DIABETIC Medicine

COMMENTARY

Glucocorticoid-induced hyperglycaemia and diabetes: Call for action

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Diabetes and hyperglycaemia are associated with increased morbidity and large healthcare and economic costs.[1] Glucocorticoid-induced diabetes and hyperglycaemia are common. Glucocorticoids are used widely to treat people with inflammatory and autoimmune conditions,[2] malignancies[3] and in hospitalised patients with COVID-19.[4] In the United Kingdom (UK), among hospitalised patients, the prevalence of glucocorticoid use is 10% in all patients[5] and 25–40% in those with diabetes.[6] This is associated with adverse metabolic outcomes including impaired glycaemic control[7] and can manifest as a new-onset diabetes (glucocorticoid-induced diabetes) or worsening hyperglycaemia in people with diabetes (glucocorticoid-induced hyperglycaemia). The hypothesised mechanism for glucocorticoid-induced diabetes and hyperglycaemia is reduced insulin sensitivity and increased gluconeogenesis. Approximately 2% of all newly diagnosed diabetes cases in the United Kingdom are related to glucocorticoid use over a mean duration of 8.9 (±1.7) years.[8] A meta-analysis by Liu et al.[9] demonstrated that the incidence of glucocorticoid-induced diabetes and hyperglycaemia is 18.6% and 32.3%, respectively, over the period of 1–12 months. Patients from the included studies were adults in outpatient and inpatient settings treated with systemic glucocorticoids for a variety of indications including haematological malignancies, rheumatoid arthritis, pemphigus, pemphigoid, systemic lupus erythematosus, respiratory and neurological conditions.[9]

Glucocorticoid-induced diabetes and hyperglycaemia is a problem in primary care and in hospital care. In primary care, optimising care for patients by preventing acute diabetic emergencies and avoiding unnecessary hospital admissions is important. In hospitalised patients, hyperglycaemia is independently associated with prolonged length of stay, infections and mortality[10] acknowledging that people with the highest blood glucose values may be particularly ill. About 22% of patients using systemic glucocorticoids are treated long term (>6 months),[11] which protracts their risk of developing diabetes. There is limited evidence of the effects of glucocorticoid-induced diabetes and hyperglycaemia on the outcomes of hospitalisation.[12] Some studies in patients with malignancies reported reduced response to chemotherapy and increased mortality.[13,14] Similarly, detrimental effects on hospitalisation outcomes were reported in patients with renal transplant[15] and acute exacerbation of chronic obstructive pulmonary disease.[16] However, these studies are limited by observational design and the fact that hyperglycaemia is more likely in severely ill patients. Clinical guidance on glucocorticoid-induced diabetes and hyperglycaemia is supported by a limited evidence base.[6] Here we discuss a lack of robust evidence in several aspects of diagnosis, monitoring and treatment of glucocorticoid-induced diabetes and hyperglycaemia and propose the way forward to address the unmet clinical needs.

Glucocorticoid-induced diabetes and glucocorticoid-induced hyperglycaemia may remain undiagnosed or are identified only when symptoms or acute complications of hyperglycaemia emerge. Numerous risk scores to identify people most likely to develop type 2 diabetes exist, and may include corticosteroid use,[17,18] but no risk score has been exclusively developed among patients who

take corticosteroids.[19] The most established risk scores including the QDScore[17] and the Cambridge score[18] contain current use of glucocorticoids. Although risk factors for glucocorticoid-induced diabetes are similar to those for type 2 diabetes,[20] new risk scores utilising routine clinical data developed specifically for patients using corticosteroids may perform better.

No evidence exists if early detection or treatment of glucocorticoid-induced diabetes improves the outcomes, but frequent blood glucose monitoring may improve early diagnosis. Glucocorticoid-induced diabetes and hyperglycaemia may resolve after stopping glucocorticoids or may persist.[7] Similarly, gestational diabetes may resolve after giving birth, but increases the risk of future type 2 diabetes, and women who had gestational diabetes are advised to monitor HbA1c annually.[21] Guidelines from the Joint British Diabetes Societies[6] recommend monitoring capillary blood glucose at least once daily among those without diabetes on systemic glucocorticoids, and if new diabetes is suspected, guidance recommends performing an oral glucose tolerance test before three months have elapsed or measuring HbA1c three months after discontinuing glucocorticoids. A major limitation of the guidelines is that they are not based on empirical evidence. It is possible that those who had a transient glucocorticoid-induced diabetes would benefit from regular monitoring of HbA1c after stopping glucocorticoid treatment, but the optimal frequency is not known, and further research is needed to address this.

There is no generally accepted treatment strategy for managing glucocorticoid-induced diabetes and hyperglycaemia, and current British recommendations are based on consensus.[6] Recent narrative reviews summarised the strategies used to manage glucocorticoid-induced diabetes and hyperglycaemia in various settings.[12,20] Differences in pharmacokinetics between glucocorticoids make managing glucocorticoid-induced diabetes and hyperglycaemia more complex according to existing guidance. For example, in people without prior diabetes on once daily glucocorticoid therapy, guidance from the Joint British Diabetes Societies recommends sulphonylureas initially if capillary blood glucose is above 12 mmol/L on two occasions in 24 h.[6] Metformin may be used given its favourable effects on insulin sensitivity[22] while dipeptidyl peptidase 4 (DPP-4) inhibitors can be effective in mild hyperglycaemia without increasing the risk of hypoglycaemia. However, none of the non-insulin agents except sulphonylurea (metformin, pioglitazone, DPP-4 inhibitors, sodium-glucose cotransporter 2 (SGLT2)-inhibitors, glucagon like peptide 1 (GLP-1) receptor agonists) are as yet recommended because they have not demonstrated efficacy in acute glucocorticoid-induced hyperglycaemia.[6] If hyperglycaemia cannot be controlled on sulphonylureas, the guidance recommends starting insulin.[6] Insulin is also recommended in the setting of glucocorticoid-induced diabetes and multiple daily doses of glucocorticoids.[6] Evidence from trials assessing the effectiveness of different insulin regimens is limited.

Glycaemic management during glucocorticoid treatment for specific indications (COVID-19, malignancies) has been described. Dexamethasone has been recommended in patients with respiratory failure associated with COVID-19.[4] However, in those with diabetes, new-onset hyperglycaemia on dexamethasone had detrimental effects on the outcomes of COVID-19 indicating that glucocorticoids should be used carefully in those with COVID-19 and diabetes to strike a balance between anti-inflammatory and hyperglycaemic effects. Rayman et al.[23] published guidance on managing glycaemia on dexamethasone treatment in the context of COVID-19 in those with and without pre-existing diabetes. The guidance highlights that if blood glucose is above 12 mmol/l among insulin-naïve individuals, NPH insulin should be used at 0.3 IU kg^{-1} day^{-1} of which 2/3 should be given in the morning. Insulin dose should be halved in people older than 70 years and in those with impaired renal function (eGFR < 30 ml min^{-1} 1.73 m^{-2}).[23] Uptitration or downtitration of 10% is recommended for every 6 mmol/l increase or decrease in blood glucose, respectively.[23] There is no universally accepted guidance on managing glucocorticoid-induced diabetes and hyperglycaemia in patients with malignancies. Previous literature largely focuses on inpatients and suggests that basal-bolus insulin is most effective in this context.[24]

How glucocorticoid-induced hyperglycaemia in people with diabetes affects future requirements for treatment, cardiometabolic risk factors over time, or health outcomes compared to people with diabetes not exposed to glucocorticoids requires clarifying. Although the efficacy of newer agents for diabetes, for example GLP-1 receptor agonists and SGLT2 inhibitors, in acute glucocorticoid-induced hyperglycaemia has not been demonstrated,[6] they have favourable effects on some of the sequalae of long-term glucocorticoid use and diabetes (obesity, hypertension, dyslipidaemia, non-alcoholic fatty liver disease, renal impairment, heart failure). However, SGLT2 inhibitors are associated with euglycaemic ketoacidosis[25] and glucocorticoids with hyperglycaemic ketoacidosis. Whether GLP-1 receptor agonists and SGLT-2 inhibitors confer benefits to those exposed to glucocorticoids has not been evaluated.

Despite being common, glucocorticoid-induced diabetes and hyperglycaemia remains a neglected clinical issue and action is needed to generate more evidence to underpin clinical guidance. Significant gaps in our understanding of the natural history of glucocorticoid-induced diabetes, its prediction and management exist despite its negative consequences including emergency department attendances, increased length of hospital stay and

diabetes-related complications. These gaps have challenged the efforts to strengthen the guidance for detecting, monitoring and managing glucocorticoid-induced diabetes. High-quality data from rigorously designed studies, both randomised controlled trials and large-scale studies using data from routine healthcare, are urgently needed to address these gaps.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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