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REVIEW ARTICLE

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Glucocorticoid-induced osteoporosis: skeletal manifestations of glucocorticoid use and 2004 Japanese Society for Bone and Mineral Research-proposed guidelines for its management

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Abstract Glucocorticoid (GC) is widely used to treat a variety of inflammatory and allergic diseases, and about 0.9% of the adult population in Japan (approximately one million people) are known to take oral GC at any given time. GC causes a number of significant side effects, among which are skeletal manifestations such as osteoporosis and degenerative bone fracture, maor complications of GC therapy. Although the population of GC-induced osteoporosis patients is estimated to be approximately one-fifth of patients with primary osteoporosis, few physicians are aware of the increased risk of fracture caused of GC, and there is inadequate information concerning the effetiveness of prevention and treatment of GC-induced osteoporosis. Recently, mechanisms of GC-induced osteoporosis have been clarified, and treatment strategies have been developed. Accordingly, the 2004 Japanese Society for Bone and Mineral Research (JSBMR)-proposed guidelines for the management and treatment of GC-induced osteoporosis have 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. The present guideline is prepared for clinical practice.

Key words Bisphosphonate · Glucocorticoid (GC) · Osteoporosis · Treatment

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Introduction

In 1950, Hench, Kendall, and Richtenstein were awarded the Nobel Prize for Medicine for their work on the identification and clinical application of synthetic glucocorticoid (GC). They determined that the administration of GC caused marked alleviation of the clinical signs and symptoms in 100 patients with rheumatoid arthritis (RA). Since then, GC has been used for a variety of acute and chronic inflammatory diseases including systemic autoimmune diseases such as RA, respiratory diseases such as asthma, renal diseases such as nephrotic syndrome, and inflammatory bowel disease.

At that time, however, they had also recognized the many adverse effects of chronic use of GC. External administration of synthetic GC induces an imbalance of internal cortisol levels and leads to a number of significant side effects, including glucose tolerance, diabetes, weight gain, hyperlipidemia, skin thinning, opportunistic infection, cataracts, hypertension, psychoses, and osteoporosis. Among them osteoporosis is an unavoidable, severe side effect of GC and is particularly destructive in postmenopausal women. Currently, about 0.9% of the total adult population in Japan (approximately one million people) are known to take oral GC at any given time, and it is estimated that GC-induced osteoporosis accounts for approximately one-fifth of all patients with primary osteoporosis.

Unfortunately, few physicians are aware of the bone loss and increased risk of fracture caused by GC, and there is inadequate information concerning the effectiveness of prevention and treatment of GC-induced osteoporosis. Recently, the mechanisms of GC-induced osteoporosis have been clarified, and treatment strategies have been developed. Accordingly, management guidelines for GC-induced osteoporosis have been established in the United States, the United Kingdom, and many other countries.[1–3] In this review we describe the mechanisms of GC-induced osteoporosis and document its management and treatment, introducing the 2004 Japanese Society for Bone and Mineral Research (JSBMR)-proposed guidelines.

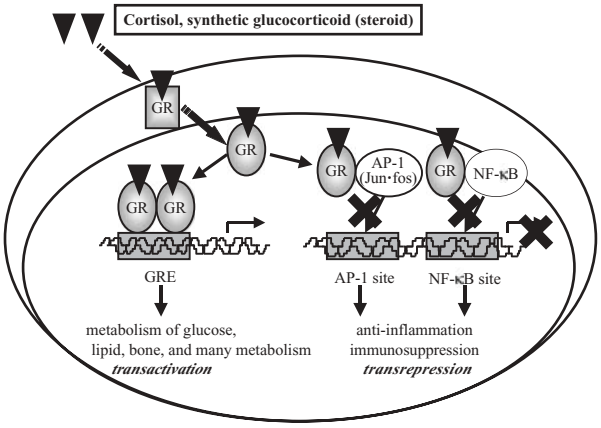

Fig. 1. Mechanisms of the physiologic and pharmacologic actions of glucocorticoid (GC). Both cortisol and synthetic GC bind to the GC receptor (*GR*). After binding to the GR, the ligand–GR complex is transported to the nucleus and binds to specific sites on steroid-regulated genes bearing GR-receptive element (*GRE*), which leads to physiologic effects of GC. The complex of synthetic GC and *GR* inhibits the transcription of inflammatory proteins by binding to *AP-1* and *NF-κB*, but it also binds to *GRE*, causing an imbalance of homeostasis

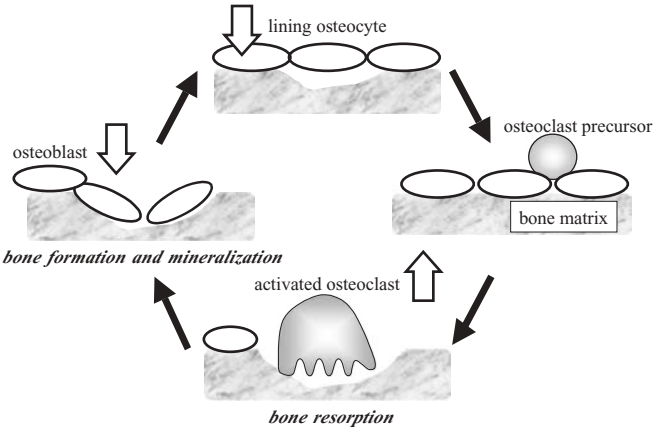

Fig. 2. Mechanisms of GC-induced osteoporosis. Bone metabolism is mediated by the two major processes of bone remodeling: *bone formation* and *bone resorption*. However, GC decreases the number of *osteoblasts*, reduces synthesis of *bone matrix* proteins from them, and enhances *bone resorption*, preventing apoptosis of matured *osteoclasts*, which results in impaired bone remodeling and incomplete repair of bone remodeling lacunae

Mechanisms of GC in physiologic and pharmacologic actions

The adrenal cortex produces three major classes of steroids: GC (cortisol); mineralocorticoids; and adrenal androgens. Thus, normal adrenal function is important for modulating intermediary metabolism and immune responses through GCs. The daily secretion of cortisol ranges between 15 and 30 mg/day [as prednisolone (PSL) 3–6 mg/day] with a circadian cycle. Both cortisol and synthetic GC bind to the glucocorticoid receptor (GR). After binding to the GR, the ligand–GR complex is transported to the nucleus, where it binds to specific sites on steroid-regulated genes bearing GR-responsive elements (GREs) and alters levels of transcription. Physiologic effects of GC include the regulation of protein, carbohydrate, lipid, and nucleic acid metabolism (Fig. 1).[4,5]

On the other hand, pharmacologic actions of synthetic GC are mediated by GR-mediated inhibition of at least two transcription factors, activating protein (AP)-1 and nuclear factor-κB (NF-κB), which stimulate the activity of various inflammatory cytokine genes such as interleukin-1 (IL-1), IL-8, tumor necrosis factor-α (TNFα), and granulocyte/macrophage colony-stimulating factor. However, the synthetic GC-GR complex binds to not only these transcription factors but also to the GRE on multiple physiologic genes, modulating intermediary metabolism or homeostasis. Thus, external administration of synthetic GC, even 1 mg of PSL, causes an imbalance of the metabolism of glucose, lipid, bone, and other substances. Among their effects, osteoporosis is an unavoidable and severe side effect of GC.[4–7]

Mechanisms of GC-induced osteoporosis

Glucocorticoid-induced osteoporosis is known to occur through a number of mechanisms. GC alters gonadal function, decreases intestinal calcium absorption, and increases renal calcium elimination, among other actions; but the major pathway of GC-induced osteoporosis is understood to be a direct effect of GC on bone metabolism: a reduction in bone formation and an increase in bone resorption.[7–10]

Bone metabolism in health and disease is based on a self-regulating cellular event. The two major processes of bone remodeling – bone formation and resorption – are closely regulated by multiple local soluble factors and systemic hormones. The initial event in bone remodeling is an increase in osteoclastic bone resorption. Osteoblasts play a central role in bone formation by synthesizing multiple bone matrix proteins and differentiating into bone cells during the bone remodeling cycle. However, uncoupling of bone remodeling caused by multiple factors often leads to an imbalance of bone homeostasis (e.g., osteoporosis).

Glucocorticoid decreases the absolute number of osteoblasts by decreasing replication and increasing premature apoptosis, which results in a short life span. It also reduces synthesis of bone matrix proteins such as type I collagen, osteocalcin, hyaluronan, and glycosaminoglycan, and it slows the production of skeletal growth factors including bone morphogenetic protein-2, insulin-like growth factor-1, and prostaglandin E_2. In contrast, GC enhances bone resorption, preventing apoptosis of matured osteoclasts, inducing production of RANKL and colony-stimulating factor-1 of osteoblasts, and decreasing osteoprotegerin expression in osteoblasts.[11] A shortened life span, reduced protein synthesis in osteoblasts, and prevention of osteoclast apoptosis results in impaired bone remodeling and severe bone loss, represented by the incomplete repair of

bone remodeling lacunae (Fig. 2). Such bone losses are initially observed in trabecular bone and subsequently followed by losses in cortical bone.

Clinical characteristics of GC-induced osteoporosis

Clinical features of GC-induced osteoporosis are mainly the following: (1) There is an initial rapid bone loss during the first 3–12 months of GC therapy. (2) Although the peak dose and cumulative dose of GC are important, a "safety dose" is not evident. (3) The incidence of vertebral fracture in GC-induced osteoporosis, even if loss of bone mineral density (BMD) is minimal, is higher than in primary osteoporosis. (4) Bisphosphonate is highly effective for increasing the BMD, decreasing bone resorption markers, and reducing vertebral fracture risk (70%–90% reduction), and it demonstrates initial preventive effects in premenopausal women, even those on high-dose GC therapy.[3,7,9,12,13]

The initial rapid bone loss of 3%–27% of the BMD is reported to occur during the first 6–12 months, and the fracture risk increases within 3 months after the initiation of GC therapy.[6,7] A higher dose of GC causes more rapid changes in BMD. We observed that, despite the use of alfacalcidol with commencement of high-dose GC therapy, about 10% bone loss occurred within the first 6 months in premenopausal women and men with systemic autoimmune diseases.[14] The relative risk (RR) for vertebral fractures is dose-dependent: 1.55, 2.59, and 5.18 for doses of <2.5, 2.5–7.5, and >7.5 mg of PSL daily, respectively. Thus, the RR for the fracture increases even in patients taking as little as 2.5 mg of PSL.[15]

Rheumatoid arthritis, by itself, causes regional and generalized bone loss; but RA patients on GC generally have lower BMD than their non-GC-user counterparts and they are at markedly higher risk for degenerative fractures. A meta-analysis concluded that the effect of GC on bones among RA patients is, at worst, modest, and a "safety dose" does not exist.[5,6,16] A dose of only 2.5 mg of PSL has almost immediate effects on serum osteocalcin levels, a major marker of bone formation, and even intraarticular injection of GC has biologic adverse effects on bone.[17] Analyses of the large United Kingdom General Practice Research Database (GPRD) also reported adverse effects of GC on bone as follows: (1) GC-induced osteoporosis occurs rapidly and is most strongly related to the daily dose (not the cumulative dose). (2) A monotonic relation is observed between clinical fractures and GC doses up to 20 mg. (3) The fracture incidence increases in a more exponential fashion thereafter. (4) A "safe" GC dose from the standpoint of bone does not exist (Fig. 3).[18]

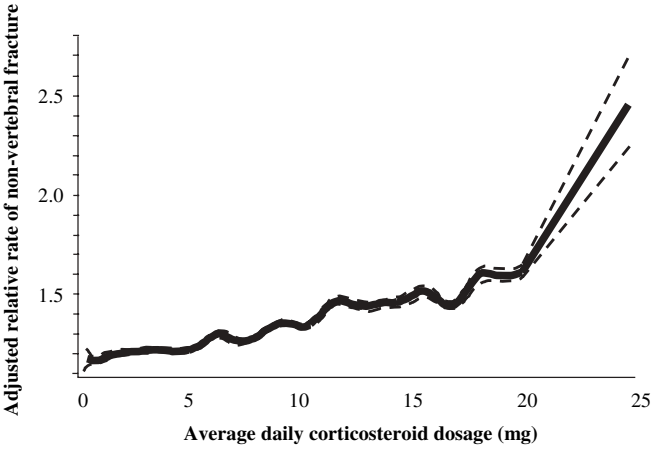

Fig. 3. Effects of a daily GC dose on nonvertebral fractures. The incidence of nonvertebral fractures of 244 235 GC users was assessed by the large United Kingdom General Practice Research Database (GPRD). *Dashed lines* represent the 95% confidence interval (CI). Adapted from van Staa et al.[15]

Longitudinal studies have noted that the cumulative dose of GC enhances the problem. The 5-year probability of having a regenerative fracture is known to be approximately 33% in female patients with RA taking an average PSL dose of 8.6 mg.[19] Other studies have indicated that more than 40% of long-term GC users ultimately experience a fracture.[20] In addition, GC-induced bone loss and fractures are known to be enhanced by multiple clinical factors, including menopause, organ dysfunction (the kidney), low body mass index (BMI), disease activity of RA, older age, disability, and immobilization, among others.[1]

Drafting the 2004 JSBMR-proposed guidelines

Management guidelines for GC-induced osteoporosis were developed and reported[21] in the United States in 1996 when the seriousness of GC-induced osteoporosis as a complication of GC therapy was recognized, and they have since been revised.[13,22–25] In Japan, the JSBMR established a study group on osteoporosis diagnostic criteria in 1999 followed by the Subcommittee to Study Diagnostic Criteria for GC-induced Osteoporosis in 2001 to examine diagnostic criteria for GC-induced osteoporosis. Finally, the present guidelines in Japan, based on evidence available at present, were prepared for clinical practice (Fig. 4).[26]

Patients studied by the subcommittee to study diagnostic criteria for GC-induced osteoporosis

The survey items for establishing the guidelines were sex, age, height, body weight, underlying disease, BMD, GC treatment history, osteoporosis treatment history, and bone fracture history. As a result, a total of 692 patients were recruited up to 2002 in addition to the 299 patients recruited in 1999 and 2000. They included 627 women and 65 men. The most common underlying disease was RA in 319 patients, and 373 patients had diseases other than RA. The latter included 162 patients with systemic lupus erythematosus, 27 with systemic sclerosis, 26 with mixed connective tissue disease, 20 with polymyositis/dermatomyositis, 16

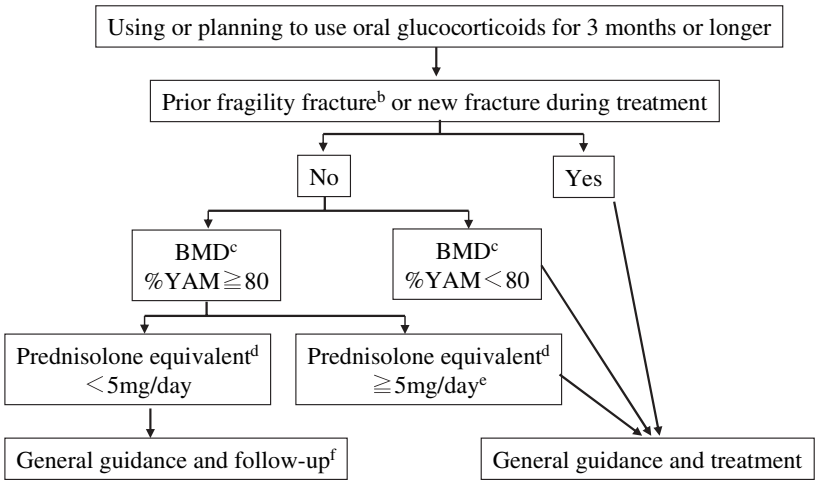

Fig. 4. Guidelines on the management and treatment of GC-induced osteoporosis (2004 edition)[a]. *BMD*, bone mineral density; *YAM*, young adult men (20–44 years old). [a]These guidelines cover patients 18 years of age and older. [b]Definition of fragility fractures is the same as that for primary osteoporosis. [c]Bone mineral density 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 fracture even when bone mineral density is high (cutoff values, %YAM 90). [f]Risk of fracture is higher in the elderly

- 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 vertebral 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

with polymyalgia rheumatica, 12 with nephrosis, 10 with asthma, 10 with idiopathic thrombocytopenic purpura, and 90 with other diseases. The results of an analysis of a 2-year follow-up survey on 220 patients administered GCs by Tanaka and Oshima[27] were added to these analytical results, and work on establishing 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 GC are a serious problem in children, but at present no evidence that can be used has been reported in Japan or elsewhere; hence, children were excluded. Because of the same lack of evidence concerning GC injected intravenously, only patients using oral GC for whom evidence is available in Japan and elsewhere were subjects. There is no evidence concerning the administration period in Japan. The most recent guidelines outside Japan cover treatment with administration for 3 months or longer.[13,23–25] In a meta-analysis of the risk of bone fractures after starting treatment with oral GC overseas, it was reported that the incidence of new vertebral fractures reaches a maximum 3–6 months after administration and forms a plateau thereafter,[16] suggesting that treatment simultaneously with or during the early stage of GC administration is important. Therefore, the subjects were patients with planned administration for 3 months or longer.

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 factures in patients with prior fragility fractures showed the highest value compared with other factors at an odds ratio of 7.92.[27] 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.[28]

Bone mineral density

The cutoff values of BMD, which can efficiently distinguish fracture and nonfracture cases, were estimated from the receiver-operating characteristic (ROC) curve based on an analysis of cases collected by the Subcommittee to Study Diagnostic Criteria. The cutoff value and the percent of young adults men (%YAM) for all patients were 0.776 g/cm^2 and 76.8%, respectively. In all patients, the cutoff value (%YAM) in the group with a PSL 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 BMDs. The results of a cross-sectional analysis of all

patients collected by the Subcommittee to Study Diagnostic Criteria showed a %YAM cutoff value of 77%, and the cutoff value in the group with a PSL equivalent dose of 5 mg/day or higher (at which it was reported, based on a meta-analysis, that the BMD rapidly decreased and bone fractures increased) was 78%. In the longitudinal analysis by Tanaka and Oshima, the %YAM cutoff value in the group with a PSL equivalent dose of 5 mg/day or higher was 80%.[27] Based on these results, a BMD of <80% (%YAM) was taken as the second evaluation criterion for starting treatment.

Dose of glucocorticoid

The number of patients collected by the subcommittee was not enough to clarify the relation between the fracture risk and the total GC dose, and the analysis could not be performed. Almost no difference was found in the relation between the fracture risk and the administration period, but this was because of insufficient data for individual patients; this point will have to be clarified in the future. Sufficient evidence on the relation between the GC dose and the fracture risk rate or its BMD cutoff value has still not been obtained in Japan, and reports from elsewhere were used for reference. The results of an overseas meta-analysis showed a reverse correlation between the BMD of the lumbar vertebrae and the total GC dose (daily dose × period), and the risk of a spinal fracture even at a daily dose of <2.5 mg of PSL equivalent was 1.55. The fracture rate increased dose-dependently and was 5.18 at a dose of 7.5 mg or higher.[16] It has been reported that a dose of ≥5.0 mg 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 (mean daily dose) as PSL equivalent. However, in a longitudinal study, the %YAM cutoff value for the BMD was 90% in the group administered a 10 mg/day or higher dose of PSL equivalent; even at a %YAM close to 100%, the risk of fracture was clearly higher in patients given GC than in those not administered GC.[27]

Old age

In the study of Tanaka and Oshima,[27] the incidence of bone fractures increased significantly with increased age, and age was identified as a risk factor for new spinal factures in patients administered GC. However, the cutoff value for age to distinguish clearly fracture and nonfracture cases could not be determined.

Treatment of GC-induced osteoporosis

General guidance

As for primary osteoporosis, it is necessary to provide guidance on improving the life style, nutrition, and exercise regimen. This guidance is based on that given for primary osteoporosis.[29]

Follow-up observation

The risk of bone fractures is higher in patients administered GC than in those who were not treated with GC. Therefore, in patients evaluated as the follow-up observation group based on the present guidelines, it is essential to conduct follow-up observations by measuring the BMD and obtain radiographs of the thoracic and lumbar vertebra on a regular basis.

Drug treatment

In prospective randomized control trials overseas[30–34] and in Japan,[14,35] evidence has been found that the bisphosphonate products etidronate, alendronate, and risedronate significantly prevent bone fractures caused by GC-induced osteoporosis. Therefore, these drugs have been recommended as first-line treatment. Active vitamin D_3 has been reported to have fracture-preventing effects, although they are inferior to those of the bisphosphonates.[36]

Vitamin K_2 also was found to have fracture-preventing effects in a longitudinal study in Japan.[27] These two vitamins have been recommended as second-line drugs. Although the parameter was BMD, it was reported based on a meta-analysis that vitamin D and bisphosphonates administered concomitantly are more effective than bisphosphonates given alone in the treatment of GC-induced osteoporosis.[37] Concomitant administration of active vitamin D_3 and bisphosphonates should be considered in patients with serious or high-risk osteoporosis.

Conclusions

Glucocorticoids are widely used to treat a variety of inflammatory and allergic diseases and are prescribed by a wide array of physicians. It is well known that GC causes a number of significant side effects, and among them are skeletal manifestations, such as osteoporosis and degenerative bone fracture, major complications of GC therapy. Recently, the mechanisms of GC-induced osteoporosis have been clarified, and treatment strategies have been developed. Accordingly, management guidelines for GC-induced osteoporosis have been established in the United States, the United Kingdom, and elsewhere. The 2004 JSBMR-proposed guidelines for the management and treatment of GC-induced osteoporosis have 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. It will be necessary to verify and revise the present guidelines based on newly collected evidence in the future.

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