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Steroids and diabetes – myth or reality

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Abstract

The label "steroid" is a general term. Glucocorticoids (GCs) are frequently prescribed anti-inflammatory and immunosuppressive drugs. In addition to their beneficial effects on disease activity, GCs have an extensive side effect profile, including adverse effects on metabolism resulting in the development of glucose intolerance and overt diabetes.

Recent developments have led to renewed interest in the mechanisms underlying these diabetogenic effects of GCs. First, dissociated glucocorticoid receptor (GR) agonists were developed which are designed to segregate the anti-inflammatory and metabolic actions of GCs, potentially rendering compounds with a higher therapeutic index.

Second, at present, 11-beta hydroxysteroid dehydrogenase type-1 inhibitors are under development. These compounds may lower tissue GC concentrations by inhibiting cortisone to cortisol conversion and are being evaluated in clinical trials as a novel treatment modality for the metabolic syndrome.

Here, we provide an up-to-date overview of the current insights regarding the mechanisms responsible for the adverse metabolic effects of GCs that may lead to steroid diabetes. Particularly, we will focus on GC-related induction of insulin resistance and pancreatic islet-cell dysfunction.

Finally, we will discuss how increased knowledge concerning the pathophysiology of steroid diabetes may result in improved treatment strategies.

Keywords: Pancreatic islet-cell dysfunction, glucocorticoids, insulin resistance, steroid diabetes

Introduction

Glucocorticoid (GC) hormones are secreted by the cortex of the adrenal gland, under control of the hypothalamic-pituitary-adrenal axis. GCs are stress hormones that facilitate a flight or fight reaction by providing substrate for oxidative metabolism by increasing hepatic glucose production, adipose tissue lipolysis and proteolysis, and by maintaining adequate blood pressure[1].

In the clinic, synthetic GCs are extensively used in the treatment of numerous disease entities due to their potent anti-inflammatory and immunosuppressive actions when administered at pharmacological dosages. GCs affect both the innate and the acquired immune system.

As such, GCs impair the ability of leukocytes to exit the bloodstream and enter sites of infection and tissue injury, resulting in suppression of the inflammatory response. In addition, GCs impair the phagocytic function of macrophages and reduce the production of inflammatory cytokines required for inflammatory responses.

Moreover, GCs reduce the activity of the acquired immune system by inducing T-cell depletion, while B-cell function is mostly minimally altered by GC treatment[2].

How do steroids affect blood glucose

Steroid treatment increases the amount of glucose produced by the liver. Steroids can also make your body produce less insulin than usual, which is the hormone that controls glucose levels in the blood.

If your body is unable to make enough insulin to deal with the increased production of glucose by the liver, your blood glucose levels will rise above normal. If you were testing your blood glucose levels before starting steroids, you may notice your blood glucose levels are raised or more difficult to control. This is called "Steroid-induced hyperglycaemia".

Predisposing factors leading to increased risk of hyperglycaemia with steroid therapy

- Pre-existing type 1 or type 2 diabetes
- People at increased risk of diabetes (e.g., 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 hyperglycemic with steroid therapy.

Steroid and diabetes – a reality

Steroids may be administered by various regimes and in variable doses. A single or short course of steroid (e.g. prednisolone) in the morning may be the commonest mode of administration. In susceptible patients, this will often result in a rise in blood glucose by late morning that continues into the evening.

Overnight the blood glucose generally falls back, often to baseline levels the next morning. Thus treatment should be tailored to treating the hyperglycaemia, whilst avoiding nocturnal and early morning hypoglycaemia. In pregnancy and other situations, a single dose or short course of steroid may be administered.

Many hospital inpatients will receive multiple daily doses of steroids. Glucose levels in most individuals can be predicted to rise approximately 4 to 8 hours following the administration of oral steroids and sooner following the administration of intravenous steroids.

Capillary blood glucose (CBG) monitoring is paramount to guiding appropriate therapeutic interventions. Conversely, glucose levels may improve to pre-steroid levels 24 hours after intravenous steroids are discontinued.

If oral steroids are weaned down over several weeks the glucose levels may decline in a dose dependent fashion. This may not always occur, particularly in those with pre-existing undiagnosed diabetes.

Glucocorticoids – estimation of diabetes risk

The GC-associated risk to develop diabetes is difficult to estimate for a number of reasons. First, patients are often treated with different GC formulations, during widely differing time periods and importantly, at different dosing regimens.

Also, patient populations have a large variety of susceptibility to develop hyperglycaemia in part due to the varying indications for GC treatment, different age groups, comorbidities and genetic factors.

Finally, since most studies measured only fasting glucose levels, steroid diabetes may go under reported in current literature. In a case control study, a 36% (OR 1.36; 95% CI 1.10-1.69) increased diabetes risk was reported.[3]

In an older population (aged >65 years), higher risks were observed (OR 2.31; 95% CI 2.11-2.54).[4]

In patients using oral GCs, a dose-dependent increase in the risk to develop diabetes requiring anti-hyperglycemic therapy was described, with ORs of 1.36 (95% CI 1.10-1.69) and 5.82 (95% CI 2.74-12.35) for lower (defined as 25 mg prednisolone equivalent) GC dosages, respectively.[5]

In GC-treated rheumatoid arthritis patients31 and primary renal disease patients, diabetes prevalence ranging between 20-40% was reported, although in the non-GC treated groups, diabetes prevalence was usually also high due to the adverse effect of systemic inflammation on glucose tolerance.[6,7]

The mechanisms underlying these so-called diabetogenic effects of GCs regarding glucose, lipid and protein metabolism were studied in the 1960-1970s and were mainly attributed to GC-induced insulin resistance at the level of liver, skeletal muscle and adipose tissue.[8,9,10,11]

Organs and pathways involved in the diabetogenc effects of glucocorticoid drugs

Glucocorticoid-induced insulin resistance

Liver

The liver is a key regulator of metabolism, within a complex regulatory network of hormonal, autonomic nervous and metabolic stimuli. Under fasting conditions, the liver maintains euglycemia by producing glucose through both gluconeogenesis and glycogenolysis. Insulin, which is secreted in response to a meal or carbohydrate load, is the most important hormone that suppresses endogenous glucose production (EGP).

On the other hand, the contra-regulatory hormones cortisol and glucagon increase EGP under fasting or hypoglycemic conditions. Thus, the liver is an important player in the diabetogenic effects induced by GC treatment[12].

Skeletal muscle

Skeletal muscle tissue is the most important site for insulin-stimulated glucose disposal in the postprandial state and thus plays a crucial role in glucose metabolism.[13] Following binding to its membrane-bound receptor, insulin stimulates glucose uptake, glucose oxidation and glycogen synthesis by phosphorylation of several proteins, usually referred to as the insulin-signalling cascade.[14]

The mechanisms by which GCs interfere with insulin signalling in skeletal muscle are yet to be elucidated. GCs could directly affect the phosphorylation of proteins involved in the insulin-signalling cascade, or indirectly through changes in lipid and protein metabolism.

As such, GCs increase plasma levels of no esterified fatty acids (NEFA) by impairing the insulin-mediated suppression of adipose tissue lipolysis (detailed below)49 and increase plasma levels of amino acids due to enhanced proteolysis.[15,16]

Both elevated NEFA and amino acids concentrations are strong inhibitors of insulin-stimulated glucose uptake.[17,18]

Adipose tissue

Although the adverse metabolic effects of elevated GC levels on glucose and protein metabolism are reasonably well defined, the effects on lipid metabolism and in particular the role of adipose tissue herein are less clear. However, several observations indicate that GCs exert unfavorable effects on adipose tissue.[19,20]

Glucocorticoid-induced islet-cell dysfunction - Pancreatic beta cells

The pancreatic beta cell plays a crucial role in glucose metabolism and in the past decades, beta-cell dysfunction has been acknowledged as the key defect underlying the development of T2DM.[21]

Under physiological conditions, insulin secretion is directly related to insulin sensitivity through a hyperbolic relation. The product of these parameters, known as the disposition index, remains constant.[22]

Thus, when the workload on the beta cell increases (by factors such as obesity, insulin resistance or low-grade inflammation), healthy beta cells can adapt by augmenting insulin secretion to meet this increased demand, thus maintaining euglycaemia.[23]

Failure of the beta cells to sufficiently secrete insulin to meet insulin demands results in glucose intolerance and T2DM[23]

Pancreatic alpha cells

By secreting glucagon, the pancreatic alpha cell has an important role in glucose metabolism.102 As previously mentioned, glucagon stimulates hepatic glucose production by promoting glycogenolysis and gluconeogenesis.

In many patients with T2DM, glucagon levels are increased in the fasted state and are incompletely suppressed in the postprandial state. Thus, elevated glucagon levels were shown to contribute importantly to both fasting and postprandial hyperglycaemia.[24]

The gut-islet axis

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are hormones secreted by the gut that are released following nutrient ingestion. GLP-1 lowers (postprandial) blood glucose through several mechanisms, including stimulation of meal-related insulin response and suppression of glucagon secretion in a glucose-dependent manner.

In addition, GLP-1 slows down gastric emptying, promotes satiety, decreases appetite and reduces body weight. In human beta cells and in vivo in animals and in humans, exogenous GLP-1 administration, in the presence of elevated glucose, acutely induces insulin secretion while prolonged GLP-1 exposure may result in increased insulin production[25].

Steroid diabetes - from mechanism to treatment

Due to these combined effects of GCs on both insulin sensitivity and islet-cell function, and due to their specific PK/PD profile, it has become clear that synthetic GCs particularly increase postprandial glucose levels, without affecting fasting glucose levels,[26]

similarly as has been observed in patients with Cushing's syndrome. This observation has important consequences. First, the incidence of steroid diabetes may be underestimated due to the fact that usually only fasting glucose levels are monitored during therapy. [27]

As such, low-dose prednisolone treatment is reported to have few side effects, while in our studies we observed various metabolic processes, particularly in the postprandial and hyperinsulinemia state, to be disturbed by low-dose prednisolone treatment[28] (Table 1).

Table 1: adverse metabolic effect of low dose glucocorticoid therapy

Liver	**Impaired suppression of glucose production by insulin**
Skeletal muscle	Reduced insulin-stimulated glucose uptake
Adipose tissue	Impaired suppression of lipolysis by insulin Increased NEFA levels during hyperinsulinemia
Beta cells	Reduced glucose-adjusted basal insulin secretion Beta cells Reduced potentiation of glucose-stimulated insulin secretion

Second, the described specific pattern of GC-induced hyperglycaemia may provide directions for the development of the dissociated GR agonists. Finally, increased insight into the mechanisms by which GCs induce hyperglycaemia may also be used for the management of steroid diabetes in clinical practice.

It is remarkable that despite the fact that GCs are well known to induce diabetes, there are very few studies that have investigated how GC-induced diabetes may best be treated, or preferentially, be prevented. Guidelines are currently solely based on expert opinions.[26,29]

Incretin-based therapies

In recent years, incretin-based therapies have become available for the treatment of T2DM. These include the injectable DPP-4 resistant GLP-1 receptor agonists and the class of oral DPP-4 inhibitors. Since GLP-1 receptor agonist treatment decreases gastric emptying, stimulates meal-related insulin secretion and reduces glucagon secretion, it addresses at least two important pathophysiological features of GC-induced hyperglycaemia. [30,31]

In addition, incretin-based therapies mainly target postprandial hyperglycaemia and, due to their glucose dependent mechanism of action, have low hypoglycemia risk.

Given these properties, incretin-based therapies may particularly be suited to treat GC-induced hyperglycaemia. The potential use of GLP-1 receptor agonists for the treatment of GC-induced hyperglycaemia was first proposed in 2007 when Ritzel and colleagues infused GLP-1 in ten patients with T2DM of whom one patient was only later found to have diabetes due to Cushing's disease.[32]

By comparing the one patient with Cushing's disease with the nine T2DM patients, the investigators studied whether the effects of GLP-1 on glucose metabolism were preserved in hypercortisolism.

In another paper, four cases of patients who were previously diagnosed with T2DM, but whose glycaemic control worsened under GC therapy, were successfully treated with exenatide twice daily.[33]

Currently, other proof-of-concept studies are ongoing in which the effects of more prolonged treatment with the DPP-4 inhibitor sitagliptin on glucose metabolism are assessed in men with the metabolic syndrome concomitantly treated with high-dose prednisolone.[34]

It will be interesting to see whether also in this population, incretin-based therapies may be useful in the treatment of GC-induced hyperglycaemia.

Future, real-life studies need to be conducted in relevant patient populations, i.e. patients taking GCs in clinical practice for inflammatory conditions. Since inflammation also negatively affects insulin secretion and sensitivity, the interactions among GCs, systemic inflammation and incretin-based drugs may yield unexpected findings.[35]

Conclusion

Knowledge regarding the diabetogenic effects of GCs has significantly been expanded in recent years, which will help the development of novel GR agonists with a more favourable therapeutic index. In addition, the increased insight into the pathophysiology of the diabetogenic effects of GC treatment should in due time result in a more tailored therapy to treat the associated hyperglycaemia. Thus we conclude by saying that there is a strong association between diabetes and steroid therapy which is not a myth, but reality

References

1. van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? Eur J Clin Invest. 2009; 39:81-93.

2. Zen M, Canova M, Campana C, et al. The kaleidoscope of glucorticoid effects on immune system. Autoimmune Rev. 2011; 10:305-10.

3. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. Diabetes Care. 2006; 29:2728-9.

4. Blackburn D, Hux J, Mamdani M. Quantification of the Risk of Corticosteroid-induced Diabetes Mellitus Among the Elderly. J Gen Intern Med. 2002; 17:717-20.

5. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J. Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med. 1994; 154:97-101.

6. Hoes JN, van der Goes MC, van Raalte DH, et al. Glucose tolerance, insulin sensitivity and beta-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose glucocorticoids. Ann Rheum Dis. 2011; 70:1887-94.

7. Uzu T, Harada T, Sakaguchi M, et al. Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. Nephron Clin Pract. 2007;105:c54-7.

8. Fain JN. Effects of Dexamethasone and 2-Deoxy-D-Glucose on Fructose and Glucose Metabolism by Incubated Adipose Tissue. J Biol Chem. 1964; 239:958-62.

9. Issekutz B, Jr., Borkow I. Effect of glucagon and glucose load on glucose kinetics, plasma FFA, and insulin in dogs treated with methylprednisolone. Metabolism. 1973; 22:39-49.

10. Kaplan SA, Shimizu CS. Effects of cortisol on amino acids in skeletal muscle and plasma. Endocrinology. 1963; 72:267-72.

11. Lecocq FR, Mebane D, Madison LL. The Acute Effect of Hydrocortisone on Hepatic Glucose Output and Peripheral Glucose Utilization. J Clin Invest. 1964; 43:237-46.

12. Barthel A, Schmoll D. Novel concepts in insulin regulation of hepatic gluconeogenesis. Am J Physiol Endocrinol Me tab. 2003;285: E685-92.

13. DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes. 1981; 30:1000-7.

14. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001; 414:799-806.

15. Lofberg E, Gutierrez A, Werner man J, et al. Effects of high doses of glucocorticoids on free amino acids, ribosomes and protein turnover in human muscle. Eur J Clin Invest. 2002; 32:345-53.

16. Short KR, Bigelow ML, Nair KS. Short-term prednisone use antagonizes insulin's anabolic effect on muscle protein and glucose metabolism in young healthy people. Am J Physiol Endocrinol Me tab. 2009;297: E1260-8.

17. Krebs M, Krssak M, Bernroider E, et al. Mechanism of amino acid-induced skeletal muscle insulin resistance in humans. Diabetes. 2002; 51:599-605.

18. Perseghin G, Petersen K, Shulman GI. Cellular mechanism of insulin resistance: potential links with inflammation. Int J Obes Relat Metab Disord. 2003;27(Suppl 3): S6-11.

19. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. Diabetes Metab Rev. 1988; 4:17-30.

20. Peckett AJ, Wright DC, Riddell MC. The effects of glucocorticoids on adipose tissue lipid metabolism. Metabolism. 2011; 60:1500-10.

21. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia. 2003; 46:3-19.

22. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes. 1993; 42:1663-72.

23. van Raalte DH, Diamant M. Glucolipotoxicity and beta cells in type 2 diabetes mellitus: Target for durable therapy? Diabetes Res Clin Pract. 2011;93(Suppl 1): S37-46.

24. Gromada J, Franklin I, Wollheim CB. Alpha-cells of the endocrine pancreas: 35 years of research but the enigma remains. Endocr Rev. 2007; 28:84-116.

25. Drucker DJ. Biological actions and therapeutic potential of the glucagon-like peptides. Gastroenterology. 2002; 122:531-44.

26. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009; 15:469-74.

27. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Me tab. 2003; 88:5593-602.

28. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009; 68:1833-8.

29. Kwon S, Her Mayer KL. Glucocorticoid-induced hyperglycemia. Am J Med Sci. 2013; 345:274-7

30. Cervera A, Wajcberg E, Sriwijitkamol A, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. Am J Physiol Endocrinol Me tab. 2008;294: E846-52.

31. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. Diabetes Care. 2011;34(Suppl 2): S279-84.

32. Ritzel RA, Kleine N, Holst JJ, Willms B, Schmiegel W, Nauck MA. Preserved GLP-1 effects in a diabetic patient with Cushing's disease. Exp Clin Endocrinol Diabetes. 2007; 115:146-50.

33. Matsuo K, Nambu T, Matsuda Y, et al. Evaluation of the effects of exenatide administration in patients with type 2 diabetes with worsened glycemic control caused by glucocorticoid therapy. Intern Med. 2013; 52:89-95.

34. http://clinicaltrials.gov/ct2/show/NCT00721552?term=SPHINX&rank=1.

35. den Uyl D, van Raalte DH, Nur Mohamed MT, et al. Metabolic effects of high-dose prednisolone treatment in early rheumatoid arthritis: Diabetogenic effects and inflammation reduction on the balance. Arthritis Rheum. 2012; 64:639-46.