



# Glucocorticoid Metabolism in Obesity and Following Weight Loss

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Glucocorticoids are steroid hormones produced by the adrenal cortex and are essential for the maintenance of various metabolic and homeostatic functions. Their function is regulated at the tissue level by 11 $\beta$ -hydroxysteroid dehydrogenases and they signal through the glucocorticoid receptor, a ligand-dependent transcription factor. Clinical observations have linked excess glucocorticoid levels with profound metabolic disturbances of intermediate metabolism resulting in abdominal obesity, insulin resistance and dyslipidaemia. In this review, we discuss the physiological mechanisms of glucocorticoid secretion, regulation and function, and survey the metabolic consequences of excess glucocorticoid action resulting from elevated release and activation or up-regulated signaling. Finally, we summarize the reported impact of weight loss by diet, exercise, or bariatric surgery on circulating and tissue-specific glucocorticoid levels and examine the therapeutic possibility of reversing glucocorticoid-associated metabolic disorders.

**Keywords:** glucocorticoids, obesity, weight loss, bariatric surgery, 11 $\beta$ -HSD1

## GLUCOCORTICOID SECRETION

Glucocorticoid hormones are a class of corticosteroids, produced by the adrenal cortex primarily under the control of the hypothalamic-pituitary-adrenal (HPA) axis (1). Briefly, corticotropin-releasing hormone (CRH) and vasopressin are released from the hypothalamus and synergistically stimulate the secretion of stored adrenocorticotrophic hormone (ACTH) from corticotrope cells in the anterior pituitary gland. Following this, ACTH is transported by the blood to the adrenal cortex, where it rapidly stimulates biosynthesis of corticosteroids such as cortisol from cholesterol (2). However, it recently became apparent (3) that the fine-tuning and regulation of the adrenal system is also controlled by ACTH-independent mechanisms. These include a temporal lag between stimulus-induced changes in circulating ACTH and in corticosteroid levels (4), adrenal corticosteroid metabolism and kinetics, and plasma protein binding (5–7). Moreover, dysregulation is observed in glucocorticoid secretion under pathological conditions (8, 9). An example of this is in obesity, where several studies in humans report (8, 10–12) an increase of cortisol secretion directly from the adrenal gland, yet the circulating plasma levels are normal, potentially due to higher metabolic clearance rate.

A variety of growth factors, neuropeptides, cytokines and adipokines have been demonstrated to affect adrenal secretions. Correspondingly, adrenocortical cells express receptors for each of these factors (13, 14). *In vitro* studies found that vital glucose regulating-peptides also have the capacity

to regulate ACTH-stimulated glucocorticoid secretion. More specifically, insulin inhibits cortisol secretion from bovine adrenocortical cells (15), while glucagon inhibits cortisol secretion from human adrenocortical cells (16, 17). The satiety factor leptin was found to directly regulate adrenal secretions via its receptors on adrenocortical cells (18, 19). Likewise, the gut-derived incretin hormone glucagon-like peptide 1 (GLP-1) was also shown to inhibit glucocorticoid release from rat adrenal cortex in response to ACTH, by decreasing the activation of adenylate cyclase and by impairing the late steps of glucocorticoid synthesis (17). Nonetheless, intracerebroventricular, intravenous, and intraperitoneal administration of GLP-1 increased circulating levels of cortisol in rats, a change preceded by an increase in ACTH levels (20, 21). The mechanisms through which circulating GLP-1 activate the HPA axis remain to be elucidated, and may provide further evidence for the beneficial effect of GLP-1 receptor agonists in obesity and type 2 diabetes (T2DM) treatment.

### 11 $\beta$ -Hydroxysteroid Dehydrogenases

Although the regulation of glucocorticoid secretion is an important means of their action, the effects of glucocorticoids on target tissues such as liver and adipose tissue are dependent on metabolism by 11 $\beta$ -hydroxysteroid dehydrogenases (11 $\beta$ -HSDs), with the notable exception of pancreatic  $\beta$ -cells (22). 11 $\beta$ -HSD1 is present in most cells and tissues and acts predominantly as an NADPH-dependent reductase to regenerate the active glucocorticoid receptor (GR) ligand cortisol (or corticosterone, in rodents) from inactive cortisone (**Figure 1**) (23). Conversely, 11 $\beta$ -HSD2 inactivates cortisol by converting it into cortisone, thereby protecting the mineralocorticoid receptor from cortisol ligands. 11 $\beta$ -HSD2 is largely expressed in the kidney, placenta, and colon whereas the principle sites of 11 $\beta$ -HSD1 expression are liver, adipose tissue and muscle (24). The A-ring reductases, 5-reductase types 1 and 2 (5R1 and 5R2) convert cortisol and cortisone to their dihydrometabolites, and these are next converted to tetrahydrometabolites through the action of 3-hydroxysteroid dehydrogenase (25, 26). Total glucocorticoid production can be estimated by analyzing the sum of glucocorticoid metabolites in a 24 h urinary sample. The relative excretion of cortisol to cortisone metabolites [(5 $\alpha$ -THF + THF + a-cortol)/(THE + a-cortolone)] reflects the global activity of 11 $\beta$ -HSD 1 (27).

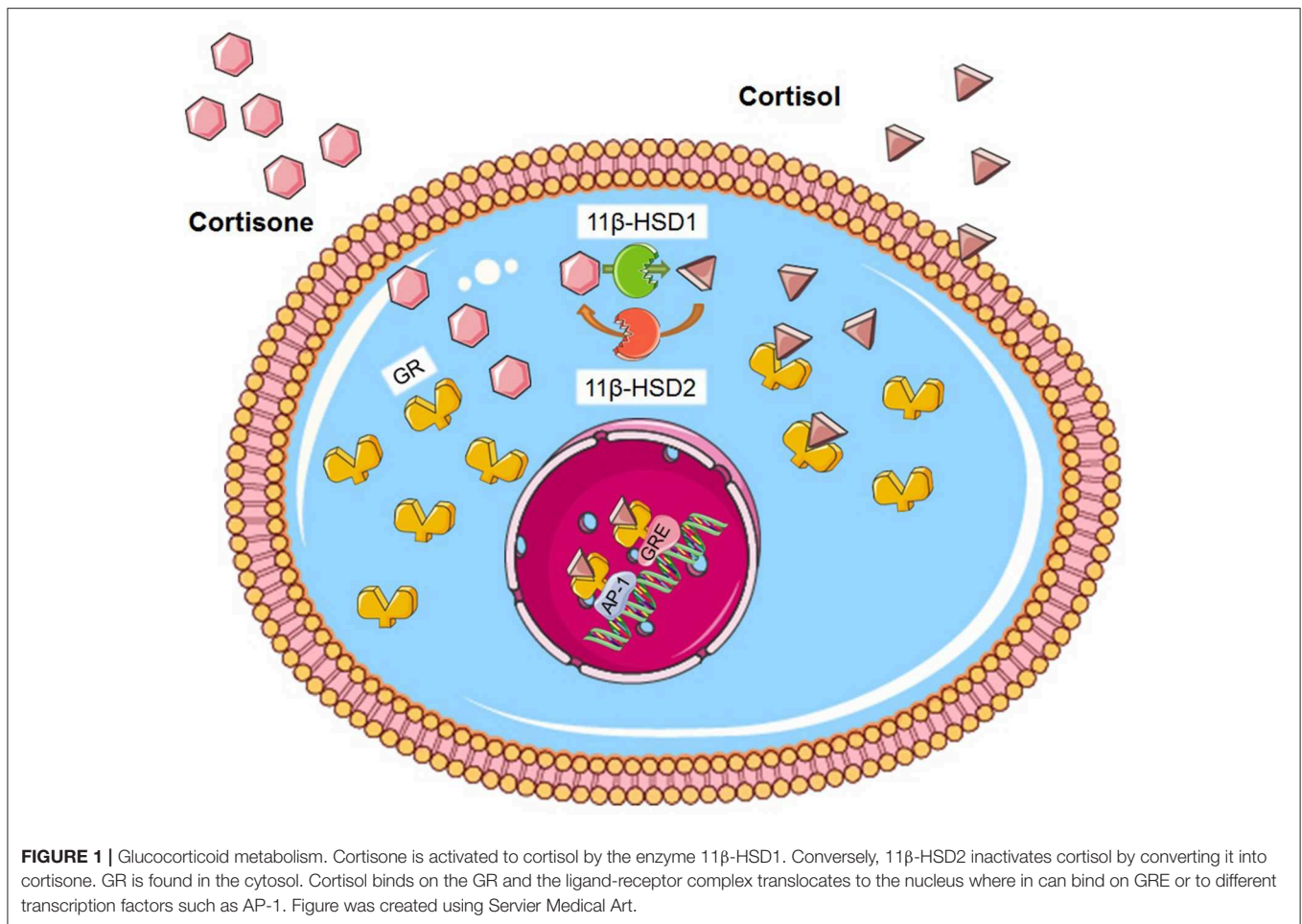
Glucocorticoid metabolism at the tissue level is dysregulated in human obesity, with increased 5-reductase activity and decreased cortisol levels in the liver (28–30). Contrariwise, 11 $\beta$ -HSD1 activity is increased in adipose tissue, which increases tissue glucocorticoid levels. Mice overexpressing 11 $\beta$ -HSD1 in adipose tissue develop visceral obesity, insulin resistance, dyslipidaemia, and hypertension (31), while liver-specific 11 $\beta$ -HSD1 overexpression results in insulin resistance and hypertension, but not obesity (32). Interestingly, 11 $\beta$ -HSD1 appears to be absent from pancreatic  $\alpha$  and  $\beta$ - cells though present in other cell types in the mouse and human islet (22, 33). Selective 11 $\beta$ -HSD1 inhibitors have been shown to lower glucose intolerance and reduce food intake and weight gain in hyperglycaemic mouse models (34–36). 11 $\beta$ -HSD1

knockout mice are resistant to hyperglycaemia when fed a high-fat diet and show reduced expression of mRNA encoding the key hepatic gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PCK1) (37). Overall, these studies place 11 $\beta$ -HSD1 in a central position of cortisol metabolism and suggest that its inhibition may be a key target for diabetes and obesity treatments, especially as a mediator of insulin sensitivity. Nonetheless, the differential regulation of 11 $\beta$ -HSD1 between organs implies a more complex pathway that may require equal attention to be paid to 11 $\beta$ -HSD2.

### Glucocorticoid Receptors (GR)

The function of glucocorticoids, both at a physiological and pharmacological level, is mediated by the GR. The GR is a member of the nuclear receptor superfamily of ligand-dependent transcription factors and its gene is regulated by both developmental and tissue-specific factors (38). Activated GR controls the expression of thousands of genes, either by inducing or inhibiting their transcription through DNA binding (39–41). The GR is composed of three main domains; the N-terminal transactivation, the central DNA-binding and the C-terminal ligand binding domains, with the central domain containing two zinc fingers. In the absence of glucocorticoids, GR is located primarily in the cytoplasm inside a large multi-protein complex. Once glucocorticoids are bound, GR dissociates from the complex and exposes two nuclear localization signals. GR then rapidly translocates into the nucleus through nuclear pores and, once inside, binds directly to glucocorticoid-responsive elements (GRE) and regulates the expression of target genes (**Figure 1**) (42). Our understanding of the role of the GR protein has changed dramatically within the last decade, as it is now accepted that the GR gene can be spliced into a large group of receptor isoforms, each with a different expression and function that widens the glucocorticoid diversity of GR action (43). Moreover, although this review focuses on the genomic mechanism of glucocorticoid function, several studies have demonstrated a rapid, non-genomic action mechanism that does not involve gene expression alteration and may involve an, as yet uncharacterised, receptor located at the plasma membrane (44–46).

Glucocorticoids acting through the GR regulate glucose metabolism in the liver, skeletal muscle, adipose tissue, and the pancreas, by controlling the expression of key enzymes. However, in obesity, cortisol levels remain at near normal concentrations, pointing to intracellular control of GR action in these circumstances. This suggests that GR polymorphisms might be responsible for the pathophysiology and evolution of obesity and diabetes (47, 48). The GR levels and activity have also been linked to diabetes pathogenesis, as increased hepatic GR mRNA induces activation of phosphoenolpyruvate carboxykinase (PEPCK), which results in hyperglycaemia and insulin resistance in diabetic obese mice and obese Zucker rats (49, 50). This observation was also made in human skeletal muscle, as increased GR was linked to the metabolic syndrome (51). Furthermore, general and hepatic inactivation of GR, achieved through the use of antagonists, was shown to improve glucose tolerance and insulin resistance in diabetic animals (52–54). The mass emerging observations on GR



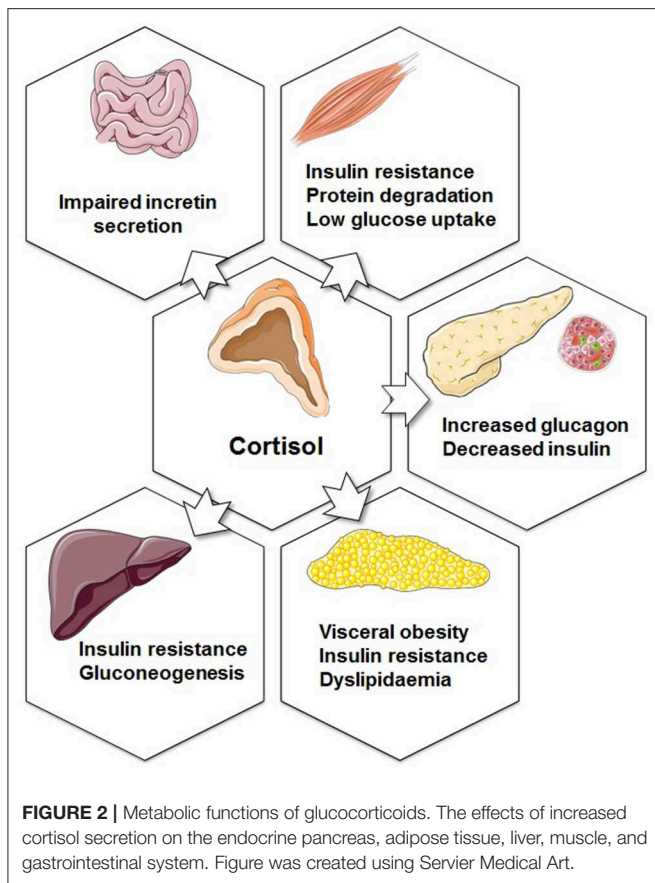
polymorphism could further indicate which receptor subtype can be a disease risk indicator, as well as improve specificity for GR antagonism treatment.

## METABOLIC FUNCTION OF GLUCOCORTICOIDS

Glucocorticoids are involved in metabolic, inflammatory, cardiovascular, and behavioral processes. Thus, as mentioned above, they modulate the transcription of a variety of genes, including cytokines and chemokines, receptors, enzymes, adhesion molecules, and inhibitory proteins. Clinical observations linking high glucocorticoid levels to the metabolic syndrome provided evidence for their role on diabetes and obesity (55). The metabolic effects of glucocorticoids are linked to physiological mechanisms that are associated with hepatic and peripheral insulin resistance, hyperglycaemia, and dyslipidaemia. In the liver, glucocorticoids stimulate gluconeogenesis by activating PEPCK and glucose-6-phosphatase (G6Pase) (56). Moreover, in the fasting condition, glucocorticoids stimulate lipolysis in adipocytes, resulting in generation of glycerol to be utilized in gluconeogenesis and free fatty acids to be oxidized

and get used as energy (57, 58). Although glucocorticoids are important for the maintenance of lipid homeostasis, excess glucocorticoids can result in an increase the circulating free fatty acids and induce lipid accumulation in skeletal muscle and liver, both of which are associated with insulin resistance (59–61). In rat skeletal muscle, glucocorticoid excess can also inhibit the translocation of GLUT4 glucose transporters to the plasma membrane in response to insulin, resulting in insulin resistance (Figure 2) (62). In human adipose tissue, glucocorticoids induce adipocyte differentiation leading to increased adiposity and insulin resistance (63–65).

The link between glucocorticoids and T2DM is strong, yet the effect of glucocorticoids on the endocrine pancreas remains controversial. The study of transgenic mice overexpressing the GR selectively in the  $\beta$ -cell indicated that glucocorticoids may directly inhibit insulin release *in vivo* (66). Correspondingly, several *in vitro* studies have demonstrated an inhibitory effect of glucocorticoids on mouse islets (67, 68). The function of 11 $\beta$ -HSD1 in mouse and human islets has been examined *in vitro*, and data suggest direct control over  $\alpha$ -cell glucagon release and a paracrine effect on insulin secretion (69). In islets obtained from diabetic obese mice, glucocorticoid administration



up regulated  $11\beta$ -HSD1 causing impaired insulin secretion. This effect was abolished by GR antagonist or an  $11\beta$ -HSD1 inhibitor (70).

Glucocorticoids have also been associated with pancreatic development. Treatment of fetal rats with dexamethasone reduced  $\beta$ -cell insulin content and examination of embryonic pancreata from glucocorticoid-treated animals revealed a decrease of insulin-producing cells and an increase in exocrine cells, possibly the result of down-regulation of pancreas maturation transcription factors such as Pdx1, Pax6, and Nkx6.1 (71, 72). However, islets from Wistar rats treated with dexamethasone for 5 days showed an enhanced insulin release in response to glucose, with an increased number of insulin granules docked at the plasma membrane observed in  $\beta$ -cells (73). Transgenic mice overexpressing  $11\beta$ -HSD1 selectively to the  $\beta$ -cell displayed a reversal of high fat-induced  $\beta$ -cell failure. This was due to the expansion of  $\beta$ -cell population and the function of small islets, the latter being linked to protein kinase A and p21 signaling pathways (74). Finally, corticosterone, cortisol, and cortisone suppressed voltage-dependent  $Ca^{2+}$  channel activity in human and rodent  $\beta$ -cells, while in parallel amplifying cAMP signals and increasing the number of membrane-docked insulin secretory granules. Interestingly, no changes were observed in glucose-stimulated insulin secretion nor in the maximal ATP/ADP responses to glucose (75).

## GLUCOCORTICOID METABOLISM IN OBESITY AND WEIGHT LOSS

### Diet and Exercise

Although a link between glucocorticoids and obesity has been reported in many studies, it is still unclear what changes following weight loss. Tomlinson et al. (76) reported the effects of weight loss on glucocorticoids in patients with obesity on very low calorie diet. Even though circulating cortisol and cortisone concentrations did not change with weight loss, the 0900h cortisol/cortisone ratio increased, indicating a shift in set-point toward cortisol generation consistent with increased  $11\beta$ -HSD1 activity. Expression of  $11\beta$ -HSD1 in whole adipose tissue did not change with weight loss but did increase in isolated adipocytes. No other corticosteroid was affected. A follow-up of this study (77) showed that total glucocorticoid secretion in this scenario decreased post-diet-induced weight loss. However, urinary steroid metabolite ratios that reflect  $11\beta$ -HSD1 activity did not change. Moreover, increased cortisol availability within adipose tissue interstitial fluid was shown after weight loss.

In men with weight loss following 6 months of dieting, cortisol production rate, free cortisol levels and metabolic clearance rate did not change when compared to baseline (78). Nonetheless, with greater weight loss and decreased body fat, both cortisol production and free cortisol levels increased, whilst adipose  $11\beta$ -HSD-1 decreased, compared to baseline (78). One week of caloric restriction in men also failed to reveal any change in cortisol levels (79). These results were further investigated in overweight/obese post-menopausal women following diet-induced weight loss with contradictory results. In one study (80),  $11\beta$ -HSD1 expression in adipose tissue was decreased post-weight loss and this reduction was correlated with a reduction in BMI between baseline and 6 months post-diet initiation. In contrast, a previous study showed that weight reduction did not impact gene expression levels of  $11\beta$ -HSD1 in adipose tissue (81).

Glucocorticoids respond acutely to changes in nutritional status, with cortisol levels increasing within minutes following a meal (82, 83). Given the discrepancies between studies, as well as differences in human and rodent data, it became clear that the type of meal in each diet had to be specified and specific dietary macronutrients were investigated with regards to their effect on metabolism (84). A high fat-low carbohydrate diet increased whole body  $11\beta$ -HSD1 activity and decreased 5 $\alpha$ - and 5 $\beta$ -reductase activities in men, compared with a moderate fat-moderate carbohydrate diet, with no effect on subcutaneous adipose tissue  $11\beta$ -HSD1 (84). In rodents, although there was no difference between low carbohydrate and moderate carbohydrate diets, hepatic  $11\beta$ -HSD1 mRNA was reduced in both diets when compared with a high fat Western diet (85).

Apart from diet, exercise is a common treatment for weight loss. However, exercise is also a form of metabolic stress which can stimulate the HPA axis and lead to increased levels of circulating glucocorticoids (86, 87). The importance of this has been investigated by separating acute intense and chronic voluntary exercises in rats on treadmill running, where intense exercise studies have shown higher corticosterone levels in urine, enlargement of the adrenal glands and reduced adrenal sensitivity

to ACTH, as indicated by low ACTH-to-glucocorticoid ratio (88, 89), whether regular and voluntary exercise increased adrenal sensitivity, demonstrating that long-term training balances glucocorticoid fluctuations (86, 90).

Although increased glucocorticoid concentration can indeed have a negative impact in pancreatic  $\beta$ -cells alone (91), regular exercise can improve insulin sensitivity and glucose tolerance and this could be attributed to tissular, rather than systemic, glucocorticoid metabolism. It has previously been shown that exercise can lead to reduced expression of the glucocorticoid receptor and  $11\beta$ -HSD1 in muscle and liver, yet unchanged circulating cortisol, in hamsters (87). Importantly, previous studies in humans and rodents have demonstrated that various types of exercise are able to improve insulin sensitivity, by recovering the function of specific insulin signaling proteins such as Akt and IRS-1 and also augment GLUT-4 expression (92–97). Insulin-stimulated glucose uptake in muscle, impaired by exposure to glucocorticoids, can also be enhanced by exercise. The effects of exercise appear to involve increased activation of insulin signal via Akt and IRS1 in rodents, as well as slow the glucocorticoid-induced muscle atrophy. This appears to improve through a combination of increases in mTOR and its downstream target p70S6K protein, and a small increase in MuRF-1 protein level, the latter a regulator of proteasome-dependent degradation of muscle proteins (94–96). To date, studies have been able to demonstrate that exercise is able to attenuate exogenous glucocorticoid-induced hyperglycaemia, while less is known about its effect on endogenous glucocorticoids.

Overall, reporting on the relationship between cortisol levels, obesity and weight loss has been challenging, especially if cortisol was measured in the serum, urine or saliva which would provide a snapshot in time rather than continuous reporting. This is most likely due to the fact that cortisol is secreted in a pulsatile manner, affected by the circadian rhythm, environmental circumstances and stress (98), which could even be diet-induced. In addition, gender and adiposity location also appear to have an effect on results. It is therefore important to remember that not all patients with obesity will demonstrate similar cortisol secretion and metabolism, especially at baseline level. Chronic cortisol measurement may provide a more appropriate and ubiquitous way to report changes in glucocorticoid metabolism, potentially by using hair cortisol measurements (99–102), which has been shown to be a novel and accurate way to measure average systemic cortisol levels.

## Bariatric Surgery

Bariatric surgery, and particularly Roux-en-Y gastric bypass (RYGB), causes sustained weight loss in individuals with morbid obesity, as well as dramatic and rapid improvement of T2DM, dyslipidaemia, hypertension and a significant reduction of cardiovascular disease and death (103). Although the effects of RYGB on diabetes were initially attributed to the substantial weight loss subsequent to post-operative restriction of nutrient intake and/or absorption, the same effect was demonstrated in rodents that did not experience weight loss, suggesting a mechanism of action that is weight independent. Moreover, the

improvements are observed within hours and days, long before substantial weight loss occurred.

In an effort to understand the underlying mechanisms of diabetes remission, this observation has since led to numerous investigations on the glucoregulatory role of the gastrointestinal tract, including the role of an increase in observed post-operative GLP-1 concentration. This includes the “hindgut hypothesis” which holds that euglycaemic effects are derived from the expedited delivery of nutrients to the distal intestine, where GLP-1 is primarily secreted, and therefore enhances the insulin signal that improves glucose metabolism (104). Few data are available regarding the specific modifications in glucocorticoid metabolism after bariatric surgery in human obesity. Given the numerous endocrine changes following surgery, one might expect to have a conclusive picture of glucocorticoid metabolism post-operatively. The fact that this is the case due to different surgical procedures, as well as alterations of the same procedures, which can cause perioperative stress and different levels of caloric restriction and weight loss.

Several observations have linked bariatric surgery to glucocorticoid metabolism, notably in the context of post-operative adipose tissue reduction. Woods et al. investigated the activity and expression of  $11\beta$ -HSD1 in hepatic and adipose tissue before and  $\sim 14$  months after RYGB, revealing a post-operative increase in hepatic  $11\beta$ -HSD1 activity, as inferred from a by raised serum cortisol/cortisone ratio (F/E) (105). However, subcutaneous adipose tissue  $11\beta$ -HSD1 activity was decreased, as showed by the tissue's F/E. Moreover, total urinary cortisol metabolites were reduced, suggesting a reduction in HPA axis activity (105). The decrease of subcutaneous adipose tissue  $11\beta$ -HSD1 activity at 1 and 2 years after gastric bypass surgery in humans has also been reported through both mRNA expression and urine and adipose tissue F/E, along with positive changes in insulin sensitivity, circulating leptin, and adiponectin, and peripheral glucocorticoid metabolism (106–108). Additionally, intra-adipose levels of cortisone, rather than cortisol, demonstrated the most obvious changes, suggesting that the altered glucocorticoid metabolism after weight loss may be an adaptive response to insufficient levels of adipose cortisol. Of note, supplementary data in Methlie et al. (108), show that obese patients at 1 year post-RYGB demonstrated a significant reduction of adipose tissue F/E, when compared to non-obese controls. This observation points to an effect potentially caused by more than surgery-induced weight loss and may include the gastrointestinal tract manipulation itself. One potential mechanism could be the effect of post-operatively increased GLP-1 on glucocorticoid regulation, as discussed before. Taken together, the reduction in glucocorticoid exposure in subjects with obesity may represent an additional possible contribution to the health benefits of bariatric surgery.

## DISCUSSION

Glucocorticoids are steroid hormones that are crucial for the preservation of homeostasis. Their physiological and therapeutic effects have made them key targets for drug development,

primarily as anti-inflammatory agents. Nonetheless, their side effects can be severe, especially in terms of metabolism. In this review, we provide an overview of the physiology glucocorticoid regulation, metabolism, and signaling pathways, as well as their effects on obesity and diabetes. We also discussed the ability of weight loss to reverse some of these effects.

Overall, high glucocorticoid levels are associated with hyperglycaemia and insulin resistance and affect key metabolic organs such as the pancreas, liver, muscle and adipose tissue (28, 30, 107, 109). Of note, the exact mechanism of glucocorticoid action remains controversial in pancreatic islets, especially in insulin secretion during glucocorticoid treatment (66–68). Glucocorticoid metabolism is largely controlled by 11 $\beta$ -HSD1 and GR and has been shown to be strongly linked to Body Mass Index, as intra-adipose cortisol levels are increased relative to inactive cortisone in the obese state, even if circulating cortisol levels remain stable. Weight loss through diet, exercise, and bariatric surgery is linked to reduced glucocorticoid secretion and function, possibly through the recovery of insulin sensitivity and function of insulin sensitivity proteins. In all three weight loss interventions, the expression levels of 11 $\beta$ -HSD1 in adipose tissue and liver remains a matter of debate, as studies report both increasing and decreasing levels (78–80, 107, 108). Moreover, acute cortisol measurements are presented, through serum and plasma samples. It is therefore vital to measure chronic cortisol levels to get a longer-term picture of cortisol alterations, and investigate the role of 11 $\beta$ -HSD1 and GR following rapid weight loss in patients, especially following bariatric surgery which is

currently the least published field. This will help us determine if the positive observations on glucocorticoid metabolism are due to weight loss or if direct or indirect gastrointestinal manipulation can also have an effect.

## AUTHOR CONTRIBUTIONS

EA prepared the first draft and revised the manuscript. LG and GR revised the manuscript.

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