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A REVIEW ON GLUCOCORTICOID-INDUCED HYPERGLYCEMIA

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ABSTRACT

To review the available literature on glucocorticoid-induced hyperglycemia and providing a strategical therapy. Glucocorticoids are widely used to treat several disease condition. The major adverse effect of glucocorticoidis hyperglycemia. Its incidence is more in long term treatment with glucocorticoid. Several risk factors like infection, keto-acidosis, cell dysfunction is associated with glucocorticoid induced hyperglycemia. So consideration should be done before the treatment with glucocorticoids. Glucocorticoid-induced hyperglycemia occurs in non-diabetic patients and also with previously known diabetes patients. The hyperglycemia induced by steroids may be symptomatic or asymptomatic. In case asymptomatic it worsen the patient's condition. So glucose level should be monitored periodically and this condition is caused by steroid effects over beta pancreatic cell, insulin sensitivity and glucose production. The dosing modification and glycemic control both play an important role in managing glucocorticoid-induced hyperglycemia and also if it is recognized early it can be effectively treated with insulin and oral hypoglycemic medications. Oral hypoglycemic agent impact the blood glucose lowering so post prandial blood glucose level is improved. If blood glucose level is not controlled by oral hypoglycemic agents insulin is suggested for further treatment. Insulin is the treatment of choice

in a patient with persistent hyperglycemia >200mg/dl, it has an immediate onset of action, and up-titration to an effective dose is relatively easy.

Keywords: Glucocorticoids, Hyperglycemia, Insulin, Oral Antidiabetic agents, Diabetes mellitus

INTRODUCTION

Steroid-induced hyperglycemia is a serious problem. Steroids are the drugs used to treat complex disease conditions like respiratory disease, rheumatoid, organ transplantation, hematologic malignancies, if DM is induced by steroids then it is called steroid Diabetics Mellitus and the widely hospitalized patients suffer side effects because of its use, in general, there are two condition due to effect of glucocorticoids, the first is hyperglycemia (if the patient was nondiabetic), here the patient experience increased blood glucose level due to the management with corticosteroid and this condition may or may not be reversible, if not reversed newly it leads to Diabetics Mellitus. This condition is common in the patient who is taking glucocorticoids as the long-term treatment if the patient already suffering from uncontrolled Diabetics Mellitus. Steroids worsen the Diabetics Mellitus over the glycemic control and lead to micro and macro vascular disease. If, no dose adjustment in corticosteroid is done**.**

A prospective, for those patients with new hyperglycemia compared with an in-hospital mortality rate of only 1.7% for those with normal glycemic control and 3% mortality rate for those with previously known diabetes and hyperglycemia (P<0.001) **[37]**. Untreated hyperglycemia results from glucocorticoid use can trigger developing diabetes. People with in-hospital hyperglycemia and previously undiagnosed diabetes should be referred to the diabetes team for follow-up and evaluation of diabetes status, with the initiation of therapeutic measures if appropriate. Targeted glycemic control therapy in hospitalized patients has been demonstrated to exert a positive effect on patient outcomes. Glucocorticoid-induced hyperglycemia can be controlled either by adjusting insulin or changing the antidiabetic regimen. So the patients were recommended to treat with glucocorticoids who develop hyperglycemia should be treated with a basal-bolus insulin regimen at a starting dose of 0.3 to 0.5 units/kg/day.

Hyperglycemia: It is defined as the blood glucose level is greater or equal to 200 mg/dl **[7]**.

Diabetes Mellitus: It is the condition of hyperglycemia ranges fasting blood glucose level greater or equal to 126mg/dl, a random

plasma glucose concentration greater or equal to 200mg/dl and plasma glucose concentration greater or equal to 200 mg/dl, 2hr after the 75g oral glucose and the Haemoglobin A1C (HBA1C) is greater or equal to 6.5 % **[8]**.

Corticosteroids:

Corticosteroids are engineered compounds and of two kinds to be specific glucocorticoid (metabolic), mineralocorticoid (electrolyte managing) principally utilized in the substitution treatment when endogenous creation is debilitated. The clinical use and the withdrawal of the drug are more complex as it exerts its action over the other organ. So treatment with corticosteroid should be done with consideration.

CLASSIFICATION OF GLUCOCORTICOIDS [17]:

SHORT ACTING: Hydrocortisone

INTERMEDIATE ACTING: Prednisolone, Methyl prednisolone,

LONG ACTING: Dexamethasone, Betamethasone.

Corticosteroids in the carbohydrate and protein metabolism:

It widely affects the metabolism of carbohydrates and protein. Glucocorticoids exert their effect as intermediatary metabolites in protecting glucose-dependent tissues (heart and brain) from starvation but, over the periphery, they diminish the glucose utilization and increase the protein breakdown and synthesis of glutamine and activate lipolysis which gives aminoacid and glycerol for gluconeogenesis (production of glucose from noncarbohydrate compound). This prompts a increase in the blood glucose level the rest is put away in the liver as glycogen. From the pharmacological action of steroids over carbohydrate and protein metabolism, it is clear that the steroid induces hyperglycaemic conditions.

Absorption:

Steroids are orally effective and water-soluble administered mostly in IV the route which rapidly achieves high concentration in the body fluid exerts prolong effect and any alteration in the chemical structure changes its absorption, time of onset, duration of action.

Transport metabolism and excretion:

Corticosteroids are reversible bonding with protein and the unbound drugs enter the cell to produce its effects. Two types of protein are present with steroid-binding capacity as CBA (corticosteroid-binding albumin) and CBG (corticosteroid-binding globulin) which relatively has low total binding capacity but has a high affinity for steroids. Its t1/2 is about 1.5 hrs longer t1/2 because intracellular receptors regulate protein synthesis so effects

remain even after the steroid is removed from the plasma.

Steroids are metabolized by hepatic microsomal enzymes and futherconjucated by glucuronic acid or sulfate and excreted through urine **[17]**.

Incidence:

Glucocorticoid induced hyperglycemia occur in about 64% patients **[11]**.

In view of the examination of the New Jersey Medicaid program proportion of 2.23 happened diabetics mellitus and companion study was finished with the patients with RA (steroids are utilized regularly and for long haul) with moderate acting glucocorticoids and the outcome was discovered twice than the normal rate **[1]**.

No association with the steroid-induced diabetics with injected, inhaled, topical glucocorticoids, glucocorticoid eyedrops and this is more common among the patients who are treated with three or more oral glucocorticosteroid (high dose) in their prescription **[2]**.

Alongside portion and term of steroid treatment age, weight, past glucose prejudice, decreased affectability to insulin, debilitated insulin discharged by beta-pancreatic cell because of the incitement of glucose, family ancestry, race matters for the steroid-prompted hyperglycemia **[3].**

Drug-induced glycemia is asymptomatic **[8]** but in certain conditions, severe fatigue nausea, blurred vision, polydipsia, polyuria, become very dehydration, common ADR affecting 20% to 40% patients without a history of DM, glucose often elevated among the patients with prediabetics and previously well-controlled diabetes during the steroid treatment **[13]**.

Risk factors:

There are several factors due to steroid-induced hyperglycemia they are infection, poor CVS condition, thrombosis, inflammation, endothelial cell dysfunction, enhanced neuronal damage after ischemic brain injury, most common is ketoacidosis or hyperosmolar coma, In nondiabetic, if the patient experiences steroid-induced hyperglycemia persistent chance to develop diabetes mellitus. Risk factors should be taken into consideration before therapy and monitor the patient hyperglycemic level frequently during the treatment **[7]**.

PATHOPHYSIOLOGY:

A study was conducted in the rodent with steroids the result was found to be i) reduce uptake and the oxidation of various metabolites ii) increase the potassium efflux and limit the calcium influx (but the insulin secretion remain unaffected by this alteration. iii) decrease the effect of calcium

ions over the insulin secretion iv) alters the parasympathetic nervous system. Indirectly the beta cell failure can derive from elevated levels of triglyceride and NEFA (NON ESTERIFIED FATTY ACIDS) the so-called lipotoxicity **[3]**. If two-week continuous exposure to the glucocorticoids causes pancreatic dysfunction in the healthy person due to the pro-apoptotic effect of glucocorticoid which causes decreased pancreatic secretion along with reduced insulin sensitivity and increased glucose production.

Inhibitionthe production and the secretion of insulin by beta-pancreatic cell:

Chronic treatment with a corticosteroid may induce beta-cell failure indirectly by lipotoxicity due to the accumulation of pancreatic fatty acids by elevating plasma levels of free fatty, triglycerides acids this causes inhibition in the production and secretion of insulin by beta-pancreatic cells **[3]**.

Reduce insulin sensitivity:

Corticosteroids incite to meddle directly with different parts of the insulin flagging course. Fringe glucose take-up was finished with GLUT4 carrier in the cell layer. Movement of the GLUT4 to the cell surface in reaction to insulin was hindered by the corticosteroid. These cause decrease glucose uptakes it also alters the protein and lipid metabolism which cause reduce insulin sensitivity in muscle **[3]**.

Increased glucose production:

Whenever the glucose is present the insulin suppresses the endogenous glucose production corticosteroids also increase the endogenous glucose production directly by activation numerous genes involved in the hepatic metabolism of carbohydrates leading to the increment in gluconeogenesis (phosphoenolpyruvate carboxy kinase and glucose 6 phosphates) and also indirectly antagonize the action of insulin and also increase gluconeogenesis from adipose tissue and muscles and the transport of the metabolites across the mitochondrial membrane which increase gluconeogenesis **[3]**.

MANAGEMENT OF GLUCOCORICOID INDUCED HYPERGLCEMIA

The administration for glucocorticoid-prompted hyperglycemia traces the utilization of the principal line oral medicines and other noninsulin treatments and talks about the proposal for insulin use when glucose targets are not met utilizing other antidiabetic specialists **[18]**.

Non Insulin Agents

Glimepiride is the first choice oral treatment for hyperglycemia arising from corticosteroid

use as their might impact blood-glucose-lowering it's immediate and postprandial hyperglycemia is improved **[20, 25]**. However, sulfonylurea may pose a risk of hypoglycemia due to long duration of action **[21]**. Metformin closely counteracts the effect of glucocorticoids by enhancing insulin sensitivity and reducing gluconeogenesis, Similarly a recent double-blind, placebo-controlled trace in which adult patients on initiation of Glucocorticoid therapy were randomized to either metformin or placebo, suggested that metformin may reduce metabolic complications of a patient requiring glucocorticoid treatment **[22]**. In any case, in patients requiring longterm glucocorticoid use in whom renal and liver capacity is adequate, metformin could be a sensible decision. Repaglinide demonstrates immediate onset of action has a low risk of hypoglycemia band can be titrated in small increments **[19, 23]**. An observational study showed that 14 out of 23 patients with new-onset diabetes after renal transplant were successfully treated with Repaglinide. After 6 months, patients receiving repaglinide had reduced their HBA1C from a mean of 7.6 % to 5.8% ($p<0.05$) **[24]**. When GC is administered in a morning daily dose, insulin secretagogues are a reasonable choice **[23, 25]**. Incretin specialists, dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins), and glucagon-like peptide (GLP-1) agonists act by invigorating insulin emission and smothering glucagon creation postprandially. In contrast, a small double-blind, placebo-controlled trial evaluating the effect of prednisolone 30 mg on glucose metabolism in 38 men with metabolic syndrome demonstrated that the addition of sitagliptin 100mg did not prevent postprandial hyperglycemia from prednisone **[26]**. Another little examination assessed 11 Japanese patients with ongoing kidney sickness who got dosed alogliptin for steroid-initiated hyperglycemia alogliptin administartion brought about diminished postprandial hyperglycemia ($P=0.0031$) diminished HBA1C ($p=0.0033$) and expanded GLP-1 focus ($P=0.0014$) **[27]**. Exenatide therapy significantly reduced the 4-hour glucose area under the curve during a meal challenge test compared with placebo plus saline ($P =0.025$), decreased insulin glucagon levels after a meal ($P=0.017$ AND $P=0.018$ respectively), and improved insulin sensitivity ($P=0.012$) **[28]**. Use of TZD (for example, rosiglitazone and pioglitazone) has also been suggested. These agents have been used for the long-term treatment of transplant–induced diabetes mellitus with some success in combination with other agents **[29, 31]**. Thiazolidinediones are

associated with fluid retention which could be exacerbated by glucocorticoids. There is also increasing concern for edema, congestive heart failure, and a possible risk of cardiovascular disease with the use of TZD **[32]**.

Insulin Agents

In the event that Glucose targets are not arrived at most extreme portions of sulfonylurea or meglitinide with or without the utilization of antidiabetes specialists, then, at that point insulin ought to be considered **[33]**. Insulin is the treatment of decision in a patient with constant hyperglycemia >200mg/dl, it has a prompt beginning of activity, and up-titration to a powerful portion is somewhat simple. The basic thought is that if we can give specific insulin simultaneously with glucocorticoid administration, we would be able to neglect the hyperglycemic effect of glucocorticoid **[34]**. Basal bolus regimens are premixed insulin appear to be a suitable and equally effective option **[33]**. It is recommended that patients treated with glucocorticoids who develop hyperglycemia should be treated with a basal/bolus insulin regimen at a starting dose of 0.3 to 0.5U/Kg/day. Recently published guidelines did not specifically comment on the potential for increased nutritional insulin needs in patients receiving glucocorticoid but recommend IV insulin infusion when the basal-bolus approach is not effective **[35]**. A preferred option for steroid-induced diabetes may be weigh based neutral protamine Hagedorn (NPH) insulin dose once daily to be given at the same time as the study. Weight-based NPH insulin at 0.1U/kg is for every 10-mg of prednisone up to a maximum of 0.4U/kg is recommended to initiate **[36]**. Just as prednisone and prednisolone have a peak action at 4-8 hours 12-16 hours, NPH insulin has a similar action profile. A suggested weight-based algorithm for insulin based on the known dose-response effects of GC on insulin sensitivity is shown in **Table 1**.

Table 1: Estimation of initial dose of insulin in glucocorticoid-induced hyperglycaemia (Suh and park, 2017)

Estimation of initial dose of insulin in glucocorticoid-induced hyperglycaemia (Suh and park, 2017)	
Prednisolone dose (mg/day)	**Insulin dose (units/ kg body weight/ day)**
40	**0.4**
30	**0.3**
20	**0.2**
10	**0.1**

For patients receiving a daily twice the dose of glucocorticoid, it may be reasonable to substitute insulin glargine or insulin detemir for NPH insulin to mirror a longer duration of hyperglycemia. Additionally if fasting blood glucose is controlled (5-7mmol/L) yet postprandial readings stay high notwithstanding the utilization of NPH insulin, then, at that point a quick acting insulin simple could be presented with lunch or evening supper (eg: insulin aspart, insulin lispro, or insulin glulisine).

Specific regiemens:

The individual with type 2 diabetes is now kept up with, on a once-day by day portion basal insulin, then, at that point on account of once-every day morning oral steroid, this ought to be changed to a morning infusion (whenever infused in the evening) and titrated vertically in additions of 10-20% dependent on the pre-evening feast glucose level **[25]**. Nateglinide is a short-acting glucose-lowering drug for the therapy of patients with type 2 DM, in a multicentered, multinational study. They didn't observe any serious adverse effects, so treatment with nateglinide may thus be suitable for glucocorticoid-induced DM in patients with primary renal disease **[1]**.

CONCLUSION

We conclude that steroid-induced hyperglycemia should be considered as it has leads to several complications if there is no consideration was taken widely with long-term use of glucocorticoids. In case of any complication, dose adjustment should be done mean while condition should be managed with hypoglycaemic drugs and insulin.

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