Inpatient glucocorticoid use: beneficence *vs* non-maleficence

Data suggest that over 12% of inpatients are taking high-dose glucocorticoids, which are a well-recognized cause of hyperglycaemia. Hyperglycaemia is associated with poor outcomes in most medical and surgical specialities, yet rates of blood glucose monitoring and appropriate management remain very low.

Glucocorticoids are widely used in several specialties for their immunosuppressive and anti-inflammatory properties. However, their use is limited by their well-recognized side-effect profile, including the development of hyperglycaemia.

The vast majority of glucocorticoid use is in the outpatient population. Epidemiological data have shown that in the UK approximately 0.75% of the population is on oral glucocorticoid treatment at any one time. This varies from about 0.2% in under 30-year-olds to 2.5% in those between 70 and 79 years old (Royal College of Physicians, 2002). Of this long-term use, 40% is used for respiratory disease, with most of the rest being used for either musculoskeletal or dermatological conditions that require immunosuppression (Royal College of Physicians, 2002). While the vast majority of glucocorticoid use is for less than 5 days, over a fifth is for over 6 months with about 4.3% being reportedly used for over 5 years (Fardet et al, 2011).

It is well recognized that long-term glucocorticoid use is associated with the development of hyperglycaemia, and observational data for many – if not most – medical and surgical conditions suggest that the additional presence of hyperglycaemia or diabetes is associated with poorer outcomes (Baker et al, 2006; Kwon et al, 2013). Thus the question arises that if so many specialties prescribe these potentially harmful drugs, should the prescribers – as they should with every other drug they prescribe – take responsibility for the potential consequences of the drug. Should patients be counselled on the potential harms of the drug? Beneficence *vs* non-maleficence?

Table 1. Relative potency and half-life of commonly used glucocorticoids

Glucocorticoid	Potency (dose equivalent)	Duration of action (half-life in hours)
Hydrocortisone	20 mg	8
Prednisolone	5 mg	16–36
Methylprednisolone	4 mg	18–40
Dexamethasone	0.75 mg	36–54
Betamethasone	0.75 mg	36–54

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Differences between glucocorticoids

Different glucocorticoids have different potencies, as shown in *Table 1*. While the majority of glucocorticoid use is in medical specialities, these steroids are also commonly used by anaesthetists as part of the enhanced recovery after surgery scheme to prevent postoperative nausea and vomiting. However, it is not known how many individuals undergoing surgery who are not previously known to have diabetes but who were given reasonably high doses of glucocorticoid have their pre- or postoperative blood glucose levels measured, despite evidence that postoperative hyperglycaemia is associated with harm (Frisch et al, 2010). Recently published data show that the prevalence of inpatients on supraphysiological glucocorticoids was over 12%, yet only about 20% of those on glucocorticoids were having their glucose monitored (Swafe et al, 2014).

Pathophysiology of glucocorticoid-induced hyperglycaemia

High-dose glucocorticoids are used predominantly for their anti-inflammatory and immunosuppressive effects. How they work is not completely understood, but it is thought that they act on glucocorticoid receptors in the cytoplasm and nucleus to suppress the expression of pro-inflammatory genes and increase the expression of anti-inflammatory genes, which in combination reduce the production of both arachidonic acid and prostaglandin pathway (Fernandes and McKay, 2013).

Glucocorticoids have several detrimental effects on carbohydrate metabolism. They promote visceral adipose tissue deposition and at the same time enhance lipolysis. They alter the levels of adipose tissue-derived cytokines and acutely increase hepatic glucose production. They also have very complex effects on beta cell function (Saltiel and Kahn, 2001; Lambillotte et al, 2008).

In the longer term they diminish the ability of insulin to initiate intracellular signalling mechanisms in the liver, adipose tissue and muscle and thereby induce insulin resistance, which in turn inhibits glucose uptake into muscles and reduces oxidative phosphorylation (Hollingdal et al, 2008; Petersons et al, 2013).

These effects have the result that, in the very earliest manifestation, is postprandial hyperglycaemia (Schacke et al, 2002). In somebody with a previous diagnosis of diabetes who develops hyperglycaemia as a result of glucocorticoid use, this would be termed glucocorticoid- induced hyperglycaemia. However, if somebody is not previously known to have diabetes but develops hyperglycaemia, this would be termed glucocorticoid-induced diabetes. The post-prandial hyperglycaemia may progress and the hyperglycaemia may just cause a transient rise in blood glucose levels or may result in hyperosmolar hyperglycaemic syndrome. The best predictors of glucocorticoid-induced diabetes are a family history of diabetes or increasing age and previous glucocorticoid use (Clement et al, 2004).

Lack of knowledge?

The vast majority of inpatient care in the UK is delivered by junior doctors. Work looking at levels of junior doctors' knowledge about diabetes, and assessing their levels of confidence in managing the condition in this group, has shown that most junior medical staff lack even a basic grasp of diabetes, and the majority have a poor understanding of its management (George et al, 2011). In addition, it is possible that senior medical staff who routinely prescribe high-dose glucocorticoids, e.g. those working in rheumatology, renal medicine, oncology, haematology, gastroenterology and respiratory medicine, may not focus on the glycaemic effects of this class of drug. It may well be that this combination of junior doctors and senior doctors being unaware of this potential effect of glucocorticoid therapy may lead to glucose not being measured.

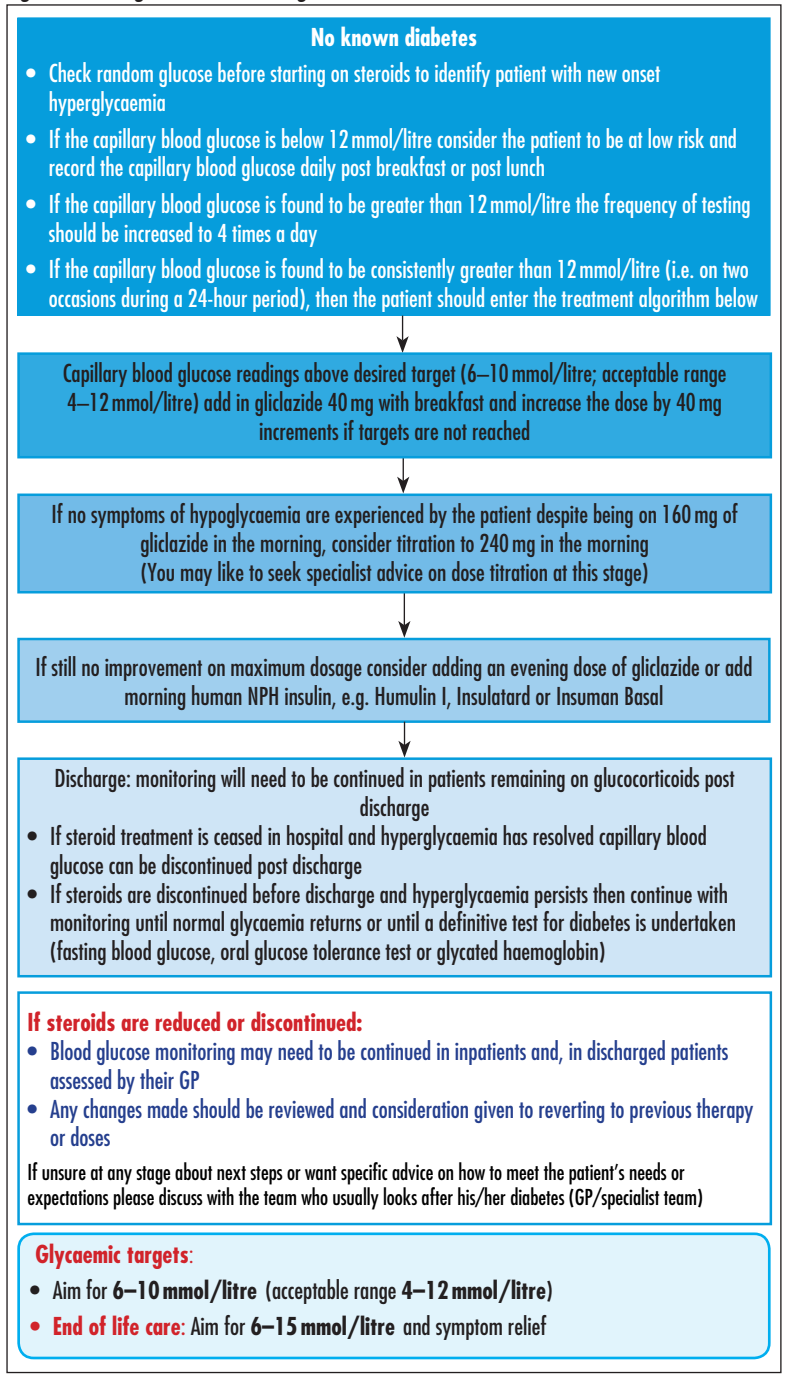
Treatment options

Previous work has shown that hyperglycaemia in medical patients is associated with increased risk of death (Baker et al, 2006). There have previously been attempts to try to find the optimal treatment for steroid-induced hyperglycaemia. The initial management would be prevention – to try to educate the teams who routinely prescribe high-dose glucocorticoids in helping to detect steroid-induced hyperglycaemia early and to initiate treatment when it is first found. In addition, there has been some work looking at a variety of different drugs used to treat this condition, but there is currently no consensus.

Thiazolidinediones work well in this condition and there is a complex interaction between glucocorticoids in the PPAR (peroxisome proliferator-activated receptor) signalling pathway that are often the therapeutic targets for this class of agents (Willi et al, 2002). However, these drugs work very slowly and so may be useful in the outpatient setting. Given the controversy surrounding this class of drugs in terms of their side-effect profile they may not be appropriate for many people. These side effects include an increase in cardiovascular death rates, increased distal forearm fracture rates, increased rates of macular oedema and bladder cancer (Ryan et al, 2006; Nissen and Wolski, 2007; Loke et al, 2009; Ferwana et al, 2013).

Sulphonylureas are widely used, but there is little published evidence for these. The Joint British Diabetes Societies have written a guideline for the management of inpatient steroid-induced hyperglycaemia which is due to be published shortly and will be freely accessible at www.diabetologists-abcd.org.uk/JBDS/JBDS.htm. Several hospitals were invited to submit their guidelines for the management of this condition to the writing group for these guidelines and almost all of them used sulphonylureas first or second line. However, very few of them gave any evidence for their use or references for this. *Figures 1–3* show the pathways for people with

Figure 1. Management of steroid (glucocorticoid)-induced diabetes.



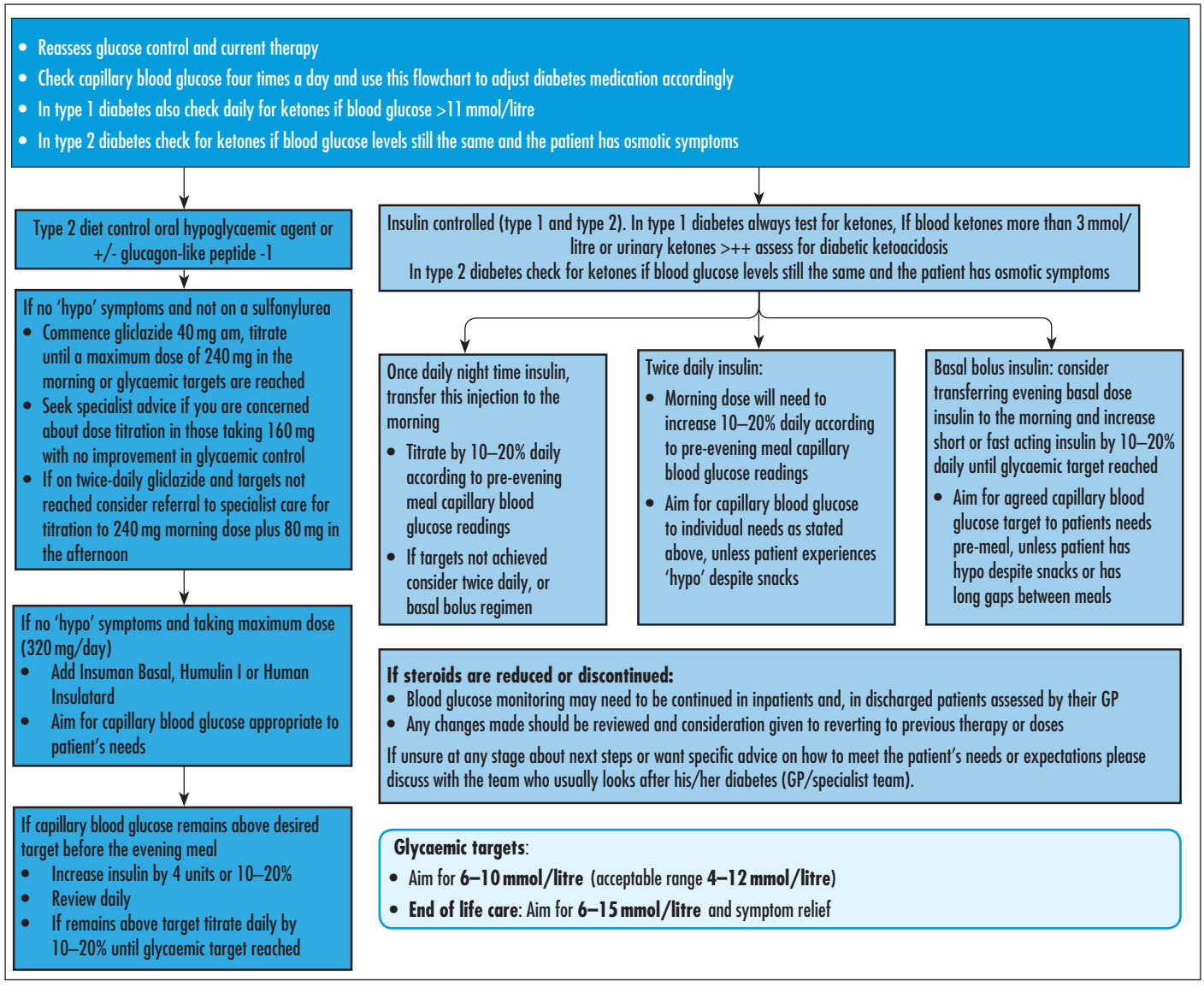
glucocorticoid-induced hyperglycaemia, glucocorticoid-induced diabetes and for the management at the end of life.

Given their mode of action, incretin-based therapies would theoretically work very well in this situation because of their ability to prevent blood glucose rising, rather than lowering blood glucose, but there is very little experience of use of either glucagon-like peptide-1 analogues or dipeptidyl peptidase-4 (DPP-4) inhibitors in this circumstance and there remain some safety concerns about their long-term use (Butler et al, 2013). There are some data for the use of DPP-4 antagonists in hospitalized patients, but very few of these individuals were reported as being on glucocorticoids (Umpierrez et al, 2013).

The best treatment, therefore, is probably insulin and this has previously been recommended in the United States as the drug of choice for glucocorticoid-induced hyperglycaemia (Hirsch and Paauw, 1997). In particular, the use of pre-meal insulin would minimize the effect of the post-prandial rise in blood glucose, although for many people receiving high-dose intravenous or multiple daily doses of oral glucocorticoids, an intravenous insulin infusion may also be appropriate. Difficulties arise because the dose of insulin required would be difficult to predict because individuals have different degrees of insulin resistance and insulin sensitivity. A variable rate intravenous insulin infusion may achieve an acceptable blood glucose concentration quicker than a multiple dose injection regimen and allow some estimate of the total daily dose of insulin that may be required. The further advantages of a variable rate intravenous insulin infusion would allow the appropriate tapering of glucose rates, thus ensuring that glycaemic control is not compromised, while minimizing the risk of hypoglycaemic episodes.

In line with the glucose targets for hospitalized patient in other guidelines, the Joint British Diabetes Societies recommend that the blood glucose level should be

Figure 2. Managing glucose control in people with known diabetes taking once-daily steroids (glucocorticoids).



6–10 mmol/litre with a range of 4–12 mmol/litre being acceptable. Once again, these may be difficult to achieve because of the added metabolic complexity of stress hyperglycaemia, altered nutritional intake and multiple interruptions to medical care while in hospital. The targets for end-of-life care are different (*Figure 3*).

For outpatient use there is the advantage of giving subcutaneous insulin, but the differences with this regimen are that higher prandial doses are required than basal insulin doses when compared with the use of a variable rate intravenous insulin infusion. However, a potential limitation for further recommendation as to which insulin to use is that no work has been done in this situation to compare human insulin to analogue insulin. There are also theoretical risks, because basal insulin will need to be given to prevent hyperglycaemia and to prevent hypoglycaemia by mismatching prandial insulin doses with carbohydrate intake. Close liaison with the specialist diabetes team would be required to ensure that the treatment is appropriate.

The American Diabetes Association has for many years suggested that people who are not known to have diabetes and who receive glucocorticoid therapy should monitor their blood glucose levels regularly (American Diabetes Association, 2014). They went on to suggest that if hyperglycaemia is persistent then basal bolus insulin may be necessary and the glycaemic goals for somebody who was not previously known to have diabetes should be the same as somebody who does have diabetes.

Of course there is almost no evidence for these recommendations, with the American Diabetes Association acknowledging that they are expert opinion only. In addition while there remains a wealth of evidence suggesting that hyperglycaemia is associated with harm, there is very little evidence to show that normalizing hyperglycaemia is associated with benefit (Umpierrez et al, 2002; Bruno et al, 2008; Dhatariya, 2013).

Conclusions

Glucocorticoid-induced hyperglycaemia and glucocorticoid-induced diabetes remain conditions which are associated with harm and can worsen the underlying condition for which the glucocorticoids are being given. The Joint British Diabetes Societies guidelines for the management of this condition in both outpatients and inpatients should help address these issues.

The Joint British Diabetes Societies guideline recommends that regular blood glucose testing be undertaken in all individuals without a previous diagnosis of diabetes who are given doses of glucocorticoids equivalent to a dose of ≥7.5 mg of prednisolone given daily either as an inpatient or as an outpatient, and that appropriate glucose-lowering medications be initiated if hyperglycaemia occurs. In addition, extra monitoring needs to take place in people with an existing diagnosis of diabetes and that appropriate adjustments made in their medication to keep them within their individualized glycaemic target. BJHM

Conflict of interest: Dr K Dhatariya is an author of the glucocorticoid associated hyperglycaemia guideline produced by the Joint British Diabetes Societies.

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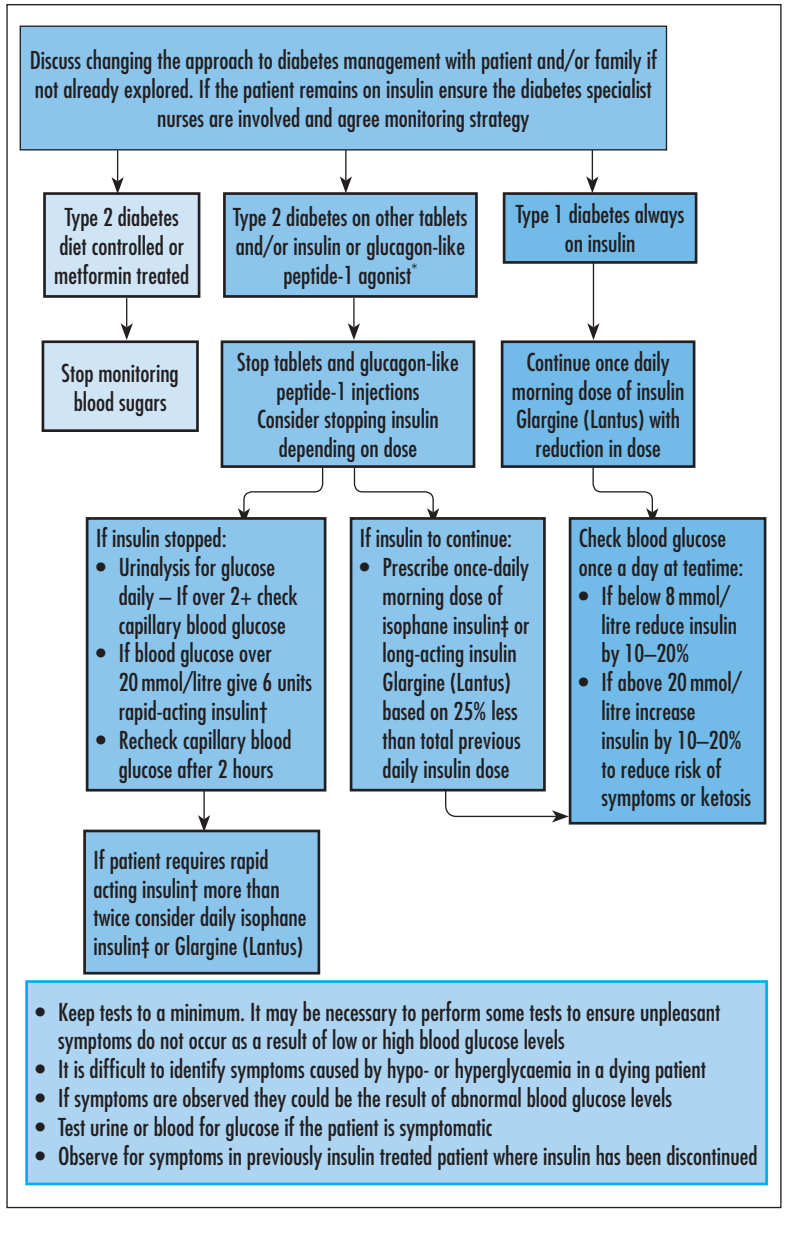
Figure 3. End of life diabetes management. For queries relating to the diabetes flowchart please contact the diabetes specialist nurses. For queries relating to palliative care please contact the palliative care team. *Bydureon (exenatide ER), Byetta (exenatide) / Victoza, (liraglutide), Lyxumia (lixisenatide); †Humalog/Novorapid/Apidra; ‡ Humulin I /Insulatard/Insuman Basal.



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KEY POINTS

- Glucocorticoid use in hospitalized inpatients is common, yet monitoring of blood glucose levels is poor.
- Hyperglycaemia is associated with poor outcomes in this group of patients.
- If a person with a previous diagnosis of diabetes develops hyperglycaemia as a result of glucocorticoid use, this is termed glucocorticoid-induced hyperglycaemia.
- If a person is not previously known to have diabetes but develops hyperglycaemia, this would be termed glucocorticoid-induced diabetes.
- The Joint British Diabetes Societies will shortly produce a guideline that standardizes the management of glucocorticoid-associated hyperglycaemia.