Steroid diabetes: from mechanism to treatment?

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ABSTRACT

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. 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.

GLUCOCORTICOIDS: A BRIEF HISTORY

In 1908, it was first established that ‘substances’ secreted by the adrenal gland were involved in glucose metabolism following studies in adrenalectomised dogs that developed hypoglycaemia. In the following decades, the critical role of the adrenal cortex in intermediary metabolism and energy homeostasis was further characterised. A major advance was made in 1936 with the simultaneous isolation of the inactive form of the adrenal hormone cortisol, known as cortisone, by the Polish-born, Swiss chemist Tadeusz Reichstein and the American chemist Edward Calvin Kendall. This breakthrough enabled further experiments into the various physiological roles of adrenal cortex hormones. The amount of cortisone that could be isolated from bovine adrenal glands, however, was small and the need to produce adrenocorticosteroids through synthetic methods...
soon became apparent. This process was fuelled by the US entry into the Second World War, when rumours circulated that Luftwaffe pilots were taking adrenal extracts to increase their resistance to oxygen deprivation at high altitudes. Although this rumour was never confirmed, it induced an all-out quest for large-scale synthesis of active adrenal hormone. By 1946, Lewis Hastings Sassert of Merck Research Laboratories succeeded in synthetically producing cortisone from desoxycholic acid. By the summer of 1948, sufficient material was produced for oral GCs in the United States alone. This was driven by observations that joint complaints were reduced by jaundice and that the newly discovered steroid cortisone seemed structurally related to bile acids. Indeed, cortisone treatment induced a spectacular reduction in joint tenderness and swelling in chronic rheumatoid arthritis patients. In the following year, the use of cortisone was successfully introduced in the treatment of other autoimmune diseases. In 1950, the ‘wonder drug’ cortisone was officially launched as a pharmacological agent. In the same year Tadeusz Reichstein, Philip Showalter Hench and Edward Calvin Kendall shared the Nobel Prize for Physiology or Medicine ‘for research on the structure and biological effects of adrenal cortex hormones’. Currently, over six decades later, GCs remain the cornerstone in the treatment of numerous diseases that cover the entire spectrum of internal medicine (table 1), resulting in an estimated ten million annual prescriptions for oral GCs in the United States alone.

**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 underreported in current literature. In a case control study, a 36% (OR 1.36; 95% CI 1.10-1.69) increased diabetes risk was reported. In an older population (aged >65 years), higher risks were observed (OR 2.31; 95% CI 2.11-2.54). In patients using oral GCs, a dose-dependent increase in the risk to develop diabetes requiring antihyperglycaemic 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 <10 mg prednisolone equivalent) and higher (defined as >25 mg prednisolone equivalent) GC dosages, respectively. In GC-treated rheumatoid arthritis patients 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.

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. After this period of intensive research on the adverse metabolic effects of GCs, a temporary decline in research on this topic was observed (figure 1).

**Table 1. Common indications for systemic glucocorticoid therapy within the field of internal medicine**

<table>
<thead>
<tr>
<th>Subspeciality</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatology</td>
<td>RA(^a), SLE(^a), GCA(^a), PMR(^a), sarcoidosis(^a)</td>
</tr>
<tr>
<td>Nephrology</td>
<td>Vasculitis/glomerulonephritis(^a)</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>IBD(^b), autoimmune hepatitis(^b)</td>
</tr>
<tr>
<td>Haematology</td>
<td>Lymphoma(^c), multiple myeloma(^c)</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>Meningitis(^b)</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>COPD(^b)</td>
</tr>
<tr>
<td>Emergency medicine</td>
<td>Anaphylactic/allergic reactions(^b)</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; GCA = giant cell arteritis; IBD = inflammatory bowel disease; PMR = polymyalgia rheumatica; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

**GLUCOCORTICOID THERAPY: SEVERE SIDE EFFECTS**

Although GCs display excellent efficacy, their use is hampered by a broad profile of sometimes serious side effects. These include, but are not limited to, osteoporosis, increased susceptibility to develop infections, glaucoma, hypertension, gastric ulcer disease, psychiatric disease, skin atrophy, skeletal muscle atrophy, fluid retention and adverse effects on metabolism. These metabolic adverse effects include the development of central adiposity, hepatic steatosis, insulin resistance, glucose intolerance and dyslipidaemia. Together, the coexistence of these abnormalities increases the risk of diabetes and cardiovascular disease. Despite the introduction of novel synthetic GC compounds designed to reduce these adverse effects, including prednisolone (1965) and dexamethasone (1966), many of the above-listed side effects remain present today, especially at higher dosages.
GLUCOCORTICOIDS AND THEIR METABOLIC EFFECTS: RENEWED INTEREST

In recent decades, there has been a renewed interest in the diabetogenic effects of GCs (figure 1). This has two important reasons. First, there is increasing evidence that endogenous hypercortisolism, whether resulting from chronic stress or excessive production in adipose tissue, may play a role in the development of (visceral) obesity, metabolic syndrome, type 2 diabetes (T2DM) and cardiovascular disease, as postulated by Björntorp. This was partly encouraged by the striking resemblance between several features of obesity and the metabolic syndrome and the phenotype of chronic GC excess (Cushing’s syndrome). Indeed, in a number of studies, elevated cortisol levels were demonstrated in T2DM patients and in individuals with cardiovascular risk factors as compared with healthy controls, and were shown to correlate with body mass index and waist circumference. Interestingly, in addition to these subtle changes in plasma cortisol levels, other groups have shown that disturbed tissue GC metabolism, especially in liver and adipose tissue, may also contribute to the current obesity/metabolic syndrome pandemic (as detailed below). Second, increased knowledge regarding tissue GC metabolism and the genomic actions of GCs has led to the development of two novel, distinct classes of therapeutic agents which currently fuel research into the metabolic effects of GCs (see below).

PHARMACOLOGICAL MODULATION OF GLUCOCORTICOID ACTION: 11-BETA HYDROXysteroid dehydrogenase Type 1 inhibitors

Intracellularly, cortisol may be regenerated from its inactive metabolite cortisone, a reaction that is catalysed by the enzyme 11-beta hydroxysteroid dehydrogenase (HSD) type 1 (figure 2), which is predominantly expressed in liver and adipose tissue. Thus, local GC concentrations may be regulated in a tissue-specific manner at the pre-receptor level. Increased activity of this enzyme was demonstrated in adipose tissue derived from rodent models of obesity and from obese humans. In addition, 11-beta HSD1 expression and activity in subcutaneous adipose tissue were shown to be positively associated with insulin resistance and obesity. Moreover, 11-beta HSD1 knock-out mice exhibited improved glucose tolerance, a more beneficial lipid profile, reduced weight gain and visceral fat accumulation following chronic high-fat feeding as compared with wild-type littermates. In contrast, mice that overexpress 11-beta HSD1 in liver or adipose tissue develop obesity and several features of the metabolic syndrome. These observations have substantiated the notion that alterations in tissue cortisol levels influence systemic metabolism and that the enzyme 11-beta HSD1 constitutes an attractive therapeutic target for the treatment of obesity and its metabolic consequences. As such, many pharmaceutical companies are currently developing 11-beta HSD1 inhibiting compounds for the treatment of obesity and the metabolic syndrome.

Pharmacological modulation of glucocorticoid action: dissociated glucocorticoid receptor agonists

Improved understanding of the genomic actions of GCs has led to the development of novel agents which are devoid of the metabolic side effects, while their anti-inflammatory action is preserved. These compounds are named dissociated glucocorticoid receptor (GR) agonists. In 1985, the GR was discovered. Subsequently, it was shown that GCs exert most of their actions by binding to this intracellular receptor after which the formed hormone-receptor complex migrates to the nucleus to regulate target gene expression. More recently, it became evident that the anti-inflammatory actions of GC drugs are largely mediated by transrepression of target genes, whereas the metabolic effects are mostly mediated by transactivation of genes. Since these genomic actions of GCs have different molecular mechanisms (figure 2), they may potentially be separated. These findings are at the basis of the novel dissociated GR agonists. Several compounds with a dissociated profile are currently under development by different pharmaceutical companies and have shown promising results in animal models.
Glucocorticoid-induced insulin resistance

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 euglycaemia 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 hypoglycaemic conditions.\(^5\)

Pharmacological dosages of GCs administered in the short term to healthy volunteers increased EGP in the fasted state in a number of studies but not in all studies.\(^5\)\(^-\)\(^5\) This increase in EGP is driven by GC-induced increment in gluconeogenesis rather than glycogenolysis.\(^6\) GCs mainly stimulate gluconeogenesis by promoting the expression and activity of key enzymes of gluconeogenesis including phosphoenolpyruvate carboxykinase (PEPCK)\(^5\)\(^5\) and glucose-6-phosphatase.\(^5\) Indeed, the PEPCK gene contains a glucocorticoid response element (GRE) in its promoter region and is considered a key player in GC-induced hyperglycaemia.\(^6\) Other mechanisms by which GCs may enhance gluconeogenesis include increased delivery of substrate for gluconeogenesis to the liver through breakdown of peripheral protein and fat stores\(^5\)\(^6\) and potentiation of the effects of other glucoregulatory hormones such as glucagon and epinephrine.\(^6\) The most prominent effects of GCs on liver glucose metabolism are evident during hyperinsulinaemic conditions. Both acute and more prolonged GC treatment were shown to blunt the suppressive effects of insulin on EGP by up to 50\%.\(^6\)\(^,\)\(^5\)\(^,\)\(^7\)\(^-\)\(^9\) The mechanisms underlying this GC-induced liver insulin resistance are currently not clarified. In rats, dexamethasone was shown to impair the insulin-signalling cascade, leading to reduced activation of insulin target proteins and genes in liver cells.\(^6\)

Thus, the liver is an important player in the diabetogenic effects induced by GC treatment. This is further illustrated by a study in rats where treatment with a liver-selective GR antagonist resulted in reduced fasting plasma glucose levels and decreased EGP during a hyperinsulinaemic-euglycaemic clamp.\(^6\) Of note, GCs also affect hepatic lipid metabolism by increasing very-low-density lipoprotein production and stimulating de novo lipogenesis; however, this topic is beyond the scope of this review and is discussed in detail elsewhere.\(^6\)

**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.\(^6\) 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.\(^7\)

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**Figure 2. Novel compounds related to glucocorticoid metabolism (simplified scheme)**

- **DNA** = deoxyribonucleic acid; **mRNA** = messenger ribonucleic acid; **GC** = glucocorticoid; **GR** = glucocorticoid receptor; **GRE** = glucocorticoid response element; **11-beta Hsd1** = 11-beta hydroxysteroid dehydrogenase type 1.  

1) At the pre-receptor levels, cortisol regeneration in tissues may be reduced by inhibition of the enzyme 11-beta hydroxysteroid dehydrogenase type 1. Given the role of disturbed tissue glucocorticoid (GC) metabolism in ‘dispaedic’ obesity and the metabolic syndrome, drugs are under development that aim to reduce the activity of 11-beta HSD1.  

2) GCs regulate target gene expression by different genomic mechanisms. Positive regulation of genes (transactivation) is mediated by binding of a ligand-activated glucocorticoid receptor (GR) homodimer to a GC response element (GRE), which is usually located in the promoter region of the target gene. Ligand-activated GR homodimers may also bind to negative GRES, leading to regression of gene transcription. Moreover, inhibition of target genes may also be achieved by interaction of GR monomers with other transcription factors via protein–protein interaction (transrepression). The transrepression pathway seems mainly responsible for GC-induced side effects, whereas the transactivation pathway is thought to primarily induce GCs anti-inflammatory effects. Dissociated GR agonists are designed to predominantly induce transrepression pathways.  

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**Organs and pathways involved in the diabetogenic effects of glucocorticoid drugs**

**Glucocorticoid-induced insulin resistance**

**Liver**

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Decades ago, cortisol was shown to reduce insulin-stimulated glucose disposal in a dose-dependent manner, a finding that was confirmed in several subsequent studies. GCs particularly impair nonoxidative glucose disposal (reflecting glycogen synthesis), whereas glucose oxidation rates remain intact. Despite the fact that GC-induced skeletal muscle insulin resistance is a well-known phenomenon, the mechanisms involved remain currently incompletely understood.

GCs may reduce skeletal muscle glucose uptake by reducing total skeletal muscle mass through GC-induced atrophy. However, since GCs reduce insulin-stimulated glucose uptake already after short-term treatment in the absence of significant decrements in skeletal muscle mass, direct effects of GCs on insulin-regulated metabolic pathways in skeletal muscle may be more important. Indeed, GCs were shown to disturb the insulin-signalling cascade in rats, resulting in impaired glucose uptake and glycogen synthesis.

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 nonesterified fatty acids (NEFA) by impairing the insulin-mediated suppression of adipose tissue lipolysis (detailed below) and increase plasma levels of amino acids due to enhanced proteolysis. Both elevated NEFA and amino acids concentrations are strong inhibitors of insulin-stimulated glucose uptake.

In addition to changes in skeletal muscle cells, GCs may also impair glucose uptake by disturbing the insulin-induced recruitment of capillaries in skeletal muscle tissue. In the last decade, it has become progressively evident that vascular tissue, and particularly endothelial cells, represent an important physiological target for insulin. Insulin exerts a vasodilatory action by promoting nitric oxide (NO) release from the endothelial cells. By recruiting capillaries to expand the endothelial transporting surface available for nutrient exchange, the vascular actions of insulin significantly contribute to overall insulin-stimulated glucose uptake. In our study, a two-week treatment with low-dose (7.5 mg daily) and high-dose (30 mg daily) prednisolone dose-dependently impaired insulin-stimulated capillary recruitment in healthy individuals as assessed by capillary microscopy. Moreover, prednisolone-induced impairment in insulin-stimulated capillary recruitment was related to changes in fasting and postprandial glucose levels as well as insulin sensitivity as measured by a hyperinsulinaemic clamp and standardised meal test.

Thus, GC-induced skeletal muscle insulin resistance is a hallmark of GC-induced hyperglycaemia; however, the alterations within skeletal muscle tissue that induce this effect are unknown. In addition, GC-induced impairment in insulin-related capillary recruitment may also partly account for the reduction in glucose uptake by skeletal muscle.

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 unfavourable effects on adipose tissue.

As such, chronic GC excess in Cushing’s syndrome or during prolonged GC treatment increases fat deposition in the visceral compartment and promotes liver fat accumulation, at the cost of subcutaneous fat deposition which, together with peripheral muscle wasting, causes the well-known Cushingoid phenotype. The GC-induced reduction in subcutaneous adipose tissue (SAT) with concomitant increase in visceral adipose tissue (VAT) is clinically relevant since VAT is well known to be associated with an untoward metabolic profile as opposed to SAT, is metabolically more active and is associated with increased cardiovascular risk. Mechanisms involved in this GC-induced specific alteration in adipose tissue distribution are yet to be clarified.

In addition to altering adipose tissue distribution, GCs may also affect adipose tissue function. Although GCs display lipogenic actions in VAT, they acutely increase fasting lipolysis rates in vitro and in vivo. GC-induced induction of whole-body lipolysis could be explained by increased activity of the key lipolytic enzymes adipose triglyceride lipase (ATGL) and hormone sensitive lipase (HSL) and possibly by augmented beta-adrenergic signalling and results in increased plasma NEFA levels. As mentioned earlier, increased NEFA levels contribute to hyperglycaemia by impairing muscle and liver insulin sensitivity.

In analogy to liver and skeletal muscle, GCs were shown to impair insulin signalling in 3T3-L1 adipocytes in vitro and in human adipose tissue in vivo (Van Raalte et al.; unpublished observations). At the level of adipose tissue, insulin inhibits adipose tissue lipolysis and stimulates triglyceride uptake. We observed that prednisolone treatment dose-dependently impaired insulin-stimulated suppression of lipolysis resulting in elevated plasma NEFA levels during hyperinsulinaemia.

In addition to regulating adipose tissue lipid metabolism, insulin also stimulates adipose tissue glucose uptake. Although the overall contribution of glucose uptake by adipose tissue in the postprandial state is thought to be relatively modest, fat cells contribute to overall glucose tolerance by a cross-talk with liver and skeletal muscle. This is most likely mediated by metabolically active
factors and hormones that are secreted by adipose tissue, collectively known as adipocytokines. As such, GCs have been shown to alter levels of various adipocytokines both in vitro and in vivo (Van Raalte, et al.; unpublished observations) towards a more diabetogenic profile. Thus, plasma concentrations of adiponectin, which are generally positively associated with insulin sensitivity, were reduced following high-dose prednisolone treatment. The pro-inflammatory adipocytokines resistin and leptin, which are usually negatively associated with insulin sensitivity, were both increased by high-dose prednisolone treatment.

In conclusion, GCs diabetogenic effects also involve actions on adipose tissue, i.e. unbefitting changes in adipose tissue distribution and induction of adipose tissue insulin resistance, which result in increased lipolysis, hyperlipidaemia and altered adipocytokine secretion by fat cells.

**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. 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. 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. Failure of the beta cells to sufficiently secrete insulin to meet insulin demands results in glucose intolerance and T2DM.

**Direct effects of glucocorticoids on beta-cell function: in vitro studies**

GCs were extensively shown to impair insulin secretion in vitro in insulinoma cell lines and in rodent-derived islets. Various aspects of the insulin secretory machinery were inhibited by GCs including glucose uptake and oxidation, membrane depolarisation and calcium-triggered insulin exocytosis. By these combined actions, GCs reduced glucose-stimulated insulin secretion (GSIS), but also inhibited the effects of numerous other insulin secretagogues. In addition to attenuating insulin secretion, GCs impaired insulin biosynthesis and induced beta-cell apoptosis following more prolonged incubation. GC-induced impairment in the function of the endoplasmic reticulum (ER), a cell organelle responsible for the synthesis of all secreted proteins, most notably insulin, may be critically involved in these conditions. GCs induce ‘ER stress’ which is characterised by an accumulation of misfolded proteins inside the organelle. This ER stress may result in reduced insulin production, but may also trigger beta-cell apoptosis. The detrimental effects of GCs on beta-cell function were further emphasised in mice that developed diabetes through impaired insulin secretion after specific overexpression of the GR in beta cells.

**Effects of glucocorticoids on beta-cell function in humans**

Also in vivo in humans, GCs acutely impair insulin secretion. High-dose prednisolone impaired first-phase glucose-stimulated insulin secretion as well insulin secretion induced by the amino acid and beta-cell membrane depolarisator arginine following a single gift as measured by a hyperglycaemic clamp study. At the same GC dose, impairment of beta-cell function during a standardised meal test was also noted, in particular, a reduction in glucose-adjusted insulin secretion (beta-cell glucose sensitivity).

More prolonged administration (maximally up to two weeks) of GCs to healthy volunteers has shown somewhat different results. Due to the induction of insulin resistance, GCs were shown to increase fasting insulin levels and insulin secretion following oral or intravenous stimulation tests. This increased beta-cell response, however, does not indicate improved beta-cell function, but rather compensation for GC-induced insulin resistance, which was evident after correction for insulin sensitivity by regression methods or by calculating a disposition index. In many studies in healthy volunteers, unchanged disposition index indicated adequate compensation for GC-induced insulin resistance. However, in susceptible populations, including obese and normoglycaemic insulin-resistant individuals or those with low glucose-stimulated insulin secretion (GSIS) prior to treatment with GCs, GSIS was not enhanced to such an extent to compensate for GC-induced impairment of insulin sensitivity. Thus, in normoglycaemic first-degree relatives of patients with T2DM and obese women, the disposition index decreased following GC treatment. In addition to glucose-stimulated insulin secretion, we studied the effects of GCs on arginine-induced insulin secretion, which may be a proxy for maximal insulin secretory capacity at a given level of hyperglycaemia. Interestingly, prednisolone dose-dependently decreased arginine-induced insulin secretion. In addition, prednisolone reduced glucose-independent insulin secretion during standardised meal tests and impaired insulin secretion induced by the incretin hormones (detailed below).

Thus, GC-induced beta-cell dysfunction is a hallmark of GC-induced hyperglycaemia; however, the effects are dependent on the duration of treatment, population exposed and the specific beta-cell parameters that are...
investigated. Finally, additional evidence for a role of beta-cell function in GC-induced diabetes comes from a study where functional single nucleotide polymorphisms in the GR gene with increased GC sensitivity were shown to be related to reduced insulin secretion during a hyperglycaemic clamp.101

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.101 Already in 1971, GCs were shown to augment glucagon levels.103 This was demonstrated both in healthy individuals treated with dexamethasone and in patients with Cushing’s syndrome. In both groups, fasting glucagon levels were increased and glucagon concentrations were incompletely suppressed following ingestion of a protein meal or following alanine infusion.103 We demonstrated that the effects of GCs on glucagon levels are dose-dependent: only high-dose (30 mg prednisolone daily), but not low-dose (7.5 mg prednisolone daily) GC treatment increased fasting and postprandial glucagon levels following a two-week treatment in healthy men.49,67,77 Interestingly, this effect of high-dose GCs on glucagon levels was already evident after a single gift.95 Thus, both fasting and postprandial hyperglucagonaemia are present in GC-induced hyperglycaemia.

The gut-islet axis

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic 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.104 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.

GLP-1 has a short half-life (1-2 minutes) since it is cleaved by the ubiquitous enzyme dipeptidyl peptidase (DPP)-4. Due to the above-mentioned beneficial effects of GLP-1 on glucose metabolism, treatment with DPP-4 resistant GLP-1, GLP-1 receptor agonists95 and DPP-4 inhibitors106 has been developed in T2DM patients, in whom the insulino tropic effects of GLP-1 are still intact, albeit to a lesser extent than in non-diabetic subjects.107 Up to recently, the effects of GC treatment on GLP-1 secretion and its insulino tropic actions had been little addressed. In rodents, GC treatment resulted in decreased mRNA stability of the preproglucagon gene, a precursor of GLP-1, resulting in reduced GLP-1 levels.108 In our study in healthy volunteers, a two-week treatment with prednisolone did not affect circulating GLP-1 concentrations during standardised meal tests, which was confirmed by others.97,109 Interestingly, however, the insulino tropic effects of GLP-1 were reduced by GC treatment, as demonstrated by reduced potentiation of glucose-stimulated insulin secretion when GLP-1 was co-infused.98 It is unclear whether this impaired incretin effect is a specific beta-cell defect induced by GC treatment or whether it may be secondary to general GC-induced beta-cell dysfunction. Thus, an impaired gut-islet axis characterised by impaired insulino tropic effects of GLP-1 is present in GC-induced hyperglycaemia. The mechanisms by which GCs are thought to induce hyperglycaemia are summarised in figure 3.

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

![Figure 3. Mechanisms of glucocorticoid-induced hyperglycaemia](image-url)
particularly increase postprandial glucose levels,\textsuperscript{192} without affecting fasting glucose levels,\textsuperscript{192} similarly as has been observed in patients with Cushing’s syndrome.\textsuperscript{192} 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. As such, low-dose prednisolone treatment is reported to have few side effects,\textsuperscript{193} while in our studies we observed various metabolic processes, particularly in the postprandial and hyperinsulinaemic state, to be disturbed by low-dose prednisolone treatment (Table 2). 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.\textsuperscript{111,114}

‘Classic’ hypoglycaemic agents

A few intervention studies that aimed to treat or prevent GC-induced hyperglycaemia have been performed in healthy individuals. In a crossover study carried out in five volunteers, a 14-day pre-treatment with the thiazolidinedione (TZD) troglitazone, but not metformin or pioglitazone, reduced hyperglycaemia during an oral dinedione (TZD) troglitazone, but not metformin or pioglitazone, reduced hyperglycaemia during an oral glucose tolerance test after three days of dexamethasone treatment at 4 mg daily.\textsuperscript{115} Another small-sized uncontrolled study also showed effectiveness of troglitazone in preventing GC-induced glucose intolerance in healthy participants treated with dexamethasone for four days.\textsuperscript{116} However, participants gained 1.7 kg of weight during the four weeks of pre-treatment with troglitazone.

In addition to weight gain, thiazolidinediones cause oedema, heart failure and bone fractures,\textsuperscript{117-118} all of which are particularly unfavourable given the side effect profile of GCs, which shares similar features. Meanwhile, the market authorisation of troglitazone (2000) and rosiglitazone (2010) was suspended in Europe due to liver toxicity and cardiovascular disease risk, respectively. Given the GC-induced increment in postprandial glucose levels, short-acting prandial insulin is currently recommended.\textsuperscript{114} However, choosing the right dosage of insulin may be challenging due to the fact that GC dosage is often tapered over time making insulin demand variable. Furthermore, insulin therapy may increase the risk of hypoglycaemia and induce weight gain, both of which are undesired side effects.

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,\textsuperscript{119} stimulates meal-related insulin secretion\textsuperscript{119} and reduces glucagon secretion,\textsuperscript{120} it addresses at least two important pathophysiological features of GC-induced hyperglycaemia.

In addition, incretin-based therapies mainly target postprandial hyperglycaemia and, due to their glucose-dependent mechanism of action, have low hypoglycaemia 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.\textsuperscript{121} 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.\textsuperscript{122} We explored the potential of GLP-1 receptor agonists to prevent GC-induced hyperglycaemia in a randomised, proof-of-concept study in eight healthy volunteers. We could show that intravenous infusion of the GLP-1 receptor agonist exenatide prevented the rise in postprandial glucose levels induced by acute treatment with high-dose prednisolone. This was achieved by preventing GC-induced hyperglucagonaemia and GC-induced beta-cell dysfunction, and by reducing gastric emptying rates.\textsuperscript{123} Currently, other proof-of-concept studies are ongoing in which the effects of more prolonged treatment with

### Table 2. Adverse metabolic effects of low-dose glucocorticoid therapy (7.5 mg prednisolone equivalent)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Postprandial hyperglycaemia\textsuperscript{7}</th>
<th>Liver</th>
<th>Skeletal muscle</th>
<th>Adipose tissue</th>
<th>Adipose tissue</th>
<th>Beta cells</th>
<th>Beta cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Impaired suppression of glucose production by insulin\textsuperscript{19}\textsuperscript{9}</td>
<td>Reduced insulin-stimulated glucose uptake\textsuperscript{49}</td>
<td>Impaired suppression of lipolysis by insulin\textsuperscript{19}</td>
<td>Increased NEFA levels during hyperinsulinaemia\textsuperscript{19}</td>
<td>Reduced glucose-adjusted basal insulin secretion\textsuperscript{19}\textsuperscript{96}</td>
<td>Reduced potentiation of glucose-stimulated insulin secretion\textsuperscript{19}\textsuperscript{97}</td>
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\textsuperscript{1}p=0.07; \textsuperscript{2}p=0.09; \textsuperscript{3}p=0.06.
the DPP-4 inhibitor sitagliptin on glucose metabolism are assessed in men with the metabolic syndrome concomitantly treated with high-dose prednisolone.\(^8\) 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.\(^{31,124}\)

**CONCLUSION**
Knowledge regarding the diabetogenic effects of GCs has signifi cantly 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 pathophysiolog y of the diabetogenic effects of GC treatment should in due time result in a more tailored therapy to treat the associated hyperglycaemia.

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**REFERENCES**


