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INVITED REVIEW

Management of glucocorticoid-induced diabetes

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ABSTRACT

Glucocorticoid-induced diabetes (GID) is a frequent metabolic complication of glucocorticoid therapy. It results from both insulin resistance and impaired insulin secretion, exacerbated by glucocorticoid use. Despite its prevalence, consensus guidelines on screening and management remain limited. GID affects approximately one in five patients receiving long-term glucocorticoid therapy. Risk factors include older age, high BMI, prediabetes, ethnicity, and high-dose systemic glucocorticoids. All patients initiated on moderate to high doses of glucocorticoids should be assessed for GID risk factors and closely monitored for the development of hyperglycemia and diabetes. In addition, glucocorticoid therapy can significantly exacerbate hyperglycemia in individuals with pre-existing diabetes, and stringent glucose monitoring is crucial. Treatment should be tailored to individual patient. Oral anti-diabetics such as metformin and sulfonylureas might be used in selected patients with mild GID. However, insulin is the primary treatment for severe hyperglycemia. Early detection and individualized management strategies are critical to mitigate GID's impact. Further research is needed to develop consensus guidelines and optimize treatment approaches.

Keywords: glucocorticoid, diabetes, hyperglycemia, risk factors, treatment.

Introduction

Glucocorticoid-induced diabetes (GID) is a well-recognized complication of glucocorticoid therapy, particularly in patients receiving long-term or high-dose glucocorticoid treatment. This review discusses the epidemiology, risk factors, diagnostic criteria, management strategies, and includes key algorithms and tables to aid in clinical decision-making.

Epidemiology

The use of glucocorticoids is common, with data from the United Kingdom and the United States of America indicating that approximately 1% of the population uses glucocorticoids [1,2]. Orally administered glucocorticoids may account for up to 2% of new-onset diabetes cases in the primary care setting [3]. There is also data showing that approximately 19% of patients on glucocorticoid therapy for more than one month could develop diabetes [4]. Hospitalized patients are particularly vulnerable, with 56% experiencing at least one hyperglycemic event when on glucocorticoids [5].

Risk Factors

Several factors contribute to the development of GID. The route of glucocorticoid administration, the dosage, and the duration of therapy are critical determinants [6]. For instance, systemic administration presents a higher risk than intra-articular or intra-lesional injections. However,

even intra-articular glucocorticoid injections may induce hyperglycemia for several days in patients with diabetes mellitus [7]. Additionally, higher doses of glucocorticoids significantly escalate the risk of hyperglycemia, particularly at doses equivalent to more than 120 mg of hydrocortisone being associated with a 10-fold increase in risk [6]. Moreover, the type of glucocorticoid administration is critical, as daily long-term use causes higher hyperglycemia risk than cyclic use. Research shows that 6 weeks of continuous glucocorticoid administration increases the risk of hyperglycemia by 50% compared to 5 days on, 15 days off usage [8]. Other risk factors for GID are older age, renal dysfunction, prediabetes, family history of diabetes, overweight or obesity, and co-administration of other medications associated with hyperglycemia risk (Table 1). Furthermore, genetic variations found in the population have been shown to be useful in predicting the metabolic responses to glucocorticoid therapy that are unique to each individual, such as hyperglycemia and diabetes mellitus [9].

Screening and Diagnosis

The diagnostic criteria for GID mirror those of common diabetes mellitus, with fasting plasma glucose (FPG) levels of ≥126 mg/dL or a 2-hour plasma glucose (2h PG) level of ≥200 mg/dL during a 75 g oral glucose tolerance test (OGTT) (Table 2).

There is no consensus regarding who should be screened for GID and when, and the American Diabetes Association (ADA) suggests 'considering' screening for diabetes in patients on long-term glucocorticoid therapy [10]. Fasting plasma glucose alone may not be the best method for screening GID, as short- and intermediate-acting glucocorticoids administered in the morning would increase plasma glucose in the afternoon or evening [6]. OGTT may therefore be a better approach for GID screening in long-term low-dose glucocorticoid users. In a study involving 150 patients who used low-dose glucocorticoids (≤10 mg/day of prednisolone) for more than 3 months, OGTT revealed that 19% had impaired glucose tolerance compared to 5% with impaired fasting glucose [11]. It is controversial whether prednisolone dosages as low as 5 mg per day could also increase the risk of GID [12,13].

Management

Management of GID should be individualized, taking into account the patient's risk factors, the type, dosage and duration of glucocorticoid treatment, and the severity of hyperglycemia. In patients without a history of diabetes, the focus should be on monitoring and early intervention. Patients with GID risk factors need a more frequent glucose monitoring, and persistent hyperglycemia (PG ≥180 mg/dL in two or more readings) require treatment [6,10] (Figure 1).

Non-Pharmacological Interventions

Lifestyle modifications, including dietary adjustments and physical activity, are essential components of GID management. However, due to the rapid onset of hyperglycemia with glucocorticoid use, these often need to be supplemented with pharmacological therapy.

Table 1. Risk factors for glucocorticoid-induced diabetes

Age	>60 years
BMI	>25 kg/m^2 (also abdominal obesity)
Hypertriglyceridemia	
Prediabetes	HbA1c >6.5%
Renal dysfunction	GFR < 40 mL/min/1.73 m^2
Family history of diabetes	
Ethnicity	e.g., black ethnic group
Concurrent medications	e.g., MMF, calcineurin inhibitors, furosemide

BMI: body mass index, GFR: glomerular filtration rate, MMF: mycophenolate mofetil.

Table 2. Diagnostic criteria for diabetes [10]

FPG	≥126 mg/dL
2-h PG during 75 g OGTT	≥200 mg/dL
Random PG in a person with classical symptoms of hyperglycemia	≥200 mg/dL
HbA1c*	≥6.5%

*The test should be performed in a laboratory using a National Glycohemoglobin Standardization Program-certified method.

FPG: fasting plasma glucose, OGTT: oral glucose tolerance test.

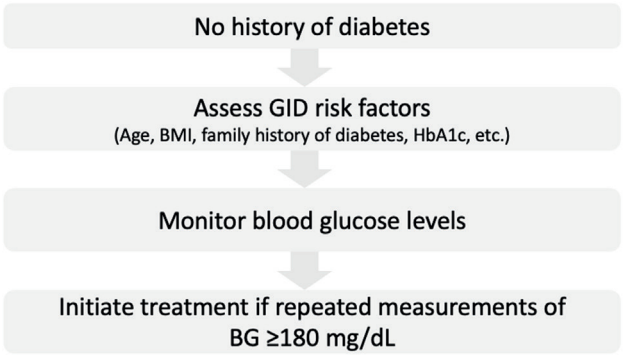

Figure 1. Diagnostic approach to glucocorticoid-induced diabetes

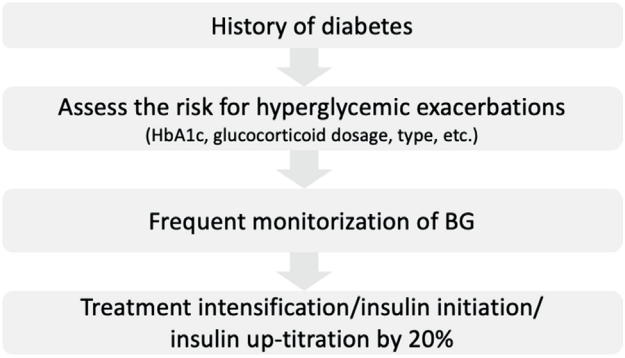

Figure 2. An approach for managing hyperglycemic exacerbations in diabetic patients induced by glucocorticoids

Pharmacological Interventions

The treatment of GID is similar to that of common diabetes in the population. However, managing GID with oral antidiabetic drugs (OADs) is challenging because being flexible with these medications in treatment is often difficult. A significant percentage of patients with GID would therefore need insulin. Still, OADs might be used in selected patients with mild hyperglycemia (BG levels <180 mg/dL) who receives low-dose glucocorticoids. On the other hand, acute severe glucocorticoid-induced hyperglycemia with PG levels exceeding 200 mg/dL requires insulin treatment [14]. In patients with diabetes, it may be advisable to intensify anti-diabetic treatment, initiate insulin therapy if it is not already being used, or increase the insulin dose if it is already being administered, even before starting glucocorticoids [6,15] (Figure 2). It should be noted that patients may need higher doses of prandial insulin rather that basal insulin, since peak concentrations of intermediate-acting glucocorticoids are reached 4 to 6 hours after administration, and last for 12 to 16 hours [6]. It is therefore common to have near-normal fasting BG measurements in the morning which tend to increase during the afternoon.

Insulin treatment should be tailored to individual patient. Insulin choices can be made based on whether the patient's glucocorticoid is short (hydrocortisone), intermediate (prednisone, methylprednisolone), or long-acting (dexamethasone). Intermediate-acting glucocorticoids like prednisolone and methylprednisolone typically begin their peak effect between 4-8 hours and last for 12-16 hours. Since the timing of the peak effect of NPH insulin coincides with this range, some experts recommend adding morning NPH insulin for patients taking a morning dose of prednisolone or methylprednisolone [16]. However, a meta-analysis revealed no advantage of NPH insulin use over insulin glargine or detemir in GID management [15]. The severity of hyperglycemia determines whether basal insulin alone will be sufficient or if bolus injections will be needed [6]. Nevertheless, "sliding scale" insulin injections should be avoided in favor of basal-bolus insulin regimens [15].

Oral anti-diabetics might be used in selected patients with mild GID. Sulfonylureas may be considered in patients using intermediate- to long-acting glucocorticoids due to their rapid onset and prolonged effect, though they carry a risk of nocturnal hypoglycemia. Glinides, which are fast-and short-acting agents administered before meals, previously offered flexibility in managing blood glucose levels in GID, although they are no longer available in some regions. Incretin-based therapies, targeting postprandial glucose, can be used, although study results are mixed; they are generally reserved for selected cases with mild glucose increase on long-term, low-dose glucocorticoids. Metformin is also an option for these patients due to its well-established efficacy in managing mild hyperglycemia. Thiazolidinediones, despite their potential as insulin sensitizers, present a double-edged sword; while they counteract some of the metabolic effects of glucocorticoids, their adverse effects—such as fluid retention, weight gain, and osteoporosis—often mirror the side effects associated with glucocorticoid therapy [6,14].

In long-term management, as the dose of glucocorticoids is tapered, the need for anti-diabetic treatment may decrease. Additionally, it is important to remember that suppression of endogenous cortisol can increase susceptibility to nocturnal hypoglycemia [17].

Conclusion

Glucocorticoid-induced diabetes is a common complication, and while a consensus on screening protocols has yet to be established, it may be prudent to consider OGTT screening in patients receiving long-term low-dose glucocorticoid therapy. All patients initiated on moderate to high doses of glucocorticoids, on the other hand, should be assessed for GID risk factors and closely monitored for the development of hyperglycemia and diabetes, with regular blood glucose monitoring being essential. In individuals with pre-existing diabetes, glucocorticoid therapy can significantly exacerbate hyperglycemia. Therefore, stringent glucose monitoring is crucial. Treatment may be tailored based on the type and dose of glucocorticoid, as well as individual patient factors. In cases of acute severe hyperglycemia, insulin remains the sole effective treatment option.

Author contribution

Study conception and design: SHO; draft manuscript preparation: SHO. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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