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Side Effects of Glucocorticoids

Irmak Sayın Alan and Bahadır Alan

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Abstract

Glucocorticoids represent the most important and frequently used class of drugs in the management of many inflammatory and immunologic conditions. Beside these beneficial effects, glucocorticoids are also associated with serious side effects. Cushing’s syndrome, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, osteoporosis, psychiatric disturbances, and immunosuppression are among the most important side effects of systemic glucocorticoids. These side effects are especially noticeable at high doses for prolonged periods. Even in low-dose therapy, glucocorticoids could lead to serious side effects. The underlying molecular mechanisms of side effects of glucocorticoids are complex, distinct, and frequently only partly understood. This comprehensive article reviews the current knowledge of the most important side effects of glucocorticoids from a clinical perspective.

Keywords: glucocorticoids, systemic, mechanisms of actions, therapeutic use, side effects

1. Introduction

The term “glucocorticoids” (GCs) represents both naturally secreted hormones by adrenal cortex and anti-inflammatory and immunosuppressive agents. Since the successful use of hydrocortisone (cortisol), the principal glucocorticoid of the human adrenal cortex, in the suppression of the clinical manifestations of rheumatoid arthritis, many synthetic compounds with glucocorticoid activity have been manufactured and tested [1]. The differences between pharmacologic effects of synthetic GCs (SGCs) result from structural variations of their basic steroid nucleus and its side groups. These structural variations may affect the bioavailability of SGCs. These include gastrointestinal or parenteral absorption, plasma half-life, and metabolism in the liver, fat, or target tissues—and their abilities to interact with the glucocorticoid receptor and to modulate the transcription of glucocorticoid—responsive genes [2]. Structural
Variations reduce the natural cross-reactivity of SGCs with the mineralocorticoid receptor (MR), eliminating the offending salt-retaining effect. In addition to these, some variations increase SGCs’ water solubility for parenteral administration or decrease their water solubility to improve topical potency [3, 4]. The main SGCs used in clinical practice together with their relative biological potencies and their plasma and biological half-lives are listed in Table 1.

GCs are 21-carbon steroid hormones. The delta-4,3-keto-11-beta,17-alpha,21-trihydroxyl configuration is required for glucocorticoid activity and is present in all natural and synthetic GCs. Approximately 90% of endogenous cortisol in serum is bound to proteins, primarily corticosteroid-binding globulin (CBG) and albumin. Conversely synthetic GCs other than prednisolone either bind weakly to albumin or circulate as free steroids, because they have little or no affinity for CBG. The free form of the GCs can easily diffuse through the membrane and can bind with high affinity to intracytoplasmic glucocorticoid receptors. GCs perform most of their effects owing to specific, immanent distributed intracellular receptors. Binding of the GCs to this receptor creates a complex, which then translocates into the nucleus, where it can interact directly with specific DNA sequences (glucocorticoid-responsive elements [GREs]) and other transcription factors. GCs are metabolized in the liver. The kidney excretes 95% of the conjugated metabolites, and the remainder is lost in the gut. Exogenous GCs have the same metabolic processes as endogenous GCs. The half-lives of synthetic GCs are generally longer than that of cortisol, which is approximately 80 minutes [8–13]. The mechanisms of actions of GCs are shown in Figure 1.

<table>
<thead>
<tr>
<th>Glucocorticoids</th>
<th>Equivalent dose (mg)</th>
<th>Glucocorticoid potency</th>
<th>HPA suppression</th>
<th>Mineralocorticoid potency</th>
<th>Plasma half-life (min)</th>
<th>Biologic half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>20.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>90</td>
<td>8–12</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25.0</td>
<td>0.8</td>
<td>0.8</td>
<td>113–200</td>
<td>80–118</td>
<td>8–12</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>5.0</td>
<td>4.0</td>
<td>4.0</td>
<td>0.3</td>
<td>60</td>
<td>18–36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>0.3</td>
<td>113–200</td>
<td>18–36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4.0</td>
<td>5.0</td>
<td>4.0</td>
<td>0.3</td>
<td>60</td>
<td>18–36</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>30</td>
<td>17</td>
<td>0</td>
<td>200</td>
<td>36–54</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6</td>
<td>25–40</td>
<td>0</td>
<td>0</td>
<td>300</td>
<td>36–54</td>
</tr>
<tr>
<td>Mineralocorticoids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>2.0</td>
<td>10</td>
<td>12.0</td>
<td>250</td>
<td>200</td>
<td>18–36</td>
</tr>
<tr>
<td>Desoxytocosterone acetate</td>
<td>0</td>
<td>20</td>
<td>20</td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Glucocorticoid equivalencies (adapted from [5–7]).
GCs are used in nearly all medical specialties for systemic therapies. GCs represent the standard therapy for reducing inflammation and immune activation in asthma, as well as allergic, rheumatoid, collagen, vascular, hematological, neurological disorders, and inflammatory bowel diseases. Also GCs are used in renal, intestinal, liver, eye, and skin diseases and in the suppression of the host-vs.-graft or graft-vs.-host reactions following organ transplantation. SGCs administered as replacement therapy in primary or secondary adrenal insufficiency (AI), and as adrenal suppression therapy in glucocorticoid resistance and congenital adrenal hyperplasia. They are also used for some diagnostic purposes, such as in establishing Cushing’s syndrome. Acute pharmacologic doses of GCs can be used in a small number of nonendocrine diseases, such as for patients suffering from acute traumatic spinal cord injury, with severe neurological deficits and bone pain even after surgery and critical illness-related cortisol insufficiency. In addition, all fetuses between 24 and 34 week gestation at risk of preterm delivery should be considered as candidates for antenatal treatment with GCs. Benefits of GCs have been showed in a number of other patients including high-risk cardiac surgery, liver failure, post-traumatic stress disorder, community acquired pneumonia, and weaning from mechanical ventilation [3, 4, 6, 7, 9, 14–18]. Common clinical uses of systemic GCs are shown in Table 2.

This comprehensive article aims to highlight the common side effects of systemic (oral and parenteral) GCs. First of all, the mechanisms of action of GCs will be described. Then the side effects of GCs will be discussed along with the pathophysiological mechanisms. While this section was being written, current literature and databases have been utilized.
<table>
<thead>
<tr>
<th>Field of medicine</th>
<th>Disorder(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy and respirology</td>
<td>• Moderate to severe asthma exacerbations</td>
</tr>
<tr>
<td></td>
<td>• Acute exacerbations of chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>• Allergic rhinitis</td>
</tr>
<tr>
<td></td>
<td>• Atopic dermatitis</td>
</tr>
<tr>
<td></td>
<td>• Urticaria/angioedema</td>
</tr>
<tr>
<td></td>
<td>• Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>• Food and drug allergies</td>
</tr>
<tr>
<td></td>
<td>• Nasal polyps</td>
</tr>
<tr>
<td></td>
<td>• Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td></td>
<td>• Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>• Acute and chronic eosinophilic pneumonia</td>
</tr>
<tr>
<td></td>
<td>• Interstitial lung disease</td>
</tr>
<tr>
<td>Dermatology</td>
<td>• Pemphigus vulgaris</td>
</tr>
<tr>
<td></td>
<td>• Acute, severe contact dermatitis</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>• Adrenal insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>• Ulcerative colitis</td>
</tr>
<tr>
<td></td>
<td>• Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td>• Autoimmune hepatitis</td>
</tr>
<tr>
<td>Hematology</td>
<td>• Lymphoma/leukemia</td>
</tr>
<tr>
<td></td>
<td>• Hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td>• Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Rheumatology/immunology</td>
<td>• Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>• Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>• Polymyalgia rheumatica</td>
</tr>
<tr>
<td></td>
<td>• Polymyositis/dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>• Polyarteritis</td>
</tr>
<tr>
<td></td>
<td>• Vasculitis</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>• Uveitis</td>
</tr>
<tr>
<td></td>
<td>• Keratoconjunctivitis</td>
</tr>
<tr>
<td>Other</td>
<td>• Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>• Organ transplantation</td>
</tr>
<tr>
<td></td>
<td>• Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>• Chronic active hepatitis</td>
</tr>
<tr>
<td></td>
<td>• Cerebral edema</td>
</tr>
</tbody>
</table>

Table 2. Common clinical uses of systemic GCs (adapted from [19]).
2. Mechanism of actions

GCs affect many, if not all, cells and tissues of the human body, thus awakening a wide variety of changes that involve several cell types concurrently [20].

2.1. Gene transcription

Binding of the receptor to GREs may cause either enhancement or suppression of transcription of responsive downstream genes. GCs inhibit the synthesis of almost all known inflammatory cytokines [21, 22].

2.2. Post-translational events

GCs also inhibit secretion and synthesis of inflammatory molecules (IL-1, IL-2, IL-6, IL-8, tumor necrosis factor, inflammatory eicosanoids, and cyclooxygenase-2) by affecting post-translational events [23].

2.3. Effect on the distribution of blood cells

The administration of glucocorticoids predictably results in neutrophilic leukocytosis, dramatic reductions in circulating eosinophils and basophils, transient minor reductions in monocytes and total lymphocytes. Acute lymphopenia normalizes by 24–48 hours. GCs have no direct effects on erythrocyte and platelet counts. But anemia and thrombocytosis can heal with improvement of chronic inflammation [24, 25].

3. Changes in cell function and survival

3.1. Neutrophils

The most important effect of GCs on neutrophils is the inhibition of neutrophil adhesion to endothelial cells. This effect reduces trapping of neutrophils in the inflamed region and probably is responsible for the characteristic hematological change—neutrophilia. GCs at pharmacologic doses, only modestly impair neutrophil functions, such as lysosomal enzyme release, the respiratory burst, and chemotaxis to the inflamed region. Lower doses do not affect these functions [26, 27].

3.2. Monocytes and macrophages

GCs antagonize macrophage differentiation and inhibit many of their functions. GCs (1) suppress myelopoiesis and inhibit expression of class II major histocompatibility complex antigens induced by interferon-γ; (2) block the release of numerous cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α; (3) suppress production and release of pro-inflammatory prostaglandins (PGs) and leukotrienes; (4) suppress phagocytic and microbicidal activities of activated macrophages; (5) reduce the clearance of opsonized bacteria by the reticuloendothelial system; (6) reduce accumulation of monocytes and macrophages in the tissues [28–31].
3.3. Eosinophils, basophils, and mast cells

GCs support eosinophil apoptosis. In addition to this, GCs decrease the accumulation of eosinophils and mast cells to the allergic reaction sites. Also, GCs inhibit IgE-dependent release of histamine and leukotriene C4 from basophils, and they also inhibit degranulation both production of cytokines and degranulation of mast cells and eosinophils [26, 32, 33].

3.4. Natural killer cells (NKC)

Total numbers of circulating NKC are not significantly altered following administration of GCs. But, sustained upregulation of NKC activation genes were observed [34].

3.5. Endothelial cells

GCs have profound effects on the activation/function of endothelial cells and certainly inhibit vascular permeability. GCs inhibit directly the expression of adhesion molecules on both leukocytes and endothelial cells. GCs inhibit endothelial adhesion, as well as indirect effects due to the inhibition of transcription on cytokines (interleukin-1 and tumor necrosis factor) which upregulate endothelial adhesion molecule expression [25].

3.6. T lymphocytes

Administration of the GCs causes a dramatic diminution of in vitro antigen responsiveness of T lymphocytes. The generation, proliferation, and function of helper and suppressor T cells and cytotoxic T cell responses are inhibited by GCs. These effects are due to the inhibition of the release of certain cytokines. GCs also inhibit the acute generation of both T helper type 1- and T helper type 2-derived cytokines by activated T cells. But the inhibitory effect on expression of T helper type 1-derived cytokines is greater [35–38].

3.7. B lymphocytes and immunoglobulin levels

GCs have gradual effects on B cell activation, proliferation, and differentiation. B lymphocytes are relatively resistant to the immunosuppressive effects of GCs in contrast to T lymphocytes. Once B cells are activated, they differentiate into immunoglobulin-secreting plasma cells. But GCs have only minimal effects on this differentiation process. The most important effect of GCs on B lymphocytes relevant with immunoglobulin production and secretion. GCs also increase immunoglobulin catabolism. A short course of treatment with GCs causes an evident and permanent decrease in serum IgG. In contrast, immunoglobulin E (IgE) levels may increase. Whether GCs inhibit immunoglobulin gene expression is not known. Consequently, low-dose GCs inhibits leukocyte traffic and cellular immune responses. But to suppress the functions of leukocytes and the humoral immune response, higher doses of GCs are needed. This variability of drug response is also obvious among different patients and diseases [39–43].

3.8. Dendritic cells and antigen presentation

GCs causes a significant reduction in circulating dendritic cells. Dendritic are the major stimulants of naive T cells by presenting antigens. As a result, GCs impair the development of immunity to first encountered antigens [44].
3.9. Fibroblasts

At supraphysiological concentrations, GCs suppress proliferation of fibroblasts and growth factor-induced DNA synthesis and protein synthesis, including synthesis of collagen and glycosaminoglycan. Also GCs have been shown to interact with two mediators of fibroplasia; transforming growth factor-β and vascular endothelial growth factor. Furthermore GCs induce fibronectin messenger RNA transcription, inhibit interleukin-1, tumor necrosis factor-α-induced metalloproteinase synthesis, and arachidonic acid metabolite synthesis [20, 28, 45, 46].

3.10. Prostaglandins

Suppression of inflammatory prostaglandins (PGs) is a major factor in the anti-inflammatory action of the GCs. The suppression of phospholipase A2 activity with GCs is mediated by the activation of inhibitors of the enzyme itself or by inhibition of enzyme synthesis. The glucocorticoid-linked lipocortin/annexin family of proteins may be involved in this process. A second step in prostaglandin synthesis is the formation of prostaglandin H2 from arachidonic acid by enzymes called cyclooxygenases. The COX-2 gene and protein are strongly upregulated in endothelial cells, fibroblasts, and macrophages, and by mediators, such as endotoxin and interleukin-1. But GCs strongly suppress the expression of COX-2 induced by inflammatory stimuli. Later, D’Adamio et al. identified a glucocorticoid-induced leucine zipper (GILZ). GILZ is a member of the leucine zipper protein family which belongs to the transforming growth factor β-stimulated clone-22 family of transcription factors. GILZ inhibits inflammatory cytokine-induced expression of COX-2, by this way mediates the anti-inflammatory effects of GCs [47–53].

4. Side effects of systemic glucocorticoids

Toxicity of GCs is one of the most common causes of iatrogenic illness associated with chronic inflammatory disorders. The side effects of GCs have been known for decades. But the exact risk-benefit ratio is incomplete and/or inconsistent, because usually it is difficult to differentiate the effects of GCs from the effects of the underlying accompanying diseases, other comorbidities,

| Onset early in therapy, essentially unavoidable | • Emotional lability | • Insomnia |
|                                               | • Enhanced appetite, weight gain, or both |
| Enhanced in patients with underlying risk factors or concomitant use of other drug | • Glucocorticoid-related acne | • Hypertension |
|                                               | • Diabetes mellitus   | • Peptic ulcer disease |
| When supraphysiologic treatment is sustained   | • Cushingoid appearance| • Myopathy |
|                                               | • Hypothalamic-pituitary-adrenal suppression | • Osteonecrosis |
|                                               | • Impaired wound healing | • Increased susceptibility to infections |
or the other medications. GCs associated side effects are dependent on both the average dose and the duration of therapy. Overall, it can be stated that prolonged application is a high-risk factor, whereas total dose is of secondary importance. Even in low-dose therapy, GCs could lead to serious side effects. The severity ranges from more cosmetic aspects (e.g. teleangiectasia, hypertrichosis) to serious disabling and even life-threatening situations (e.g. gastric hemorrhage). Single or multiple side effects can occur [12, 54, 55]. The side effects of GCs are the major limiting factor for the use of these agents. An overview of the most common and serious side effects of GCs is summarized in Table 3.

5. Adrenal insufficiency (AI)

The most common cause of AI is the chronic administration of high doses of GCs. This is called iatrogenic or tertiary AI. Exogenous GCs causes a significant suppression of the hypothalamic-pituitary-adrenal axis (HPA) even in small doses for only few days. Consequently, the adrenal cortex loses the ability to produce cortisol in the absence of adrenocorticotrophic hormone (ACTH). When the suppression of ACTH levels prolongs, this situation causes atrophy of the adrenal cortex and secondary adrenal insufficiency. The use of systemic GCs results in higher systemic levels of corticosteroids than in cases of compartmental use, as a result leads to higher percentages of AI. Adrenal suppression is more likely in the following situations: (1) longer duration of treatment. The influence of smaller doses over longer durations is highly variable. After long-term systemic therapy with GCs (more than 1 year), AI has to be expected in 100% of the patients. (2) Supraphysiologic doses, stronger formulations, and longer acting formulations (Table 4). If the patients are taking doses of prednisone of ≥20 mg daily for ≥3 weeks, this situation should be considered as adrenal suppression. AI lasting for more than 4 weeks has been demonstrated after treatment with high-dose dexamethasone for 28 days [57–64].

Adrenal suppression is less likely in the following situations: (1) regimens that mimic the diurnal rhythm of cortisol (higher dose in the morning, lower dose in the afternoon) and (2) alternate-day dosing of steroids. The possible risk of this side effect is unknown. At the same time, individual responses to GCs may be highly different. The clinical presentation of AI is variable; many of the signs and symptoms are non-specific and can be mistaken for symptoms of intercurrent illness or the underlying condition being treated with GCs. Signs and symptoms of AI

### Table 3. The most common and serious side effects of GCs (adapted from [56]).

<table>
<thead>
<tr>
<th>Delayed and insidious, probably dependent on cumulative dose</th>
<th>Rare and unpredictable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atherosclerosis</td>
<td>• Glaucoma</td>
</tr>
<tr>
<td>• Cataracts</td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Fatty liver</td>
<td>• Growth retardation</td>
</tr>
<tr>
<td>• Skin atrophy</td>
<td>• Osteoporosis</td>
</tr>
<tr>
<td>• Osteoporosis</td>
<td>• Pseudotumor cerebri</td>
</tr>
<tr>
<td>• Growth retardation</td>
<td>• Psychosis</td>
</tr>
</tbody>
</table>

Pharmacokinetics and Adverse Effects of Drugs - Mechanisms and Risks Factors
and adrenal crisis are listed in Table 5. AI often occurs when the exogenous GCs are withdrawn too rapidly or, in the case of stressful conditions (e.g., surgery and infection), when higher levels of GCs may be required. In addition to AI and adrenal crisis decreased ACTH level related with the suppression of the HPA axis, leads to reduced general steroid-hormone production. This situation favors further side effects, such as hypogonadism and osteoporosis [55, 65–68].

### Table 4. The supraphysiologic dosing and interconversion of SGCs (adapted from [66, 67, 69]).

<table>
<thead>
<tr>
<th>Dose</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>≤7.5 mg prednisone equivalent/day</td>
</tr>
<tr>
<td>Medium</td>
<td>&gt;7.5 mg but ≤30 mg prednisone equivalent/day</td>
</tr>
<tr>
<td>High</td>
<td>&gt;30 mg but ≤100 mg prednisone equivalent/day</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;100 mg prednisone equivalent/day</td>
</tr>
<tr>
<td>Pulse therapy</td>
<td>≥250 mg prednisone equivalent/day for 1 day or a few days</td>
</tr>
</tbody>
</table>

Prednisone or prenisolone 5 mg/prednisolone 20 mg/dexamethasone 0.75 mg.

### Table 5. Signs and symptoms of adrenal insufficiency and adrenal crisis (adapted from [72]).

<table>
<thead>
<tr>
<th>Adrenal suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weakness/fatigue</td>
</tr>
<tr>
<td>• Malaise</td>
</tr>
<tr>
<td>• Nausea</td>
</tr>
<tr>
<td>• Vomiting</td>
</tr>
<tr>
<td>• Diarrhea</td>
</tr>
<tr>
<td>• Abdominal pain</td>
</tr>
<tr>
<td>• Headache (usually in the morning)</td>
</tr>
<tr>
<td>• Fever</td>
</tr>
<tr>
<td>• Anorexia/weight loss</td>
</tr>
<tr>
<td>• Myalgia</td>
</tr>
<tr>
<td>• Arthralgia</td>
</tr>
<tr>
<td>• Psychiatric symptoms</td>
</tr>
<tr>
<td>• Poor linear growth in children</td>
</tr>
<tr>
<td>• Poor weight gain in children</td>
</tr>
<tr>
<td>• Clinical signs of Cushing syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adrenal crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypotension</td>
</tr>
<tr>
<td>• Decreased consciousness</td>
</tr>
<tr>
<td>• Lethargy</td>
</tr>
<tr>
<td>• Unexplained hypoglycemia</td>
</tr>
<tr>
<td>• Hyponatremia</td>
</tr>
<tr>
<td>• Seizure</td>
</tr>
<tr>
<td>• Coma</td>
</tr>
</tbody>
</table>

and adrenal crisis are listed in Table 5. AI often occurs when the exogenous GCs are withdrawn too rapidly or, in the case of stressful conditions (e.g., surgery and infection), when higher levels of GCs may be required. In addition to AI and adrenal crisis decreased ACTH level related with the suppression of the HPA axis, leads to reduced general steroid-hormone production. This situation favors further side effects, such as hypogonadism and osteoporosis [55, 65–68].
5.1. Steroid withdrawal or adrenal insufficiency?

When GCs are tapered and their effects decline, patients might experience lethargy, myalgias, nausea, vomiting, and postural hypotension. In this situation, increasing the dose of GCs to prevent AI may delay recovery of the adrenal function. The treatment plan should be made by evaluating the risk/benefit ratio. At this point, patients may just need reassurance, symptomatic treatment, or if necessary, a brief (1-week) increase of the previous lowest dose, followed by reevaluation. Maximal caution is advised with any taper. Fortunately, the adrenal cortex repairs the ability to secrete sufficient amounts of cortisol for some period of time. Repair of endogenous cortisol secretion is expected after stopping the exogenous GCs. But the recovery time may vary among patients. The inhibition of the HPA axis function induced by exogenous GCs may persist for 6–12 months after treatment is withdrawn. In conclusion, all patients using GCs are at risk for AI. Clinicians should inform patients about the risk, signs, and symptoms of AI; and consider testing patients after cessation of high dose or long-term treatment with GCs [68].

6. Weight gain and lipodystrophy

GCs have reciprocal effects on adipose tissue metabolism, promoting both lipolysis and lipogenesis/adipogenesis, inducing irregularity of adipose tissue distribution (i.e. lipodystrophy). These effects are shown in Figure 2 (adapted from [69]). About 60–70% of patients treated with GCs for a long-term period report weight gain. This is different from classical weight gain. A central hypertrophy of adipose tissue develops. Characteristic findings are facial adipose tissue (moon face), truncal obesity and dorsocervical adipose tissue (buffalo hump). In contrast, peripheral and subcutaneous adipose tissues get thinner. This specific changes are called Cushingoid features and related with lipodystrophy induced by GCs. Weight gain is the most common self-reported side effect. About two-thirds of patients exhibit Cushingoid features within the

![Figure 2. Mechanisms of glucocorticoid-induced weight gain and lipodystrophy.](image-url)
first 2 months of therapy with GCs. These side effects are dependent on both the dose and duration of GCs. The risk of weight gain increases from the use of 5 to 7.5 mg per day of prednisone (or an equivalent). The risk of these side effects are higher in younger patients, females, those with a higher baseline body mass index, those with a higher initial caloric intake (>30 kcal/kg/day), and those with a baseline higher leptin and lower resistin levels. More importantly, these side effects are related with high blood pressure, blood glucose and triglyceride levels, and low high-density lipoprotein cholesterol levels (cardiovascular risk factors). Therefore, treatment with GCs increases the risk of coronary heart disease, cardiac insufficiency, and stroke [70–74].

7. Cardiovascular disease

GCs have complex, and often conflicting, influences on cardiovascular disease (CVD) and cardiovascular risk. Patients chronically using exogenous GCs are at higher risk of CVD, such as coronary artery disease, heart failure, and stroke. In patients with rheumatoid arthritis, chronic obstructive pulmonary disease, and other conditions who were exposed to chronic exogenous GCs, a case-control study found a dose-response relationship between daily glucocorticoid dose and the risk of heart failure. The risk of ischemic heart disease was also increased. Patients taking ≥7.5 mg of prednisone per day or the equivalent had a significantly higher mixed risk of myocardial infarction, angina, coronary revascularization, hospitalization for heart failure, transient ischemic attack, and stroke. Exposure to GCs within the preceding 6 months was related with increased cardiovascular risks. The risks were higher with continuous use than intermittent use. The relationship between cardiovascular risk and GCs is confounded by the underlying inflammatory disease (e.g. rheumatoid arthritis and systemic lupus erythematosus). Because of chronic inflammation and treatment with higher doses of GCs, chronic inflammatory conditions may further increase the incidence of CVD. This increased risk is cumulative and dose-dependent, is mainly observed during the first month of treatment and is reduced when treatment is interrupted. In patients with inflammatory arthritis, increased mortality from heart disease has been established. Moreover, an association between GCs and the risk for atrial fibrillation and flutter has been established by several studies. Pulse GCs are additionally related with CVD. Sudden death caused by pulse dose GCs has been reported. But this tends to occur in patients with underlying CVD. Therefore, patients with underlying severe cardiac and renal disease should be closely monitored during pulse therapy with GCs [75–78].

Cardiovascular side effects of GCs can be explained by two mechanisms: (1) direct influence on the function of the heart and vasculature and (2) increasing cardiovascular risk factors. Glucocorticoid receptor is known to be expressed in the heart. By this way GCs exert direct effects on cardiomyocytes. The interaction of GCs with the vascular wall is impaired in CVD. Some well-known cardiovascular risk factors, such as hypertension, insulin resistance, hyperglycemia, and dyslipidemia are more commonly observed in glucocorticoid exposed people. The main effects of GCs on cardiovascular risk are likely due to interaction with the kidney, liver, adipose tissue, and central nervous system. The effects of GCs on homeostasis are presumably due to renal sodium retention and intravascular volume overload. There is also evidence for additional, non-renal mechanisms. This confirms that GCs can interact directly with the cells of the heart and vascular wall. By this way, GCs may alter their function and structure. In patients with...
chronic inflammatory disease, carotid plaque and arterial distensibility (independent of cardiovascular risk factors and clinical manifestations) have been established. In patients with systemic lupus erythematosus administration of GCs decreased the effectiveness of pravastatin [79–83].

8. Hyperglycemia and diabetes

GCs are the most common cause of drug-induced hyperglycemia and diabetes. Hyperglycemia and diabetes induced by GCs, is defined as an abnormal increase in blood glucose associated with the use of GCs in a patient with or without a prior history of hyperglycemia or diabetes. GCs cause an exaggerated postprandial hyperglycemia and insensitivity to exogenous insulin. Thus, GCs have a greater effect on postprandial compared to fasting glucose. Postprandial hyperglycemia (defined as blood glucose 200 mg/dL 2 hours after a meal) is a much more sensitive indicator for hyperglycemia and diabetes induced by GCs. The exact prevalence is not known. The incidence of hyperglycemia and diabetes in hospitalized patients treated with GCs without a known history of diabetes is >50%. GCs increases by two- to fourfold the risk of hyperglycemia and diabetes in non-diabetic subjects. Treatment with exogenous GCs disrupts the glycemic balance of known diabetics [84–87].

Development of glucocorticoid-induced diabetes depends on the dose and duration of exposure. A study found that the risk for hyperglycemia increased substantially with increasing daily steroid dose. The risk may change with the type of the GCs, related with biochemical properties (e.g. potency of the anti-inflammatory and metabolic effects and duration of the effects). But, there is little difference between the GCs most frequently used (i.e. prednisone, prednisolone, and methylprednisolone). The effects of GCs on glucose excursions are observed within hours (6–8 hours) of exposure. The predisposing factors for hyperglycemia and diabetes induced by GCs have been suggested to be overweight, old age, non-white ethnicity, previous glucose intolerance, reduced sensitivity to insulin or impaired insulin secretion stimulated by glucose, female sex, Down syndrome, puberty, the severity of the disease itself, a family history of diabetes, type A30, B27, and Bw42 human leukocyte antigens (HLA); and receiving a kidney transplant from a deceased donor. Solid organ transplant patients treated with GCs, 10–20% of them develop diabetes, especially within the first months of exposure. Other immunosuppressive agents can also disrupt glycemic control through other mechanisms. Usually, hyperglycemia and diabetes induced by GCs improves with dose reductions and usually reverses when therapy is discontinued, but patients with high risk may develop persistent diabetes [88–91].

The pathophysiology of glucocorticoid-induced diabetes involves (1) increase in insulin resistance and (2) reduced glucose uptake in muscle and adipose tissue (via insulin-sensitive glucose transporter type 4) as a consequence GCs cause decreasing glucose uptake and glycogen synthesis. On the other hand GCs have profound and reciprocal effects on glyceroneogenesis in liver and adipose tissue. GCs increase the amount of fatty acids released into the blood. Increased fatty acids interfere with glucose utilization and causes insulin resistance, particularly in skeletal muscle. (3) Increased glucose production, increased hepatic gluconeogenesis via peroxisome proliferator-activated receptor α. (4) Direct effects on pancreatic β cells including inhibition of the production and secretion of insulin, a proapoptotic effect on β cells, a reduction in insulin
biosynthesis, and β cell failure. (5) GCs may modulate the expression and activity of adipokines, such as adiponectin, leptin, and resistin. By this way GCs may disrupt insulin sensitivity and may also reduce the insulinotropic effects of glucagon-like peptide-1 [92–97].

9. Osteoporosis and osteonecrosis

9.1. Osteoporosis

GCs are the most common cause of secondary osteoporosis and nontraumatic osteonecrosis. GCs increase fracture risk in both adult men and women, regardless of bone mineral density (BMD) and prior fracture history. But fracture risk is related to the dose and duration of GCs, age, and body weight. Risk factors for osteoporosis induced by GCs are shown in Table 6. GCs cause significantly stronger losses of trabecular than of cortical bone. Fractures are most common in regions of the skeleton that are predominantly cancellous, such as the vertebral bodies and ribs. After discontinuation of GCs, fracture risk gradually declines to baseline over a year or two [98–100].

GCs induce osteoclastic activity initially (first 6–12 months), followed by a decrease in bone formation. GCs decrease bone formation by inhibiting osteoblastic activity in the bone marrow, suppressing osteoblast function, decreasing osteoblast life span, and promoting the apoptosis of osteoblasts and osteocytes. The effect of GCs on bone turnover is complex and can be divided into two groups (Table 7) [101–103].

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>Elderly patients receiving glucocorticoid therapy have a 26-fold higher risk of vertebral fractures than younger patients and a shorter interval between initiation of treatment and the occurrence of fracture</td>
</tr>
<tr>
<td>Low body mass index</td>
<td>Significant risk factor for GIO and probably fractures as well</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>Rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease, chronic pulmonary disease, and transplantation are independent risk factors</td>
</tr>
<tr>
<td>Family history of hip fracture, prevalent fractures, smoking, excessive alcohol consumption, frequent falls</td>
<td>All are independent risk factors for osteoporosis but have not been well studied in patients receiving glucocorticoids</td>
</tr>
<tr>
<td>Glucocorticoid receptor genotype</td>
<td>Individual glucocorticoid sensitivity may be regulated by polymorphisms in the glucocorticoid receptor gene</td>
</tr>
<tr>
<td>11β-HSD isoenzymes</td>
<td>11β-HSD1 expression increases with aging and glucocorticoid administration and thereby enhances glucocorticoid activation</td>
</tr>
<tr>
<td>Glucocorticoid dose (peak, current, or cumulative, duration of therapy, interval)</td>
<td>There may be no safe dose, although this is somewhat controversial. However, the risk of fracture unarguably escalates with increased doses and duration of therapy. Alternate day or inhalation therapy does not spare the skeleton</td>
</tr>
<tr>
<td>Low BMD</td>
<td>Glucocorticoid-induced fractures occur independently of a decline in bone mass but patients with very low bone density may be at higher risk</td>
</tr>
</tbody>
</table>

11β-HSD, 11β-hydroxysteroid dehydrogenase; BMD, bone mineral density.

Table 6. Risk factors for glucocorticoid-induced osteoporosis (adapted from [99]).
16.4. Purpura

When severe dermal atrophy and loss of intercellular substance occur by GCs, blood vessels lose their surrounding dermal matrix. The fragility of dermal vessels causes purpura. The dorsum of the hands, forearms, sides of the neck, face, and lower legs (sun exposed areas) are the most common affected sites [143].

17. Psychiatric and cognitive disturbances

Systemic GCs induce dose-dependent a wide range of psychiatric and cognitive disturbances, including memory impairment, agitation, anxiety, fear, hypomania, insomnia, irritability, lethargy, mood lability, and even psychosis [144].

17.1. Behavioral effects

Increase in appetite resulting with weight gain is the most common behavioral side effect of long-term exposure to GCs. Weight gain does not correlate with the cumulative dose. Sleep disturbances are the second most common behavioral side effects of GCs and dose-dependent. The evening dose induces sleeplessness [145, 146].

17.2. Psychic effects

Psychic side effects (PSE) of GCs are quantitatively/qualitatively distinct forms. Symptoms range from an initial slight increase in the overall sense of well-being (independent of improvement in their underlying disease activity) or low-grade mood changes, such as euphoria, grandiosity, emotional lability, depressed or elated mood, up to severe psychiatric disorders, and suicidality. The frequency ranges from 1.3 to 62% in adults. The predicted threshold dose for PSE is ≥20 mg/day of prednisone (or equivalent), but can be seen at very low dosages. PSE commonly develop within the first weeks of exposure, but may occur within few days or at any point during treatment, including withdrawal (especially after long-term and high dose exposures). A family history of depression, previous neuropsychiatric disorders, and alcoholism has also been reported as risk factors for the development of PSE. Women were more likely to develop depression, whereas men were more likely to develop mania. The risk of depression, mania, delirium, confusion, and disorientation increases, but suicidal behavior and panic disorder decreases with age. PSE often disappears shortly after dose reduction or discontinuation. Switching to alternative GCs may be helpful. Clinicians should ask about a prior history of psychiatric disorder and refer patients to a psychiatrist [147–149].

17.3. Cognitive effects

Cognitive impairment is a common, dose-dependent side effect of GCs. Common symptoms are deficits in attention, concentration, memory retention, mental speed, and efficiency. Prolonged exposure to moderate/high doses of GCs may cause cumulative and long-lasting effects on specific brain areas. Low doses of GCs do not affect adult cognitive functions in both short- and long-term exposure. Older patients appear to be more sensitive to memory impairment with short-term exposure [149].
18. Monitoring and prevention of side effects

The same total dose of GCs among systemic treatments has different side effects. Split-dose regimens are more toxic than single daily-dose protocols. Both these protocols are more toxic than alternate-day treatment programs. In daily treatment regimens, SGCs with long biologic half-lives (e.g. dexamethasone) have a greater potential for side effects than analogs do with intermediate biologic half-lives (e.g. prednisone). High doses of systemic GCs can be administered for less than a week with partial safety, even though the same dose of drug administered for a more prolonged period will result in presumably, clinically significant side effects. The lowest dose of GCs should be used for the shortest period of time that is needed to achieve the treatment goals. Preexisting comorbid conditions (diabetes mellitus, hypertension, dyslipidemia, heart failure, cataract or glaucoma, peptic ulcer disease, use of nonsteroidal anti-inflammatory drugs, low bone density, or osteoporosis) may increase risk when GCs are required. To provide an optimal therapy, patient education is very important. Patients should be informed about the side effects of GCs. GCs generally stimulate the appetite, causes weight gain, elevated blood pressure, and glucose levels. Therefore, patients should be informed about the importance of diet when therapy is begun. The symptoms and signs of side effects related with GCs, should also be explained to the patients [32, 51–53]. For systemic therapy, the choice of specific GCs depends, partially, on clinical variables like underlying or accompanying diseases. Hydrocortisone is usually used for physiologic replacement and “stress” coverage in patients with HPA suppression. Hydrocortisone has a short biologic half-life and causes sodium and potassium retention. Thus, this agent is not commonly used for systemic immunosuppressive or anti-inflammatory treatment. Fluorinated analogs, such as dexamethasone, have a long biologic half-life and little sodium-retaining potency. But long biologic half-life, may be associated with a greater potential for side effects. As a result, this group of SGCs is not commonly used in prolonged daily therapy regimens [54].

19. Concluding remarks

To reduce the incidence and severity of these side effects (described above); they should be well known. Besides, dose of GCs should be decreased carefully. According to the patients’ risk factors taking general preventive measures are important.

Author details

Irmak Sayın Alan* and Bahadır Alan

*Address all correspondence to: irmaksayin@yahoo.com

1 Okan University, Medical Faculty, Department of Internal Medicine, Istanbul, Turkey
2 Okan University, Medical Faculty, Department of Cardiology, Istanbul, Turkey
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