Journal of Diabetes

Journal of Diabetes **10** (2018), 546–555

ORIGINAL ARTICLE

Longitudinal study of short-term corticosteroid use by working-age adults with diabetes mellitus: Risks and mitigating factors

Highlights
- Adults with diabetes mellitus have a greater risk of fracture, venous thromboembolism, and sepsis than those without diabetes; the use of corticosteroids, even for short durations, increases this risk.
- Vitamin D mitigated the risk of fracture in patients with diabetes who used corticosteroids, and statins decreased the likelihood of hospitalization for sepsis in corticosteroid users with diabetes.
- Corticosteroids should be used with caution in patients with diabetes and mitigating factors should be considered.

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Received 22 August 2017; revised 24 October 2017; accepted 21 November 2017.

doi: 10.1111/1753-0407.12631

Abstract

Background: This study assessed the frequency of short-term oral corticosteroid use in adults with diabetes, examined the incidence of fractures, venous thromboembolism (VTE), and hospitalization for sepsis after corticosteroid use, and evaluated whether preventative medications mitigated adverse events.
Methods: A longitudinal study (2012–14) was conducted of 1 548 945 adults (aged 18–64 years) who received healthcare coverage through a large national health insurer. Incidence rate ratios (IRR) were calculated using conditional Poisson regression.
Results: Short-term oral corticosteroids were used by 23.9%, 20.8%, and 20.9% of adults with type 2 diabetes, type 1 diabetes, and no diabetes, respectively, during the 3-year period ($P < 0.001$). Baseline risks of fracture, VTE, and sepsis were greater for individuals with than without diabetes ($P < 0.001$). The combined effect of having diabetes and using corticosteroids was greater than the sum of the individual effects (synergy indices of 1.17, 1.23, 1.30 for fracture, VTE, and sepsis, respectively). The IRR for VTE in the 5–30 days after corticosteroid use was 3.62 (95% confidence interval [CI] 2.41–5.45). Fractures increased in the 5–30 days after corticosteroid use (IRR 2.06; 95% CI 1.52, 2.80), but concomitant use of ergocalciferol mitigated this risk (IRR 1.13; 95% CI 0.12, 11.07). The risk of hospitalization for sepsis was elevated with corticosteroid use (IRR 3.79; 95% CI 2.05, 7.01), but was mitigated by the concomitant use of statins.
Conclusions: Short-term oral corticosteroid use is common in adults with diabetes and is associated with an elevated, but low, risk of adverse events. The findings suggest that preventative medications may mitigate risk.

Keywords: corticosteroids, diabetes mellitus, drug-related side effects and adverse reactions, statins, vitamin D.

Introduction

Oral corticosteroids decrease insulin secretion, promote gluconeogenesis and glycogenolysis, and diminish hepatic and skeletal muscle insulin sensitivity;[1] therefore, their use in patients with diabetes mellitus requires close surveillance. Guidelines for diabetes management include recommendations for careful monitoring of blood glucose when beginning the use of oral corticosteroids and for caution when insulin dosing corrections are made to compensate for the anticipated hyperglycemia.[2–4] This is notable because corticosteroid use is common;[5–7] for example, approximately one-fifth of the US working-age population uses short-term corticosteroids.[8]

Aside from hyperglycemia, the pleiotropic side effects of long-term oral corticosteroid use are well recognized.[9] The use of oral corticosteroids for short periods has been generally considered safe, but recently has been implicated in the risk of adverse events (AEs), albeit at rather low frequencies.[8] Because AEs may occur infrequently, it is not always possible to evaluate such risks within the context of a randomized controlled trial due to low statistical power. Trials also impose a challenge for the evaluation of patient safety due to the dissimilarity of trial participants to the wider population of patients who may be taking the medications. Moreover, many trials do not assess all risks; for example, investigators found that venous thromboembolism (VTE) was not reported in 89% of randomized controlled trials.[10] Therefore, the evaluation of patient safety is often undertaken during the post-trial period using data from a larger population of users.

We were particularly interested in the safety of medications in the young and middle-aged adult populations with diabetes because of the lack of studies in adults of working age. We obtained data from a large, national sample of American adults who received private healthcare coverage. The purpose of the present study was twofold: (i) to assess the frequency of short-term oral corticosteroid use in adults with diabetes; and (ii) to examine the incidence of fractures, VTE, and hospitalization for sepsis by corticosteroid use. In addition, we assessed whether there were potential mitigating factors that may affect this risk.

Methods

A longitudinal study was conducted using de-identified data collected from 1 January 2012 through 31 December 2014 from adults (18–64 years of age) who received healthcare coverage through a large national health insurer (obtained through OptumInsight, Eden Prairie, MN, USA). The study was reviewed by the University of Michigan Institutional Review Board for oversight regarding human subjects, designated as exempt from further review, and given a waiver for informed consent. There were 1 548 945 adults in the database, and the study methods have been described in detail elsewhere.[8] Briefly, adults with 3 years of continuous enrollment with the national health insurer were included to assess corticosteroid use and the incidence of fracture, VTE, and hospitalization for sepsis. Because we were studying incident events, those individuals who experienced fractures, VTE or sepsis in 2011 were excluded from the study. Over the 3-year period of the study (2012–14), the first occurrence for each outcome was extracted so as to not capture follow-up visits for the same event.

Oral corticosteroid use of short duration (<30 days) was extracted from pharmacy files, indicating the type of prescription(s) and the date(s) when filled. Patients who were prescribed oral corticosteroids for ≥30 days cumulatively over the study period were excluded, as were those who received any oral corticosteroids during the year prior to the start of the study (in 2011). The oral corticosteroids identified were betamethasone, dexamethasone, methylprednisolone, triamcinolone, prednisone, prednisolone, hydrocortisone, and cortisone. We focused on oral corticosteroids that were swallowed (e.g. tablets, capsules, elixirs) and excluded all other forms of corticosteroids, including aerosols, creams, drops, suspended drops, lotion, spray, and vials.

Patients with type 1 diabetes mellitus (T1DM) were defined as individuals who had at least two International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; https://www.cdc.gov/nchs/icd/icd9cm.htm, accessed 12 May 2017) codes indicating T1DM on different dates, with the use of insulin (Table 1). Patients with type 2 diabetes mellitus (T2DM) were identified as individuals with records of at least two ICD-9-CM codes indicating T2DM on different dates, regardless of type of antidiabetic medication used (Table 1). Outcomes (fracture, VTE, sepsis) were also ascertained through ICD-9-CM codes. For sepsis, hospital admissions were used in which the principal diagnosis was sepsis. Fractures of the torso and limbs were included from injury codes (Table 1).

There were no missing values for age or gender. There were complete data regarding diagnoses and medication prescriptions that were filled by the participants within this health insurance plan during the time period of the study.

Statistical analysis

There were several phases to the statistical analyses. In the first phase, we examined the frequency (%) of

Table 1 Identification of conditions in the study

Condition	Codes
Diabetes	Minimum of two diagnoses of ICD-9-CM codes on different dates: 250xx
Type 1 diabetes	Minimum of two diagnoses of ICD-9-CM codes on different dates: 250x1 or 250x3, with the use of insulin
Type 2 diabetes	Minimum of two diagnoses of ICD-9-CM codes on different dates: 250x0 or 250x2 with x = 0–9, regardless of antidiabetic medications used
Fractures	ICD-9-CM codes: 7331x or 805xx–829xx
Venous thromboembolism	ICD-9-CM codes: 4151x, 4511x, 4512x, 25181, 25183, 45184, 45189, 4519x, 4532x, 4534x, 45380, 45382–45389 or 4539x
Hospitalization for sepsis	ICD-9-CM codes: 78552, 99591 or 99592, as principal diagnosis

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification (https://www.cdc.gov/nchs/icd/icd9cm.htm, accessed 12 May 2017).

corticosteroid use (with 95% exact confidence intervals [CI]), stratified by type of diabetes, gender, and age category. To assess differences in the frequency of use by subgroup, Pearson's Chi-squared tests were used.

In the second phase of the analyses, we assessed the frequency of AEs (fractures, VTE, and hospitalization for sepsis). Both cumulative incidence (%) and rates (events/1000 person-years) were calculated with 95% CIs, stratified by type of diabetes. Incidence rate ratios (IRR) were also calculated, comparing the event rate in corticosteroid users with that in non-steroid users, with stratification by type of diabetes. The interaction between steroid use and diabetes on AEs was determined by using the synergy index on an additive scale.[11] A synergy index >1.0 indicates a positive interaction; that is, the combined effect of having diabetes and using corticosteroids would be greater than the sum of the individual effects of these two factors. In addition, we examined the association between corticosteroid use and AEs when stratified by the type of antidiabetic medication used (i.e. ever used during the study period); odds ratios (ORs) were generated from a logit model with adjustment for age, gender, and race. Heterogeneity by type of antidiabetic medication was evaluated using Cochran's Q test and the I^2 statistic, which measures the percentage of variation in the ORs (across the various antidiabetic medications) that is due to heterogeneity rather than random error.

In the third phase of the analyses, the association between corticosteroid use and AEs was evaluated. Using a self-controlled case series design, the incidence of AEs after corticosteroid use was calculated and compared with the incidence of AEs during the time period when the corticosteroid was not used. That is, the incidence of events was compared in different time windows within the same person. We assessed risk of AEs in the 5–30, 31–90, and 91–180 days after the corticosteroid prescription was filled. The reference (comparator) period was 5–180 days prior to when the corticosteroid prescription was filled. Conditional (fixed) Poisson regression was used for the analyses, offset by the natural logarithm of the time under observation. Incidence rate ratios were generated with 95% CI comparing the risk of AEs when using versus not using corticosteroids. Because this was a within-person comparison, gender, race, genetic profile, history of past medical conditions, and past health-related behaviors remained the same. Other non-steroidal medications that were significantly associated with the outcomes were included as time-varying covariates.

In a secondary analysis of patients with diabetes, the self-controlled case series design was extended to examine whether the use of preventative medications at the same time as the corticosteroids affected the results. Specifically, concomitant use (prescription filled 0–30 days prior to the corticosteroid prescription) of vitamin D and statin was determined. Use of corticosteroids with vitamin D was of interest for the assessment of fractures. Use of corticosteroids with statin was of interest for VTE and sepsis. Statistical methods were similar to those described above (i.e. fixed Poisson regression with an offset). In addition, we used a cohort design to further investigate the association between concomitant medications and AEs (comparing users with non-users) in which logistic regression was used. Alpha was set at 0.05, two-tailed. All analyses were conducted in Stata/MP 14.2 (StataCorp, College Station, TX, USA).

Results

In the present study, 8.1% (126 091/1 548 945) of adults had diabetes mellitus. Of those with diabetes, 87.4% (110 141/126 091) had T2DM and 12.6% (15 950/126 091) had T1DM. The mean (± SD) age of those with T2DM, with T1DM, and those without diabetes was 53.3 ± 8.2), 49.5 ± 11.4, and 43.6 ± 12.1 years, respectively. Men were more likely to have diabetes

than women (60% males with T1DM, 59% males with T2DM, 54% males without diabetes; $P < 0.001$).

Within this database, 21.1% (327 452/1 548 945) used corticosteroids for <30 days. Individuals with T2DM were more likely to use corticosteroids than those with T1DM and those without diabetes ($P < 0.001$ for both). The frequency of corticosteroid use is given in Table 2, by diabetes type, gender, and age categories. Women with T2DM were frequent users of short-duration corticosteroids (28.4% during the 3-year study period). Across both gender and age categories, individuals with T2DM were more frequent users of corticosteroids than either those with T1DM or those without diabetes. The mean (± SD) duration of corticosteroid therapy in patients with diabetes was 6.7 ± 3.0 days, whereas the median (interquartile range) duration was 6 days (5–7 days).

Rates of fracture, VTE, and hospitalization for sepsis are given in Table 3. Adults with T1DM had greater rates of AEs than those with T2DM and those without diabetes ($P < 0.001$ for both). In adults with T1DM who used corticosteroids, 12.5% experienced a fracture, 4.6% experienced VTE, and 4.4% were hospitalized for sepsis during the study period. This compares with 7.2%, 2.6%, and 1.4%, respectively, for adults with T2DM. The IRRs indicate that the risks of AEs were significantly elevated in patients with diabetes (both T1DM and T2DM) and in corticosteroid users (vs non-users without diabetes), although the strength of the association was greater in those with T1DM (Table 3). For example, the risk of VTE was sevenfold greater in patients with T1DM who used corticosteroids than in non-users without diabetes. All outcomes exhibited positive interactions (synergy indices of 1.17, 1.23, and 1.30 for fracture, VTE, and sepsis, respectively). Therefore, the combined effect of having diabetes and using corticosteroids was greater than the sum of the individual effects.

When stratified by the type of antidiabetic medication used, the association between corticosteroid use and AEs remained (Fig. 1). The results indicate that there was no significant heterogeneity in the ORs, regardless of the outcome ($P = 0.360$ for fracture, $P = 0.962$ for VTE, $P = 0.465$ for sepsis). The I^2 (measure of inconsistency) for fracture, VTE, and sepsis was 9.0%, 0%, and 0%, respectively. Therefore, the odds for developing the three AEs were significantly elevated for corticosteroid users (vs non-users), regardless of the type of antidiabetic medication used during the period of the study.

The results from the self-controlled case series are listed in Table 4. The risk of AEs was greatest during the 5- to 30-day period after the corticosteroid prescription was filled for those with diabetes (IRR 2.06 for fracture, IRR 3.62 for VTE, and IRR 3.79 for sepsis). For all three outcomes, the IRRs tended to decrease over time. The results for those without diabetes are given in Table 5, indicating that the relative risk of AEs was similar for those with and without diabetes, although the underlying baseline risk (cumulative incidence) was was greater in those with diabetes (Table 3).

We also evaluated the addition of potential preventative medications on the relationship between corticosteroids

Table 2 Short-duration oral corticosteroid use by type of diabetes, age, and gender

	Steroid use	No steroid use	*P*-value
Overall			
Type 1 diabetes	3316/15 950 (20.8)	12 634/15 950 (79.2)	
Type 2 diabetes	26 300/110 141 (23.9)	83 841/110 141 (76.1)	
No diabetes	297 836/1 422 854 (20.9)	1 125 018/1 422 854 (79.1)	<0.001
Women			
Type 1 diabetes	1553/6449 (24.1)	4896/6449 (75.9)	
Type 2 diabetes	12 699/44 676 (28.4)	31 977/44 676 (71.6)	
No diabetes	153 780/653 890 (23.5)	500 110/653 890 (76.5)	<0.001
Men			
Type 1 diabetes	1763/9501 (18.6)	7738/9501 (81.4)	
Type 2 diabetes	13 601/65 465 (20.8)	51 864/65 465 (79.2)	
No diabetes	144 056/768 964 (18.7)	62 4908/76 8964 (81.3)	<0.001
Age < 40 years			
Type 1 diabetes	476/3106 (15.3)	2630/3106 (84.7)	
Type 2 diabetes	1735/7410 (23.4)	5675/7410 (76.6)	
No diabetes	97 028/521 916 (18.6)	424 888/521 916 (81.4)	<0.001
Age ≥ 40 years			
Type 1 diabetes	2840/12 844 (22.1)	10 004/12 844 (77.9)	
Type 2 diabetes	24 565/102 731 (23.9)	78 166/10 2731 (76.1)	
No diabetes	200 808/900 938 (22.3)	700 130/900 938 (77.7)	<0.001

Unless indicated otherwise, data show the *n*/*N* (row percentages), where n is the number of patients who used or did not use steroids and N is the number of patients in the category (type 1 diabetes, type 2 diabetes, or no diabetes).

Table 3 Frequency of adverse events by corticosteroid use and type of diabetes

	No. events	No. patients	Cumulative incidence (%)	Incidence rate* (95% CI)	IRR (95% CI)	Synergy index† (95% CI)
Fracture						
No steroids, no diabetes	45 969	1 125 018	4.1	13.9 (13.8, 14.0)	1.00 (reference)	
No steroids, T1DM	1161	12 634	9.2	32.2 (30.4, 34.1)	2.31 (2.18, 2.45)	
No steroids, T2DM	4223	83 841	5.0	17.2 (16.7, 17.8)	1.24 (1.20, 1.28)	
Steroids, no diabetes	17 784	297 836	6.0	20.7 (20.3, 21.1)	1.49 (1.46, 1.52)	
Steroids, T1DM	414	3316	12.5	43.3 (37.7, 49.6)	3.11 (2.70, 3.57)	
Steroids, T2DM	1892	26 300	7.2	26.3 (24.7, 27.9)	1.89 (1.78, 2.01)	1.17 (1.12, 1.23)
Venous thromboembolism						
No steroids, no diabetes	7136	1 125 018	0.6	2.1 (2.1, 2.2)	1.00 (reference)	
No steroids, T1DM	341	12 634	2.7	9.1 (8.2, 10.1)	4.30 (3.85, 4.79)	
No steroids, T2DM	1418	83 841	1.7	5.7 (5.4, 6.0)	2.68 (2.53, 2.84)	
Steroids, no diabetes	3513	297 836	1.2	4.1 (3.9, 4.3)	1.93 (1.84, 2.03)	
Steroids, T1DM	151	3316	4.6	14.8 (11.8, 18.6)	6.98 (5.48, 8.76)	
Steroids, T2DM	679	26 300	2.6	8.8 (7.9, 9.8)	4.15 (3.73, 4.61)	1.23 (1.16, 1.29)
Hospitalization for sepsis						
No steroids, no diabetes	2271	1 125 018	0.2	0.7 (0.6, 0.7)	1.00 (reference)	
No steroids, T1DM	441	12 634	3.5	11.8 (10.8, 13.0)	17.58 (15.84, 19.47)	
No steroids, T2DM	870	83 841	1.0	3.5 (3.2, 3.7)	5.16 (4.77, 5.58)	
Steroids, no diabetes	1040	297 836	0.3	1.3 (1.2, 1.4)	1.98 (1.81, 2.16)	
Steroids, T1DM	146	3316	4.4	16.7 (13.5, 20.7)	24.87 (19.79, 30.89)	
Steroids, T2DM	370	26 300	1.4	5.3 (4.7, 6.1)	7.94 (6.89, 9.11)	1.30 (1.23, 1.37)

*Per 1000 person-years at risk.
†Synergy between diabetes and steroid use on an additive scale.
CI, confidence interval; IRR, incidence rate ratio; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

and AEs in individuals with diabetes. In the present study, 11.4% (14 376/126 091) of individuals with diabetes used vitamin D, and 97.6% of the prescriptions were for 50 000 IU ergocalciferol weekly (mean [± SD] number of refills 5.7 ± 7.2). Results from the self-controlled case series (Table 4) indicate that adults with diabetes had a twofold increase in the incidence of fracture in the 5- to 30-day period after the corticosteroid prescription was filled. However, those patients with diabetes who were taking vitamin D with the corticosteroids did not experience an increased risk (IRR 1.13). Those taking corticosteroids without vitamin D had an elevated risk (IRR 2.09). We also examined the risk of fracture using the conventional cohort design, comparing individuals with diabetes who used with those who did not use the medications (Table 6). The risk of fracture was lowest (4.4%) in adults with diabetes who used vitamin D but no corticosteroids. The highest risk of fracture was 8.1% in adults with diabetes who used corticosteroids but no vitamin D. The odds of fracture were 1.37-fold greater in those using corticosteroids without vitamin D than in those who did not use either of these medications.

In this database, 61.4% (77 419/126 091) of individuals with diabetes ever used statins during the 3-year study period. The risk of VTE was elevated (IRR 3.62) during the 5- to 30-day period after the corticosteroid was taken (Table 4), but this risk declined over time. Results from the self-controlled case series indicated that the addition of statins did not appreciably affect the rate ratios for VTE; the risk remained elevated regardless of statin use. For sepsis, however, the use of corticosteroids without statin yielded a significant IRR of 4.91 (Table 4). When patients with diabetes used statins concomitantly with the corticosteroids, there was no significant elevation in sepsis risk.

We also evaluated corticosteroids with statins using the conventional cohort approach (Table 6). The greatest risk of an AE occurred in adults with diabetes who used corticosteroids without statins (3.3% for VTE, 2.1% for sepsis). The odds of VTE were 51% greater in those using corticosteroids without statins compared with those using neither (Table 6). However, the odds of VTE were not elevated when the corticosteroids were used with statins (OR 1.04). In addition, the odds of hospitalization for sepsis were lower when statins were used concomitantly with corticosteroids (OR 0.77) than when using neither; the (multiplicative) interaction term between corticosteroids and statins was significant ($P = 0.013$). The use of statins modified the association between corticosteroids and hospitalization for sepsis.

Discussion

In the present study, adults with diabetes were found to be frequent users of short-term oral corticosteroids. Use

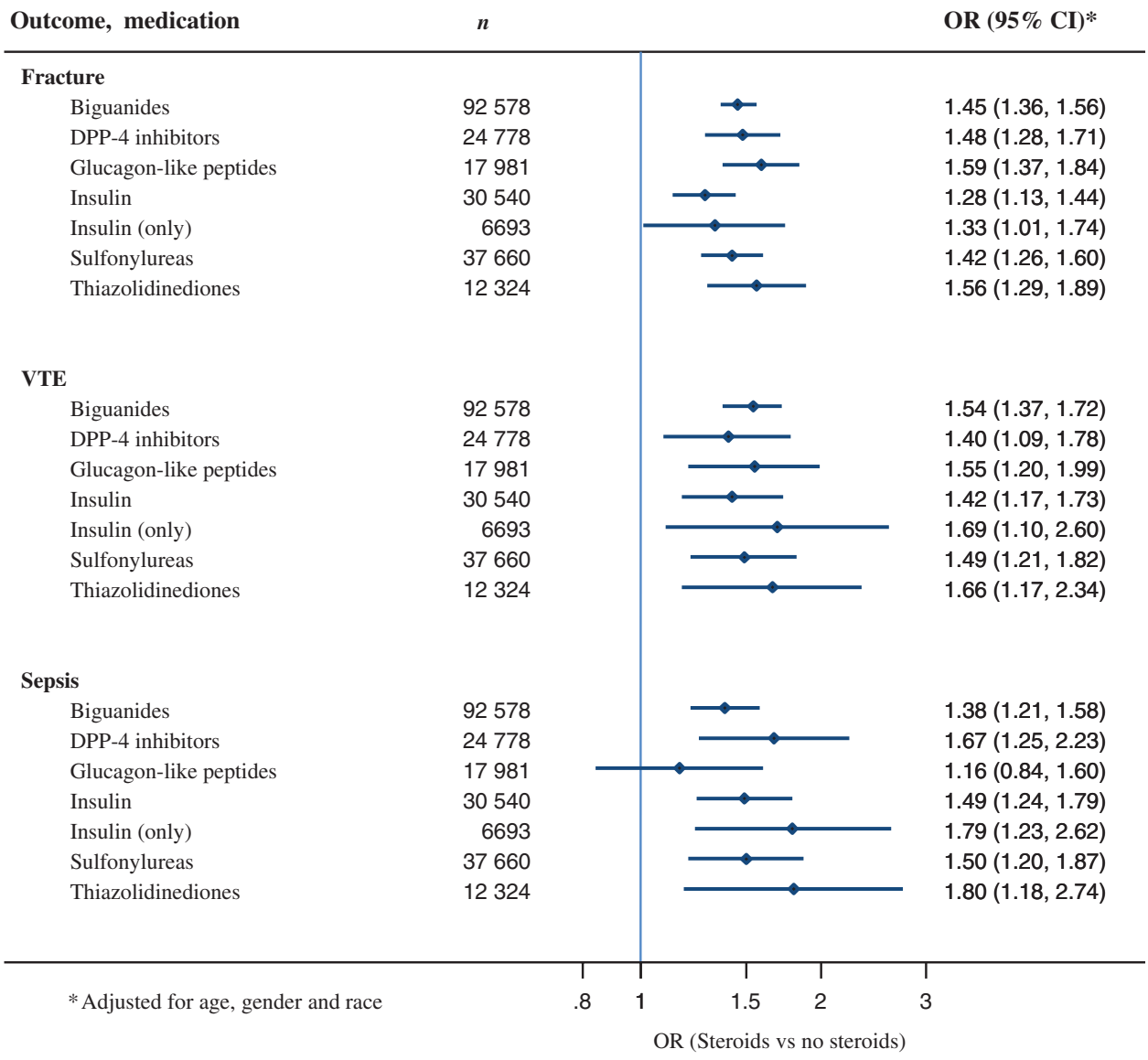

Figure 1 Odds ratios (ORs) for the association between corticosteroid use and adverse events according to type of antidiabetic medication. CI, confidence interval; DPP-4, dipeptidyl peptidase 4.

was particularly common in T2DM, affecting one in four patients, whereas use occurred in one of five individuals with T1DM, and in one of five people without diabetes. Short-term use was higher in middle-aged adults compared with younger adults, and was frequent in women with T2DM, affecting 28.4% during the 3-year study period.

The higher rates of fracture, VTE, and hospitalization for sepsis in patients with diabetes confirm results from previous investigations.[12–14] However, the present study extends the current literature with the finding of synergy between diabetes and corticosteroid use. The risks of AEs were more elevated with these two factors together than for each one separately. This suggests that efforts to prevent adverse outcomes with oral corticosteroids may be better targeted to individuals with diabetes than those without. Patients with T1DM may particularly benefit because of their higher baseline risk. For individuals with T2DM, the elevation in risk of AEs after corticosteroid use remained, regardless of the type of antidiabetic medications used.

Although there was an elevated risk of AEs after corticosteroid use, the findings suggest that certain concomitant medications could possibly mitigate risk. When individuals with diabetes used both corticosteroids and ergocalciferol (50 000 IU weekly), there was

Table 4 Incidence rate ratios for adverse events associated with corticosteroids and concomitant medications in individuals with diabetes

	5–30 days*		31–90 days*		91–180 days*	
Event and medications	IRR† (95% CI)	*P*-value	IRR† (95% CI)	*P*-value	IRR† (95% CI)	*P*-value
Fracture						
Corticosteroids	2.06 (1.52, 2.80)	<0.001	1.66 (1.29, 2.13)	<0.001	1.46 (1.16, 1.84)	0.001
Corticosteroids and vitamin D	1.13 (0.12, 11.07)	0.915	0.37 (0.03, 4.44)	0.436	0.14 (0.01, 2.82)	0.197
Corticosteroids and no vitamin D	2.09 (1.53, 2.84)	<0.001	1.70 (1.32, 2.19)	<0.001	1.50 (1.19, 1.89)	0.001
Venous thromboembolism						
Corticosteroids	3.62 (2.41, 5.45)	<0.001	1.51 (1.00, 2.28)	0.049	0.90 (0.60, 1.36)	0.613
Corticosteroids and statin	3.86 (1.74, 8.59)	0.001	1.43 (0.58, 3.52)	0.440	1.41 (0.68, 2.94)	0.353
Corticosteroids and no statin	3.33 (2.05, 5.42)	<0.001	1.51 (0.95, 2.42)	0.083	0.73 (0.44, 1.21)	0.223
Sepsis						
Corticosteroids	3.79 (2.05, 7.01)	<0.001	2.64 (1.44, 4.85)	0.002	1.64 (0.89, 3.00)	0.110
Corticosteroids and statin	1.62 (0.45, 5.85)	0.458	1.91 (0.68, 5.39)	0.219	1.02 (0.33, 3.09)	0.978
Corticosteroids and no statin	4.91 (2.31, 10.46)	<0.001	2.73 (1.26, 5.94)	0.011	1.99 (0.92, 4.30)	0.078

*The reference period was 5–180 days prior to prescription date.
†Sepsis was adjusted for antibiotics, 5-hydroxytryptamine 5-HT_3 receptor antagonists, antidepressants, anti-inflammatory agents, antimuscarinics, opiate agonists, and phenothiazine. Venous thromboembolism was adjusted for antibiotics, androgens, anxiolytics, anti-inflammatory agents, azoles, calcium channel blockers, coumarin, diuretics, opiate agonists, and platelet aggregation inhibitors. Fractures were adjusted for anti-inflammatory agents, cyclo-oxygenase 2 inhibitors, and opiate agonists.
CI, confidence interval; IRR, incidence rate ratio.

no elevated risk of fracture, but when corticosteroids were used without ergocalciferol there was a twofold increased risk of fracture. Data from the National Health and Nutrition Examination Survey, a nationally representative sample, demonstrated an association between corticosteroid use and 25-hydroxyvitamin D (25(OH)D) deficiency.[15] In a meta-analysis of 25 studies, adults receiving corticosteroid therapy were found to have low serum 25(OH)D levels that were insufficient to prevent osteoporosis.[16]. The US Preventive Services Task Force reviewed the data and found inconclusive evidence regarding vitamin D supplementation on the risk of fractures in older adults, but there were no trials in high-risk populations of middle-aged adults.[17] The present study found several high-risk populations in adults aged 18–65 years; these include corticosteroid users and individuals with diabetes. The results, suggesting that the use of 50 000 IU ergocalciferol may mitigate the effects of corticosteroid use in middle-aged adults with diabetes, should be confirmed in randomized controlled trials. Ergocalciferol is associated with minimal risk and it is significant that 42% of Americans (in general) are vitamin D deficient, as are 82% of African Americans and 69% of Hispanics in the US.[18]

We also found that the use of statins affected the association between corticosteroids and hospitalization

Table 5 Incidence rate ratios for adverse events associated with short-term oral corticosteroid use by diabetes

	5–30 days*		31–90 days*		91–180 days*	
Adverse event and condition	IRR† (95% CI)	*P*-value	IRR† (95% CI)	*P*-value	IRR† (95% CI)	*P*-value
Fracture						
Diabetes	2.06 (1.52, 2.80)	<0.001	1.66 (1.29, 2.13)	<0.001	1.46 (1.16, 1.84)	0.001
No diabetes	1.85 (1.66, 2.05)	<0.001	1.37 (1.25, 1.51)	<0.001	1.27 (1.17, 1.39)	<0.001
Venous thromboembolism						
Diabetes	3.62 (2.41, 5.45)	<0.001	1.51 (1.00, 2.28)	0.049	0.90 (0.60, 1.36)	0.613
No diabetes	3.25 (2.66, 3.98)	<0.001	1.43 (1.15, 1.76)	0.001	1.21 (0.99, 1.47)	0.065
Sepsis						
Diabetes	3.79 (2.05, 7.01)	<0.001	2.64 (1.44, 4.85)	0.002	1.64 (0.89, 3.00)	0.110
No diabetes	6.10 (4.07, 9.15)	<0.001	2.88 (1.86, 4.47)	<0.001	1.92 (1.26, 2.93)	0.003

*The reference period was 5–180 days prior to prescription date.
†Sepsis was adjusted for antibiotics, 5-hydroxytryptamine 5-HT_3 receptor antagonists, antidepressants, anti-inflammatory agents, antimuscarinics, opiate agonists, and phenothiazine. Venous thromboembolism was adjusted for antibiotics, androgens, anxiolytics, anti-inflammatory agents, azoles, calcium channel blockers, coumarin, diuretics, opiate agonists, and platelet aggregation inhibitors. Fractures were adjusted for anti-inflammatory agents, cyclo-oxygenase 2 inhibitors, and opiate agonists.
CI, confidence interval; IRR, incidence rate ratio.

Table 6 Frequency of adverse events for individuals with diabetes by type of medication

	No. events	No. patients	% With AEs	OR* (95% CI)	*P*-value
Fracture					
No corticosteroids, no vitamin D	4928	86 103	5.7	1.0 (reference)	
No corticosteroids, vitamin D	456	10 372	4.4	0.75 (0.68, 0.83)	<0.001
Corticosteroids, no vitamin D	2068	25 612	8.1	1.37 (1.30, 1.45)	<0.001
Corticosteroids, vitamin D	238	4004	5.9	0.98 (0.86, 1.12)	0.798
Venous thromboembolism					
No corticosteroids, no statins	821	37 792	2.2	1.0 (reference)	
No corticosteroids, statins	938	58 683	1.6	0.66 (0.60, 0.72)	<0.001
Corticosteroids, no statins	356	10 880	3.3	1.51 (1.33, 1.71)	<0.001
Corticosteroids, statins	474	18 736	2.5	1.04 (0.92, 1.16)	0.533
Sepsis					
No corticosteroids, no statins	689	37 792	1.8	1.0 (reference)	
No corticosteroids, statins	622	58 683	1.1	0.52 (0.46, 0.58)	<0.001
Corticosteroids, no statins	224	10 880	2.1	1.14 (0.98, 1.33)	0.090
Corticosteroids, statins	292	18 736	1.6	0.77 (0.67, 0.88)	<0.001

*Odds ratio (OR) adjusted for age, gender, and race.
AEs, adverse events; CI, confidence interval.

for sepsis. Both the self-controlled case series (within-person approach) and the cohort study (between-person approach) suggested that statins modified this association. Previous studies have shown that statins decrease the rate of severe sepsis and intensive care admissions.[19–21] Moreover, rates of hospitalization for infection have been found to be significantly elevated in patients who use corticosteroids,[22] and extended corticosteroid use has long been associated with immunosuppression and higher infection rates.[1] Because statin use is recommended for many adults with diabetes (based on the estimated 10-year cardiovascular disease risk),[23,24] randomized trials may be necessary to more clearly delineate potential benefits of adding statins to short-term corticosteroids for those patients with diabetes who are not currently receiving statins.

There are limitations of the present study. Information was not available on levels of C-peptide and glutamic acid decarboxylase autoantibodies for all individuals with diabetes. The use of ICD-9-CM diagnosis codes and medication use to discern diabetes may have resulted in some misclassification. However, validation studies indicate that the use of 250xx diagnosis codes for diabetes (captured over a 1-year period) had a sensitivity of 97%, specificity of 97%, and positive predictive value of 98%.[25] In a study to distinguish diabetes type, the use of two or more T1DM codes yielded a sensitivity of 90%[26] and a positive predictive value of 91.3% for the identification of T1DM.[27] A prescription for insulin had a sensitivity of 95% for T1DM.[26]

Another limitation of the present study is that we could not rule out confounding by indication; that is, the illness that prompted the patient's visit to the physician could be a contributing factor of the AE. However, infection, thromboembolism, and decreases in bone density are all listed as possible AEs on Food and Drug Administration package inserts of corticosteroids, indicating prior evidence of association.[28,29] With the use of short-term oral corticosteroids, we found that the absolute risk of such AEs was modest; for example, of 1000 patients with T1DM who used corticosteroids, 43 experienced a fracture over a 1-year period. This compared with 32 patients experiencing a fracture who did not use corticosteroids.

The use of a self-controlled case series is a particularly strong design for addressing other confounding factors. The present findings cannot be explained by dissimilarities in genetic profiles for different individuals because the comparison was within the same person. Similarly, other personal characteristics, such as past history of VTE, history of cancer, former smoking habits, and past personal characteristics, were controlled. Because the comparator is the person him/herself, these factors (and the interactions among such factors) are held constant.

We conclude that the use of oral corticosteroids for short durations is common in patients with diabetes and is associated with an elevated (but modest) risk of fracture, VTE, and hospitalization for sepsis. The addition of ergocalciferol to prevent fractures and the addition of statins to prevent hospitalization for sepsis should be investigated in randomized trials, particularly in patients with diabetes who use corticosteroids.

Acknowledgements

The authors' are supported by grants from the National Institutes of Health (ULTR000433 to AMMR), the

United States Department of Veterans Affairs Health Services Research and Development Service (Career Development Grant Award [CDA 11-217] to AKW). Data acquisition, and statistical and administrative support were supported by the Institute for Healthcare Policy and Innovation at the University of Michigan. These funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Disclosure

The authors report no conflicts of interest.

References

1. Fardet L, Kassar A, Cabane J, Flahault A. Corticosteroid-induced adverse events in adults: Frequency, screening and prevention. *Drug Saf*. 2007; **30**: 861–81.
2. Moghissi ES, Korytkowski MT, DiNardo M et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care*. 2009; **32**: 1119–31.
3. National Institute for Health and Care Excellence (NICE). *Type 2 Diabetes in Adults: Management*. NICE Guideline no. 28. London : NICE; 2015.
4. Redmon B, Caccamo D, Flavin P et al. *Diagnosis and Management of Type 2 Diabetes Mellitus in Adults*, 16th edn. Institute for Clinical Systems Improvement, Bloomington, 2014.
5. Fardet L, Petersen I, Nazareth I. Description of oral glucocorticoid prescriptions in general population. *Rev Med Interne*. 2011; **32**: 594–9.
6. Sturkenboom MC, Verhamme KM, Nicolosi A et al. Drug use in children: Cohort study in three European countries. *BMJ*. 2008; **337**: a2245.
7. Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocorticoid usage in the United States: A general population perspective. *Arthritis Care Res*. 2013; **65**: 294–8.
8. Waljee AK, Rogers MA, Lin P et al. Short term use of oral corticosteroids and related harms among adults in the United States: Population based cohort study. *BMJ*. 2017; **357**: j1415.
9. Fardet L, Fève B. Systemic glucocorticoid therapy: A review of its metabolic and cardiovascular adverse events. *Drugs*. 2014; **74**: 1731–45.
10. Danka J, Stuijver F, Romualdi E et al. Under-reporting of venous and arterial thrombotic events in randomized clinical trials: A meta-analysis. Internal. *Emerg Med*. 2015; **10**: 219–46.
11. Knol MJ, VanderWeele TJ, Groenwold RH et al. Estimating measures of interaction on an additive scale for preventive exposures. *J Epidemiol*. 2011; **26**: 433–8.
12. Bertoni AG, Saydah S, Brancati FL. Diabetes and the risk of infection-related mortality in the US. *Diabetes Care*. 2001; **24**: 1044–9.
13. Nicodemus KK, Folsom AR. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. *Diabetes Care*. 2001; **24**: 1192–7.
14. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: The longitudinal investigation of thromboembolism etiology. *Arch Intern Med*. 2002; **162**: 1182–9.
15. Skversky AL, Kumar J, Abramowitz MK, Kaskel FJ, Melamed ML. Association of glucocorticoid use and low 25-hydroxyvitamin D levels: Results from the National Health and Nutrition Examination Survey (NHANES): 2001–2006. *J Clin Endocrinol Metab*. 2011; **96**: 3838–45.
16. Davidson ZE, Walker KZ, Truby H. Clinical review: Do glucocorticosteroids alter vitamin D status? A systematic review with meta-analyses of observational studies. *J Clin Endocrinol Metab*. 2012; **97**: 738–44.
17. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: An updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011; **155**: 827–38.
18. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res*. 2011; **31**: 48–54.
19. Almog Y, Shefer A, Novack V et al. Prior statin therapy is associated with a decreased rate of severe sepsis. *Circulation*. 2004; **110**: 880–5.
20. Hackam DG, Mamdani M, Li P, Redelmeier DA. Statins and sepsis in patients with cardiovascular disease: A population-based cohort analysis. *Lancet*. 2006; **367**: 413–8.
21. Martin CP, Talbert RL, Burgess DS, Peters JI. Effectiveness of statins in reducing the rate of severe sepsis: A retrospective evaluation. *Pharmacotherapy*. 2007; **27**: 20–6.
22. Smitten AL, Choi HK, Hochberg MC et al. The risk of hospitalized infection in patients with rheumatoid arthritis. *J Rheumatol*. 2008; **35**: 387–93.
23. Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; **129** (Suppl. 2): S1–45.
24. US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016; **316**: 1997–2007.
25. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Med Care*. 2005; **43**: 480–5.
26. Klompas M, Eggleston E, McVetta J, Lazarus R, Li L, Platt R. Automated detection and classification of type 1 versus type 2 diabetes using electronic health record data. *Diabetes Care*. 2013; **36**: 914–21.

27. Zhong VW, Pfaff ER, Beavers DP et al. Use of administrative and electronic health record data for development of automated algorithms for childhood diabetes case ascertainment and type classification: The SEARCH for Diabetes in Youth Study. *Pediatr Diabetes*. 2014; **15**: 573–84.
28. Curtis JR, Westfall AO, Allison J et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Care Res*. 2006; **55**: 420–6.
29. Ericson-Neilsen W, Kaye AD. Steroids: Pharmacology, complications, and practice delivery issues. *Ochsner J*. 2014; **14**: 203–7.