Terminology

- **Steroid-induced diabetes**. Develop diabetes in relation to steroid therapy without a previous diagnosis of diabetes.
- **Steroid-induced hyperglycaemia**. A rise in blood glucose levels in response to steroid treatment, including those with pre-existing diabetes who suffer a deterioration in glycaemic control.

What and why

- Glucocorticoids (steroids) mimic the action of cortisol, the endogenous corticosteroid produced in the adrenal cortex. Mineralocorticoids (aldosterone *in vivo*) act via the kidneys to influence electrolyte balance.
- Steroids exert a powerful effect on carbohydrate metabolism, largely by increasing insulin resistance and facilitating hepatic glucose production. They therefore predispose to hyperglycaemia and diabetes.
- The mechanism of action of steroids means that glucose levels will typically rise 4–8 hours after taking oral steroids. Hyperglycaemia induced by steroids mainly produces rises in post-prandial blood glucose levels, rather than fasting blood glucose levels.[1]
- Prednisolone is the most commonly used steroid in primary care, accounting for over 90% of cases of steroid usage in the UK. Respiratory conditions are responsible for around 40% of cases of steroid use within the community.[2]
- A meta-analysis of studies in individuals without diabetes treated with systemic steroids found that the rates of steroid-induced hyperglycaemia and steroid-induced diabetes were 32.3% and 18.6%, respectively.[3]
- Steroid-induced diabetes may frequently go undiagnosed.

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Citation: Morris D (2022) How to diagnose and manage steroid-induced diabetes and hyperglycaemia. *Diabetes & Primary Care* **24**: 143–5

Use of glucocorticoids in primary care

Glucocorticoids are used for their anti-inflammatory and immunosuppressant activity (see conditions below). Whilst the majority of steroid courses are of short duration (e.g. rescue therapy for acute exacerbations of asthma and COPD), longer courses (e.g. for polymyalgia rheumatica) require greater surveillance and care, with dose tapering to avoid consequences of adrenal suppression. Around 22% of steroid use continues beyond 6 months.[2]

- Respiratory conditions (e.g. asthma, COPD)
- Polymyalgia rheumatica (and giant cell arteritis)
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Myasthenia gravis
- Sarcoidosis
- Autoimmune renal disease
- Inflammatory bowel disease
- Inflammatory and autoimmune skin conditions
- Allergic reactions
- Post-transplant treatment regimens
- Addison's disease
- End-of-life care

Equivalent doses of glucocorticoids (based on anti-inflammatory activity)[2]

Steroid	Equivalent doses (potency) (mg)	Half-life (duration of action) (hours)
Prednisolone	5	16–36
Hydrocortisone	20	8
Dexamethasone	0.75	36–54
Methylprednisolone	4	18–40
Betamethasone	0.75	26–54

Box A. Risk factors for steroid-induced diabetes[2,3]

- Dose, potency and duration of steroid therapy
- High BMI
- Increasing age
- Family history of type 2 diabetes
- Ethnicity – South-east Asian, Afro-Caribbean, Chinese
- Impaired glucose regulation (pre-diabetes, non-diabetic hyperglycaemia): HbA_{1c} 42–47 mmol/mol
- Previous history of gestational diabetes or polycystic ovarian syndrome
- Previous history of steroid-induced hyperglycaemia

Who should be screened for steroid-induced hyperglycaemia?

- Individuals at high risk (see above) taking more than a brief course of oral steroids.
- Supraphysiological doses of steroid include, for example, prednisolone ≥5 mg daily.
- Higher doses, greater potency and longer duration of use increase risk of steroid-induced diabetes.[2,4]

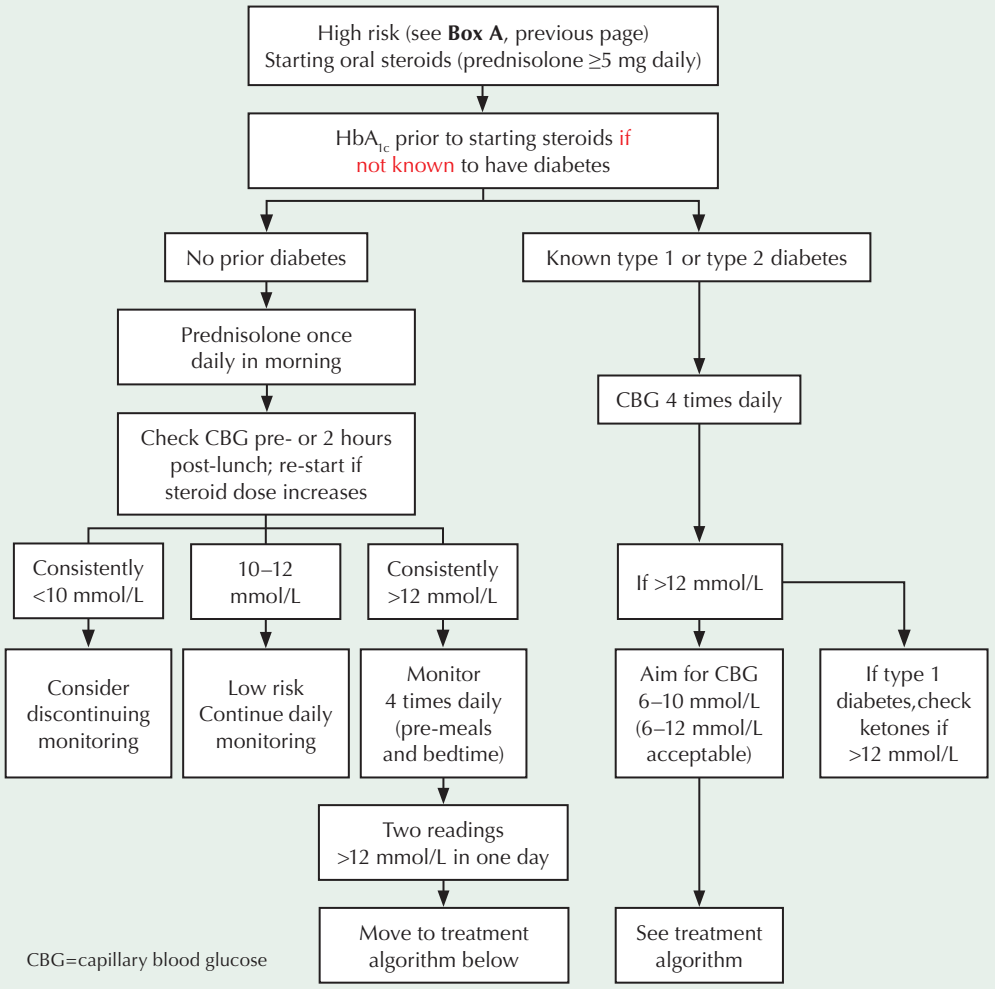
Why is steroid-induced hyperglycaemia important?

- Hyperglycaemia can induce symptoms of thirst, polyuria, weight loss and fatigue.
- Risk of progression to hyperglycaemic hyperosmolar state (HHS) or diabetic ketoacidosis (DKA).
- Increased risk of infection.
- Steroid-induced diabetes increases risk of microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (cardiovascular) complications.

Important side-effects from use of steroids

- Diabetes
- Hypertension
- Osteoporosis
- Muscle wasting
- Weight gain
- Cushing's syndrome
- Acne, skin thinning, striae
- Dyspepsia, peptic ulceration
- Candidiasis
- Hypothalamic–pituitary–adrenal suppression
- Mood disturbance
- Increased susceptibility to infection (risk of severe chickenpox, measles)

Glucose monitoring and targets in people receiving oral steroid therapy[3]

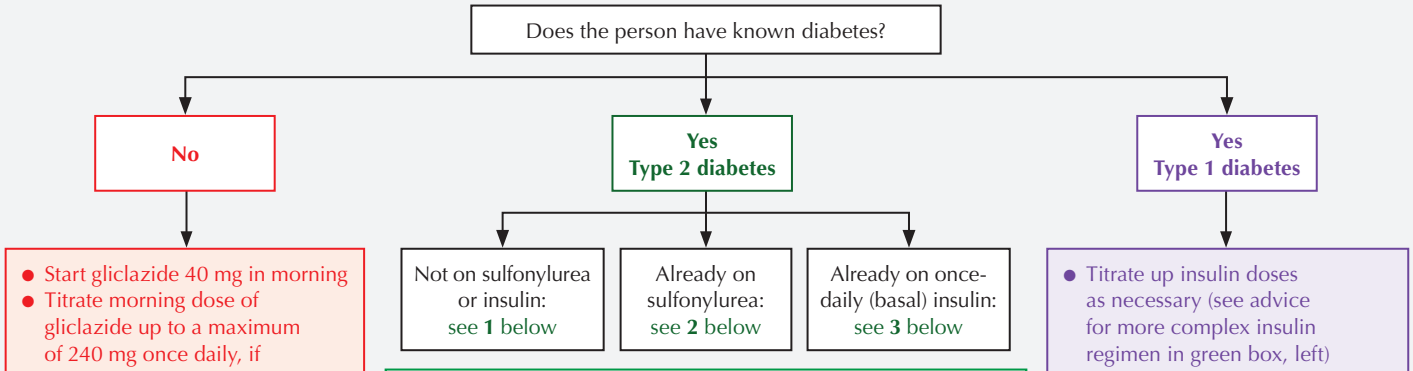


CBG=capillary blood glucose

For prednisolone, an intermediate-acting glucocorticoid, taken once daily in the morning, the rise in glucose levels will be most evident from lunchtime through to the evening, with glucose levels falling overnight. For dexamethasone, with a longer half-life, steroid-induced hyperglycaemia will persist throughout 24 hours, with less of a decline overnight. Glucose levels can rise rapidly during steroid therapy, so capillary blood glucose (CBG) should be used for monitoring and venous blood glucose levels for diagnosis, rather than HbA_{1c}.

Diagnosis steroid-induced diabetes:
Laboratory venous glucose levels ≥11.1 mmol/L
(If asymptomatic, re-check to confirm diagnosis)

Managing steroid-induced hyperglycaemia



- Start gliclazide 40 mg in morning
- Titrate morning dose of gliclazide up to a maximum of 240 mg once daily, if necessary to achieve glycaemic target (see **Box B**, right)
- If glycaemic control not achieved with gliclazide, initiate or refer for insulin therapy

- Titrate up insulin doses as necessary (see advice for more complex insulin regimen in green box, left)

1. If not on sulfonylurea (SU) or insulin:
- Start gliclazide 40 mg in morning
- Titrate morning dose of gliclazide up to a maximum of 240 mg once daily, if necessary to achieve glycaemic target
- If necessary, add evening dose of 80 mg gliclazide or add morning dose of human NPH insulin

2. If already on SU:
- Titrate up dose of SU to maximum
- If on maximum dose of SU, consider adding human NPH insulin

3. If already taking once-daily (basal) insulin:
- Switch evening basal insulin to morning
- Titrate up dose of basal insulin to achieve glycaemic target
- If glycaemic targets not achieved, consider twice-daily biphasic (mixed) insulin or basal–bolus insulin regimen

If already on a more complex insulin regimen:
- Morning dose of a twice-daily biphasic insulin can be titrated up
- If twice-daily biphasic insulin insufficient to achieve glycaemic control, consider basal–bolus insulin regimen
- If on basal–bolus regimen, consider switching basal insulin to morning and titrating up rapid-acting insulins, as necessary

Box B
- **Flowchart appropriate for once-daily morning dose of prednisolone**
- Target glucose levels: 6–10 mmol/L ideal; 6–12 mmol/L acceptable; 6–15 mmol/L end-of-life care (individualise, as necessary)
- Human NPH insulin=Humulin I, Insulatard, Insuman Basal
- At any stage discuss with specialist diabetes team if concerns or problems
- Flowchart not appropriate for people who have COVID-19 and are taking dexamethasone

Adapted from JBDS-IP (2022).[2]

Treatments for hyperglycaemia induced by steroids

There is little robust evidence to direct management of people with hyperglycaemia related to steroid use.

CBG readings guide management, not HbA_{1c}. For a once-daily morning dose of prednisolone, the challenge is to control hyperglycaemia from late morning to evening, whilst minimising the risk of nocturnal hypoglycaemia.

Lifestyle

- Reinforce the importance of a healthy lifestyle.
- Encourage avoidance of sugary foods and drinks, and promote consumption of wholemeal, high-fibre, starchy carbohydrates (that cause a slow rise in blood glucose levels).

Sulfonylureas and meglitinides[1,2]

- Sulfonylureas (e.g. gliclazide, glipizide, glimepiride) are first-choice oral treatment.
- Impact on blood-glucose lowering is immediate and post-prandial hyperglycaemia is improved.
- For introduction and titration of gliclazide, see **Managing steroid-induced hyperglycaemia** algorithm (previous page).
- For higher doses of prednisolone, starting and titration doses may be increased.
- Warn people about the risk of hypoglycaemia, how to identify this and how to manage it.
- The meglitinide repaglinide is an alternative option, with quicker onset and shorter duration of action than SUs.
  - Give with lunch and evening meal to specifically target the post-prandial hyperglycaemia induced by steroids.[3]

Other non-insulin therapies[1,2,5]

- If SU at maximum dose, other agents (used in type 2 diabetes) may be uptitrated or added to achieve target glucose levels (evidence base is limited in this situation).
- Metformin can be added (or dose uptitrated to 1 g twice daily in those with pre-existing type 2 diabetes) provided renal function is satisfactory and gastrointestinal symptoms are tolerated. Slow onset of action.
- Pioglitazone, in the absence of heart failure or left ventricular dysfunction, fracture risk and unexplained haematuria, may be added. Slow onset of action; weak evidence base.
- The evidence for use of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors in steroid-induced hyperglycaemia is limited.

Insulin[2,3,5]

- If glucose targets are not reached on maximum doses of SU (or meglitinide), with or without the use of other glucose-lowering agents, consider insulin.
- If CBG levels are high, then insulin may be the best initial option. Insulin use is increasingly likely the higher the dose and potency of the steroid.
- Insulin has an immediate onset of action.
- Education around blood glucose monitoring, adjustment of insulin dose, recognition and management of hypoglycaemia, advice on injection technique and sharps disposal, and discussion of insurance and driving regulations will be required. Refer if necessary to the diabetes specialist nurse/community diabetes specialist team.
- Human NPH (isophane) insulin (Humulin I, Insulatard, Insuman Basal) administered once daily in the morning is the insulin of choice. The activity of an intermediate-acting insulin matches the hyperglycaemic profile induced by a morning dose of oral steroid. Used in this manner, the risk of nocturnal hypoglycaemia is reduced.
- Starting dose of NPH insulin is usually 10 units. Subsequently, the insulin dose can be increased (or decreased) in 10–20% increments according to pre-evening meal CBG.
- For intensification of insulin regimens, see **Managing steroid-induced hyperglycaemia**.

More complex steroid regimens[2,3,5]

- If multiple daily doses of prednisolone (or other shorter-acting steroid), then blood glucose levels are likely to be elevated throughout a 24-hour period. Commence gliclazide 40 mg (or 80 mg) twice daily (depending on steroid dose) titrating up to 160 mg twice daily, as necessary. Other oral therapies are unlikely to help quickly.
- Twice-daily NPH insulin or a single morning dose of a longer-acting basal insulin analogue could be chosen (e.g. insulin glargine, insulin detemir).
- More complex insulin regimens can be introduced, as necessary, to achieve satisfactory glycaemic control.

Diabetes already treated with insulin[2]

- If a person with type 2 diabetes is already maintained on a once-daily basal insulin then, in the case of a once-daily oral steroid, this should be switched to a morning injection (if injected in the evening) and titrated upward in increments of 10–20% based on an afternoon glucose level.
- When a basal insulin proves insufficient, consider moving to a more complex insulin regimen (see **Managing steroid-induced hyperglycaemia**).
- Involve the diabetes specialist team as necessary.

Steroid treatment in end-of-life care[2,6]

- Steroids are frequently used in palliative care, providing symptomatic relief of nausea, anorexia, weight loss and fatigue.
- High-dose dexamethasone is used for primary or metastatic brain tumours. Risk of steroid-induced diabetes or worsening of hyperglycaemia in existing diabetes is particularly high in this situation.
- CBG in the range 6–15 mmol/L may be a suitable target, although individual circumstances must always be prioritised. Aim to avoid symptomatic hyperglycaemia (including the possibilities of DKA or HHS), whilst minimising the risk of hypoglycaemia.
- Treatment strategies are similar to those outlined earlier. Algorithms for steroid-induced hyperglycaemia and advice on monitoring and treatment withdrawal are included in the Diabetes UK *End of Life Guidance* document.[6]

Reducing steroid therapy[2]

- Individuals receiving high dose steroids for 2 weeks or less can safely undergo abrupt cessation of therapy.
- For steroid courses longer than 2 weeks, the dose must be tapered slowly to counter the risks of adrenal suppression.
- When reducing corticosteroid dose, a corresponding down-titration of doses of insulin and sulfonylurea will be necessary to avoid hypoglycaemia. Careful monitoring of CBG levels during this period is essential to achieve this safely. It may take a few days before the reduction in steroid dose translates into reduced blood glucose levels.
- JBDS suggests that for a weekly 5 mg reduction in prednisolone from a 20 mg daily regimen, a 20–25% reduction in insulin dose or a 40 mg reduction in gliclazide is appropriate.
- Following cessation of steroid therapy (and corresponding reduction in glucose-lowering medication) monitoring may need to be continued if CBG >12 mmol/L. Some people may have had unrecognised type 2 diabetes prior to steroid treatment and will need continued treatment.
- For people without pre-existing diabetes, HbA_{1c} should be measured 3 months following steroid therapy as a definitive test for diabetes status. If diabetes is suspected earlier than this, a fasting blood glucose test would be appropriate.
- Even if normoglycaemia (without medication) is achieved, retinopathy and other microvascular complications may occur/progress.[7] The recommended coding is "Diabetes in remission" to ensure surveillance continues.

Dexamethasone treatment in severe COVID-19 infection

- Dexamethasone can reduce mortality in severe COVID-19 infection and is usually given in hospital settings.[8]
- The risks of DKA and HHS are increased.
- The aim is to keep CBG <10 mmol/L.
- SUs are not recommended. Metformin (risk of lactic acidosis) and SGLT2 inhibitors (risk of DKA) should be discontinued. Insulin is the treatment of choice.
- Glucose levels may fall quickly following steroid cessation. Careful glucose monitoring is required, with appropriate reduction in insulin dose. Shared management with specialist teams is usual.

Resources

- *Steroid induced diabetes: Dietary advice* patient leaflet: bit.ly/3zCmgrN
- *Steroid-induced diabetes* patient information from Diabetes UK: bit.ly/3JbP9hJ

References

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[2]Joint British Diabetes Societies for inpatient care (2022) *Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy*. bit.ly/3vkPQ2l

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[4]Clore JN, Thurby-Hay L (2009) *Endocr Pract* **15**: 469–74

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[6]Diabetes UK (2021) *End of life guidance for diabetes care* (4th edition). bit.ly/3O2H9QT

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[8]Recovery Collaborative Group; Horby P et al (2021) *N Engl J Med* **384**: 693–704