

Incretin Based Therapy in the Management of Steroid Induced Diabetes Mellitus

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Abstract: Corticosteroid-induced hyperglycemia is a common medical problem which can cause frequent hospitalizations and therefore relates to an increase in morbidity. Metformin, sulfonylureas, thiazolidinediones and insulin are well known available therapies for the treatment of steroid induced hyperglycemia.

Incretin based therapies are a newly developing strategies with a considerable importance in the treatment regimen as well. This review aims at discussing the pathophysiology of steroid induced hyperglycemia in addition to the available therapies used for treatment, focusing on incretin therapies.

Keywords: Hyperglycemia, corticosteroids, incretins, diabetes mellitus.

INTRODUCTION

Glucocorticoids are the most commonly used medications all over the world. They are used to treat a variety of medical diseases such as exacerbation of obstructive pulmonary disease, autoimmune diseases, rheumatologic diseases, neurologic diseases as well as inflammatory bowel diseases.

With the widespread use of steroids, the side effects of those medications became more prevalent throughout time. Common encountered side effects of glucocorticoids use are weight gain, Cushingoid features, gastritis, gastrointestinal bleed, osteoporosis, myopathy in addition to infections and hyperglycemia.

The importance of steroid induced hyperglycemia has been appreciated since a long time, a study dating back to 1994 evaluated 11 855 patients receiving hypoglycemic therapy receiving steroids. It showed that the relative risk of development of hyperglycemia was 2.23 compared to nonusers [2].

The length of corticosteroid course, its dose and its potency are major predictors of the development of steroid induced diabetes mellitus.

MECHANISMS OF STEROID INDUCED HYPERGLYCEMIA

Corticosteroids cause hyperglycemia by increasing gluconeogenesis, and this is mainly caused by the activation of genes participating in the metabolism of carbohydrates in the liver [20]. They suppress phosphoenolpyruvate carboxykinase gene expression, the enzyme responsible of controlling the release of free fatty acid from adipose tissue and its synthesis in the liver thus leading to an increase in fatty

acid in the blood interfering with the utilization of glucose and inducing insulin resistance [1].

Glucocorticoids interfere with the insulin signaling cascade, at the level of glycogen synthase kinase-3 and glycogen synthase as well as GLUT4 translocation thereby affecting the insulin mediated uptake of glucose into the cells [1].

In addition, steroids increase the effects of other counter-regulatory hormones, such as glucagon and epinephrine, enhancing the endogenous production of glucose [20].

Acute treatment with glucocorticoid leads to the inhibition of cell function while prolonged glucocorticoids use leads to partial recovery of beta cell function. *In vitro* studies showed that it mainly binds to insulin receptors causing impairment in endoplasmic reticulum homeostasis leading therefore to beta cell death [1]. Glucocorticoids were also reported to increase glucagon secretion at baseline in addition to its secretion following meals [4].

Glucocorticoids potency affect the degree of hyperglycemia. In addition, Increasing glucocorticoid dosage causes insulin resistance and therefore leads to glucose intolerance and diabetes in patients at risk. For example, treatment with prednisolone causes a reduction in C peptide which was dose dependent. Similarly, fasting glucagon levels increases as the dose of prednisolone increases, whereas postprandial glucagon levels increases by prednisolone at a dose of 30 mg [17].

Steroids were shown to impair the effect of incretin. This was demonstrated in a prospective trial that subjected 10 healthy non-diabetic men to 12 weeks of oral prednisolone in addition to intake of high-energy diet, and absence of strenuous physical activity; the patients were subjected to 75 oral glucose tolerance test and intravenous glucose infusion. An increase in glucose-dependent insulinotropic polypeptide response was documented during oral glucose tolerance test (OGTT), demonstrating an impairment of the incretin effect [9].

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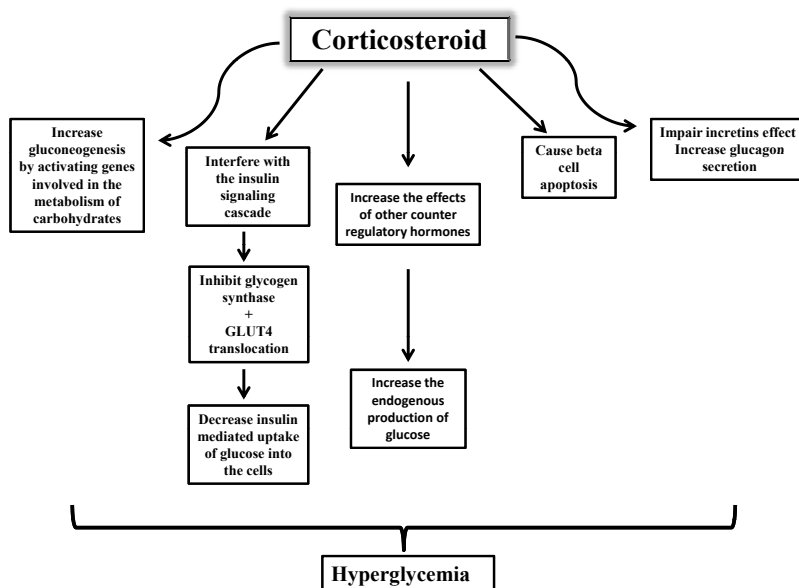


Fig. (1). Mechanisms of Steroid Induced Hyperglycemia.

In a study involving first degree relatives of patients with type 2 diabetes, 75 g oral glucose tolerance test, an isoglycaemic intravenous glucose test and a mixed meal were conducted on 20 patients in order to observe the effect dexamethasone in increasing insulin resistance and specifically its effect on incretin levels.

After receiving dexamethasone, half of the patients enrolled had increased insulin resistance but normal glucose tolerance, while the other half who had an equal increase in insulin resistance developed impaired glucose tolerance. After treatment with dexamethasone, incretin effects decreased significantly after treatment. In addition, patients had an enhanced response of total glucagon-like peptide-1 and glucose-dependent insulinotropic peptide to the OGTT [18].

In another study involving 10 non-diabetic adult, glucose homeostasis was dysregulated (including insulin resistance and reduced postprandial glucose tolerance) using prednisolone, high-calorie diet, and relative physical inactivity, the intervention also resulted in exaggerated postprandial glucagon dependant insulinotropic polypeptide (GIP) and glucagon responses [16].

Immunosuppressive therapy which is used commonly with corticosteroids such as tacrolimus and mycophenolate mofetil has also been documented to suppress insulin production and secretion adding to the effect of steroid [1].

THERAPY FOR STEROIDS INDUCED HYPERGLYCEMIA

The options for therapy of steroids induced hyperglycemia include: combination of basal and prandial insulin since the hyperglycemia is transient; in addition, short acting secretagogues targeting post prandial hyperglycemia are commonly used [1].

Metformin can be used because of enhancing insulin sensitivity. However, there are no published trials of its use [19].

Troglitazone, the first clinically applied drug of thiazolidinedione derivatives, was shown to improve dex-

amethasone -induced insulin resistance, which in turn was not improved by metformin or pioglitazone. This finding was explained by the fact that troglitazone administration decreased the serum concentration of orally administered dexamethasone, and this is secondary to the enhancement of its metabolism by CYP3A4 as was demonstrated *in vivo* studies. However, troglitazone is no longer available for therapy because of its liver toxicity. On the contrary, pioglitazone does not enhance the activity of CYP3A4 and therefore does not affect pharmacokinetics of dexamethasone [5].

INCRETIN BASED THERAPY

Glucagon dependant insulinotropic polypeptide (GIP) and glucagon like polypeptide-1 are both secreted following ingestion of a meal and act on islet -cells acting through their corresponding receptors. Incretin-receptor activation induces beta-cell proliferation and inhibits apoptosis.

GIP promotes energy storage *via* direct actions on adipose tissue, and enhances bone formation by stimulating osteoblast proliferation and inhibiting their apoptosis.

In contrast, GLP-1 regulates glucose by slowing of gastric emptying and *via* glucose-dependent inhibition of glucagon secretion. It also promotes satiety and weight reduction as was shown in both preclinical and clinical studies [8].

GLP-1 and synthetic dipeptidylpeptidase- 4 resistant GLP-1 receptor agonists (GLP-1 RAs), known as exenatide, decrease blood glucose by increasing insulin secretion and production and inhibiting glucagon secretion, and delaying gastric emptying [8].

INCRETIN BASED THERAPY FOR THE USE OF GLUCOCORTICOID INDUCED HYPERGLYCEMIA

Exenatide is a GLP-1 receptor agonist that increases glucose-dependent insulin secretion and decreases glucagon secretion after a meal. It therefore decreases serum glucose level. As discussed earlier, it delays gastric emptying and acts centrally to promote satiety. In diabetic patients, it was

shown to reduce HbA1c (range; -0.4% to -1.3%), it also significantly decreased fasting and postprandial blood glucose levels and is the only antidiabetic agent (together with liraglutide; a human GLP-1 analogue) to promote weight loss [10].

In vitro studies showed that the GLP-1 receptor agonist exendin-4 was shown to prevent beta-cell apoptosis that was caused by steroid administration *in vitro* [7]. Another trial showed that one dose of exenatide was able to decrease glucose intolerance and insulin resistance in mice [14]. *In vivo* it was found to improve beta cell function.

In a 52 week trial involving 69 diabetic patients randomized to receive exenatide or insulin glargine, beta cell function secretion was 2 fold greater in the group that received exenatide as compared to the group that received insulin after 4 weeks off the drug therapy [6].

A recent randomized placebo controlled trial evaluated the effect of exenatide compared to placebo (saline) in 8 healthy young men after a challenge with 80 mg of oral prednisolone for 3 consecutive days. As expected, steroid increased postprandial glucose significantly ($p = 0.012$). This increase was prevented by the use of exenatide when compared to no significant effect with placebo. Exenatide reduced steroid induced hyperglucagonemia during the meal challenge and delayed gastric emptying significantly. It also significantly improved C-peptide secretion [3].

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent the inactivation of glucagon-like peptide-1 (GLP-1), thereby enhancing the action of these two stated molecules, stimulating insulin secretion and inhibiting glucagon secretion [15].

In animal based studies, DPP4 was found to have a very important role in regulating the expression of factors related to steroid metabolism such as Cyp51 [12].

Hidekatsu *et al.* showed significant response in an 80 year old woman with steroid induced diabetes after starting DPP 4 inhibitor (sitagliptin) which was translated in a decrease in the requirement of rapid acting insulin and the postprandial glucose level by 150 mg/dL. This effect was not observed after the addition of metformin, nateglinide or pioglitazone [11, 15].

GLP 1 Agonist vs. DPP 4

In a 2-week duration randomized controlled trial, exenatide was shown to be superior than sitagliptin in lowering postprandial glucose. It also had a more potent effect in increasing insulin secretion and reducing postprandial glucagon secretion in type2 diabetic obese patients. Exenatide slowed gastric emptying and reduced caloric intake. This effect was not observed in the sitagliptin group [13].

The cost of DPP 4 inhibitors and GLP 1 agonists ranges between 60 to 130 \$ monthly for DPP 4 inhibitors, and up to 200\$ monthly for the GLP 1 agonists. The enteral route of administration of DPP 4 inhibitors, their weight neutral effect and their low risk of hypoglycemia favor their use when compared to other oral hypoglycemic agents and insulin therapies. As for GLP 1 agonists, their beneficial effect on

weight and similarly the low incidence of hypoglycemia may balance their increased cost in some circumstances. Therefore, harms and benefits of each medication should be well balanced before its administration.

CONCLUSION

In conclusion, patients treated with corticosteroids may benefit from incretin based therapy such as dipeptidyl peptidase (DPP)-4 inhibitors and GLP 1 agonists as shown by several small animal and human trials. They showed particular benefit regarding their effect on postprandial glycemia, and their lack of risk of hypoglycemia related to glucose-dependent effects. However, the potential risk of pancreatitis should be kept in mind accompanying the use of DPP 4 inhibitors. They should also be avoided in patients with suspected pancreatic disease. Further large randomized controlled trials are needed in order to validate their use in patients on steroid therapy. Finally, for patients with moderate or severe hyperglycemia, insulin or insulin analogues should still be the preferred treatment regimen [20].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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