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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.