

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

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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 cut-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

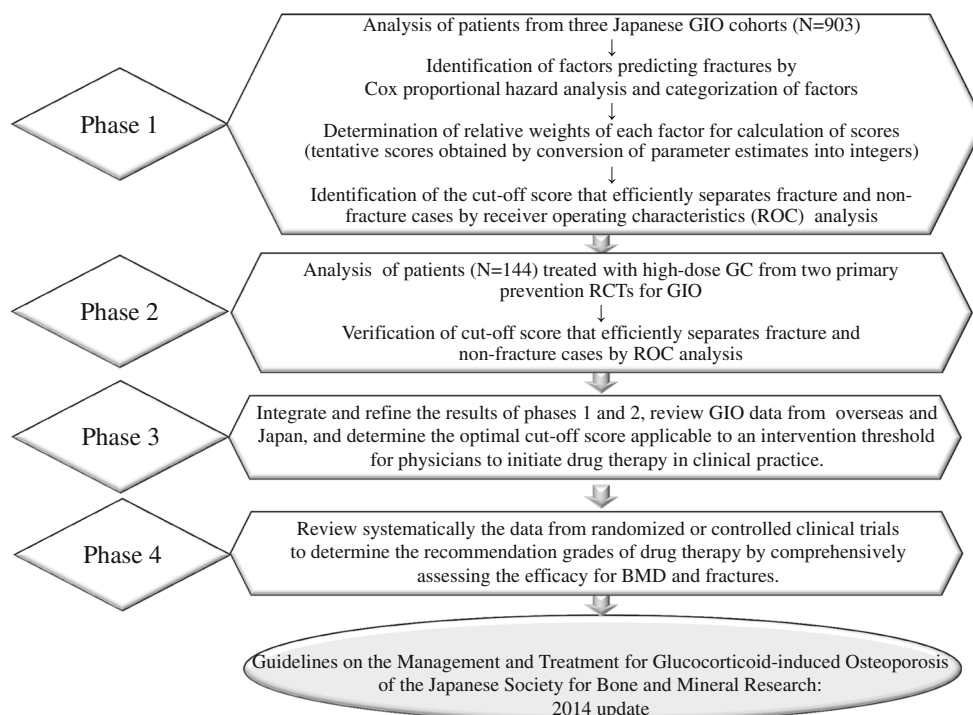


Table 2 Characteristics of patients analyzed to identify the optimal cutoff score for pharmacological intervention

	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)

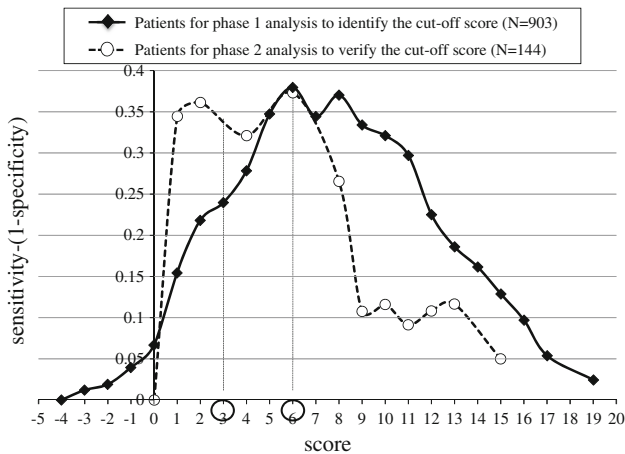


Fig. 2 Identification of the optimal cutoff score to separate fracture and non-fracture cases by receiver operating characteristics analysis. The score of the maximum value of sensitivity-(1-specificity) was 6 by both phase 1 and phase 2 analyses. A score 3 was adopted in the updated guideline as the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

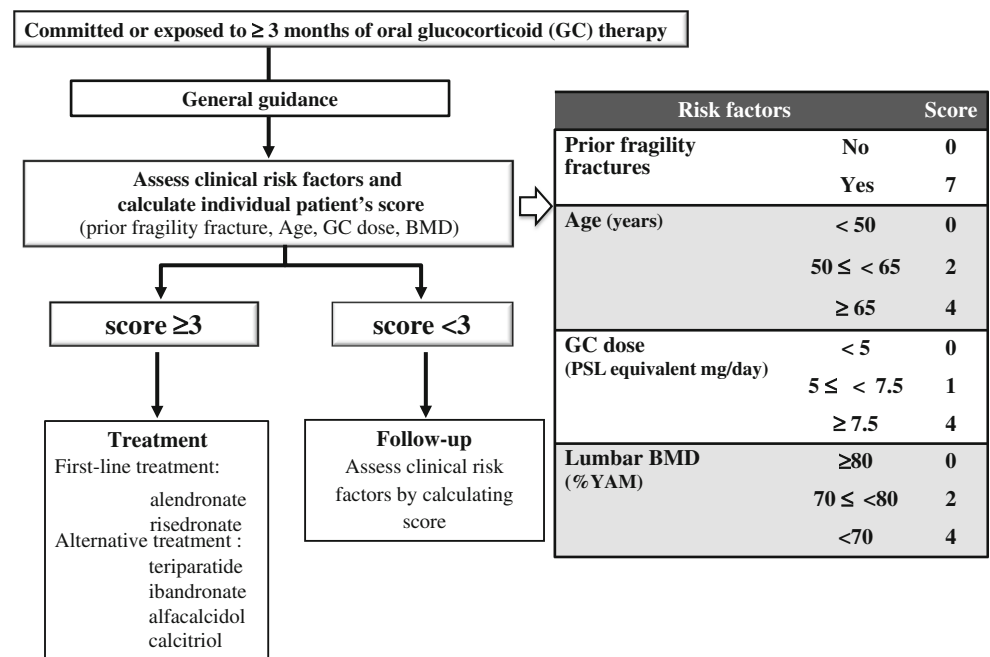
All patients who are committed to or exposed to GC therapy should be encouraged to reduce risk factors and

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 outweighs 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 the US 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.

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