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SPECIAL REPORT

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# Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004)

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## Introduction

Osteoporosis is the most frequent adverse effect of glucocorticoids. Management guidelines were developed [1] in the United States in 1996 when the seriousness of glucocorticoid-induced osteoporosis as a complication of glucocorticoid therapy was recognized, and they have since been revised [2–6]. In Japan, the Japanese Society for Bone and Mineral Research established a study group on osteoporosis diagnostic criteria in 1999 and then the Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis in 2001 to examine diagnostic criteria for glucocorticoid-induced osteoporosis, and the present guidelines were developed for clinical practice (Fig. 1).

## Guidelines on the management and treatment of glucocorticoid-induced osteoporosis

### Drafting policy

The Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis was initially organized to determine diagnostic criteria. However, guidelines on glucocorticoid-induced osteoporosis in various countries

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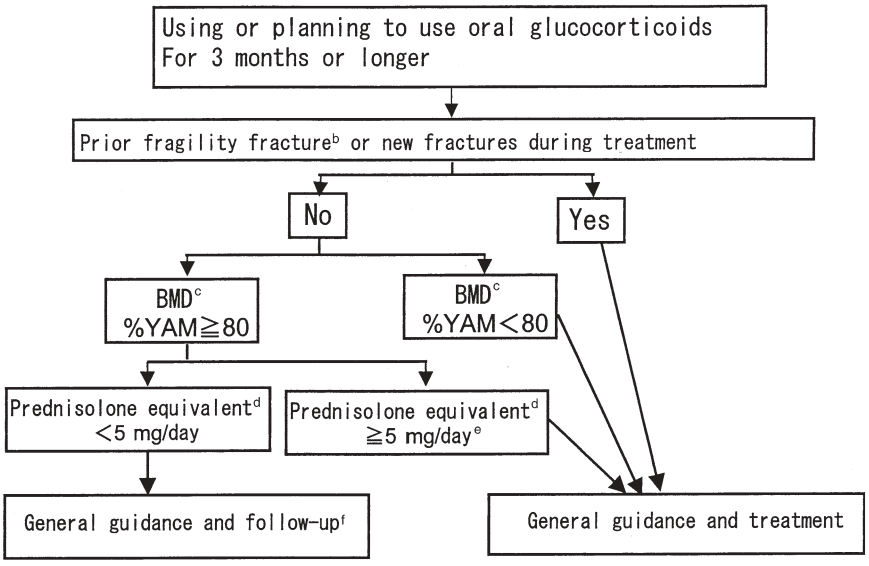
**Fig. 1.** Guidelines on the management and treatment of corticosteroid-induced osteoporosis (2004 edition)[a]




- General guidance
  Lifestyle guidance, nutritional guidance, and exercise therapy are based on those for primary osteoporosis
- Follow-up observation
  Bone mineral density measurements and thoracic and lumbar vertebra X-rays are performed on a regular basis (every 6 months or 1 year)
- Drug treatment
  1. Bisphosphonates are first-line drugs
  2. Active vitamin $D_3$ and vitamin $K_2$ are second-line drugs

YAM, young adult mean (20–44 years old); BMD, bone mineral density
[a] These Guidelines cover patients 18 years of age and older
[b] Definition of fragility fractures is the same as that for primary osteoporosis
[c] Bone mineral density (BMD) measurements are based on those for primary osteoporosis (2000 revised edition)
[d] Mean daily dose
[e] Patients administered 10 mg or more per day are at risk of fractures even when bone mineral density is high (cut-off value, %YAM90)
[f] Risk of fractures is higher in the elderly

are guidelines for primary and secondary prevention and do not specify diagnostic criteria. The subcommittee discussed this point, and a draft of management and therapeutic guidelines in Japan based on evidence available at present was prepared.

## Patients studied by the Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis

The survey items were sex, age, height, body weight, underlying disease, bone mineral density (type of instrument used, region, measured value), glucocorticoid treatment history (dose, mean dose for 6 months until measurement of bone mineral density, maximum dose throughout administration period, total administration period, total dose, pulse therapy within 1 year, use of glucocorticoids for inhalation), osteoporosis treatment history, and fracture history. The facilities connected with the Subcommittee, that is, Osaka City University, Kawasaki Medicine University, Kyushu University, Kyushu University Hospital at Beppu, Kinki University, Sapporo Yamanoue Hospital, Research Institute and Practice for Involutional Diseases, Tokyo Metropolitan Tama Geriatric Hospital, Tokyo Metropolitan Geriatric Medical Center, Hamamatsu University School of Medicine, Fujita Health University, and Radiation Effects Research Foundation, were requested to conduct the survey. As a result, a total of 692 patients were recruited up to 2002 in addition to the 299 patients recruited in 1999 and 2000, including 627 women and 65 men. The most common underlying disease was rheumatoid arthritis (RA) in 319 patients, and 373 patients had diseases other than RA; these included 162 cases of systemic lupus erythematosus (SLE), 27 of progressive systemic sclerosis (PSS), 26 with mixed connective tissue disease (MCTD), 20 with polymyositis/dermatomyositis (PM/DM), 16 with polymyalgia rheumatica (PMR), 12 with nephrosis, 10 with asthma, 10 with idiopathic thrombocytopenic purpura

(ITP), and 90 with other diseases. The results of an analysis of a 2-year follow-up survey on 220 patients administered glucocorticoids by Tanaka and Oshima [7] were added to these analytical results, and work on establishment of the guidelines proceeded.

## Evidence for drafting the guidelines

### *Subjects*

These guidelines cover men and women 18 years of age or older. Growth disorders caused by glucocorticoids are a serious problem in children, but at present no evidence that can be used has been reported in Japan or overseas, and children were excluded. Because of the same lack of evidence concerning glucocorticoids injected intravenously, only patients using oral glucocorticoids for which evidence is available in Japan and overseas were subjects. There is no evidence concerning the administration period in Japan. The most recent guidelines of the United States, UK, and Canada cover treatment with administration for 3 months or longer [3–6]. In a meta-analysis of the risk of bone fractures after starting treatment with oral glucocorticoids overseas, it was reported that the incidence of new vertebral bone fractures reaches a maximum at 3–6 months after administration and forms a plateau thereafter [8], suggesting that treatment simultaneously with or in the very early stage of glucocorticoid administration is important. Therefore, the subjects were patients with planned administration for 3 months or longer (see Fig. 1).

### *Prior fragility fractures*

The results of an analysis in a 2-year longitudinal study by Tanaka and Oshima showed that the risk of new bone fractures in patients with prior fragility fractures showed the highest value compared with other fractures at an odds ratio of 7.92 [7]. Among the patients collected by the Subcommittee to Study Diagnostic Criteria, the 154 cases (103 cases of RA, 51 cases of collagen disease) that could be analyzed longitudinally for 2 years had a high odds ratio of 5.22. Therefore, the first evaluation criterion for starting treatment was patients with prior fragility fractures and patients with new bone factures during treatment. The definition of a fragility fracture is the same as that for primary osteoporosis [9].

### *Bone mineral density*

Table 1 shows the cut-off values of bone mineral density (BMD), which can efficiently separate fracture and nonfracture cases, estimated from the receiver-operating characteristic (ROC) curve based on an analysis of cases collected by the Subcommittee to Study Diagnostic Criteria. The cut-off value for all patients was 0.776 g/cm$^2$. When the patients were divided into those with RA, the most common underlying disease, and those with diseases other than RA, the cut-off values were 0.744 g/cm$^2$ and 0.820 g/cm$^2$, respectively. In cases with SLE, the most common underlying disease other than RA, the cut-off value was 0.841 g/cm$^2$. Judging from these results, it appeared necessary to set different cut-off values for RA and for other underlying diseases. Table 2 shows the results of an investigation of this point with respect to age. In Table 2, all patients were grouped by age from those less than 40 to those 70 years of age and older. The cut-off values of bone mineral density in fracture and nonfracture cases were obtained by age and expressed as percent (%) young adult mean (YAM). When the level of differences in cut-off values (%YAM) was examined for age differences of 10 years, the values were 6.5% for patients in their forties and in their fifties and 7.1% for patients in their fifties and in their sixties. The mean age of RA patients was 60.4 years and that for diseases other than RA 48.8 years, an age difference of 11.6 years. The cut-off values were 73.6% for RA and 81.1% for diseases other than RA, a difference of 7.5%; i.e., this difference was almost the same as that for age, and the difference in cut-off values of RA and diseases other than RA is not considered as a difference caused by differences in disease but a difference due to age.

**Table 1.** Cut-off values of bone mineral density (BMD) to efficiently separate fracture and nonfracture cases

| | | BMD (g/cm$^2$) | T score | % YAM |
|---|---|---|---|---|
| Primary osteoporosis | | 0.708 | −2.60 | 70% |
| Osteopenia | | 0.809 | −1.70 | 80% |
| Glucocorticoid-treated patients | All patients | 0.776 | −1.97 | 76.8% |
| | RA | 0.744 | −2.24 | 73.6% |
| | Non-RA | 0.820 | −1.60 | 81.1% |
| | SLE | 0.841 | −1.43 | 83.2% |

YAM, young adult mean; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

**Table 2.** Cut-off values of bone mineral density by age and underlying disease of patients administered glucocorticoid

| Age (all patients) | %YAM | | Mean age (years) | | Underlying disease |
|---|---|---|---|---|---|
| Less than 40 years old | 86.9 | | | | |
| Forties | 85.9 | | | | |
| | 6.5 | | | | |
| Fifties | 79.4 | 81.1 | 48.8 | | Non-RA |
| | 7.1 | 7.5 | | 11.6 | |
| Sixties | 72.3 | | | | |
| | | 73.6 | 60.4 | | RA |
| Seventies and older | 69.3 | | | | |

**Table 3.** Cut-off values of bone mineral density by dose of glucocorticoids

| | Daily dose (prednisolone equivalent) (mg) | %YAM (T score) |
|---|---|---|
| All patients | ≧5 | 77.7 (−1.90) |
| | ≧7.5 | 80.3 (−1.67) |
| | ≧10 | 82.1 (−1.52) |
| RA | ≧7.5 | 75.1 (−2.12) |
| Non-RA | ≧5 | 81.8 (−1.55) |
| | ≧7.5 | 82.6 (−1.48) |

Table 3 shows the relationship between glucocorticoid dose and the cut-off values. In all patients, the cut-off value (%YAM) in the group with a prednisolone equivalent dose of 5 mg/day or higher was 77.7%, that in the group with a dose of 7.5 mg/day or higher was 80.3%, and that in the group with a dose of 10 mg/day or higher was 82.1%. These results showed that as the daily dose increased, factures occurred at higher bone mineral densities. For RA, the cut-off value was 75.1% in the group with a prednisolone equivalent dose of 7.5 mg/day or higher, and for diseases other than RA, it was 81.8% in the group with a dose of 5 mg/day or higher and 82.6% in the group with a dose of 7.5 mg/day or higher. The results of a cross-sectional analysis of all patients collected by the Subcommittee to Study Diagnostic Criteria showed a cut-off value of %YAM 77%, and the cut-off value in the group with a prednisolone equivalent dose of 5 mg/day or higher, at which it was reported based on a meta-analysis that the bone mineral density rapidly decreased and bone fractures increased, was 78%. It was clear that it is not necessary to consider differences in cut-off values due to differences in underlying diseases. In the longitudinal analysis by Tanaka and Oshima, the cut-off value in the group with a prednisolone equivalent dose of 5 mg/day or higher was %YAM 80% [7]. Based on these results, bone mineral density of less than %YAM 80% was taken as the second evaluation criterion for starting treatment.

*Dose of glucocorticoids*

The number of patients collected by the Subcommittee was not enough to clarify the relationship between the fracture risk and the total glucocorticoid dose, and the analysis could not be performed. Almost no difference was found in the relationship between the fracture risk and the administration period, but this was because of insufficient data on individual patients, and the relationship will have to be clarified in the future. Sufficient evidence on the relationship between the glucocorticoid dose and fracture risk rate or its cut-off value of bone mineral density has still not been obtained in Japan, and overseas reports had to be used for reference. The results of an overseas meta-analysis showed a reverse correlation between the bone mineral density of the lumbar vertebra and the total dose of glucocorticoid (daily dose × period), and the risk of a spinal fracture even at a daily dose of less than 2.5 mg of prednisolone equivalent was more than 1.0, i.e., 1.55. The fracture rate increased dose dependently and was 5.18 at 7.5 mg or higher doses [8]. It has been reported that a dose of 5 mg or higher is the threshold value for increased fracture risk. Therefore, the third evaluation criterion for the start of treatment was proposed as a dose of 5 mg/day or higher (mean daily dose) as prednisolone equivalent (see Fig. 1). However, in a longitudinal study, the cut-off value of bone mineral density was %YAM 90% in the group administered a 10 mg/day or higher dose of prednisolone equivalent, and even at a %YAM close to 100%, the risk rate of fractures was clearly higher in the patients given glucocorticoid than in patients not administered glucocorticoids [7].

*Old age*

In the study by Tanaka and Oshima [7], the incidence of bone fractures increased significantly with increase in age, and age was identified as a risk factor of new spinal fractures in patients administered glucocorticoids; however, a cut-off value of age to clearly separate fracture and nonfracture cases could not be determined.

*Treatment of glucocorticoid-induced osteoporosis*

*General guidance.* In the same way as with primary osteoporosis, it is necessary to provide guidance on improvements in lifestyle and on nutrition, as well as exercise therapy. This guidance is based on that given for primary osteoporosis [10].

*Follow-up observation.* The risk of bone fractures is higher in patients administered glucocorticoid than in those who were not treated with glucocorticoid. Therefore, in patients evaluated as the follow-up observation group based on the present guidelines, it is essential to conduct follow-up observation by measuring bone mineral density and taking X-rays of the thoracic and lumbar vertebra on a regular basis.

*Drug treatment.* In prospective randomized control trials (RCT) overseas [11–15] and in Japan [16,17], evidence that the bisphosphonate products etidronate, alendronate, and risedronate significantly prevent bone fractures caused by glucocorticoid-induced osteoporosis has been reported. Therefore, these drugs have been recommended as first-line drugs at present. Active vitamin $D_3$ has been reported to have fracture-preventing effects, although these are inferior to those of the bisphosphonates [18], and vitamin $K_2$ has also been found to have fracture-preventing effects from a longitudinal study in Japan [7]. These two vitamins have been recommended as second-line drugs. Although the parameter was bone mineral density, it was reported based on a meta-analysis that vitamin D and bisphosphonates administered concomitantly are more effective than bisphosphonates alone in the treatment of glucocorticoid-induced osteoporosis [19]. Concomitant administration of active vitamin $D_3$ and bisphosphonates should be considered in patients with serious or high-risk osteoporosis. When bisphosphonates are difficult to administer to postmeno-

pausal women because of problems such as side effects, selection of raloxifene, a selective estrogen receptor modulator (SERM) [4,20,21] may be considered; however, therapeutic evidence of SERM for glucocorticoid-induced osteoporosis is still insufficient and further study will be necessary.

## Conclusion

The 2004 edition of the guidelines on the management and treatment of glucocorticoid-induced osteoporosis has been developed based on the results of a longitudinal study by subcommittee members and the results of an analysis of patients collected by the Subcommittee to Study Diagnostic Criteria for Corticosteroid-Induced Osteoporosis, together with evidence obtained overseas and in Japan at present. It will be necessary to verify and revise the present guidelines based on newly collected evidence in the future.

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