Chapter 6

Side Effects of Glucocorticoids

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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**.

Glucocorticoids	Equivalent dose (mg)	Glucocorticoid potency	HPA suppression	Mineralocorticoid potency	Plasma half-life (min)	Biologic half-life (h)
Short-acting						
Cortisol	20.0	1.0	1.0	1.0	90	8–12
Cortisone	25.0	0.8		0.8	80–118	8–12
Intermediate-acting						
Prednisone	5.0	4.0	4.0	0.3	60	18–36
Prednisolone	5.0	5.0		0.3	115–200	18–36
Triamcinolone	4.0	5.0	4.0	0	30	18–36
Methylprednisolone	4.0	5.0	4.0	0	180	18–36
Long-acting						
Dexamethasone	0.75	30	17	0	200	36–54
Betamethasone	0.6	25–40		0	300	36–54
Mineralocorticoids						
Fludrocortisone	2.0	10	12.0	250	200	18–36
Desoxycorticosterone acetate	0			20	70	

Table 1. Glucocorticoid equivalencies (adapted from [5–7]).

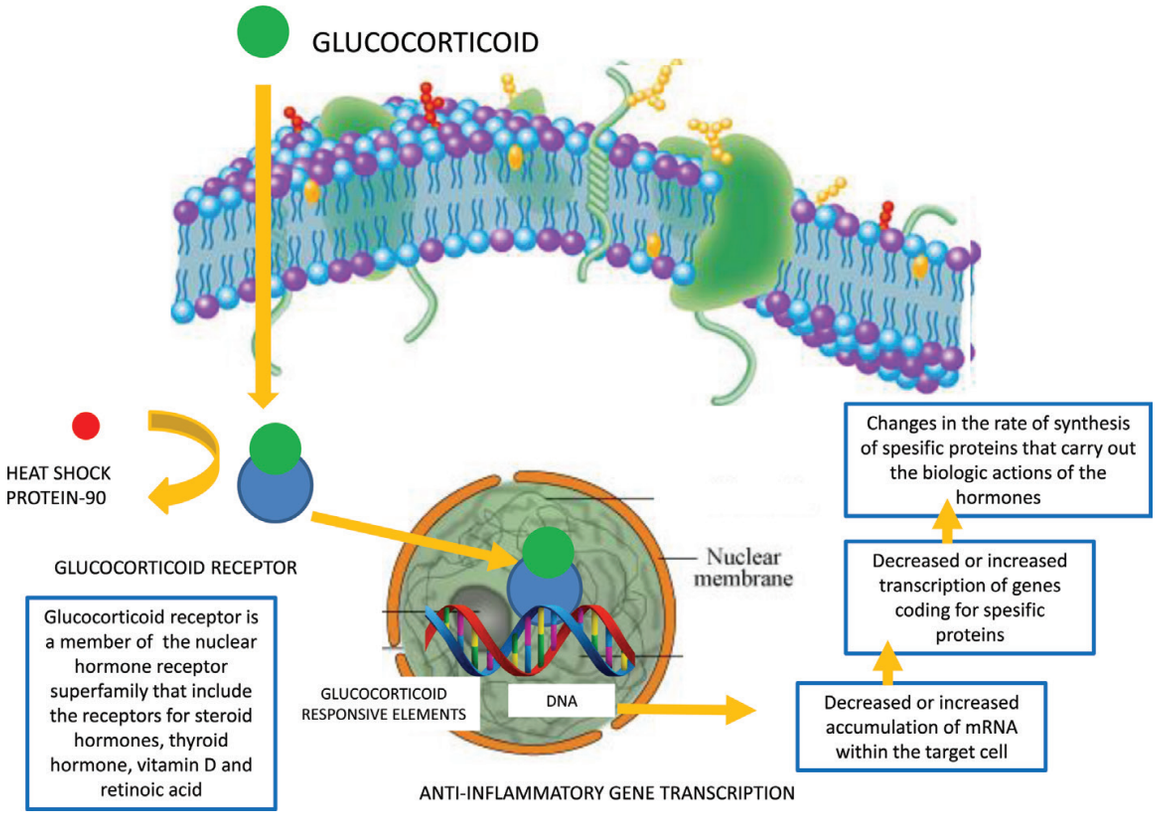

Figure 1. The mechanisms of actions of GCs.

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.

Field of medicine	Disorder(s)
Allergy and respirology	• Moderate to severe asthma exacerbations
	• Acute exacerbations of chronic obstructive pulmonary disease
	• Allergic rhinitis
	• Atopic dermatitis
	• Urticaria/angioedema
	• Anaphylaxis
	• Food and drug allergies
	• Nasal polyps
	• Hypersensitivity pneumonitis
	• Sarcoidosis
	• Acute and chronic eosinophilic pneumonia
	• Interstitial lung disease
Dermatology	• Pemphigus vulgaris
	• Acute, severe contact dermatitis
Endocrinology	• Adrenal insufficiency
	• Congenital adrenal hyperplasia
Gastroenterology	• Ulcerative colitis
	• Crohn's disease
	• Autoimmune hepatitis
Hematology	• Lymphoma/leukemia
	• Hemolytic anemia
	• Idiopathic thrombocytopenic purpura
Rheumatology/immunology	• Rheumatoid arthritis
	• Systemic lupus erythematosus
	• Polymyalgia rheumatica
	• Polymyositis/dermatomyositis
	• Polyarteritis
	• Vasculitis
Ophthalmology	• Uveitis
	• Keratoconjunctivitis
Other	• Multiple sclerosis
	• Organ transplantation
	• Nephrotic syndrome
	• Chronic active hepatitis
	• Cerebral edema

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

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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) supress 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 naïve 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
- Enhanced appetite, weight gain, or both
- Insomnia

Enhanced in patients with underlying risk factors or concomitant use of other drug

- Glucocorticoid-related acne
- Diabetes mellitus
- Hypertension
- Peptic ulcer disease

When supraphysiologic treatment is sustained

- Cushingoid appearance
- Hypothalmic-pituitary-adrenal suppression
- Impaired wound healing
- Myopathy
- Osteonecrosis
- Increased susceptibility to infections

Delayed and insidious, probably dependent on cumulative dose	
• Atherosclerosis	• Growth retardation
• Cataracts	• Osteoporosis
• Fatty liver	• Skin atrophy
Rare and unpredictable	
• Glaucoma	• Pseudotumor cerebri
• Pancreatitis	• Psychosis

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

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 prolonges, 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

Dose	Definition
Low dose	≤7.5 mg prednisone equivalent/day
Medium	>7.5 mg but ≤30 mg prednisone equivalent/day
High	>30 mg but ≤100 mg prednisone equivalent/day
Very high	>100 mg prednisone equivalent/day
Pulse therapy	≥250 mg prednisone equivalent/day for 1 day or a few days
Prednisone or prenisolone 5 mg≈/hydrocortisone 20 mg≈/dexamethasone 0.75 mg.	

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

Adrenal suppression	•Weakness/fatigue
	• Malaise
	• Nausea
	• Vomiting
	• Diarrhea
	• Abdominal pain
	• Headache (usually in the morning)
	• Fever
	• Anorexia/weight loss
	• Myalgia
	• Arthralgia
	• Psychiatric symptoms
	• Poor linear growth in children
	• Poor weight gain in children
	• Clinical signs of Cushing syndrome
Adrenal crisis	• Hypotension
	• Decreased consciousness
	• Lethargy
	• Unexplained hypoglycemia
	• Hyponatremia
	• Seizure
	• Coma

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

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

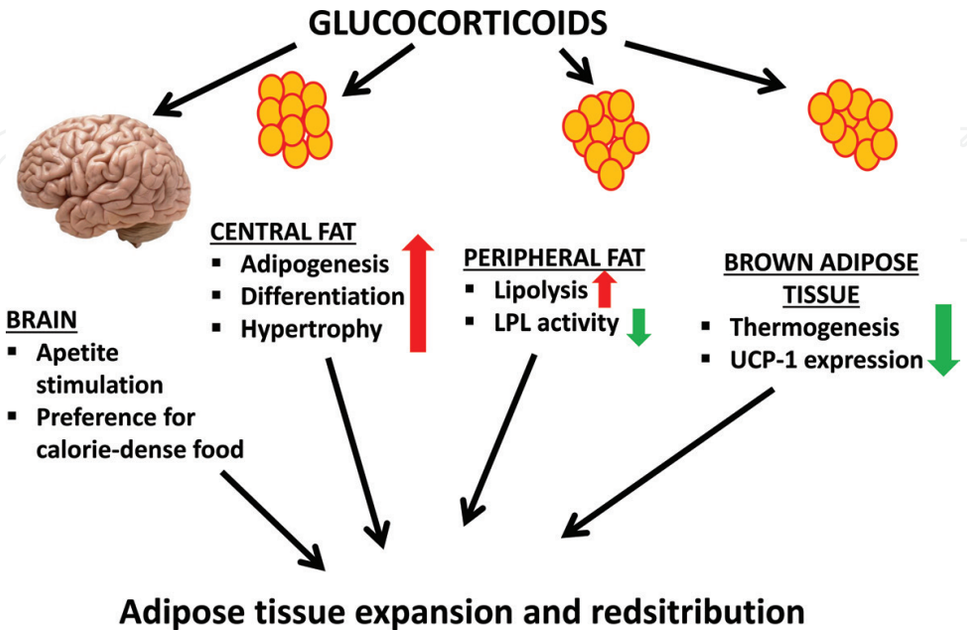

Figure 2. Mechanisms of glucocorticoid-induced weight gain and lipodystrophy.

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].

Risk factor	Explanation
Advancing age	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
Low body mass index	Significant risk factor for GIO and probably fractures as well
Underlying disease	Rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease, chronic pulmonary disease, and transplantation are independent risk factors
Family history of hip fracture, prevalent fractures, smoking, excessive alcohol consumption, frequent falls	All are independent risk factors for osteoporosis but have not been well studied in patients receiving glucocorticoids
Glucocorticoid receptor genotype	Individual glucocorticoid sensitivity may be regulated by polymorphisms in the glucocorticoid receptor gene
11β-HSD isoenzymes	11β-HSD1 expression increases with aging and glucocorticoid administration and thereby enhances glucocorticoid activation
Glucocorticoid dose (peak, current, or cumulative, duration of therapy, interval)	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
Low BMD	Glucocorticoid-induced fractures occur independently of a decline in bone mass but patients with very low bone density may be at higher risk

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

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

Direct effects	Indirect effects
1. Decreased bone formation • Inhibition of osteoblasts replication • Inhibition of osteoblastic apoptosis • Inhibition of bone matrix synthesis 2. Increased bone reabsorbtion • Stimulation of osteoclast synthesis	1. Decrease in net intestinal Ca^{2+} absorbtion 2. Inhibition of renal Ca^{2+} re-absorbtion 3. Stimulation of parathyroid hormone secretion 4. Inhibition of growth hormone secretion

Table 7. Effects of glucocorticoids on bone metabolism (adapted from [103]).

1. Dose and duration of therapy
2. Intra-articular administration
3. Polymorphisms in VEGF, GR, 11β-HSD2, COL2A1, PAI1, P-glycoprotein
4. Underlying disorders: renal insufficiency, transplantation, graft vs. host disease, inflammatory bowel disease, HIV, acute lymphoblastic leukemia, excessive alcohol intake, hypercoagulable states, sickle cell disease, radiation exposure
5. Dexamethasone causes greater skeletal complications than prednisone
VEGF: vascular endothelial growth factor; GR: glucocorticoid receptor; 11β-HSD2: 11β-hydroxysteroid dehydrogenase type2; COL2A1: collagen type II; PA1: plasminogen activator inhibitor 1; HIV: human immunodeficiency virus.

Table 8. Risk factors for glucocorticoid-induced osteonecrosis (adapted from [99]).

9.2. Osteonecrosis

The most common joint involved is the hip and GCs are the second most common cause. The incidence of osteonecrosis induced by GCs increase with higher doses and prolonged treatment. But can be seen with short-term exposure to high doses, and without osteoporosis. Osteonecrosis develops in 9–40% of adult patients receiving long-term GCs. Risk factors are shown in **Table 8** [104–106].

10. Hypertension

Glucocorticoid-induced elevation in blood pressure is classified as secondary hypertension and is a major risk factor for cardiovascular diseases. Blood pressure in humans is subjected to tight control by several physiologic systems that have pleiotropic effects and interact together in a complex fashion. GCs can cause hypertension by influencing these systems in different ways. One possible mechanism is the in vitro affinity of the non-selective mineralocorticoid receptor (MR) for the GCs. As a result, stimulation of the MR by exogenous GCs leads to renal Na^+ retention, volume expansion, and finally to an increase in blood pressure. Vascular tone (imbalance between vasoconstriction and vasodilation), centrally mediated mechanisms, renin-angiotensin system activation, cardiac hypercontractility, and endothelial cell dysfunction may also play a role. Enhanced reactive oxygen species and reduced nitric oxide (NO)

bioavailability are the most important factors for endothelial cell dysfunction. The risk of hypertension is 2.2 times higher in patients treated with GCs, whatever the duration of exposure. The risk seems to increase with duration of exposure and daily dosage. A family history of essential hypertension may also predispose hypertension induced by GCs. People with glucocorticoid-induced lipodystrophy are at higher risk [107–110].

11. Dyslipidemia

GCs have a very important role in energy homeostasis and on lipid metabolism. Chronic exposure to exogenous GCs is a secondary cause of dyslipidemia. But the degree of lipid abnormalities in different clinical conditions is quite variable. These variabilities are related with the heterogeneity of the populations treated in terms of age, sex, underlying condition, glucocorticoid dose, and concomitant medications. All possible changes in lipid profile (i.e. isolated increase of triglyceride levels, increase of both cholesterol and triglycerides levels, absence of changes in lipid parameters, and improvement in lipid profile with increased HDL cholesterol) have been reported, excluding organ transplant recipients. Because transplanted patients concomitantly treated with other immunosuppressive drugs with side effects on the lipid metabolism (e.g. cyclosporine), which is a confounding factor. People with glucocorticoid-induced lipodystrophy are more likely to develop an unfavorable lipid profile. But interestingly, findings from the Third National Health and Nutrition Examination Survey suggest that GCs may have a beneficial effect on lipid profile in adults ≥60 years of age. GCs stimulate lipolysis and modulate free fatty acid (FFA) mobilization through various mechanisms. These mechanisms are summarized in **Figure 2**. Stimulation of lipolysis depends on dose and duration. Therefore in patients treated with GCs at high doses or for prolonged periods, regular monitoring of lipid profile is recommended [111–114] (**Figure 3**).

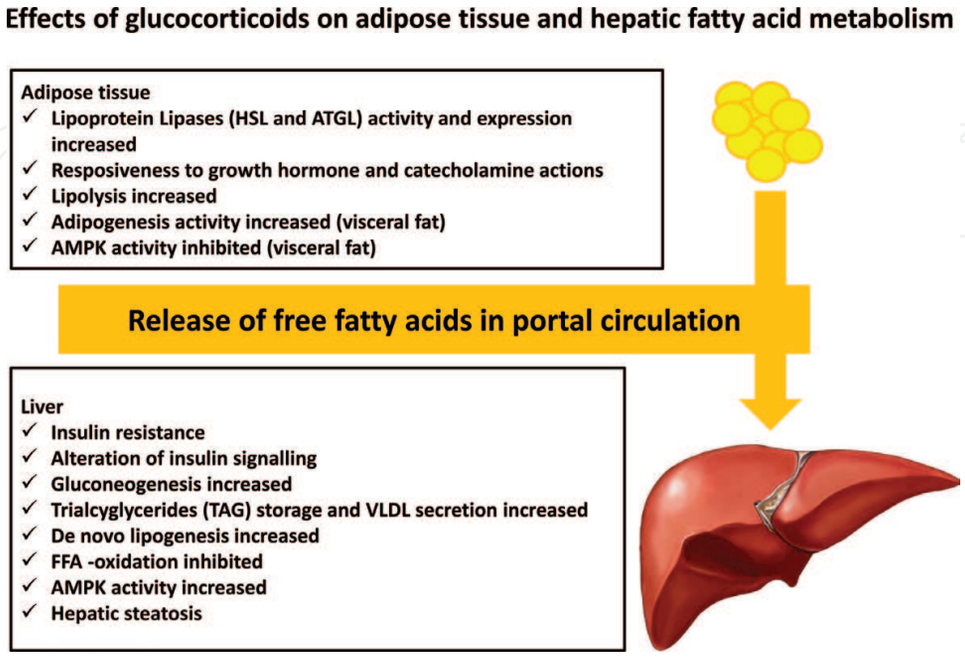

Figure 3. Effects of glucocorticoids on adipose tissue and hepatic fatty acid metabolism (adapted from [115]).

12. Gastrointestinal side effects

Side effects of GCs on the gastrointestinal system include peptic ulcers (PU), upper gastrointestinal bleeding (UGB), and pancreatitis.

12.1. PU

There is conflicting evidence related with the risk of PU for patients treated with glucocorticoid monotherapy. In a case-control study, there was no increased risk of PU at any dose or duration of glucocorticoid monotherapy. But in the same study, the combination of GCs with nonsteroidal anti-inflammatory drugs (NSAID), there was a significantly increased risk of peptic ulcer. Treatment with GCs may cause gastric irritation, more than PU [116, 117].

12.2. UGB

The incidence of UGB is low in patients treated with GCs alone and without a prior history of bleeding, but notably higher in patients receiving concomitantly anticoagulants and NSAIDs, and those with a history of bleeding. In the presence of different underlying diseases, such as rheumatoid arthritis, treatment with GCs may represent a more important risk factor for gastrointestinal complications than NSAIDs. In animal studies, GCs have been shown to increase gastric acid secretion, to reduce gastric mucus, to cause gastrin and parietal cell hyperplasia, and to delay the healing of ulcers [118–120].

12.3. Pancreatitis

Although the exact mechanism is unknown, incidence of GCs induced pancreatitis is well established in the medical literature. One case-control study showed that the risk of acute pancreatitis was increased among current users of oral GCs compared with nonusers. This risk was highest 4–14 days after drug dispensation and the risk gradually decreased thereafter. Pancreatitis, commonly reported in chronic exposure to GCs, especially in large doses for a wide variety of diseases [121].

13. Ocular side effects

13.1. Glaucoma

GCs induce morphological and functional changes in the trabecular meshwork (TM). These mechanisms are considered to be the leading cause of increased intraocular pressure during treatment with GCs. Systemic GCs are associated with a high incidence of glaucoma. All doses of GCs increase the risk for glaucoma. Nevertheless, doses of hydrocortisone 40 mg per day (prednisone 10 mg equivalent) were associated with an almost twofold increased risk. In patients over 40 years of age and with certain systemic diseases (e.g. diabetes mellitus, high myopia, connective tissue disease particularly rheumatoid arthritis), as well as relatives of patients with primary open-angle glaucoma (POAG), the risk for glaucoma induced by GCs increases. Glaucoma may lead to increased intraocular pressure, optic disc cupping, severe optic nerve damage, but considered a *silent* disease. *Because* there are no evident *symptoms*

until visual loss. Discontinuation of GCs leads to reversal of intraocular hypertension within a few weeks, but the optic nerve damage is often permanent [122, 123].

13.2. Cataracts

Posterior subcapsular cataracts (PSC) induced by GCs appears bilaterally and is distinguishable from the more common types of cataract. Increased glucose levels, caused by an increased gluconeogenesis rate; inhibition of Na^+/K^+-ATPase; increased cation permeability; inhibition of glucose-6-phosphate-dehydrogenase; inhibition of RNA synthesis; loss of ATP; and covalent binding of steroids to lens proteins are the possible mechanisms. These changes are specific for PSC induced by GCs. The risk appears to be both duration and dose-dependent. PSC is more likely to occur at higher doses of GCs. But as with other side effects, lower doses (<5 mg prednisone per day) have been linked to PSC [123, 124].

13.3. Central serous chorioretinopathy (CSCR)

CSCR is also associated with systemic GCs. Symptoms are central visual blur and reduced visual acuity. GCs should be used cautiously in patients with a history of CSCR [125].

Exophthalmos and chorioretinopathy rarely occur. Consequently, before treatment with GCs, clinicians should ask about the history of glaucoma, cataracts, and CSCR; and patients with risk factors should be referred to ophthalmologic examination.

14. Immunosuppression and risk of infection

There are multiple anti-inflammatory and immunosuppressive effects of GCs (**Table 9**) [126]. These mechanisms may predispose patients to infections. The overall risk of infections is 50–60% higher in the patients exposed to GCs. The risk of infections can be related with dose and duration of GCs. Infection rates were not increased in patients given a daily dose of <10 mg or a cumulative dose of <700 mg of prednisone. But the exact dosages and duration that substantially change the benefit-risk ratio for GCs varies by the personal and the underlying risk factors. The risk factors for infections are the underlying disorders (especially rheumatoid arthritis and systemic lupus erythematosus), patient age, lower functional status, and concomitant use of immunosuppressive or biologic therapies. In addition, a low albumin level is strongly associated with the risk of infection, because of direct (i.e. as an etiological factor) or indirect (i.e. by being a marker of the malnutrition-inflammation syndrome) effects. Furthermore, a low albumin level is associated with a higher free glucocorticoid fraction. Due to the inhibition of cytokine release and associated reduction in inflammatory and febrile responses, patients treated with GCs may not be presented with obvious signs and symptoms of infection. Therefore, it may be difficult to detect infections at an early stage. In addition to serious bacterial infections, the increase in risk is much higher for opportunistic infections (e.g. *Pneumocystis jiroveci* pneumonia, herpes zoster tuberculosis, listeriosis, aspergillosis, nontuberculous mycobacterial disease, invasive fungal infections), and in specific populations (e.g. allogeneic bone marrow transplant and solid organ transplant). Reactivation of cytomegalovirus with GCs is a serious problem especially in solid organ transplant recipients [127–131].

Lymphocytes

- Reversible lymphopenia, CD4 depletion (>50% reduction)
- Decreased proliferation and migration of lymphocytes
- Impaired delayed-type hypersensitivity
- Impaired natural killer cell cytotoxicity
- Decreased lymphokine production (interleukin-2, TNFα,interleukin-12, interferon γ)
- Th1/Th2 dysregulation of T-helper cells (decreased Th1 and increased Th2 cytokine production)
- Impaired phagocyte effector cell function and cellular immune response

Monocytes/macrophages

- Reversible monocytopenia (>40% reduction)
- Impaired phagocytosis and oxidative killing
- Decreased chemotaxis and migration to sites of inflammation
- Impaired formation of nitric oxide
- Impaired maturation of monocytes to macrophages
- Inhibition of pro-inflammatory cytokine production(interleukin-1, interleukin-6, TNFα)

Neutrophils

- Impaired phagocytosis, degranulation, and oxidative burst
- Reduced cytokine production
- Impaired formation of nitric oxide
- Defective adherence to endothelium, extravasation,chemotaxis
- Inhibition of apoptosis

Other immune effector cells

- Decreased counts for alveolar dendritic cells, central nervous system microglial cells, and Langerhans' epidermal cells
- Impaired antigen-presenting capacity of dendritic and Langerhans' cells (decreased expression of MHC II on their surface)
- Defective microglial cell-killing capacity (impaired nitric oxide formation)

Other effects

- Inhibition of prostaglandin production
- Inhibition of host's inflammatory response
- Attenuation of clinical (i.e. fever) and radiological signs of infection
- Potential delay of diagnosis

Table 9. Immunosuppressive effects of glucocorticoids (adapted from [126]).

15. Myopathy

GCs have direct catabolic effects on skeletal muscles. These catabolic effects are mediated by several cellular mechanisms. GCs inhibit the glucose uptake in skeletal muscles, by this way stimulate protein catabolism and inhibit protein synthesis in muscles. These direct effects causes muscle weakness. Besides, it was shown that GCs increase the transcription of genes encoding components of the ubiquitin-proteasome pathway, thereby increasing the proteolytic capacity of muscle cells. Transactivation of certain genes through glucocorticoid receptors also contributes to muscle atrophy. GCs inhibit the production by the muscle of IGF-I, a growth factor that stimulates the development of muscle mass by increasing protein synthesis and myogenesis, while decreasing proteolysis and apoptosis. In addition, GCs stimulate the production of myostatin, a growth factor that inhibits the muscle mass development by downregulating the proliferation and protein synthesis [132–135].

Myopathy usually develops over several weeks to months with the use of GCs. The typical clinical features are proximal muscle weakness and atrophy in both the upper and lower

extremities. Quadriceps and other pelvic girdle muscles are more severely affected. Myalgias and muscle tenderness are not seen. Although there is some variation in the dose and duration of GCs prior to the onset of muscle weakness, the higher the dose of GCs used related with the more rapid the onset. But it is more common in patients treated with ≥10 mg/day of prednisone or equivalent. The severity and the mechanism for the catabolic effect of GCs may differ with age. Creatine phosphokinase, aldolase, aspartate aminotransferase, lactate dehydrogenase (LDH), LDH isoenzymes, and changes in urinary excretion of creatine neither correlate with the degree of muscle weakness, nor discriminate between patients receiving small and large doses of GCs. So there is no definitive diagnostic test for myopathy induced by GCs. Diagnosis is to exclude other possible etiologic factors. Weakness of peripheral and respiratory muscles may have significant clinical effects, such as loss of quality of life, fatigue, impaired wound healing, compromised lung function, and poor immune response. Treatment is discontinuation of GCs or dose reductions immediately. Symptoms generally improve within 3–4 weeks of dose reductions, and often resolve after discontinuation of GCs [136–138].

16. Cutaneous side effects

The most important cutaneous side effects of systemic GCs are skin atrophy-fragility, irreversible striae rubrae distensae (red striae), purpura, and delayed wound healing. A rare but unimportant side effect is hypertrichosis. Fortunately, hypertrichosis is usually reversible and disappears after discontinuation of GCs. The potency and duration of therapy determine the occurrence and severity of cutaneous lesions.

16.1. Skin atrophy

All parts of the skin involved become thin and fragile. Women seem to be more susceptible to this side effect. Suppression of cutaneous cell proliferation and protein synthesis causes skin atrophy. Further effects of GCs on the skin are a decreased synthesis of epidermal lipids, as well as an increased transepidermal water loss [139, 140].

16.2. Striae

These are visible linear scars that form in areas of dermal damage, presumably during mechanical stress. Stria means scar tissue. For this reason, once developed, they are permanent. In the differential diagnosis, excessive weight gain and pregnancy should be excluded [141].

16.3. Delayed wound healing

The effects of GCs on wound healing are multifactorial. GCs prevent the early inflammatory phase, which is essential for wound repair. GCs also affect keratinocytes (epidermal atrophy and delayed reepithelialization), fibroblasts (reduced collagen and ground substance, resulting in dermal atrophy, and striae), and vascular connective tissue support (telangiectasia, purpura, and easy bruising). According to delayed granulation, tissue formation of GCs impairs angiogenesis. Furthermore GCs have impact on wound healing by the regulation of pro-inflammatory cytokines, growth factors, matrix proteins, and matrix proteases [142].

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.

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