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Complications of Short-Course Oral Corticosteroids for Eosinophilic Chronic Rhinosinusitis during Long-Term Follow-Up

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Abstract: The literature strongly recommends the use of oral corticosteroids in the management of patients with eosinophilic chronic rhinosinusitis (CRS) with nasal polyps. Although potential complications associated with the long-term use of oral corticosteroids for the treatment of CRS have been suggested, no studies have described these effects in detail. Forty-three patients with a mean age of 51 years with eosinophilic CRS were retrospectively evaluated after surgery. Short-course oral prednisolone (PSL, 0.5 mg/kg of body weight) was provided for one week when anosmia and eosinophilic mucin and/or nasal polyps were present. The postoperative follow-up period ranged from 12 to 108 months (average: 62 months). HbA1C showed normal ranges in all except one patient, who had a diabetic pattern of HbA1C of 6.5%. Five patients had serum cortisol levels below the cutoff value. However, re-examination of the serum cortisol and adrenocorticotropic hormone stimulation test showed normal ranges in all five patients who had initially shown abnormal values of serum cortisol. Thus, adrenal insufficiency in all the patients was negligible. Five (3 women and 2 men) out of the 15 patients (6 women and 9 men) who participated in bone mineral density measurement showed significant reductions, suggesting the presence of osteoporosis. Patients taking long-term and repeated short-course use of oral corticosteroids for refractory nasal polyps of eosinophilic CRS are likely to have a potentially increased risk for osteoporosis.

Keywords: eosinophilic chronic rhinosinusitis; nasal polyps; oral corticosteroid; osteoporosis; bone mineral density; cortisol; postoperative follow-up

1. Introduction

Chronic rhinosinusitis (CRS) is defined as persistent inflammation of the nasal and paranasal cavity mucosa lasting three or more months [1]. Based on an epidemiological study in the United States, about 29.2 million adults (prevalence: 14.2%) have CRS. The prevalence and medical costs of CRS are increasing and have become an important social issue [2]. The histomorphological patterns of chronic rhinosinusitis with nasal polyps are characterized by the predominance of eosinophils and mixed mononuclear cells but a relative paucity of neutrophils [3], and therefore can be designated as eosinophilic CRS. Mucosal infiltration with eosinophils in CRS with nasal polyps may have a poorer surgical outcome and is frequently associated with bronchial asthma [4].

Eosinophilic CRS is characterized by eosinophilic inflammation driven by Th2 cytokines [5]. Since glucocorticosteroids have potent anti-inflammatory effects, including decreasing inflammation mediated by eosinophils [6,7], they are the most common first-line treatment for CRS with nasal

polyps [8]. Placebo-controlled studies showed that topical corticosteroid therapy reduced the recurrence of polyps after surgery [9,10]. However, since topical corticosteroid therapy is not effective in all patients, systemic glucocorticosteroids are sometimes used. A randomized, controlled, double-blind study demonstrated improved nasal symptom scores when compared to the placebo with a 14-day treatment with 50 mg prednisolone (PSL) [11]. Although short courses of 5–14 days of oral corticosteroids are recommended for safe use in CRS with nasal polyps [8], repeated or prolonged use of oral steroids may be associated with an increased risk of systemic side effects [12]. Other studies with level-2 evidence showed positive changes in the majority of the parameters evaluated [11,13,14]. Thus, analysis of the data supports the use of oral steroids in patients with CRS and with nasal polyps for immediate and short-term periods.

The anti-inflammatory effects of oral steroids cannot be separated from their metabolic effects. Repeated or prolonged use of oral steroids may be associated with an enhanced risk of systemic side effects. At three to six months after the end of the oral steroid treatment period for CRS, increases in insomnia and gastrointestinal disturbance have been suggested as adverse effects [11,13,15]. Potential complications associated with the long-term use of oral corticosteroids for the treatment of CRS have been suggested [16]. The prevalence of adrenal insufficiency and low bone mass were recognized in patients with CRS with nasal polyps taking oral steroids [17,18]. Conversely, no systemic or local side effects of steroid treatment were seen in any patients [14,19]. Thus, whether the long-term use of oral corticosteroid for the treatment of eosinophilic CRS causes adverse effects is still controversial. In general, the main adverse effects of corticosteroid oral treatment include disturbance in glucose metabolism, suppression of the hypothalamic pituitary adrenal axis, osteoporosis or changes in bone mineral density (BMD), growth retardation in children, and cataracts and glaucoma [12,20,21].

In the present study, we evaluated the systemic adverse effects during long-term follow-up with intermittent and repeated short-course use of oral corticosteroids in refractory nasal polyps of eosinophilic CRS. Moreover, to evaluate the prevalence of adverse systemic effects during long-term follow-up, we calculated the relationship between the cumulative doses of PSL and the presence of osteoporosis in addition to the risk factors for osteoporosis.

2. Materials and Method

2.1. Patients

This study of a series of cases was approved by the ethics committee of the Juntendo University Faculty of Medicine. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of 17-180 (Project identification code). All subjects entered the study after providing informed consent.

Eosinophilic CRS was diagnosed based on the criteria of the Japanese Epidemiological survey of Refractory Eosinophilic Chronic Rhinosinusitis Study (JESREC) study [22]. Patients with specific types of CRS with nasal polyps, including aspirin sensitivity and cystic fibrosis, were excluded. Patients with eosinophilic CRS requiring oral corticosteroids postoperatively were recruited from the Department of Otorhinolaryngology of the Juntendo University Faculty of Medicine and the study was conducted between January 2007 and October 2016.

2.2. Study Protocol

Endoscopic sinus surgery was performed under general anesthesia according to our previous paper [23]. We used standard postoperative management as follows. All patients received an intranasal corticosteroid preparation of two puffs of fluticasone (100 μg) daily in each nostril as well as a saline nasal douche after surgery. A short-course of oral PSL (0.5 mg/kg of body weight) was prescribed for 5–10 days when anosmia and eosinophilic mucin and/or nasal polyps were present. Furthermore, levofloxacin (200 mg) was orally administered twice per day when massive, purulent nasal discharge occurred.

2.3. Outcome Measures

Details of the dose and duration of oral corticosteroid therapy were obtained for each patient from their clinical records. Lifetime cumulative doses of PSL were calculated, plus duration of therapy as the total period that continuous or intermittent corticosteroids had been taken. The criteria for diagnosing glucocorticoid-induced diabetes mellitus was defined as a fasting blood glucose level of ≥6.9 mmol/mol and HbA1c ≥65 mmol/mol [24]. The cutoff value for serum cortisol in the morning, used to define adrenal insufficiency, was 4.5 μg/dL. A rapid adrenocorticotropic hormone (ACTH test) was performed by measuring the serum cortisol concentrations immediately before and 30 and/or 60 min after the intravenous injection of cosyntropin (Cortrosyn; 0.25 mg). A normal response to the rapid ACTH test was defined as an increase in the serum cortisol concentration of at least 550 nmol/L (20 μg/dL). Bone mineral density (BMD) was measured at the anterior-posterior lumbar spine (L2–L4) by dual energy X-ray absorptiometry (Hologic Discovery A QDR, Hologic, Inc., Marlborough, MA, USA) using the same scanner for all patients. Lumbar spine BMD was computed from vertebrae that were unaffected by bone fracture or osteoarthritis using regression analysis [25]. BMD was expressed in absolute values as a T score and Z score matched for race and sex from peak bone mass (T score) or matched for age (Z score). Osteoporosis was defined as a T score of less than −2.5.

2.4. Statistical Analysis

The data were expressed as the mean ± S.D. Statistical analyses were evaluated using StatMate IV for Windows. One-way analysis of variance (ANOVA) followed by Fisher's exact test were used for 2-group comparison of age, body mass index, peripheral blood eosinophil, cumulative PSL dose, or duration of an oral corticosteroid. Pearson's chi-square test was used for 2-group comparison of gender. Pearson's correlation coefficient was used to examine the relationship between cumulative PSL and BMD. Differences were considered to be significant if $p < 0.05$.

3. Results

Forty-three patients with eosinophilic CRS requiring oral corticosteroids postoperatively (26 males and 17 females, ranging from 22 to 73 years, mean age of 51 years) were enrolled between January 2007 and October 2016. All 43 patients with eosinophilic CRS were taking frequent intermittent courses of an oral corticosteroid. The cumulative PSL dose ranged from 2.5 g to 22.7 g (mean: 12.8 g), with a duration of administration of 12 to 108 months (mean: 62 months), and daily dose of 5 to 30 mg.

The demographic and baseline clinical profiles are shown in Table 1. The proportion of male patients was 60%. Blood examination was performed before the administration of oral corticosteroids and demonstrated a mean total Immunoglobulin E of 387 IU/mL and a mean eosinophil of 8.7%. The comorbidity of allergic rhinitis and bronchial asthma was found to be 23 and 58%, respectively.

Table 1. Baseline demographics and clinical information (n = 43 patients).

Baseline Demographics and Clinical Information	
Male, no. (%)	26 (60)
Age, mean (min., max.)	51 (22, 73)
Serum eosinophil (%), mean (min., max.)	8.7 (0.3, 19.1)
Total IgE (IU/ml), mean (min., max.)	387 (18, 2288)
History of bronchial asthma, no. (%)	18 (42)
History of allergic rhinitis, no. (%)	10 (23)
History of eosinophilic otitis media, no. (%)	3 (0.7)

The distributions of HbA1c, serum cortisol level, and BMD are shown in Figure 1. HbA1c showed normal ranges in all except one patient. The patient revealed glucocorticoid-induced diabetes mellitus based on a fasting blood glucose of 126 mg/dL and a HbA1C of 6.5 mmol/mol. Five of the 19 patients had serum cortisol levels below the cutoff value. However, re-examination of the serum cortisol and

ACTH stimulation test showed normal ranges for all five patients initially showing abnormal values of serum cortisol. Thus, the adrenal insufficiency in all patients was negligible.

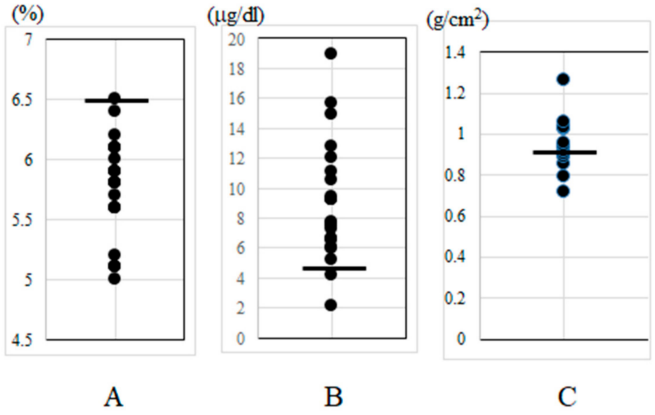

Figure 1. Scatterplots of (**A**) HgA1c, (**B**) serum cortisol, and (**C**) bone mineral density. Horizontal bars denote the normal limit.

Five (3 women and 2 men) of the 15 patients (6 women and 9 men) who participated in BMD measurement showed a significant reduction (33.3%) in bone density, suggesting the presence of osteoporosis. No vertebral fracture was observed in the present study. There were no significant differences in age, sex, peripheral blood eosinophil, cumulative PSL dose, or duration of oral corticosteroid between the groups with or without the presence of osteoporosis (Table 2). However, a significant increase in body mass index was observed in the group with the presence of osteoporosis but not in those without osteoporosis ($p < 0.01$). The cumulative PSL dose tended to be related to the reduction in BMD, but not significantly (Figure 2, $r = -0.28$, $p = 0.434$).

Table 2. Risk factors of osteoporosis.

	n	Osteoroporosis(+)	Osteoroporosis(−)
Age, mean (SD)	15	53.0 (11.5)	50.2 (11.5)
Sex, women versus men	15	3 vs 2	3 vs 7
Body mass index, kg/m^2, mean (SD)	15	0.79 (0.08)	1.01 (0.1)
Peripheral blood eosinophils, /μL, mean (SD)	15	726 (430)	942 (370)
Cumulative PSL dose, g, mean (SD)	15	14.2 (7.6)	11.2 (4.9)
Duration of PSL, mth, mean (SD)	15	67.6 (36.1)	55.0 (24.3)

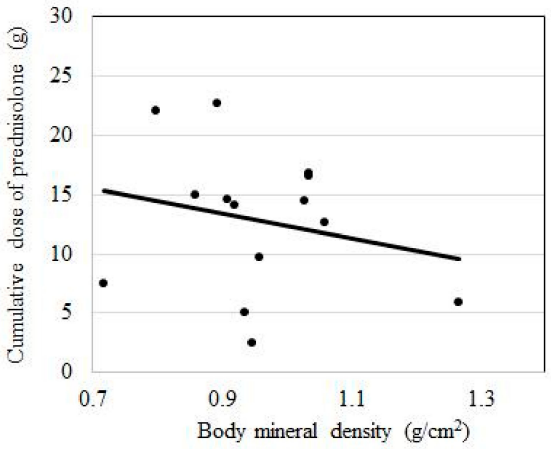

Figure 2. Relationship between cumulative prednisolone (PSL) and body mineral density ($r = -0.028$, $p = 0.434$).

4. Discussion

This study first revealed the prevalence of systemic adverse effects of frequent intermittent courses of oral corticosteroids for the prior 12 months, at least in patients with refractory nasal polyps from eosinophilic CRS. Based on a review of the literature [16], 16 articles were identified that evaluated the use of oral corticosteroids in patients with CRS and nasal polyps. However, no consensus was found to exist regarding the dosage or duration of the use of oral corticosteroids in the management of CRS and nasal polyps. All the studies highlighted benefits with very few adverse effects, and no severe adverse events were reported. We focused on glucose metabolism, suppression of the hypothalamic pituitary adrenal axis, and osteoporosis as adverse events.

Glucocorticoids are the main cause of drug-induced hyperglycemia/diabetes mellitus. The mechanisms that have been proposed to explain glucocorticoid-induced diabetes mellitus include decreased peripheral insulin sensitivity, increased hepatic glucose production, and inhibition of pancreatic insulin production and secretion [26]. Glucocorticoid-induced diabetes mellitus is common, but detection is generally difficult in a clinical setting due to the benign and asymptomatic profile. In the present study, we found only one out of 43 patients (2.3%) with glucocorticoid-induced diabetes mellitus. The frequency of glucocorticoid-induced diabetes mellitus in the present study was apparently lower than in a survey in Japan, which reported an incidence of approximately 6%–9% [27].

The use of corticosteroids is associated with numerous side effects and is considered to be the most common cause of adrenal insufficiency [28]. Chronic use of corticosteroids inhibits the function of the hypothalamic-pituitary-adrenal axis via negative feedback. Adrenal insufficiency is a serious, potentially life-threatening side effect of corticoid use. In asthma patients, the percentage of adrenal insufficiency ranges from 2.4% (low dose corticosteroids) to 21.5% (high dose corticosteroids), and according to treatment duration, from 1.4% (<28 days) to 27.4% (>1 year). These findings suggest that the risk of adrenal insufficiency cannot be excluded regardless of the dose or treatment duration [20]. A previous study [17] of patients with CRS with nasal polyps stated that asymptomatic adrenal insufficiency had a high prevalence of 48.8%. In contrast, in the present study, the use of oral corticosteroids in patients with eosinophilic CRS resulted in negligible adrenal insufficiency. However, oral corticosteroids should be used judiciously, understanding the potential complications of adrenal insufficiency associated with their long-term use.

Oral corticosteroid treatment has been associated with osteoporosis and an increased risk of fracture [29]. Bonfils et al. [17] reported a high prevalence of osteoporosis and osteopenia (12.2% and 48.8%, respectively) compared with the normal population. Patients with CRS with nasal polyps had taken at least four courses of oral steroid during the previous 12 months. Each course included PSL at 1 mg/kg body weight/day for 6–10 days. Rajasekaran et al. [18] evaluated the degree of osteoporosis in patients with CRS with and without nasal polyps, who had taken oral steroid (>5 mg daily) for at least three months. The overall prevalence of low bone density or osteopenia or osteoporosis was 38.6%. The cumulated steroid correlated strongly with bone density. In this study, we evaluated the effect of a short-course of 5–10 days of oral corticosteroids for at least 12 months based upon the bone metabolism assessed by objective measures of BMD. Approximately 30% of our subjects had a diagnosis of osteoporosis, but no subject had a vertebral fracture. No relationship was found between the cumulative PSL dose and BMD. Thus, long-term oral corticosteroid use, either short-course or daily-course, had an osteoporosis prevalence of 10%–30% in eosinophilic CRS. In patients taking long-term oral corticosteroids for chronic lung diseases, 58% had osteoporosis and 61% had a vertebral fracture. Furthermore, a high cumulative PSL dose is related to a low BMD [12]. Thus, the prevalence of osteoporosis in eosinophilic CRS is comparable to that in lung diseases, whereas the presence of vertebral fracture is completely different between upper and lower airway disorders. Nevertheless, the present study, a limited number of patients showed a trend of reduced BMD in relation to PSL use. Notably, low BMD is a risk factor for future fractures and appropriate treatment for osteoporosis is required.

This study has several limitations that need further investigation. First, the present study is a retrospective analysis of a series of cases. A case/control study with odds ratio calculation or a cohort study with relative risk calculation would be necessary to confirm our preliminary findings. Second, the present study evaluated the relationship between the adverse effects and cumulative dose of corticosteroid. However, the adverse effects of oral corticosteroid may depend on the daily dose, regimen of administration (continuous or frequent intermittent), or duration, which were not evaluated here. A larger sample size sufficient to classify differences in the types of dose and duration of oral corticosteroid therapy will allow the determination of the ideal dose with minimal adverse effects. Third, bone metabolism may be influenced by lifetime cigarette consumption, alcohol intake, calcium intake, age at menopause, exercise, glucose metabolism, and hypothalamic pituitary adrenal axis. Considering these multifactorial causes of the adverse effects may be necessary using a multivariable analysis including other variables that can influence the results.

5. Conclusions

Patients taking long-term and repeated short-course oral corticosteroids for refractory nasal polyps of eosinophilic CRS are likely to show a potentially increased risk for osteoporosis. However, no consensus exists on the dose and duration of oral corticosteroids prescription. Future research, including randomized controlled trials, registry studies, and prospective evaluations, are required to clarify the risk of osteoporosis in eosinophilic CRS patients.

Author Contributions: K.I. was involved in all stages of the study. R.M., S.I., H.H., N.O., H.O., Y.K., and A.S. were involved in data collection and laboratory examination. R.M. was involved in drafting the manuscript. All authors provided final approval for the publication of this manuscript. All authors read and approved the final manuscript.

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