Risk of Diabetes Associated With Prescribed Glucocorticoids in a Large Population

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The burden of diabetes is increasing (1), as is the frequency of atopic disease (2), which is often treated with glucocorticoid drugs. Because of this, we asked, "What proportion of incident diabetic cases in a population is associated with prescribed glucocorticoid drugs?"

RESEARCH DESIGN AND METHODS

— A nested case-control study was implemented using The Health Improvement Network (3), which is a database containing electronic medical records from family practices in the U.K. (4). Data analyzed included medical diagnostic codes recorded for each consultation, as well as hospital referrals and discharges, and drug codes for all prescriptions issued by the practice. Primary care electronic records were subject to several validation studies (5). This study was approved by the South East Research Ethics Committee. The study population was drawn from 114 family practices with 644,495 registered patients aged ≤100 years. Diabetic case subjects were selected if the date of the first clinical diagnosis of diabetes was between 1 November 2003 and 31 October 2004 and if they were aged between 30 and 89 years at diagnosis and were never prescribed insulin or diagnosed with type 1 diabetes. Two control subjects were randomly selected for each case. The control subjects were matched for age, sex, and practice and were never diagnosed with diabetes or prescribed oral antidiabetic drugs or insulin.

The entry date to the study was the earliest date in the Windows-based medical record or the date of the first prescription following registration up to a maximum of 10 years before the diabetes diagnosis date. Prescriptions for glucocorticoids were counted separately by route of administration including oral, inhaled, topical, ophthalmic, and injected. Initial analysis showed that the relative risk of diabetes increased up to three prescriptions and then remained approximately constant. The cumulative number of glucocorticoid prescriptions was analyzed using the categories none, one or two, and three or more. In addition, the cumulative oral dose was estimated by multiplying, for each prescription, the quantity prescribed by the equivalent dose of hydrocortisone for the preparation. To address problems of confounding (6), propensity scores were estimated as the probability of each subject being prescribed glucocorticoids based on the recorded pattern of medical events and coprescribing in that subject. All medical events, including practice consultations, hospital referrals, and discharges, during the study period were counted separately for the 20 main headings from the clinical terms classification (7). These headings provide a similar classification to the chapter headings of the International Classification of Diseases. All nonglucocorticoid prescriptions were counted separately for the 15 major chapter headings from the British National Formulary (8), which classify drugs according to major indications (gastrointestinal, cardiovascular, respiratory, etc.). Initially, logistic regression models were fitted with glucocorticoid prescriptions as dependent variables and, as predictors, dummy variables summarizing all coprescribing and comorbid medical events, as well as age-group, sex, smoking, and BMI category, the latter including categories for missing values. Propensity scores (9) were estimated, for each mode of glucocorticoid administration separately, as the residuals from the logistic model and were divided into seven categories. Odds ratio (OR) of diabetes associated with glucocorticoids were then estimated adjusting for propensity score category using conditional logistic regression. Population-attributable risks (PARs) were estimated using the formula [(OR − 1)/OR] × Pe, where Pe is the proportion of cases exposed to glucocorticoids (10).

RESULTS

— There were 2,647 case subjects who were diagnosed with diabetes and 5,294 matched control subjects. The mean (±SD) age was 62.4 ± 13.1 years, and 49% were women. The mean duration of analysis time contributed by each subject was 8.9 ± 1.7 years. Respiratory disease was recorded on one or more occasion for 62.2% of case subjects and 54.5% of control subjects, musculoskeletal disease 71.2 and 64.4%, skin disease 58.1 and 51.2%, and diseases of nervous system and sense organs 56.4 and 51.0%, respectively ($P < 0.001$ for each comparison).

The proportion of case subjects receiving three or more glucocorticoid prescriptions (Table 1) was <10%, except for inhaled (12.6%) and topical (26%) preparations. After adjusting for propensity score category, there was no association of diabetes with injected, inhaled, or topical glucocorticoids or glucocorticoid eye drops. The adjusted OR for diabetes associated with three or more oral glucocorticoid prescriptions was 1.36 ([95% CI 1.10–1.69], $P = 0.005$), and the PAR was 2.0%. Estimates for the PAR based on

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Abbreviations: PAR, population attributable risk; .

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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the upper and lower confidence limits for the OR were 0.7–3.1%. The adjusted OR of diabetes associated with a cumulative oral dose equivalent to ≥2.5 g hydrocortisone was 1.25 (1.01–1.54), with 7.6% of case subjects exposed, giving an estimated PAR of 1.5%. The median equivalent dose of hydrocortisone for subjects in this category was 9.9 g (interquartile range 4.7–22.0).

CONCLUSIONS — The study draws on prospectively recorded prescribing information from a large population in primary care. Based on clinical data, both exposure and outcome were measured imprecisely and the frequency of diabetic hyperglycemia may be underestimated. We adjusted for all recorded medical diagnoses and coprescribing, but clinical records contain missing and misclassified values that lead to residual confounding. Only a minority of glucocorticoid-treated patients received high doses (11), but calculations based on the cumulative equivalent dose of oral hydrocortisone gave a consistent estimate for the PAR. We did not have information concerning prescriptions from hospital-based services where higher doses of glucocorticoids may be prescribed, but in the U.K., most ambulatory prescriptions are generally issued in primary care. Misclassification of glucocorticoid exposure may generally contribute to underestimation of associations. However, the proportion of case subjects exposed to oral glucocorticoids was low and the PAR insensitive to varying the magnitude of the estimated OR.

The present analyses, using two different methods to quantify exposure, show that orally administered glucocorticoids may be associated with up to 2% of incident cases of diabetes in a primary care population. From the population perspective, there is either minimal or no association of incident diabetes with prescribing of glucocorticoid-containing inhalers, topical preparations, eye drops, or infrequent glucocorticoid injections for musculoskeletal disorders. We have not evaluated whether these treatments may exacerbate preexisting diabetes.

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Table 1—*Risk of diabetes associated with prescribing of glucocorticoids with different routes of administration*

		Glucocorticoids (route of administration)									
		Oral	*P* value	Injected	*P* value	Inhaled	*P* value	Topical	*P* value	Eye drops	*P* value
Exposed to ≥3 prescriptions	Case subjects (*n* = 2,647)	205 (7.7)		67 (2.5)		333 (12.6)		688 (26.0)		44 (1.7)	
	Control subjects (*n* = 5,294)	260 (4.9)		104 (2.0)		468 (8.8)		1,085 (20.5)		90 (1.7)	
Unadjusted model	1–2 prescriptions	1.28 (1.07–1.52)	0.006	1.35 (1.14–1.61)	0.001	1.18 (0.88–1.58)	0.277	1.24 (1.10–1.39)	<0.001	1.17 (0.95–1.45)	0.145
	≥3 prescriptions	1.69 (1.39–2.05)	<0.001	1.36 (0.99–1.88)	0.056	1.50 (1.29–1.74)	<0.001	1.50 (1.33–1.69)	<0.001	0.99 (0.69–1.43)	0.961
Adjusted model*	1–2 prescriptions	1.04 (0.87–1.26)	0.655	1.18 (0.99–1.42)	0.070	0.91 (0.67–1.23)	0.524	1.02 (0.90–1.15)	0.764	1.04 (0.84–1.29)	0.714
	≥3 prescriptions	1.36 (1.10–1.69)	0.005	1.14 (0.81–1.59)	0.457	1.12 (0.90–1.39)	0.310	1.10 (0.95–1.27)	0.199	0.86 (0.59–1.26)	0.448

Data are *n* (%) or OR (95% CI). Data are for 2,647 incident diabetic case subjects and 5,294 nondiabetic control subjects. OR compared with no prescriptions for reference. *Adjusted for propensity score category derived from 20 classes of comorbidity, 15 classes of coprescribing, smoking, and BMI.