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

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Glucocorticoids are effective for treating several respiratory diseases. However, they can cause hyperglycemia. This study determined 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 between January 2003 and December 2008. Patients whose initial random glucose level exceeded 200 mg/dL or who had pre-existing diabetes were excluded. 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 with respiratory diseases met the inclusion criteria. Their median age was 55 yr, and 139 were female. 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. Multivariate logistic regression identified older age (odds ratio 1.05, 95% confidence interval 1.02-1.09) as a risk factor for S-DM. S-DM is frequent among patients with respiratory diseases treated with glucocorticoid. Clinicians should be aware of the possibility of S-DM, especially among elderly patients.

Key Words: Diabetes; Glucocorticoids; Hyperglycemia; Respiration Disorders; Steroids

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-

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ed with glucocorticoid included idiopathic interstitial pneumonia, 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/m^2)	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 ± 25.5	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%)	2 (6.5%)	8 (4.1%)	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)	179 (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.

Table 2. Predictors of steroid-induced DM (multivariable analysis)

Parameters	Odds ratio	95% confidence interval	*P* value
Age* (yr)	1.05	(1.02-1.09)	0.006
Sex, Male	1.70	(0.48-5.99)	0.41
Smoking	1.36	(0.29-6.32)	0.70
Pack-years	1.02	(0.99-1.05)	0.22
Hyperlipidemia	2.12	(0.47-9.47)	0.33
Idiopathic interstitial pneumonias	1.19	(0.36-3.86)	0.78
Endobronchial tuberculosis	0.38	(0.06-2.31)	0.30

*(year X + 1 vs year X).

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 hypoglycemic agents and insulin were initiated.

DISCUSSION

Glucocorticoids can cause hyperglycemia via insulin resistance, which augments hepatic gluconeogenesis and lowers glucose uptake by peripheral tissues such as muscle cells and adipocytes (2, 6). For these reasons, it is not uncommon to observe abnormal glucose tolerance among patients receiving steroid therapy. In the present study of 231 patients with respiratory diseases who received glucocorticoid, 34 (14.7%) of the patients experienced S-DM. Given that the incidence of S-DM in other conditions requiring glucocorticoids, such as connective tissue diseases, was between 0.4% and 54% (7-11), the proportion of patients with respiratory disease treated with steroid who developed S-DM in our study is comparable. The wide variability may reflect different study populations, doses of glucocorticoid, duration of follow-up, and different diagnostic criteria for S-DM.

Proposed risk factors for S-DM included old age, high BMI, impaired glucose tolerance before therapy, cumulative dose, and long duration of steroid therapy. However, these results were not always consistent across studies (10-13). In our series of 231 patients treated with steroid for respiratory diseases, only old age was an independent risk factor for S-DM.

Glucose tolerance declines progressively with age, resulting in a high incidence of type 2 diabetes and impaired glucose tolerance in the old population (14, 15). According to the Korean National Health and Nutrition Examination Survey (16), 45% of Koreans 65 yr and older meet the diagnostic criteria for type 2 diabetes or impaired glucose tolerance. With aging, beta-cell function declines, and basal insulin secretion level decreases (17). In addition, the interaction of many factors associated with aging likely contributes to the altered glucose tolerance. These factors include obesity, decreased physical activity, medications, and coexisting illness (18). Considering the vulnerability of the aged population to glucose intolerance, the association of S-DM and age in our study can be understood.

To appreciate our results correctly, we should consider the limitations of this study. The effects of glucocorticoid on glucose metabolism are greater in the postprandial state than when fasting (10, 11, 19). In our study, however, we monitored fasting blood glucose rather than the postprandial plasma glucose level. In this context, our study could underestimate the incidence of S-DM.

In conclusion, S-DM is frequent among patients with respiratory diseases treated with glucocorticoid. Clinicians should be aware of the possibility of steroid-induced DM, especially among old patients.

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AUTHOR SUMMARY

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