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Optimum management of glucocorticoid-treated patients

Subbulaxmi Trikudanathan and Graham T McMahon*

SUMMARY

Glucocorticoids are taken by approximately 2% of the US adult population at any given time. The powerful anti-inflammatory and immunosuppressive benefits of these drugs must, however, be weighed against their multisystem adverse effects. Clinicians should always prescribe the lowest possible dose for the shortest possible time. Patients should be informed of the short-term and long-term adverse effects to expect, particularly if the dose of glucocorticoids is expected to exceed the equivalent of approximately 7.5 mg prednisone daily for 2 months or more. At the commencement of glucocorticoid therapy, a patient's blood pressure, lipid profile, 25-hydroxyvitamin D_3 level and fasting glucose level should be measured and baseline bone densitometry performed. Bisphosphonate therapy should be initiated for postmenopausal women and men with a bone density T-score below –1 or for those with a history of fracture. Regular ophthalmic screening for cataracts and glaucoma is warranted, and patients at high-risk of gastric ulceration (especially patients simultaneously taking nonsteroidal anti-inflammatory drugs) should receive proton-pump inhibitors. Prophylaxis against opportunistic infections is appropriate for high-risk populations, such as organ-transplant recipients. Trimethoprim plus sulfamethoxazole can be given to high-risk populations, such as organ transplant recipients. The duration of weaning from glucocorticoid treatment should be proportionate to treatment duration. Appropriate preventive therapy can mitigate many of the adverse effects associated with glucocorticoid therapy.

KEYWORDS adverse effects, clinical practice, corticosteroid, glucocorticoid, prophylaxis

REVIEW CRITERIA

A list of the major adverse associations of glucocorticoid treatment was retrieved from the pharmacopoeia. A PubMed search for each of these adverse events combined with a search term for glucocorticoids ("glucocorticoids" or "corticosteroids" or "prednis*" or "dexamethasone"). Only studies that involved adult humans and that were written in the English language were considered. Summaries were screened for suitability before being summarized and added to the text.

S Trikudanathan is a Member of the Faculty in the Department of Medicine at the Tufts University School of Medicine, and practices clinical medicine at the St Elizabeth's Medical Center, Boston. GT McMahon is a Member of the Faculty in the Division of Endocrinology at the Brigham and Women's Hospital, and an Assistant Professor of Medicine at Harvard Medical School, Boston, MA, USA.

Correspondence
*Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, 221 Longwood Avenue, RF-291, Boston, MA 02115, USA
gmcmahon@partners.org

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INTRODUCTION

The availability of disease-modifying drugs has diminished the clinical dependency on glucocorticoids for disease management; however, glucocorticoids are still taken by around 2% of adults in the US at any given time.[1,2] Glucocorticoids offer strong anti-inflammatory effects by negatively regulating cytokine release from the cells of the immune system. The drugs are clinically useful in the management of many clinical conditions, including rheumatoid arthritis and asthma, and for the immunosuppressive treatment of organ transplant recipients. Consequently, glucocorticoids are available in many formulations with differing pharmacokinetic and pharmacodynamic profiles, and glucocorticoid and mineralocorticoid activities (Table 1). Healthy adults typically produce the equivalent of 10 mg hydrocortisone daily.[3]

Oral glucocorticoids are, unfortunately, associated with multisystem adverse effects that limit their widespread use. This Review will focus on what is known about these adverse effects and provide recommendations for the care of adult patients who require long-term treatment with glucocorticoids (Table 2).

MUSCULOSKELETAL EFFECTS

Glucocorticoids have notable effects on the skeleton. They induce an early increase in bone resorption followed by a progressive decline in bone formation that especially affects trabecular bone. The decline in bone density and the associated increase in the risk of fracture are both dose-dependent, and the risks increase with doses higher than the equivalent of 7.5 mg prednisone daily.[4,5]

Glucocorticoids impair the replication, differentiation and function of osteoblasts.[6] By activation of caspase 3—a key mediator of apoptosis—these drugs also raise the rate of apoptosis of osteocytes and osteoblasts, and thereby substantially reduce bone formation and increase bone fragility.[7,8] Furthermore, glucocorticoids increase the expression of macrophage colony-stimulating

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Table 1 Available glucocorticoids and their relative potencies.

Drug	Anti-inflammatory action	Hypothalamic–pituitary–adrenal suppression	Approximate equivalent dose (mg)	Duration of action (h)
Hydrocortisone	1	1	20.0	12
Prednisone	3	4	5.0	12–36
Prednisolone	3	4	5.0	12–36
Methylprednisolone	6	4	4.0	12–36
Dexamethasone	26	17	0.7	>48

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factor and RANK-ligand (also known as tumor necrosis factor ligand superfamily member 11) and decrease the expression of osteoprotegerin (also known as tumor necrosis factor receptor superfamily member 11B). These expression effects induce osteoclastogenesis and diminish osteoclast apoptosis.[9] Chronic therapy with glucocorticoids increases the prevalence of osteocyte and osteoblast apoptosis and leads to the accumulation of the apoptotic osteoclasts. The result is disruption of lacunocanalicular circulation and microdamage to the bone.[10]

Glucocorticoids also suppress insulin-like growth factor I (IGF-I) activity and thereby reduce the synthesis of type 1 collagen. Use of these drugs indirectly induces osteopenia by decreasing intestinal calcium absorption and increasing renal calcium elimination, and also by reducing the production of estrogen and testosterone.[11,12] Furthermore, steroid-induced muscle weakness increases the risk of falls.

Meta-analyses have shown an increased risk of fracture among patients treated with glucocorticoids (relative rate between 1.3 and 1.9 for all fractures, 1.6 for hip fractures and 2.6 for vertebral fractures).[4,13] A high prevalence of asymptomatic vertebral fractures has been observed among postmenopausal women receiving long-term glucocorticoid therapy.[14] Whether the risk of glucocorticoid-associated fracture differs between the sexes is unclear. Some studies have shown that women are more susceptible, whereas other studies have found no major differences in risk between men and women. In a meta-analysis that examined the epidemiology of glucocorticoid-associated osteoporosis, age and sex did not influence the effects of cumulative dose on bone density.[4] Vertebral fractures seem to occur at higher bone density levels among patients treated with glucocorticoids than women with postmenopausal osteoporosis, which suggests an effect of glucocorticoids on bone quality.[15]

A baseline measurement of BMD at the lumbar spine and hip is generally recommended at the commencement of long-term glucocorticoid therapy. Prophylactic bone-protection strategies are recommended for patients starting an equivalent of at least 5 mg prednisone daily for a minimum of 3 months.[16] In addition, guidelines advocate smoking cessation, reduction of alcohol consumption and initiation of weight-bearing exercises. Daily calcium (1,000–1,500 mg) and vitamin D_3 (≥800 IU/day, titrated to a 25-hydroxyvitamin D_3 level of ≥62.4 nmol/l) supplements should be offered to all patients who are started on long-term glucocorticoids.

For glucocorticoid-treated patients with additional bone density risk factors, such as postmenopausal women with a bone density T-score of more than 1.0–1.5 SD below the peak bone mass, guidelines recommend that bisphosphonate therapy be started.[16,17] Bisphosphonates inhibit osteoclast-mediated bone absorption and prevent osteocyte and osteoblast apoptosis by the activation of extracellular kinases.[18] In clinical trials, risedronate significantly increased vertebral and femoral bone density and decreased the relative risk of new vertebral fractures.[19,20] Similarly, alendronate was more effective in the prevention of glucocorticoid-induced bone loss among patients with rheumatic diseases than was alfacalcidol.[21] Premenopausal women who are being considered for bisphosphonate therapy should be adequately counseled about long-term implications of exposure to these drugs.

Teriparatide—a recombinant human protein that contains peptides 1–34 of the parathyroid hormone—holds promise for its anabolic effect on bone formation. A study in 2007 demonstrated

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Table 2 Strategies to reduce the risk of known glucocorticoid-associated adverse events.

System affected	Adverse event	Risk factors	Strategy
Musculoskeletal	Osteoporosis	Low bone mass	Supplemental calcium and vitamin D_3. Add bisphosphonates if T-score is below –1 in postmenopausal women and men
	Osteonecrosis	Younger age	Typically joint replacement
	Myopathy	Older age Poor nutritional status Malignancy	Exercise program, nonfluorinated glucocorticoids
Cardiovascular	Hypertension, hyperlipidemia	Family history of cardiovascular disease	Standard risk-factor modification
Gastrointestinal	Gastritis, ulceration	History of gastrointestinal ulceration, synchronous use of NSAIDs	Proton-pump inhibitors in high-risk patients
	Steatohepatitis	Obesity	Routine monitoring of liver tests
Dermatologic	Subcutaneous atrophy	Water-soluble preparations	Use deep-gluteal injection
	Skin cancers	Fair complexion, family history, transplantation	Sun block
Ocular	Cataract, raised intraocular pressure	Older age	Regular ophthalmic screening
Endocrine	Cortisol deficiency	Glucocorticoid with long half-life	Taper should be prolonged if treatment is prolonged. Use glucocorticoid with short half-life during taper
	Precipitation or exacerbation of diabetes	Older age, obesity, prediabetes, family history, personal history of gestational diabetes	Self-monitoring of blood glucose. Augment hypoglycemic therapy expectantly
Infection	Opportunistic infection	Open portal for infection	Alternate-day glucocorticoid administration. Add trimethoprim plus sulfamethoxazole
Psychiatric	Psychosis	Acute, high-dose glucocorticoids	Neuroleptics or lithium if glucocorticoid dose must be continued

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

that teriparatide was more effective than alendronate in increasing bone density. Compared with alendronate treatment, use of teriparatide was also associated with significantly fewer new vertebral fractures, but there was no difference in the number of nonvertebral fractures between the groups.[22] Bone loss related to glucocorticoid treatment might be largely reversible because fracture risk decreases over time after treatment is discontinued.[13]

Avascular necrosis is a serious but rare complication of glucocorticoid use. This disorder most typically affects the hip joints of younger patients treated with high-dose therapy.[23] In a prospective study of patients with systemic lupus erythematosus receiving high-dose methylprednisolone, one-third developed changes to the femoral head that were detectable on MRI, although most of the affected patients were asymptomatic.[24,25]

Steroid-induced myopathy was originally described by Cushing in 1932 in a patient with pituitary adenoma and occurs in up to 11% of patients treated with high-dose glucocorticoids.[26] As with other complications, the onset of myopathy is associated with the duration of treatment and the cumulative dose. Patients who develop this complication note the insidious onset of a symmetric weakness that typically involves the proximal lower extremities and that can progress to involve the proximal shoulder girdle. Myopathy has been reported to affect the respiratory muscles in a small number of corticosteroid-treated patients even when the

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proximal-muscle weakness is mild or absent.[27,28] Risk factors for the development of steroid-induced myopathy include older age, poor nutritional status and coexisting malignancy.[29]

Glucocorticoids have a direct catabolic effect on skeletal muscles. These drugs interact with intracellular receptors to enhance the expression level of glutamine synthetase, which increases glutamine production by muscle.[30] The degree of corticosteroid-induced muscle atrophy correlates with the degree of increased expression of glutamine synthetase.[31,32] Administration of growth hormone and recombinant IGF-I prevented glucocorticoid-induced muscular wasting in rats by decreasing glutamine synthetase activity in muscle.[33,34] IGF-I signaling also increases the activity of Akt1 (RAC-α serine/threonine protein kinase), a signaling molecule that suppresses catabolic pathways and induces muscle hypertrophy.[35]

Glucocorticoid-induced myopathy cannot be definitively diagnosed from the findings of any biochemical test,[36] although nonspecific type II fiber atrophy is typically present in muscle biopsy samples.[37] Alternate-day dosing and reduced dosing can decrease the incidence of glucocorticoid-induced myopathy but might not control symptoms of disease. Discontinuation or dose reduction of glucocorticoids improves muscle strength. If patients cannot be weaned from glucocorticoids, substitution of fluorinated glucocorticoids (e.g. dexamethasone or triamcinolone) with nonfluorinated glucocorticoids (e.g. prednisone or hydrocortisone) seems to reverse some of the muscle weakness.[26,38] Increased muscle stimulation by endurance training and increased physical activity could also attenuate glucocorticoid-induced muscle atrophy.[32]

INFECTIOUS COMPLICATIONS

Glucocorticoid therapy increases susceptibility to infections, predominantly because phagocyte function is impaired and cell-mediated immunity is suppressed. In a study of more than 6,000 patients with rheumatoid arthritis being treated with prednisone, a dose-related relationship was observed between prednisone use and the risk of hospitalization with pneumonia.[39] Similar findings were noted in a study of 223 patients with systemic lupus erythematosus; the frequency of all infections and specifically bacterial and opportunistic infections increased with increasing glucocorticoid dose.[40]

An association between glucocorticoid use and increased risk of infection was also found in a meta-analysis of 71 controlled clinical trials. The authors of that report documented that the overall rate of infection was 12.7% in the glucocorticoid-treated group as compared with 8.0% in the control group. However, the rate of infection was higher only in patients with a daily dose that exceeded a threshold of 10 mg daily or in those with a cumulative dose that exceeded 700 mg prednisone.[41] Patients with neurologic disease seemed to have an especially high risk of infection, which suggests that the type and severity of the underlying disease may influence the susceptibility to infection.

Glucocorticoids inhibit neutrophil migration to inflammatory sites and reduce the bactericidal activity of neutrophils. The presence of neutrophilia as a result of glucocorticoid therapy can occur in the absence of infection as a consequence of neutrophil demargination and accelerated release of mature neutrophils from the bone marrow. A superimposed infectious process is suggested if 'band' forms of neutrophils are present in the blood and/or metamyelocytes in proportions that exceed 6% of leukocytes.[42] A study that used microarray techniques to analyze glucocorticoid-induced gene-expression patterns in human monocytes found that glucocorticoid therapy induced differentiation and reprogramming of monocytes but did not cause global monocyte suppression.[43]

Treatment with glucocorticoids does not seem to increase the risk of all infections equally. Some researchers have recommended that T-helper-cell concentrations in the blood be monitored to prospectively identify patients at high risk of infection. Lymphocytopenia (<600 cells/μl), a low $CD4^+$ T-cell count (<250 cells/μl) and glucocorticoid therapy equivalent to more than 10 mg prednisolone per day seem to be indicative of a high risk of infection.[44]

Glucocorticoids suppress $CD4^+$ lymphocyte levels in the lungs and blood and attenuate surveillance carried out by alveolar macrophages to detect infections. These effects particularly increase the risk of *Pneumocystis jiroveci* pneumonia. Early clinical observations suggested that cases of pneumocystis pneumonia increased during glucocorticoid taper among patients with primary brain tumors;[45,46] furthermore, in a large consecutive series, over 90% of patients who developed pneumocystis pneumonia but who were not infected with HIV

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had been treated with glucocorticoids in the preceding month.[47]

Antibiotic prophylaxis should be considered for patients with brain tumors and organ transplant recipients who have received long-term glucocorticoid therapy—especially during the tapering phase of steroid treatment.[48] Prophylactic treatment with trimethoprim plus sulfamethoxazole (one double-strength tablet comprising 160 mg trimethoprim plus 800 mg sulfamethoxazole given three times a week, or one single-strength tablet daily) has been shown to be highly effective in reducing the incidence of *P. jiroveci* pneumonia among chronically glucocorticoid-treated patients.[49] Dapsone (100 mg daily) or aerosolized pentamidine are alternative treatments for patients allergic to sulfamethoxazole, although these drugs seem to be less effective and less-well tolerated.

No studies have shown that glucocorticoid-treated patients have an increased risk of developing new tuberculosis or re-activating old tuberculosis, but clinicians should maintain a low threshold of suspicion in appropriate clinical circumstances.[50,51] For patients who are stabilized on a chronic dose of glucocorticoids, alternate-day administration of therapy is associated with fewer infections than once-daily therapy.[52]

GASTROINTESTINAL EFFECTS

Glucocorticoid use has been widely considered to increase the risk of gastritis, ulcer formation, and gastrointestinal bleeding from perforated peptic ulcers. Although the molecular mechanisms that underlie these steroidal effects have not been elucidated, studies in animals have shown that glucocorticoids increase gastric acid secretion and inhibit the reparative mechanisms involved in ulcer healing. Glucocorticoids suppress the protective functions of prostaglandins via inhibition of phospholipase A_2 in the arachidonic acid pathway by a similar mechanism to that of nonsteroidal anti-inflammatory drugs (NSAIDs). Glucocorticoid-induced ulcers are typically gastric, multiple, have little scar tissue and present without induration at the ulcer site. They are usually asymptomatic and might not be discovered until major complications such as hemorrhage or perforation occur.

A large pooled analysis that evaluated 3,064 glucocorticoid-treated patients found that more than twice as many glucocorticoid-treated patients had gastrointestinal ulcers than controls not receiving glucocorticoid therapy (1.8% versus 0.8%, relative risk of 2.3) and 60% more in the treatment group had bleeding than controls.[53] By contrast, a meta-analysis concluded that use of glucocorticoids did not significantly increase the risk of peptic ulceration; however, the patients studied were not endoscopically screened.[54]

Risk factors for the development of glucocorticoid-induced ulcers include concomitant usage of NSAIDs, a total dose equivalent to greater than 1,000 mg prednisone, a duration of therapy longer than 30 days and a history of peptic ulcer disease.[55] Concurrent NSAID and glucocorticoid administration seems to be associated with an especially high risk; for example, in a cohort of elderly Medicaid recipients, the risk of ulceration was over 14-fold higher in patients treated concurrently with glucocorticoids and NSAIDs than in those who used neither drug.[56] This pattern of risk might account for the increased risk of ulceration observed among patients who are treated in rheumatology clinics that often co-prescribed the two drugs.

Co-prescription of proton-pump inhibitors has become commonplace for patients treated with glucocorticoids and NSAIDs concurrently or for corticosteroid-treated patients who have a history of gastrointestinal ulceration or hemorrhage.[57] Other more uncommon gastrointestinal complications associated with glucocorticoid use include pancreatitis, perforation of colonic diverticular abscesses and fatty liver.

CARDIOVASCULAR EFFECTS

The long-term cardiovascular risk in glucocorticoid-treated patients was highlighted by the findings of a cohort study published in 2004.[58] Compared with patients who were not treated with glucocorticoids, treated patients had a dose-dependent increase in the rate of cardiovascular events that reached a rate ratio as high as 4.5 at high doses. Although these data are observational and may be confounded by the conditions that triggered glucocorticoid use, there is reason to believe that cardiovascular disease and glucocorticoid therapy are linked.[59] Glucocorticoid treatment is independently associated with cardiovascular risk factors such as hypertension,[60] hyperlipidemia[61] and hyperglycemia.[62] Glucocorticoids seem to have a direct effect on atherogenesis, vascular function, and vascular remodeling following intravascular

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injury or ischemia. These effects are mediated by both glucocorticoid and mineralocorticoid receptors and modified by local metabolism of glucocorticoids by the 11β-hydroxysteroid dehydrogenase enzymes.[59]

Patients with particular polymorphisms in the glucocorticoid receptor gene could be particularly susceptible to glucocorticoid-mediated cardiovascular risk. One such polymorphism—the *Bcl*1 polymorphism—involves a *Bcl*1 restriction site in intron 2 and is a C to G nucleotide change 646 bp downstream from exon 2. Patients with this polymorphism and those with the N363S (1220A>G) variant of the glucocorticoid receptor have increased sensitivity to glucocorticoids and have a tendency towards hypertension, visceral obesity and hyperinsulinemia.[63] The ER22/23EK polymorphisms of the glucocorticoid receptor are associated with relative resistance to glucocorticoids, and patients with these polymorphisms have a propensity toward reduced waist and hip circumferences and body weight.[63] Appropriate risk-factor modification and pharmacologic therapy would be expected to be beneficial for affected patients who require long-term glucocorticoid treatment.

DERMATOLOGIC COMPLICATIONS

Glucocorticoid therapy can lead to skin thinning, striae, telangiectasis, acneiform eruption and rosacea. Atrophy of the epidermis and the dermis can result in the irreversible striae rubrae distensae. Telangiectasiae are frequently visible through the thinned skin, and mild trauma can damage local blood vessels leading to the development of purpura.[64] Cushingoid features such as truncal obesity, dorsocervical fat pad, hypertrichosis, moon face and weight gain can occur rapidly in patients treated with more than 7.5 mg of prednisone daily. One study found that moon facies developed in 13% of patients who took the equivalent of 5–15 mg prednisone for up to 60 days.[65] Compared with daily glucocorticoid administration, alternate-day administration causes less suppression of the hypothalamic–pituitary–adrenal axis and results in a lower incidence of the Cushingoid appearance.[52]

Nitric oxide has been reported to have a critical role in the accumulation of collagen around wounds and on the acquisition of mechanical strength.[66,67] Glucocorticoids impair wound healing by inhibiting nitric oxide synthesis in a dose-dependent manner.[68] When glucocorticoids are used, they can delay wound contraction, inhibit fibroblast proliferation, matrix synthesis and angiogenesis, and affect the recovery of epithelialisation.[67,68] Changes in suture techniques that involved creation of a pedunculated seromuscular flap[69] or polyglycolic acid mesh reinforcement[70] significantly improved the strength of small-bowel anastomoses in animals treated with glucocorticoids.

Organ transplant recipients are at a significantly increased risk of nonmelanoma skin cancers and non-Hodgkin's lymphoma; in part this increase in risk is related to the cumulative doses of immunosuppressive drugs, including glucocorticoids. A large population-based case–control study that examined glucocorticoid use in nontransplant recipients showed that the use of oral glucocorticoids, but not inhaled glucocorticoids, was associated with an increased risk of both squamous cell and basal cell cancers though to a lesser extent than that experienced by organ transplant recipients;[71] the finding was duplicated in a different study.[72] Immunosuppression induced by use of oral glucocorticoids is hypothesized to enable these cancers to emerge because of impaired immunosurveillance. Sun block is an appropriate preventative recommendation.

Local subcutaneous atrophy after glucocorticoid injection is relatively frequent in young women and girls who are given less-water-soluble preparations;[73,74] therefore, deep-gluteal rather than deltoid injection sites are preferred for intramuscular administration.

OCULAR COMPLICATIONS

Cataracts are among the most common adverse effects of long-term treatment with glucocorticoids; they are distinguishable from senile cataracts by their posterior subcapsular location.[5] Glucocorticoids also increase intraocular pressure in a dose-dependent manner;[75,76] patients with a family history of glaucoma are most predisposed. Intraocular edema as a consequence of glucocorticoid treatment can lead to serous chorioretinopathy, a condition in which the retina and choroid separate.[77]

PSYCHIATRIC COMPLICATIONS

Many patients experience a mild euphoria when glucocorticoid treatment is initiated. Psychiatric adverse effects of glucocorticoid treatment include a wide array of symptoms that range from depression to mood swings, hypomania

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and frank psychosis. These symptoms are dose-dependent and often appear in the first two weeks of treatment.[78,79] Whether prior psychiatric problems or any specific underlying diseases increase a patient's risk of developing psychiatric adverse effects is unclear.[78,80] Individuals with glucocorticoid receptor variants such as the *Bcl*1 and ER22/23EK polymorphisms have an increased susceptibility to the development of major depression; the role that these polymorphisms have in the risk of depression associated with exogenous glucocorticoid treatment remains speculative.[81]

Glucocorticoid doses exceeding the equivalent of 40 mg prednisone daily are associated with a considerable risk of psychosis, particularly within the first 5 days of treatment.[82] Patients with steroid psychoses present with a constellation of symptoms including emotional lability, anxiety, insomnia, depression, agitation, and auditory and visual hallucinations. Tricyclic antidepressants exacerbate these symptoms by increasing the translocation of corticosteroids receptors from the cytoplasm to the nucleus and increasing the rate of mRNA production;[83,84] therefore, their coadministration should be avoided.[85,86] Dose reduction or discontinuation of glucocorticoids can ameliorate the symptoms. When discontinuation is not possible, neuroleptics or lithium can be successful when prescribed in consultation with a psychiatrist.[78] Small trials have also shown the beneficial effect of lamotrigine and olanzipine in improving mood and cognitive performance among patients who required long-term treatment with glucocorticoids.[87,88]

Evidence indicates that memory retrieval is impaired by glucocorticoid treatment.[89,90] The effect can be measured as early as the first dose[91] and persists beyond 1 year of treatment.[92] Elderly patients are more susceptible to memory impairment at low doses than are younger patients .

HYPERGLYCEMIA

Glucocorticoid therapy may precipitate new-onset diabetes or exacerbate pre-existing diabetes.[54,62] Glucocorticoids seem to increase peripheral insulin resistance, increase hepatic glucose production and inhibit pancreatic insulin secretion; in animal models these effects are dependent on peroxisome proliferator-activated receptor α and the vagal afferent pathway.[93,94] Increased age, a high BMI, a family history of diabetes mellitus, impaired glucose tolerance and prior history of gestational diabetes are predisposing factors for the development of new-onset diabetes.[62] Findings from a population-based study indicate that the risk of developing hyperglycemia is doubled in glucocorticoid-treated patients compared with untreated patients and the magnitude of risk increases substantially with increasing glucocorticoid dose.[95] If a patient develops diabetes he or she typically does so within the first 6 weeks of glucocorticoid therapy, but metabolic emergencies, for example diabetic ketoacidosis, can occur more rapidly in patients who already have type 1 diabetes.

Detection of new-onset diabetes is important during high-dose, short-term glucocorticoid therapy, as well as during intermittent therapy and therapy exceeding 1 month. Self-monitoring of blood glucose levels should be encouraged for all patients with hyperglycemia. Fasting glucose levels are often not substantially affected, especially in patients receiving glucocorticoids once daily in the morning.[96] Mild hyperglycemia can often be managed with oral hypoglycemic agents, diet and exercise. Patients previously taking insulin typically require dose escalation up to twice the previously established dose requirement.[97] Many patients who were not previously taking insulin will require initiation of insulin therapy to maintain glycemic control. The hyperglycemic effect of glucocorticoids seems to be readily reversible, and typically resolve within 2 days of discontinuation of the glucocorticoid.[98] Consequently, oral hypoglycemics or insulin should be modified as the glucocorticoid dose is reduced or stopped.

ADRENAL SUPPRESSION

Chronic glucocorticoid treatment results in atrophy of the zona fasciculata, and increases the risk of acute cortisol insufficiency if the glucocorticoid is stopped acutely. The risk of adrenal suppression corresponds to the duration of therapy and the cumulative dose received. The zona fasciculata seems to retain normal function until the daily dose exceeds the equivalent of 5 mg prednisone daily.[99] The duration of suppression correlates with the half-life of the glucocorticoid. Evening dosing will suppress the normal circadian burst of adrenocorticotropin each morning, and the rhythm will remain suppressed for a duration that approximates the half-life of the administered glucocorticoid.[100,101]

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Patients with subnormal cortisol levels typically complain of lethargy, malaise, nausea, myalgias, arthralgias, headache and fever, symptoms that seem to correspond to increasing circulating concentrations of interleukin 6.[102] As the glucocorticoid deficit becomes more profound, hypotension can occur. During periods of physiologic stress, the daily maintenance dose should be doubled. Parenteral glucocorticoids are indicated if the patient develops sufficient diarrhea or vomiting to make absorption questionable.

The zona fasciculata of the adrenal gland tends to recover quickly when the duration of suppression is no more than 1 week.[103] Glucocorticoid dose can be safely tapered over 72 h in patients who have been treated for less than 2 weeks; a slower tapering regimen over 8–12 weeks is indicated for patients who have been treated with suppressive doses for more than 1 year. One study showed that the spontaneous recovery of the pituitary–adrenal axis from glucocorticoid-induced suppression may take as long as 9 months.[104] Once a patient's dose has been tapered to an equivalent of 5 mg prednisone daily, reduction of the dose by 1 mg/month is safe.[105] Use of equivalent doses of shorter-acting glucocorticoids (such as hydrocortisone) more than once daily might accelerate adrenal recovery.

A morning endogenous cortisol level above 276 nmol/l suggests recovery of the adrenal gland if the patient is otherwise well.[106] Recovery can be confirmed if a stimulation test with 250 μg adrenocorticotropin generates a 1 h poststimulation cortisol level of more than 552 nmol/l.[107]

CONCLUSIONS

Glucocorticoids are highly effective drugs, but their use can cause substantial adverse effects, even at low doses. The risk of adverse effects increases with increasing exposure. When appropriate, disease-modifying agents and alternative immunosuppressive therapies can be used to replace or diminish the reliance on high glucocorticoid doses. Acutely, high-dose glucocorticoid use can lead to psychosis and predispose susceptible patients to sepsis. Over the longer term, glucocorticoid treatment increases the risk of fractures and incident diabetes, among many other complications. Many of these adverse events can be averted by use of the lowest possible dose for the shortest possible duration of time, and by the initiation of appropriate preventive therapy.

KEY POINTS

- Glucocorticoids should be prescribed at the lowest possible dose for the shortest possible time
- Appropriate baseline tests for patients initiating chronic glucocorticoid therapy include lipid profile, vitamin D3 level, fasting glucose level, and bone densitometry
- Bisphosphonate therapy is appropriate for glucocorticoid-treated men or postmenopausal women who have a bone density T-score of less than –1
- Prophylaxis against opportunistic infections is appropriate for high-risk patients
- The duration of weaning from glucocorticoids should correlate with the duration of treatment
- Proton-pump inhibitors are appropriate for patients receiving concurrent nonsteroidal anti-inflammatory drugs

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Competing interests
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