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Review Article

Steroids Induced Hyperglycemia: Its Effects and Management

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Abstract

Steroids are medications that have been widely utilized for a number of ailments, both acute and chronic. The action of endogenous steroids, nuclear hormones that penetrate cell membranes to bind to certain glucocorticoid receptors in the cytoplasm of target cells to form glucocorticoid-receptor (GR) complexes, is mimicked by synthetic glucocorticoids. The translocated activated GR complex regulates DNA transcription in the cell nucleus. The main factor for drug-induced hyperglycemia is steroids. They not only worsen hyperglycemia in those who already have diabetes mellitus (DM), but they can also lead to DM in people who've not previously experienced it. Their incidence can reach up to 46% of patients, and their glucose levels can rise by up to 68% over baseline. Steroid effects are often narrow and reversible. Drug-induced diabetes is supposed to go away as steroid doses are decreased because their impact on endocrine metabolism returns to normal; however, this is often not the case. The synthesis of lipolysis, proteolysis, and hepatic glucose is increased by glucocorticoids (GCs) because they act as a substrate for oxidative stress metabolism. A wide range of medical conditions has been treated with GCs. Although steroid-induced hyperglycemia has been proven to be medically effective, it is still a widespread and potentially dangerous issue that must be taken into consideration when administering any GC dose. The most common scenario requires the use of insulin, particularly when the serum glucose level is greater than 200 mg/dL.

Keywords: Steroids, Glucocorticoids, Hyperglycemia, Resistance, Insulin

INTRODUCTION

Despite multimorbidity being common, clinical guidelines are typically written as though patients had only a single ailment, and the overall impact of treatment recommendations from several clinical guidelines is hardly taken into consideration.[1, 2]

A simple application of recommendations from several single-disease clinical guidelines in patients with different illnesses may lead to complex multiple-drug regimens (polypharmacy), that carry the risk of unintentionally harmful medication combinations.[3,4,5]

Previous studies of the effects of adhering to single illness guidelines in people with multimorbidity have generally considered single hypothetical patients with carefully chosen multiple ailments; a scenario that is likely to overestimate the scope of the issue. [5,6]

According to US population survey data, Lorgunpai and colleagues have found a significantly higher incidence of drug-disease interactions, or "therapeutic competition," with a fifth of older American adults receiving prescriptions for medications that could aggravate one condition.[7]

The American Geriatrics Society has identified drug-disease and drug-drug interactions as essential components of the best therapy for older persons with multiple chronic diseases.[8]

DRUG-DISEASE INTERACTIONS:

Whenever time a patient takes a medication, the medication must pass through their particular body. Depending on the bacteria that live in the intestines, the patient's age, or the overall condition of their excretory organs, such as the liver or kidneys, a drug's metabolism can differ from patient to patient. Chemical reactions happen while the drug circulates throughout the body, making it water soluble so that it may finally be eliminated and won't build up in the bloodstream to harmful levels. However, this process sometimes doesn't go as predicted due to various disease conditions. [9]

Several molecules with a variety of physiological functions are referred to be steroids. More specifically, a class of chemicals known as corticosteroids includes both hormones which are produced naturally and in laboratories. In general, glucocorticoids regulate metabolism and inflammation, while mineralocorticoids regulate sodium and water balance. The selection of steroid compounds is based on how well they will work for a particular treatment. Corticosteroids have effects that range from exclusively glucocorticoid effects to exclusively mineralocorticoid effects. For example, although having strong anti-inflammatory characteristics, a substance might also contain mineralocorticoid activity, which has a negative impact on blood pressure.

Steroids are medications that have been widely utilized for a number of ailments, both acute and chronic. [10]

Despite their effectiveness, the wide range of side effects, which can be categorized into three groups: immediate, gradual, and idiosyncratic, limit their use. Symptoms that appear right away include fluid retention, impaired vision, changes in mood, insomnia, weight gain, and immune response modification. The impacts on endocrine metabolisms, such as hyperglycemia, and osteopenia leading to osteoporosis, dyslipidemia, central obesity, and adrenal suppression, manifest more gradually. Likewise considered to have a gradual beginning include dyspepsia, skin thinning, and acne. Cataracts, open-angle glaucoma, avascular necrosis, and psychosis are a few of the idiosyncratic effects.[11,12]

STEROID MECHANISM OF ACTION:

The action of endogenous steroids, nuclear hormones that penetrate cell membranes to bind to certain glucocorticoid receptors in the cytoplasm of target cells to form glucocorticoid-receptor (GR) complexes, is mimicked by synthetic glucocorticoids. The translocated activated GR complex regulates DNA transcription in the cell nucleus. Anti-inflammatory proteins are subsequently transactivated as a result, while pro-inflammatory proteins are transrepression. Steroid injection affects insulin resistance by interfering with insulin receptors in the liver, muscles, and adipose tissue, as well as modulating beta-cell activity, which affects how carbohydrates are metabolized. In "at-risk persons," these actions promote hyperglycemia. [13]

Steroid dose equivalents:

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

N.B. potency relates to anti-inflammatory action, which may not equate to a hyperglycemic effect [13]

The main factor for drug-induced hyperglycemia is steroids. They not only worsen hyperglycemia in those who already have diabetes mellitus (DM), but they can also lead to DM in people who've not previously experienced it. [10,14] Their incidence can reach up to 46% of patients, and their glucose levels can rise by up to 68% over baseline. [15-17]

Acute consequences including nonketotic hyperosmolar condition, diabetic ketoacidosis, and in rare cases mortality, especially in patients with pre-existing DM, can also be precipitated in some populations by them. [18]

Predisposing factors leading to increased risk of hyperglycemia with steroid therapy:

- Pre-existing type 1 or type 2 diabetes
- People at increased risk of diabetes (eg. obesity, family history of diabetes, previous gestational diabetes, ethnic minorities, polycystic ovarian syndrome)
- Impaired fasting glucose or impaired glucose tolerance, HbA1c 42-47mmol/mol
- People previously hyperglycaemic with steroid therapy
- Those identified to be at risk utilizing the University of Leicester/Diabetes UK diabetes risk calculator (riskscore.diabetes.org.uk) [19]

EFFECTS OF STEROIDS-HYPERGLYCEMIA:

Despite its prevalence, little is known about how steroid-associated hyperglycemia affects clinical comorbidities and mortality. Similar to other patients, diabetic patients have a typical cardiovascular risk factor for both microvascular and macrovascular problems. Increasing LDL cholesterol, endothelial dysfunction, activation of the clotting cascade, increased production of pro-inflammatory cytokines, and oxidative stress that leads to the advancement of the macrovascular disease have all been linked to higher cardiovascular mortality. [20]

According to numerous studies, both diabetic and non-diabetic patients who experience a brief increase in serum glucose also experience acute inflammatory reactions and endothelial dysfunction.[21] Acute hyperglycemia in a hospitalized patient is linked to longer hospital stays, more frequent Emergency room visits, a higher chance of admission to critical care, a higher risk of infection, slower wound healing, and higher hospital death rates. [21,22,23]

The use of GC can cause persistent hyperglycemia, which can lead to hyperglycemic hyperosmolar states in susceptible populations like the elderly. The above states may necessarily require repetitive hospital admissions for aggressive hydration and insulin therapy as well as an increase in complications from inpatient hyperglycemia.[21] Furthermore, steroid hyperglycemia is a potent indicator of graft failure in the transplant population, with a 2- to 3-fold greater risk of fatal and non-fatal cardiovascular events in comparison to non-diabetic patients. [25,26]

PHARMACOKINETICS AND PHARMACODYNAMICS:

Adrenal-derived steroids are produced from cholesterol, and they are secreted based on a circadian cycle and pulsatile ultradian rhythm. The range of normal secretion is between 8 to 15 mg/dl, with 10% of that amount circulating in free form and the remaining 90% bound to carrier proteins, namely albumin and cortisol-binding globulin.

Depending on the type of GCs utilized, the plasma half-life ranges from 80 to 270 minutes, and indeed the effect in tissues lasts for 8 to 12 hours. They are metabolized in the liver, and the kidneys are primarily responsible for excreting their conjugated metabolites. [27,28,29]

Depending on the type of steroid used—intermediate-acting or long-acting GCs—insulin resistance develops mostly postprandial and in various manners. Methylprednisolone and prednisone are categorized as intermediate-acting GCs, with a peak of the effect occurring 4-6 hours after the treatment. When they are given in a single dose, their influence on glucose levels is primarily felt during the afternoon and night without altering fasting glucose. However, when given in

divided dosages, they result in chronic hyperglycemia. Dexamethasone belongs to the class of long-acting GCs and has steroid hyperglycemia persisting for more than 24 hours with a mild decrease during an overnight fast. [27,28,29]

Steroid effects are often narrow and reversible. Drug-induced diabetes is supposed to go away as steroid doses are decreased because their impact on endocrine metabolism returns to normal; however, this is often not the case. [30,31]

There is not much research that talks about how long-term GC consumption affects pancreatic function and the initiation of DM. According to new statistics available, GCs are expected to have the biggest effects when given immediately, specifically during the second and fourth week, with the majority of patients experiencing spontaneous remission when a phenomenon of adaptation decreases how much glucose levels rise. [32,33]

PATHOPHYSIOLOGY:

The synthesis of lipolysis, proteolysis, and hepatic glucose is increased by GCs because they act as a substrate for oxidative stress metabolism.[13] Because steroids raise insulin resistance, which can range from 60% to 80% depending on the dose and type used, the mechanism causing glucose intolerance with GC administration is comparable to that of type 2 DM. [2,35] The enzymatic activity of 11-hydroxysteroid dehydrogenase, which is divided into two types and expressed in the liver and adipose tissue, is one of the important factors that alter the biological effects of steroids. Type 1 amplifies the local action of steroids to convert cortisone to cortisol, while type 2 predominates in renal tissue and minimizes the effect of converting cortisol to cortisone.[34]

The biggest glycogen reserve in the body is found in skeletal muscle, which accounts for 80% of postprandial glucose storage. Insulin and the availability of the glucose transporter type 4 (GLUT4) in the cell membrane are absolutely necessary for its storage. Steroids induce insulin resistance by directly interfering with signaling cascades, particularly the GLUT4 transporter, in muscle cells. As a result, insulin-stimulated glucose uptake is reduced by 30%–50%, and insulin-stimulated glycogen synthesis is reduced by 70%. [36,37]

Contrarily, steroids cause protein catabolism, which raises serum amino acids and disrupts insulin signaling in muscle cells. Protein catabolism results in an increase in serum amino acids. Additionally, they enhance lipolysis, which raises serum-free fatty acids and triglycerides. The liver utilizes gluconeogenesis and glycogenolysis to maintain euglycemia while an individual is fasting; these processes are inhibited by insulin when a person eats. Through the induction of enzymes that promote gluconeogenesis, increased lipolysis and proteolysis, increased mitochondrial activity, the enhancement of the effects of counter-regulatory hormones such as glucagon and epinephrine, and the induction of insulin resistance via the nuclear peroxisome proliferator-activated receptor (PPAR) α, GCs counteract the metabolic effects of insulin, particularly in the postprandial state. [34,38,37]

Steroids have direct impacts on different adipokines: (1) they increase the expression of resistin and adipokines, which alter glucose tolerance; (2) they decrease the expression of adiponectin, which increases insulin sensitivity; and (3) they increase the expression and secretion of leptin. They also decrease the production of insulin, and it is assumed that they decrease cell mass by causing beta cells to undergo apoptosis. Similar to the way the pancreatic beta cell increases insulin secretion in response to a decline in insulin sensitivity to maintain glucose homeostasis, but often this increase is insufficient to overcome insulin resistance, resulting in hyperglycemia. [34,35]

GCs cause a state of hyperinsulinism as a result of increased insulin resistance, as evidenced by the aforementioned. Whenever this mechanism arises in healthy individuals, it is counteracted by an increase in pancreatic insulin production, which maintains serum glucose levels within the normal range.[21] However, this balancing effect is lost in sensitive populations, such as normoglycemic individuals who have decreased insulin sensitivity and a low rate of production of the same before using steroids, leading to hyperglycemia. [34]

TREATMENT:

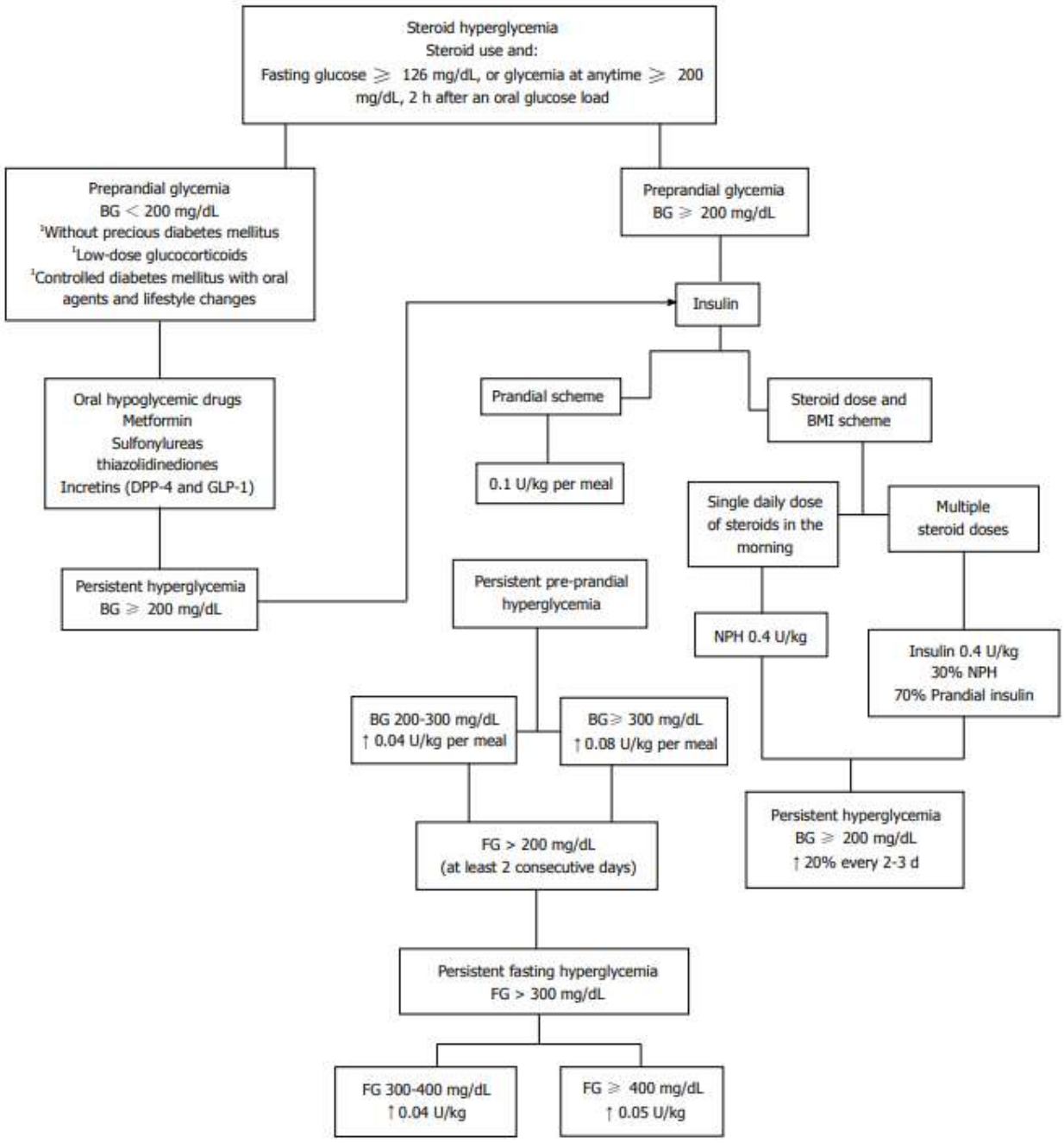
The approach to hyperglycemia should always be personalized due to variations in steroid dose and the employed strategy. [39]

The best treatment strategy for each patient must be determined after a comprehensive assessment 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, as well as the mechanism of action, pharmacokinetics, and pharmacodynamics of the various hypoglycemic drugs.. [37]

The first decision to be made when deciding on the appropriate treatment plan is whether to employ oral hypoglycemic medications or insulin. (Figure 1).

Algorithm for the management of glucocorticoids-induced hyperglycemia:

Figure 1



[Figure1 Adapted from] Glucocorticoid-induced hyperglycemia management algorithm. In cases of nocturnal hyperglycemia attributed to long-acting steroid treatment, glargine and other analogs may be suggested. [40] Calculatation 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.

CONCLUSION:

A wide range of medical conditions has been treated with GCs. Although steroid-induced hyperglycemia has been proven to be medically effective, it is still a widespread and potentially dangerous issue that must be taken into consideration when administering any GC dose. Although it occurs frequently, little is known about how steroid-related hyperglycemia affects clinical comorbidity and mortality. Since this would enable early detection and efficient treatment in these patients, a thorough understanding of the mechanisms causing steroid hyperglycemia is necessary. The most common scenario requires the use of insulin, particularly when the serum glucose level is greater than 200 mg/dL. However, in order to consider lifestyle modifications and oral hypoglycemic medications as alternate therapeutic options, a personalized strategy must be employed with each patient.

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