Age, Initial Dose and Dose Increase are Independent Risk Factors for Symptomatic Vertebral Fractures in Glucocorticoid-Treated Male Patients

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Abstract

Objective The incidence and risk factors for symptomatic vertebral fracture were analyzed in glucocorticoid-treated male patients.

Methods This was an observational cohort study at Shimoshizu National Hospital in Japan. Analyzed were 161 male patients newly treated with high-dose glucocorticoid (≥20 mg/day prednisolone equivalent) (initial age: 53.5±16.9, initial glucocorticoid dose: 38.9±12.9 mg/day (0.66±0.23 mg/kg/day), follow-up time: 70.4±52.5 months) and 33 male patients with no glucocorticoid (initial age: 52.7±13.0, follow-up time: 76.4±62.7 months). The vertebral fracture was determined by x-rays.

Results Symptomatic vertebral fractures occurred more frequently in the high-dose glucocorticoid group (21.1%) than in the no glucocorticoid group (3.0%). Using Cox model, the adjusted hazard ratio (HR) for the high-dose glucocorticoid group was 8.16 (95% confidence interval: 1.09-60.86) relative to the no glucocorticoid control group. In the high-dose glucocorticoid group, Kaplan-Meier analyses demonstrated that the incidence of fractures in the patients with glucocorticoid dose increase was significantly higher in comparison with those with no glucocorticoid dose increase. Cox model demonstrated that the risk was independently higher in every 10-year increment of initial age with HR 1.58 (1.18-2.13), in every 10 mg increment of initial dose of prednisolone with HR 2.03 (1.43-2.88), in every dose increase of glucocorticoid increase with HR 3.63 (2.04-6.46), and with each 1-gram decrease of cumulative dose of glucocorticoid with HR 0.88 (0.84-0.93).

Conclusion In male patients, high-dose glucocorticoid causes a significantly high prevalence of symptomatic vertebral fractures, and the independent risk factors are age, initial glucocorticoid dose, glucocorticoid dose increase, and decrease of cumulative glucocorticoid dose.

Key words: symptomatic vertebral fracture, osteoporosis, glucocorticoid, collagen vascular disease, male, risk factor

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Introduction

Glucocorticoid-induced osteoporosis was first described by Cushing over 70 years ago, a study in which patients with excess endogenous glucocorticoid were reported to develop bone fractures in Cushing’s disease (1). In the past decades, glucocorticoid-induced osteoporosis and bone frac-
tures have drawn considerable attention, since synthetic glucocorticoids have been widely used in patients with autoimmune, pulmonary and gastrointestinal diseases, as well as in patients with organ transplants and neoplastic diseases (1-4). Several large-scale cross-sectional studies and meta-analyses have demonstrated that glucocorticoid treatment induced osteoporosis and increased the risk of vertebral fractures (3, 5, 6). Recently, we clarified the incidence and the risk factors for symptomatic vertebral fracture during high-dose glucocorticoid treatment in the Chiba-Shimoshizu Rheumatic Cohort (CSRC) (7-10).

The autoimmune diseases frequently require immunosuppressive treatment with long-term high-dose glucocorticoid which results in the glucocorticoid-induced osteoporosis. Although the pathogenesis of autoimmune diseases is multi-factorial with genetic predisposition and environmental triggers contributing to disease progression (11), both experimental and clinical lines of evidence suggest that autoimmunity is influenced by gender (12), as immune-reactivity is more enhanced in females than in males, and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren’s syndrome occur significantly and more frequently in females than in males (12). As a result, the characteristics of glucocorticoid-induced osteoporosis have been less known in male patients, although Kanis et al reported that glucocorticoid treatment is associated with a significantly increased risk of fractures in both genders (5).

In the present study, we investigated the incidence and risk factors for the symptomatic vertebral fracture in the long-term use of high-dose glucocorticoid in male patients, sub-analyzing the Chiba-Shimoshizu Rheumatic Cohort of 20 years in Japan.

Subjects and Methods

Subjects

Chiba-Shimoshizu Rheumatic Cohort (CSRC) was conducted by the Department of Rheumatology of a highly specialized rheumatic center at Shimoshizu National Hospital (Chiba, Japan) in order to investigate the prognosis, the complications and the side effects of treatment in the rheumatic diseases. These patients had been mostly referred to our center for the treatment of rheumatic diseases involving multiple organs. Most of the patients were diagnosed as having collagen vascular disease such as systemic lupus erythematosus, Sjögren’s syndrome, polymyositis/dermatomyositis, rheumatoid arthritis, systemic sclerosis, or the granulomatous vasculitic conditions exemplified by Wegener’s granulomatosis. A total of 2631 patients were registered to CSRC between 1986 and 2006. Among the patients, we defined the male patients, who were newly treated with an initial dose of \( \geq 20 \) mg prednisolone (PSL) equivalent per day for at least more than 6 months without prior prophylactic treatment with bisphosphonate to prevent bone loss, as the high-dose glucocorticoid group in this study.

Study design

This was a 20-year observational study. Study subjects were generally followed up once every month or two months. The follow-up period for each patient started with the initial administration of glucocorticoid. Study subjects were monitored regarding age, body weight, height, smoking, and alcohol use. Alcohol use was defined as consumption exceeding 4 units (or equivalent) per week. A unit of alcohol was defined as 20 g of pure alcohol. Body mass index (BMI) was also calculated. We defined glucocorticoid dose increase as the reintroduction of \( \geq 20 \) mg of glucocorticoid per day (PSL equivalent) due to increased disease activity in patients whose doses were once tapered to <20 mg of glucocorticoid 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.

Symptomatic vertebral fracture

Symptomatic vertebral fracture was defined as vertebral deformity with a clinical symptom that was confirmed by thoracolumbar x-rays in patients with a backache. Lateral thoracolumbar x-rays 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 (13) 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 mean ± SD. Differences in baseline characteristics among groups were evaluated by chi-square test, Student’s t-test, or ANOVA followed by Tukey’s honestly significant difference test. Differences in the incidences of vertebral fractures were compared between groups by the Kaplan-Meier method and evaluated by the log-rank test. Differences at P values <0.05 were considered statistically significant.

Hazard ratio with 95% confidence interval was estimated by Cox regression model. The ratio was adjusted for sex, BMI, initial age, smoking, alcohol use, initial glucocorticoid dose, cumulative glucocorticoid dose, glucocorticoid pulse therapy and the number of glucocorticoid dose increases. All statistical calculations were performed with IBM SPSS Statistics 18 (SPSS Inc., Chicago, Illinois) and STATISTICA Standard 6.0 (StatSoft Inc., Tulsa, Oklahoma).

Results

Patient characteristics

We followed both 161 male patients on high-dose glucocorticoid therapy (initial age: 53.5±16.9 years) and 33 male patients designated as no glucocorticoid controls (initial age:
52.7±13.0) between 1986 and 2006 in CSRC.

The major anthropometric and clinical data of the study patients are shown in Table 1. There was a wide age range at entry to the study (18-87 years). The high-dose glucocorticoid and no glucocorticoid control groups were similar in terms of initial age, BMI, rate of alcohol use and follow-up time. Patients in the high-dose glucocorticoid group had a higher rate of smoking (Table 1). In the high-dose glucocorticoid group, the mean initial daily glucocorticoid dose was estimated to be 23.4 g (PSL equivalent). The disease activity-related glucocorticoid dose increase involving re-introduction of 20 mg/day or higher (PSL equivalent) occurred in 51 patients (31.7%). Glucocorticoid pulse therapy was given to 13.0% of the patients over the entire study.

The underlying diseases were diverse among the patients in both groups, consisting of rheumatoid arthritis 24.2% (control: high-dose, 60.6%:16.8%), microscopic polyangiitis 13.4% (0%:16.1%), systemic lupus erythematosus 12.9% (3.0%:14.9%), polymyositis/dermatomyositis 10.3% (0%:12.4%), polymyalgia rheumatica 6.7% (3.0%:7.5%), systemic sclerosis 6.2% (9.1%:5.6%), Churg-Strauss syndrome 5.7% (0%:6.8%), Sjögren’s syndrome 4.6% (18.2%:0.9%), adult-onset Still’s disease 3.6% (0%:4.3%), Behçet’s disease 3.1% (0%:3.7%) and others 9.3 % (6.1%:9.9%).

### Incidence of Symptomatic Vertebral Fracture

During the 20 years of following this cohort, symptomatic vertebral fractures occurred in 21.1% of the high-dose glucocorticoid group, which was significantly higher than the 3.0% in the no glucocorticoid group. The cumulative incidence of symptomatic vertebral fractures was analyzed with the Kaplan-Meier curves, as shown in Fig. 1. The high-dose glucocorticoid group had a significantly higher incidence of symptomatic vertebral fractures in comparison with the no glucocorticoid control group (p<0.05); 8.2% vs. 3.0% at 12 months, 13.5% vs. 3.0% at 36 months, 17.7% vs. 3.0% at 60 months, 27.9% vs. 3.0% at 120 months, and 35.9% vs. 3.0% at 180 months, respectively (Fig. 1). Cox model demonstrated that the unadjusted hazard ratio (HR) of the high-dose glucocorticoid group was 7.84 (95% confidence interval: 1.07-57.34) relative to the no glucocorticoid control group, and the adjusted HR for age, BMI, smoking and alcohol use was 8.16 (1.09-60.86) (Table 2).

In the high-dose glucocorticoid group, the fracture group had significantly higher initial age, mean daily glucocorticoid dose, and proportion of glucocorticoid dose increase in comparison to the no fracture group. No significant differences were observed between the two groups in BMI, alcohol use, smoking, initial glucocorticoid dose, cumulative glucocorticoid dose, and glucocorticoid pulse therapy (Table 3).

In order to analyze the effect of glucocorticoid dose increase, male patients newly treated with high-dose glucocorticoid were categorized into groups with and without glucocorticoid dose increase (Table 4). The two groups were of similar initial age, BMI, prevalence of smoking and alcohol use, and initial glucocorticoid dose. However, the group with glucocorticoid dose increase had a higher glucocorticoid daily dose, a higher glucocorticoid cumulative dose and higher prevalence of glucocorticoid pulse therapy (Table 4). The symptomatic vertebral fractures occurred in 22.9% of the group with the glucocorticoid dose increase, which was significantly higher than the 3.0% in the group with no glucocorticoid dose increase (Table 4). Kaplan-Meier analysis demonstrated that the group with glucocorticoid dose increase had a significantly higher proportion of patients with symptomatic vertebral fractures in comparison with the no dose increase group (p<0.05), as shown in Fig. 2.
Risk factors for symptomatic vertebral fracture

The risk factors of symptomatic vertebral fracture in male patients newly treated with high-dose glucocorticoid were evaluated by Cox regression model for initial age, BMI, initial smoking, initial alcohol use, initial dose, glucocorticoid pulse therapy, number of glucocorticoid dose increase, and glucocorticoid cumulative dose, as shown in Table 5. The risk for symptomatic vertebral fracture was independently higher in every 10-year increment of the initial age with HR 1.58 (1.18-2.13), in every 10-mg increment of the initial dose of PSL with HR 2.03 (1.43-2.88) and in every glucocorticoid dose increase with HR 3.630 (2.04-6.46). However, the symptomatic vertebral fracture risk was independently higher with each 1-gram decrease of cumulative glucocorticoid dose (prednisolone equivalent) with HR 0.88 (0.84-0.93), indicating that higher age, higher initial glucocorticoid dose, glucocorticoid dose increase, and lower cumulative glucocorticoid dose were factors for fracture risk. On the other hand, BMI, smoking, alcohol use and glucocorticoid pulse therapy were not associated with symptomatic vertebral fractures.

Discussion

In the present study, symptomatic vertebral fractures occurred more frequently in male patients with the high-dose glucocorticoid than in those without glucocorticoid. The Cox model demonstrated that age, initial glucocorticoid dose, glucocorticoid dose increase, and decrease of cumulative glucocorticoid dose are the risk factors for the symptomatic vertebral fractures in male patients newly treated with high-dose glucocorticoid.

Kanis et al reported that the glucocorticoid treatment is associated with a significantly increased risk of fractures in both genders (5), which is comparable with our findings that
male glucocorticoid users had a significantly higher risk than those without glucocorticoid in CSRC. Recently, the risk of bone fragility was also reported in male patients treated with glucocorticoid (14).

Although the presence of gender difference on the risk of fracture has been debated in glucocorticoid-induced osteoporosis (4-6, 13, 15), we recently demonstrated the female-dependent risk by analyzing CSRC (7, 8, 10). The CSRC was one of the longest longitudinal studies (20 years) focusing on the symptomatic vertebral fracture as a primary endpoint. It covered a large number of new glucocorticoid users with a wide age range, and high dose of glucocorticoid. These factors might enable us to detect the gender difference on glucocorticoid-induced vertebral fracture (7, 8, 10).

The age-dependent risk for symptomatic vertebral fractures was also demonstrated during high-dose glucocorticoid treatment in CSRC (7-10). We previously demonstrated the age dependency of symptomatic vertebral fracture 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 those aged 18-31 years (p<0.01), and symptomatic vertebral fractures occur within a shorter period of glucocorticoid treatment as patients’ age increased (9).

The significantly positive correlation between fracture risk and greater numbers of glucocorticoid dose increases is one of the important findings, which was also observed in our previous studies of CSRC (7, 8, 10). The increased fracture risk with intermittent high-dose oral glucocorticoid therapy was recently demonstrated by others (16), indicating that the exposure to high glucocorticoid dose during a certain period of time might be enough to cause bone damage. The significant correlation between the glucocorticoid dose and the number of dose increases may be linked to both activity and the type of the underlying disease, 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 was reported to be independent of glucocorticoid treatment (2, 17-21). From this

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**Table 3.** Characteristics of Symptomatic Fracture and Non-fracture Groups of Vertebrae in Male Patients at Baseline and during High-dose Glucocorticoid Treatment

<table>
<thead>
<tr>
<th></th>
<th>Fracture group</th>
<th>No fracture group</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Initial age (years)</td>
<td>59.7±13.3</td>
<td>51.8±17.4</td>
<td>p&lt;0.05 (1)</td>
</tr>
<tr>
<td>BMI</td>
<td>21.4±3.5</td>
<td>21.9±3.1</td>
<td>N.S. (1)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>50.0</td>
<td>48.0</td>
<td>N.S. (2)</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>50.0</td>
<td>46.5</td>
<td>N.S. (2)</td>
</tr>
<tr>
<td>Initial daily dose of PSL (mg/day)</td>
<td>41.8±13.1</td>
<td>38.1±12.8</td>
<td>N.S. (1)</td>
</tr>
<tr>
<td>Mean daily dose of PSL (mg)</td>
<td>22.5±11.6</td>
<td>14.4±6.8</td>
<td>p&lt;0.001 (1)</td>
</tr>
<tr>
<td>Cumulative dose of PSL (g)</td>
<td>23.5±20.5</td>
<td>23.4±16.1</td>
<td>N.S. (1)</td>
</tr>
<tr>
<td>GC pulse therapy (%)</td>
<td>20.6</td>
<td>11.0</td>
<td>N.S. (2)</td>
</tr>
<tr>
<td>Number of GC dose increases (0/1/2/3/4)</td>
<td>15/13/5/0/1</td>
<td>95/21/8/3/0</td>
<td>p&lt;0.01 (2)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. BMI, body mass index; PSL, prednisolone; GC, glucocorticoid

1) Unpaired t test, 2) Chi-square test.

**Table 4.** Characteristics of Male Patients with and without GC dose Increase at Baseline and during High-dose Glucocorticoid Treatment

<table>
<thead>
<tr>
<th></th>
<th>GC dose increase group</th>
<th>No GC dose increase group</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>51</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Number of GC dose increases (0/1/2/3/4)</td>
<td>0/34/13/3/1</td>
<td>110/0/0/0/0</td>
<td></td>
</tr>
<tr>
<td>Initial age (years)</td>
<td>52.4±14.5</td>
<td>54.0±17.9</td>
<td>N.S. (1)</td>
</tr>
<tr>
<td>BMI</td>
<td>22.3±3.2</td>
<td>21.6±3.2</td>
<td>N.S. (1)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>45.1</td>
<td>50.0</td>
<td>N.S. (2)</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>49.0</td>
<td>46.4</td>
<td>N.S. (2)</td>
</tr>
<tr>
<td>Initial daily dose of PSL (mg/day)</td>
<td>41.4±14.5</td>
<td>37.7±12.0</td>
<td>N.S. (1)</td>
</tr>
<tr>
<td>Mean daily dose of PSL (mg)</td>
<td>19.0±10.3</td>
<td>14.7±7.4</td>
<td>p&lt;0.01 (1)</td>
</tr>
<tr>
<td>Cumulative dose of PSL (g)</td>
<td>34.1±19.9</td>
<td>18.4±12.9</td>
<td>p&lt;0.001 (1)</td>
</tr>
<tr>
<td>GC pulse therapy (%)</td>
<td>23.5</td>
<td>8.2</td>
<td>p&lt;0.05 (2)</td>
</tr>
<tr>
<td>Vertebral fracture (%)</td>
<td>22.9</td>
<td>9.7</td>
<td>p&lt;0.01 (2)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. BMI, body mass index; PSL, prednisolone; GC, glucocorticoid

1) Unpaired t test, 2) Chi-square test.
A negative correlation between cumulative glucocorticoid dose and fracture risk was unexpectedly observed in the present study and in other studies of CSRC (7, 8, 10), whereas positive correlations between cumulative dose and fracture risk were contrarily found in previous studies (22-24). Although its pathophysiological basis is hard to determine in the present study, there may be some genetic or environmental risk factors in the fracture group. These factors may shorten the duration to produce vertebral fracture and thus also reduce the cumulative dose of glucocorticoid. As a result, the cumulative dose might be negatively associated with fracture risk (7, 8, 10).

The pathogenesis of glucocorticoid-induced osteoporosis was unclear in the present study. Recent evidence indicated that the effect of glucocorticoid on inhibition of bone formation appears to be more important than that on stimulation of bone resorption (2), and the direct effect of glucocorticoid on both osteoblastic lineage and osteocytes appears to be critical. Glucocorticoid is known to reduce the mature osteoblast pool, and to impair osteoblastic differentiation and maturation (2). In this respect, it is of therapeutic interest that teriparatide, which stimulates bone formation, was reported to reduce the risk of vertebral fractures in
glucocorticoid-induced osteoporosis (25).

The present study has several limitations. First, the fracture risk in the present study might be lower than the fracture risk between the high-dose glucocorticoid group and healthy population since we compared the fracture risk between the patients with and without glucocorticoid in the cohort. In addition, it is well known that vertebral fracture associated with glucocorticoid therapy is often asymptomatic (2, 26, 27). Because we used symptomatic vertebral fracture determined by clinical observation followed by x-rays as an end-point, the fracture incidences observed might be less than those that actually occurred. Second, the gonadal function was not examined in this study, although hypogonadism is one of the common causes for the osteoporosis, and low testosterone levels are known to be correlated with the fracture in men (28, 29). Third, bone mineral density was not included as a parameter in our study, since our cohort started from 1986 and we could not measure the bone mineral density. The correlation between bone mineral density and glucocorticoid-induced fracture risk has been discussed for years, and the recent data have suggested that bone strength is determined by not only bone mineral density but also bone quality, and bone quality may in fact be critical for glucocorticoid-induced fracture risk instead of bone mineral density (5). Actually, it was reported that the values of lumbar bone mineral density were not associated with vertebral fractures in glucocorticoid-treated male patients (14).

In conclusion, high-dose glucocorticoid causes a significantly high prevalence of symptomatic vertebral fractures in male patients treated with high-dose glucocorticoid. Age, initial glucocorticoid dose, glucocorticoid dose increase, and decrease of cumulative glucocorticoid dose are independent risk factors.

The authors state that they have no Conflict of Interest (COI).

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References