Diabetes and steroids: Storm conditions

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Article points

1. Steroids are often used in the management of long-term conditions, cancer and also end-of-life care.
2. Hyperglycaemia is common in people using steroid therapy. People known to have diabetes should receive advice on how to manage their diabetes when using steroid therapies.
3. Healthcare professionals need to be aware of the impact of steroid use on glycaemic control and introduce glucose monitoring in susceptible individuals.
4. The risk of steroid-induced diabetes is high in specific patient groups.
5. Diabetes screening using HbA_{1c} is recommended prior to using steroid therapy in individuals not previously known to have diabetes.

Key words

- Diabetes
- Steroids
- Steroid-induced hyperglycaemia
- Steroid-induced diabetes

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The use of glucocorticosteroids (steroids) can be problematic in people with diabetes because of their hyperglycaemic effects. These can cause glucose control to be become unsettled and lead to steroid-induced hyperglycaemia. As well as having an effect on people with known diabetes, steroids may also cause hyperglycaemia in people without known diabetes. Steroid-induced hyperglycaemia is a short-term effects of steroids, but it may lead to longer-term steroid-induced diabetes. This article describes the effects of steroid treatment on glucose control and the action of commonly used steroid therapies. It also highlights the patient groups who are most likely to use steroids. It offers guidance on screening and monitoring, and on the use of glucose-lowering therapies to reduce hyperglycaemia in people not previously known to have diabetes, as well in those with an existing diagnosis of diabetes and in those in end-of-life care.

The attainment of good glycaemic control in people with diabetes can be troublesome at times. Add in to the mix the hyperglycaemic effect of glucocorticosteroid (steroid) treatments and glucose control becomes harder to control, and can result in steroid-induced hyperglycaemia. The use of steroids can also have a hyperglycaemic effect in some individuals not previously known to have diabetes. This may be a short-term effect during the course of steroids and the weeks following, or it may result in steroid-induced diabetes.

This article describes the effects of steroid treatment on glucose control and the action of commonly used steroid therapies. It also highlights the patient groups who are most likely to use steroids. It offers guidance on screening and monitoring, and in the use of glucose-lowering therapies to reduce hyperglycaemia in people not previously known to have diabetes, as well in those with an existing diagnosis of diabetes and in those in end-of-life care.

Glucocorticosteroids (steroids)

Synthetic steroids mimic the effect of endogenous steroids produced in the adrenal glands. They reduce inflammation and so are commonly used in people with rheumatoid or neurological conditions, and in those with asthma, chronic obstructive airways or other lung diseases. In addition, they help suppress the immune system so are often part of chemotherapy regimens and are used in transplant patients (Hwang and Weiss, 2014; Joint British Diabetes Societies for Inpatient Care [JBDS-IP], 2014). Steroids can be used in pregnancies with a risk of early delivery as they are used to aid lung maturity of the unborn child (Institute for Quality and Efficiency in Health Care, 2008)

Steroids use can lead to beta cell destruction

(Gittoes et al, 2010) resulting in increased insulin resistance and hyperglycaemia in those with an existing diagnosis of diabetes and in those not previously known to have the condition. The adrenal glands produce cortisol that is equivalent to about 7.5 mg of prednisolone daily (Gittoes et al, 2010). Any doses higher than this will lead to problems with carbohydrate metabolism. Doses of more than 7.5 mg of prednisolone for more than 2 weeks will cause adrenal suppression (Gittoes et al, 2010).

There is widespread use of steroids in the inpatient population, with some studies citing 40–60% of diabetes referrals, due to new-onset diabetes or worsening of type 2 diabetes control (Donihi et al, 2006; Hwang and Weiss, 2014). In the UK, prevalence of steroid use in inpatients varies between 10–30% (JBDS-IP, 2014). The National Diabetes Inpatient Audit identified a figure of 16% in their snapshot audit of 2013 (Heath and Social Care Information Centre, 2014). In the outpatient setting, 40% of steroid use is said to be in people with respiratory problems.

Both the duration of time on steroid therapy and the potency of the specific drug used contribute to the risk of the progression on to steroid-induced diabetes. It is clear that some individuals are more at risk of developing hyperglycaemia when steroids are used (see *Box 1*).

Box 1. Individuals at greater risk of hyperglycaemia following steroid treatment (Joint British Diabetes Societies for Inpatient Care, 2014).

- Pre-existing type 1 or type 2 diabetes.
- People at increased risk of diabetes (e.g. obesity, family history of diabetes, previous gestational diabetes, ethnic minorities, polycystic ovarian syndrome).
- Impaired fasting glucose or impaired glucose tolerance, HbA_{1c} 42–47 mmol/mol (6–6.5%).
- People previously hyperglycaemic with steroid therapy.
- Those identified to be at risk utilising the University of Leicester/Diabetes UK diabetes risk calculator (riskscore.diabetes.org.uk).

Table 1. Steroid dose equivalents (Joint British Diabetes Societies for Inpatient Care, 2014).

Steroid	Potency (equivalent doses)	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	26–54

Steroids can be given orally or intravenously and in variable doses; the most common regimen used is a single dose or a short-course of oral steroid therapy, such as prednisolone, in the morning. These doses are often given for short periods of time and the dose is reduced gradually over several weeks. People with cancer may be treated with steroids as part of their chemotherapy regimen, and the duration and dosage in these individuals depends on the particular cancer treatment regimen.

In susceptible individuals, the use of once-daily prednisolone often leads in a rise in blood glucose by late morning that continues into the evening (JBDS-IP, 2014). Overnight, the blood glucose generally reduces and is usually back to baseline levels by the next morning. Therefore, diabetes treatment should be tailored to treating the hyperglycaemia, while avoiding nocturnal and early morning hypoglycaemia. In pregnancy and other situations, a single dose or short course of steroid may be given. Many hospital inpatients will receive multiple daily doses of steroids. The potency and duration of action varies for each drug (*Table 1*).

It is predicted that, in most individuals, blood glucose levels rise approximately 4–8 hours following oral steroids. The effect occurs sooner following the administration of intravenous steroids (JBDS-IP, 2014). Regular capillary blood glucose (CBG) monitoring is

essential to guiding the appropriate diabetes treatment. In some cases, glucose levels can improve to pre-steroid levels 24 hours after intravenous steroids are discontinued, such as when used in pregnancy. If oral steroids are titrated down over several weeks, as is common practice, it is important that diabetes treatment is also reduced in tandem with steroid reduction as the glucose levels may lower in a dose dependent fashion. This may not always happen, particularly in those with pre-existing undiagnosed diabetes.

Steroids and side effects (British National Formulary, 2016)

The risk of side effects when using steroid therapies will depend on the particular drug used, the dose given and frequency and the duration of treatment.

Common side effects of oral steroids include:

- Increased appetite.
- Gastric ulceration.
- Acne.
- Rapid mood swings.
- Bruising to skin.
- Delayed wound healing.
- Osteoporosis.
- Hypertension.
- Cushing-like appearance.
- Hyperglycaemia.
- Reduced growth in children.

Box 2. Frequency of blood glucose testing after starting steroid treatment (Joint British Diabetes Societies for Inpatient Care, 2014).

Monitoring in those with a pre-existing diabetes diagnosis (steroid-induced hyperglycaemia).

- Test four times a day, before or after meals, and before bed, irrespective of background diabetes control.
- If the capillary glucose is found to be consistently greater than 12 mmol/L on two occasions during 24 hours, then the patient should enter the treatment algorithm (see Algorithm 1: Managing steroids in people with known diabetes. Page 131).

Monitoring in those without a previous diabetes diagnosis (steroid-induced diabetes).

- Monitoring should occur at least once daily, preferably prior to lunch or evening meal, or alternatively 1–2 hours post lunch or evening meal. If the initial blood glucose is less than 12 mmol/L, continue to test once prior to or following lunch or evening meal.
- If a subsequent capillary blood glucose is found to be greater than 12 mmol/L, then the frequency of testing should be increased to four times daily (before meals and before bed).
- If the capillary glucose is found to be consistently greater than 12 mmol/L (i.e. on two occasions during 24 hours), then the patient should enter the treatment algorithm (see Algorithm 2: Steroid-induced diabetes. Page 132).

Glucose targets

For the diabetes inpatient population, blood glucose targets of 6–10 mmol/L are recommended, accepting a range of 4–12 mmol/L (JBDS, 2013). However, these targets would need to be relaxed in individuals where "tight" control would lead to an unacceptable risk of hypoglycaemia, such as in the frail, older person, those with dementia or at risk of falling, and those in end-of-life care. Individualised targets for community-based individuals would need to be determined by the GP or specialist commencing the steroid treatment.

Monitoring

It is recognised that a person without a previous diabetes diagnosis is often referred late to hospital or community diabetes teams and often when steroid therapy has already resulted in hyperglycaemia (JBDS-IP, 2014). The JBDS-IP group gives consensus guidance on management and treatment pathways. They recommend that an HbA_{1c} test be taken where possible prior to starting steroid treatments. Once steroids are prescribed, it is recommended that blood glucose monitoring be commenced, with the frequency depending on whether the individual has steroid-induced hyperglycaemia or steroid-induced diabetes (*Box 2*).

Treatment pathways for people with known diabetes and steroid-induced diabetes

The foundation of all diabetes treatment relies on effective patient education. People with diabetes should be made aware that steroid treatment could increase blood glucose levels and know how to manage this. A patient leaflet for people

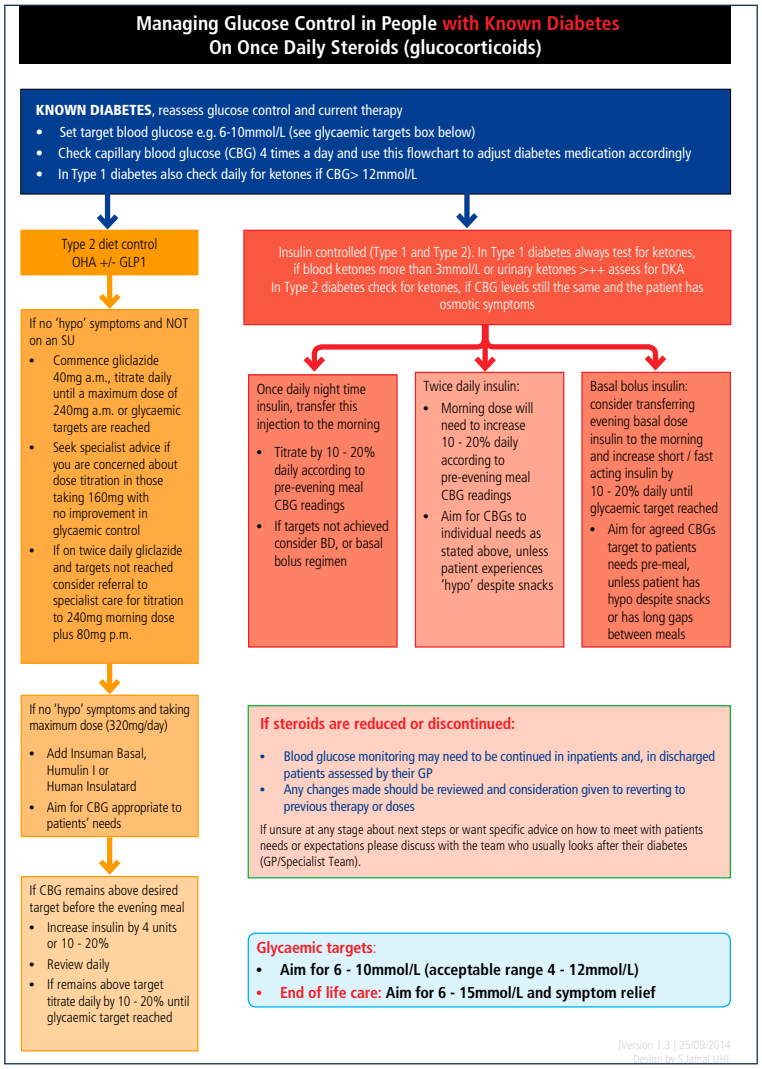
with type 2 diabetes is available for download (Training, Research and Education for Nurses in Diabetes-UK [TREND-UK], 2015). People without a previous diabetes diagnosis and who experience hyperglycaemia should be made aware that any rises in blood glucose may be temporary, or may result in a permanent diagnosis of steroid-induced diabetes. Lifestyle management remains at the core of all treatment; however, diabetes oral or insulin therapies may need to be instigated or increased.

Once-daily steroid therapy

The treatment of choice of diabetes oral therapy is a sulphonylurea. They promote insulin release from the pancreatic beta cells and have a fast mode of action. The most commonly used sulphonylurea is gliclazide, with a staring dose of 40 mg with breakfast in the newly diagnosed on once-daily prednisolone. This dose can gradually be titrated to 240 mg in the morning, providing there is no hypoglycaemia. If needed, an additional evening dose could also given of up to 80 mg, with the maximum dose being 320 mg per day (JBDS-IP, 2014). Other agents are not recommended for various reasons relating to pharmacokinetics (*Table 2*).

Table 2 . Guidance for the use of diabetes oral therapies (Joint British Diabetes Societies for Inpatient Care, 2014).

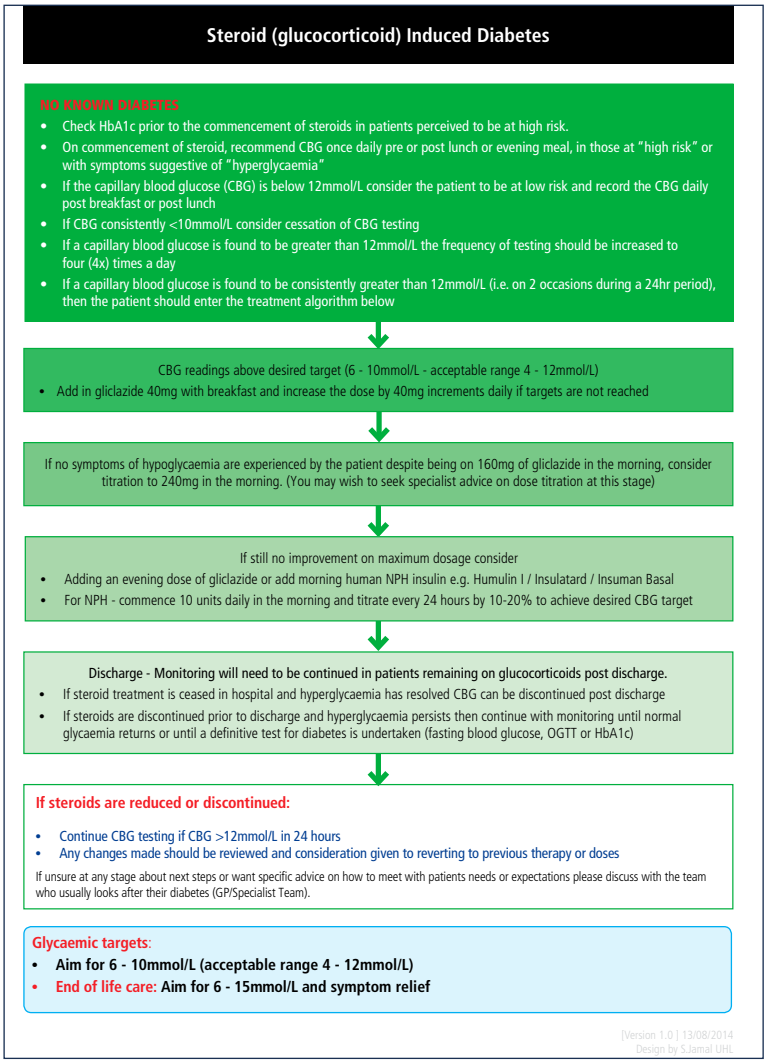
Metformin	Metformin should be gradually titrated and therefore is unlikely to achieve the fast reduction in blood glucose that is required.
Glitazones (e.g pioglitazone)	Pioglitazone takes several weeks to reach maximum effect, so reduction in hyperglycaemia would be slow. Cannot be used in those with heart failure and fluid retention or those with bladder cancer. There is a risk of bone fracture.
Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide receptor agonists	No evidence to support the use in those using steroids.
Sodium-glucose co-transporter 2 inhibitors	No evidence to support the use in those using steroids



Algorithm 1. Treatment for people with known diabetes (Joint British Diabetes Societies for Inpatient Care, 2014).

Insulin therapy

In the insulin naïve person, if glycaemic control is not optimal despite oral treatment or if the individual has diabetes symptoms, the morning administration of basal human insulin is recommended, with a starting dose of 10 units. A daily titration of 10–20% is recommended, as long as there are no episodes of hypoglycaemia



Algorithm 2. Steroid-induced diabetes (Joint British Diabetes Societies for Inpatient Care, 2014).

and until glycaemic targets are achieved (Dashora and Taylor, 2004; JBDS-IP, 2014).

Multiple daily doses of steroids

Oral therapies are not likely to be effective in these individuals, so insulin will be the mainstay of treatment. A basal regimen, twice daily or multiple-dose regimen will probably be needed to reduce hyperglycaemia in these patients. In acutely unwell patients, the use of an intravenous insulin infusion may be required.

Special groups

Steroids used during pregnancy

Insulin is the mainstay of diabetes management in pregnancy. Doses may have to be increased significantly by 40% (JBDS-IP, 2014; NICE, 2015) or more at the time of the first steroid injection to reduce hyperglycaemia and resulting risks of macrosomia to the fetus, for a period of 24–72 hours. The use of an intravenous insulin infusion may be required to combat the hyperglycaemia resulting from steroid use. The diabetes team should always be involved in the management of these individuals.

Steroids used in end-of-life care

The aim of treatment at end of life is to prevent hypoglycaemia and ensure symptomatic relief, rather than aim for tight glycaemic control. Steroids, such as dexamethasone or prednisolone, are frequently used in end-of-life care to reduce symptoms relating to the individual's presiding condition. The impact of steroids on glucose control can cause, in addition, hyperglycaemic symptoms and, if there is over-treatment with glucose lowering therapies, hypoglycaemia. Therefore, the treatment pathways offered by the JBDS-IP group recommend reduced glycaemic targets; blood glucose readings of 6–15 mmol/L to reduce the risk of unpleasant diabetes symptoms (Diabetes UK, 2013).

Steroid reduction and cessation

It is important that in all individuals, whether managed by oral or insulin therapies, regular monitoring is in place when steroids are reduced or stopped. This will identify the risk of hypoglycaemia and aid diabetes treatment plans.

Follow-up plans

People who have commenced steroid therapies in hospital should be discharged with a clear management plan for follow up.

Pre-existing diabetes

Those with a pre-existing diabetes diagnosis should be aware that diabetes treatment should be reduced in tandem with any reduction in steroid therapy. They should continue to monitor blood glucose and get advice regarding their diabetes management. JBDS-IP gives clear guidance on the amount of blood glucose testing and glucose targets required in these individuals. Monitoring and screening for those at risk of steroid-induced

Box 3. Follow-up reviews in those at risk of steroid-induced diabetes (Joint British Diabetes Societies for Inpatient Care, 2014).

Steroids commenced and patient discharged

- Standard education for patient and carer.
- Blood glucose testing once daily (pre- or post-lunch or evening meal).
- If blood glucose readings greater than 12 mmol/L, increase frequency of testing to four times daily.
- If two consecutive blood glucose readings greater than 12 mmol/L in a 24 hour period, follow algorithm for management of steroid-induced diabetes (Algorithm 2).

Patient discharged on decreasing dose of steroid above 5 mg once daily

- Standard education for patient and carer, including advice on hypoglycaemia.
- Continue capillary blood glucose (CBG) monitoring until blood glucose normalises (4–7 mmol/L).
- Review by agreed individual (for example, GP, Diabetologist or DSN) at an appropriate juncture to consider down-titration of anti-hyperglycaemic therapy.

Patient discharged following steroid cessation

- If hyperglycaemia persists
  - -CBG testing until return to normoglycaemia (4–7 mmol/L) **OR** until a definitive diagnosis of diabetes is given.
  - -If hyperglycaemia resolved, stop CBG testing and arrange definitive test for diabetes at 3 months.

diabetes is shown in *Box 3*.

If patients are commenced on steroids in the outpatient or GP setting, it is advised that blood glucose monitoring be commenced and a blood glucose meter issued.

Screening for diabetes

An HbA_{1c} reading should be taken three months after the steroids are discontinued. However, if there are indications that a confirmation of diabetes diagnosis is required before that, then a fasting glucose or oral glucose tolerance test may be appropriate, in line with local or national guidance.

Summary

Managing diabetes can be difficult and turbulent at times; the addition of steroid treatment may lead to "storm conditions" in the management of diabetes. It is important that healthcare professionals and people either living with diabetes or those regularly taking steroid therapies without an existing diabetes diagnosis are aware of the risk of hyperglycaemia.

There are no existing policies relating to the management of either steroid-induced hyperglycaemia or steroid-induced diabetes, but consensus guidance is available in the UK (JBDS-IP, 2014). An audit will be needed to ascertain whether the guidance is effective and further investigation into treatment pathways are required for those people on more than once-daily steroids. ■

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