Variation in glucocorticoid sensitivity and the relation with obesity

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Summary
Increasing evidence points to a relation between increased glucocorticoid (GC) exposure and weight gain. In support, long-term cortisol measurements using hair analysis revealed that many individuals with obesity appear to have cortisol values in the high physiological range. The mechanisms behind this relationship need to be determined in order to develop targeted therapy to reach sustainable weight loss in these subgroups.

The effect of GCs is not only determined by the plasma concentration of GCs but also by individual differences in GC sensitivity and the target tissue, which can be analyzed by functional GC assays. GC sensitivity is influenced by multiple genetic and acquired (e.g., disease-related) factors, including intracellular GC availability, hormone binding affinity, and expression levels of the GC receptors and their isoforms, as well as factors involved in the modulation of gene transcription. Interindividual differences in GC sensitivity also play a role in the response to exogenous GCs, with respect to both therapeutic and adverse effects.

Accordingly, in this review, we summarize current knowledge on mechanisms that influence GC sensitivity and their relationships with obesity and discuss personalized treatment options targeting the GC receptor.

KEYWORDS
cortisol, glucocorticoid sensitivity, glucocorticoids, obesity

1 INTRODUCTION

Glucocorticoids (GCs) are steroid hormones and essential for life. They are involved in reproduction, metabolism, growth, coagulation, bone turnover, stress, cognition, water and electrolyte homeostasis, and inflammatory and immune responses.\textsuperscript{1,2} Synthetic derivatives of GCs are widely used in clinical practice because of their immunosuppressive and anti-inflammatory properties, for example, in the treatment of inflammatory diseases, autoimmune disorders, and hematological cancers.\textsuperscript{3}

Dysregulation of GC production results in distinct clinical disease phenotypes, with features resembling Cushing's syndrome (characterized by GC excess) or adrenal insufficiency (characterized by GC deficiency).\textsuperscript{4} GCs follow secretion patterns showing

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circadian and ultradian rhythms and are also induced in response to inflammation and other stressors, be it emotional or physical. However, if the stressor exceeds a temporal threshold or certain severity, GC secretion can become, in part, maladaptive, leading to adverse effects, such as anxiety and cognitive dysfunction, mood alteration, immune suppression, and insulin resistance associated with central obesity. Chronically increased cortisol levels, exemplified by Cushing’s, are consistently associated with weight gain.

The metabolic effects of GCs are many and involve many organs and tissues. For example, elevated cortisol levels can modulate adipose tissue functioning. GCs seem to have tissue specific effects, whereby high levels promote preferential expansion of unfavorable visceral adipose depots while impairing favorable brown adipose tissue function and promote a “brown to white” phenotypic conversion. Similarly, studies in rodent models of Cushing’s syndrome have demonstrated that systemic high levels of endogenous cortisol lead to white adipose tissue growth, reduced insulin tolerance, and hyperglycemia. This can eventually stimulate development of (components of the) metabolic syndrome (MetS), including abdominal obesity, hypertension, dyslipidemia, and insulin resistance. The correspondence of MetS to the signs and symptoms of the Cushing’s syndrome suggests that GC signaling also plays a role in obesity in general. In this respect, it is interesting that long-term GC measurements in scalp hair revealed that around half of the individuals with obesity of our Dutch patient cohort appear in the high physiological range, whereas the other half is in the normal physiological range.

However, the ultimate response to GCs is not only determined by the serum/blood concentration of GCs but also by individual differences in tissue-specific GC sensitivity, influenced by genetic and acquired (e.g., disease-related) factors. GCs act mainly by modulating gene expression via transactivation and transrepression mechanisms. The beneficial or harmful effects of GCs are dependent on the specific cellular signaling pathways that are activated. Many of the molecular mechanisms underlying the interindividual variation in GC sensitivity in different tissues/processes are still unknown. Insights in such mechanisms might offer personalized therapy and diagnostic options in patients with obesity.

In this article, we will summarize the current knowledge, primarily focusing on human studies, on mechanisms behind interindividual differences in GC sensitivity in relation to obesity. The review includes differences in GC receptor-mediated signaling, association of genetic polymorphisms and mutations and assays to measure GC sensitivity. Gaining insight into the signaling mechanisms is essential to understand the contribution of subtle increases in endogenous GCs and/or exogenous GC use to increased cardiometabolic risks in obesity. In addition, it may also help in understanding how to improve the balance between the beneficial and harmful effects of exogenous GCs, as many patients rely on such treatments. Altered sensitivity to GCs may exacerbate metabolic sequelae in vulnerable individuals, such as those with obesity, possibly necessitating personalized dosing strategies.

## 2 | Endogenous GC Mechanisms of Action

The production of endogenous GCs is under control of the hypothalamus–pituitary–adrenal (HPA) axis. The hypothalamic corticotropin-releasing hormone (CRH) stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). Thereafter, ACTH activates the cAMP (adenosine 3’5’-cyclic monophosphate) pathway in cells within the zona fasciculata of the adrenal cortex, which leads to production and secretion of GCs. The most important GC in humans is cortisol. An increase in levels of cortisol inhibits the release of CRH and ACTH via negative feedback mechanisms at the level of the hypothalamic paraventricular nucleus (PVN) (inhibition of CRH) and the pituitary gland (inhibition of ACTH).

Cortisol is highly lipophilic and therefore mostly bound to corticosteroid-binding globulin (CBG) when transported via blood. Approximately 90% of circulating cortisol is bound to CBG, 6% is bound with a low affinity to albumin, and only 4% is free and biologically active. Cortisone is the biologically inactive form of cortisol and can act as a reservoir of inactive precursor steroid. The ratio of cortisone/cortisol is tissue specific and is regulated by expression levels and activity of the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes. 11β-HSD type 1 (11β-HSD1) can (locally) convert cortisone to active cortisol, whereas 11β-HSD2 can inactivate cortisol and locally prevent GC action in specific tissues. 11β-HSD1 is mainly expressed in metabolic target tissues including liver (highest expression and affecting systemic cortisone/cortisol ratios), adipose tissue, and central nervous system, whereas 11β-HSD2 is expressed mainly in epithelial tissues such as the kidney (highest expression), colon, salivary, and sweat glands.

### 2.1 | The glucocorticoid receptor

Unbound GCs can diffuse across the plasma membrane of many types of cells and exert their effect upon binding to the glucocorticoid receptor (GR) or mineralocorticoid receptor (MR). GR and MR are expressed in many tissues, where they can interact with each other in synergy or in opposition. The affinity of cortisol for the GR is about 10-fold lower compared with the MR; hence, GR is only partially occupied when GC levels are low. The MR is occupied substantially even under basal conditions (late evening), whereas at stress levels/or the circadian peak of GC secretion (morning), the GR is gradually activated. Cortisol and aldosterone have the same binding affinity for MR. However, under normal conditions, 11β-HSD2 can inactivate cortisol, which allows aldosterone to bind the MR in target cells, for example, epithelial cells. The GR is expressed in nearly all organs and cells in the body, including the pituitary gland and PVN. Accordingly, the GR has a central role in negative feedback regulation of GC production, via action at the (core of the) HPA axis. Because both elevated cortisol levels and synthetic GCs affect predominantly the GR, below we will focus on mechanisms and processes that relate to GR, but very similar principles apply to MR.
The human GR (hGR), encoded by the NR3C1 gene located on chromosome 5q31–32 and consisting of nine exons, belongs to the nuclear hormone receptor subfamily 3 (Figure 1). It consists of an N-terminal transactivation domain (NTD), a central DNA-binding domain (DBD), and a C-terminal ligand-binding domain (LBD).2,3 The NTD is involved in the transcriptional activation of GR target genes; the DBD recognizes and binds DNA target sequences, also known as GC response elements (GREs), and the LBD is responsible for the binding of GCs and transcriptional activity. The DBD and LBD are separated by the hinge region, of which the function is still unclear, but which is subject to posttranslational modification (suggesting a role beyond linking the other domains).2,3

The best characterized signaling mode of the GR is the genomic pathway (Figure 2). The GR, in its quiescent state, is located in the cytoplasm bound to a chaperone complex. This complex consists of, among others, the heat shock protein 90 (hsp90), hsp70, and FK506 binding protein 5 (FKBP5). On binding of GCs, the GR undergoes conformational changes, leading to its dissociation from the chaperone complex and translocation of the ligand-receptor complex into the nucleus. Within the nucleus, the complex can bind to GREs and to other transcription factors and stimulate and repress expression of many different target genes.2,3

Transactivation by the GR via GREs is thought to play a major role in most unfavorable metabolic effects of GCs. In addition, the GR can cause transrepression of target genes by binding to other specific “negative GREs” (nGREs).2,3 The accessibility of GREs and nGREs contributes to the tissue and cell specific effects of GCs.4 On the other hand, the GR can also transrepress GC-mediated reactions independent of nGREs by protein–protein interaction with transcription factors, for example, AP-1 (activating protein-1) and NF-xB (nuclear factor-xB). GCs can also exert their effects via membrane GR, a non-genomic signaling mechanism that is more rapid, but much less understood than the genomic signaling mode.2,3

Both the therapeutic and adverse effects of GCs are mediated by genomic and non-genomic mechanisms. The GR can increase the expression of anti-inflammatory proteins (transactivation) or decrease the production of pro-inflammatory proteins (transrepression). The interindividual and tissue-specific responses after GR activation are partly due to different GRE accessibility, different repertoires of interacting proteins, and GR isoforms.2,3

2.2 | GR isoforms

The GR exists as multiple protein isoforms (Figure 1), all derived from the NR3C1 gene.2,3 The multiple isoforms are formed by alternative splicing and translation initiation mechanisms and posttranslational modifications.3,4 The levels of expression of the different GR isoforms vary among tissues.3,4

| GR Isoform | NTD  | DBD  | H    | LBD  |
|------------|------|------|------|------|
| Grα        | 1    | 421  | 486  | 528  | 777  |
| Grβ        | 1    | 421  | 486  | 528  | 742  |
| Grγ        | 1    | 421  | 486  | 528  | 778  |
| GrA        | 1    | 592  | 421  | 486  | 528  | 777  |
| GrP        | 1    | 592  | 421  | 486  | 528  | 777  |

Alternative exon 9β
Arginine insertion between exon 3 and 4
Exon 5, 6 and 7 are skipped
Intron 7 is kept and exon 8 and 9 are removed

FIGURE 1 Glucocorticoid receptor (GR) isoforms and NR3C1 polymorphisms. GRα is known as the classical GR, consists of nine exons, and has three main domains, N-terminal transactivation domain (Exon 2) (NTD), a central DNA-binding domain (Exons 3 and 4) (DBD), and a C-terminal ligand-binding domain (Exons 5–9) (LBD). Alternative splicing, translation initiation mechanisms, and posttranslational modifications result in multiple isoforms: GRβ, GRγ, GR-A, and GR-P. The location of four NR3C1 polymorphisms, N363S and BclI, associated with glucocorticoid hypersensitivity, and exon 9β and ER22/23EK, associated with glucocorticoid hyposensitivity, is illustrated. DBD, central DNA-binding domain; H, hinge region; LBD, C-terminal ligand-binding domain; NTD, N-terminal transactivation domain.
Alternative splicing of the GR generates two main isoforms defined at the mRNA level, GRα and GRβ, which are similar through amino acid 1–727 but differ in their C-termini. The GRα is known as the classical GR and is mainly located in the cytoplasm in the absence of hormone. It binds GCs, translocates into the nucleus, and activates gene expression. The GRβ can be located either in the cytoplasm or nucleus and is a dominant negative inhibitor of GRα. In addition to negatively regulating the actions of GRα, GRβ also exerts its own independent effects. It has been reported that the ratio of GRα and GRβ expression in various cells is critical for GC sensitivity, in particular in inflammatory contexts. Under normal conditions, the expression of GRα is much greater than the expression of GRβ in most cells and tissues, making cells sensitive for GCs. However, it is hypothesized that an increase in expression of GRβ can lead to GC resistance in immune cells.

Other isoforms generated by alternative splicing are GR-P, GRγ, and GR-A. The GRγ is widely expressed and able to bind GCs and DNA, and it is often associated with GC resistance. The isoforms GR-P and GR-A miss large regions of the LBD and do not bind GCs. Little is known about GR-A, but GR-P was reported to increase the activity of GRα. The interaction of GR-P with GRα may therefore also play an important role in GC sensitivity. Strikingly, alternative translation initiation starting sites in GRα mRNA produce an additional eight GR N-terminal translational isoforms (GRα-A, GRα-B, GRα-C1, GRα-C2, GRα-C3, GRα-D1, GRα-D2, and GRα-D3) that may be present for all splice variants. These translational isoforms are less well characterized, but also differ in the expression patterns, and are known to be involved in GC sensitivity.

### 3 | GENETIC MUTATIONS AND POLYMORPHISMS IN ASSOCIATION WITH GC SENSITIVITY

#### 3.1 | GC sensitivity

Multiple factors influence individual GC effects at the tissue level, including intracellular GC availability (dependent on, e.g., 11β-HSD activity and metabolic clearance rate), hormone binding affinity, expression levels of the GC receptors and isoforms and factors involved in the modulation of gene transcription. The diversity of these mechanisms also causes interindividual variability in GC sensitivity to be tissue specific.

#### 3.2 | GR resistance

Generalized hyposensitivity or resistance to GCs is a rare, familial, or isolated condition with only a few dozen cases previously reported. To compensate for the resistance to GCs, levels of circulating cortisol and ACTH concentrations are elevated. Despite biochemical hypercortisolism, no classical phenotype of Cushing’s syndrome is observed. However, there is a large variation in clinical manifestations that can range from completely asymptomatic to hyperandrogenism, fatigue, hypertension, hypokalemic alkalosis, and/or (apparent) mineralocorticoid excess.
Generalized GC resistance is most often the result of mutations in the GR LBD or—in its milder forms—polymorphisms in the NR3C1 gene (discussed later in the article).2,15,48

### 3.3 | GR hypersensitivity

Similarly, GC hypersensitivity syndrome, also referred to as cortisol hyperreactive syndrome or normocortisolemic Cushing's syndrome, is also rare. It is characterized by the appearance of Cushingoid features and normal to low serum cortisol levels.4,5 Cultured skin fibroblasts from the earliest reported patient showed hyperreactivity to GCs in vitro.5 Another case showed increased numbers of GRs per cell (observed in peripheral lymphocytes) with normal binding affinity.57 Interestingly, GC hypersensitivity seems to predominantly affect the peripheral tissues but not the hypothalamus and pituitary glands; hence, the negative feedback loop is largely intact, and suppression of the HPA axis is disproportional to the clinical signs.54 These cases illustrate the need for clinical awareness of GC hypersensitivity in patients suspected of Cushing's syndrome, when cortisol levels are low and exogenous GC use is excluded.

GR gain-of-function mutations in the NR3C1 gene are observed in congenital GC hypersensitivity. To our knowledge, only few gain-of-function mutations have been described.41,58 A heterozygous D401H mutation detected in Exon 2 of the GR gene showed increased transcriptional activity, normal ligand-binding affinity, and normal nuclear translocation. The D401H mutation is associated with an increased risk of obesity, hypertension, and other characteristics of the MetS.58

### 3.4 | Polymorphisms associated with GC sensitivity

Polymorphisms in the GR gene are associated with differential GC sensitivity, altered metabolic profiles, and differences in body composition, although causality has not been unambiguously demonstrated (Figure 1) (Table 1).48,59-63 Two well-characterized polymorphisms in GRα that are associated with hypersensitivity to GCs are N363S and BclI, with allele frequencies in the general (Caucasian) population of 4.5% and 38% (6% and 47% in heterozygous carriers), respectively.15,48 Both polymorphisms are associated with an adverse lipid profile, abdominal obesity, hyperinsulinemia, and hypertension.59,60,64

The N363S polymorphism (rs56149945), located in Exon 2, causes an increase in transactivation capacity of the GR, which is thought to be responsible for most metabolic effects of GCs, but has no apparent effect on the transrepression capacity.61,65,66 The N363S polymorphism is associated with an increase in low-density lipoprotein (LDL) cholesterol levels in elderly and a higher body mass index (BMI).67,68 It is speculated that heterozygous carriers of the N363S polymorphism who develop obesity store fat more effectively via activation of lipogenesis.64,69

In addition, several polymorphisms in the GR gene are correlated with a relative GC resistance. Polymorphisms related to GC hypo-sensitivity are the 9β and the ER22/23EK variants, with allele frequencies in the general (Caucasian) population of 16.5% and 2.5% (28% and 5% in heterozygous carriers), respectively.75

The polymorphism in exon 9β (rs6198) of the GR gene increases stability of the mRNA such as the GRβ mRNA.74 Because the GRβ is a dominant negative inhibitor of GRα, the 9β polymorphism may contribute to GC hyposensitivity as has been demonstrated in vitro.41,74 In the Caucasian population, the rs6198 polymorphism is associated with a more favorable phenotype including less central obesity in women and a better lipid profile in men, although this may be different in other ethnic groups. However, a haplotype comprising this polymorphism was found to be associated with a more pro-inflammatory system and cardiovascular disease.75,76

The reduction in sensitivity to GCs in carriers of the ER22/23EK (rs6189 and rs6190) polymorphism is reflected by a smaller decrease in cortisol concentrations and higher serum concentrations of cortisol after a 1 mg dexamethasone (DEX) suppression test.77 In contrast to the N363S polymorphism, the ER22/23EK polymorphism causes a reduction in transactivation capacity of the GR, but has no effect on

| TABLE 1 | Polymorphisms in the NR3C1 gene associated with glucocorticoid (GC) sensitivity |
| --- | --- | --- | --- |
| Polymorphism | GC sensitivity | Effects on body composition and metabolic profile | References |
| N363S | Increased | Increased LDL cholesterol levels in elderly, higher BMI, and hypertension | 64,65,67,68 |
| BclI | Increased | Increased insulin resistance, BMI, abdominal obesity, total body fat, and hypertension | 64,71,72 |
| 9β | Decreased | Reduction in central obesity and a beneficial lipid profile | 76 |
| ER22/23EK | Decreased | Lower fasting insulin levels and LDL cholesterol concentrations. Sex-specific beneficial body compositional changes | 77,79 |

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; Bcl, Bcl family member; ER, estrogen receptor; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; N363S, a single nucleotide polymorphism in exon 2 of the GR gene; MetS, metabolic syndrome; rs, reference single nucleotide polymorphism.
transrepression. Interestingly, Russcher et al. showed in vitro that the ER22/23EK polymorphism is associated with an increase in the expression of the translational isoform GRα-A at the expense of GRα-B, which can lead to an overall decrease in transcriptional activity. This seems a plausible mechanism to explain the association between the ER22/23EK polymorphism and GC resistance. In vivo studies have shown that heterozygous carriers of the ER22/23EK polymorphism have lower fasting and non-fasting insulin, slightly lower fasting glucose levels, and lower total and LDL cholesterol concentrations compared with non-carriers. These findings suggest that ER22/23EK carriers are more resistant to the effects of GCs and have better metabolic profiles.

In addition, beneficial body composition was observed in ER22/23EK carriers around young-adult age compared with noncarriers. Male carriers were taller and had more muscle strength and female carriers were likely to have smaller waist and hip circumferences.

The aforementioned polymorphisms N363S, Bcl, 9β, and ER22/23EK seem to influence GC sensitivity and have differential effects on the metabolic profile (Table 1). A profile of the NR3C1 gene polymorphisms may provide an indication of risks for diseases related to obesity and adverse cardiometabolic profiles, leading to more targeted therapy.

4 | ASSAYS TO MEASURE GC SENSITIVITY

In addition to inter- and intraindividual differences, GC sensitivity may also be tissue specific. GC sensitivity can be measured in vivo and in vitro. It is therefore important to select the appropriate test, depending on the clinical need.

4.1 | In vivo evaluation of GC sensitivity

GC sensitivity of the GR can be measured in vivo by oral or intravenous DEX suppression test (DST). This test assesses the negative feedback action mediated by DEX, a synthetic GC, via the GR as indicated by the suppression of HPA axis activity. Insufficient suppression of cortisol after DST (in the absence of signs of Cushing’s syndrome) suggests GC resistance. A modification of this test using very low dose DEX (0.25 mg) is often used to assess hypersensitivity.

The DST is limited to the indication of GC sensitivity that is either genetically determined or specific at the level of the pituitary gland and—for the higher dose—the hypothalamus, whereas local (acquired) GC resistance may not be sufficiently represented. It has been amply demonstrated that GC sensitivity results may vary between tissues as observed in the reported differences between in vivo and in vitro measurements in the same individual.

4.2 | In vitro evaluation of GC sensitivity

Differences in GR activity can result from a decrease in GR affinity for GCs or number of GRs, impaired translocation of the GR into the nucleus, receptor thermolability, or a change in protein–protein interaction with coactivators. The relative expression of the different GR isoforms can be assessed in various tissues or peripheral blood mononuclear cells (PBMCs) by quantitative reverse transcription polymerase chain reaction (qRT-PCR). It has been suggested that the number of GR in PBMCs represents individual responsiveness to GCs in vivo and in vitro.

Several in vitro functional assays have been developed to assess GR sensitivity to GCs in different target tissues such as in PBMCs. The DEX Inhibition of Lymphocyte Proliferation Assay (DILPA) assessed the extent of inhibition of phytohemagglutinin (PHA) induced T-lymphocyte proliferation by DEX. These assays have been superseded by nonradioactive modifications such as the BLISS (BrdU Lymphocyte Incorporation Steroid Sensitivity) assay, performed in PBMCs. Despite showing promise in the identification of GC non-responders, this assay needs further validation of its efficacy.

Another in vitro bioassay measured the GR-mediated transactivation or transrepression of GC-responsive genes, such as GC-induced leucine zipper (GILZ) or interleukin (IL)-2, respectively, in PBMCs. This assay demonstrated an association between in vitro GC sensitivity and clinical GC therapy outcome in rheumatoid arthritis. However, other studies using this assay have reported a lack of correlation between GILZ and IL-2 expression and also with the outcome of the DST. In vivo, GCs can inhibit the expression of pro-inflammatory mediators such as IL-2. On the other hand, transactivation of regulatory molecules such as GILZ has also been demonstrated to have beneficial effects by indirectly repressing the expression of cytokines. This suggests that transactivation, transrepression, and regulation of the HPA axis are complex, partially independent, processes. Nevertheless, these bioassays might be useful in developing prediction models to optimize the type and dosage of GCs to balance their therapeutic and adverse effects in patients.

Expression of a single or few genes does not fully recapitulate the complexity of the molecular response to physiological triggers, such as cortisol. Other studies have performed transcriptome analysis of DEX-treated PBMCs to capture the dynamic transcriptional response to GR activation. RNA sequencing in cultured lung carcinoma cells identified several new and potentially important genes (e.g., PER1, ZFP36, and BIRC1) that are responsive to GCs. Importantly, dose and time after DEX treatment were crucial determinants of GR-mediated transcriptional changes. Thus, whereas transcriptomic analysis of DEX-stimulated PBMCs may identify key genes involved in altered GC signaling, the results emphasize the importance of the dose and time after treatment underscoring the complexity of the effects induced by GC.

5 | INDIVIDUAL DIFFERENCES IN GC SENSITIVITY AND THEIR RELATIONSHIPS TO BODY WEIGHT AND METABOLIC FEATURES

The associations between increased fasting plasma cortisol levels and high blood pressure and insulin resistance and lipid levels, including increased triglycerides, LDL, and high-density lipoprotein (HDL)
cholesterol levels have been well described. However, the relation between cortisol levels as measured in blood, saliva and urine, and obesity is inconsistent. This can be attributed to the circadian secretion pattern of cortisol as well as the variation caused by circumstances such as acute stress. In contrast, the correlation between cortisol levels measured in hair (that are assumed to represent long-term exposure to cortisol) and BMI and waist-to-hip ratio is demonstrated to be more robust across different populations. An increment of 9.8% in hair cortisol level was associated with 2.5 kg/m² higher BMI, cross-sectionally. In addition, elevated hair cortisol levels were also related to a higher prevalence of MetS. We previously reported that about half of the individuals with obesity have an elevated long-term cortisol level compared with individuals with overweight or normal weight. The elevated cortisol, at systemic (e.g., in Cushing’s syndrome) or local levels (e.g., overactivity of 11β-HSD1), may result in preferential expansion of visceral fat depots. Furthermore, previously described GR gene variations might enhance sensitivity of individuals for the biological effects of cortisol increasing their propensity to weight gain and obesity. On the other hand, obesity itself can also lead to increased chronic stress. Social stigma related to obesity is associated with increased stress and higher long-term cortisol levels, which might contribute to a vicious circle. This effect may be exacerbated by the use of exogenous GCs prescribed for comorbidities related to obesity, such as arthrosis and asthma. In this context, we have previously reported significantly higher use of medication containing corticosteroids in individuals with obesity. Paradoxically, half of the individuals with obesity in our previously described study had normal long-term cortisol levels. Although this dichotomy in cortisol levels in obesity is under investigation, the strong association of elevated cortisol with metabolic dysfunction in human and animal studies suggests that at least a proportion of the individuals may benefit from cortisol-reducing therapies.

Exogenous GCs are widely used potent anti-inflammatory drugs with multiple indications and many administration forms. Increased levels of endogenous cortisol and chronic exposure to certain exogenous GCs have more or less similar biological effects, because exogenous corticosteroids also bind to the GR with varying affinity. However, in contrast to endogenous GCs, exogenous GCs (except hydrocortisone and prednisolone) are not bound to CBG and are not metabolized by 11β-HSD2.

Side effects of GC treatment are common: abdominal weight gain, metabolic side effects, diabetes mellitus, neuropsychiatric (e.g., depression), musculoskeletal, gastrointestinal, cardiovascular, dermal, ocular, or immunological in nature. Therefore, it is not surprising that associations have been found between obesity and GC use. In our large study comprising 140,879 adult participants from the Lifelines Cohort from the northern Netherlands, we found that use of locally applied GCs, particularly inhaled types, and/or systemic GCs was associated with higher likelihood of having MetS, higher BMI, and other adverse cardiometabolic traits, especially among women. In addition, we found in the same cohort associations between, in particular, inhaled and systemic corticosteroids and reduced executive cognitive functioning and a higher likelihood of mood and anxiety disorders. Nevertheless, unlike systemic use and prolonged use of higher dosages of locally applied GCs, where a causal role in the manifestation of adverse effects have been demonstrated, such a relation is yet to be shown for local administration of GCs.

Interestingly, long-term cortisone levels measured in scalp hair were suppressed in users of inhaled, nasal, or topical corticosteroids, which suggests mild adrenal suppression due to exogenous GCs. This warrants caution with the use of exogenous GCs, in particular also in individuals with increased GR sensitivity where it may lead to substantial weight gain and other adverse effects.

6.1 Innovative strategies for exogenous synthetic GC use

In the past, novel synthetic derivatives of GCs have been developed that distinguish between GR signaling modes. These compounds have been termed “dissociated ligands,” selective GR modulators, or more recently selective GR agonists (SEGRAs). These compounds are currently being investigated for improvement in therapeutic efficacy, that is, anti-inflammatory effects coupled with minimal adverse side effects. Whereas the side effects of GCs are thought to be mainly due to transactivation of genes, their desirable therapeutic effects have been attributed to transrepression. The original notion has been to favor transrepression over transactivation, but current insights suggest that this is likely overly simplistic. The role of transactivation in suppressing inflammation is increasingly evident from animal models. Transactivation of anti-inflammatory genes may also be necessary for full anti-inflammatory efficacy. This may change the view on developing new GC therapies with reduced side effects.

The adverse side effects from prolonged and/or high dosage treatment with GCs are not only caused by the broad pharmacological activity but also by the variation in biodistribution. In order to get more insight into this variation, there is a clinical need for biomarkers. To balance efficacy versus toxicity of GC treatment, liposomes are now being studied as targeted drug delivery systems to enhance the biodistribution and target site accumulation of GCs. Also, coadministration of other drugs may be a way to prevent side effects: A promising recent study showed that metformin administration can improve some of the metabolic profile and clinical outcomes for GC-treated patients with inflammatory disease.

7 CONCLUDING REMARKS

The net effect of endogenous and exogenous GCs on various aspects of physiology is determined by individual differences in GC sensitivity brought about by genetic and acquired (e.g., disease-related) factors
including intracellular GC availability, hormone binding affinity, expression levels of the GR and isoforms, factors involved in the modulation of gene transcription, 11β-HSD activity, and metabolic clearance rate.\textsuperscript{15,16,41,45,46}

The complex relation between GCs and obesity is most likely bidirectional. However, the central question that is still under investigation is to what extent an increased sensitivity to GCs leads to (abdominal) obesity or vice versa whether obesity leads to a self-sustaining vicious circle characterized by high cortisol levels leading to fat redistribution and associated metabolic sequelae. It would be interesting to assess the relation of GC sensitivity with long-term cortisol levels measured in scalp hair in the context of obesity. Furthermore, transcriptome analysis of patient tissues, to capture the dynamic transcriptional response to GR activation, might shed further light on the mechanisms of GC sensitivity in obesity and help to design improved personalized treatment options.

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CONFLICTS OF INTEREST
All authors declare that they have no conflict of interest.

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