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Use of parenteral glucocorticoids and the risk of new onset type 2 diabetes mellitus: A case-control study

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ABSTRACT

Background: Use of oral glucocorticoids (GCs) has been associated with hyperglycaemia and type 2 diabetes mellitus (T2DM). However, unlike oral GCs, there is minimal or no data on the effect of parenteral GC use on T2DM.

Objective: To assess the association between use of parenteral GCs and the risk of receiving a first prescription of a non-insulin antidiabetic drug (NIAD) as a proxy for new onset of T2DM.

Methods: A population based case-control study was performed using the Clinical Practice Research Datalink (CPRD). Cases (n = 177,154) were defined as patients >18 years of age who had their first ever NIAD prescription between January 1987 and October 2013. Controls were matched by age, gender and general practitioner practice. Conditional logistic regression analyses were used to estimate the risk of NIAD prescription and use of parenteral GCs. Our analyses were statistically adjusted for lifestyle factors, comorbidities and concomitant drug use.

Results: Although this study confirmed that oral GCs increases the risk of receiving a first prescription of a NIAD (OR 2.63 [95% CI 2.53–2.73]), there was no association between the use of parenterally administered GCs and the risk of receiving a first prescription of a NIAD (OR 0.88 [95% CI 0.76–1.02]). The number of GC prescriptions was not associated with risk of new onset T2DM compared to no parenteral GCs use; neither the type of GC.

Conclusion: Our study does not demonstrate an association between the use of parenteral GCs and the risk of new onset of T2DM.

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1. Introduction

Glucocorticoids (GCs) are widely used as treatment for many diseases because of their anti-inflammatory and immunosuppressive properties. Despite their efficacy, their use has been associated with various side effects, including hyperglycaemia and induction of type 2 diabetes mellitus (T2DM) [1–7].

The risk of developing GC-induced diabetes has previously been described in multiple observational studies. A case-control study demonstrated that orally administered GCs may be associated with up to 2% of incident cases of diabetes in a primary care population [1]. Two other observational studies showed a two-fold increased risk of T2DM with oral GC use [6,3]. The main determinants of developing diabetes are the daily dose of GCs, type of GC, a longer duration of treatment, continuous use, an older age, a higher glycosylated haemoglobin (HbA1c) level at baseline, a higher Body Mass Index (BMI), family history of diabetes or race [5,7,8].

Multiple mechanisms have been suggested to be involved in the development of GC-induced T2DM, such as increased hepatic glucose production, inhibition of glucose uptake in muscles and adipose tissue, and decreased beta-cell function [7]. GCs can induce diabetogenic side effects through interactions with the regulation of glucose homeostasis. Under conditions of excess and/or long-term treatment, GCs can induce peripheral insulin resistance by impairing insulin signalling, which results in reduced glucose in the cells and elevated endogenous glucose production. Furthermore, GCs can promote abdominal obesity, elevate plasma fatty acids and triglycerides. In response to GC-induced peripheral insulin resistance and in an attempt to maintain normoglycaemia, pancreatic β-cells undergo several adaptations which results in hyperinsulinaemia. Failure of β-cells to compensate for this situation favours glucose homeostasis disruption, which can result in hyperglycaemia [9,10].

Similar to oral GCs, parenteral GCs are used mainly as pulse therapy in patients with rheumatoid arthritis and in patients with osteoarthritis. In a previous study, 50% of patients with osteoarthritis who underwent a knee or hip replacement surgery had received parenteral GCs in the 2-years prior to surgery [11]. Previous studies have also demonstrated that the use of parenteral GCs is associated with hyperglycaemia in patients with diabetes and in patients without diabets. Intravenous administration of high dose (1 g) methylprednisolone for a period of three days in non-diabetic patients resulted in significant increase of fasting glucose levels [12]. Administration of methylprednisolone acetate at the knee joint in well controlled diabetic patients showed a significant increase in blood glucose levels with peak values seen between 2 and 24 h following the injection. This increase usually lasted between 2and 5 days [13,14]. Furthermore, elevated glucose levels were seen in both diabetic and non-diabetic patients after injection of three 5.625 mg cortivazole injections (85 mg prednisolone-equivalent) at the shoulder joint at 3-day interval. No significant effect on cholesterol or triglyceride levels have been found [15].

However, unlike oral GCs, there is minimal or no data regarding the incidence of new onset of T2DM among parenteral GC users. Due to the different routes of administration and different dose regimes, the risk of T2DM may differ from oral GCs. Therefore, the objective of this study was to assess the association between use of parenteral GCs and the risk of receiving a first prescription of a non-insulin antidiabetic drug (NIAD) as a proxy for new onset T2DM.

2. Methods

2.1. Data sources

A case-control study was performed using the Clinical Practice Research Datalink (CPRD). The CPRD is a large primary care database containing medical records registered by over 674 general practitioners (GP) in the UK. It represents 6.9% of the total British population. In the UK, GPs play a key role in the healthcare system as they are responsible for primary care and specialist referrals. Consequently, this database provides information on a wide range of medical records, including diagnoses, prescriptions, specialist referrals, and laboratory test results [16]. The study protocol was approved by the Independent Scientific Advisory Committee (ISAC), protocol number: 16_091R.

2.2. Study population

All patients (males and females aged >18 years), between January 1987 and October 2013, who had their first ever prescription record of a NIAD were defined as a case. The first prescription record of a NIAD was used as a proxy for new onset of T2DM. NIADs included metformin, sulphonylurea, Glucagon-like peptide-1 (GLP-1) analogues, Dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, thiazolidinediones, and acarbose. The index date was defined as the date of the first NIAD prescription. A minimum period of 12 months of follow-up before the index date was required to ensure that we were dealing with new onset of T2DM. For each T2DM patient, one control patient without a NIAD or insulin prescription prior to the index date was selected and matched by year of birth, sex, and GP practice using incidence density sampling.

2.3. Exposure assessment

Use of oral and parenteral (intraarticular/intrabursal/periarticular/intramuscular/intradermal) GCs was determined by reviewing prescriptions before the index date (Supplementary Table 1 and Supplementary Table 2). Current users comprised all patients with at least one recorded prescription within the 90-day period before index date. Recent users were those who received a GC between 91 days and 180 days before index date, but without a prescription in the 90-day period before index date. Past users were defined as patients who had a last GC prescription more than 180 days before the index date.

2.4. Covariates

We reviewed the literature to identify risk factors for T2DM. Risk factors including BMI (most recent prior to index date) and smoking status were used as potential confounders. Furthermore, a history of comorbidities such as heart failure, angina pectoris, acute myocardial infarction (AMI), hypertension, hypercholesterolemia, arrhythmia, cerebrovascular, osteoarthritis, systemic lupus erythematosus, rheumatoid arthritis, transplantation, retinopathy and neuropathy ever before index date were also included. Drugs which may induce hyperglycaemia [17], such as loop diuretics, beta-blockers, antipsychotics, protease inhibitor, other GC drugs (oral, nasal, dermal, etc.) and other drugs such as calcium channel blockers, RAAS inhibitors, statins in the six months prior to index date were also considered as potential confounders.

2.5. Statistical analysis

Conditional logistic regression analyses (using SAS version 9.3, PHREG procedure) were used to assess the association between new onset of T2DM and use of oral and parenteral (intraarticular/intrabursal/periarticular/intramuscular/intra dermal) GCs, expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). In all analyses, covariates were included as confounders if they independently changed the beta-coefficient for current GC exposure by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature. To determine whether a duration-response relationship was present we stratified the current oral and parenteral GC users by number of prescriptions ever before index date (1–4, 5–8, >8 prescriptions). To determine whether there is a difference between the various parenteral GCs, current users were be stratified by type of parenteral GC (triamcinolone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone).

3. Results

Between January 1987 and October 2013, 177,154 cases and 177,154 controls were identified. The characteristics of cases and controls are summarized in Table 1. Age, gender and smoking status distribution were similar among cases and controls. Cases had a higher average BMI (31.4 kg/m^2 [cases] vs 26.5 kg/m^2 [controls]), average HbA1c (8.6% [cases] vs 6.3% [controls]) and average fasting glucose level (10.1 mmol/L [cases] vs. 5.3 mmol/L [controls]) compared to controls. Similarly, a history of comorbidities and drug use was found to be higher among the cases than among the controls. A history of other GC use within 6 months before the index date was higher among the cases (17.0%) as compared to the controls (9.5%).

Current use of oral GCs was associated with an increased risk of receiving a first NIAD prescription (OR 2.63 [95% CI 2.53–2.73]), Table 2. After adjusting for relevant confounders the corresponding adjusted (adj.) OR was 2.55 (95% CI 2.43–2.68). The risk of first NIAD prescription decreased with increasing number of parenteral GC prescriptions compared to patients without oral GCs use; adj. OR was 3.38 (95% CI 3.11–3.68) in group with 1–4 prescriptions, adj. OR 3.09 (95% CI 2.72–3.52) in group with 5–7 prescriptions and adj. OR 2.04 (1.91–2.18) in the group with >8 prescriptions.

Table 3 shows an association between the use of parenteral GCs and receiving a first NIAD prescription, crude OR 1.29 [95% CI 1.15–1.44]. However, after full statistical adjustment for confounders no association was found (OR 0.88 [95% CI 0.76–1.02]). There was no difference in the effect on risk of first NIAD prescription with increasing number of parenteral GC prescriptions compared to patients without parenteral GC use. Furthermore, there was no difference between the different parenteral GC substances (Table 4).

4. Discussion

This study found no association between the use of parenterally administered GCs and the risk of receiving a first prescription of a NIAD as a proxy for new onset T2DM. An increase in the number of GC prescriptions or the type of parenteral GC was not associated with risk of new onset T2DM compared to no parenteral GC use. However, in line with other observational studies, we found an increased risk of GC-induced diabetes among oral GC users compared to non-users [1,6,3]. This provides evidence for the 'assay sensitivity' of our data source, study design and definitions of exposure and outcome.

We did not find an association between the use of parenteral GCs and new onset of T2DM. First, this may be explained by the short duration and intermittent use of parenteral GCs. The effect of GCs is usually transient and reversible. As GC doses are reduced, their effect on endocrine metabolism returns to baseline and drug induced diabetes is expected to resolve [8]. Among oral GC users, a continuous GC scheme and long duration have been described as predictors for T2DM [5,7]. Blackburn et al. showed that the incidence of T2DM increase in time among oral GC users. The incidence of T2DM increased after >3 months of GC use among oral GC users compared with the reference group. The number needed to harm (NNH) for continuous use of oral GCs over 1, 2 and 3 years were 41, 23 and 16 respectively [3]. In our study approximately 85% of the cases currently using a parenteral GC had 1–4 prescriptions prior to index date. When a parenteral GC was prescribed more than one time to a single patient, the average days between each prescription was 439 days. This intermittent use and short duration of parenteral GC use may be too short to affect the development of T2DM. Furthermore, the risk of new onset of T2DM within current GC users with >8 prescriptions was increased (OR 1.55 [95% CI 0.70–3.43]). This effect, however, was not statistically significant, possibly due to a small sample size. Secondly, most of the parenteral GCs are locally administered. Of the parenteral GCs, methylprednisolone was mostly used in both cases and controls (about 65%). In general, this GC is used intra-articularly or intramuscularly. A previous study showed that intra-articularly administered GCs increased glucose concentrations in patients with controlled diabetes [13]. However, compared to continuous use of oral GC, when using

Table 1 – Baseline characteristics of cases (NIAD users) and controls (none NIAD users).

Characteristic	Controls n = (%) n = 177154	Cases n = (%) n = 177154
Mean age at index date (years, (SD))	60.8 (15.0)	60.8 (15.0)
Gender, females	83,359 (47.1)	83,359 (47.1)
Smoking status		
Never	77,842 (43.9)	71,544 (40.4)
Current	34,349 (19.4)	32,667 (18.4)
Ex	45,412 (25.6)	64,476 (36.4)
Missing	19,551 (11.0)	8467 (4.8)
BMI (kg/m^2, mean, (SD))	26.5 (4.9)	31.4 (6.6)
By category		
<25.0 kg/m^2	58,027 (32.8)	22,597 (12.8)
25–29.9 kg/m^2	54,671 (30.9)	53,338 (30.1)
30–34.9 kg/m^2	20,258 (11.4)	46,940 (26.5)
≥35.0 kg/m^2	7757 (4.4)	40,473 (22.8)
BMI missing	36,441 (20.6)	13,806 (7.8)
HbA1c most recent within the year prior to index date		
HbA1c (mean, (SD))	6.3 (1.2)	8.6 (1.8)
By category		
<6.5%	2334 (1.3)	5138 (2.9)
6.5–7.9%	712 (0.4)	37,484 (21.2)
8.0–9.4%	216 (0.1)	27,313 (15.4)
≥9.5	86 (0.0)	24,119 (13.6)
HbA1c missing	173,806 (98.1)	83,100 (46.9)
Fasting glucose most recent within the year prior to index date		
Fasting glucose (mean, (SD))	5.3 (0.8)	10.1 (4)
By category		
<6.0 mmol/L	8748 (4.9)	2075 (1.2)
6.0–7.4 mmol/L	1181 (0.7)	8329 (4.7)
7.5–8.9 mmol/L	98 (0.1)	9080 (5.1)
≥9.0 mmol/L	39 (0.0)	17,814 (10.1)
Fasting glucose missing	167,088 (94.3)	139,856 (78.9)
History of comorbidity ever before index date		
T2DM	1955 (1.1)	133,069 (75.1)
Retinopathy	902 (0.5)	9161 (5.2)
Neuropathy	1258 (0.7)	3528 (2.0)
Angina	11,193 (6.3)	20,290 (11.5)
AMI	6186 (3.5)	11,880 (6.7)
Heart failure	4173 (2.4)	8528 (4.8)
Hypercholesterolemia	9025 (5.1)	16,572 (9.4)
Hypertension	44,686 (25.2)	82,665 (46.7)
Arrhythmia	8403 (4.7)	12,919 (7.3)
Cerebrovascular disease	8115 (4.6)	12,489 (7.0)
Osteoarthritis	28,248 (15.9)	35,440 (20.0)
Rheumatoid arthritis	2549 (1.4)	2919 (1.6)
Transplantation	210 (0.1)	412 (0.2)
History of drug use within 6 months before index date		
Loop diuretics	9178 (5.2)	21,481 (12.1)
Calcium channel blockers	19,204 (10.8)	38,179 (21.6)
Beta-blockers	17,922 (10.1)	35,116 (19.8)
RAAS inhibitors	25,596 (14.4)	65,994 (37.3)
Statins	25,241 (14.2)	76,753 (43.3)
Antipsychotics	2404 (1.4)	4367 (2.5)
Use of other glucocorticoids (oral, dermal, nasal etc.)	16,787 (9.5)	30,073 (17.0)

Abbreviations: SD = standard deviation, BMI = body mass index, HbA1c = Glycated Haemoglobin, AMI = acute myocardial infarction, T2DM = Type 2 Diabetes Mellitus, T1DM = Type 1 Diabetes Mellitus, RAAS = renin-angiotensin-aldosterone-system.

Table 2 – Use of oral GCs and risk of first NIAD prescription.

Oral GC use	Controls (n = 177154)	Cases (n = 177154)	Crude OR	(95%CI)	Adjusted OR[a]	(95% CI)
Never	156,679	146,700	Reference		Reference	
Past	15,104	18,988	1.37	(1.34–1.40)	1.04	(1.01–1.07)
Recent	1426	1946	1.48	(1.38–1.59)	1.14	(1.04–1.25)
Current	3945	9520	2.63	(2.53–2.73)	2.55	(2.43–2.68)
By no of prescriptions ever before index date						
1–4	1162	3438	3.23	(3.02–3.45)	3.38	(3.11–3.68)
5–8	492	1421	3.15	(2.84–3.49)	3.09	(2.72–3.52)
>8	2291	4661	2.22	(2.11–2.33)	2.04	(1.91–2.18)
By type of GC, most recent prior to index date						
Triamcinolone	0	0	–	–	–	–
Prednisolone	3640	8426	2.52	(2.43–2.63)	2.33	(2.22–2.46)
Methylprednisolone	4	6	1.70	(0.47–6.12)	4.37	(0.68–28.17)
Hydrocortisone	81	206	2.69	(2.08–3.48)	2.41	(1.73–3.35)
Dexamethasone	94	738	8.49	(6.85–10.53)	15.16	(11.80–19.47)
Betamethasone	17	28	1.77	(0.97–3.24)	1.56	(0.71–3.42)
Cortisone	5	6	1.24	(0.38–4.05)	1.00	(0.26–3.79)
Fludrocortisone	104	110	1.15	(0.88–4.50)	1.48	(1.05–2.10)

Abbreviations: GCs = glucocorticosteroids, BMI = body mass index, RAAS = renin-angiotensin-aldosterone-system, OR = odds ratio, CI = confidence interval.

[a] Adjusted for: BMI and smoking status. History of disease ever before index date: angina, heart failure, hypertension, neuropathy, osteoarthritis. Drug use in 6 months prior to index date: loop diuretics, RAAS-inhibitors, statins, calcium channel blockers.

Table 3 – Use of parenteral GCs and risk of first NIAD prescription by number of parenteral GC prescriptions.

GC use	Controls (n = 177154)	Cases (n = 177154)	Crude OR	(95% CI)	Adjusted OR[a]	(95% CI)
Never	167,423	164,615	Reference		Reference	
Past	8656	11,191	1.34	(1.30–1.38)	1.02	(0.98–1.06)
Recent	503	639	1.32	(1.18–1.49)	0.91	(0.77–1.06)
Current	572	709	1.29	(1.15–1.44)	0.88	(0.76–1.02)
By no of prescriptions ever before index date						
1–4	507	601	1.23	(1.09–1.38)	0.87	(0.74–1.03)
5–8	46	76	1.73	(1.20–2.50)	0.76	(0.48–1.23)
>8	19	32	1.76	(0.99–3.10)	1.55	(0.70–3.43)

Abbreviations: NIAD = Non-insulin antidiabetic drug, GCs = Glucocorticosteroids, BMI = body mass index, RAAS = renin-angiotensin-aldosterone-system, OR = odds ratio, CI = confidence interval.

[a] Adjusted for: BMI and smoking status. History of disease ever before index date: angina, heart failure, hypertension, neuropathy, osteoarthritis. Drug use in 6 months prior to index date: loop diuretics, RAAS-inhibitors, statins, calcium channel blockers, other glucocorticoids.

Table 4 – Use of parenteral GCs and risk of first NIAD prescription by substance of parenteral GC.

GC use	Controls (n = 177154)	Cases (n = 177154)	Crude OR	(95% CI)	Adjusted OR [a]	(95% CI)
Never	167,423	164,615	Reference		Reference	
Past	8656	11,191	1.34	(1.30–1.38)	1.02	(0.98–1.06)
Recent	503	639	1.32	(1.18–1.49)	0.91	(0.77–1.06)
Current	572	709	1.29	(1.15–1.44)	0.88	(0.76–1.02)
By type of GC, most recent prior to index date						
Triamcinolone	140	175	1.29	(1.03–1.61)	0.87	(0.65–1.18)
Prednisolone	8	18	2.33	(1.01–5.37)	2.28	(0.79–6.60)
Methylprednisolone	370	462	1.30	(1.13–1.49)	0.86	(0.72–1.04)
Hydrocortisone	54	54	1.04	(0.72–1.52)	0.83	(0.50–1.38)
Dexamethasone	0	0	–		–	

Abbreviations: NIAD = Non-insulin antidiabetic drug, GC = Glucocorticosteroid, BMI = body mass index, RAAS = renin-angiotensin-aldosterone-system, OR = odds ratio, CI = confidence interval.

[a] Adjusted for: BMI and smoking status. History of disease ever before index date: angina, heart failure, hypertension, neuropathy, osteoarthritis. Drug use in 6 months prior to index date: loop diuretics, RAAS-inhibitors, statins, calcium channel blockers, other glucocorticoids.

GCs locally the time exposed to sufficiently high concentrations may be too short to have systemic effects and to develop T2DM. After administration of methylprednisolone intra-articularly, peak levels were observed after 2–12 h and complete clearance from the blood after 5 days.[18–20] After oral administration of methylprednisolone, peak concentrations were observed after 1.5 h and its elimination half-life is 1.8 h [21].

Our study has several strengths and limitations. To our knowledge, this is the first study that evaluated the association between use of parenteral GCs and new onset of T2DM. It was conducted using the world's largest primary care database which is representative for 6.9% of the British population. This enabled us to assess the risk of T2DM in 12,539 users of parenteral GCs. Third, we have evaluated the effect of duration of parenteral GC use and risk of T2DM by stratifying our analyses by number of prescriptions.

A limitation of this study is that the causal interpretation of the findings will be restricted. Although we corrected for relevant covariates, confounding remains a considerable concern in observational studies. Due to limited availability of data we were unable to control for some factors, such as ethnicity, and genetic factors. This may influence the results, since ethnicity and genetic factors are important risk factors for developing T2DM [8]. In the United Kingdom, South Asian and Black communities are two to four times more likely to develop T2DM than those with a Caucasian background [22,23] Since the majority of British population includes Caucasians [24], ethnicity is not likely to be an important limitation in our study. We did not stratify by gender as this has not been described as a risk factor for glucocorticoid induced diabetes mellitus [8].

Confounding by indication may be another concern in observational studies. GCs are mostly prescribed in patients with rheumatoid arthritis, systemic lupus erythematosus and other inflammatory disease. These patients are at increased risk of developing cardiovascular disease and T2DM because of their pathological background. Based on this knowledge, GC users are, due to their co-morbidity, more likely to develop T2DM [25]. However, these factors did not change the beta-coefficient of current GC use with >5% compared to the crude analysis. Therefore, they were not included as relevant confounders. Furthermore, patients with inflammatory diseases may have higher endogenous GC levels caused by disease-related stress, which may increase serum glucose levels. As this is possibly present in the cases, this may also lead to confounding by indication.

Misclassification of exposure may also be of concern. Prescription data were used to determine exposure. However, the nature of this data does not allow us to confirm compliance of medication. Furthermore, since CPRD database does not contain prescription data from hospitals or day care clinics, we were not able to include parenteral GC administrations in hospitals in our analysis. These factors may have led to underestimation of the exposure. However, since most locally used parenteral GCs are administered by nurses or GPs in the primary care setting, this is unlikely to have influenced the results. A dose-response relationship could not be accurately ascertained given the limitations in data availability regarding the different routes of administration and different dose regimes of parenteral GCs. A first NIAD prescription could be considered to be an inadequate definition of new onset of T2DM. The earlier stages of T2DM are usually either undetected or treated with non-pharmacological methods. Therefore, at the time of first prescription the disease has likely been present for some time may therefore be of concern. However, a first NIAD prescription provides a clear date at which a stage of the disease is reached that requires pharmacological treatment. Fasting glucose or HbA1c levels do not provide such a clear and unambiguous cut-off. Furthermore, NIAD use has been previously used in CPRD studies to define T2DM [26,27]. Since antidiabetics are taken exclusively to treat diabetes, the possibility of misclassifying non-diseased subjects as diseased subjects is minimal. Finally, we were not able to determine the effect of intravenous use of GCs on T2DM. Since intravenous GCs are administered in hospitals and hospital data is limited in the CPRD database [28], we only focused on locally (intraarticular/intrabursal/periarti cular/intramuscular/intradermal) used parenteral GCs in the primary care line setting.

In conclusion, this case-control study does not demonstrate a statically significant increase in the risk for new onset of T2DM among current users of parenteral GCs compared to non-users. This is in contrast to our findings demonstrating an association between oral GC use and the risk of T2DM. Since this was the first observational study assessing the effects of parenteral use of GCs on onset of TD2M, more studies are necessary to confirm the absence of possible metabolic side effects of parenteral GCs.

Conflicts of interest

JN, AK, PS, BvdB and FV: None

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2018.02.010.

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