Incidence and Risk Factors of Steroid-induced Diabetes in Patients with Respiratory Disease

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INTRODUCTION

Since the introduction of glucocorticoids in the 1950s, they have played a pivotal role in the treatment of various inflammatory diseases, including respiratory diseases. As they decrease inflammation and minimize tissue damage (1), glucocorticoids have been used widely to treat idiopathic interstitial pneumonia, chronic obstructive pulmonary disorders, endobronchial tuberculosis, sarcoidosis, hypersensitivity pneumonitis, and other respiratory diseases.

However, glucocorticoids have various adverse effects. They can cause glaucoma, fluid retention, increased blood pressure, increased blood sugar, menstrual irregularities, weight gain, stomach pain, insomnia, and infection. Impaired glucose metabolism is one of the commonest adverse effects. Glucocorticoids not only exacerbate hyperglycemia in patients with known diabetes mellitus (DM), but also cause DM in patients without documented hyperglycemia before the initiation of glucocorticoid therapy (2). The hyperglycemic condition is transient in many cases, but some patients may develop polydipsia, polyuria, and repeated infections. Especially in the elderly, there is a risk of precipitating hyperglycemic hyperosmolar states, including coma. In the long-term, the overall burden of repeated increases in blood glucose may increase cardiovascular risk (3, 4) and the risk of microvascular complications (5).

This study examined the incidence and clinical risk factors of steroid-induced DM in patients treated with glucocorticoid therapy for various respiratory diseases.

MATERIALS AND METHODS

Patients

We included adult patients (age > 20 yr) with respiratory diseases who were newly started on glucocorticoids from January 2003 through December 2008 at three hospitals affiliated with Seoul National University, Korea: Seoul National University Hospital, Seoul National University Bundang Hospital, and Seoul National University Boramae Hospital. The respiratory diseases treat-
ed with glucocorticoid included idiopathic interstitial pneumonitis, endobronchial tuberculosis, sarcoidosis, and hypersensitivity pneumonitis. Patients with asthma and chronic obstructive pulmonary disease (COPD) were not included, not only because they frequently used inhaled steroid, but also because their use of systemic steroid was usually short term.

Patients with respiratory diseases treated with systemic glucocorticoid exceeding a prednisolone-equivalent dose of 20 mg/day for at least for 4 weeks were included in the analysis. Patients with pre-existing diabetes or an initial random glucose level exceeding 200 mg/dL before initiating steroid therapy were excluded. We also excluded patients who were treated with steroid for other than lung diseases, such as malignancy, rheumatoid arthritis, transplantation, and nephrotic syndrome.

The demographic characteristics, clinical findings, and laboratory results were obtained from a retrospective review of the medical records. In addition, detailed information on the use of glucocorticoid (daily dose, duration of treatment, and cumulative dose) was collected.

Steroid-induced DM (S-DM) was defined as a fasting glucose concentration above 126 mg/dL or a random glucose concentration exceeding 200 mg/dL at least twice after beginning steroid treatment.

Statistical analysis

The chi-squared test was used to compare categorical variables, and the t-test to compare continuous variables between patients with and without S-DM. The variables analyzed included age, sex, body mass index (BMI), underlying lung diseases, daily and cumulative dose of steroid, duration of treatment, and initial random serum glucose level. To identify predictors of S-DM, multiple logistic regression models were constructed that included any variables with \( P < 0.10 \). Statistical significance was considered if \( P < 0.05 \). All statistical analyses were performed using SPSS® (Version 12.0, Chicago, IL, USA).

Ethics statement

The study protocol was approved by the institutional review boards of the Seoul National University Hospital (H-0906-059-284), Seoul National University Bundang Hospital (B-1001-092-103), and Seoul National University Boramae Hospital (06-2010-4).

RESULTS

Incidence of steroid-induced diabetes

The analysis included 231 patients with respiratory diseases who started taking systemic glucocorticoid during the study period. Their median age was 55 yr (range 22–85 yr), and 139 were female (60.2%). The baseline clinical characteristics and laboratory findings of the study population are summarized in Table 1. Respiratory diseases requiring glucocorticoid treatment included idiopathic interstitial pneumonia (125 patients), endo-

| Table 1. Baseline demographic and clinical characteristics of the patients with respiratory diseases treated with steroid |
|---------------------------------------------------------------|
| **Characteristics** | **All patients** | **Patients with steroid-induced DM** | **Patients without steroid-induced DM** | **P value** |
| Number of subjects | 231 | 34 | 197 |  |
| **Demographic characteristics** |  |  |
| Age, yr (median, range) | 55 (22-85) | 65 (50-81) | 53 (22-85) | < 0.001 |
| Male sex (%) | 92 (39.8%) | 18 (52.9%) | 74 (37.6%) | 0.09 |
| Body mass index (kg/m²) | 23.2 ± 3.7 | 23.6 ± 3.2 | 22.9 ± 3.8 | 0.53 |
| Current or ex-smoker | 80 (34.6%) | 19 (55.9%) | 61 (31%) | 0.005 |
| Pack-years | 10.7 ± 20.2 | 23.1 ± 26.5 | 8.5 ± 18.4 | 0.004 |
| **Respiratory diseases requiring steroid treatment** |  |  |
| Idiopathic interstitial pneumonitis | 125 (54.1%) | 27 (79.4%) | 98 (49.7%) | 0.001 |
| Endobronchial tuberculosis | 60 (26.0%) | 2 (5.9%) | 58 (29.4%) | 0.004 |
| Sarcoidosis | 43 (18.6%) | 5 (14.7%) | 38 (19.3%) | 0.53 |
| Hypersensitive pneumonitis | 3 (1.3%) | 0 | 3 (1.5%) | > 0.99 |
| **Comorbidities** |  |  |
| Hypertension | 35 (15.4%) | 8 (25.0%) | 27 (13.8%) | 0.12 |
| Hyperlipidemia | 12 (5.3%) | 4 (12.5%) | 8 (4.1%) | 0.07 |
| Chronic kidney disease | 11 (4.8%) | 1 (3.0%) | 10 (5.1%) | > 0.99 |
| Chronic liver disease | 3 (1.3%) | 0 | 3 (1.5%) | > 0.99 |
| Malignancy | 10 (4.4%) | 1 (3.0%) | 9 (4.6%) | 0.63 |
| **Initial laboratory findings** |  |  |
| Random glucose (mg/dL) | 101 (59-198) | 108 (76-190) | 100 (59-198) | 0.12 |
| Creatinine (mg/dL) | 0.9 (0.4-1.5) | 0.9 (0.6-1.4) | 0.9 (0.4-1.5) | 0.71 |
| Cholesterol (mg/dL) | 178 (88-331) | 186 (121-283) | 178 (88-331) | 0.22 |
| **Use of glucocorticoid (median, range)** |  |  |
| Total dose* (mg) | 4,965 (560-32,585) | 5,454 (940-23,590) | 4,880 (560-32,585) | 0.60 |
| Daily dose (mg) | 21.4 (6-64.4) | 24.6 (7-58.9) | 20.4 (6-64.4) | 0.25 |
| Total duration (days) | 193 (28-1,869) | 168 (33-1,408) | 198 (28-1,869) | 0.91 |

*Equivalent dose of prednisolone.
bronchial tuberculosis (60 patients), sarcoidosis (43 patients), and hypersensitivity pneumonitis (three patients).

The median random glucose before initiating glucocorticoid in the 231 patients was 101 mg/dL (range 59–198 mg/dL). The median cumulative prednisolone-equivalent dose of glucocorticoid was 4,965 mg (range 560-32,585 mg), and the median duration of steroid treatment was 193 days (range 28-1,869 days). S-DM was diagnosed in 34 (14.7%) out of 231 patients.

Risk factors of steroid-induced diabetes
The patients who developed S-DM were older than the patients who did not (65 vs 53 yr, P < 0.001). In addition, idiopathic interstitial pneumonitis was more common (79.4% vs 49.7%, P = 0.001), and endobronchial tuberculosis was less common (5.9% vs 29.4%, P = 0.004) among patients with S-DM than among those without S-DM. However, neither the cumulative dose nor the duration of glucocorticoid use was associated with the development of S-DM (Table 1).

Multiple logistic regression analysis revealed that only older age (odds ratio [OR] 1.05, 95% confidence interval [CI] 1.02–1.09) was an independent risk factor for developing S-DM (Table 2).

Evolution of steroid-induced diabetes
The median time of onset of S-DM was 91.5 days (range 15-1,733 days); 18 patients (52.9%) were diagnosed in the first 3 months, and five patients (14.5%) after 1 yr. Among the 23 patients followed for longer than 6 months after the diagnosis of S-DM, 10 were treated with oral hypoglycemic drugs and five with insulin. The other eight patients were observed without treatment. Treatment for S-SM could be stopped after a median of 202 days (range 47-1,621 days) in seven of the 15 patients in whom hy-
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AUTHOR SUMMARY

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We investigated the incidence and risk factors of steroid-induced diabetes mellitus (S-DM) in patients treated with glucocorticoid for respiratory diseases. A retrospective study examined patients with respiratory diseases treated with a prednisolone-equivalent glucocorticoid dose exceeding 20 mg/day for at least 4 weeks. S-DM was defined as a fasting glucose concentration exceeding 126 mg/dL or a random glucose concentration exceeding 200 mg/dL at least twice after beginning steroid treatment. A total of 231 patients met the inclusion criteria. The median cumulative prednisolone-equivalent glucocorticoid dose was 4,965 mg, and the median duration of steroid treatment was 193 days. S-DM was diagnosed in 34 (14.7%) of 231 patients. Older age was identified as a risk factor for S-DM. In conclusion, clinicians should be aware of the possibility of S-DM for patients with respiratory diseases, especially among patients.