthritis (RA) was common in cohorts A, B, and C. In particular, RA patients accounted for 75 % of cohort B. Therefore, the GC dose in these cohorts was as low as 5–12 mg/day and

the mean of lumbar BMD was around 80 % of the YAM. In contrast, the major underlying diseases of cohorts D and E were systemic lupus erythematosus (SLE), polymyositis/dermatomyositis, and vasculitis syndrome, which are usually treated with high doses of GCs. Because of differences in the underlying diseases, the patients in cohorts D and E were younger than those in cohorts A, B and C. Also, the baseline mean lumbar BMD of cohorts D and E was more than 90 % of the YAM.

Since the instruments used for BMD measurement by DXA varied among the participating institutions, BMD data were expressed as %YAM. Assessment and definition of vertebral fractures were done according to the criteria for primary osteoporosis in the JSBMR guideline on the prevention and treatment of osteoporosis [18].

Process of updating guidelines

The committee revised the guidelines according to the 4-phase process shown in Fig. 1.

Phase 1 involved the analysis of patients from three Japanese GIO cohorts (cohorts A, B and C), excluding the two cohorts enrolled to study the primary prevention of GIO. A total of 903 patients were analyzed by the Cox proportional hazard model to identify factors predicting fractures. First, the hazard ratio of each fracture predictor was obtained as a continuous variable. Then the factors were categorized with appropriate references and hazard ratios were calculated for each reference. For calculation of the risk score, the relative weight of a factor for predicting fracture was determined and a tentative score was assigned by conversion of parameter estimates. In brief, tentative scores were calculated 10 times for each parameter estimate, decimals were rounded, and the score was rounded to the next integer. The final score was calculated as the tentative score divided by 2 with rounding of decimals, and it was rounded to an integer <10. Then the cu-off score that efficiently separated patients with fracture from non-fracture patients was determined by receiver operating characteristic (ROC) analysis.

Phase 2 involved analysis of patients from the other two Japanese GIO cohorts (cohorts D and E), who were participants in RCTs on the primary prevention of GIO. The proportion of RA patients was high and the mean GC dose was<10 mg/day (prednisolone equivalent) for the cohorts analyzed in phase 1. Therefore, in order to verify that the cutoff score obtained in phase 1 could be applied to patient populations receiving high-dose GC therapy, and that the cutoff score could be used for both patients committed and exposed to GC therapy, phase 2 involved analysis of patients receiving primary prevention of GIO during treatment with GC for systemic collagen vascular diseases, such as SLE, polymyositis/dermatomyositis and vasculitis syndrome. The cutoff score that efficiently separated patients with fracture from non-fracture patients was analyzed by same process as that used in phase 1.

In phase 3, the committee integrated the findings from phases 1 and phase 2, refined the results by adding the evidence about GIO from Japan and overseas, and

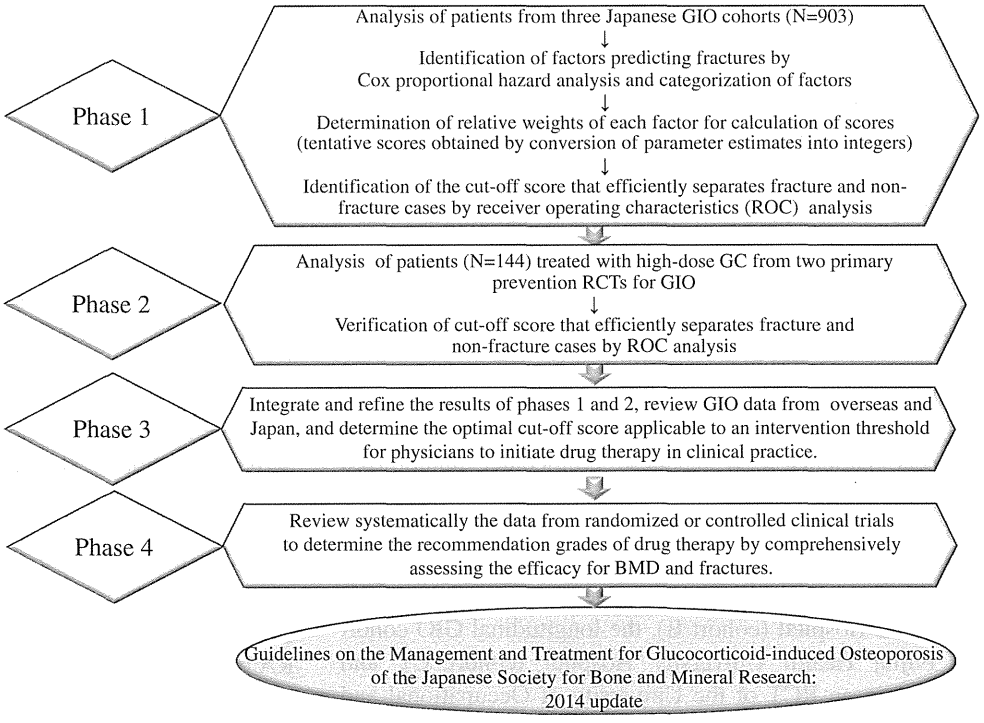

Fig. 1 The guidelines were updated in four steps: phase 1 to phase 4. Details of each phase are mentioned in the text

Table 2 Characteristics of patients analyzed to identify the optimal cutoff score for pharmacological intervention

	Male	Female
Number of subjects	117	786
Age/years (range)	59.8 ± 13.3 (17–83)	56.8 ± 12.8 (18–92)
Percentage with menopause (%)	–	81.7 %
GC dose (mg/day)[a]	10.4 ± 13.4 (0–80)	7.0 ± 7.9 (0–60)
<5	26 (22.2 %)	237 (30.2 %)
5 ≤ < 7.5	42 (35.9 %)	331 (42.1 %)
≥7.5	49 (41.9 %)	218 (27.7 %)
Methylprednisolone pulse therapy	6 (5.1 %)	14 (1.8 %)
Lumbar bone mineral density (%YAM)	87.6 ± 16.8	79.7 ± 15.6
Prior fragility fracture	23 (19.7 %)	188 (23.9 %)
New fracture	27 (23.1 %)	129 (16.4 %)
Underlying disease		
RA	66 (56.4 %)	510 (64.9 %)
SLE	10 (8.5 %)	106 (13.5 %)
PM/DM	13 (11.1 %)	24 (3.1 %)
Vasculitis syndrome	4 (3.4 %)	4 (0.5 %)
PMR	1 (0.9 %)	14 (1.8 %)
Miscellaneous	21 (17.9 %)	80 (10.2 %)
Overlap		
RA + PM/DM	0	1
RA + Miscellaneous	1	36
SLE+PM/DM	0	1
SLE + Miscellaneous	0	8
PM/DM + Miscellaneous	0	2
RA + PM/DM + Miscellaneous	1	1
Medications for osteoporosis		
None	52 (44.4 %)	241 (30.7 %)
Aminobisphosphonates	29 (24.8 %)	199 (25.3 %)
Non-aminobisphosphonates	16 (13.7 %)	150 (19.1 %)
SERM	0	6 (0.8 %)
Active vitamin D3	16 (13.7 %)	173 (22.0 %)
Vitamin K2	4 (3.4 %)	16 (2.0 %)
Miscellaneous	0	1 (0.13 %)

In patients receiving methylprednisolone pulse therapy, 50 mg/day (1 mg/kg body weight) was set as the usual dose following pulse therapy for analytical convenience

RA rheumatoid arthritis, *SLE* systemic lupus erythematosus, *PM/DM* polymyositis/dermatomyositis, *PMR* polymyalgia rheumatica

[a] Prednisolone equivalent mg/day

determined the optimal cutoff score that was applicable as an intervention threshold for physicians to initiate drug therapy in clinical practice.

Table 3 Predictors of fracture

Factor		Hazard ratio	95 % confidence interval	*P* value
Age	1 year increase	1.024	1.008–1.040	0.025
GC dose[a]	1 mg/day increase	1.038	1.024–1.051	<0.0001
Lumbar bone mineral density (%YAM)	1 % increase	0.979	0.968–0.991	0.006
Prior fragility fracture	+	3.412	2.409–4.832	<0.0001
Bisphosphonate therapy	+	0.472	0.302–0.738	0.001

[a] Prednisolone equivalent

Phase 4 involved assessing pharmacological interventions for the prevention and treatment of GIO. The data from randomized or controlled clinical trials performed overseas and in Japan were reviewed systematically. The investigation attempted to determine whether pharmacological intervention was effective for both BMD and fracture, as well as for both primary and secondary prevention. The committee determined the grade of recommendation for each drug by comprehensively assessing the beneficial effects on BMD and fractures when the drug was employed for prevention and treatment of GIO.

Results

Phase 1 analysis

Identification of fracture predictors

The committee analyzed 903 patients from three Japanese cohorts. As shown in Table 2, 87 % of the patients were female, and the mean age of each cohort was 56–60 years. The major underlying disease was rheumatoid arthritis. In about 30 % of patients, the GC dose was <5 mg/day (prednisolone equivalent), with about 40 % of patients receiving a dose of 5–7.5 mg/day, and about 30 % of patients using 7.5 mg/day or more. Few patients were on high dose of GC therapy.

When clinical characteristics were analyzed by using the Cox proportional hazard model, the age, GC dose, lumbar BMD, and prior fragility fracture were identified as factors that predicted future fractures (Table 3). As the age increased by 1 year, the fracture risk increased by 2.4 %. Similarly, as the GC dose increased by 1 mg prednisolone equivalent/day, the fracture risk increased by 3.8 %. Conversely, as lumbar BMD increased by 1 %, the fracture risk decreased by 2.1 %.

Table 4 Categorization of the predictors of fractures

Factors	Reference	Hazard ratio	95 % confidence interval	*P* value
Age (years)				
50 ≤ < 65	<50	1.446	0.86–2.427	0.16
65≤		2.108	1.214–3.660	0.08
GC dose (mg/day)[a]				
5 ≤ < 7.5	<5	1.149	0.754–1.756	0.5186
7.5≤		2.166	1.405–3.338	0.0005
Lumbar bone mineral density (%YAM)				
70 ≤ < 80	80≤	1.373	0.896–2.104	0.1452
<70		1.863	1.244–2.790	0.0025
Prior fragility fracture				
+	−	3.485	2.457–4.943	<0.0001
Bisphosphonate therapy				
+	−	0.481	0.307–0.753	0.061

[a] Prednisolone equivalent

Table 5 Scores for the categories of each fracture predictor

Predictor	Parameter estimates by logistic regression	Tentative score[a]	Final score[b]
Age (years)			
<50			0
50 ≤ < 65	0.36890	4	2
65≤	0.74589	8	4
GC dose (mg/day)[c]			
<5			0
5 ≤ < 7.5	0.13867	2	1
7.5≤	0.77294	8	4
Lumbar bone mineral density (%YAM)			
80≤			0
70 ≤ < 80	0.31724	4	2
<70	0.62218	7	4
Prior fragility fractures			
−			0
+	1.24846	13	7
Bisphosphonate therapy			
−			0
+	−0.73190	−8	−4

[a] Calculated 10 times for each parameter estimate, decimals rounded off, and rounded up to the next integer

[b] Tentative score divided by 2, decimals rounded off, and rounded to an integer <10

[c] Prednisolone equivalent

If there was a history of prior fragility fracture, the fracture risk increased by 3.4 times compared with that for patients who had no history of fracture. In contrast, use of bisphosphonates decreased the fracture risk by 52.8 %.

Categorization of fracture predictors

When the hazard ratio for age was calculated versus <50 years, the fracture risk was 1.446 times higher at age 50–65 years and was 2.108 times higher at age ≥65 years. For the GC dose and lumbar BMD, hazard ratios were calculated versus a prednisolone dose <5 mg/day and versus %YAM ≥80 %, respectively. The hazard ratios are shown in Table 4. In patients with a history of fragility fractures, the future fracture risk was 3.485 times higher than in patients without prior fragility fractures. In contrast, treatment with bisphosphonates decreased the fracture risk to 0.481 times compared with that for patients not on bisphosphonates (Table 4).

Tentative scores obtained by conversion of parameter estimates

Parameter estimates for each risk factor obtained by logistic regression were converted to tentative scores by the formula described in the "Methods," and are shown in Table 5. Final scores were obtained by modification of the tentative scores as shown in Table 5 and were employed for further analysis. As a result, an age 65 years or older, a GC dose of more than 7.5 mg/day (prednisolone equivalent), a BMD of <70 % relative to the YAM, and fragility fracture were assigned high scores as independent risk factors for fracture.

Determining the optimal score for discrimination between fracture and non-fracture patients

Using the final scores, receiver operating characteristic (ROC) analysis was performed to obtain the optimal cutoff score. The score with the highest value (0.380) for sensitivity-(1-specificity) was shown to be a score of 6 (Table 6; Fig. 2). At a score of 6, the sensitivity, 1-specificity, true positive rate (%), true negative rate (%), false positive rate (%), and false negative rate (%) were 0.712, 0.332, 71.2, 66.8, 33.1, and 28.8 %, respectively. The area under the ROC curve (a measure of how well the score distinguished fracture and non-fracture groups) was 0.741.

Phase 2 analysis

Verification of the phase 1 results

The validity of the optimal cutoff score for setting the intervention threshold was assessed in the following manner by using the data from different patient groups.

The subjects consisted of 144 patients from the two RCTs on primary prevention, which were the primary prevention trial of the University of Occupational and Environmental Health and a multicenter study on the efficacy of alendronate and alfacalcidol (GOJAS) for primary prevention. The

Table 6 Determination of the optimal cut off score by receiver operating characteristics (ROC) analysis

X	Probability	1-specificity	Sensitivity	Sensitivity-(1-specificity)	True positive	True negative	False positive	False negative
19.0000	0.701	0.001	0.026	0.024	4	746	1	152
17.0000	0.615	0.004	0.058	0.054	9	744	3	147
16.0000	0.569	0.012	0.109	0.097	17	738	9	139
15.0000	0.521	0.019	0.147	0.129	23	733	14	133
14.0000	0.474	0.031	0.192	0.162	30	724	23	126
13.0000	0.426	0.058	0.244	0.186	38	704	43	118
12.0000	0.380	0.076	0.301	0.225	47	690	57	109
11.0000	0.336	0.100	0.397	0.297	62	672	75	94
10.0000	0.295	0.141	0.462	0.321	72	642	105	84
9.0000	0.256	0.166	0.500	0.334	78	623	124	78
8.0000	0.222	0.220	0.590	0.370	92	583	164	64
7.0000	0.190	0.258	0.603	0.344	94	554	193	62
6.0000	**0.162**	**0.332**	**0.712**	**0.380**	**111**	**499**	**248**	**45**
5.0000	0.138	0.396	0.744	0.347	116	451	296	40
4.0000	0.117	0.542	0.821	0.278	128	342	405	28
3.0000	0.098	0.639	0.878	0.240	137	270	477	19
2.0000	0.083	0.724	0.942	0.218	147	206	541	9
1.0000	0.069	0.807	0.962	0.154	150	144	603	6
0.0000	0.058	0.908	0.974	0.067	152	69	678	4
−1.0000	0.048	0.948	0.987	0.039	154	39	708	2
−2.0000	0.040	0.975	0.994	0.019	155	19	728	1
−3.0000	0.033	0.988	1.000	0.012	156	9	738	0
−4.0000	0.028	1.000	1.000	0.000	156	0	747	0

Bold values indicate the highest value of sensitivity-(1-specificity)

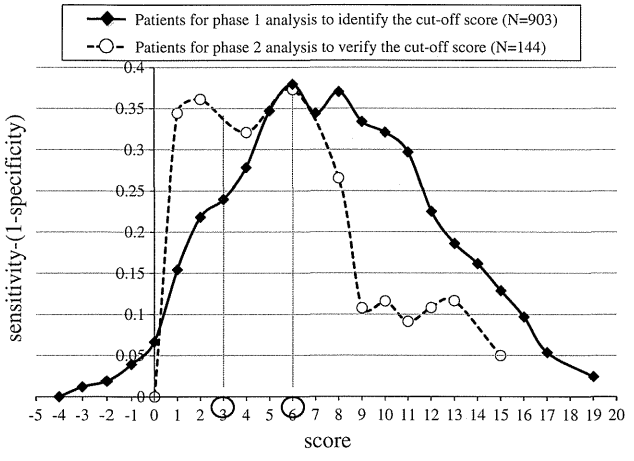

Fig. 2 Identification of the optimal cutoff score to separate fracture and non-fracture cases by receiver operating characteristics analysis. The score of the maximum value of sensitivity-(1-specificity) was 6 by both phase 1 and phase 2 analyses. A score 3 was adopted in the updated guideline as the optimal cutoff score and is shown in the graph

characteristics of these subjects are shown in Table 7. All of the subjects were female patients, except for one male, and mean age was about 10 years younger than that of the subjects in the phase 1 analysis. Underlying diseases were generally systemic collagen vascular diseases, such as SLE and polymyositis/dermatomyositis, and there were only four patients with RA. Accordingly, all except one of the patients were taking GC doses of more than 7.5 mg/day (prednisolone equivalent). The clinical profiles of the patients in the phase 1 and 2 analyses differed with regard to age, GC doses, and underlying diseases.

Verification of the optimal cutoff score from Phase 1

ROC analysis indicated that the score with the highest value (0.373) for sensitivity-(1-specificity) was a score of 6 (Table 8; Fig. 2) and this finding corresponded to the result obtained in phase 1. At the score 6, the sensitivity, 1- specificity, true positive rate (%), true negative rate (%), false positive rate (%), and false negative rate (%) were 0.600, 0.227, 60.0, 77.3, 22.7, and 40.0 %, respectively. The area under the ROC curve (an indicator of accuracy) was 0.741.

Determining the optimal cutoff score for intervention and outline of the updated guidelines (phase 3)

Patients covered by the guidelines

The updated guidelines cover men and women aged 18 years or older who are using or planning to use GC for more than

Table 7 Characteristics of patients analyzed to verify the cutoff score for verification

	Male	Female
Number of subjects	1	143
Age/years (range)	57.0	48.3 ± 15.7 (18–84)
Percentage of menopause (%)	–	49.0 %
GC dose (mg/day)[a]	40	44.7 ± 17.7 (0–160)
<5	0	0
5 ≤ < 7.5	0	1 (0.7 %)
≥7.5	1	137 (99.3 %)
Methylprednisolone pulse therapy	0	6 (4.1 %)
Lumbar bone mineral density (%YAM)	86.8	94.8 ± 15.9
Prior fragility fracture	0	10 (7.0 %)
New fracture	0	16 (11.2 %)
Underlying disease		
RA	0	4 (2.8 %)
SLE	0	48 (33.6 %)
PM/DM	1	36 (25.2 %)
Vasculitis syndrome	0	17 (11.9 %)
PMR	0	1 (0.7 %)
Miscellaneous	0	31 (21.7 %)
Overlap		
RA + SLE	0	2
SLE+PM/DM	0	1
Medications for osteoporosis		
None	0	1 (0.7 %)
Aminobisphosphonates	0	50 (35.7 %)
Non-aminobisphosphonates	0	34 (24.3 %)
SERM	0	0
Active vitamin D3	1	54 (38.6 %)
Vitamin K2	0	0
Miscellaneous	0	1 (0.7 %)

In patients receiving methylprednisolone pulse therapy, 50 mg/day (1 mg/kg body weight) was set as the usual dose following pulse therapy for analytical convenience

RA rheumatoid arthritis, *SLE* systemic lupus erythematosus, *PM/DM* polymyositis/dermatomyositis, *PMR* polymyalgia rheumatica

[a] Prednisolone equivalent mg/day

3 months. New evidence regarding GIO in children has not been reported in Japan or overseas since the 2004 JSBMR guidelines were published, and the cohorts used to identify risk factors for fractures and set the cutoff score for pharmacological intervention when updating these guidelines did not include any children. Therefore, children were excluded from coverage by the guidelines. With regard to the GC administration route, currently available evidence is limited to oral administration, and there is insufficient data about intravenous or inhaled GCs. The risk of vertebral fractures was found to increase rapidly within 3–6 months after the start of oral GC therapy by an epidemiological study [2], and the framework for development of national guidelines on the management of GIO provided by the Joint IOF-ECTS Working Group covers men and women considering oral GC therapy for 3 months or longer [14]. Although analysis of 903 cases in phase 1 failed to demonstrate that the duration of GC therapy was a factor predicting fractures, the updated JSBMR guidelines are designed for patients who are exposed to or committed to oral GC therapy for more than 3 months.

Determination of the optimal cutoff score for pharmacological intervention and development of the guidelines

The committee analyzed 903 patients in cohorts A, B, and C, which included a high percentage of RA patients using rather low GC doses, to determine the intervention threshold score, and the cutoff score obtained that efficiently separated fracture and non-fracture cases was a score of 6. Then, verification of this score was performed by analyzing 144 patients from cohorts D and E, in which the majority of patients had systemic collagen vascular diseases and were on high-dose GC therapy. As a result, a score of 6 was confirmed to discriminate fracture and non-fracture cases. Thus, the results of both analyses were consistent.

The committee then discussed the optimal score for pharmacological intervention on the basis of a score of 6. The following issue was raised regarding a score of 6 as an intervention threshold; the score of a woman aged from 50 to under 65 years would be <6, even if she had osteopenia (BMD 70–79 %) or was taking prednisolone at a moderate dose (5–7.5 mg/day). Therefore, the committee concluded that it was preferable for the sensitivity of the optimal cutoff score to be more than 80 % from a clinical point of view. Accordingly, the guidelines were updated on the basis of a score of 3 as the optimal cutoff score for pharmacological intervention. The Guidelines on the Management and Treatment of Glucocorticoid-Induced Osteoporosis of the Japanese Society for Bone and Mineral Research (2014 update) are shown in Fig. 3. An age of 65 years or older, prednisolone ≥7.5 mg/day (or its equivalent), prior fragility fracture, and lumbar BMD <70 % of the YAM are all assigned a score ≥3 as single risk factors, so drug therapy should be started for subjects with any of these factors.

General guidance and treatment/follow-up

General guidance

All patients who are committed to or exposed to GC therapy should be encouraged to reduce risk factors and

Table 8 Verification of the optimal cutoff score by receiver operating characteristics (ROC) analysis

X	Probability	1-Specificity	Sensitivity	Sensitivity-(1-specificity)	True positive	True negative	False positive	False negative
		0.000	0.000	0.000	0	119	0	15
15.0000	0.508	0.017	0.067	0.050	1	117	2	14
13.0000	0.406	0.017	0.133	0.117	2	117	2	13
12.0000	0.358	0.025	0.133	0.108	2	116	3	13
11.0000	0.312	0.042	0.133	0.091	2	114	5	13
10.0000	0.270	0.084	0.200	0.116	3	109	10	12
9.0000	0.232	0.092	0.200	0.108	3	108	11	12
8.0000	0.197	0.135	0.400	0.266	6	103	16	9
6.0000	**0.140**	**0.227**	**0.600**	**0.373**	**9**	**92**	**27**	**6**
4.0000	0.098	0.479	0.800	0.321	12	62	57	3
2.0000	0.067	0.639	1.000	0.361	15	43	76	0
1.0000	0.055	0.656	1.000	0.345	15	41	78	0
0.0000	0.046	1.000	1.000	0.000	15	0	119	0

Bold values indicate the highest value of sensitivity-(1-specificity)

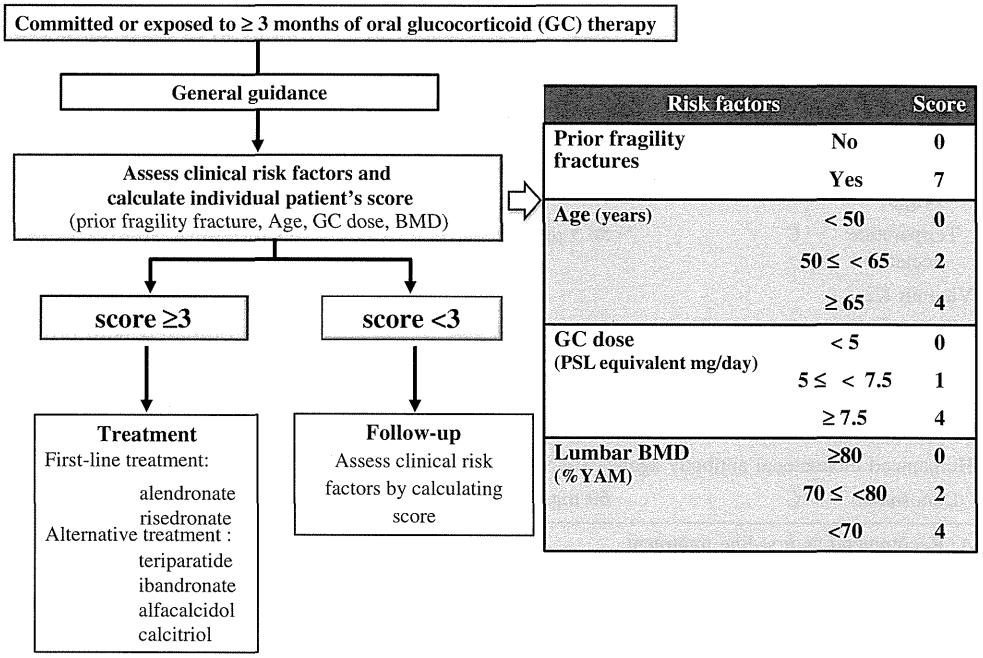

Fig. 3 Guidelines on the Management and Treatment for Glucocorticoid-Induced Osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update. *GC* glucocorticoid, *PSL* prednisolone, *BMD* bone mineral density

modify their lifestyle, regardless of the GC dose or duration of GC therapy. It is important to provide guidance on improvement of nutrition, including dietary calcium intake, body weight, smoking, alcohol intake, and exercise, for the management of GIO similar to that for management of primary osteoporosis [18].

Monitoring and follow-up

Monitoring is necessary to verify the efficacy of drug therapy. To carefully assess the development of new fractures and changes of BMD, regular radiographic examination and BMD measurement should be scheduled every 6–12 months. Even in patients who are judged to have a low fracture risk and are being observed without pharmacological intervention, the fracture risk should be assessed by the scoring method in the JSBMR guidelines at appropriate intervals, considering their GC dose and other risk factors.

Recommendations of pharmacotherapy for GIO (phase 4)

As shown in Table 9, the committee has limited the pharmacological interventions recommended in the updated guidelines to agents that are currently approved for the treatment of osteoporosis in Japan.

Table 9 Pharmacological recommendations for glucocorticoid-induced osteoporosis

Medications	Recommendation grade[a]	Dose and administration
Bisphosphonates		
Alendronate	A	5 mg daily, 35 mg weekly, oral
		900 μg every 4 weeks, iv infusion
Risedronate	A	2.5 mg daily, 17.5 mg weekly, 75 mg monthly, oral
Etidronate	C	200 mg, 400 mg 2 weeks per 3 months, oral
Minodronate	C	1 mg daily, 50 mg every 4 weeks, oral
Ibandronate	B	1 mg monthly, iv
Active vitamin D3 analog		
Alfacalcidol	B	0.25 μg, 0.5 μg, 1 μg daily, oral
Calcitriol	B	0.25 μg, 0.5 μg daily, oral
Eldecalcitol	C	0.5 μg, 0.75 μg daily, oral
Teriparatide [recombinant human parathyroid hormone (1–34)]		
Teriparatide (rDNA origin)	B	20 μg daily, sc
Teriparatide acetate	C	56.5 μg, weekly, sc
Vitamin K2		
Menatetrenone	C	45 mg daily, oral
Selective estrogen-receptor modulators (SERM)		
Raloxifene	C	60 mg daily, oral
Bazedoxifene	C	20 mg daily, oral
Humanized monoclonal antibody against RANKL		
Denosumab	C	60 mg every 6 months, sc

A: Recommend as first-line treatment

B: Recommend as alternative treatment if there is a contraindication or early intolerance to first-line treatment, or an inadequate response to first-line treatment

C: Insufficient or limited evidence to recommend for the treatment of GIO

[a] Recommendation grade

Alendronate and risedronate have been shown to prevent a decrease of lumbar and femoral BMD [19–26]. The efficacy of these drugs has been proven in both primary and secondary prevention studies. In addition, reduction of vertebral fractures was demonstrated in these studies, although not as a primary endpoint. Therefore, both alendronate and risedronate are recommended as first-line treatment. Since both daily and once-weekly oral alendronate have been shown to be effective for GIO [22], the committee did not alter the grade of recommendation for bisphosphonates on the basis of regimens.

Cyclical etidronate has been shown to be effective for preventing vertebral and femoral bone loss in randomized prospective controlled studies [27, 28], so this drug was recommended as first-line therapy in the 2004 JSBMR guidelines. However, reduction of vertebral fractures was only found to be significant in post-menopausal women by sub-analysis, and not in the whole patient population [27]. Therefore, the evidence was judged to be insufficient for recommending etidronate in the updated guidelines.

Efficacy of minodronate for GIO has not been investigated sufficiently, so this drug is not recommended in the new guidelines.

Ibandronate has been shown to be effective for secondary prevention of GIO by increasing vertebral and femoral BMD and reducing vertebral fractures compared with alfacalcidol [29–31]. However, data on primary prevention are limited to one study with a small number of patients [32]. For this reason, ibandronate is considered to be an alternative option for individuals with contraindications to or early intolerance of first-line treatment.

With regard to active vitamin D3 derivatives (alfacalcidol and calcitriol), there is evidence demonstrating effectiveness for lumbar and femoral BMD, and evidence of vertebral fracture reduction, albeit not as a primary endpoint, has been reported in placebo-controlled or comparator studies [33–35]. A meta-analysis showed that active vitamin D3 derivatives achieved a greater increase of BMD and more effective reduction of vertebral fracture risk compared with no treatment or calcium alone [36, 37], so these drugs are also alternative treatments.

The effect of eldecalcitol on GIO has not been evaluated and there are no available clinical data. In addition, it may have the risk of further increasing urinary calcium excretion, so eldecalcitol is not recommended in the guidelines.

Teriparatide [rDNA origin] has been shown to be effective at increasing vertebral and femoral BMD and for reducing vertebral fractures in secondary prevention studies [11, 12, 38–40], although the latter outcome was not a primary endpoint. Teriparatide was more effective than alendronate for secondary prevention of GIO, but no studies have been conducted with respect to primary prevention. The safety and efficacy of this drug have not been evaluated beyond 2 years of treatment. Since treatment with teriparatide is limited to no longer than 2 years during a patient's lifetime and there is no evidence on how to determine the optimal timing of its use, this agent is only recommended as alternative treatment in patients with a contraindication or early intolerance to first-line treatment or those showing an inadequate response to first-line treatment. It is also unclear what the optimal drug treatment would be following teriparatide. Some studies suggest that anti-resorptive therapy, such as bisphosphonates, should be considered following the permitted 2-year treatment duration [40, 41].

The efficacy of teriparatide acetate for GIO has not been evaluated. Because there are no available clinical data, the committee has not recommended it this time.

Because vitamin K2 was shown to have a similar fracture-preventing effect to etidronate in a Japanese longitudinal cohort study, it was recommended as an alternative drug in the 2004 guidelines. However, there are no additional data to verify the effectiveness of vitamin K2 for GIO, and a prospective randomized controlled study has not been conducted to assess its effect on reducing fractures. Accordingly, evidence about the effect of vitamin K2 on GIO was judged to be insufficient for it to be recommended, as was decided for etidronate.

Selective estrogen receptor modulators (SERMs) and denosumab, a fully human monoclonal antibody to RANKL, were also not recommended in the new guidelines because of insufficient data in relation to GIO.

Safety of treating GIO

Bisphosphonates-related osteonecrosis of the jaw (BRONJ)

There are accumulating reports on osteonecrosis of the jaw developed in patients with cancer or osteoporosis who have been treated with intravenous or oral bisphosphonates after invasive dental procedures such as tooth extraction [42]. The incidence of BRONJ is very low and is estimated to be between 1/10,000 and 1/100,000 person-years based on reports from overseas, while the nationwide retrospective cohort survey conducted by the Japanese Society of Oral and Maxillofacial Surgeons demonstrated an incidence ranging from 0.01 to 0.02 % in Japan [43]. Although GC therapy has been cited as a risk factor for BRONJ, there is no evidence that osteonecrosis of the jaw is more common in bisphosphonate-treated patients taking GCs than in those treated with bisphosphonates alone. Since an increased fracture risk is associated with long-term GC therapy for more than 3 months and efficacy of bisphosphonates for the prevention and treatment of GIO has been established, the benefit of bisphosphonate therapy definitely overweighs the risk. With regard to the definition, clinical characteristics, risk factors, precautions when initiating bisphosphonates, and how long to suspend bisphosphonate therapy before dental procedures and when to resume it, the standard position paper from the allied task force committee of JSBMR should be helpful as a reference for physicians [44].

Atypical femoral fractures (AFFs)

Atypical femoral fractures (AFFs), which are located in the subtrochanteric region and diaphysis of the femur, have been reported in patients taking bisphosphonates or denosumab [45–47]. However, AFFs also occur in patients without exposure to these osteoporosis medications. AFFs are fractures that occur suddenly with minimal or no trauma, and are often preceded by prodromal thigh or groin pain for several weeks. According to the second report of the American Society for Bone and Mineral Research [47], based on recent evidence, AFFs may represent stress or insufficiency fractures.

AFFs are rare, accounting for approximately 1 % of all hip and femoral fractures, and few serious cases may be encountered in the clinical setting. Although GCs have been proposed as a risk factor for the development of AFFs, a recent controlled study revealed that GC use was not associated with an increased risk of AFFs in patients taking bisphosphonates [46].

Although the relative risk of AFFs is increased in patients taking bisphosphonates, the absolute risk has been reported to be low, ranging from 3.7 to 50 per 100,000 person-years [47]. Since longer-term use of bisphosphonates may be associated with a higher risk of AFFs, further imaging examination should be considered in patients using bisphosphonates who develop unexplained dull pain or aching in the thigh or groin region.

Safety of drug therapy in premenopausal women who want to become pregnant

Although there is limited evidence about the efficacy of drug therapy for GIO in premenopausal women, no clinical trials of bisphosphonates or other drugs have been specifically designed with premenopausal women as the primary target population. In addition, there is currently little evidence about the safety of bisphosphonates or other drugs before and during pregnancy or while breast-feeding. Because of inadequate evidences, the guidelines do not provide any recommendations on drugs for premenopausal women who want to become pregnant.

Bisphosphonates are incorporated into the bone matrix, and then are gradually released over a period of weeks to years. Therefore, there is a theoretical risk of fetal harm, but human preconception and first trimester bisphosphonate use in case reports and prospective cohort studies with a small sample size have demonstrated no significant adverse effects on the fetus, neonate or mother [48–51], as reported in animal studies. The ACR 2010 guidelines recommended alendronate (grade A) and risedronate or teriparatide (grade C) for selected premenopausal women of childbearing potential who are taking more than 7.5 mg/day of prednisolone, have a history of fragility fractures and are clearly at higher risk for additional fractures [13]. However, bisphosphonates, including the first-line

medications alendronate and risedronate, have been assigned to pregnancy category C by theUS Food and Drug Administration (FDA), and it is not clear how long bisphosphonates should be suspended before pregnancy. Therefore, these drugs should be used carefully before pregnancy and only in specific cases when there are no alternatives and the benefits outweighs the risks, and these agents should be avoided during pregnancy. In addition, informed consent is necessary [13, 52].

Bisphosphonates might be transferred from mother to infant in breast milk. However, the clinical risk is not expected to be high, since the bisphosphonate concentration in milk was below the detection limit, absorption by neonates would be expected to be very low as in adults, and bisphosphonates may form complexes with calcium from breast milk in the gastrointestinal tract. However, considering the lack of adequate evidence regarding the safety of bisphosphonates in relation to breast-feeding, these drugs should be used with great caution during lactation [52, 53].

Discussion

The Committee of the JSBMR has updated the guidelines on the management and treatment of glucocorticoid-induced osteoporosis and has incorporated a new scoring method. In the updated guidelines, the committee established an intervention threshold by analyzing five Japanese GIO cohorts from primary and secondary prevention studies, and then by comprehensively assessing fracture risk using the scoring methods. Age, GC dose, lumbar BMD, and prior fragility fractures were identified as factors predicting future fracture, and each factor was scored according to the category. As a result, the fracture risk for an individual can be calculated as the sum of the scores for each risk factor. Since an age of 65 years or older, prednisolone dose of 7.5 mg/day or more and a history of fragility fracture are independent risk for future fractures, initiation of drug therapy can be decided more easily without evaluation of BMD by DXA when one of these risk factors exists.

During the process of updating the guidelines, the pharmacological threshold was identified by analyzing three GIO cohorts with a high percentage of RA patients and Low GC doses. This threshold was subsequently verified by using data on two primary prevention GIO cohorts using high-dose GC therapy for systemic collagen vascular diseases. As a result, the thresholds obtained from analyses of these two different patient populations were identical. Therefore, the recommendations in the guidelines cover patients with various underlying diseases treated with low to high doses of GC, and can be applied to both primary and secondary prevention of GIO.

The medications recommended in the guidelines are limited to those approved for the treatment of osteoporosis in Japan. Among these agents, the committee comprehensively reviewed validity for both primary and secondary prevention, and assessed the benefit for both BMD and fracture prevention based on the results of clinical studies performed in Japan and overseas. Then they recommended the drugs judged to be most effective based on current knowledge. The recommendations shall be revised suitably when new evidence regarding the effectiveness of therapy is accumulated.

Finally, recommendations in the guidelines are provided to aid the physician in decision-making for the management of GIO, and do not replace an experienced physician's judgment in the care of patients with GIO.

Conflict of interest Y. S. has received research funding from Mitsubishi-Tanabe, Eisai, AbbVie, Pfeizer, Ono, Toyama Chemical, Japan Blood Products Organization, Takeda, Chugai, and Astellas, and has received honoraria or fees for promotional materials from Pfizer, Takeda, Eisai, and Mitsubishi-Tanabe. S. S. has received consulting fees, speaking fees, and/or honoraria from Asahi Kasei Pharma, Astellas, Chugai, Daiichi-Sankyo Eizai, Eli Lilly Japan, MSD, Ono, Pfizer, Takeda, Teijin Pharma. S. F. has received speaking fees, and/or honoraria from Daiichi-Sankyo and Ono. H. N. has received speaking fees from Abbvie, Chugai, Astellas, Takeda, Pfizer, Janssen, Eisai, Daiichi-Sankyo., Teijin, Lilly, Ono, and Asahikasei. I. T. has received speaking fees, and/or honoraria from Chugai, Astellas, Takeda, Mitsubishi-Tanabe, Pfizer, Eisai, Daiichi-Sankyo, Eizai, Asahikasei, Teijin, Eli Lilly Japan , Taisho-Toyama, Ono and MSD. K. O. has received consulting fees, speaking fees, and/or honoraria from Chugai, Eli Lilly Japan, MSD, Pfizer, Teijin Pharma. R. T. has received speaking fees from Astellas, Daiichi-Sankyo and Eli Lilly. T. M. has received speaking fees, and/or research funding from Chugai, Takeda, Pfizer, Eisai, Daiichi-Sankyo, Taisho-Toyama, Teijin Farma, MSD, Ono and Elilly Japan. Y. T. has received consulting fees, speaking fees, and/or honoraria from Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi-Tanabe, Pfizer, Janssen, Eisai, Daiichi-Sankyo, UCB, GlaxoSmithKline, Bristol-Myers.

References

1. Weinstein RS (2011) Glucocorticoid-induced bone disease. N Engl J Med 365:62–70
2. Van Staa TP, Leukens HGM, Cooper C (2002) The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 13:777–787
3. LoCascio V, Bonucci E, Imbimbo B, Ballanti P, Adami S, Milani S, Tartarotti D, DellaRocca C (1990) Bone loss in response to long-term glucocorticoid therapy. Bone Miner 8:39–51
4. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C (2003) Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 48:3224–3229
5. American College of Rheumatology Task Force on Osteoporosis Guidelines (1996) Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 39:1791–1801
6. Adachi JD, Olszynski WP, Hanley DA, Hodsman AB, Kendler DL, Siminoski KG, Brown J, Cowden EA, Goltzman D, Ioannidis G, Josse RG, Ste-Marie LG, Tenenhouse AM, Davison KS,

Blocka KL, Pollock AP, Sibley J (2000) Management of corticosteroid-induced osteoporosis. Sem Arthritis Rheum 29:228–251
7. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis (2001) Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis 2001 update. Arthritis Rheum 44:1496–1503
8. Royal College of Physicians (2002) Glucocorticoid-induced osteoporosis: Guidelines on Prevention and Treatment. Bone and Tooth Society of Great Britain. National Osteoporosis Society and Royal College of Physicians, London
9. Nawata H, Soen S, Takayanagi R, Tanaka I, Takaoka K, Fukunaga M, Matsumoto T, Suzuki Y, Tanaka H, Fujiwara S, Miki T, Sagawa A, Nishizawa Y, Seino Y (2005) Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004). J Bone Miner Metab 23:105–109
10. Kanis JA (2007) On behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary health care level. WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield
11. Saag KG, Shane E, Boonen S, Marín F, Donley DW, Taylor KA, Dalsky GP, Marcus R (2007) Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med 357:2028–2039
12. Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, Krege JH, Krohn K, Warner MR (2009) Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum 60:3346–3355
13. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, Curtis JR, Furst DE, McMahon M, Patkar NM, Volkmann E, Saag KG (2010) American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res 62:1515–1526
14. Lekamwasam S, Adachi JD, Agnusdei D, Bilezikian J, Boonen S, Borgström F, Cooper C, Diez Perez A, Eastell R, Hofbauer LC, Kanis JA, Langdahl BL, Lesnyak O, Lorenc R, McCloskey E, Messina OD, Napoli N, Obermayer-Pietsch B, Ralston SH, Sambrook PN et al (2012) A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 23:2257–2276
15. Kirigaya D, Nakayama T, Ishizaki T, Ikeda S, Satoh T (2011) Management and treatment of osteoporosis in patients receiving long-term glucocorticoid treatment: current status of adherence to clinical guidelines and related factors. Intern Med 50:2793–2800
16. Guzman-Clark JR, Fang MA, Sehl ME, Traylor L, Hahn TJ (2007) Barriers in the management of glucocorticoid-induced osteoporosis. Arthritis Rheum 57:140–146
17. Compston J (2011) Clinical question: what is the best approach to managing glucocorticoid-induced osteoporosis. Clin Endocrinol (Oxf) 74:547–550
18. The Ad Hoc Committee to develop Guidelines for Prevention and Treatment of Osteoporosis (The Japanese Society for Bone and Mineral Research/Japan Osteoporosis Society Collaborative Initiative.) (2011) Guidelines for Prevention and Treatment of Osteoporosis, 2011th edn. Life Science, Tokyo
19. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, Thamsborg G, Liberman UA, Delmas PD, Malice MP, Czachur M, Daifotis AG (1998) Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med 339:292–299
20. Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, Lane NE, Kaufman JM, Poubelle PE, Hawkins F, Correa-Rotter R, Menkes CJ, Rodriguez-Portales JA, Schnitzer TJ, Block JA, Wing J, McIlwain HH, Westhovens R, Brown J, Melo-Gomes JA et al (2001) Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum 44:202–211
21. de Nijs RN, Jacobs JW, Lems WF, Laan RF, Algra A, Huisman AM, Buskens E, de Laet CE, Oostveen AC, Geusens PP, Bruyn GA, Dijkmans BA, Bijlsma JW, STOP Investigators (2006) Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. N Engl J Med 355:675–684
22. Stoch SA, Saag KG, Greenwald M, Sebba AI, Cohen S, Verbruggen N, Giezek H, West J, Schnitzer TJ (2009) Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: a 12-month randomized, placebo-controlled clinical trial. J Rheumatol 36:1705–1714
23. Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, Zizic TM, Wallach S, Sewell KL, Lukert BP, Axelrod DW, Chines AA (1999) Risedronate therapy prevents corticosteroid-induced bone loss: a twelve month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 42:2309–2318
24. Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, Eusebio RA, Devogelaer JP (2000) Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res 15:1006–1013
25. Reid DM, Adami S, Devogelaer JP, Chines AA (2001) Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy. Calcif Tissue Int 69:242–247
26. Eastell R, Devogelaer JP, Peel NF, Chines AA, Bax DE, Sacco-Gibson N, Nagant de Deuxchaisnes C, Russell RG (2000) Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. Osteoporos Int 11:331–337
27. Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R, Kendler DL, Lentle B, Olszynski W, Ste-Marie LG, Tenenhouse A, Chines AA (1997) Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 337:382–387
28. Roux C, Oriente P, Laan R, Hughes RA, Ittner J, Goemaere S, Di Munno O, Pouillès JM, Horlait S, Cortet B (1998) Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. J Clin Endocrinol Metab 83:1128–1133
29. Ringe JD, Dorst A, Faber H, Ibach K, Sorenson F (2003) Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from long-term comparative study. Osteoporos Int 14:801–807
30. Ringe JD, Dorst A, Faber H, Ibach K, Preuss J (2003) Three-monthly ibandronate bolus injection offers favourable tolerability and sustained efficacy advantage over two years in established corticosteroid-induced osteoporosis. Rheumatology 42:743–749
31. Hakala M, Kröger H, Valleala H, Hienonen-Kempas T, Lehtonen-Veromaa M, Heikkinen J, Tuomiranta T, Hannonen P, Paimela L, ONCE trial group (2012) Once-monthly oral ibandronate provides significant improvement in bone mineral density in postmenopausal women treated with glucocorticoids for inflammatory rheumatic diseases: a 12-month, randomized, double-blind. Placebo-controlled trial. Scand J Rheumatol 41:260–266
32. Fahrleitner-Pammer A, Piswanger-Soelkner JC, Pieber TR, Obermayer-Pietsch BM, Pilz S, Dimai HP, Prenner G, Tscheliessnigg KH, Hauge E, Portugaller RH, Dobnig H (2009) Ibandronate prevents bone loss and reduces vertebral fracture risk in male cardiac transplant patients: a randomized double-blind, placebo-controlled trial. J Bone Miner Res 24:1335–1344

33. Reginster JY, Kuntz D, Verdickt W, Wouters M, Guillevin L, Menkès CJ, Nielsen K (1999) Prophylactic use of alfacalcidol in corticosteroid-induced osteoporosis. Osteoporos Int 9:75–81
34. Ringe JD, Cöster A, Meng T, Schacht E, Umbach R (1999) Treatment of glucocorticoid-induced osteoporosis with alfacalcidol/calcium versus vitamin D/calcium. Calcif Tissue Int 65:337–340
35. Sambrook PN, Kotowicz M, Nash P, Styles CB, Naganathan V, Henderson-Briffa KN, Eisman JA, Nicholson GC (2003) Prevention and treatment of glucocorticoid-induced osteoporosis.: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. J Bone Miner Res 18:919–924
36. Amin S, Lavalley MP, Simms RW, Felson DT (2002) The comparative efficacy of drug therpies used for the management of corticosteroid-induced osteoporosis: a meta-regression. J Bone Miner Res 17:1512–1526
37. de Nijs RN, Jacobs JW, Algra A, Lems WF, Bijlsma JW (2004) Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D3 analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies. Osteoporos Int 15:589–602
38. Langdahl BL, Marin F, Shane E, Dobnig H, Zanchetta JR, Maricic M, Krohn K, See K, Warner MR (2009) Teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. Osteoporos Int 20:2095–2104
39. Devogelaer JP, Adler RA, Recknor C, See K, Warner MR, Wong M, Krohn K (2010) Baseline glucocorticoid dose and bone mineral density response with teriparatide or alendronate therapy in patients with glucocorticoid-induced osteoporosis. J Rheumatol 37:141–148
40. Karras D, Stoykov I, Lems WF, Langdahl BL, Ljunggren Ö, Barrett A, Walsh JB, Fahrleitner-Pammer A, Rajzbaum G, Jakob F, Marin F (2012) Effectiveness of teriparatide in postmenopausal women with osteoporosis and glucocorticoid use: 3-year results from the EFOS study. J Rheumatol 39:600–609
41. Rittmaster RS, Bolognese M, Ettinger MP, Hanley DA, Hodsman AB, Kendler DL, Rosen CJ (2000) Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. J Clin Endocrinol Metab 85:2129–2134
42. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL et al (2007) Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 22:1479–1491
43. Urade M, Tanaka N, Furusawa K, Shimada J, Shibata T, Kirita T, Yamamoto T, Ikebe T, Kitagawa Y, Fukuta J (2011) Nationwide survey for bisphosphonate-related osteonecrosis of the jaws in Japan. J Oral Maxillofac Surg 69:e364–e371
44. Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, Taguchi A, Toyosawa S, Nagata T, Urade M (2010) Bisphosphonate-related osteonecrosis of the jaw: position paper from the Allied Task Force Committee of Japanese Society for Bone and mineral Research, Japan Osteoporosis Society, Japanese Society for Oral and Maxillofacial Radiology and Japanese Society of Oral and Maxillofacila Surgeons. J Bone Miner Metab 28:365–383
45. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster D, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Koval K, Lane JM, McKiernan F, McKinney R, Ng A et al (2010) Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 25:2267–2294
46. Schilcher J, Michaëlsson K, Aspenberg P (2011) Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 364:1728–1737
47. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW, Ebeling PR, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J (2014) Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 29:1–23
48. Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D, Moretti M, Koren G, Ito S (2009) Pregnancy outcome following in utero exposure to bisphosphonates. Bone 44:428–430
49. Ornoy A, Wajnberg R, Diav-Citrin O (2006) The outcome of pregnancy following pre-pregnancy or early pregnancy alendronate treatment. Reprod Toxicol 22:578–579
50. Chan B, Zacharin M (2006) Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: a report of four cases. J Clin Endocrinol Metab 91:2017–2020
51. Munns CF, Rauch F, Ward L, Glorieux FH (2004) Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. J Bone Miner Res 19:1742–1745
52. Siminoski K, Fitzgerald AA, Flesch G, Gross MS (2000) Intravenous pamidronate for treatment of reflex sympathetic dystrophy during breast feeding. J Bone Miner Res 15:2052–2055
53. MaNicholl DM, Heaney LG (2010) The safety of bisphosphonate use in premenopausal women on corticosteroids. Curr Drug Saf 5:182–187

Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2014;81:251–257
DOI: 10.1159/000357142

Received: July 30, 2013
Accepted: November 5, 2013
Published online: February 26, 2014

Serum Fibroblast Growth Factor 23 Is a Useful Marker to Distinguish Vitamin D-Deficient Rickets from Hypophosphatemic Rickets

Takuo Kubota[a, b] Taichi Kitaoka[a] Kohji Miura[a] Makoto Fujiwara[a] Yasuhisa Ohata[a] Yoko Miyoshi[a] Keiko Yamamoto[a] Shinji Takeyari[c] Takehisa Yamamoto[c] Noriyuki Namba[a] Keiichi Ozono[a]

[a]Department of Pediatrics, Graduate School of Medicine, and [b]First Department of Oral and Maxillofacial Surgery, Graduate School of Dentistry, Osaka University, and [c]Department of Pediatrics, Minoh City Hospital, Osaka, Japan

Key Words
Vitamin D · Fibroblast growth factor 23 · Rickets · Hypophosphatemia · Children

Abstract
Background/Aims: Vitamin D-deficient rickets (DR) has recently re-emerged among developed countries. Vitamin D deficiency can influence biochemical results of patients with fibroblast growth factor 23 (FGF23)-related hereditary hypophosphatemic rickets (HR), making differential diagnosis difficult. In the present study we evaluated the utility of serum FGF23 levels in the diagnosis of DR and during its treatment. ***Methods:*** The study group comprised 24 children with DR and 8 children with HR. Serum FGF23 levels and bone metabolism-related measurements were assessed. ***Results:*** Serum FGF23 levels in patients with DR were less than 19 pg/ml, while those in patients with HR were more than 57 pg/ml. There were significant differences in serum levels of calcium, phosphate, parathyroid hormone, and 1,25-dihydroxyvitamin D, as well as tubular maximum phosphate reabsorption per glomerular filtration rate between patients with DR and HR, but these values were not fully mutually exclusive. In addition, serum FGF23 and phosphate levels were increased following treatment. ***Conclusion:*** Serum FGF23 level is the most critical biochemical marker for distinguishing DR from HR and might be a good indicator of biochemical response to the intervention. Serum FGF23 levels show utility for the diagnosis of DR and in the assessment of its response to treatment.

Introduction

Rickets is caused by defective mineralization in the growth plate of cartilage and in the matrix of bone in a growing child [1, 2]. Bowed legs, enlargement of the wrists and knees, rachitic rosary, craniotabes, growth retardation, delayed initiation of walking, and waddling gait are often associated with rickets. Diagnosis of rickets requires radiographic signs such as cupping, splaying, or fraying in the metaphysis of a long bone.

The most common cause of rickets is vitamin D deficiency, although genetic or acquired disorders of the gut, liver, kidney, and metabolism of vitamin D can cause rickets [2]. Increased numbers of patients with vitamin D deficiency have been reported among children in recent years throughout the world [3–5], including Japan [6–9]. Circulating 25-hydroxyvitamin D [25(OH)D] concentration is the best clinical indicator of vitamin D repletion in the body. Vitamin D deficiency is diagnosed by the mea-

KARGER

1663–2818/14/0814–0251$39.50/0

E-Mail karger@karger.com
www.karger.com/hrp

Keiichi Ozono, MD, PhD
2-2 Yamadaoka
Suita, Osaka 565-0871 (Japan)
E-Mail keioz@ped.med.osaka-u.ac.jp

surement of serum 25(OH)D concentration below 20 ng/ml in adults [10, 11]. In addition, many experts have commonly proposed a cutoff value of 20 ng/ml for serum 25(OH)D concentration to designate vitamin D deficiency in children [12, 13]. Treatment of vitamin D deficiency with native vitamin D or active vitamin D is effective for the correction of rickets [8, 14].

X-linked hypophosphatemic rickets (HR) is the most common form of heritable rickets and is manifested by fibroblast growth factor 23 (FGF23) excess and renal phosphate wasting [15, 16]. Clinical and radiographic features are mostly similar to vitamin D-deficient rickets (DR). Biochemical findings include hypophosphatemia and low-to-normal circulating 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. Serum concentrations of parathyroid hormone (PTH) are usually normal or modestly elevated in some cases. Other forms of FGF23-related hereditary HR have been described, including an autosomal dominant form caused by mutations in FGF23 and autosomal recessive forms caused by mutations in dentin matrix protein 1 and in ectonucleotide pyrophosphatase/phosphodiesterase 1. The prevalence of these forms of HR appears much less than that of X-linked HR. Serum FGF23 concentrations are increased in patients with HR [17, 18]. FGF23 decreases serum phosphate concentrations by the inhibition of renal proximal tubular phosphate reabsorption and the suppression of 25(OH)D-1α-hydroxylase [19]. Vitamin D and phosphate are necessary for the treatment of HR [15, 20].

In collaboration with other institutes, we previously reported on the diagnostic utility of serum FGF23 measurement in patients with hypophosphatemia [21]. However, it remains unclear whether serum FGF23 measurement is useful for differentiating DR and HR, especially in the case of comorbidity of HR plus vitamin D deficiency. Thus, in the current study, we report the diagnostic utility of serum FGF23 measurements to distinguish patients with DR from those with HR.

Subjects and Methods

Subjects

This study included 32 patients who attended Osaka University Hospital or Minoh City Hospital (Osaka, Japan) from January 2003 through June 2012 and who were diagnosed with DR or HR based on clinical, laboratory, and radiographic findings, as well as clinical course. In detail, the diagnostic criteria of DR included radiographic signs such as cupping, splaying, or fraying in the metaphysis of a long bone, high serum levels of alkaline phosphatase (AP) and PTH, and low 25(OH)D levels. Vitamin D deficiency was defined as serum 25(OH)D levels less than 20 ng/ml [13]. The diagnosis of DR was confirmed by no recurrence of rickets after discontinuation of treatment. The diagnostic criteria of HR included radiographic signs such as cupping, splaying, or fraying in the metaphysis of a long bone, low serum phosphate concentrations, and tubular maximum phosphate reabsorption per glomerular filtration rate (TmP/GFR), high AP levels, and normal levels of PTH, 1,25(OH)$_2$D, and 25(OH)D. Although 2 patients did not meet the criteria of HR due to low 25(OH)D levels, they were diagnosed with HR because of high FGF23 levels and resistance to α-calcidol treatment. Other disorders which could develop rickets were excluded, including malabsorption, liver and renal tubular diseases, parathyroid disorders, type I and II vitamin D-dependent rickets, hypophosphatasia, primary disorders of bone matrix, drug-induced mineralization defects, and tumors. Twenty-four patients (11 boys, 13 girls) were diagnosed with DR and 8 (2 boys, 6 girls) with HR. Seven of the 8 patients with HR were sporadic, while 1 patient inherited HR from her mother. Physical examinations were made, and blood and urine samples were taken. Radiography demonstrated rachitic signs in the metaphysis of a long bone in all the patients. Complaints, feeding type before solid food, restricted and/or unbalanced diet, and sunlight exposure were evaluated for DR patients. Dietary content and sun exposure were based on information obtained from parents or guardians. When patients were not given some foods because of concern about allergy, it was considered as a restricted diet. When patients did not take certain foods, it was considered as an unbalanced diet. Playing outside twice a week or less was regarded as insufficient sun exposure. Laboratory data without serum FGF23 levels of 3 DR patients and those with serum FGF23 levels of 2 HR patients were included in previous publications by our group [9, 21]. Measurement of serum FGF23 levels was approved by the institutional review board of Osaka University Hospital and written informed consent was obtained from the parents or guardians of the patients. Patients with DR were treated with α-calcidol suspension because neither cholecalciferol nor ergocalciferol suspension is available on prescription or on the market in Japan.

Measurements

Laboratory measurements included serum levels of calcium (reference range: 8.4–10.0 mg/dl), phosphate (4.2–6.2 mg/dl for the age of 1 year), AP (353–1,009 U/l for the age of 1 year), PTH (10–60 pg/ml), 1,25(OH)$_2$D (20–60 pg/ml), 25(OH)D (the lower limit, 20 ng/ml [13]), and FGF23 (10–50 pg/ml for adults [21]), as well as TmP/GFR (2.7–6.3 mg/dl for the ages 1–24 months [22]) and urine calcium/creatinine ratio (U-Ca/Cr). TmP/GFR was calculated from the formula: TmP/GFR = serum phosphate – urine phosphate × serum creatinine/urine creatinine [23]. Serum 25(OH)D levels were measured in 3 out of 8 with patients with HR. Serum FGF23 levels were measured by an ELISA method that recognizes only full-length biologically active FGF23 (Kainos Laboratories, Japan). The lowest reportable value of FGF23 was 10 pg/ml. Serum 25(OH)D levels were measured by a competitive immunoluminometric direct assay (LIAISON 25OH Vitamin D TOTAL Assay; DiaSorin, USA, 20 samples) and by competitive protein-binding assays (Mitsubishi Chemical Medience, Japan, 6 samples; BML, Japan, 1 sample) because of differences of assay costs.

Statistics

Data were analyzed by a Mann-Whitney U test, ROC analysis, or paired t test using JMP (SAS Institute, USA) and SPSS (IBM SPSS, USA) statistical software.

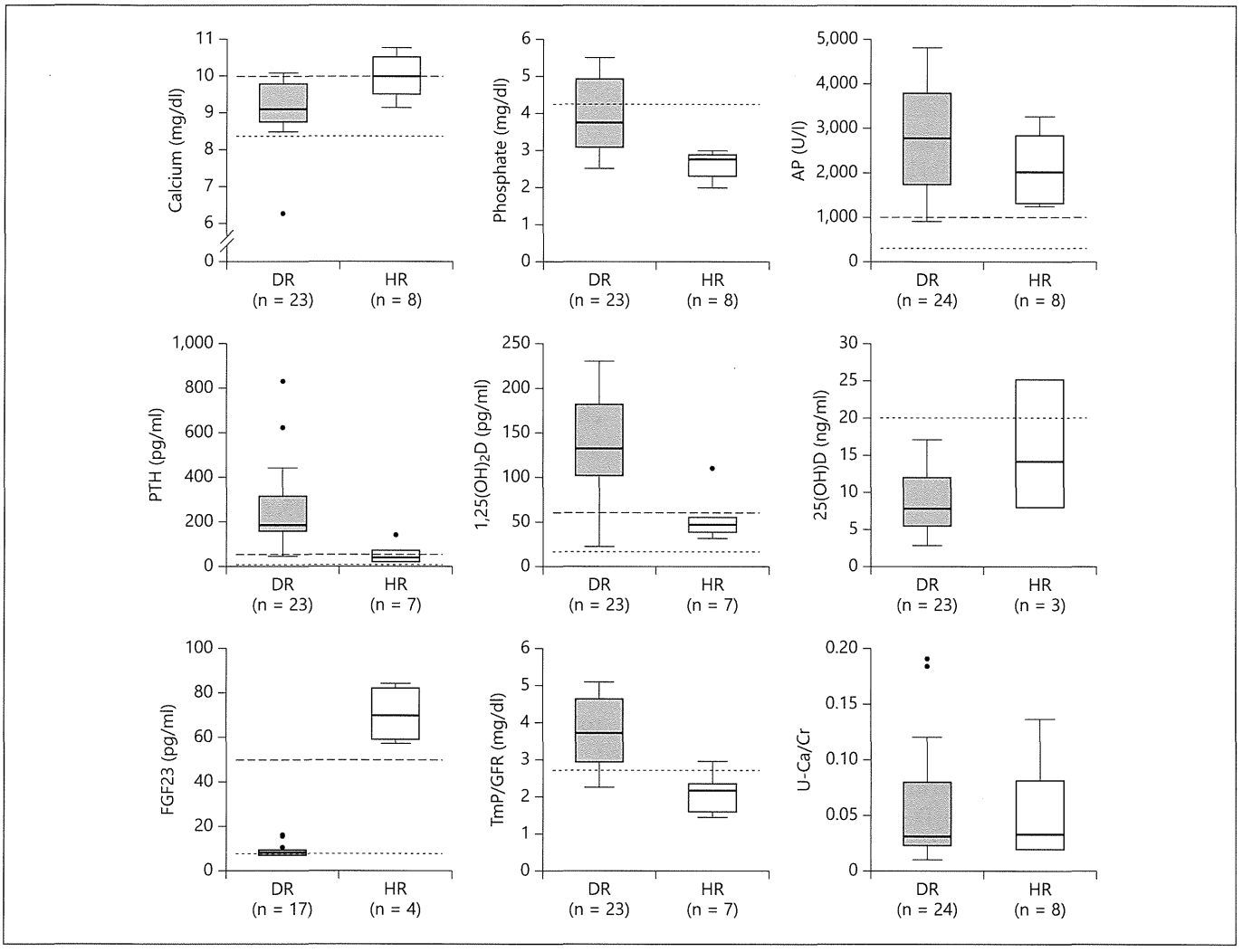

Fig. 1. Biochemical measurements of patients with DR and HR before treatment. Note that only the serum FGF23 level is exclusive between DR and HR. The data are presented as box plots. $p < 0.01$ for calcium, phosphate, PTH, $1,25(OH)_2D$, FGF23, and TmP/GFR. Dashed and dotted lines are the upper and lower limit of reference ranges, respectively.

Results

Clinical Features of DR Patients

Clinical features, including complaints, feeding type before solid foods, restricted and/or unbalanced diet restriction, and sunlight exposure were evaluated in the 24 DR patients. Complaints consisted of bowed legs (n = 18, 75%), elevated serum AP level (n = 5, 21%), and convulsions (n = 1, 4%). Feeding type before solid food was exclusively breast milk (n = 21, 89%) and breast plus formula milk (n = 1, 4%). Twelve patients (50%) had a restricted and/or unbalanced diet. There were 6 patients (25%) with insufficient sun exposure.

Characteristics of DR and HR Patients

There were no differences in age, height, and weight between DR and HR patients. Age was 17 ± 7 (mean ± SD) months, height was −1.3 ± 1.5 SD score (SDS), and weight was −0.5 ± 1.3 SDS in DR patients compared to age 21 ± 8 months, height −1.9 ± 1.0 SDS, and weight −0.1 ± 0.8 SDS in HR patients.

Utility of Serum FGF23 Levels to Distinguish HR and DR Patients

Laboratory findings of DR and HR patients were determined before treatment (fig. 1). Serum calcium concentration was lower in patients with DR than those