Inhaled Corticosteroids and the Risks of Diabetes Onset and Progression

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ABSTRACT

BACKGROUND: Systemic corticosteroids are known to increase diabetes risk, but the effects of high-dose inhaled corticosteroids are unknown. We assessed whether the use and dose of inhaled corticosteroids increase the risk of diabetes onset and progression.

METHODS: We formed a new-user cohort of patients treated for respiratory disease during 1990-2005, identified using the Quebec health insurance databases and followed through 2007 or until diabetes onset. The subcohort treated with oral hypoglycemics was followed until diabetes progression. A nested case-control analysis was used to estimate the rate ratios of diabetes onset and progression associated with current inhaled corticosteroid use, adjusted for age, sex, respiratory disease severity, and co-morbidity.

RESULTS: The cohort included 388,584 patients, of whom 30,167 had diabetes onset during 5.5 years of follow-up (incidence rate 14.2/1000/year), and 2099 subsequently progressed from oral hypoglycemic treatment to insulin (incidence rate 19.8/1000/year). Current use of inhaled corticosteroids was associated with a 34% increase in the rate of diabetes (rate ratio [RR] 1.34; 95% confidence interval [CI], 1.29-1.39) and in the rate of diabetes progression (RR 1.34; 95% CI, 1.17-1.53). The risk increases were greatest with the highest inhaled corticosteroid doses, equivalent to fluticasone 1000 µg per day or more (RR 1.64; 95% CI, 1.52-1.76 and RR 1.54; 95% CI, 1.18-2.02; respectively).

CONCLUSIONS: In patients with respiratory disease, inhaled corticosteroid use is associated with modest increases in the risks of diabetes onset and diabetes progression. The risks are more pronounced at the higher doses currently prescribed in the treatment of chronic obstructive pulmonary disease.

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KEYWORDS: Asthma; Chronic obstructive pulmonary disease; Drug safety; Glucocorticoids; Observational studies

Inhaled corticosteroids are commonly used and effective medications for the treatment of asthma. Their indication and effectiveness in treating chronic obstructive pulmonary disease (COPD) are controversial.1,2 While these drugs are recommended primarily for patients with more severe COPD who have frequent exacerbations,3 they are nevertheless widely used for this condition.2 Moreover, higher doses of inhaled corticosteroids are commonly used in COPD, with recent trials involving doses of 1000 µg of fluticasone per day for 2-3 years.4,5 Such high doses have been associated with significant systemic effects such as pneumonia, glaucoma, cataracts, adrenal suppression, and accelerated bone turnover.6-10

The question of the association between inhaled corticosteroid use and the induction and worsening of diabetes has been rekindled recently. This issue is particularly relevant to patients with COPD, a major cause of chronic disability whose prevalence increases steadily with age, similarly to type 2 diabetes.11-13 Moreover, both the prevalence and incidence of type 2 diabetes are higher in patients with
COPD \cite{14,15} Therefore, the co-existence of these 2 chronic conditions among the elderly becomes important if corticosteroid medications used in the treatment of COPD also are associated with deterioration in glycemic control.

Major randomized trials in COPD did not report excess rates of adverse events of diabetes associated with inhaled corticosteroid use.\cite{4,5,16} These trials, while large, may not have had sufficient power to detect this excess risk. Observational studies on this issue, while reporting an excess incidence of diabetes associated with the use of oral corticosteroids, did not find an excess incidence with use.\cite{17,18} These studies, conducted using data from the 1990s, could not, however, assess the higher doses of inhaled corticosteroids currently being used. A recent observational study conducted in the Veterans Affairs database found that inhaled corticosteroid use was not associated with a change in serum glucose concentration in patients who do not also have diabetes, but a change was observed in a dose-response manner in patients with existing diabetes.\cite{19}

We therefore conducted a population-based cohort study of patients treated for respiratory disease to assess whether the use and the dose of inhaled corticosteroids increase the risk of new diabetes onset and, among patients who also have existing type 2 diabetes, whether inhaled corticosteroid use leads to the need for insulin.

**METHODS**

**Data Source**

We used the computerized databases of the Régie de l’assurance maladie du Québec, the agency responsible for administering the universal health insurance program of the province of Québec, Canada, for all its 7 million residents. The databases contain information on demographics and all medical services rendered, along with the diagnostic code of the service (International Classification of Diseases-9th revision), for all residents of the Province. The prescription drugs database includes outpatient prescription medications dispensed to all people aged 65 years or older, all social welfare recipients and, since 1996, all other residents who choose to join the provincial drug plan. In 2002, this drug plan was covering more than 3 million people: 545,651 individuals on welfare, 883,483 individuals aged 65 years or more, and 1,725,331 individuals without access to private group insurance.\cite{20} Information obtained from the Quebec prescription claims databases has been validated previously.

These databases have been used previously to conduct epidemiological studies of the risks of glaucoma, cataracts, fractures, and pneumonias associated with inhaled corticosteroids.\cite{6,7,10,21,22}

**Study Design**

We first formed a population-based cohort of all people in the population covered during 1990-2005 dispensed 3 or more prescriptions for respiratory medications in a 1-year period. Cohort entry was defined by the date of the third prescription for a respiratory medication. Subjects with a diagnosis of diabetes or a dispensed prescription for an antidiabetic drug before or on the day of cohort entry were excluded to allow the identification of new-onset diabetes. The remaining subjects were followed until the first antidiabetic medication after cohort entry, death, or until December 31, 2007. The antidiabetic agents included oral hypoglycemic agents, namely sulfonylureas, metformin, thiazolidinediones, and insulin.

To assess the risk of diabetes progression, we formed the subcohort of patients dispensed a prescription for an oral hypoglycemic agent during follow-up and defined as cohort entry the date of their first such prescription. Subjects whose first antidiabetic medication was insulin were thus excluded. The remaining subjects were followed until the first prescription for insulin (as an indicator of disease progression) after cohort entry, death, or until December 31, 2007.

In view of the large sizes of the 2 cohorts, a nested case-control analysis within each cohort was performed. For each case, 10 controls matched on age (within 1 year) and calendar time were selected at random from all subjects who entered the cohort in the same month as the case and at risk (alive and without the outcome of interest) on the date the case event occurred (index date). When fewer than 10 potential controls were available for a case, all members of the risk set were included as controls for that case.

**Inhaled Corticosteroid Exposure**

All prescriptions for inhaled corticosteroids, alone or in a combination inhaler, dispensed before the index date were identified and their doses obtained. These include inhaled beclometasone, budesonide, triamcinolone, fluticasone, and flunisolide. All doses of inhaled corticosteroids were converted to fluticasone equivalents according to defined daily doses of the most recent prescription in the 30 days before the index date, and categorized as: high (fluticasone...
1000 µg per day or more), moderate (500-999 µg per day), and low (<500 µg per day).

Data Analysis

Conditional logistic regression was used to estimate the adjusted rate ratios of diabetes onset and progression associated with current use and dose of inhaled corticosteroid. Current use was defined as a prescription in the 30 days before the index date. The rate ratios were adjusted for age (by design), sex, severity of respiratory disease, and co-morbidity. Severity of respiratory disease was measured by the number of dispensed prescriptions for beta-agonists, ipratropium bromide, theophylline, and cromolyns; the number of prescriptions for oral corticosteroids, for antibiotics; the presence of a hospitalization with a primary diagnosis of COPD or asthma; all measured in the year before the index date. Co-morbidity included cardiac disease defined by a prescription for cardiotropes, antihypertensives, diuretics or vasodilators; central nervous system drugs included benzodiazepines, major tranquilizers, anticonvulsants, and drugs for parkinsonism; osteoporosis drugs included calcium, vitamin D, and bisphosphonates; antirheumatic drugs included gold salts, methotrexate, azathioprine, hydroxychloroquine, and chloroquine. Nonsteroidal anti-inflammatory drugs, anti-depressive agents, and narcotics were considered as separate categories. All other prescriptions were regrouped.

Several sensitivity analyses were performed. First, to assess the possible contamination by concurrent oral corticosteroid use, the analysis was stratified by their use in the year before the index date. The analysis was also stratified according to the probability of asthma or COPD as the underlying respiratory diagnosis. Subjects were considered as probable COPD if they were at least 55 years old at cohort entry, but with no mention of asthma, either as the primary or a secondary diagnosis during hospitalization. All other subjects were considered to have probable asthma.

RESULTS

The cohort included 388,584 patients treated with respiratory medications, after excluding 39,068 already treated for diabetes. At cohort entry, the patients were 50.5 (± 27.5) years of age and 46% were men. The mean duration of follow-up was 5.5 years, during which 30,167 patients initiated treatment with antidiabetic medication. Thus, the overall incidence rate of new diabetes onset was 14.2 per 1000 per year. The subcohort of patients treated exclusively with oral hypoglycemic agents included 27,416 subjects, of which 2099 were subsequently given insulin during follow-up. Thus, the incidence rate of diabetes progression was 19.8 per 1000 per year.

Table 1 describes the characteristics of these cases of new diabetes onset and of diabetes progression, and their

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of New Cases of Treated Diabetes and Their Matched Controls, and Cases of Diabetes Progression and Their Matched Controls, At or In the Year Before the Index Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Diabetes Onset</td>
<td>Diabetes Progression</td>
</tr>
<tr>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Number</td>
<td>30,167</td>
</tr>
<tr>
<td>Age in years (mean ± SD)</td>
<td>66.3 ± 15.0</td>
</tr>
<tr>
<td>Follow-up in years (mean ± SD)</td>
<td>4.7 ± 3.7</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>41.4</td>
</tr>
<tr>
<td>COPD probable* (%)</td>
<td>16.8</td>
</tr>
<tr>
<td>Markers of respiratory disease severity in the year before index date</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for asthma or COPD (%)</td>
<td>19.9</td>
</tr>
<tr>
<td>Number of prescriptions (mean ± SD):</td>
<td></td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>0.9 ± 3.7</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>0.8 ± 2.0</td>
</tr>
<tr>
<td>Other respiratory drugs</td>
<td>4.3 ± 7.7</td>
</tr>
<tr>
<td>Treatment for other diseases in the year before index date (%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac drugs</td>
<td>69.0</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>24.9</td>
</tr>
<tr>
<td>Central nervous system drugs</td>
<td>10.8</td>
</tr>
<tr>
<td>Osteoporosis drugs</td>
<td>11.5</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>37.9</td>
</tr>
<tr>
<td>Narcotics</td>
<td>10.6</td>
</tr>
<tr>
<td>Antirheumatic drugs</td>
<td>1.2</td>
</tr>
<tr>
<td>Other drugs</td>
<td>18.5</td>
</tr>
</tbody>
</table>

*COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs.

*Individuals who entered the cohort after the age of 55 years and without mention of asthma during a hospitalization.
matched controls. Cases and controls were aged 66 (± 15) years, and the time to treatment initiation with antidiabetic medication was 4.7 years. The cases had more severe respiratory disease, with a higher frequency of asthma/COPD hospitalization and greater number of prescriptions for respiratory drugs, including oral corticosteroids and antibiotics. The cases had slightly higher prevalence of co-morbidity.

Table 2 shows that, after adjustment for differences in the covariates, current use of inhaled corticosteroids was associated with a significant 34% increase in the rate of diabetes (rate ratio [RR] 1.34; 95% confidence interval (CI), 1.29-1.39). There was a dose-response relationship, with the increase in the rate of diabetes greatest with the highest doses of inhaled corticosteroids, equivalent to fluticasone 1000 µg per day or more (RR 1.64; 95% CI, 1.52-1.76). The Figure displays the adjusted rate ratio as a function of the dose, along with 95% confidence limits for the fitted dose-response curve.

Table 3 shows that the current use of inhaled corticosteroids is also associated with a 34% increase in the rate of diabetes progression defined as a first prescription for insulin among users of oral hypoglycemic agents (RR 1.34; 95% CI, 1.17-1.53), and a 54% increase corticosteroid dose (RR 1.54; 95% CI, 1.18-2.02). Sensitivity analyses excluding subjects using oral corticosteroids concurrently in the year before the index date show that the rate ratio of diabetes onset associated with current inhaled corticosteroid use was comparable (RR 1.28; 95% CI, 1.22-1.34). Moreover, this rate ratio was similar in patients with probable asthma (RR 1.39; 95% CI, 1.31-1.49) or probable COPD (RR 1.28; 95% CI, 1.22-1.34).

**DISCUSSION**

Using a large population-based cohort of asthma and COPD patients, we found that the use of inhaled corticosteroids is associated with a significant 34% increase in the risk of incident diabetes, defined as initiation of antidiabetic medications. This risk increased with higher doses of inhaled corticosteroids, with 1000 µg of fluticasone per day or equivalent associated with 64% increase in the risk. Moreover, we found that in patients already treated for diabetes with oral hypoglycemic agents, the risk of progression to insulin also increased by 34% with the use of inhaled corticosteroids, with the higher doses associated with a 54% increase in this risk.

Clearly, systemic corticosteroids are associated with insulin resistance and hyperglycemia. Therefore, it is not surprising that inhaled corticosteroids, especially at high doses which have clear systemic effects,8 might result in hyperglycemia and earlier need for therapy or its intensification. This is of concern because duration of diabetes is associated with the likelihood of complications. While Slator et al19 were only able to show an effect of inhaled corticosteroids on blood sugar in patients already treated for diabetes, this may have been due to lack of power because they included only 1,698 subjects.19 Dendukuri et al17 also using the Quebec health administrative databases and with a
inhaled corticosteroid use. With an incidence rate of excess rates of adverse events of diabetes associated with inhaled corticosteroids in COPD did not previously identify by its treatment with medications, with the dispensing of inhaled corticosteroids. Their study, however, identified by its treatment with medications, with the dis-similar design, did not find an association of diabetes, as these trials, the Towards a Revolution in COPD Health increase in the risk. To put this in perspective, the largest of randomization followed for 1 year, or 4,200 patients fol-lowed for 3 years, to have sufficient power to detect a 50% sponse. Interestingly, their study reported a trend, although not significant, toward an excess risk of diabetes with high-dose beclomethasone. A similar study in Ontario again did not find a risk for inhaled corticosteroids, but this was carried out in an earlier time period when lower doses of less potent inhaled corticosteroids predominated.

It is not surprising that the major randomized trials of inhaled corticosteroids in COPD did not previously identify excess rates of adverse events of diabetes associated with inhaled corticosteroid use. With an incidence rate of diabetes of 14.2/1000/year in this cohort of patients with asthma or COPD, these trials, while large, did not have sufficient power to detect the observed excess risk. We would need a trial of 12,000 patients free of diabetes at randomization followed for 1 year, or 4,200 patients fol-lowed for 3 years, to have sufficient power to detect a 50% increase in the risk. To put this in perspective, the largest of these trials, the Towards a Revolution in COPD Health trial, which included over 6,000 patients over 3 years, of which 3,000 were exposed to inhaled corticosteroids, reported an excess risk of pneumonia on the basis of a 3-year cumulative incidence of pneumonia in the placebo group of 12.3%, in contrast to the 3-year cumulative incidence of diabetes of 4.2% estimated from our study.

The dose-response effect of inhaled corticosteroid use that we found on both the incidence and progression of diabetes is particularly important in the risk-benefit equation for patients with COPD. Indeed, while inhaled corticoste-roids are very effective for the treatment of asthma, their effectiveness in treating COPD is controversial. The fact that inhaled corticosteroids are now commonly combined in a single device with a long-acting bronchodilator, the latter recommended earlier in COPD, has resulted in inhaled corticosteroids now being used by over 70% of COPD patients. Moreover, these combined medications contain high doses of inhaled corticosteroids, as high as 1000 μg of fluticasone per day. Consequently, the widespread use of inhaled corticosteroids at higher doses in patients with COPD, along with the elevated incidence of diabetes in this age group and their uncertain effectiveness, can have an impact on the risk-benefit profile of inhaled corticosteroids in COPD.

This study has strengths and limitations. We assembled a large population-based cohort of close to 400,000 patients observed over 18 years. This size and long-term follow-up of the cohort enabled the identification of a large number of incident cases of diabetes that allowed very precise estimates of the risk associated with varying doses of inhaled corticosteroids. While we adjusted the risk estimates for several major confounders, there may be some residual confounding from unmeasured covariates. Indeed, low doses of inhaled corticosteroids were associated with a small excess risk of diabetes onset but not progression, although the latter analysis had insufficient power to detect small increases in risk. However, while the risks observed at the higher doses are consistent with the risks associated with low doses of prednisone, the smaller risk associated with lower doses of inhaled corticosteroids could also represent some residual confounding. Information on obesity was not available in the databases. Obesity may have been a con-founder because it is a risk factor for diabetes; while in asthma, obesity is associated with more severe asthma and may lead to prescribing inhaled corticosteroids more frequently or at higher doses. The lack of a difference in the risk estimates between individuals more likely to have COPD and those more likely to have asthma suggests that obesity was not a significant confounder because in COPD, low body mass index, rather than obesity, is a marker of severity.

We defined the incidence of diabetes by a first-time treatment with antidiabetic medications. This definition underestimates the more broad definition of diabetes measured

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude Rate Ratio</th>
<th>Adjusted* Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled corticosteroid use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No current use (%)</td>
<td>84.1</td>
<td>89.8</td>
<td>1.00</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Current use† (%)</td>
<td>15.9</td>
<td>10.2</td>
<td>1.68</td>
<td>1.34</td>
<td>1.17-1.53</td>
</tr>
<tr>
<td>Low dose (%)</td>
<td>0.8</td>
<td>0.6</td>
<td>1.33</td>
<td>1.08</td>
<td>0.63-1.87</td>
</tr>
<tr>
<td>Medium dose (%)</td>
<td>11.4</td>
<td>7.6</td>
<td>1.61</td>
<td>1.30</td>
<td>1.12-1.52</td>
</tr>
<tr>
<td>High dose (%)</td>
<td>3.8</td>
<td>2.0</td>
<td>2.11</td>
<td>1.54</td>
<td>1.18-2.02</td>
</tr>
</tbody>
</table>

CI = confidence interval.
*Adjusted for all of the factors listed in Table 1.
†Current use refers to a prescription in the 30 days before the index date.
by serum glucose levels, as these are not recorded in administrative databases. Nevertheless, our definition of diabetes is a harder measure that most likely represents the more serious cases requiring pharmacological treatment. Our estimates of the risk of diabetes associated with current inhaled corticosteroid use may, therefore, be underestimated by this under-ascertainment of the incidence of diabetes.

In conclusion, high doses of inhaled corticosteroids commonly used in patients with COPD are associated with an increase in the risk of requiring treatment for diabetes and of having to intensify therapy to include insulin. Therefore, patients instituting therapy with high doses of inhaled corticosteroids should be assessed for possible hyperglycemia and treatment with high doses of inhaled corticosteroids limited to situations where the benefit is clear.

References