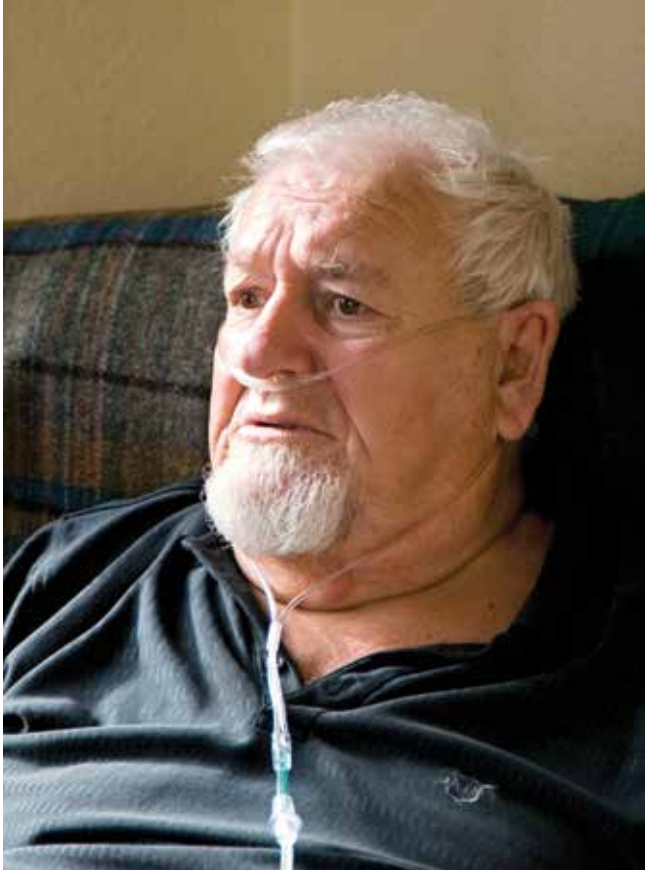
Glucocorticoid-induced hyperglycaemia

Common but easily missed

TIEN F. LEE BEng, MSc, BM BS
LI M. NG MB BS
STEPHEN N. STRANKS MB BS, FRACP



Screening for glucocorticoid-induced hyperglycaemia is important because hyperglycaemia is associated with reduced quality of life, increased rates of infections, poor wound healing, falls and increased long-term risks of macrovascular complications. Management includes general lifestyle modifications, consideration of oral hypoglycaemic agents and/or insulin, and cardiovascular risk factor management.

Glucocorticoids such as prednisolone and dexamethasone are commonly used for a variety of chronic diseases including chronic obstructive pulmonary disease and inflammatory rheumatological disease. In hospitalised patients receiving glucocorticoids, diabetes incidence rates of 64 to 71% have been reported.[1] Glucocorticoids are by far the most common cause of drug-induced diabetes, and the prevalence may be underestimated because of measurement of fasting plasma glucose levels as a screening test. The odds ratio for the development of new-onset diabetes in patients taking glucocorticoids has been reported to be 1.36 to 2.31.[1]

Key points

- **Glucocorticoid-induced hyperglycaemia is common and the diagnosis is often missed.**
- **Patients should ideally be screened for pre-existing diabetes before commencing glucocorticoids.**
- **Blood glucose levels tend to rise postprandially, particularly in the afternoon and evening, in patients taking a morning dose of prednisolone (e.g. in people with chronic obstructive pulmonary disease). Fasting blood glucose levels may be affected in patients taking high doses or long-acting glucocorticoids.**
- **Screening for glucocorticoid-induced hyperglycaemia should be performed by:**
  - **measuring plasma glucose levels two hours after lunch or dinner (≥11.1 mmol/L)**
  - **measuring random evening plasma glucose levels (≥11.1 mmol/L)**
  - **performing a standardised oral glucose tolerance test.**
- **Asymptomatic patients require two abnormal plasma glucose levels for a definitive diagnosis.**
- **Measurement of fasting plasma glucose levels has poor sensitivity for diagnosing glucocorticoid-induced hyperglycaemia.**
- **Management of people with glucocorticoid-induced hyperglycaemia should include general lifestyle modifications, consideration of oral hypoglycaemic agents and/or insulin, and cardiovascular risk factor management.**

ENDOCRINOLOGY TODAY 2014; 3(2): 26-30

Dr Lee is an Endocrinology Advanced Trainee at the Southern Adelaide Diabetes and Endocrine Services, Flinders Medical Centre, Adelaide. Dr Ng is a GP Registrar at the Sturt Fleurieu Education and Training, Adelaide.
Associate Professor Stranks is the Director of Southern Adelaide Diabetes and Endocrine Services and Associate Professor at Flinders University of South Australia, Adelaide, SA.

General practitioners have a unique position in providing continuity of care and can play a major role in screening for glucocorticoid-induced hyperglycaemia. Management of patients with glucocorticoid-induced hyperglycaemia may require a referral to an endocrinologist or physician.

Who to screen?

Screening for glucocorticoid-induced hyperglycaemia is important because hyperglycaemia is associated with reduced quality of life, increased rates of infections, poor wound healing, falls and increased long-term risks of macrovascular complications. Patients taking high doses of glucocorticoids or with pre-existing diabetes may also present acutely with diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome.

Patients who are elderly, those with risk factors for type 2 diabetes (obesity, positive family history, previous gestational diabetes) and those who are likely to receive a prolonged course or high doses of glucocorticoid therapy are at greatest risk and should be screened for glucocorticoid-induced hyperglycaemia. Patients receiving intermittent but recurring glucocorticoid therapy (e.g. in patients receiving high doses of glucocorticoid therapy as part of a chemotherapy protocol) also warrant screening. Young patients with no risk factors for diabetes or comorbid metabolic risk factors receiving only a short course (<three weeks) of glucocorticoids may not require screening; however, there are currently no consensus guidelines on this.

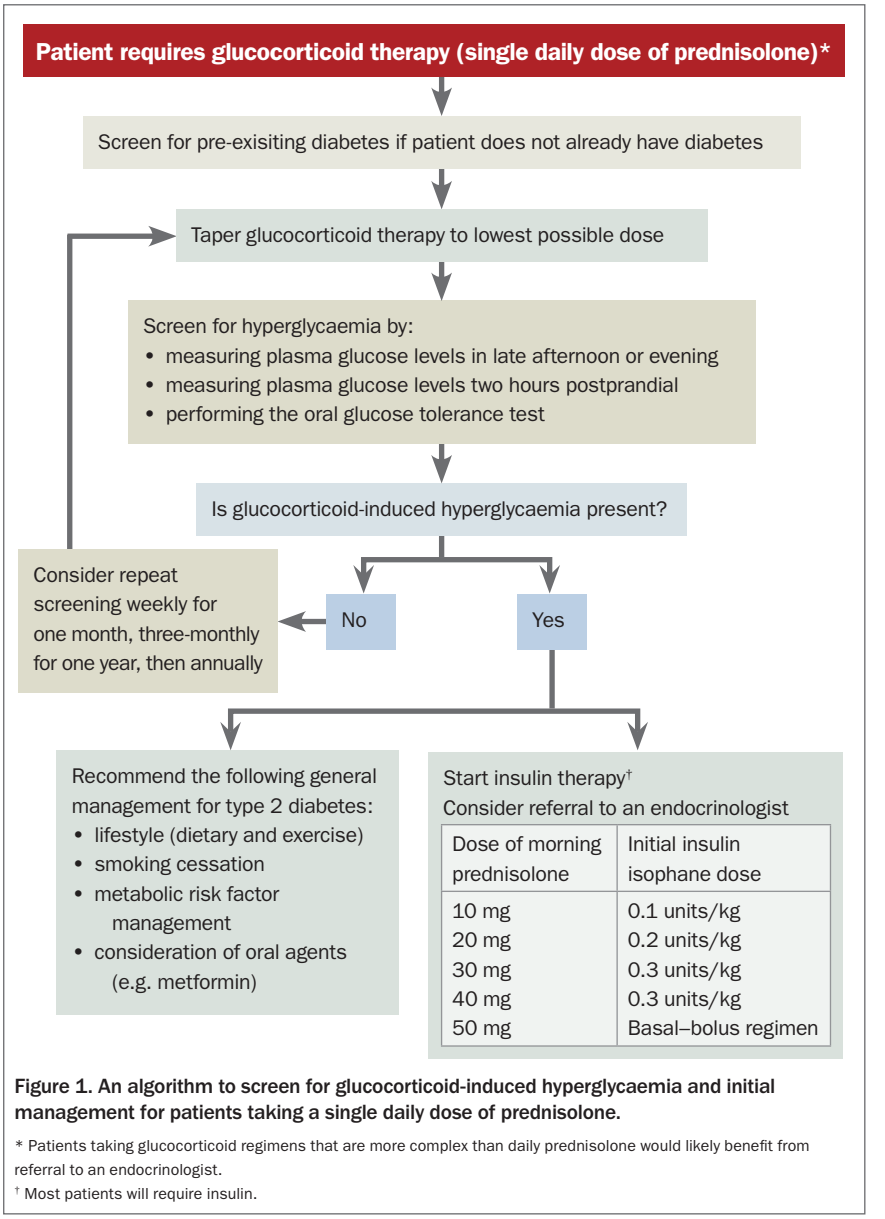


Figure 1. An algorithm to screen for glucocorticoid-induced hyperglycaemia and initial management for patients taking a single daily dose of prednisolone.

* Patients taking glucocorticoid regimens that are more complex than daily prednisolone would likely benefit from referral to an endocrinologist.

† Most patients will require insulin.

How to screen?

A recommended method for screening for glucocorticoid-induced hyperglycaemia is shown in Figure 1. For patients without known impaired glucose tolerance or diabetes, undiagnosed impaired glucose metabolism should ideally be excluded before initiation of glucocorticoid therapy based on the RACGP guidelines (see Figure 2).[2]

Continuous monitoring of circadian glycaemic patterns in patients receiving morning prednisolone for chronic obstructive pulmonary disease (COPD) has shown elevation of afternoon and evening plasma glucose levels with relative sparing of the fasting blood glucose level.[3] Postprandial hyperglycaemia was also noted. This coincides with a study on the use of long-term low-dose prednisolone in patients with inflammatory rheumatological disease, which showed raised postprandial glucose levels without higher levels of HbA_{1c} or fasting plasma glucose.[4] Measurement of afternoon or evening plasma glucose levels, measurement of two-hour postprandial blood glucose levels or the oral glucose tolerance test should therefore be used to screen for glucocorticoid-induced hyperglycaemia. In a general practice setting, patients can be referred for a plasma glucose measurement towards the end of the work day at a laboratory. As per the World Health Organization guidelines, diagnosis of new-onset diabetes requires two abnormal readings in an asymptomatic patient. An oral glucose tolerance test is also acceptable, although it would be more time consuming, costly and inconvenient for the patient.

Measurement of fasting plasma glucose levels or HbA_{1c} in isolation should be discouraged when screening for glucocorticoid-induced hyperglycaemia. Measurement of fasting blood glucose levels has

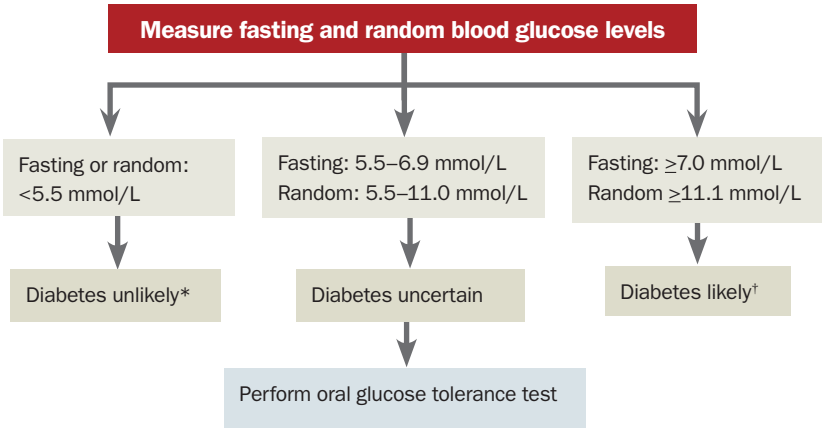


Figure 2. Screening for diabetes.[2]

* Retest yearly if patient is at high risk, 3-yearly if increased risk.

† Two abnormal plasma glucose levels if asymptomatic or one normal plasma glucose level if symptomatic is required for a diagnosis of diabetes.

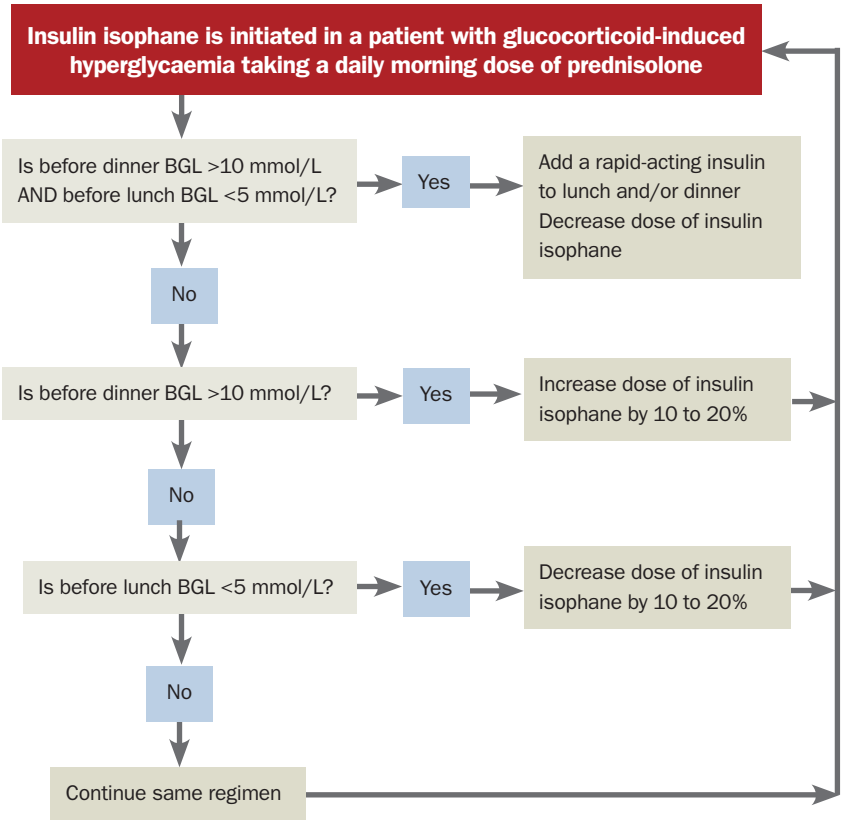


Figure 3. A simplified dose-adjustment protocol for insulin isophane in patients taking daily morning prednisolone.

Abbreviation: BGL = blood glucose level.

been reported to miss up to 51% of new-onset diabetes in a study on post-transplant patients.[5] Measurement of HbA_{1c} may not detect recent-onset hyperglycaemia and cannot be used in patients with any condition that increases red blood cell turnover, which might be common in patients requiring glucocorticoid therapy.

For patients with known impaired glucose tolerance or diabetes who are testing only morning capillary glucose levels, additional finger-prick tests should be performed, ideally postprandially.

Management

Unfortunately, there is a paucity of scientific data to guide specific treatment of patients with glucocorticoid-induced hyperglycaemia. Management principles are therefore extrapolated from patients with type 2 diabetes, modified somewhat by the documented effects of glucocorticoids on carbohydrate metabolism. Glucocorticoids induce diabetes by increasing insulin resistance and, at least acutely, reducing insulin secretion.

A simplified approach to the management of glucocorticoid-induced hyperglycaemia in patients receiving a daily single morning dose of prednisolone is shown in Figures 1 and 3. Management can be initiated by a GP who has an interest in diabetes, ideally in conjunction with an experienced diabetes educator. General management includes education, lifestyle management, counselling and metabolic risk factor management. The use of an insulin-sensitising agent, such as metformin, should also be considered. Other oral diabetes therapies may be of some use but have limited efficacy and may have side effects (particularly weight gain and increased fracture risk with thiazolidinediones, and hypoglycaemia and weight gain with sulfonylureas), which render their risk/benefit profile unfavourable.

Despite the lack of trials, insulin is considered to be the agent of choice for the management of glucocorticoid-induced hyperglycaemia. This is because it provides greatest flexibility for patients taking intermittent glucocorticoid therapy, greater dosing flexibility and more rapid onset and offset

of action.[1] Insulin therapy may be initiated in hospital and some patients may require referral to an endocrinologist for ongoing management. This is particularly the case for patients receiving multiple daily doses of glucocorticoids or having poorly controlled diabetes at baseline.

The initial bodyweight-dependent dose of insulin isophane can be based on the suggestions by Clore (see Figure 1).[6] Intermediate-acting insulin is preferred over longer-acting insulin for patients on morning prednisolone due to the relative sparing of fasting blood glucose levels. If a patient is already taking insulin and will only receive intermittent glucocorticoids (such as with chemotherapy or exacerbations of airway diseases), an easy approach is to add the intermediate-acting insulin to the patient's regular insulin regimen, and taper it when the glucocorticoid dosage is also reduced. Complex cases will likely benefit from a referral to an endocrinologist.

Titration of a patient's intermediate-acting insulin can be carried out using a simple protocol (see Figure 3), assuming a typical eating pattern with three main meals per day at regular hours. In such a patient, the before lunch blood glucose level tends to be the lowest reading due to the peak effect of the morning intermediate-acting insulin and the delayed effects of oral glucocorticoids. This delayed effect of prednisolone makes insulin isophane a better choice than mixed insulin in most cases. If further control is required after providing maximal morning intermediate-acting insulin, an ultra-rapid insulin can be added at lunch and/or dinner time.

For patients taking high doses of glucocorticoids (>50 mg prednisolone or equivalent) or longer-acting glucocorticoids, such as dexamethasone, a basal bolus schedule should be considered and initiated as for a typical patient with diabetes. Dose adjustments with higher short-acting doses at lunch and dinner will generally be required to attain reasonable glycaemic control when prednisolone is administered in the morning.

Finally, the patient should be informed to reduce his or her insulin dose as glucocorticoid dosing is reduced. The simplest approach would be a proportionate reduction in the insulin dosage, and then for further optimisation based on the resulting blood glucose levels.

Ongoing research

There is no evidence demonstrating superiority of any antihyperglycaemic agents. However, recent research, especially on newer agents that work on the incretin pathway, shows promise. For example, vildagliptin, a dipeptidyl peptidase-4 inhibitor, has been separately shown to be effective in reducing HbA_{1c} in patients with new-onset diabetes after heart transplant and kidney transplant.[7,8] In a small study, exenatide has also been shown to prevent prednisolone-induced glucose intolerance and islet-cell dysfunction in healthy humans.[9]

There is also a potential weight-reduction benefit over insulin with the use of glucagon-like peptide-1 agonists.

Conclusion

GPs can play a key role in screening and detecting of people with glucocorticoid-induced hyperglycaemia. Ideally, patients should be screened for pre-existing diabetes before starting glucocorticoids. Screening for glucocorticoid-induced hyperglycaemia should be performed by:

- measuring plasma glucose levels two hours after lunch or dinner (≥11.1 mmol/L)
- measuring random evening plasma glucose levels (≥11.1 mmol/L)
- performing a standardised oral glucose tolerance test.

Management of people with glucocorticoid-induced hyperglycaemia should include general lifestyle modifications, consideration of oral hypoglycaemic agents and/or insulin, and cardiovascular risk factor management. **ET**

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COMPETING INTERESTS: Dr Lee has received honoraria and sponsorship from Novo Nordisk. Dr Ng: None. Associate Professor Stranks has received lecture fees from Sanofi, Novo Nordisk and Diamond Pharma. He is a member of the Advisory Board for Eli Lilly and Sanofi and the Sustain Chief Investigator for Novo Nordisk. He has received honoraria from Novo Nordisk and research support from Sanofi.