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Risk of corticosteroid-induced hyperglycemia requiring medical therapy among patients with inflammatory eye diseases

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Contributions

Design and conduct of the study (JDU, YD, GSY, JHK); collection, management, analysis, and interpretation of the data (JDU, YD, GSY, ED, SG, JTR, EBS, JET, CSF, DAJ, GAL, RBN, JHK); preparation, review, or approval of the manuscript (JDU, YD, GSY, ED, SG, JTR, EBS, JET, CSF, DAJ, GAL, RBN, JHK)

Institutional Review Board Approval

The project was conducted in accordance with the principles of the Declaration of Helsinki, with the approval of the governing Institutional Review Boards of each institution, each of which has granted waiver of consent, allowing all living and deceased patients to be included.

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Abstract

Objective—To identify the incidence and risk factors for corticosteroid-induced hyperglycemia requiring medical therapy among patients with inflammatory eye diseases.

Design—Retrospective cohort study.

Participants—Patients with ocular inflammation followed at five United States tertiary centers who initially were neither diabetic nor taking hypoglycemic medications.

Methods—Eligible patients who used oral corticosteroids during follow-up were identified and followed longitudinally for initiation of hypoglycemic medication over one year after beginning corticosteroids. The remaining eligible patients were followed for one year after their initial visit. Survival analysis was used to calculate the risk of hyperglycemia requiring medical therapy, and to identify potential risk factors.

Main Outcome Measures—Initiation of hypoglycemic medications.

Results—Among 2,073 non-diabetic patients treated with oral corticosteroids, 25 (1.21%) initiated hypoglycemic therapy compared with 5 (0.19%) of 2,666 patients not treated with oral corticosteroids (relative risk (RR) = 4.39, 95% Confidence Interval (CI) = 1.68 – 11.5). Relative risk tended to be higher in association with higher initial doses (For initial doses <40 mg of prednisone/day, RR=3.23, 95% CI: 1.08–9.64; for initial prednisone dose ≥40 mg/day, RR=5.51, 95% CI: 2.01–15.1). Other risk factors for the initiation of hypoglycemic therapy included older age (RR (per each additional 10 years) = 1.46, 95% CI = 1.15 – 1.85, $p = 0.002$) and African-American race (RR = 2.94, 95% CI = 1.34 – 6.43, $p = 0.007$).

Conclusions—These results suggest that the absolute risk of corticosteroid-induced hyperglycemia that is detected and treated with hypoglycemic therapy in the tertiary ocular inflammation setting is low (an excess cumulative risk on the order of 1% within one year), although on a relative scale it is approximately 4.4-fold higher than in patients not treated with oral corticosteroids. Higher age and African-American race also were risk factors. Physicians who use systemic corticosteroids for ocular inflammatory diseases should be aware of this risk, and should consider surveillance for hyperglycemia among high-risk patients. However, given the low absolute risk, routine laboratory monitoring or referral for monitoring may not be necessary for low risk patients.

INTRODUCTION

In the United States, the incidence of uveitis is estimated to be between 25.6 and 52 cases per 100,000 persons per year^{1,2}. Scleritis, pemphigoid, and other forms of ocular inflammatory diseases add to the burden of ocular inflammatory disease. Systemic corticosteroid therapy is indicated for severe cases of each of these conditions³. Such therapy usually is effective for suppressing active inflammation³, but is known to predispose patients to a number of side effects, including the risk of corticosteroid-induced diabetes mellitus (DM)^{4,5}. While the use of topical corticosteroids only rarely is associated with incident DM⁶, systemic corticosteroids have been reported to be the most common cause of drug-induced diabetes mellitus⁷. Because systemic corticosteroids are a mainstay of

treatment for inflammatory eye diseases, the risk of a clinically important degree of corticosteroid-induced hyperglycemia is highly relevant to ophthalmologists.

Previous small clinical studies have described the risk of corticosteroid-induced diabetes in systemic disease cohorts.^{8–11} Because a cohort with mostly local ocular disease may have a different degree of risk than patients with systemic diseases, we set out to identify the risk of hyperglycemia requiring glucose-lowering therapy among patients receiving oral corticosteroids for the indication of ocular inflammatory disease, and to identify predisposing risk factors in this clinical setting.

METHODS

Overview

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort is a large retrospective cohort of patients with non-infectious ocular inflammation seen at five tertiary centers in the United States. The study's methods have been described in detail previously¹². Eligible patients had a non-infectious ocular inflammatory diagnosis (uveitis, scleritis, cicatrizing conjunctivitis of mucous membrane pemphigoid, and other conjunctival, corneal, optic nerve, and orbital inflammatory diseases). Patients known to have human immunodeficiency virus infection were excluded from the study.

For most patients, participating centers had managed systemic therapy administered for ocular inflammatory diseases directly, and their detailed records regarding the use of systemic corticosteroids (among other medications) were available for review. Data about demographic, clinical, and treatment characteristics were harvested from medical records by a structured, protocol-driven review of every visit of every patient, conducted by expert reviewers.¹² All eligible patients identified were studied. All medications in use—including corticosteroids, insulin, and oral hypoglycemic agents—were entered for every clinic visit. Quality control features built into the data system required immediate correction or verification of unlikely values. Records of patients who had been seen at more than one of the participating centers were merged so as to avoid duplication.

In order to address the incidence of clinically important hyperglycemia, patients were followed for initiation of hypoglycemic medication therapy within 12 months after starting oral corticosteroids for the first time during the study, or for 12 months after study entry (for those never observed to take corticosteroids). Patients were excluded from the study if they met the following exclusion criteria: 1) age 17 years or younger, 2) documented medical history of type I or II diabetes mellitus prior to initiating corticosteroid therapy; 3) use of hypoglycemic medication at the initial visit, 4) patients without at least 1 follow-up visit.

Statistical Analysis

Hyperglycemia risk for patients with/without oral corticosteroid use was estimated through calculation of proportions and through a person-year analysis assuming a Poisson distribution. Their cumulative incidence of hyperglycemia (use of hypoglycemic medication) over time within 12 months of initial corticosteroid use was estimated through Kaplan-Meier analysis. The association of corticosteroid use and other potential risk factors with development of hyperglycemia was evaluated through the calculation of relative risk (RR) and their 95% confidence intervals (CI), via univariate and multivariate Cox regression models. The patient characteristics significantly associated with incident hyperglycemia ($p < 0.05$) in univariate analysis were included in a multivariate Cox regression model; the final model was simplified by only keeping the statistically significant risk factors from multivariate analysis. All the statistical analyses were performed using SAS v9.1 (SAS Inc., Cary, NC).

RESULTS

Patient Characteristics

Demographic information regarding patients in this study is given in Table 1. A total of 4,739 patients with ocular inflammation met eligibility criteria for this analysis, after excluding those with no follow-up visits, those with known diabetes mellitus, and those taking hypoglycemic drugs at the initiation of oral corticosteroid therapy (or at the initial visit for those never observed to take oral corticosteroid therapy). Of these, 2,073 (44%) were treated with oral corticosteroids during observation. Most eligible study patients were female (64%) and Caucasian (74%). These patients had been diagnosed with uveitis (77%), scleritis (15%), mucous membrane pemphigoid (6%), or other forms of ocular inflammation (3%). Most (73%) were free of associated systemic inflammatory disease; spondyloarthropathy (6%), sarcoidosis (6%), and rheumatoid arthritis (4%) were the most common systemic inflammatory conditions encountered.

Risk of Corticosteroid-Induced Hyperglycemia

Of the 2,073 patients who took systemic corticosteroids, 25 (1.21%) initiated hypoglycemic medications within 12 months after starting the corticosteroids, versus 5 (0.19%) of the 2,666 patients who did not take systemic corticosteroids (relative risk (RR) = 4.39, 95% CI = 1.68 – 11.5, $p=0.003$; Table 1). The incidence rate for hyperglycemia among patients from the time of initiating systemic corticosteroids was 22.6 per 1,000 person-years compared with 5.2 per 1,000 person-years in patients not using systemic corticosteroids (ratio of incidence rates = 4.37, 95% CI = 1.87 – 11.3, $p=0.0001$). The cumulative incidence was 1.93% (95% CI: 1.24%-2.99%) in the year following initiation of oral corticosteroid treatment, and 0.65% (95% CI: 0.24%-1.74%) within one year absent oral corticosteroid treatment. Compared to patients not taking systemic corticosteroids, the relative risk for initiating hypoglycemic medications was 3.23, 95% CI = 1.08–9.64, $p=0.04$ among patients initially taking less than 40 mg/day of oral prednisone and 5.51, 95% CI = 2.01–15.1, $p=0.001$ among patients initially taking greater than or equal to 40 mg/day of oral prednisone (see Figure 1).

The 25 patients starting hypoglycemic medications in association with corticosteroid use were followed over a total of 28.96 person-years thereafter. Of these, 15 were observed to subsequently discontinue these medications; the Kaplan-Meier estimate of the proportion stopping within one year after having started hypoglycemic medications was 62.7% (95% CI: 42.0%-83.2%). Among 13 of these with subsequent follow-up, cessation of hypoglycemic medications in 11 was associated with tapering of corticosteroids (a similar proportion of those who did not stop hypoglycemic medications tapered corticosteroids as well). Among the five patients starting hypoglycemic medications absent use of oral corticosteroids, none were observed to stop hypoglycemic medications, although 4/5 had less than one year's follow-up.

Risk Factors for Incident Hyperglycemia

Crude associations between potential risk factors (age, gender, race, ocular inflammatory diagnosis, and presence of systemic inflammatory disease) for the development of hyperglycemia are given in Table 1, and multivariate adjusted results are given in Table 2. In addition to use of oral corticosteroids, factors associated with increased risk of hyperglycemia were increasing age (adjusted RR = 1.46 per each ten years of increasing age, 95% CI = 1.15 – 1.85; see Figure 2) and African-American race (adjusted RR = 2.94 with respect to other races, 95% CI = 1.34 – 6.43; see Figure 3). Compared with uveitis, scleritis (RR = 2.91, 95% CI = 1.25 – 6.80, $p=0.014$) and other inflammatory eye diseases (RR = 4.90, 95% CI = 1.43 – 16.8, $p=0.012$) were significantly associated with incident

hyperglycemia in univariate analyses; however, these associations were abrogated by adjusting for use of corticosteroids, age, and African-American race. Female sex (RR = 0.87, 95% CI = 0.41 – 1.83, $p = 0.71$) and diagnosis with a systemic inflammatory disease (RR = 0.64, 95% CI = 0.31 – 1.32, $p = 0.23$) were not significant risk factors for the development of corticosteroid-induced hyperglycemia.

DISCUSSION

The results of this multicenter, retrospective cohort study indicate that the risk of hyperglycemia requiring treatment with hypoglycemic medications is approximately 4.4-fold higher following initiation of systemic corticosteroids in patients being treated for inflammatory eye diseases, with higher doses being associated with higher risk. Even so, the absolute risk is low (an attributable risk of 1.18% within one year of treatment). The risk of hyperglycemia also increased monotonically with age and was nearly 3-fold higher amongst African-Americans than among other races (mostly Caucasians). The majority of patients requiring hypoglycemic medications subsequently stopped them within one year, usually in association with tapering of corticosteroids.

The incidence of corticosteroid-induced hyperglycemia in our study is much lower than reported in previous small clinical series of patients with systemic diseases. Uzu 2008 reported that 41% of 42 patients with primary renal disease being treated with corticosteroids subsequently developed diabetes. Patients in this study were treated with both oral and occasionally very high dose intravenous corticosteroids. Age and body mass index were the only other identifiable significant risk factors. Information regarding body mass index was not available in our database. Similarly Iwamoto 2004 reported that 52% of 25 patients with various neurologic diseases being treated with oral and intravenous corticosteroids developed corticosteroid-induced diabetes. Age and serum cholesterol level after corticosteroid therapy were the only significant risk factors for hyperglycemia in this study. Dose and duration of corticosteroid therapy were not found to be significant risk factors. Panthakalam 2004 reported that 8.8% of 102 patients with rheumatoid arthritis developed corticosteroid-induced diabetes and that 6 of 6 patients with pre-existing diabetes experienced worsening of their disease. Our study did not evaluate the risk of worsening diabetes amongst those already known to be diabetic.

Although the risk of developing diabetes appears much lower in our study, the results of these studies cannot be directly compared to ours, because they diagnosed diabetes based on blood glucose levels, whereas our study only examined the initiation of hypoglycemic medication. It is likely that several patients in our study developed hyperglycemia that would have met the criteria used for diabetes diagnosis used in the other studies had they been screened repeatedly for hyperglycemia in the hospitalized setting, but which never came to clinical attention in the outpatient setting, or else was not judged to require hypoglycemic medication because of an expectation of improvement with tapering of systemic corticosteroids. Moreover, corticosteroid treatment for patients with ocular inflammatory diseases may be less intensive than the approach used for other illnesses, which may have reduced the risk of corticosteroid-induced diabetes. Because ocular inflammation is not life-threatening, and often can be addressed with topical and periocular corticosteroids in addition to systemic corticosteroid-sparing therapies, clinicians would have had greater freedom to taper corticosteroids and may have been able to avert corticosteroid-induced hyperglycemia requiring hypoglycemic medications for many cases. Additionally, the study centers were chosen for the study based on their frequent use of corticosteroid-sparing immunosuppressive therapy for ocular inflammatory diseases, and frequent recourse to such therapy (in approximately 25% of patients) also may have reduced the risk of corticosteroid-induced diabetes^{12,13}.

Using a retrospective, case-control approach to this question, Gurwitz et al examined a random sample of 11,855 patients enrolled in the New Jersey Medicaid Program aged 35 years or older over a 10 year period who had recently initiated a hypoglycemic medication (event)¹¹. The odds ratio for development of hyperglycemia requiring treatment was 2.23 (95% CI = 1.92 – 2.59) compared to those not taking corticosteroids, a value more similar to that obtained in our study, though somewhat lower. Risk increased with average daily corticosteroid dose, African-American race, and nursing home residence, but (in contrast to our results) age was not found to be a significant risk factor. Indications for corticosteroid therapy were unavailable in the study. Our study instead looked at patients with a unifying diagnoses and examined them over time to see which patients with the exposure (corticosteroid use) subsequently developed the event (initiation of hyperglycemic mediation). The data obtained from our study are based upon office visits, in which all relevant changes to the medical history are available, whereas the Gurwitz study may have missed patients who were on hypoglycemic medications or corticosteroids, but did not receive them from Medicaid.

There are several limitations to this study. Our absolute risk results should be interpreted as reflecting the risk of hyperglycemia of a degree sufficient to come to clinical attention and require therapy; temporary elevations in blood glucose that did not cause clinical symptoms would be missed with this approach. Relative risk estimates associated with risk factors would be less affected by this limitation than absolute risk estimates. Also, as a retrospective study, patients were considered to have had an event only if hypoglycemic therapy was initiated between the initial visit for ocular inflammation and sustained until a follow-up visit. Furthermore, it is possible that some patients already had diabetes and/or were already on hypoglycemic therapy at the initial visit, but that this information was missing from the medical record. Such errors would tend to inflate estimates of the absolute risk of hyperglycemia, and to blunt risk factor associations (since the errors would affect both groups), leading to underestimates of risk ratios, rather than creating spurious associations. However, because the practices involved are run in a manner resembling rheumatology practices, such omissions likely would be infrequent, as also is suggested by the low absolute risk observed. Conversely, because patients not requiring oral corticosteroids may have been followed less frequently, episodes of hypoglycemic therapy may have been missed more frequently in the untreated group, which would tend to inflate the relative risk of hyperglycemia following corticosteroid therapy. The data available did not provide the opportunity to adjust for some reported risk factors, such as body mass index, cholesterol level, or family history of diabetes. If these factors were distributed unevenly between groups, unrecognized confounding could have affected the associations observed. However, given the likelihood that risk factors for corticosteroid-induced diabetes would have tended to deter use of systemic corticosteroids, unmeasured confounding would have been more likely to reduce the relative risk of hyperglycemia with corticosteroid therapy rather than produce spurious associations. It is reassuring that the other risk factors implicated in this analysis generally were consistent with those seen in prior reports^{8–11}. Most patients receiving treatment were free of systemic morbidity and were relatively young, so the relatively favorable results observed may reflect a lesser risk of corticosteroid-induced hyperglycemia in such patients than in patients with systemic diseases studied in other reports. The participating centers also pioneered corticosteroid-sparing approaches to the management of ocular inflammatory diseases, so the results reflect an approach which minimizes the dose and duration of systemic corticosteroids.

In summary, patients with inflammatory eye diseases managed at tertiary uveitis centers experienced in the use of corticosteroid and corticosteroid-sparing therapy had a low absolute risk of developing hyperglycemia requiring treatment following oral corticosteroid treatment (attributable risk of ~1% within 12 months). However, the *relative* risk for

hyperglycemia that required treatment was 4.4 times greater with systemic corticosteroid therapy, and higher initial doses tended to be associated with higher risk, confirming that there is a heightened risk of hyperglycemia with this approach. The risk of hyperglycemia was increased further with increasing age and African-American race. Ophthalmologists managing ocular inflammation patients with systemic corticosteroids should be aware that corticosteroid therapy increases the risk for clinically important hyperglycemia—especially among patients whose older age and African-American descent put them at higher risk. Clinicians managing systemic corticosteroid therapy in such patients should include monitoring for hyperglycemia (via questioning patients for hyperglycemic symptoms and laboratory testing when indicated) and/or seek medical consultation when appropriate. However, given the low absolute risk, routine laboratory monitoring or medical consultation for low risk patients may not be necessary.

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Figure 1.
Kaplan-Meier plot showing cumulative incidence of hyperglycemia requiring treatment by oral corticosteroid use.

Figure 2. Kaplan-Meier plot showing cumulative incidence of hyperglycemia requiring treatment when separated by age.

Figure 3.
Kaplan-Meier plot showing cumulative incidence of hyperglycemia requiring treatment when separated by race.

Table 1

Patient characteristics as potential risk factors for incident hyperglycemia (use of hypoglycemic medications) among patients with ocular inflammatory diseases *

Variable	n	Incident Hyperglycemia (%)	Relative Risk (95% CI)	P value
Age (continuous, 10 years increase)	4,739	30 (0.60)	1.39 (1.12–1.71)	0.002
Gender				0.71
Male	1,700	11 (0.60)	1.00	0.71
Female	3,039	19 (0.60)	0.87 (0.41 – 1.83)	0.27
Race				
White	3,491	20 (0.60)	1.00	0.024
African- American	664	10 (1.50)	2.40 (1.12 – 5.13)	NA
Hispanic	198	0 (0.0)	NA	NA
Other	224	0 (0.0)	NA	NA
Unknown	162	0 (0.0)	NA	0.037
Ocular Inflammatory Diagnosis				
Uveitis	3,632	16 (0.40)	1.00	
Scleritis	693	8 (1.20)	2.91 (1.25 – 6.80)	0.014
MMP	284	3 (1.10)	1.92 (0.56 – 6.58)	0.31
Other	130	3 (2.30)	4.90 (1.43 – 16.8)	0.012
Any Associated Systemic Inflammatory Diseases				
No	3,472	18 (0.50)	1.00	0.23
Yes	1,267	12 (0.90)	0.64 (0.31 – 1.32)	0.004
Oral Corticosteroid Use				
No	2,666	5 (0.19)	1.00	
Initial prednisone dose <40 mg/day	1,012	9 (0.89)	3.23 (1.08 – 9.64)	0.04
Initial prednisone dose ≥ 40 mg/day	1,061	16 (1.51)	5.51 (2.01–15.1)	0.001

* CI: confidence interval; NA: not available (because no hypoglycemia event was observed in this group, relative risk and the associated p-value could not be calculated); MMP: mucous membrane pemphigoid. Of the 4,739 patients, 460 were from Oregon Health & Sciences University, 2,226 were from Massachusetts Eye & Ear Infirmary, 508 were from the National Eye Institute, 1,325 from the Wilmer Eye Institute, and 220 from the Scheie Eye Institute.

Table 2

Adjusted relative risk for hyperglycemia within 12 months among patients with ocular inflammatory diseases

Variable	Adjusted relative risk (95% Confidence Interval)	P value
Age , (per 10 years'-increase)	1.46 (1.15 – 1.85)	0.002
Race		
Non-African-American	1.00	
African-American	2.94 (1.34 – 6.43)	0.007
Inflammatory Diagnosis		0.18
Uveitis	1.00	
Scleritis	2.11 (0.88 – 5.05)	0.09
Mucous Membrane Pemphigoid	1.18 (0.31 – 4.52)	0.81
Other	3.11 (0.88 – 10.9)	0.08
Oral Corticosteroid Use		0.004
None	1.00	
Initial prednisone dose <40 mg/day	3.21 (1.06 – 9.77)	0.04
Initial prednisone dose ≥ 40 mg/day	5.54 (2.00 – 15.3)	0.001