Incidence of Symptomatic Vertebral Fracture with High-dose Glucocorticoid Treatment in the Chiba-Shimoshizu Rheumatic Cohort between 1986 and 2006

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Abstract. We investigated the incidence of symptomatic vertebral fracture in patients who required long-term high-dose glucocorticoid (GC) treatment. The patients with collagen vascular diseases (aged 18 years or older) were registered to Chiba-Shimoshizu Rheumatic Cohort from 1986 to 2006. The study included the patients who were newly treated with the initial dose more than 20 mg prednisolone equivalent per day at least for more than 6 months. Among 700 patients (female/male: 539/161, mean age: 46.7 years, mean initial GC dose: 39.9 mg/day), 167 patients (23.8%) had at least one symptomatic vertebral fracture. Age and daily GC dose were significantly higher in the symptomatic fracture group than the no symptomatic fracture group. Cox regression model demonstrated that the relative risk for symptomatic vertebral fracture is independently higher in female patients, and in patients with initial higher age, and in those patients with initial higher GC dose and GC dose-increase, but lower with cumulative higher GC dose. High-dose GC treatment causes significantly high prevalence of symptomatic vertebral fracture in patients with collagen vascular disease. Age, female, higher initial GC dose and GC dose-increase are the risk factors for the symptomatic vertebral fracture in those patients.

Key words: Symptomatic vertebral fracture, Osteoporosis, Glucocorticoid, Collagen vascular disease

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GLUCOCORTICOID (GC) -induced osteoporosis was first described by Cushing over 70 years ago, in which patients with excess endogenous GC was reported to develop bone fractures in Cushing's disease [1]. In the past decades, GC-induced osteoporosis and bone fractures have drawn attention, since synthetic GCs have been widely used in patients with autoimmune, pulmonary and gastrointestinal diseases, as well as in patients with organ transplants and neoplas-

tic diseases [1-8].

Collagen vascular diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, polymyositis/dermatomyositis, systemic sclerosis, and granulomatous vasculitic conditions exemplified by Wegener's granulomatosis are associated with immune dysregulation. They are chronic and sometimes involve multiple organs, thus occasionally life-threatening. To control disease activity, an immunosuppressive regimen with long-term and high-dose GC is necessary, but the treatment causes high incidence of osteoporosis [9-15].

In the present study, we investigated the risk factors of symptomatic vertebral fracture implicated in long-term use of high-dose GC in patients with collagen vascular diseases, analyzing a cohort at Shimoshizu National Hospital in Japan between 1986 and 2006.

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Abbreviations: CSRC, Chiba-Shimoshizu Rheumatic Cohort; GC, glucocorticoid; PSL, prednisolone

Subjects and Methods

Subjects

A total of 2631 patients was registered in the Chiba-Shimoshizu Rheumatic Cohort (CSRC) in the Department of Rheumatology of a highly specialized rheumatic center, Shimoshizu National Hospital (Chiba, Japan), between 1986 and 2006. These patients were mostly referred to our center for treatment of collagen vascular diseases involving multiple organs. All patients were diagnosed as having collagen vascular diseases such as systemic lupus erythematosus, Sjogren's syndrome, polymyositis/dermatomyositis, rheumatoid arthritis, systemic sclerosis, or the granulomatous vasculitic conditions exemplified by Wegener's granulomatosis. Among the patients, those (aged 18 years or older) who were newly treated with high-dose GC were included in the study. They were treated with an initial dose of 20 mg or higher prednisolone (PSL) equivalent per day for at least 6 months without prior prophylactic treatment with bisphosphonate, hormone replacement therapy, or selective estrogen receptor modulator to prevent bone loss.

Study design

This was a 20-year observational study in patients receiving high-dose GC therapy. Study subjects were generally followed up every one or two months. The follow-up period for each patient started with the initial administration of GC. Study subjects were monitored regarding gender, age, body weight, height, and clinical characteristics such as underlying disease, initial smoking, and initial alcohol use. Body mass index (BMI) was also calculated. We defined a GC dose-increase as the re-introduction of more than 20 mg of GC per day (PSL equivalent) due to increased disease activity in patients whose doses were once tapered to less than 20 mg of GC per day. In the fracture patients, the daily dose of PSL (mg/day) and the cumulative dose of PSL (g) were calculated from the data until fracture. This study was approved by the Ethics Committee of Shimoshizu National Hospital. The informed consent was waived.

Symptomatic vertebral fracture

A symptomatic vertebral fracture was defined as

vertebral deformity that was confirmed by physical examination and spine x-ray in patients with sudden severe backache. Lateral thoracolumbar radiograms of the spine were graded independently by a radiologist. Vertebral deformity was semi-quantitatively assessed by a method similar to that described by Genant *et al.* [16], and deformity was positively confirmed if there was more than a 20% reduction in anterior, middle or posterior vertebral height.

Statistical analysis

Data were expressed as means $\pm$ SD. Potential risk factors for symptomatic vertebral fracture (age, gender, underlying disease, cumulative GC dose, mean daily GC dose, GS pulse therapy, numbers of GC dose-increase, smoking, and alcohol use) were first assessed in a univariate analysis. Differences in baseline characteristics were evaluated between two groups of patients by chi-square test and univariate analysis was performed with Student's t-test.

The no symptomatic vertebral fracture ratios were compared between the groups (smoking vs. no smoking, alcohol use vs. no alcohol used, and the groups with and without dose-increase) with the Kaplan Meier method and evaluated with log-rank test. Difference with p value <0.05 was considered to be statistically significant.

The hazard ratio of symptomatic vertebral fracture was estimated for each risk factor with Cox regression model with 95% confidence interval. The ratios were adjusted for gender, BMI, initial age, smoking, alcohol use, initial GC dose, cumulative dose of GC, GC pulse therapy and number of GC dose-increase. All statistical calculations were performed with SPSS (SPSS Inc., Chicago, IL), STATISTICA (StatSoft, Tulsa, OK), and/or MedCalc (MedCalcSoftware, Mariakerke, Belgium) computer software.

Results

Patient characteristics

In this study, a total of 700 patients (539 females, 161 males; initial age: 46.7 ± 16.6 yrs) were followed up over a 20 year period. The initial age of patients ranged widely (18-88 years), and the mean age of study population was relatively young, with more than 50% being

Table 1. Characteristics of symptomatic fracture and no symptomatic fracture groups of vertebrae at baseline and during the GC treatment

	Fracture group	No fracture group	Difference P value
Number of patients	167	533	
Gender (female/male)	133/34	406/127	N.S. ²⁾
Initial age (year)	56.3±14.0	43.6±16.3	P<0.001 ¹⁾
BMI	21.2±3.2	21.5±3.2	N.S. ¹⁾
Smoking (%)	41 (24.6%)	134 (25.1%)	N.S. ²⁾
Alcohol use (%)	32 (19.2%)	94 (17.6%)	N.S. ²⁾
Initial dose of PSL (mg/day)	39.0±14.8	40.1±13.8	N.S. ¹⁾
Daily dose of PSL (mg/day)	20.5±11.6	13.2±6.4	P<0.001 ¹⁾
Cumulative dose of PSL (g)	24.5±21.5	33.3±25.5	P<0.001 ¹⁾
GC pulse therapy (%)	25 (15.0%)	75 (14.1%)	N.S. ²⁾
Number of GC dose-increase (0/1/2/3/4)	73/64/21/6/3	357/102/47/23/4	P<0.001 ¹⁾

Data are expressed as mean ± SD.

BMI, body mass index; PSL, prednisolone; GC, glucocorticoid

¹⁾Unpaired t test, ²⁾Chi square test.

younger than age 50. Among those, 77% was female, 18% used alcohol and 25% smoked initially.

About one third of the patients had systemic lupus erythematosus (33.0%) as the underlying disease, and the rest of the patients had Sjogren's syndrome (11.7%), polymyositis/dermatomyositis (11.0%), rheumatoid arthritis (9.6%), systemic sclerosis (5.7%), mixed connective tissue disease (5.1%), Wegener's granulomatosis (0.9%), and others (23.0 %).

The initial GC dose was a high 39.9 ± 14.1 mg/day on average and the mean daily GC dose was 14.9 ± 8.6 mg/day (PSL equivalent). Among the patients, 38.6% required dose-increase and 14.3% required GC pulse therapy during the study period. Cumulative GC dose was estimated to be 31.2 ± 24.9 g (PSL equivalent) on average.

Incidence of symptomatic vertebral fracture

Among 700 patients, 167 patients (23.8%) had at least one symptomatic vertebral fracture during the study period, indicating that incidence of symptomatic vertebral fracture was high. The fracture group had significantly higher mean age, higher daily dose, lower cumulative dose, and higher number of GC dose-increase in comparison to the no fracture group. No significant differences were observed between the two groups in gender, BMI, use of alcohol, smoking, initial GC dose and GC pulse therapy (Table 1).

When the patients were categorized into the groups with and without GC dose-increase, the two groups had similar BMI, use of alcohol, and smoking. However, the group with dose-increase had a higher percent of females, lower age, and higher initial dose, higher daily dose, higher cumulative dose, longer observation period, and higher rate of GC pulse therapy as shown in Table 2. According to the Kaplan-Meier analysis, the group with dose-increase had significantly lower no symptomatic vertebral fracture ratio in comparison to the group without dose-increase ($P<0.05$) as shown in Figure 1A. On the other hand, Kaplan-Meier analyses demonstrated that no significant differences were found between smoking and no smoking, and between alcohol use and no alcohol use as shown in Figures 1B and C.

Risk factors for symptomatic vertebral fracture

The risk factors of symptomatic vertebral fracture were evaluated with Cox regression models for gender, initial age, BMI, smoking, initial alcohol use, initial dose, cumulative dose, number of GC dose-increase, and GC pulse therapy, as shown in Table 3. The risk for symptomatic vertebral fracture was independently higher in female patients with hazard ratio (HR) 1.774 (1.133-2.777, 95% CI), in every 10-year increment of the initial age with HR 1.787 (1.577-2.024, 95% CI), in every 5 mg/day of initial GC dose

Table 2. Characteristics of patients with and without GC dose-increase at baseline and during GC treatment

	No dose-increase group	Dose-increase group	Difference P value
Number of patients	430	270	
Gender (female/male)	320/110	219/51	p<0.05 ²⁾
Initial age (years)	49.4 ± 16.8	42.3 ± 15.5	p<0.001 ¹⁾
BMI	21.5 ± 3.3	21.3 ± 3.1	N.S. ¹⁾
Smoking (%)	111 (25.8%)	64 (23.7%)	N.S. ²⁾
Alcohol use (%)	72 (16.7%)	54 (20.0%)	N.S. ²⁾
Observation period (months)	83.0 ± 63.3	134.7 ± 72.9	p<0.001 ¹⁾
Initial dose of PSL (mg/day)	38.0 ± 12.5	42.8 ± 15.8	p<0.001 ¹⁾
Daily dose of PSL (mg/day)	13.8 ± 7.4	16.8 ± 9.8	p<0.001 ¹⁾
Cumulative dose of PSL (g)	23.1 ± 19.3	44.1 ± 27.2	p<0.001 ¹⁾
GC pulse therapy (%)	42 (9.8%)	58 (21.5%)	p<0.001 ²⁾
Vertebral fracture (%)	73 (17.0%)	94 (34.8%)	p<0.001 ²⁾

Data are expressed as mean ± SD.

BMI, body mass index; PSL, prednisolone; GC, glucocorticoid

¹⁾Unpaired t test, ²⁾Chi square test

Table 3. Evaluation of risk factors for symptomatic vertebral fracture using Cox proportional hazard regression model

Variables	Hazard ratio (95% confidence interval)	P- values
Female	1.774 (1.133-2.777)	P<0.05
BMI (every 1 BMI)	0.981 (0.933-1.031)	N.S.
Initial age (every 10 years)	1.787 (1.577-2.024)	P<0.001
Smoking	1.353 (0.889-2.059)	N.S.
Alcohol use	1.083 (0.660-1.777)	N.S.
Initial dose of PSL (ever 5mg/day)	1.241 (1.157-1.332)	P<0.001
Number of GC dose-increase	2.457 (2.054-2.939)	P<0.001
GC pulse therapy	1.317 (0.830-2.090)	N.S.
Cumulative dose of PSL (every 1g)	0.922 (0.908-0.935)	P<0.001

BMI, body mass index; PSL, prednisolone; GC; glucocorticoid.

Hazard ratio of risk factors was calculated using Cox proportional hazard regression model (confidence interval of 95%).

(prednisolone equivalent) with HR 1.241(1.157-1.332, 95% CI) and in every GC dose-increase with HR 2.457 (2.054-2.939, 95% CI). However, the symptomatic vertebral fracture risk was independently higher in decrease of every gram of cumulative GC dose (prednisolone equivalent) with HR 0.922 (0.908-0.935, 95% CI), indicating that GC dose increase, higher age, female, higher initial GC dose and lower cumulative GC dose were factors for fracture risk. In contrast, BMI, smoking, alcohol use and GC pulse therapy were not associated with vertebral fracture.

Discussion

In the present study, the prevalence of symptomatic vertebral fracture was high (23.8%) in Japanese patients with collagen vascular diseases, and required the treatment of initial high dose of GC (more than 20 mg PSL equivalent) daily. Risk factors for symptomatic vertebral fracture were found to be age, female, higher initial GC dose, and greater number of GC dose-increase. Lower cumulative GC dose was associated with the group with symptomatic vertebral fracture.

Fig. 1. Kaplan-Meier estimates of the no symptomatic vertebral fracture ratio in patients (A) with and without GC dose-increase, (B) between smoking and no smoking, and (C) between alcohol use and no alcohol use.

The collagen vascular diseases are chronic and occasionally life-threatening, thus requiring long term high-dose GC treatment [11, 12, 17, 18]. The mean initial daily dose (39.9 ± 14.1 mg/day), daily doses (14.9 ± 8.5 mg/day) and cumulative dose (31.2 ± 25.0 g) of the present study were approximately two times higher than those used in previous large population studies [19, 20]. The doses and periods may be high enough to produce rapid damage to the bone structure. The incidence of symptomatic vertebral fracture was markedly higher (23.8%) in the present study than the 12.3%

and 9.1% found in the patients with systemic lupus erythematosus both in a large US population-based study of the 1994 National Health Interview Survey [13], and in the patients of a cross sectional study of a large UK cohort of patients with systemic lupus erythematosus [15], respectively.

Symptomatic vertebral fracture in our study occurred in both age- and female-dependent manners. However, the results of previous studies and the meta-analyses on risk factors for vertebral fractures involving GC treatment were controversial [5, 7, 20, 21].

Naganathan *et al.* observed that the incidence of vertebral deformities was higher in GC users age 60 and older than the younger users [19]. On the other hand, Peel *et al.* observed the opposite results in a study of 76 postmenopausal women with steroid-treated rheumatoid arthritis (aged 50-79 years), where the vertebral deformity was most prevalent in the patients aged 50-59 years [22]. Recently, we also demonstrated the age-dependency of symptomatic vertebral fracture with high-dose GC treatment using the age quartiles in the sub-analysis of CSRC, in which the hazard ratio was 26-fold higher in patients aged 60-88 than in patients aged 18-31 years ($P < 0.01$) [23]. In addition, symptomatic vertebral fractures occur within shorter period of GC treatment as patients' age increased [23].

The association between gender and fracture risk has also been debated. Female as well as duration of GC administration and age were associated with bone fractures in patients with rheumatoid arthritis according to the multivariate analyses [24], whereas no significant difference in GC-induced fracture risk was reported between male and female in some studies [8,19] and meta-analysis [20, 21]. The possible explanation for age- and gender-dependence of GC-induced fracture in the present study could be the style, design and size of study. GC-induced fracture in the previous large-scale studies were mostly examined in cross-sectional and population-based manners [8,20,21,25-30]. A majority of longitudinal studies on bone fracture were on small-scale and included relatively few new GC users [20]. The present study covered a large number of 700 new GC users with the mean age of a much younger and wider range [46.7 (18-88) years] compared with other studies. The present longitudinal study had one of the longest study periods, 20 years. We also reported the female-dependent risk of symptomatic vertebral fracture in the elderly in the sub-analysis of CSRC [31].

Although the pathophysiological relevance in the relation between gender or age and GC-induced osteoporosis was not elucidated, the effect of GC on inhibition of bone formation appears to be more important than that on stimulation of bone resorption [3], and the direct effect on both osteoblastic lineage and osteocytes appears to be critical. GC is known to reduce the mature osteoblast pool, and to impair osteoblastic differentiation and maturation [3]. It is of therapeutic interest to note that teriparatide, which stimulates bone formation, was reported to reduce the risk of vertebral

fractures in GC-induced osteoporosis [32]. Thus, the association of bone formation to our findings, age and gender dependence in fracture risk must be examined in the future.

The correlation between fracture risk and GC dose (accumulative or daily) is of clinical importance. In the present study, both the higher initial dose and the greater numbers of GC dose-increase were two independent risk factors. The increased fracture risk with intermittent high-dose oral GC therapy was recently demonstrated by others [33], indicating that the exposure to high GC dose during a long period of time might produce the bone damage. However, the very high GC dose with a short period of exposure may not be what induces the damage, since GC pulse therapy was not correlated to bone fracture.

Both the activity and type of underlying disease may influence the GC dose and the number of dose-increase, which in turn may affect the degree of bone damage. In previous studies, bone loss in inflammatory bowel disease, rheumatoid arthritis, and chronic obstructive pulmonary disease is reported to be independent of GC treatment [3, 7, 34-37]. The systemic release of inflammatory cytokines affect bone formation and bone resorption, and seems to underlie the pathophysiology of bone loss [35, 37]. In these aspects, a subgroup analysis of the type and activity of diseases is necessary in the future.

We found an unexpected negative correlation between cumulative GC dose and fracture risk in the present study, whereas the positive correlations between cumulative dose and fracture risk were contrarily found in previous studies [38-40]. Especially, a strong relationship between daily dose and fracture risk and a weak correlation between cumulative dose and fracture risk were found in a large population-based cohort study in UK [8]. Although it is difficult to determine the basis for the negative association in the present study, there are several possible explanations. 1. There may be some genetic or environmental risk factors in the vertebral fracture group, which may shorten the duration to produce vertebral fracture. As a result, the cumulative dose might be negatively associated with fracture risk. 2. GC might be masking the symptomatic vertebral fracture through the reduction of pain and causing the underestimation, since GC is used to control many types of acute pain including cancer [41, 42] by reducing local production of inflammatory cytokines. However, this explanation

seems unlikely, since long-term GC administration is reported to have no effect on acute nociceptive thresholds in rats [43].

Our study has several limitations. Although the correlation between bone mineral density and GC-induced fracture risk has been discussed for years [21], we have no data on bone mineral density in the study subjects. Recent evidence has suggested that bone strength is determined by both bone mineral density and bone quality, and that bone quality may be more critical for GC-induced fracture risk than bone mineral density [21]. Recently, it has been known that vertebral fracture associated with GC therapy often is asymptomatic [3, 44, 45]. Since the clinical observation of the condition initiated the diagnostic procedure for symptomatic vertebral fracture in the present study, the fracture incidences observed might be less than the degree of actual occurrence.

The treatment of GC-induced osteoporosis has been extensively studied for the past several decades, and guidelines on the management and treatment of GC-induced osteoporosis have been published in Western countries and Japan [46, 47]. In general, the management of patients exposed to GC includes general health measures, sufficient calcium, and vitamin D,

and reducing the therapeutic regimen to the minimal effective dose [5]. The pharmacological treatment of GC-induced osteoporosis involves the use of bisphosphonates [5]. Our data may indicate the use of bisphosphonates should be considered soon after beginning GC therapy, especially with high-dose.

In conclusion, Japanese patients with collagen vascular diseases, who require long-term high-dose GC treatment, have a high risk of symptomatic vertebral fractures. Since the independent risk factors include female gender, initial age, high initial dose and high number of GC dose-increase, the methods of GC treatment, and the age- and gender-dependent bone strength of the patient may influence GC-induced osteoporosis.

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