CLINICAL RESEARCH STUDY

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The Association of Inhaled Corticosteroid Use with Serum Glucose Concentration in a Large Cohort

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ABSTRACT

BACKGROUND: Inhaled corticosteroids (ICSs) are widely used in the treatment of obstructive lung disease. ICSs have been shown to be systemically absorbed. The association between ICS and serum glucose concentration is unknown.

METHODS: To explore the association of ICS dosing with serum glucose concentration, we used a prospective cohort study of US veterans enrolled in 7 primary care clinics between December 1996 and May 2001 with 1 or more glucose measurements while at least 80% adherent to ICS dosing. The association between ICS dose from pharmacy records standardized to daily triamcinolone equivalents and serum glucose concentration was examined with generalized estimating equations controlling for confounders, including systemic corticosteroid use.

RESULTS: Of the 1698 subjects who met inclusion criteria, 19% had self-reported diabetes. The mean daily dose of ICS in triamcinolone equivalents was 621 μg (standard deviation 555) and 610 μg (standard deviation 553) for subjects with and without diabetes, respectively. After controlling for systemic corticosteroid use and other potential confounders, no association between ICS and serum glucose was found for subjects without diabetes. However, among subjects with self-reported diabetes, every additional 100 μg of ICS dose was associated with an increased glucose concentration of 1.82 mg/dL (*P* value .007; 95% confidence interval [CI], 0.49-3.15). Subjects prescribed antiglycemic medications had an increase in serum glucose of 2.65 mg/dL (*P* value .003; 95% CI, 0.88-4.43) for every additional 100 μg ICS dose.

CONCLUSION: Among diabetic patients, ICS use is associated with an increased serum glucose concentration in a dose-response manner.

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Inhaled corticosteroids (ICSs) are commonly prescribed to patients with both asthma[1] and chronic obstructive pulmonary disease (COPD).[2] ICSs decrease mortality in patients with asthma[3,4] and are indicated among patients with COPD with severe airflow obstruction and frequent exacerbations.[2,5] Several studies have examined the systemic effects of ICSs on the adrenal axis, skin, bone mineral density, fractures, and cataracts.[6-15] In addition to these effects of ICSs, systemic corticosteroids lead to a decrease in glucose control.[16] Case reports of 1 patient describe loss of glucose control associated with ICSs,[17,18] but no study has examined the association between ICS and serum glucose levels.

The Lung Health Study II did not demonstrate an increased risk for a new diagnosis of diabetes mellitus associated with ICS use.[19] Similarly, receiving a prescription for an ICS was not associated with an increased risk of receiving a new prescription for antiglycemic medications.[20] Oral corticosteroid use was associated with an increased risk of new-onset diabetes compared with proton pump inhibitor users, but no association was detected for ICS use.[21] The steps between diagnosis and receipt of medications for diabetes require a number of processes, such as medical and laboratory evaluations, proper interpretation, and intervention. These steps may lower the sensitivity of measures, such as new diagnoses of diabetes or new receipt of an

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antiglycemic medication to detect changes in overall glucose control. We sought to examine the association between ICS and glucose concentration using data collected from the Department of Veterans Affairs with comprehensive medication and laboratory assessments.

MATERIALS AND METHODS

Setting

The subjects were identified from the Ambulatory Care Quality Improvement Project trial, a randomized controlled trial of quality improvement interventions in the primary care setting. Subjects had at least 1 outpatient visit to the general internal medicine clinic at 1 of 7 participating Department of Veterans Affairs medical centers in the previous year.[22] The intervention had no effect on main trial outcomes.[23] Subjects were enrolled from February 1997 to December 1999 with data available 1 year before entry. Inpatient and outpatient administrative and pharmacy data were regularly extracted from the Veterans' Health Information System Technology Architecture (VISTA) computerized medical record system. The study protocol was approved by the Institutional Review Board at the University of Washington (Seattle, Wash).

CLINICAL SIGNIFICANCE

- Inhaled corticosteroid use is associated with higher serum glucose concentrations among patients with diabetes.
- This association is dose-dependent.
- Clinicians can anticipate an increase in serum glucose for patients using inhaled corticosteroids and should adjust serum glucose monitoring accordingly.

Subjects

All subjects who were taking an ICS based on pharmacy records (described below) and who had at least 1 serum glucose measurement during routine care were potentially eligible (Figure 1). Subjects were excluded if information regarding self-reported diabetes at the beginning of the study period was missing.

Medication Data

All prescriptions that were filled during the study period were obtained from VISTA and updated regularly. Information collected included medication name and category, date on which the prescription was filled, medication dose, and supply duration (days supply). The study period was divided into 30-day ascertainment intervals that began at an index date that corresponded to the return date of a self-report health care checklist from subjects. Medication exposure and glucose measurements were assessed for each 30-day interval.

Subjects could contribute to analyses if they filled more than 1 prescription for ICSs and had enough medication available to last at least 80% of the 30-day interval when a serum glucose measurement was obtained during routine practice. Pharmacy records were examined for at least 6 months before trial enrollment for dispensed prescriptions using published algorithms[24] to determine whether medication was available in each 30-day interval, taking into account both the accrual of additional prescriptions (oversupply) and the date prescriptions were filled (Figure 2).

The exposure variable for this study was the daily ICS dose a subject was taking in triamcinolone (TAC) microgram equivalents. The concentration of ICS prescriptions from different formulations (beclomethasone, flunisolide, and fluticasone) were converted to micrograms of TAC through published equivalents (1 μg of TAC equals 1 μg of flunisolide, 0.5 μg of beclomethasone, and 0.25 μg of fluticasone).[25] Daily dose was calculated for each time interval by dividing the total number of micrograms (based on ICS strength and canisters dispensed) by the day's supply.

Outcome Variable

Serum glucose measured during routine outpatient clinical practice was the primary outcome measure. It is not known if the subject was fasting at the time of serum glucose measurement. To minimize the confounding effect of systemic corticosteroid use, glucose values obtained 30 days before a hospital admission, during a hospitalization, and 90 days after an admission were excluded. Glucose levels were matched to intervals that subjects had an ICS available for at least 80% of the interval. If more than 1 glucose value was available during this time period, the average glucose measurement for that specific time period was used.

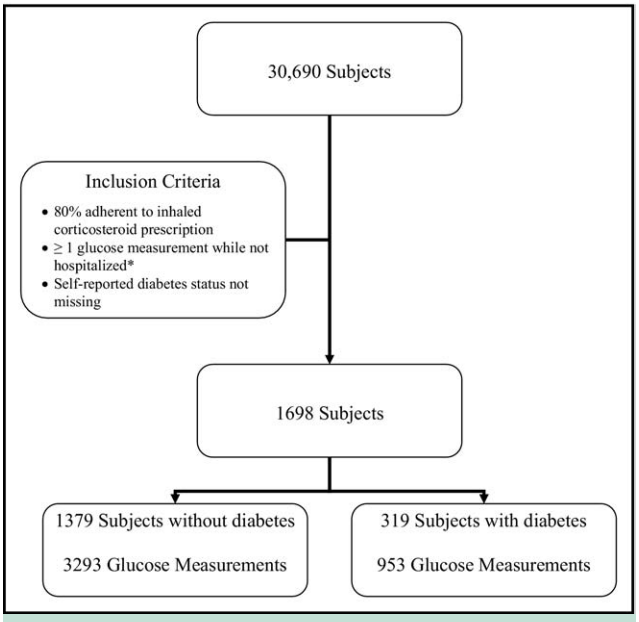

Figure 1 Flow chart of study design. *Excluded serum glucose measurements 30 days prior, during, and 90 days after a hospitalization.

Covariates

Baseline data for prescription of insulin and oral antiglycemic medications prescribed in the 90 days before the index date were collected from VISTA. Similar data were collected for short- and long-acting β-agonists, ipratropium, and theophylline prescriptions. Any outpatient dispensation of systemic corticosteroids (oral, intramuscular, or intravenous) during the study period was recorded as a dichotomous variable. Proxy measures of disease severity from VISTA were recorded, including hospitalizations and outpatient visits for any cause, as well as COPD-specific, in the year before study entry. COPD visits or admissions were defined by a primary diagnosis of COPD (International Classification of Diseases Ninth Revision (ICD-9): 491, 492, or 496). The extent of comorbid disease, using the Deyo adaptation of the Charlson comorbidity score, was calculated for each subject on the basis of inpatient and outpatient ICD-9 codes in the year before study entry.[26,27]

Baseline characteristics and health history were taken from self-report at the time of study enrollment. This information included age at entry, gender, race/ethnicity, highest education level achieved, and current annual income in $10,000 increments. Subjects also reported if they had ever been given a diagnosis of diabetes mellitus or COPD. Finally, subjects reported their current smoking status as current, former, or never.

Study Design/Analysis

The association between ICS dose and serum glucose was regressed using generalized estimating equations with a linear link to account for the repeated measures design of this study.[28] Models were constructed parsimoniously, excluding variables that were not confounders if they did not change the threshold level of significance or point estimates by more than 10%. Final equations were adjusted for the outpatient use of systemic corticosteroids during the study, age at entry, COPD-specific outpatient visits made during the year before study entry, Charlson score, annual income in $10,000 increments, and race/ethnicity. Short acting β-agonists, total hospitalizations, COPD-specific hospitalizations, and total outpatient visits did not confound the relation between ICS dose and serum glucose, so were not included in the final model. We did not find any substantial deviation from linearity for the association between ICS dose and serum glucose after examining multiple other models. An assessment for effect modification for both self-report of diabetes at study entry and use of diabetes medication in the 90 days before study entry was performed. All tests were 2 tailed using robust standard errors to minimize assumptions about equal variance in the subjects,[29] and a P value of less than .05 was considered statistically significant. The analyses were conducted using STATA SE-9 MP Special Edition (StataCorp, College Station, Tex).

RESULTS

There were 1698 subjects who met inclusion criteria, having at least 1 outpatient serum glucose measurement during a 30-day time interval when they were at least 80% adherent to use of an ICS. Table 1 shows the demographic charac-

Table 1 Baseline Characteristics of the Cohort Stratified by Self-Reported Diabetes Mellitus

Characteristics[a]	Subjects without DM	Subjects with DM
No.	1379	319
Demographics		
Age: Mean, SD	65.4 (10.8)	66.4 (9.9)
Male %	97%	97%
White %	82%	74%
Socioeconomic Variables		
Education (HS or less) (%)	62%	56%
Income < $30,000/y: (%)	89%	87%
Medical History		
COPD		
Self-report (%)	85%	83%
ICD-9 code (%)[b]	87%	85%
Smoking		
Never smokers (%)	8%	11%
Former smokers (%)	63%	65%
Current smokers (%)	27%	22%
Comorbidities		
Health care use/assessment in year before entry		
Primary Care Visits		
Total visits: Mean, SD	2.1 (1.8)	2.7 (2.2)
COPD related: Mean, SD	0.7 (0.9)	0.6 (1.0)
Hospitalizations		
All: Mean, SD	0.4 (0.9)	0.5 (1.0)
COPD related: Mean, SD	0.07 (0.3)	0.05 (0.3)
Charlson index score: Mean, SD	1.8 (1.3)	2.8 (1.8)
Medications		
TAC 100 μg equivalents: Mean, SD	610 (555)	621 (553)
Pulmonary Medication in 90 Days before Entry		
Short-acting ß-agonists (%)	71%	66%
Canisters received: Mean, SD	3.4 (3.5)	3.0 (3.2)
Anticholinergics (%)	51%	45%
Canisters received: Mean, SD	2.3 (3.0)	2.1 (3.0)
Long-acting ß-agonists (%)	4%	6%
Theophylline (%)	28%	28%
Systemic corticosteroid use during study (%)	43%	40%
Diabetes Medications in 90 Days before Entry		
Insulin (%)	0.22%	27%
Oral antiglycemics (%)	0.8%	49%

DM = diabetes mellitus; HS = high school; SD = standard deviation; ICD-9 = International Classification of Diseases Ninth Revision; COPD = chronic obstructive pulmonary disease; TAC = triamcinolone.

[a]Less than 5% missing data for all variables except Charlson, 6.6% and 16.9% with and without DM, respectively, and education, 6.3% and 7.3% with and without DM, respectively.

[b]Assessed in the year before study entry.

Table 2 Association of Serum Glucose (milligrams/deciliter) with Inhaled Corticosteroid Dose and Confounders Stratified by Self-reported Diabetes Mellitus[a]

Variable	β	P[b]	95% CI[b]
Subjects with Diabetes			
TAC[c] 100 μg equivalents	1.82	.007	0.49-3.15
Age (y)	−0.34	.399	−1.13 to 0.45
Systemic corticosteroid use (yes/no)	−4.16	.461	−15.22 to 6.91
COPD outpatient visits[d] (No.)	−4.90	.143	−11.46 to 1.66
Charlson Score[d]	−0.66	.774	−5.16 to 3.84
Income[e]	−5.85	.041	−11.45 to −0.24
Subjects without Diabetes			
TAC[c] 100 μg equivalents	−0.35	.078	−0.74 to 0.04
Age (y)	−0.10	.495	−0.38 to 0.18
Systemic corticosteroid use (yes/no)	1.07	.611	−3.04 to 5.17
COPD outpatient visits[d] (No.)	−0.04	.969	−1.96 to 1.88
Charlson Score[d]	1.46	.036	0.10-2.81
Income[e]	−0.57	.456	−2.08 to 0.94

CI = confidence interval; TAC = triamcinolone; COPD = chronic obstructive pulmonary disease.
[a]Race/ethnicity confounder not shown.
[b]Robust standard errors.
[c]TAC.
[d]Assessed in the year before study entry.
[e]Measured in $10,000 increments.

teristics of the population stratified by self-reported diabetes status. Subjects had an average age of approximately 65 years, of whom the large majority carried a diagnosis (either by self-report or ICD-9 code) of COPD. Subjects with self-reported diabetes made up 19% of the population. Approximately 90% were current or former smokers. There were few hospitalizations in the year before entry for all subjects.

The average daily dose of ICS measured in TAC equivalents was 621 μg (standard deviation [SD] 555) and 610 μg (SD 553) for subjects with and without self-reported diabetes, respectively. More than 65% of the subjects filled at least 1 prescription for short-acting bronchodilators in the 90 days before entering the study. Six percent of the subjects with diabetes and 4% of those without diabetes were taking a long-acting β-agonist, whereas 28% were taking theophylline in both groups (Table 1). Subjects without diabetes had an average of 3.1 (SD 2.63) serum glucose measurements available for analysis, and subjects with diabetes had an average of 3.9 (SD 3.11). The average serum glucose concentration was 170 mg/dL (SD 74) and 112 mg/dL (SD 34) for subjects with and without diabetes, respectively.

After controlling for age, systemic corticosteroid use, COPD outpatient visits, Charlson score, income, and race/ethnicity, ICS dose was not associated with serum glucose concentration (β coefficient 0.37 mg/dL increase for every 100 μg TAC equivalent increase; $P = .279$; 95% confidence interval [CI], −0.30 to 1.03) overall in the cohort.

Among participants with self-reported diabetes, each 100 μg TAC equivalent increase in dose was associated with a 1.82 mg/dL increase in serum glucose concentration ($P = .007$; 95% CI, 0.49-3.15) (Table 2). Among subjects without self-reported diabetes, ICS dose was not associated with serum glucose concentration (β coefficient 0.35 mg/dL decrease for every 100 μg TAC equivalent increase; $P = .078$; 95% CI, −0.74 to 0.04). Figure 2 represents and compares the adjusted associations from the regression model. The regression results were unchanged when the subject with diabetes with a glucose measurement greater than 800 mg/dL was removed in a sensitivity analysis.

For subjects prescribed antiglycemic medications in the 90 days before study entry, each TAC 100 μg equivalent increase was associated with a 2.65 mg/dL increase in serum glucose concentrations ($P = .003$; 95% CI, 0.88-4.43) (Table 3). For subjects not prescribed diabetes medications in the 90 days before entry, ICS dose was not associated with serum glucose concentration (β coefficient 0.17 mg/dL decrease for every 100 μg TAC equivalent increase; $P = .504$; 95% CI, −0.33 to 0.68).

DISCUSSION

We found a significant association between ICS dose and higher serum glucose levels among diabetic patients but did not see this association among nondiabetic individuals. Other studies have not shown an association between ICS and markers of glucose control,[19-21] although these outcomes may be insensitive measures of the effect of ICS on serum glucose. Although the results of this study are consistent with the known effects of systemic corticosteroids, the association observed between ICS and serum glucose might or might not be causal.

The magnitude of the association between ICS and serum glucose might appear small, but it can be clinically meaningful over the range of ICS dosing among patients with diabetes, especially because we found no evidence for a plateau in serum glucose concentrations. For example, among subjects with self-reported diabetes, applying our described association to the dose of ICS used in a recent

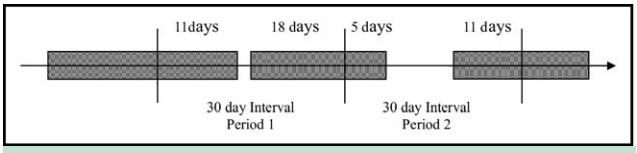

Figure 2 Example of ICS exposure during two 30-day intervals. Each box represents the amount of time a subject was prescribed an ICS. The subject would be classified as > 80% adherent during period 1 because he filled a prescription for 29 of 30 days but < 80% adherent during period 2 (16/30 days). A serum glucose level measured during period 1 would be included in the analysis, whereas one measured in period 2 would not.

Table 3 Association of Serum Glucose (milligrams/deciliter) with Inhaled Corticosteroid Dose and Confounders Stratified by Use of Antiglycemic Medications[a]

Variable	β	P[b]	95% CI[b]
Subjects Prescribed Antiglycemic Medication[c]			
TAC[d] 100 μg equivalents	2.65	.003	0.88-4.43
Age (y)	−0.37	.325	−1.12 to 0.37
Systemic corticosteroid use (yes/no)	13.24	.125	−3.68 to 30.16
COPD outpatient visits[e] (No.)	−6.06	.028	−11.47 to −0.65
Charlson Score[e]	−1.65	.511	−6.57 to 3.27
Income[f]	−6.81	.025	−12.79 to −0.84
Subjects Not Prescribed Antiglycemic Medication[g]			
TAC[d] 100 μg equivalents	0.17	.504	−0.33 to 0.68
Age (y)	0.00	1.000	−0.21 to 0.21
Systemic corticosteroid use (yes/no)	0.92	.672	−3.35 to 5.19
COPD outpatient visits[e] (No.)	−1.18	.287	−3.35 to 0.99
Charlson Score[e]	2.22	.003	0.74-3.70
Income[f]	0.40	.662	−1.40 to 2.20

CI = confidence interval; TAC = triamcinolone; COPD = chronic obstructive pulmonary disease.

[a]Race/ethnicity confounder not shown.

[b]Robust standard errors.

[c]Subjects receiving a prescription for insulin or oral antiglycemic medication in the 90 days before study entry.

[d]TAC.

[e]Assessed in the year before study entry.

[f]Measured in $10,000 increments.

[g]Subjects not receiving a prescription for insulin or oral antiglycemic medication in the 90 days before study entry.

study (500 μg of fluticasone twice daily, equal to 4000 TAC equivalents),[25,30] we would estimate that ICS use may potentially contribute to an increase of serum glucose concentration of 72.8 mg/dL (95% CI, 19.5-126.2).

Our results are consistent with studies showing an association between ICS use and bone density, fractures, skin changes, myocardial infarctions, and markers of inflammation,[8-14,31-33] as well as the relationship between systemic corticosteroids and glucose control.[16] Among subjects without diabetes, a previous study demonstrated that ICS use was associated with higher glucose concentrations after an oral glucose test compared with pretreatment values for subjects with COPD, perhaps related to a decrease in insulin sensitivity.[34]

However, non-biologic explanations also are possible. For example, type 2 diabetes has been associated with reduced lung function.[35-41] Because ICS prescription and dose are likely related to poor lung function, subjects with more severe diabetes might have worse lung function and symptoms and require higher doses of ICS. Although the findings may be secondary to this residual confounding, our proxy measures of symptoms and disease burden were similar among subjects with and without diabetes.

Our results might illustrate a form of bias by indication. For example, patients who are adherent to higher doses of ICS may experience a greater burden of pulmonary symptoms, which in turn distracts them from tighter management of coexisting diabetes. This case of competing priorities has been demonstrated in other settings,[42] and although the association in this case is not biologically causal, it may indicate a limited capacity for the patient and health care system to adequately address several diseases simultaneously. Close attention to diabetic control among patients taking ICSs would still be important, but for reasons other than a direct biologic mechanism.

Our study has several strengths. We used information from a large outpatient cohort that was followed for several years. We likely had near complete information medication exposures, including medication adherence.[43] Our large sample size permitted examination of ICS use over a wide dose range, and our measurement permitted a dose-response analysis. We carefully restricted our sample to those who had enough medication to be adherent for the majority of the assessment period with a validated algorithm.[24] We did not limit this study to subjects with COPD, although only a minority was likely taking ICSs for asthma.

Because patients are often provided a home supply of systemic corticosteroids for acute exacerbations, we could not assess the timing or actual dose of systemic corticosteroid use. Nevertheless, we attempted to minimize its confounding effect in multiple ways. First, we excluded glucose measurements associated with a hospitalization. Second, we adjusted for systemic corticosteroid use during the study period. Third, because subjects with more severe disease may receive systemic corticosteroids more frequently, we also adjusted using proxy measures of disease severity, such as number of outpatient visits for COPD. Although a similar percentage of subjects with and without diabetes were prescribed systemic corticosteroids, our results may be subject to unmeasured confounding if subjects with diabetes received higher doses.

Our results may not be generalizable to other populations receiving ICSs because our population was composed of older men who received ICSs mainly for treatment of COPD. The subjects with diabetes in this population had poor diabetic control and the analysis ended in 2001, so subjects may have had less attention placed on strict glucose control than would be practiced currently. We assumed patients who filled a prescription took it as directed. Finally, we did not examine glycosylated hemoglobin or fasting serum glucose concentrations, which may be better clinical measures of diabetes control than random serum glucose measurements.

CONCLUSIONS

Our findings demonstrated that among patients with diabetes, ICSs were associated with higher serum glucose concentra-

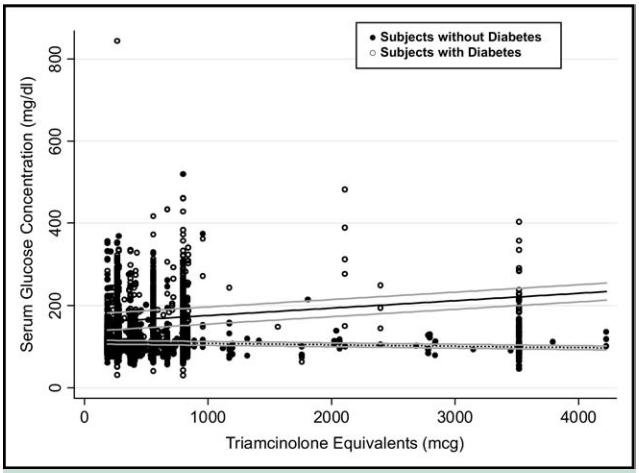

Figure 3 Association between serum glucose concentration and ICS use measured in TAC microgram equivalents for subjects with a self-reported history of diabetes compared with those without diabetes. The solid regression line presents subjects with diabetes, and the dotted line presents subjects without diabetes (both adjusted for age, systemic corticosteroid use, COPD outpatient visits, Charlson score, income, and race/ethnicity). The gray lines present the 95% CIs for the forecasted predicted values.

tions and this association was dose-dependent (Figure 3). Given the association between ICS dose and serum glucose among patients with diabetes, clinicians may want to more closely monitor serum glucose levels among patients with diabetes who were prescribed inhaled corticosteroids.

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