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Topical Corticosteroids and the Risk of Diabetes Mellitus

A Nested Case-Control Study in the Netherlands

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Abstract

Background: The relationship between topical corticosteroid use, potency, treatment duration, concomitant exposure to systemic corticosteroids, and risk of diabetes has been incompletely studied.

Objective: To investigate an association between intense, longstanding topical corticosteroid use and diabetes mellitus.

Methods: Data for this nested case-control study were obtained from the PHARMO Record Linkage System, including linked drug dispensing and hospital records of >2.5 million individuals in defined areas of the Netherlands. Users of topical corticosteroids during 1992–2004, without diabetes, with ≥2 topical corticosteroid dispensings and ≥4 years of follow-up were selected. Diabetes onset was defined as first occurrence (index date) of an antidiabetic drug dispensing or hospitalization for diabetes. Cases were matched 1 : 4 by age and sex to controls, with ≥2 topical corticosteroid dispensings and similar follow-up duration. Use of topical corticosteroids and systemic corticosteroids and/or inhaled corticosteroids as co-medication was classified as current, recent and past/never (≤2 years, 2–4 years and >4 years ago, respectively). Multivariate regression analyses were adjusted for co-medication and co-morbidity.

Results: Among 192 893 incident topical corticosteroid users, 2212 developed diabetes and could be matched to 8582 controls. Current topical corticosteroid use was associated with an (unadjusted) 1.24-fold increased risk of diabetes (unadjusted OR 1.24; 95% CI 1.11, 1.40). The odds ratio increased to 1.32 with >180 days of topical corticosteroid use (95% CI 1.14, 1.54) and to 1.44 with a cumulative topical corticosteroid load (combined potency and amount) of 731–1460 mg (95% CI 1.21, 1.72). Among past/never users of systemic corticosteroids and/or inhaled corticosteroids, current use of topical corticosteroids remained associated with a 1.27-fold increased diabetes risk (unadjusted OR 1.27; 95% CI 1.10, 1.47) compared with past users of topical corticosteroids.

Conclusion: An increased risk of new-onset diabetes may be an important consideration in the treatment of patients with topical corticosteroids, especially when intense skin treatment is needed. Future studies are needed to endorse these findings in other populations.

Background

Systemic effects of topical corticosteroids for skin diseases have been known for decades. Their use is associated with clinical signs of Cushing's syndrome and adrenal suppression.[1-4] Consequently, endogenous hypercortisolism and suppression of the hypothalamic-pituitary-adrenal (HPA) axis cannot be ignored as clinically relevant systemic effects of intense topical corticosteroid treatment.[3-6] It has also been suggested that HPA axis disturbances are associated with disturbances in endogenous insulin secretion,[7] insulin resistance[8] and overt diabetes mellitus.[9] Systemic effects are most prevalent for the fluorinated topical corticosteroid classes that are characterized by greatest potency and strongest systemic absorption. Systemic absorption of topical corticosteroids correlates with increasing duration and cumulative dose of treatment.[10] With a systemic absorption fraction of 4–19% over a period of 24 hours, topical hydrocortisone treatment was accompanied by a pharmacologically significant systemic dose.[10] Treatment with oral and inhaled corticosteroids, especially fluticasone propionate, has also been associated with HPA axis disturbances[11,12] and diabetes.[13-15] The biological mechanism underlying adverse systemic effects of topical corticosteroids may be similar to that with systemic exposure to oral and inhaled corticosteroids. Because the risk of systemic effects increases with high doses and prolonged use of systemic corticosteroids,[2] a dose-response relationship would support a possible association between topical corticosteroid use and diabetes.

Epidemiological evidence for a possible association between use of topical corticosteroids and diabetes is, however, scarce. Disturbances of glucose metabolism and diabetes with intense use of topical corticosteroids have been described in a limited number of case reports.[2,5,16,17] One epidemiological study from the UK Health Improvement Network failed to demonstrate an association of diabetes with topical corticosteroid use.[15] No other pharmacoepidemiological investigation thus far has formally addressed the relationship between topical corticosteroid use, potency, treatment duration, concomitant exposure to systemic corticosteroids, and risk of diabetes. At the same time, the prevalence of use of topical corticosteroids as well as the incidence of diabetes (mainly type 2) are enormous.[18] In order to contribute to the understanding of the epidemiology of diabetes, we investigated the hypothesis that treatment with topical corticosteroids is associated with an increased risk of new-onset diabetes in a dose-dependent manner.

Methods

Data Source

This study was conducted with data from the PHARMO Record Linkage System (PHARMO RLS), which includes several linked databases, among which are drug dispensing records and hospital records from more than three million individuals in defined areas in the Netherlands. The drug dispensing histories contain data on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens and the duration of use of the drug. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital records include detailed information concerning primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification

(ICD-9-CM).[19] For a detailed description of the PHARMO database, we refer to earlier work.[20]

Design

This was a nested case-control study within a retrospective cohort of users of topical corticosteroids.

Study Cohort

The study cohort included new users of topical corticosteroids (ATC code D07A, D07B, D07C and D07X) between 1 January 1992 and 31 December 2004 with a follow-up registration of at least 4 years and without diabetes in the 1-year period before the start of topical corticosteroid use, i.e. no use of antidiabetic drugs (ATC code A10, i.e. insulins and analogues, blood glucose lowering drugs and other drugs used in diabetes) or diabetes-related hospitalization (hospitalization for diabetes [ICD-9-CM code 250], diabetic retinopathy [ICD-9-CM code 362.0], diabetic cataract [ICD-9-CM code 366.4], diabetes during pregnancy [ICD-9-CM code 648] or insulin intoxication [ICD-9-CM code 962.3]). New users of topical corticosteroids were defined as those who had not been dispensed a topical corticosteroid during at least 1 year prior to their first dispensing for topical corticosteroids. Age was not part of the eligibility criteria. Cohort members were followed from the start of topical corticosteroid use until the earliest onset of diabetes (as defined in the following section), transferring out of the pharmacy or end of the study period (December 2004).

Cases and Controls

Any individual in the cohort of topical corticosteroid users was deemed a diabetes case if all of the following conditions were met. Firstly, they were prescribed antidiabetic drugs (as defined in the previous section) followed by a second prescription within 1 year. The date of the first antidiabetic drug dispensing was defined as the date of the diagnosis of diabetes and used in the study as the index date. Secondly, the index date was preceded by at least 4 years in the cohort. Thirdly, at least two topical corticosteroid dispensings before the index date were present. Each case was matched by age (± 2 years) and sex to four controls. Controls were selected from all cohort members who were present on the case's index date, did not have diabetes (as defined in the previous section) at any time during follow-up, had at least two topical corticosteroid dispensings before the case's index date and had at least the same duration of follow-up. Selected controls were assigned the same index date as the case they were matched to.

Topical Corticosteroid Exposure

Exposure to topical corticosteroids was considered with respect to various aspects of its intensity, namely recency, cumulative duration, average potency and cumulative load.

Recency

Current users of topical corticosteroids were defined as patients having at least one topical corticosteroid dispensing during the 2-year period before the index date. Recent users were defined as patients having a prescription in the 4-year period before, but not during the 2-year period before the index date, and past users as patients who had used topical corticosteroids only before the 4-year period before the index date.

Cumulative Duration

Many patients use topical corticosteroids on an intermittent or sporadic basis, based on the typical disease course of most dermatological conditions.[21] For topical applications, the bodily location and amount of drugs to be applied per day is not recorded. Assuming an average daily dose of 1 g,[22] the duration of use of a topical corticosteroid dispensing (in days) was calculated as the total dispensed amount (in grams) divided by this average daily dose (1 g/day). For each current or recent user of topical corticosteroids, the cumulative duration of use in the 4-year period before the index date was calculated as the sum of all topical corticosteroid use in this period. For past users of topical corticosteroids, the cumulative duration of use during the 4-year period prior to the index date was 0 days. The cumulative duration of topical

corticosteroid use was categorized into 0, 1–60, 61–180 and >180 days. In the calculation of cumulative duration we did not assume continuous use, but only summed the days of use in the 4-year period before the index date. The pattern of use is not known and variable. A person with 60 days of cumulative use, for example, may have used topical corticosteroids every day for 30 days and thereafter 2 days a week for 15 weeks, or may have used topical corticosteroids very sporadically, 1–2 days a month during the 4-year period.

Average Potency

Individual topical corticosteroids were classified into potency groups according to the WHO ATC index. In sum, the ATC-4 code is based on the first four characters of the ATC code, with the character at the fourth level indicating the strength of corticosteroids (e.g. 'weak' – ATC-4 code D07AA; 'moderately potent' – ATC-4 code D07AB; 'potent' – ATC-4 code D07AC; and 'very potent' – ATC-4 code D07AD), corresponding to a potency score of 1 (for 'weak') through 4 (for 'very potent'). For each current or recent user of topical corticosteroids, the average potency score over the 4-year period prior to the index date was calculated as a function of dose and duration of use. It was calculated as the sum of grams of ointment multiplied by the potency and divided by the cumulative duration of use of topical corticosteroids during this period. For past users of topical corticosteroids, the average potency score during that period was 0. The average potency was categorized into 0, 1, 2, 3 and 4.

Cumulative Load

Load of a topical corticosteroid dispensing was calculated as total dispensed amount (in grams) multiplied by potency score.[23] In recent and current users of topical corticosteroids, the cumulative load was calculated as the sum of all topical corticosteroid loads over the 4-year period prior to the index date. For past users of topical corticosteroids, the cumulative load of topical corticosteroids during that period use was 0 days. The cumulative load was categorized into 0, 1–90, 91–180, 181–365, 366–730, 731–1460 and >1460 mg.

Covariates

Co-medication with systemic corticosteroids (ATC code H02AB) and/or inhaled corticosteroids (ATC code R03BA) was also considered. Use of systemic and/or inhaled corticosteroids was classified similarly to topical corticosteroid use, i.e. 'current users of systemic corticosteroids and/or inhaled corticosteroids' (≤2 years before index date), 'recent users of systemic corticosteroids and/or inhaled corticosteroids' (2–4 years) and 'past or never users of systemic corticosteroids and/or inhaled corticosteroids' (>4 years). Current, recent and past/never use of the most potent inhaled corticosteroid fluticasone propionate (ATC-code R03BA05) was considered specifically. Note that all users of systemic and/or inhaled corticosteroids also used topical corticosteroids at any given time during the study.

In addition, the following covariates were considered: sex, age at index date, year of index date, prescriber of first topical corticosteroid dispensing, follow-up duration, number of all hospitalizations during the 1-year period before the index date and co-medication use in the 4-year period before the index date. The latter included the following drugs known to influence the glucose metabolism: thiazide diuretics, α-adrenergic receptor antagonists, β-adrenergic receptor antagonists, antiepileptics and antipsychotics. The antipsychotic drugs were divided into two groups: atypical antipsychotics and conventional antipsychotics.[13,24,25]

Statistical Analysis

The association between topical corticosteroid use and new-onset diabetes was studied using univariate and multivariate conditional logistic regression (PROC PHREG, SAS v8.2; SAS Institute Inc., Cary, NC, USA). Covariates defined above that were univariately associated with new-onset diabetes were included in the multivariate model. Use of fluticasone propionate was analysed in a separate model. Effects of cumulative duration of topical corticosteroid use, average potency of topical corticosteroids and cumulative load were studied with multivariate regression analyses and tested across ordinal categories using

p for trend. In addition, stratification by combined systemic corticosteroids and/or inhaled corticosteroids was used to show the impact of these co-medications on the association between topical corticosteroid use and new-onset diabetes.

Results

Patient Characteristics

Among 192 893 incident topical corticosteroid users, 7862 patients developed diabetes. Of these, 2212 cases had at least 4 years of follow-up since the start of topical corticosteroid use, and at least two topical corticosteroid dispensings before the index date (date of first diabetes hospitalization or drug dispensing). The 2212 cases were matched to a total of 8582 controls. Table I shows the characteristics of cases and controls. About 58% of cases and controls were females; about 59% were ≥65 years. The vast majority of first topical corticosteroid dispensings were prescribed by general practitioners, among both cases and controls. During the 4-year period before the index date, systemic corticosteroids were used by 23% of cases and 17% of controls ($p < 0.01$), whereas inhaled corticosteroids were used by 18% of cases and 13% of controls ($p < 0.01$). Other frequently used co-medications included β-adrenergic receptor antagonists (cases 38%; controls 24%; $p < 0.01$) and thiazide diuretics (cases 9%; controls 5%; $p < 0.01$).

Association between Use of Topical Corticosteroids and New-Onset Diabetes

The association between use of topical corticosteroids and new-onset diabetes is shown in the top section of table II. The risk of new-onset diabetes among current users of topical corticosteroids was increased 1.2-fold compared with past users of topical corticosteroids (unadjusted odds ratio [OR] 1.24; 95% CI 1.11, 1.40). Results were

Table I. Characteristics of cases with new-onset diabetes mellitus and their age- and sex-matched controls among users of topical corticosteroids

Characteristic	Cases (n = 2212)		Controls (n = 8582)	
	no.	%	no.	%
Female sex	1286	58.1	5025	58.6
Age ≥65 years	1297	58.6	4981	58.0
Mean age [years (SD)]	55.1 (15.7)		54.5 (15.5)	
Year of index date <2000[a]	688	31.1	2678	31.2
Year of first use of topical corticosteroids <1996[b]	1718	77.7	7220	84.1
Prescriber general practitioner[c]	1924	87.0	7725	90.0
Duration of follow-up ≥8 years[d]	555	25.1	2710	31.6
≥1 Hospitalization within 1 year before index date	548	24.8	1320	15.4
Drug history within 4 years before index date				
systemic corticosteroids	510	23.1	1493	17.4
inhaled corticosteroids	389	17.6	1103	12.9
thiazide diuretics	188	8.5	413	4.8
α-adrenergic receptor antagonists	45	2.0	70	0.8
β-adrenergic receptor antagonists	839	37.9	2079	24.2
antiepileptics	99	4.5	321	3.7
antipsychotics, conventional	96	4.3	234	2.7
antipsychotics, atypical	16	0.7	34	0.4

a Minimum 1996, maximum 2003.

b Minimum 1992, maximum 1999.

c First dispensing.

d Minimum 4 years, maximum 12 years.

Table II. Association between recency, cumulative duration, average potency score, and cumulative load of topical corticosteroids and new-onset diabetes mellitus

Parameter	Cases		Controls		OR (95% CI)	OR_{adj}[a] (95% CI)
	no.	%	no.	%		
Recency of topical corticosteroid use						
Past	499	22.5	2219	25.8	1.00 (Ref.)	1.00 (Ref.)
Recent	462	20.9	1852	21.6	1.12 (0.97, 1.30)	1.11 (0.96, 1.29)
Current	1251	56.6	4511	52.6	1.24 (1.11, 1.40)	1.20 (1.07, 1.36)
Cumulative duration of topical corticosteroid use (days)[b]						
0	499	22.5	2219	25.9	1.00 (Ref.)	1.00 (Ref.)
1–60	831	37.6	3299	38.4	1.14 (1.00, 1.29)	1.13 (0.99, 1.28)
61–180	484	21.9	1716	20.0	1.26 (1.10, 1.46)	1.23 (1.06, 1.42)
>180	398	18.0	1348	15.7	1.32 (1.14, 1.54)	1.24 (1.06, 1.45)
Average potency score of topical corticosteroid used[b]						
0	499	22.6	2219	25.9	1.00 (Ref.)	1.00 (Ref.)
1	380	17.2	1353	15.8	1.27 (1.09, 1.47)	1.25 (1.07, 1.46)
2	734	33.2	2826	32.9	1.16 (1.02, 1.32)	1.15 (1.00, 1.31)
3	498	22.5	1787	20.8	1.25 (1.08, 1.44)	1.20 (1.04, 1.38)
4	101	4.6	397	4.6	1.15 (0.91, 1.46)	1.08 (0.85, 1.39)
Cumulative load of topical corticosteroid used (mg)[b]						
0	499	22.6	2219	25.9	1.00 (Ref.)	1.00 (Ref.)
1–90	343	15.5	1464	17.1	1.05 (0.90, 1.23)	1.03 (0.88, 1.21)
91–180	260	11.8	1106	12.9	1.04 (0.88, 1.24)	1.04 (0.87, 1.23)
181–365	371	16.8	1299	15.1	1.29 (1.11, 1.50)	1.27 (1.09, 1.49)
366–730	303	13.7	1084	12.6	1.26 (1.07, 1.48)	1.25 (1.06, 1.47)
731–1460	238	10.8	736	8.6	1.44 (1.21, 1.72)	1.38 (1.15, 1.66)
>1460	198	9.0	674	7.9	1.33 (1.10, 1.60)	1.21 (0.99, 1.47)

a Adjusted for use of systemic corticosteroids and/or inhaled corticosteroids (defined as current use, recent use and past/never use), use of thiazide diuretics, α- and β-adrenergic receptor antagonists, and antipsychotics in the 4-year period before the index date, prescriber and number of hospitalizations in the 1-year period before the index date.

b Measured in the 4-year period before the index date.

Current = 0–2 years before index date; **OR** = odds ratio; **OR_{adj}** = adjusted OR; **Past** = no topical corticosteroid use during the 4 years before index date; **Recent** = 2–4 years before index date; **Ref.** = reference category.

similar after adjustment for use of systemic and/or inhaled corticosteroids and other covariates.

Cumulative Duration, Potency and Load of Topical Corticosteroid Use

Subsequently in table II, the association between use of topical corticosteroids and diabetes is further investigated in relation to cumulative duration of topical corticosteroid use, average potency and cumulative load (potency and amount combined). A higher cumulative duration of topical corticosteroid use was associated with a higher risk for new-onset diabetes (p for trend <0.02). With a cumulative duration of use increasing from 1 to >180 days (reference category = 0 days), the OR increased from 1.14 (95% CI 1.00, 1.29) to 1.32 (95% CI 1.14, 1.54). There was no association between increasing average potency score and a higher diabetes risk (p for trend >0.05). A higher cumulative load of topical corticosteroids was associated with a statistically significantly increased risk of new-onset diabetes ($p < 0.001$). A cumulative load of 181–365 mg was associated with a 1.3-fold increased risk of new-onset diabetes (unadjusted OR 1.29; 95% CI 1.11, 1.50) and a cumulative load of 731–1460 mg was associated with a 1.4-fold increased risk of

new-onset diabetes (unadjusted OR 1.44; 95% CI 1.21, 1.72). Adjustment for use of systemic and/or inhaled corticosteroids and other covariates did not substantially change these ORs for cumulative duration, average potency score or cumulative load of topical corticosteroids.

Association between Use of Topical Corticosteroids and New-Onset Diabetes, Stratified by Use of Systemic and/or Inhaled Corticosteroids

Current use of systemic corticosteroids and current use of inhaled corticosteroids were each associated with a similarly increased risk of new-onset diabetes compared with past/never use (unadjusted OR 1.59; 95% CI 1.40, 1.82 and 1.50; 95% CI 1.30, 1.72, respectively). For current use of systemic and/or inhaled corticosteroids combined, the risk was also increased 1.6-fold (unadjusted OR 1.56; 95% CI 1.39, 1.75). Current use of the potent inhaled corticosteroid fluticasone was associated with a 1.7-fold increased risk of new-onset diabetes compared with past/never used (unadjusted OR 1.72; 95% CI 1.39, 2.14).

We analysed to what extent risk of new-onset diabetes with use of topical corticosteroids was independent of systemic and/or inhaled corticosteroid use. In addition to the multivariate regression results (see table II), we further demonstrated this association by stratification of systemic and/or inhaled corticosteroid use in table III. Among 'past/never users of systemic corticosteroids and/or inhaled corticosteroids', current use of topical corticosteroids remained associated with a 1.3-fold increased risk of new-onset diabetes compared with past use of topical corticosteroids (unadjusted OR 1.27; 95% CI 1.10, 1.47). This OR remained similar when risk factors other than systemic corticosteroids and/or inhaled corticosteroids use were adjusted for as well (adjusted OR 1.23; 95% CI 1.06, 1.43). Within the stratum 'recent users of systemic corticosteroids and/or inhaled corticosteroids', topical corticosteroid use was not associated with risk of new-onset diabetes, but the numbers were small. Within the stratum 'current users of systemic corticosteroids and/or inhaled corticosteroids', results were essentially similar to those in 'past/never users of systemic corticosteroids and/or inhaled corticosteroids'. Restricting the inhaled corticosteroid users to users of fluticasone propionate only did not change these results (data not shown).

Discussion

In the present study, an association between the use of topical corticosteroids and new-onset diabetes was found among current users of topical corticosteroids. The association remained statistically significant among those who had never used systemic and/or inhaled corticosteroids, or had used them >4 years ago. The association increased with cumulative duration of use and with the cumulative load of drug applied over time (potency combined with amount). This argues for a dose-response relationship and therefore for the possibility that diabetes is a real adverse effect of the intense and longstanding use

Table III. Association between topical corticosteroid use and new-onset diabetes mellitus, within strata of patients also using systemic and inhaled corticosteroids

Systemic corticosteroid and/or inhaled corticosteroid use	Recency of topical corticosteroid use				
	past	recent		current	
	OR (95% CI)	OR (95% CI)	OR_{adj}[a] (95% CI)	OR (95% CI)	OR_{adj}[a] (95%CI)
Past/never (n = 8022)	1.00 (Ref.)	1.06 (0.88,1.27)	1.04 (0.87,1.25)	1.27 (1.10,1.47)	1.23 (1.06, 1.43)
Recent (n = 668)	1.00 (Ref.)	0.56 (0.11, 2.79)	0.81 (0.08, 8.39)	0.63 (0.18, 2.25)	1.01 (0.12, 8.48)
Current (n = 2104)	1.00 (Ref.)	1.64 (1.04, 2.59)	1.73 (1.06, 2.80)	1.13 (0.77, 1.66)	1.33 (0.88, 2.02)

a Adjusted for use of thiazide diuretics, α- and β-adrenergic receptor antagonists, and antipsychotics in the 4-year period before the index date, prescriber and number of hospitalizations in the 1-year period before the index date.

Current = 0–2 years before index date; **OR** = odds ratio; $\mathbf{OR_{adj}}$ = adjusted OR; **Past** = no topical corticosteroid use during the 4 years before index date; **Past/never** = no sytemic corticosteroid and/or inhaled corticosteroid use during the 4 years before index date; **Recent** = 2–4 years before index date; **Ref.** = reference category.

of topical corticosteroids. In contrast, Gulliford et al.[15] failed to demonstrate an association of diabetes with topical corticosteroid use. However, exposure was determined over a period of 9 years on average and no distinction was made between current use and past use. Furthermore, as mentioned in their discussion, exposure and outcome were measured imprecisely, there were missing data for covariates, and corticosteroids were used in relatively low doses.

Strengths of this study include the data collection from daily practice in an open-access healthcare system. Using routinely recorded data, there is no information bias. Furthermore, the whole spectrum of patients of all ages receiving topical corticosteroid therapy was covered. A heterogeneous population of corticosteroid users was studied that was likely to consist predominantly of patients with inflammatory dermatoses such as atopic dermatitis and other forms of eczema, and psoriasis. Those who received one or more dispensings for topical corticosteroids in the most recent 2 years were considered as 'current users'. This definition implies a rather conservative approach in the sense that it may include the intermittent and sporadic users as well as non-adherent users. It is known from clinical practice and adherence studies that only about 50% of cases normally finish the prescribed quantity of topical corticosteroid ointment or cream.[21,26] It is likely that this has introduced some degree of so-called non-differential misclassification: adherence is likely to be similar for topical corticosteroid users with and without diabetes. The observed statistical association between current topical corticosteroid use and diabetes as observed may therefore have been diluted; in other words, it may have been stronger in reality.

Use of systemic corticosteroids and/or inhaled corticosteroids was an important covariate in this study and adjusted for in the multivariate analyses. In addition, the association between use of topical corticosteroids and new-onset diabetes was studied stratified by use of systemic corticosteroids and/or inhaled corticosteroids. However, the dose of systemic corticosteroid and/or inhaled corticosteroid was not considered. Other relevant confounding variables were either taken into account by the matching procedure (sex, age, follow-up duration) or multivariate adjustment (prescriber, number of hospitalizations, use of drugs known to influence glucose metabolism). Drugs that interfere with glucose metabolism may be used in conjunction with topical corticosteroids, and hence might lead to an increased incidence of diabetes. However, use of these drugs in the 4-year period prior to the index date was adjusted for in multivariate regression. Residual confounding, for example by dose, and confounding due to unknown residual factors can nonetheless never be fully excluded. For example, we did not have information about body mass index and family history of diabetes. Both of these might be associated with long-term treatment with topical corticosteroids or its main indications, mainly inflammatory dermatoses such as atopic dermatitis and, less often, psoriasis. In contrast to atopic dermatitis, clinical studies suggested that moderate to severe psoriasis is associated with increased body mass index and signs of insulin resistance.[27-29] Therefore, these factors are likely to be relevant confounders, but only for a relatively small proportion of this study sample. It remains controversial whether obesity and diabetes precede the onset of psoriasis or whether they reflect an altered lifestyle and impaired quality of life of psoriasis patients. Future studies to confirm or refute the association reported here might therefore also investigate other diseases that, theoretically, may be expected to be not associated with corticosteroid exposure, e.g. musculoskeletal diseases and osteoporosis.

Various potential sources of bias that often play a role in observational studies were avoided as far as this was possible.[30] Patients with latent diabetes and patients in early stages of the disease might be more likely to seek medical help than others, for example because of overweight or perhaps even because of skin problems related to developing diabetes (protopathic bias). They might therefore be more likely to be treated with topical corticosteroids than others. This would lead to a disproportionally high frequency of topical corticosteroid users among these latent

cases. We addressed this by the requirement that cases should be at least 4 years in the study before being designated as a new diabetes case. This avoids the inclusion of latent diabetes cases and bias. The diagnosis was new, and it was either confirmed by a specialist or it was at least severe enough to require medical treatment. Patients with diet-controlled diabetes are missed by our case definition. However, this is likely to be only a small number of patients because in the end the majority of diabetic patients need oral antidiabetic drugs.

Despite considerable clinical experience with topical corticosteroids, few epidemiological data are available to help clinicians make informed decisions regarding optimal use and safety in the longer term.[31] A systematic review that included 83 randomized clinical trials concerning topical corticosteroid treatment for atopic dermatitis yielded no evidence for the occurrence of local adverse effects. However, for all trials included in the review, the maximum trial follow-up period was limited to 18 weeks.[32] More recent systematic reviews concluded that local adverse effects are related to the use of topical corticosteroids and also appear to be potency dependent. These adverse effects were poorly characterized, however, and evidence of good quality was lacking for many of these publications.[33,34] Only one large-scale (multicentre) observational study is, to our knowledge, available, encompassing 1271 patients; this study and two trials showed that risk of local adverse effects (mainly corticosteroid-induced skin atrophy) is not negligible and increases with potency class and duration of topical corticosteroid treatment.[23] Two double-blind, randomized trials with 16 weeks' follow-up found no evidence for skin atrophy with topical fluticasone application twice a week.[35,36] With regard to systemic adverse effects other than HPA axis disturbances, an association between the use of topical corticosteroids and both glaucoma and cataract has been reported but could not be substantiated by literature review.[33]

The evidence base for the long-term safety of topical corticosteroids is therefore limited.[33,34] Nevertheless, disproportional concern about adverse effects of topical corticosteroids ('topical corticosteroid phobia') has been highlighted in Dutch consensus guidelines.[37,38] Patients' concern about local and systemic adverse effects was quantified by a questionnaire study involving 200 patients with atopic dermatitis. It found perceived risk of local adverse effects to be out of proportion with actual risk in clinical practice.[39] The current findings, however, do not give solid ground to the explanation that most patients' concerns are disproportional to the risk involved.[40] As long as effective long-term management of atopic dermatitis using topical corticosteroid treatment is a challenge, patients' concerns about prolonged treatment remain legitimate.[31]

Conclusion

In conclusion, an increased risk of new-onset diabetes may be an important consideration in the treatment of patients with topical corticosteroids, especially when diabetes risk is already increased and when intense skin treatment is needed. Future studies are needed to endorse these findings in other populations.

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