Current Perception of Steroid Induced Hyperglycemia

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Abstract

Although steroid medications are frequently recommended to treat inflammatory illnesses and prevent organ transplant rejection, they also increase the risk of hyperglycemia and type 2 diabetes. Through steroid signaling in metabolic organs and tissues (liver, adipose tissue, muscle, bone, and pancreatic beta-cells), as well as indirectly through inter-organ hormone and metabolite flow, steroid-induced hyperglycemia appears. Due to context-dependent considerations, there is no universal agreement on the best screening frequency for steroid-induced hyperglycemia, despite the recommendation to analyze postprandial glucose rather than fasting glucose. Although different steroid doses and types require different hypoglycemic medications (such as insulin sensitizers and insulin) to achieve adequate glucose control. The development of selective steroid modulators that separate the anti-inflammatory from the diabetogenic effects of steroids remains difficult; nevertheless, novel pharmacological targets that inhibit diabetogenic effects are soon to be available.

Keywords: *Steroid, Hyperglycemia, Diabetes mellitus, Treatment, Insulin*

INTRODUCTION

Drugs known as steroids have been used widely to treat a wide range of acute and chronic conditions(1). They are the mainstay in the treatment of many inflammatory diseases because, at supraphysiological levels, they inhibit the production of pro-inflammatory cytokines, T-cell activity, and antibody Fc receptor expression, which activate anti-inflammatory and immunosuppressive processes(2,3).

Much research has attempted to assess the impact of corticosteroids on the natural course of the disease since December 2019, when many instances of severe pneumonia brought on by the SARS-CoV-2 coronavirus were reported in China (4–6). The notion that the harm brought on by the illness is closely tied to the aggressive inflammatory response induced underlies the justification for the use of dexamethasone in patients with severe infection (7). The positive anti-inflammatory impact of dexamethasone (6 mg daily) has been emphasized in results from the randomized assessment of CovID-19 treatment (RECOVERY) study and other clinical studies in lowering the mortality of patients hospitalized with COVID-19. As a result, the administration of medications with strong anti-inflammatory actions may lessen the disastrous effects brought on by immune system overactivity and hasten the recovery of these individuals (8,9). However, the results that have been released thus far are ambiguous and conflicting.

The impact of inhaled corticosteroids on the replication of the SARS-CoV was examined in an in vitro investigation by Matsuyama et al. According to this study, ciclesonide inhibits SARS-CoV-2 viral replication by interacting with the recently identified coronavirus protein NSP15 during biogenesis. In contrast to systemic corticosteroids, ciclesonide is less likely to inhibit the immune system when inhaled, which is predicted to minimize viral multiplication and host inflammation in the lungs (10). Later, several case reports employing this medicine by Iwabuchi et al. were published, with encouraging outcomes (11).

When Lee et al. performed a meta-analysis of papers from January 2002 to March 2020 that included patients with severe coronavirus pneumonia, they discovered that those who received corticosteroid treatment had higher fatality rates, longer hospital stays, and rates of related subsequent bacterial infections (12). Similar findings were revealed by following meta-analyses (13,14). Even still, studies of other coronavirus epidemics were included in all meta-analyses, and there was still a dearth of thorough research that precisely evaluated how these drugs affected life-threatening SARS-CoV-2 infections.

Even while long-term steroid therapy has high therapeutic effectiveness for the treatment of inflammatory illnesses, it is constrained by a wide spectrum of side effects. According to estimates, between 40% and 56% of all inpatient consultations to endocrinology services are for newly developed or worsened diabetes brought on by the start of steroid usage (15). Hospital results may suffer if hyperglycemia hazards are not understood, even in patients without diabetes. According to prospective, observational research, patients with new hyperglycemia had a 16% in-hospital mortality rate, compared to 1.7% for those with normal glycemic control and 3% for those who had previously been diagnosed with diabetes and hyperglycemia ($P<0.001$) (16). Diabetes may also be brought on by untreated hyperglycemia brought on by steroid usage. An extensive case-control study has shown that oral steroid medication had an odds ratio of 1.36 for acquiring new-onset diabetes (17). Additionally, it has

been demonstrated that using steroids increases the chance of developing new cases of diabetes in senior people by 2.31 odds compared to those who do not use steroids (18).

PATHOPHYSIOLOGY

The synthesis of lipolysis, proteolysis, and hepatic glucose is increased by GCs because they act as a substrate for oxidative stress metabolism(19). Given that steroids enhance insulin resistance, which can range from 60% to 80% depending on the amount and type used(20,21), the mechanism causing glucose intolerance following GC treatment is comparable to that of type 2 DM.

The enzymatic activity of 11-hydroxysteroid dehydrogenase, which is divided into two types and expressed in the liver and adipose tissue and amplifies the local action of steroids to convert cortisone to cortisol, is one of the notable factors that modify the biological effects of steroids(19). Type 2 predominates in renal tissue and lessens the effect of converting cortisone to cortisol.

Skeletal muscle is the greatest store of glycogen in the body and is in charge of storing 80% of postprandial glucose. Its storage is entirely reliant on the availability of the glucose transporter type 4 (GLUT4) in the cell membrane and the presence of insulin. Steroids cause insulin resistance by directly interfering with signaling cascades, particularly the GLUT4 transporter, in muscle cells. As a result, insulin-stimulated glucose uptake and glycogen synthesis are reduced by 30 percent to 50 percent and 70 percent, respectively(22,23). Contrarily, steroids cause protein catabolism, which raises blood amino acids and disrupts insulin signaling in muscle cells. Protein catabolism results in a rise in serum amino acids. Last but not least, they boost lipolysis, which raises serum-free fatty acids and triglycerides. These inhibit the entrance and storage of intramuscular glucose while promoting the accumulation of intramyocellular lipids (acetyl coenzyme A, diacylglycerol, and ceramide)(19).

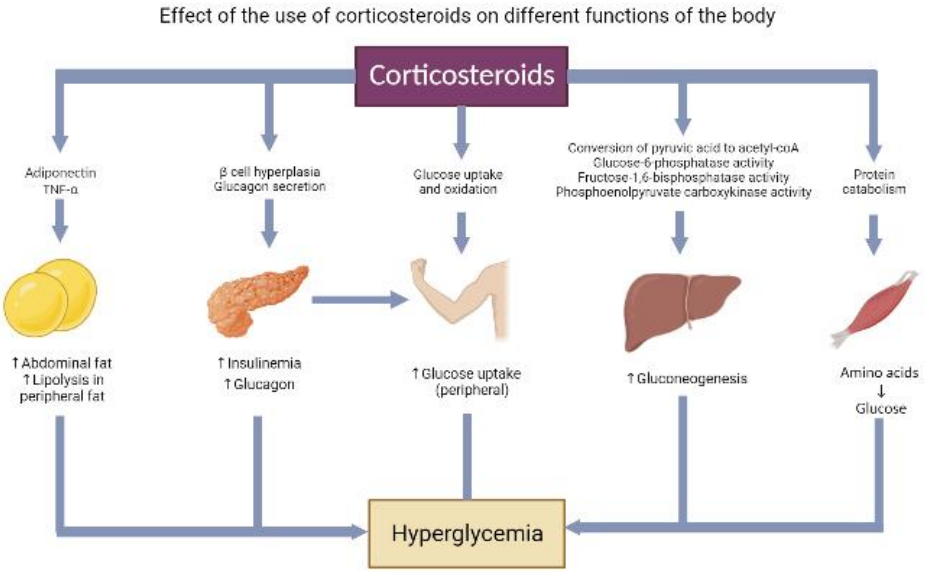
The liver uses gluconeogenesis and glycogenolysis to maintain euglycemia when a person is fasting; these processes are inhibited by insulin when a person eats. Through the induction of enzymes that promote gluconeogenesis, increased lipolysis and proteolysis, increased mitochondrial activity, the enhancement of the effects of counterregulatory hormones like glucagon and epinephrine, and the induction of insulin resistance via the nuclear peroxisome proliferator-activated receptor (PPAR)α (19,23,24), GCs counteract the metabolic effects of insulin, particularly in the postprandial state.

At the level of adipose tissue, they encourage visceral fat accumulation while decreasing peripheral reserves. Steroids have direct effects on many adipokines, including (1) elevating the expression of resistin and adipokines, which affect glucose tolerance, (2) lowering the expression of adiponectin, which increases insulin sensitivity, and (3) elevating the expression and secretion of leptin. The increase in triglyceride hydrolysis in adipocytes is also a result of them[4]. Increased plasma levels of unsaturated fatty acids, which accumulate in muscle cells and decrease glucose absorption by interfering with insulin signaling, are the end outcome of these effects(20,25).

It has been established that GCs modify pancreatic beta cell function by decreasing the expression of GLUT2 and glucokinase receptors while boosting the activity of glucose-6-phosphate dehydrogenase, which has an impact on β-oxidation. Additionally, they decrease the

production of insulin, and it's believed that by causing beta cells to undergo apoptosis, they also decrease the number of cells in the body. Similarly, the pancreatic beta cell generally increases insulin production in response to a decline in insulin sensitivity to maintain glucose homeostasis. However, occasionally, this increase is insufficient to make up for the rise in insulin resistance, which results in hyperglycemia(19,21).

Based on the above-mentioned, GCs cause hyperinsulinism by causing an increase in insulin resistance. The compensation for this process in healthy individuals is an increase in pancreatic insulin production, which keeps blood glucose levels within the normal range(20). However, this countering impact is lost in sensitive groups, such as normoglycemic people with decreased insulin sensitivity and a low rate of synthesis of the hormone before steroid administration, leading to hyperglycemia(19).



PHARMACOKINETICS AND PHARMACODYNAMICS

Contrary to expectations, there is surprisingly limited human data on the pharmacodynamics of GC-induced glucose intolerance despite the extensive history of clinical and experimental work with GCs. However, a logical time course for GC effects on glucose tolerance may be inferred from what has been documented. The plasma half-life of the regularly prescribed GCs prednisone or prednisolone is 2.5 hours, and plasma concentrations peak at about an hour after oral dosing (26). Dexamethasone has a similar pharmacokinetic profile as other steroids (27). When it comes to glucose tolerance, however, the pharmacodynamic profiles are longer and consistent with the genetic effects of the medications modulating gluconeogenesis and peripheral insulin sensitivity. Prednisone and prednisolone have effects that peak at 4 to 8 hours after administration and last for around 12 to 16 hours (26). This pattern, which resembles that of NPH insulin, serves as the foundation for our suggestions, which are discussed in the next portion of this review. Even though there are pharmacodynamic data on dexamethasone's impact on glucose levels, a recent study found that insulin levels were considerably higher 20 hours after dexamethasone was administered to healthy volunteers (28). According to this research, corticosteroids have a longer-lasting impact on insulin resistance than prednisone.

EFFECTS OF STEROID HYPERGLYCEMIA

Despite its prevalence, little is understood about how steroid-associated hyperglycemia affects clinical comorbidities and mortality. Rheumatic illnesses are the main cause of premature mortality in these people since they are a known significant cardiovascular risk factor. As a result, it is believed that having inflammatory illnesses and steroid-induced hyperglycemia concurrently may have harsher cardiovascular effects(3,29). The typical cardiovascular risk factor for microvascular and macrovascular problems is also present in diabetic patients.

Increased cardiovascular mortality has been linked to fluctuations in serum glucose levels, which are linked to elevated LDL cholesterol, endothelial dysfunction, activation of the coagulation cascade, increased production of pro-inflammatory cytokines, and oxidative stress, which leads to the progression of macrovascular disease(2). According to several studies, both diabetic and non-diabetic patients have transitory elevations in blood glucose that are linked to acute inflammatory reactions and endothelial dysfunction(20).

Acute hyperglycemia in hospitalized patients is linked to longer hospital stays more frequent ER visits, a higher risk of admission to critical care, a higher risk of infection, slower wound healing, and higher hospital mortality rates(16,30,31). Persistent hyperglycemia caused by GC usage can lead to hyperglycemic hyperosmolar states in vulnerable groups, such as the elderly, necessitating recurrent hospital hospitalizations for rigorous hydration and insulin treatment as well as a rise in consequences from inpatient hyperglycemia(32). A powerful predictor of graft failure in the transplant population, steroid hyperglycemia is also associated with a 2- to 3-fold greater risk of fatal and nonfatal cardiovascular events compared to non-diabetic patients(33,34).

TREATMENT OF STEROID HYPERGLYCEMIA

Patients should be examined for pre-existing diabetes mellitus (measurements of fasting plasma glucose and HbA1c1c) and risk factors for hyperglycemia, such as age, BMI, and family history, before beginning therapy with steroids(35,36). A minimum of 1-3 days following the start of steroid treatment, plasma glucose levels ought to be checked(20,37). If a patient is hospitalized or already has T2DM, monitoring their plasma glucose levels more frequently is advised(38,39). After the first year, monitoring should be done annually at regular intervals of three to six months(37). Similar to other types of diabetes mellitus, the following criteria must be met to diagnose steroid-induced diabetes mellitus: fasting plasma glucose concentration ≥7.0 mM, random plasma glucose concentration ≥11.1 mM, HbA1c1c ≥6.5% (48 mmol/mol), or plasma glucose concentration ≥11.1 mM 2 hours after an oral glucose tolerance test (OGTT)(40). Postprandial glycemia is more significantly impacted by steroid exposure than fasting glucose(20). Because fasting plasma glucose is measured more frequently than the time-consuming OGTT, the prevalence of steroid-induced hyperglycemia is likely underestimated(41). The best way to identify steroid-induced diabetes mellitus is to determine postprandial glycemia 2 hours after lunch and/or to perform an OGTT(41,42). The Joint British Diabetes Societies' management recommendation states that treatment should begin when plasma glucose levels are repeatedly less than ≥12 mM. A glucose level of ≤10 mM is the target of hypoglycemic therapy in steroid-induced hyperglycemia(38,43).

The effectiveness of oral hypoglycaemic medicines on steroid-induced hyperglycemia has only been sporadically studied in clinical trials. Because there are so many different variables at play, there is currently no universally accepted consensus on the best course of action for treating this illness. Many oral hypoglycaemic medications have a slow onset of action and limited dose titration flexibility, making it challenging to match the hypoglycaemic medication to the hyperglycaemic oscillation brought on by steroids(20). In addition to taking into account the underlying patient comorbidities, concurrent drug use, and the severity of the hyperglycemia brought on by the administration of steroids, individualized treatments are required. Short- and intermediate-acting steroids can cause quick and substantial changes in glycemia, with maxima occurring within 4–8 hours of the administration and falling during the night(38,44). They are frequently transiently supplied with a high initial dose and decreased over time. To reduce the incidence of nocturnal hypoglycemia, hypoglycaemic medications with high potency and rapid onset should be used(20,38). Hyperglycemia can last for up to 24 hours in individuals using long-acting steroids or those who take numerous doses each day. As a result, therapies with a protracted duration of action are preferred because they allow for flexible-dose modifications without worsening other steroid-dependent side effects(45). The kind of steroid, as well as the pharmacokinetics and pharmacodynamics of the various hypoglycaemic medications, should be taken into account when designing treatments to address the pattern of steroid-induced hyperglycemia(41).

Table: Hypoglycaemic agents in steroids-induced hyperglycemia and diabetes mellitus

Drug class	**Evidence in patients with steroid-induced diabetes mellitus**	**Suitable for the type of Steroid drug?**	**Advantages**	**Disadvantages**
Sulfonylureas	Improved fasting glucose(46)	Intermediate-acting (two or more daily doses) or long-acting steroids; intra-articular steroids	Immediate onset of action	Long-acting; high risk Of hypoglycemia; not specific to postprandial glucose
Glinides	Improved postprandial glucose(47) and mean glucose(47,48); improved mean HbA1c, in combination with other immunosuppressants(49)	Short-acting steroids	Immediate onset of action; short-acting; targets postprandial glucose; low risk of hypoglycemia	Frequent dosing; high cost

Incretin-based therapy: GLP1 receptor agonists	Improved mean and postprandial glucose(50,51); reduced the insulin dose and injection frequency in combination with basal-bolus insulin(52)	Intermediate-acting or long-acting steroids	Immediate onset of action; targets postprandial glucose; low risk of hypoglycemia	Limited evidence; gastrointestinal and renal adverse effects; high cost
Incretin-based therapy: DPP4is	Improved(53,54) or unaffected(55,56) postprandial glucose; improved mean glucose(54) and HbA1c levels(53)	Intermediate-acting or long-acting steroids	Immediate onset of action; targets postprandial glucose; low risk of hypoglycemia	Contradictory evidence; high cost
metformin	Improved postprandial glucose(57); improved AUC of glucose during OGTT(58), fast glucose, and HbA1c levels(59)	Intermediate-acting steroids	Low risk of hypoglycemia; low cost	Slow onset of action; avoid use in renal impairment
Thiazolidinediones	Improved AUC of glucose during OGTT and HbA1c, levels(60) in combination with insulin(61)	Intermediate-acting steroids	Low risk of hypoglycemia	Slow onset of action; promotes weight gain (shared adverse effects with steroids)
SGLT2is	No improvement in mean glucose when used as an add-on to other hypoglycemics(62)	Insufficient data (has not been tested without other hypoglycemic agents)	Immediate onset of action; Low risk of hypoglycemia	Limited evidence; promotes bone fracture (shared adverse effects with

				steroids)
α-Glucosidase inhibitors	Improved postprandial glucose levels in combination with glinides(48)	Insufficient data (has not been tested without other hypoglycemic agents)	Immediate onset of action; Targets postprandial glucose: low risk of hypoglycemia	Limited evidence; only provides weak hypoglycemic effect

CONCLUSION

Due to their potent immunosuppressive and anti-inflammatory properties, Steroids are essential. However, their therapeutic effectiveness has been reduced due to the negative metabolic side effects of prolonged usage, such as hyperglycemia and diabetes mellitus. The steroid-induced hyperglycemia's underlying molecular pathways are complex and involve several organs. It is challenging to determine which individuals may have negative metabolic consequences since organs and tissues either fail to remain responsive to insulin or encourage insulin resistance through inter-organ interaction. Due to this information gap, steroid exposure-related hyperglycemia and diabetes mellitus have been poorly managed clinically. It is important to develop global standards that take into account the individual patient's therapeutic tolerance, steroid treatment variations, genetic predisposition, and concomitant conditions.

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