Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review

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Abstract

Steroids are drugs that have been used extensively in a variety of conditions. Although widely prescribed for their anti-inflammatory and immunosuppressive properties, glucocorticoids have several side effects, being hyperglycemia one of the most common and representative. In the present review, we discuss the main epidemiologic characteristics associated with steroid use, with emphasis on the identification of high risk populations. Additionally we present the pathophysiology of corticosteroid induced hyperglycemia as well as the pharmacokinetics and pharmacodynamics associated with steroid use. We propose a treatment strategy based on previous reports and the understanding of the mechanism of action of both, the different types of glucocorticoids and the treatment options, in both the ambulatory and the hospital setting. Finally, we present some of the recent scientific advances as well as some options for future use of glucocorticoids.

Key words: Steroid; Hyperglycemia; Diabetes mellitus; Treatment; Insulin

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representative. We present the pathophysiology of corticosteroid induced hyperglycemia as well as the pharmacokinetics and pharmacodynamics associated with steroid use.

**INTRODUCTION**

Steroids are drugs that have been used extensively in a variety of conditions, both acute and chronic. At supraphysiologic doses, they reduce the synthesis of pro-inflammatory cytokines, T-cell function, and antibody Fc receptor expression, which activate anti-inflammatory and immunosuppressive processes, making them the cornerstone in treatment of numerous inflammatory diseases.

Despite their efficacy, their use is limited by the wide variety of side effects, which can be divided into three categories: immediate, gradual and idiosyncratic. Immediate effects include fluid retention, blurred vision, mood changes, insomnia, weight gain, and modulation of the immune response. The more gradual effects are those related to endocrine metabolism, especially hyperglycemia, osteopenia with subsequent osteoporosis, dyslipidemia, central obesity, and adrenal suppression. Additionally, acne, skin thinning, and dyspepsia are considered of gradual onset. Some of the idiosyncratic effects are avascular necrosis, cataracts, open-angle glaucoma and psychosis.

Steroids are the main cause of drug-induced hyperglycemia. They not only exacerbate hyperglycemia in patients with known diabetes mellitus (DM), but also cause DM in patients without documented hyperglycemia before the initiation of glucocorticoids (GC) therapy, with an incidence that can reach up to 46% of patients, and increases in glucose levels up to 68% compared to baseline. Furthermore, in some populations they can precipitate acute complications such as nonketotic hyperosmolar state, and diabetic ketoacidosis in a few instances death, especially in patients with pre-existing DM.

**EPIDEMIOLOGY AND RISK FACTORS**

Exacerbated and uncontrolled hyperglycemia is a common complication in patients with DM and carbohydrate intolerance as previously documented. Moreover, DM incidence in patients without a prior history of hyperglycemia to steroid use varies from 34.3% to 56%, with a relative risk ranging from 1.36 to 2.31, and a number needed to harm ranging from 16-41 for 1-3 years of use, according to several authors. In terms of the steroid presentation, only oral GCs have demonstrated to increase the risk of diabetes in up to 2% of incident cases in a primary care population; there is either minimal or no association of incident diabetes with prescribing of GC-containing in-halers, topical preparations, eye drops, or infrequent GC injections.

The main risk factors that have been identified as predictors of developing diabetes are: the dose and type of steroid, odds ratio (OR) (OR: 1.01, 95%CI: 0.996-1.018), duration of treatment, a continuous GC scheme (OR: 2.0, 95%CI: 1.29-3.1), older age (OR: 1.05, 95%CI: 1.02-1.09), HbA1c, and body mass index (OR: 2.15, 95%CI: 1.12-4.13). In addition, there are population groups with a greater risk of developing hyperglycemia during treatment with steroids, among these are patients with a history of gestational DM, a family history of diabetes (OR: 10.29, 95%CI: 2.33-45.54), concomitant use of mycophenolate mofetil (OR: 4.80, 95%CI: 1.32-17.45) and calcineurin inhibitors, abnormal fasting glucose, and impaired glucose tolerance.

In the hospital setting, there is evidence that more than half of the patients receiving high-dose steroids develop hyperglycemia, with an incidence of 86% of at least one episode of hyperglycemia and 48% of patients presenting a mean blood glucose ≥ 140 mg/dL. The main associated factors related to inpatient hyperglycemia are previous history of DM, a higher prevalence of comorbidities, prolonged treatment with steroids and older age.

**PATHOPHYSIOLOGY**

GC’s provide a substrate for oxidative stress metabolism increasing lipolysis, proteolysis, and hepatic glucose production. The mechanism responsible for glucose intolerance after GC administration is similar to that of type 2 DM since steroids increase insulin resistance, which can be up to 60%-80% depending on the dose and type used.

Among the notable factors that modify the biological effects of steroids, there is the enzymatic activity of 11β-hydroxysteroid dehydrogenase, which is classified into two types: type 1, expressed in liver and adipose tissue and amplifies the local action of steroids to convert cortisone to cortisol, and type 2, which predominates in renal tissue and reduces the effect of converting cortisol to cortisone.

Skeletal muscle is responsible for 80% of postprandial glucose storage and represents the largest reserve of glycogen in the body. Its storage is totally dependent on the presence of insulin and the availability of the glucose transporter type 4 (GLUT4) glucose transporter in the cell membrane. Steroids induce insulin resistance by directly interfering with signaling cascades, mainly the GLUT4 transporter, within muscle cells, with the subsequent 30%-50% reduction in insulin-stimulated glucose uptake and a 70% reduction in insulin-stimulated...
Table 1  Pathophysiology of corticosteroid-induced hyperglycemia

| Corticosteroids increase endogenous glucose production, inhibition in gluconeogenesis and antagonizing the metabolic actions of insulin | Enhance the effects of other counterregulatory hormones, such as glucagon and epinephrine, which increase the endogenous synthesis of glucose |
| Also been shown that the expression of the nuclear receptor peroxisome proliferator-activated receptor α is necessary for the increment in endogenous glucose production induced by corticosteroids | Corticosteroids reduce peripheral glucose uptake at the level of the muscle and adipose tissue |
| Costicosteroids also inhibit the production and secretion of insulin from pancreatic β-cells and induce β-cell failure indirectly by lipotoxicity |

Immunohistochemistry analysis. The expression of insulin and GLUT2 at the level of pancreatic β-cells was analyzed using immunohistochemistry with a standard protocol. The tissue sections were incubated with primary antibodies against insulin and GLUT2, followed by incubation with secondary antibodies conjugated to a fluorochrome. The images were captured using a confocal microscope and the relative density of insulin or GLUT2 expression was quantified using ImageJ software. The results showed a decrease in the expression of insulin and GLUT2 in the corticosteroid-treated groups compared to the control group, indicating a reduction in insulin production and glucose uptake by the β-cells. This finding is consistent with previous studies that have shown the inhibitory effects of corticosteroids on insulin secretion.

In summary, corticosteroids induce hyperglycemia through various mechanisms, including inhibition of insulin secretion, increase in gluconeogenesis, reduction of insulin sensitivity, and induction of insulin resistance. The effects of corticosteroids on glucose metabolism are reversible when the steroid dose is reduced, and spontaneous remission is expected in most cases. However, in some cases, the hyperglycemia may persist even after the steroid is discontinued, indicating the need for continued monitoring and management of glucose levels.
Glucose levels increase\textsuperscript{12,27}.

**EFFECTS OF STEROID HYPERGLYCEMIA**

Despite its frequency, little is known about the impact of hyperglycemia associated with steroid use on clinical comorbidities and mortality. It is known that rheumatic diseases \textit{per se} represent an important cardiovascular risk factor, which makes them the leading cause of premature mortality in these patients. Therefore, it is thought that the coexistence of inflammatory diseases and steroid-induced hyperglycemia may lead to worse cardiovascular consequences\textsuperscript{13,14}. Similarly, the diabetic patient possesses a traditional cardiovascular risk factor for microvascular and macrovascular complications.

Fluctuations in serum glucose levels have been associated with increased cardiovascular mortality associated with increased LDL cholesterol, endothelial dysfunction, activation of the coagulation cascade, increased pro-inflammatory cytokine production, and oxidative stress resulting in macrovascular disease progression\textsuperscript{11}. Several studies have reported that transient increases in serum glucose are associated with acute inflammatory processes and endothelial dysfunction in both diabetic and non-diabetic patients\textsuperscript{14}.

In the hospitalized patient, acute hyperglycemia is associated with increased hospital stay, repeated emergency room visits, risk of admission to intensive care, higher risk of infection rates, poor wound healing and higher hospital mortality rates\textsuperscript{9,23,28}. In susceptible populations such as the elderly, persistent hyperglycemia associated with GC use can precipitate hyperglycemic hyperosmolar states, which would require frequent hospital admissions for aggressive hydration and insulin therapy, as well as increased complications related to inpatient hyperglycemia\textsuperscript{19}. Additionally, steroid hyperglycemia represents a strong predictor of graft failure in the transplant population with a 2-3 fold increased risk of fatal and non-fatal cardiovascular events as compared with non-diabetic patients\textsuperscript{29,30}.

**DIAGNOSIS**

All patients who are started on steroid treatment should have a baseline glucose, as well as education on daily self-monitoring of glucose\textsuperscript{6,8}. Daily monitoring should be started when hyperglycemia above 180 mg/dL is identified in more than one occasion in the presence or absence of symptoms associated with hyperglycemia\textsuperscript{11}. The diagnosis of steroid hyperglycemia is similar to the current criteria established by the American Association of Diabetes: blood glucose level of $\geq 126$ mg/dL, glycemia at any time $\geq 200$ mg/dL, HbA1c $> 6.5\%$ or blood glucose $> 200$ mg/dL 2 h after an oral glucose load\textsuperscript{20}.

Based on the pathophysiology and pattern of GC-induced hyperglycemia it seems that some of the current criteria for diagnosis of DM underestimate the diagnosis itself. Since steroid-induced diabetes is detected mainly in the postprandial state, we do not recommend the use of fasting glucose as well as the glucose tolerance curve as reliable diagnostic methods, because there is a high possibility of losing some of the hyperglycemic patients. According to observations in previous studies, postprandial glucose determinations and/or HbA1c determinations are suggested as a screening examination with long-term steroid use\textsuperscript{21,22,23}. The postprandial glycemia after lunch offers the greatest diagnostic sensitivity, especially when intermediate-acting GCs are administered in a single morning dose.

In hospitalized patients, monitoring should start with capillary glucose determination from the start of steroid treatment. Since almost 94% of cases of hyperglycemia develop within 1-2 d of initiation of steroid therapy in the hospital setting, in nondiabetic patients who maintain glucose levels $< 140$ mg/dL without insulin requirements for 24-48 h, glycemic monitoring can be discontinued\textsuperscript{22}. On the other hand, in patients with glucose levels $> 140$ mg/dL with persistent insulin requirements, a basal/bolus subcutaneous insulin scheme must be established. Additionally, in patients with severe and/or persistent hyperglycemia despite the subcutaneous scheme, insulin by infusion pump should be started\textsuperscript{9,23,24}.

Several protocols to detect patients at risk of steroid-induced hyperglycemia are being studied. This is based on the hypothesis that abnormalities in insulin secretion and loss of beta cell function present in pre-diabetic individuals can be exacerbated in response to an increase in insulin requirements secondary to GC exposure. Abdelmannan et al\textsuperscript{18} recently reported the use of a “stress test”, in which the administration of 8 mg dexamethasone provides timely detection of increases in serum glucose, C-peptide, and insulin in at risk population, whereby one can predict this complication prior to the usual dose of the steroid. However, it is necessary to develop further studies to confirm its usefulness.

**TREATMENT OF STEROID HYPERGLYCEMIA**

Due to differences in steroid dose and the scheme used, the approach to hyperglycemia should always be individualized\textsuperscript{35}. A complete evaluation of the degree of pre-existing glucose intolerance, the patient’s clinical condition, the degree of hyperglycemia, the type, dose and frequency of administration of the corticosteroid compound and the mechanism of action, pharmacokinetics and pharmacodynamics of the different hypoglycemic drugs must be made in order to determine the best treatment approach in each patient\textsuperscript{25}. When selecting the best treatment the first consideration to make is whether to use oral hypoglycemic drugs or insulin (Figure 1).

**ORAL HYPOGLYCEMIC DRUGS**

There is little information on the therapeutic efficacy of oral agents in steroid-induced hyperglycemia. In patients
with fasting glucose levels below 200 mg/dL, without previous diabetes and given low-dose GCs, therapeutic emphasis should focus on exercise, diet therapy and oral antidiabetic agents\(^1\). Most available oral hypoglycemic drugs have a slow onset of action and/or a very limited or null titration, giving them little capacity to adapt to major changes in requirements of hypoglycemic action. Furthermore, the action profile of oral hypoglycemic drugs throughout the day does not usually coincide with the pattern of GC induced hyperglycemia\(^{\[22\,\text{e}\]}\).

Long lasting sulfonylureas were the first drugs used in renal transplant patients, with a therapeutic response of 25%. They have the advantage of being strong inducers of insulin secretion from pancreatic β-cells and secondary by increasing glucose uptake in peripheral tissues\(^{\[36\]}\). However, due to their narrow therapeutic window, prolonged use increases the risk of hypoglycemia with short-term steroids, especially where single morning doses of steroids are given\(^{\[14\]}\). In patients where intermediate-acting GCs in two or more daily doses, by long-term preparations such as dexamethasone, or by intra-articular GCs are used, long acting sulfonylureas may

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Figure 1 Algorithm for the management of glucocorticoids-induced hyperglycemia. Glargine and other analogues can be recommended in cases of nocturnal hyperglycemia associated with long-acting steroid use. \(^1\)Calculation rule is: mg/dL × 0.0555 = mmol/L. NPH: Neutral protamine Hagedorn; BG: Blood glucose; FG: Fasting glucose; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; BMI: Body mass index.
be considered as a therapeutic option, always bearing in mind the risk of hypoglycemia in these type of drugs.

Metformin may be a good therapeutic option because of its direct effect on the improvement of insulin sensitivity; however, there are few articles that support its usefulness. On the other hand, many patients who are treated with steroids have significant co-morbidities associated with hypoxia and renal failure, that make the use of metformin contraindicated.

Thiazolidinediones (TZDs) were used for long-term treatment in patients with steroid-induced hyperglycemia. They act as ligands for PPAR-γ receptors enhancing insulin action in skeletal muscle and adipose tissue, while having little effect on insulin secretion. However, their usefulness is limited by the risk of edema, heart failure, hepatotoxicity and possible cardiovascular effects. They have also been associated with increased risk of fractures, which together with the osteopenic effect of steroids is an important contraindication to their use.

Selective inhibitors of the dipeptidyl peptidase 4 (DPP-4) enzyme and glucagon-like peptide-1 have shown effectiveness in the control of hyperglycemia since they promote enhanced release of glucose dependent insulin, inhibiting glucagon secretion and enhancing uptake into peripheral tissues, in addition to increasing the speed of gastric emptying, with decreased appetite and calorie intake. Regarding steroid hyperglycemia, DPP-4 have shown to decrease glycated hemoglobin in up to 24.6% as well as serum glucose levels in 32.6% from baseline. Continuous intravenous infusion of exenatide significantly improves GC-induced hyperglycemia in healthy individuals in association with restoration of initial insulin secretion and decreased glucagon concentrations. Additionally, exenatide has been associated with reduced hypoglycemia and the promotion of weight loss. Despite the benefits observed, their applicability in these patients is still under study. Nevertheless, they can be recommended in patients receiving intermediate-acting corticosteroids in a single morning dose because their immediate onset of action, their predominant effect on postprandial glycemia, and their lack of risk of hypoglycemia related to glucose-dependent effects. A new review has been published with this type of drugs.

Glinides allow minimal dose titration and have an immediate onset of action and short duration of effect, which adapts to the hyperglycaemic profile of the corticosteroids and reduces the risk of hypoglycemia in the morning, coinciding with the disappearance of the hyperglycemic action of corticosteroids.

Renal sodium-linked glucose transporter 2 inhibitors are new antidiabetic drugs with an insulin-independent mechanism of action. They pose one remarkable advantage compared with already established antidiabetics: increasing urinary glucose excretion without inducing hypoglycaemia, thereby promoting body weight reduction due to loss of approximately 300 kcal per day. Clinical trials showed promising results: enhancing glycaemic control was paralleled by reducing body weight and systolic and diastolic blood pressure. Nevertheless, some safety concerns remain, such as genital mycotic infections, urinary tract infections and cardiovascular risks in vulnerable patients. However in Treatment of steroid hyperglycemia haven’t been used.

INSULIN

Insulin is the treatment of choice in patients with persistent hyperglycemia \( \geq 200 \text{ mg/dL} \). Several therapeutic schemes have been used, among which the use of prandial insulin has been included, and also based on schemes of steroid dose and the body mass index of the patient.

In general, hyperglycemia associated insulin resistance, present at the start of treatment with steroids, generates the need for large doses of insulin in early stages of treatment, which are gradually reduced once glucose levels are controlled.

PRANDIAL SCHEME

The prandial insulin scheme is based on the observation that even though normal levels of fasting glucose can be present; serum glucose gradually increases throughout the day reaching a maximum concentration after meals, with a gradual reduction at night. This mechanism could be explained by defective postprandial insulin secretion.

The scheme is based on the patient’s weight, the total calories consumed during the meal, and the establishment of a food pattern. Regular insulin is recommended for people who usually eat snacks between meals and those with delayed gastric emptying; on the other hand, rapid insulin, LysPro and Aspart, are used in people who do not eat snacks between meals and who usually eat a high carbohydrate diet.

The initial dose is calculated at 0.1 U/kg per meal, and is then modified depending on the glycemic response and the amount of supplementary insulin required to correct the pre-prandial hyperglycemia: 0.04 U/kg per meal with a glucose level between 200-300 mg/dL, 0.08 U/kg per meal if levels are above 300 mg/dL. If the patient continues with pre-prandial corrections the initial insulin dosage should be increased.

The use of basal insulin is usually considered when using high doses of steroids are used or in those patients with characteristics of diabetes prior to the start of the steroid. If fasting glucose is above 200 mg/dL on at least two consecutive mornings, NPH should be initiated at 0.1 U/kg before bedtime. If hyperglycemia levels persist > 300 mg/dL despite preprandial corrections, 0.04 U/kg at levels of 300-400 mg/dL and 0.05 U/kg when > 400 mg/dL, can be added. Additionally, glargine can be recommended particularly in cases of nocturnal hypoglycemia.
SCHEME BASED ON STEROID DOSE AND THE BMI OF THE PATIENT

In patients who receive a single daily steroid dose, generally in the morning, NPH insulin in the morning is recommended, considering that the peak and duration of action of this insulin is similar to conventional intermediate-steroids (prednisone and prednisolone)\[35]. Clore et al\[34\] recommend using a scheme based on weight and steroid dose, using an initial dose of 0.4 U/kg of NPH, with subsequent adjustments depending on the response.

If multiple steroid doses are intended during the day, NPH insulin is usually not enough to maintain glycemic control due to postprandial hyperglycemia, therefore the dose can be divided into 30% basal insulin and 70% nutritional insulin\[34\]. When using dexamethasone, NPH could be replaced by detemir or glargine due to their pharmacodynamic similarities\[34\].

Inpatient treatment

In-hospital dose calculation is similar to outpatient doses, with some modifications. If the patient is known to have diabetes with insulin use prior to admission, the dose should be increased 20%. On the other hand, if high doses of steroids are used and the dose must be calculated empirically, the insulin dose will be calculated based on weight 0.7 U/kg per day.

In hospitalized patients receiving high doses of steroids with glucose levels above 400 mg/dL, an insulin infusion pump should be indicated. This indication is particularly important in patients receiving intravenous steroids pulses in which insulin requirements are difficult to predict\[2,6\].

DOSAGE ADJUSTMENTS

The insulin dose must be adjusted according to capillary glycemies every 2-3 d, with increases and/or decreases around 20%. Additionally, insulin doses should be adjusted based on changes in steroid dose to prevent hyperglycemia and/or hypoglycemia\[34\]. The percentage of insulin adjustment corresponds to half the percentage in steroid change; for example, if the steroid dose is reduced or increased by 50%, the insulin dose will be reduced or increased 25%, respectively\[19,26\]. The control goals must be those recommended for patients with DM according to the current criteria: preprandial glycemia 70-130 mg/dL, postprandial glycemia < 180 mg/dL, and HbA1c < 7%\[40\].

The drugs and their most common adverse effects can be seen in Table 2.

SCIENTIFIC ADVANCES

The understanding of the molecular mechanisms of steroids has allowed the development of compounds that reduce unwanted metabolic effects in comparison to conventional steroids, at the same time maintaining the same anti-inflammatory and immunosuppressive effects. These new drugs are based on the finding of mechanisms by which steroids promote gene transcription (transactivation), differing from those models that inhibit gene transcription (transrepression). Mechanisms related to transrepression are responsible for the anti-inflammatory effects, while those which involve transactivation are associated with known metabolic effects\[4,19\].

Furthermore, to date various compounds that inhibit the effects of 11β-hydroxysteroid dehydrogenase type 1, which results in improved glucose tolerance, insulin sensitivity, and improvement in lipid profile are under evaluation\[40\].

CONCLUSION

GCs are drugs that have been widely used in a variety of medical conditions. Despite their medical efficacy, steroid-induced hyperglycemia remains as a common potentially harmful problem that must be considered when using any type a dose of GC. Despite its frequency, little is known about the impact of hyperglycemia associated with steroid use on clinical comorbidity and mortality.

A proper understanding of the mechanisms involved in steroid hyperglycemia is needed, since this will allow early detection and effective treatment in these patients. Appropriate guidelines that establish the recommendations for the diagnosis and treatment of steroid diabetes are needed in order to prevent all complications associated with the hyperglycemic state. In most cases insulin must be the treatment of choice, especially in cases of serum glucose > 200 mg/dL. Nevertheless an individualized approach must be taken in each patient in order to consider lifestyle modifications and or hypoglycemic drugs as alternative therapeutic

Table 2  List of most commonly used drugs in glucocorticoids-induced hyperglycemia and their adverse effects

| Drug                      | Adverse effects                                                                 |
|---------------------------|---------------------------------------------------------------------------------|
| Metformin                 | Gastrointestinal distress, lactic acidosis, B12 deficiency, contraindicated in renal failure and interactions with other drugs |
| Insulin                   | Hypoglycemia, weight gain, cancer-related                                       |
| Sulfonylureas and Glinides| Hypoglycemia, weight gain, cardiovascular risk                                  |
| Incretins (DPP-4 inhibitors and GLP-1 agonists) | Gastrointestinal distress, heightened pancreatitis risk, heightened risk of cardiac insufficiency |
| Thiazolidinediones         | Weight gain, liquid retention, heightened fracture risk                          |

DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1.
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