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REVIEW

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.[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]

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.[3] In the following decades, the critical role of the adrenal cortex in intermediary metabolism and energy homeostasis was further characterised.[4] 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[5] and the American chemist Edward Calvin Kendall.[6] 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.[7] In 1946, Lewis Hastings Sarett of Merck Research Laboratories succeeded in synthetically producing cortisone from desoxycholic acid.[8]

By the summer of 1948, sufficient material was produced to initiate the first studies in humans. The newly produced cortisone indeed improved the symptoms of Addison's disease.[9] In addition, rheumatologist Philip Showalter Hench, a friend and collaborator of Kendall, tested cortisone in patients with rheumatoid arthritis. This was driven by observations that joint complaints were reduced by jaundice[10] 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.[11] In the following year, the use of cortisone was successfully introduced in the treatment of other autoimmune diseases.[12] 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*),[13-25] resulting in an estimated ten million annual prescriptions for oral GCs in the United States alone.

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

Subspeciality	Indication
Rheumatology	RA[13], SLE[14], GCA[15], PMR[16], sarcoidosis[17]
Nephrology	Vasculitis/glomerulonephritis[18]
Gastroenterology	IBD[19], autoimmune hepatitis[20]
Haemato-oncology	Lymphoma[21], multiple myeloma[22]
Infectious diseases	Meningitis[23]
Pulmonology	COPD[24]
Emergency medicine	Anaphylactic/allergic reactions[25]

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

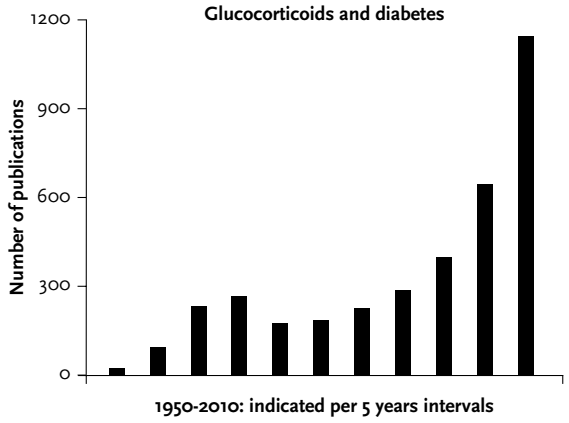
Although GCs display excellent efficacy, their use is hampered by a broad profile of sometimes serious side effects. These include, but are not limited to, osteoporosis, increased susceptibility to develop infections, glaucoma, hypertension, gastric ulcer disease, psychiatric disease, skin atrophy, skeletal muscle atrophy, fluid retention and adverse effects on metabolism.[26] These metabolic adverse effects include the development of central adiposity, hepatic steatosis, insulin resistance, glucose intolerance and dyslipidaemia.[1] Together, the coexistence of these abnormalities increases the risk of diabetes[1] and cardiovascular disease.[27] 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: 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.[28] In an older population (aged >65 years), higher risks were observed (OR 2.31; 95% CI 2.11-2.54).[29] 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.[30] In GC-treated rheumatoid arthritis patients[31] and primary renal disease patients,[32] 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.[33-36]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*).

Figure 1. *The number of new publications on PubMed with search terms 'glucocorticoids' and 'diabetes' shown per five-year intervals. The numbers indicate publications in the specific five-year interval and do not indicate accumulated numbers. After 1975, the amount of research performed on the topic declined somewhat, but in recent years, the subject has received full attention*



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 Bjorntorp.[37] 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,[38] and were shown to correlate with body mass index and waist circumference.[37] 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).[39] 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).

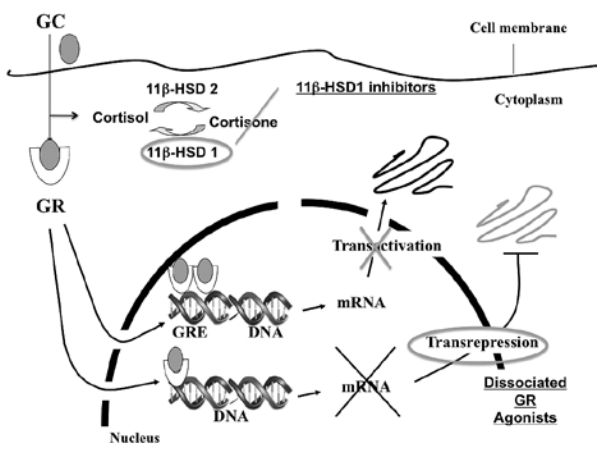
PHARMACOLOGICAL MODULATION OF GLUCOCORTICOID ACTION: 11-BETA HYDROXYSTEROID DEHYDROGENASE TYPE-1 INHIBITORS

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.[40] 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.[40] 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.[41]

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.[42] In 1985, the GR was discovered.[43] 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.[26,42] 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[42] and have shown promising results in animal models,

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



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 'idiopathic' 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 transactivation pathway seems mainly responsible for GC-induced side effects, whereas the transrepression pathway is thought to primarily induce GC's anti-inflammatory effects. Dissociated GR agonists are designed to predominantly induce transrepression pathways. 11beta-HSD1 = 11-beta hydroxysteroid dehydrogenase type 1; DNA = deoxyribonucleic acid; GC = glucocorticoid; GR = glucocorticoid receptor; GRE = glucocorticoid response element; mRNA = messenger ribonucleic acid

where they reduced inflammation without altering glucose levels.[44] However, to enable further development of these compounds for use in humans, insight into the mechanisms underlying the classical GC-induced side effects proved mandatory. To this end, research has specifically focused on the identification of biomarkers that in a dose-dependent manner reflect or predict the occurrence of side effects of the classic GR agonists, in order to compare these adverse effects with novel GR agonists in the future.

ORGANS AND PATHWAYS INVOLVED IN THE DIABETOGENIC 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 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.[45]

Pharmacological dosages of GCs administered in the short term to healthy volunteers increased EGP in the fasted state in a number[46-49] but not in all studies.[50-53] This increase in EGP is driven by GC-induced increment in gluconeogenesis rather than glycogenolysis.[54] GCs mainly stimulate gluconeogenesis by promoting the expression and activity of key enzymes of gluconeogenesis including phosphoenolpyruvate carboxykinase (PEPCK)[55] and glucose-6-phosphatase.[56] Indeed, the PEPCK gene contains a glucocorticoid response element (GRE) in its promoter region and is considered a key player in GC-induced hyperglycaemia.[57] 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[58] and potentiation of the effects of other glucoregulatory hormones such as glucagon and epinephrine.[59] 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%.[46,47,49] 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.[60]

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.[61] 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.[62]

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.[63] 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.[64]

Decades ago,[46] cortisol was shown to reduce insulin-stimulated glucose disposal in a dose-dependent manner, a finding that was confirmed in several subsequent studies.[49,65-67] GCs particularly impair nonoxidative glucose disposal (reflecting glycogen synthesis), whereas glucose oxidation rates remain intact.[49,68] 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.[69] 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.[70]

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)[49] and increase plasma levels of amino acids due to enhanced proteolysis.[71,72] Both elevated NEFA and amino acids concentrations are strong inhibitors of insulin-stimulated glucose uptake.[73,74]

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.[75,76] 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.[77] 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[78] and protein[79] metabolism are reasonably well defined, the effects on lipid metabolism and in particular the role of adipose tissue herein are less clear.[80] 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.[81] 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.[82] 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*[80] and *in vivo*.[62] 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[80] 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*[83] 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.[84] We observed that prednisolone treatment dose-dependently impaired insulin-stimulated suppression of lipolysis resulting in elevated plasma NEFA levels during hyperinsulinaemia.[49]

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,[63] fat cells contribute to overall glucose tolerance by a cross-talk with liver and skeletal muscle.[85] 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*[86] 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,[87] were reduced following high-dose prednisolone treatment. The pro-inflammatory adipocytokines resistin and leptin, which are usually negatively associated with insulin sensitivity,[87] were both increased by high-dose prednisolone treatment.

In conclusion, GCs diabetogenic effects also involve actions on adipose tissue, i.e. unbeneficial 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.[88] 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.[89] 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.[90] 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.[1] In addition to attenuating insulin secretion, GCs impaired insulin biosynthesis and induced beta-cell apoptosis following more prolonged incubation.[91] 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.[92] 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.[93]

Effects of glucocorticoids on beta-cell function in humans

Also *in vivo* in humans, GCs acutely impair insulin secretion.[94] 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.[95] 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).[96]

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.[65-67,96-98] 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[66] or those with low glucose-stimulated insulin secretion (GSIS)[48] 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[65] and obese women,[99] 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.[100] Interestingly, prednisolone dose-dependently decreased arginine-induced insulin secretion.[67] In addition, prednisolone reduced glucose-independent insulin secretion during standardised meal tests[67,96] and impaired insulin secretion induced by the incretin hormones (detailed below).[98]

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.[102] 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 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.[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.

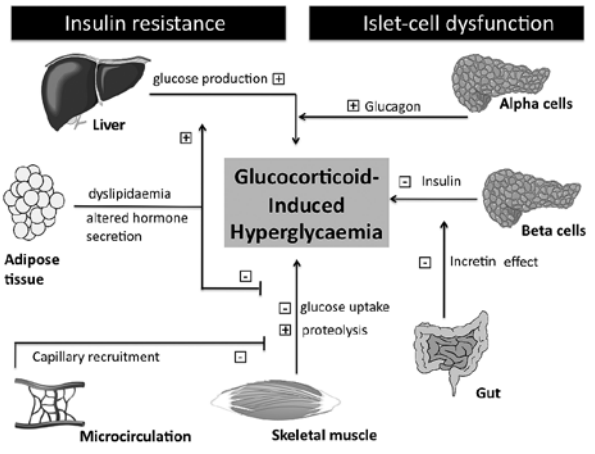
GLP-1 has a short half-life (1-2 minutes) since it is cleaved by the ubiquitous enzyme dipeptidyl peptidase (DPP)-4. Due to the above-mentioned beneficial effects of GLP-1 on glucose metabolism, treatment with DPP-4 resistant GLP-1, GLP-1 receptor agonists[105] and DPP-4 inhibitors[106] has been developed in T2DM patients, in whom the insulinotropic 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 insulinotropic 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,[67] which was confirmed by others.[97,109] Interestingly, however, the insulinotropic 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 insulinotropic 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*



Glucocorticoids (GCs) induce their diabetogenic effects both by inducing insulin resistance at the level of liver, skeletal muscle and adipose tissue, and by impairing pancreatic islet-cell dysfunction.

particularly increase postprandial glucose levels,[110] without affecting fasting glucose levels,[111] similarly as has been observed in patients with Cushing's syndrome.[112] 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,[113] 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.[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 glucose tolerance test after three days of dexamethasone treatment at 4 mg daily.[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.[116] However, participants gained 1.7 kg of weight during the four weeks of pre-treatment with troglitazone.

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

	Postprandial hyperglycaemia[67]
Liver	Impaired suppression of glucose production by insulin[49]
Skeletal muscle	Reduced insulin-stimulated glucose uptake[$49]
Adipose tissue	Impaired suppression of lipolysis by insulin[49]
Adipose tissue	Increased NEFA levels during hyperinsulinaemia[49]
Beta cells	Reduced glucose-adjusted basal insulin secretion[#67]
Beta cells	Reduced potentiation of glucose-stimulated insulin secretion[‡67]

[$]p=0.07; [#]p=0.09; [‡]p=0.06.

In addition to weight gain, thiazolidinediones cause oedema, heart failure and bone fractures,[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.[111] 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,[119] stimulates meal-related insulin secretion[105] and reduces glucagon secretion,[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.[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.[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.[95]

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.[123] 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 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.

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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. Autoimmun Rev. 2011;10:305-10.
3. Bierry H, Malloizel, L. Hypoglycemic après décapsulation, effets de l'injection d'adrénaline sur les animaux décapsules. Co R Soc Biol. 1908;65:232-4.
4. Long C, Katzin B, Fry, E. The adrenal cortex and carbohydrate metabolism. Endocrinology. 1940;26:309-44.
5. Reichstein T. Über bestandteile der nebennieren-rind, VI. Trennungsmethoden sowie isolierung der substanzen Fa, H und J. Helvetica Chimica Acta. 1936;19:1107-26.
6. Mason HI, Myers CS, Kendall EC. The chemistry of crystalline substances isolated from the suprarenal gland. J Biol Chem. 1936;114:613-31.
7. Hillier SG. Diamonds are forever: the cortisone legacy. J Endocrinol. 2007;195:1-6.
8. Sarett L. Partial synthesis of pregnene-4-triol-17(beta), 20(beta), 21-dione-3,11 and pregnene-4-diol-17(beta), 21-trione-3,11,20 monoacetate? J Biol Chem. 1946;162:601-31.
9. Perera GA, Pines KL, Hamilton HB, Vislocky K. Clinical and metabolic study of 11-dehydro-17-hydroxycorticosterone acetate (Kendall compound E) in hypertension, Addison's disease and diabetes mellitus. Am J Med. 1949;7:56-69.
10. Hench PS. Effect of Jaundice on Rheumatoid Arthritis. Br Med J. 1938;2:394-8.
11. Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin. 1949;24:181-97.
12. Hench PK, Kendall EC, Slocumb CH, Polley HF. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions. Arch Intern Med (Chic). 1950;84:545-666.
13. Bijlsma JW, van der Goes MC, Hoes JN, Jacobs JW, Buttgereit F, Kirwan J. Low-dose glucocorticoid therapy in rheumatoid arthritis: an obligatory therapy. Ann N Y Acad Sci. 2010;1193:123-6.
14. Parker BJ, Bruce IN. High dose methylprednisolone therapy for the treatment of severe systemic lupus erythematosus. Lupus. 2007;16:387-93.
15. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet. 2008;372:234-45.
16. Hernandez-Rodriguez J, Cid MC, Lopez-Soto A, Espigol-Frigole G, Bosch X. Treatment of polymyalgia rheumatica: a systematic review. Arch Intern Med. 2009;169:1839-50.
17. Baughman RP, Costabel U, du Bois RM. Treatment of sarcoidosis. Clin Chest Med. 2008;29:533-48, ix-x.
18. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116:488-98.
19. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W, American Gastroenterological A. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology. 2006;130:940-87.
20. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011;60:1611-29.
21. Tilly H, Vitolo U, Walewski J, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii78-82.
22. Harousseau JL, Dreyling M, Group EGW. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v155-7.
23. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267-84.
24. Celli BR, MacNee W, Force AET. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932-46.
25. Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. Immunol Allergy Clin North Am. 2007;27:309-26, viii.
26. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther. 2002;96:23-43.
27. Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol. 2007;157:545-59.
28. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. Diabetes Care. 2006;29:2728-9.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.

34. 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.

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

36. 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.

37. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? Obes Rev. 2001;2:73-86.

38. Reynolds RM, Walker BR, Syddall HE, Whorwood CB, Wood PJ, Phillips DI. Elevated plasma cortisol in glucose-intolerant men: differences in responses to glucose and habituation to venepuncture. J Clin Endocrinol Metab. 2001;86:1149-53.

39. Seckl JR. 11beta-hydroxysteroid dehydrogenases: changing glucocorticoid action. Curr Opin Pharmacol. 2004;4:597-602.

40. Morton NM, Seckl JR. 11beta-hydroxysteroid dehydrogenase type 1 and obesity. Front Horm Res. 2008;36:146-64.

41. Pereira CD, Azevedo I, Monteiro R, Martins MJ. 11beta-Hydroxysteroid dehydrogenase type 1: relevance of its modulation in the pathophysiology of obesity, the metabolic syndrome and type 2 diabetes mellitus. Diabetes Obes Metab. 2012;14:869-81.

42. Schacke H, Berger M, Rehwinkel H, Asadullah K. Selective glucocorticoid receptor agonists (SEGRAs): novel ligands with an improved therapeutic index. Mol Cell Endocrinol. 2007;275:109-17.

43. Hollenberg SM, Weinberger C, Ong ES, et al. Primary structure and expression of a functional human glucocorticoid receptor cDNA. Nature. 1985;318:635-41.

44. van Lierop MJ, Alkema W, Laskewitz AJ, et al. Org 214007-0: a novel non-steroidal selective glucocorticoid receptor modulator with full anti-inflammatory properties and improved therapeutic index. PLoS One. 2012;7:e48385.

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

46. Rizza RA, Mandarino LJ, Gerich JE. Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a postreceptor detect of insulin action. J Clin Endocrinol Metab. 1982;54:131-8.

47. Rooney DP, Neely RD, Cullen C, et al. The effect of cortisol on glucose/glucose-6-phosphate cycle activity and insulin action. J Clin Endocrinol Metab. 1993;77:1180-3.

48. Wajngot A, Giacca A, Grill V, Vranic M, Efendic S. The diabetogenic effects of glucocorticoids are more pronounced in low- than in high-insulin responders. Proc Natl Acad Sci U S A. 1992;89:6035-9.

49. van Raalte DH, Brands M, van der Zijl NJ, et al. Low-dose glucocorticoid treatment affects multiple aspects of intermediary metabolism in healthy humans: a randomised controlled trial. Diabetologia. 2011;54:2103-12.

50. Nielsen MF, Caumo A, Chandramouli V, et al. Impaired basal glucose effectiveness but unaltered fasting glucose release and gluconeogenesis during short-term hypercortisolemia in healthy subjects. Am J Physiol Endocrinol Metab. 2004;286:E102-10.

51. Miyoshi H, Shulman GI, Peters EJ, Wolfe MH, Elahi D, Wolfe RR. Hormonal control of substrate cycling in humans. J Clin Invest. 1988;81:1545-55.

52. Schneiter P, Tappy L. Kinetics of dexamethasone-induced alterations of glucose metabolism in healthy humans. Am J Physiol. 1998;275(5 Pt 1):E806-13.

53. Wajngot A, Khan A, Giacca A, Vranic M, Efendic S. Dexamethasone increases glucose cycling, but not glucose production, in healthy subjects. Am J Physiol. 1990;259(5 Pt 1):E626-32.

54. Bollen M, Keppens S, Stalmans W. Specific features of glycogen metabolism in the liver. Biochem J. 1998;336(Pt 1):19-31.

55. Jin JY, DuBois DC, Almon RR, Jusko WJ. Receptor/gene-mediated pharmacodynamic effects of methylprednisolone on phosphoenolpyruvate carboxykinase regulation in rat liver. J Pharmacol Exp Ther. 2004;309:328-39.

56. Vander Kooi BT, Onuma H, Oeser JK, et al. The glucose-6-phosphatase catalytic subunit gene promoter contains both positive and negative glucocorticoid response elements. Mol Endocrinol. 2005;19:3001-22.

57. Vegiopoulos A, Herzig S. Glucocorticoids, metabolism and metabolic diseases. Mol Cell Endocrinol. 2007;275:43-61.

58. Kraus-Friedmann N. Hormonal regulation of hepatic gluconeogenesis. Physiol Rev. 1984;64:170-259.

59. Dirlewanger M, Schneiter PH, Paquot N, Jequier E, Rey V, Tappy L. Effects of glucocorticoids on hepatic sensitivity to insulin and glucagon in man. Clin Nutr. 2000;19:29-34.

60. Saad MJ, Folli F, Kahn JA, Kahn CR. Modulation of insulin receptor, insulin receptor substrate-1, and phosphatidylinositol 3-kinase in liver and muscle of dexamethasone-treated rats. J Clin Invest. 1993;92:2065-72.

61. Zinker B, Mika A, Nguyen P, et al. Liver-selective glucocorticoid receptor antagonism decreases glucose production and increases glucose disposal, ameliorating insulin resistance. Metabolism. 2007;56:380-7.

62. Macfarlane DP, Forbes S, Walker BR. Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. J Endocrinol. 2008;197:189-204.

63. 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.

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

65. Henriksen JE, Alford F, Ward GM, Beck-Nielsen H. Risk and mechanism of dexamethasone-induced deterioration of glucose tolerance in non-diabetic first-degree relatives of NIDDM patients. Diabetologia. 1997;40:1439-48.

66. Larsson H, Ahren B. Insulin resistant subjects lack islet adaptation to short-term dexamethasone-induced reduction in insulin sensitivity. Diabetologia. 1999;42:936-43.

67. van Raalte DH, Kwa KA, van Genugten RE, et al. Islet-cell dysfunction induced by glucocorticoid treatment: potential role for altered sympathovagal balance? Metabolism. 2013;62:568-77.

68. Henriksen JE, Alford F, Vaag A, Handberg A, Beck-Nielsen H. Intracellular skeletal muscle glucose metabolism is differentially altered by dexamethasone treatment of normoglycemic relatives of type 2 diabetic patients. Metabolism. 1999;48:1128-35.

69. Khaleeli AA, Edwards RH, Gohil K, et al. Corticosteroid myopathy: a clinical and pathological study. Clin Endocrinol (Oxf). 1983;18:155-66.

70. Ruzzin J, Wagman AS, Jensen J. Glucocorticoid-induced insulin resistance in skeletal muscles: defects in insulin signalling and the effects of a selective glycogen synthase kinase-3 inhibitor. Diabetologia. 2005;48:2119-30.

71. Lofberg E, Gutierrez A, Wernerman 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.

72. 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 Metab. 2009;297:E1260-8.

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

74. 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.

75. Barrett EJ, Eggleston EM, Inyard AC, et al. The vascular actions of insulin control its delivery to muscle and regulate the rate-limiting step in skeletal muscle insulin action. Diabetologia. 2009;52:752-64.

76. Kubota T, Kubota N, Kumagai H, et al. Impaired insulin signaling in endothelial cells reduces insulin-induced glucose uptake by skeletal muscle. Cell Metab. 2011;13:294-307.

77. van Raalte DH, Diamant M, Ouwens DM, et al. Glucocorticoid treatment impairs microvascular function in healthy men in association with its adverse effects on glucose metabolism and blood pressure: a randomised controlled trial. Diabetologia. 2013;56:2383-91.

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

79. Hamel FG, Fawcett J, Bennett RG, Duckworth WC. Control of proteolysis: hormones, nutrients, and the changing role of the proteasome. Curr Opin Clin Nutr Metab Care. 2004;7:255-8.

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

81. Rockall AG, Sohaib SA, Evans D, et al. Computed tomography assessment of fat distribution in male and female patients with Cushing's syndrome. Eur J Endocrinol. 2003;149:561-7.

82. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2010;11:11-8.

83. Turnbow MA, Keller SR, Rice KM, Garner CW. Dexamethasone down-regulation of insulin receptor substrate-1 in 3T3-L1 adipocytes. J Biol Chem. 1994;269:2516-20.

84. Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA. Insulin effects in muscle and adipose tissue. Diabetes Res Clin Pract. 2011;93(Suppl 1):S52-9.

85. Abel ED, Peroni O, Kim JK, et al. Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature. 2001;409:729-33.

86. Fasshauer M, Paschke R. Regulation of adipocytokines and insulin resistance. Diabetologia. 2003;46:1594-603.

87. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11:85-97.

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

89. 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.

90. 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.

91. Ranta F, Avram D, Berchtold S, et al. Dexamethasone induces cell death in insulin-secreting cells, an effect reversed by exendin-4. Diabetes. 2006;55:1380-90.

92. Linssen MM, van Raalte DH, Toonen EJ, et al. Prednisolone-induced beta cell dysfunction is associated with impaired endoplasmic reticulum homeostasis in INS-1E cells. Cell Signal. 2011;23:1708-15.

93. Davani B, Portwood N, Bryzgalova G, et al. Aged transgenic mice with increased glucocorticoid sensitivity in pancreatic beta-cells develop diabetes. Diabetes. 2004;53(Suppl 1):S51-9.

94. Kalhan SC, Adam PA. Inhibitory effect of prednisone on insulin secretion in man: model for duplication of blood glucose concentration. J Clin Endocrinol Metab. 1975;41:600-10.

95. van Raalte DH, van Genugten RE, Linssen MM, Ouwens DM, Diamant M. Glucagon-like peptide-1 receptor agonist treatment prevents glucocorticoid-induced glucose intolerance and islet-cell dysfunction in humans. Diabetes Care. 2011;34:412-7.

96. van Raalte DH, Nofrate V, Bunck MC, et al. Acute and 2-week exposure to prednisolone impair different aspects of beta-cell function in healthy men. Eur J Endocrinol. 2010;162:729-35.

97. Hansen KB, Vilsboll T, Bagger JI, Holst JJ, Knop FK. Reduced glucose tolerance and insulin resistance induced by steroid treatment, relative physical inactivity, and high-calorie diet impairs the incretin effect in healthy subjects. J Clin Endocrinol Metab. 2010;95:3309-17.

98. Hansen KB, Vilsboll T, Bagger JI, Holst JJ, Knop FK. Impaired Incretin-Induced Amplification of Insulin Secretion after Glucose Homeostatic Dysregulation in Healthy Subjects. J Clin Endocrinol Metab. 2012;97:1363-70.

99. Besse C, Nicod N, Tappy L. Changes in insulin secretion and glucose metabolism induced by dexamethasone in lean and obese females. Obes Res. 2005;13:306-11.

100. Ward WK, Bolgiano DC, McKnight B, Halter JB, Porte D, Jr. Diminished B cell secretory capacity in patients with noninsulin-dependent diabetes mellitus. J Clin Invest. 1984;74:1318-28.

101. van Raalte DH, van Leeuwen N, Simonis-Bik AMC, et al. Glucocorticoid Receptor Gene Polymorphisms are Associated with Reduced First-phase Glucose-Stimulated Insulin Secretion and Disposition Index in Women, but not in Men. Diabet Med. 2012;29:e211-6.

102. 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.

103. Wise JK, Hendler R, Felig P. Influence of glucocorticoids on glucagon secretion and plasma amino acid concentrations in man. J Clin Invest. 1973;52:2774-82.

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

105. van Genugten RE, van Raalte DH, Diamant M. Does glucagon-like peptide-1 receptor agonist therapy add value in the treatment of type 2 diabetes? Focus on exenatide. Diabetes Res Clin Pract. 2009;86(Suppl 1):S26-34.

106. van Genugten RE, van Raalte DH, Diamant M. Dipeptidyl peptidase-4 inhibitors and preservation of pancreatic islet-cell function: a critical appraisal of the evidence. Diabetes Obes Metab. 2012;14:101-11.

107. Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epi-phenomenon of impaired beta-cell function? Diabetes. 2010;59:1117-25.

108. Zhang R, Packard BA, Tauchi M, D'Alessio DA, Herman JP. Glucocorticoid regulation of preproglucagon transcription and RNA stability during stress. Proc Natl Acad Sci U S A. 2009;106:5913-8.

109. Hansen KB, Vilsboll T, Bagger JI, Holst JJ, Knop FK. Increased postprandial GIP and glucagon responses, but unaltered GLP-1 response after intervention with steroid hormone, relative physical inactivity, and high-calorie diet in healthy subjects. J Clin Endocrinol Metab. 2011;96:447-53.

110. Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN. Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. J Clin Endocrinol Metab. 2011;96:1789-96.

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

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

113. 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.

114. Kwon S, Hermayer KL. Glucocorticoid-induced hyperglycemia. Am J Med Sci. 2013;345:274-7.

115. Morita H, Oki Y, Ito T, Ohishi H, Suzuki S, Nakamura H. Administration of troglitazone, but not pioglitazone, reduces insulin resistance caused by short-term dexamethasone (DXM) treatment by accelerating the metabolism of DXM. Diabetes Care. 2001;24:788-9.

116. Willi SM, Kennedy A, Wallace P, Ganaway E, Rogers NL, Garvey WT. Troglitazone antagonizes metabolic effects of glucocorticoids in humans: effects on glucose tolerance, insulin sensitivity, suppression of free fatty acids, and leptin. Diabetes. 2002;51:2895-902.

117. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2004;27:256-63.

118. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Arch Intern Med. 2008;168:820-5.

119. 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 Metab. 2008;294:E846-52.

120. 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.

121. 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.

122. 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.

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

124. den Uyl D, van Raalte DH, Nurmohamed 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.