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Prevention and treatment of systemic glucocorticoid side effects

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Abstract

Background—Systemic glucocorticoids are used in dermatologic practice for various diseases including connective tissue disorders, bullous diseases, and many other dermatologic conditions. Patients with these diseases are at times treated with long-term courses of glucocorticoids, which place them at increased risk for glucocorticoid-induced side effects. Therefore, dermatologists must be knowledgeable of risks related to glucocorticoid use and be familiar with guidelines to manage them.

Objective—To provide an update of recent advances in the prevention and treatment of major glucocorticoid-induced side effects.

Methods—Review of the literature

Results—Data regarding the prevention and treatment of glucocorticoid-induced side effects are presented.

Conclusion—This review should help dermatologists optimally manage and prevent glucocorticoid-induced side effects.

Introduction

Glucocorticoids are commonly used to treat severe skin diseases. They are effective because of their immunosuppressive and anti-inflammatory effects. Prolonged high-dose glucocorticoid therapy has many potential side effects. Side effects resulting from glucocorticoid use are common and potentially serious. We summarize guidelines on the prevention and treatment of some of the major glucocorticoid-induced side effects, including those related to the musculoskeletal, endocrine, cardiovascular, and central nervous systems.

Prevention and treatment of systemic glucocorticoid side effects

Musculoskeletal

Osteoporosis—Bone loss is one of the most common and debilitating side effects associated with prolonged high-dose glucocorticoid therapy [1]. Glucocorticoids reduce bone formation and increase bone resorption [2–6]. Bone loss associated with glucocorticoid therapy is most pronounced in the first few months after initiating treatment. A study showed that patients receiving high-dose glucocorticoid therapy (mean=21mg/day prednisone) lost a mean of 27% of their lumbar spine bone density during the first year of treatment [7]. The rate of bone loss slows considerably thereafter [4,8–9] and bone density can increases after discontinuation of glucocorticoids [10]. The glucocorticoid-induced bone

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loss is dose-dependent and patients taking higher doses have significantly increased risk of bone loss relative to patients using glucocorticoids at lower doses [7,10–12].

The prevention and treatment of glucocorticoid-induced bone loss include decreasing the dose of glucocorticoid, calcium and vitamin D supplementation, and pharmacologic therapy to prevent further bone loss or increase bone density [13]. The duration of glucocorticoid therapy and the glucocorticoid dose should be as low as possible, because even low-dose glucocorticoid replacement therapy can decrease bone mineral density [14]. Alternative therapy with other medications is recommended. The published data on alternate-day glucocorticoid therapy suggests that this therapy can also produce osteoporosis [15–16]. Short-term high-dose pulse glucocorticoid therapy is preferred over continuous therapy with oral glucocorticoids [17]. In all individuals on glucocorticoid therapy, general principles include avoiding smoking and excess alcohol, weight-bearing exercises, and taking proper precautions to prevent falls. Multiple treatments have been introduced to prevent or treat bone loss and will be reviewed here.

Calcium and vitamin D: Calcium supplementation is recommended in all individuals treated with glucocorticoids, because glucocorticoids decrease intestinal calcium absorption and increase renal calcium excretion. The American College of Rheumatology Ad Hoc Committee on Osteoporosis suggests that individuals receiving glucocorticoids maintain a calcium intake of 1000 to 1500 mg/day and vitamin D intake of 800 IU/day through either diet or supplements [18]. A study assessed the effects of calcium and vitamin D on bone density of patients with rheumatoid arthritis and the relation between this effect and low-dose glucocorticoid use [12]. A total of 96 patients with rheumatoid arthritis, 65 of whom receiving prednisone at a mean dosage of 5.6 mg/day, were randomly assigned to calcium carbonate (1000 mg/day) and vitamin D3 (500 IU/day) or placebo, and followed for 2 years. Patients receiving prednisone therapy who were given placebo lost bone in the lumbar spine and trochanter at a rate of 2.0 and 0.9 percent per year, respectively, whereas patients receiving prednisone therapy who were given calcium and vitamin D3 gained bone in the lumbar spine and trochanter at a rate of 0.72 and 0.85 percent per year, respectively. In patients receiving prednisone therapy, bone density of the femoral neck did not increase with calcium and vitamin D3. Calcium and vitamin D3 did not improve bone density at any site in patients who were not receiving prednisone. Calcium and vitamin D is generally not sufficient to prevent bone loss in patients treated with high-dose glucocorticoids.

Active vitamin D metabolites: The data on the role of active vitamin D metabolites, such as calcitriol (1, 25-dihydroxy vitamin D), in the prevention of glucocorticoid-induced bone loss and fracture is not sufficient. The combination of calcitriol and calcium protect against spine bone loss more than calcium alone in patients receiving glucocorticoids [4,19]. Active vitamin D metabolites are associated with an increased risks for hypercalcemia and hypercalciuria in patients with an already increased rate of urinary calcium excretion [20], and have been largely replaced by other safer and more effective available therapies [19,21].

Bisphosphonates: Bisphosphonates are a class of drugs that are favorably used in the prevention and treatment of glucocorticoid-induced bone loss. The mechanism for the majority of the effects of these drugs is thought to be via their ability to prevent osteoclastic bone resorption [22]. Alendronate and risedronate are the most commonly used bisphosphonates in osteoporosis.

In a study of 477 patients on glucocorticoids, 17 to 83 years of age, who were randomly assigned to receive one of two doses of alendronate or placebo, bone density in the lumbar spine increased by 2.1 and 2.9 percent over 48 weeks, respectively, in the groups that received 5 and 10 mg of alendronate per day ($P<0.001$), while decreased by 0.4 percent in

the placebo group [23]. The bone density of the femoral neck, trochanter, and total body also increased significantly in the alendronate group. There were also proportionally fewer new vertebral fractures in the alendronate group than in the placebo group (2.3% vs. 3.7%). In a two-year randomized trial comparing once-weekly (70mg) and daily alendronate (10mg) in postmenopausal women, once-weekly regimen is therapeutically as effective as daily dosing [24]. However, once-weekly administration of alendronate is more convenient for patients and can enhance their adherence to therapy.

The efficacy of risedronate in patients receiving glucocorticoids was demonstrated in 2 one-year randomized, placebo-controlled studies. In a study of 224 patients receiving glucocorticoids, bone density of the lumbar spine did not change significantly in the risedronate treated groups (2.5 or 5 mg), and decreased by 2.8 percent in the placebo group [8]. In another study of 290 patients treated with high-dose glucocorticoids (≥ 7.5 mg/day prednisone or equivalent for six or more months), lumbar spine, femoral neck, and trochanter bone mineral density increased by 2.9, 1.8, and 2.4 percent, respectively, in the risedronate group (5 mg), while remaining unchanged in the placebo group [9]. A decrease in the incidence of vertebral fractures by 70% was observed in the risedronate group in the later study.

Ibandronate is a newer and highly potent bisphosphonate and every three month IV ibandronate (2mg) has been shown to be efficacious and well-tolerated for prevention and treatment of glucocorticoid-induced osteoporosis [25–26].

Other bisphosphonates used in the prevention and treatment of glucocorticoid-induced osteoporosis include pamidronate, zoledronic acid, etidronate, and clodronate. The efficacy of oral and intravenous pamidronate in preventing glucocorticoid-induced osteoporosis has been demonstrated [27–28]. Oral pamidronate is not available in the United States and intravenous infusions are very expensive. Intravenous bisphosphonates may be associated with flu-like symptoms and hypocalcemia. Flu-like symptoms can be prevented by acetaminophen. Hypocalcemia is more likely to occur in patients with vitamin D deficiency and can be prevented by calcium and vitamin D supplementation. Intravenous bisphosphonates are reasonable options in some patients who do not tolerate oral bisphosphonates. Zoledronic acid is one of the other IV bisphosphonates currently marketed in the United States. Etidronate has been largely replaced by alendronate and risedronate which are more potent. Clodronate, a novel drug used for inhibiting osteoclastic activity, has been shown to increase bone density in asthmatic patients treated with continuous oral and inhaled glucocorticoids [29]. Clodronate is not available in the United States. For further information regarding dose and administration of bisphosphonates, please refer to Table 1.

Bisphosphonates or active vitamin D metabolites?—Bisphosphonates are usually preferred over active vitamin D metabolites. In an 18-month trial in 201 patients with rheumatic diseases, who were randomly assigned to either alfacalcidol or alendronate, alendronate was more effective in the prevention of glucocorticoid-induced bone loss than was alfacalcidol. At 18 month, the absolute group difference in bone density was 4.0 percent [21].

In another study, 38 patients with glomerular disease receiving high-dose glucocorticoids were randomized into three groups: risedronate alone, alfacalcidol alone, and the combination of both agents. Risedronate (2.5 mg/day) was more effective than alfacalcidiol in preventing bone loss in the lumbar spine, and the combined therapy was better than risedronate monotherapy, especially in patients treated with pulse steroids [30]. Also, in another study of 114 patients with chronic kidney disease (creatinine clearance ≥30 ml/min/1.73 m^2), risedronate (2.5 mg daily) was more effective than alfacalcidiol on the lumbar

spine. The combination of risedronate and alfacalcidiol was similar to risedronate monotherapy for preventing or reversing bone loss [31].

In a randomized trial in 104 patients with established glucocorticoid-induced osteoporosis, three-monthly IV ibandronate (2 mg) was more effective than oral daily alfacalcidiol (1 mg) in improving spine, femoral neck, and calcaneal bone density after two and three years[25–26].

Hormone replacement: Glucocorticoid therapy reduces serum sex hormone levels due to its effect on the hypothalamic-hypophysial axis [32]. In a retrospective study of 15 postmenopausal or amenorrheic women taking glucocorticoids, bone density significantly increased in women treated with estrogen, while it decreased in women who didn't receive estrogen [33]. However, considering its unfavorable risk-benefit profile, long-term hormone replacement therapy is no longer recommended as a first-line therapy for prevention of postmenopausal osteoporosis. American College of Rheumatology Ad Hoc Committee on Osteoporosis suggests that premenopausal women taking glucocorticoids who have menstrual irregularities receive an oral contraceptive when there is no contraindication [18]. However, there is no evidence to support estrogen therapy in premenopausal women with normal menstrual cycles.

In a randomized, placebo-controlled trial of androgens in 51 men on glucocorticoids, lumbar spine bone density and muscle mass increased significantly in men treated with testosterone [34]. Testosterone can be considered for prevention of osteoporosis in men taking high-dose steroids who become hypogonadal.

Parathyroid hormone: Parathyroid hormone promotes both bone formation and resorption; however, intermittent administration promotes bone formation more than resorption. In a recent 18-month randomized, controlled trial, teriparatide (20 μg subcutaneously daily) was compared with alendronate (10 mg orally daily) in 428 women and men with osteoporosis who had received glucocorticoids for at least 3 months (5 mg or more of prednisone equivalent daily). Both treatments significantly increased lumbar spine bone density which was the primary outcome of the study. However, bone mineral density at the lumbar spine increased more in patients receiving teriparatide than in those receiving alendronate (7.2+/−0.7% vs. 3.4+/−0.7%, $P<0.001$) [35].

Calcitonin: Calcitonin attenuates bone loss by directly reducing osteoclastic resorption. It also reduces the pain in patients who have pain-causing fractures. In a two-year prospective trial in 44 steroid-dependent asthmatic patients, patients were randomly treated with either salmon calcitonin nasal spray (200 IU every other day) or calcium alone [36]. Bone density in the calcitonin group increased by 2.7% in the first year, while in the group receiving calcium alone it decreased by 2.8%. Calcitonin maintained bone mass in a steady state during the second year, while bone loss continued in the calcium alone group. However, the lack of efficacy of calcitonin on the rate of vertebral or nonvertebral fractures does not permit its recommendation as a first line therapy for the prevention or treatment of glucocorticoid-induced osteoporosis. Calcitonin can be considered in patients who cannot tolerate oral or intravenous bisphosphonates or when bisphosphonates are contraindicated. Due to its ability to reduce bone pain, calcitonin can also be considered in patients who have sustained an acute fracture.

Thiazide diuretics and dietary sodium restriction: Glucocorticoids cause hypercalciuria. Thiazides and dietary sodium restriction both reduce urinary calcium excretion, and may have a favorable effect on calcium homeostasis in patients receiving glucocorticoids. A study investigating the effect of thiazide diuretics and dietary sodium restriction on calcium

metabolism in patients taking glucocorticoids suggested that this regimen may have a beneficial effect on calcium balance in patients receiving glucocorticoids by decreasing the fractional excretion of calcium and increasing intestinal calcium absorption [37]. However, their effect on bone density is uncertain. A meta-analysis attempting to explore this uncertainty indicated that current thiazide users have a 20% reduction in osteoporotic fracture risk and that use of long-term thiazides may also reduce osteoporotic fracture risk by 20%, but short-term use has not been shown to be protective against osteoporotic fracture [38]. Thiazides and sodium restriction can be considered in patients with substantial hypercalciuria or hypertension.

The American College of Rheumatology recommendations for prevention of glucocorticoid-induced osteoporosis [18]

- Candidates for therapy:
  - Patients initiating glucocorticoids (prednisone equivalent of 5 mg/day or higher) with plans for treatment for more than three months
  - Patients taking long-term glucocorticoids (prednisone equivalent of 5 mg/day or higher)
- Guidelines:
  - Modify lifestyle risk factors (avoiding smoking and excess alcohol, weight-bearing exercises).
  - Initiate Calcium (1000 to 1500 mg/day) and Vitamin D (800 IU/day) supplementation.
  - Prescribe bisphosphonates (use with caution in premenopausal women because of insufficient data on the potential for harm to the fetus in women who become pregnant while currently or recently receiving bisphosphonates).
  - Replace gonadal sex hormones if deficient.
  - Consider calcitonin as second-line agent if bisphosphonates are contraindicated or not tolerated.
  - In patients on long-term glucocorticoids (prednisone equivalent of 5 mg/day or higher), measure bone mineral density (BMD) at lumbar spine and/or hip at the initiation of glucocorticoid therapy. If T-score is below −1, then prescribe bisphosphonate or calcitonin. Repeat bone densitometry every year as long as glucocorticoid therapy continues.

Myopathy—Glucocorticoids use can cause myopathy by direct catabolic effect on skeletal muscle via activation of the glucocorticoid receptor [39–40]. Blockade of the glucocorticoid receptor has been shown to prevent myopathy in the rat [39]. Subjects with glucocorticoid-induced myopathy typically present with proximal muscle weakness and atrophy in both the upper and lower extremities. The onset of symptoms is usually subacute and over several weeks or months. Higher doses of glucocorticoids are associated with earlier onset of symptoms [41]. The diagnosis of glucocorticoid-induced myopathy is one of exclusion. The symptoms improve within three to four weeks after reduction in glucocorticoid dose and resolves after discontinuation of glucocorticoids [42]. Moderate exercise has also been demonstrated to attenuate glucocorticoid-induced muscle atrophy [43].

Critical illness myopathy, the most common form of intensive care unit (ICU)-acquired myopathy, has been attributed in part to IV glucocorticoids. An interaction between

glucocorticoids and neuromuscular blocking agents, which are widely used in ICU, appears to be involved. The occurrence and severity of myopathy is correlated with glucocorticoid dose [44–47]. The most common presenting symptoms of critical illness myopathy include flaccid quadriparesis and difficult weaning from mechanical ventilation [45–46]. The onset of symptoms is typically acute and over several days. Critical illness myopathy is associated with increased mortality, prolonged ventilator dependence, and prolonged ICU stays. Treatment of critical illness myopathy includes discontinuation or reduction of glucocorticoids and aggressive management of medical comorbidities. Symptoms usually improve over weeks to months; however, severe necrotizing myopathy may never recover [48].

Avascular necrosis—Glucocorticoids are a common cause of avascular necrosis, particularly in the femoral head. The overall incidence of glucocorticoid-induced avascular necrosis is low. The mechanism by which glucocorticoids cause avascular necrosis is not fully understood. A study proposed that glucocorticoids induce damage in venous endothelial cells, leading to stasis, increased intraosseous pressure, decreased arterial perfusion and finally, infarction of the bone [49]. Direct toxic effect on bone cells and increased osteocyte apoptosis may also contribute to glucocorticoid-induced avascular necrosis [50].

The incidence of avascular necrosis appears to increase with increasing glucocorticoid dosage and duration. However, low doses and short-term therapy can also cause avascular necrosis. In one prospective study, mean daily prednisone dose in the highest month of therapy was higher than 40mg/day in 93% and higher than 20 mg/day in all patients with avascular necrosis [51]. Another study investigating the relationship between glucocorticoid therapy and occurrence of avascular necrosis in patients with systemic lupus erythematos(i)us (SLE) suggested that the initial dose may be more important than the total dose or duration of therapy [52]. The glucocorticoid dose during the initial period of therapy in 17 SLE patients who developed avascular necrosis was compared with that of 25 SLE control patients. The dosage of glucocorticoids used in the first one, three, and six months of therapy was substantially higher in the patients with avascular necrosis than in the control patients. The duration of therapy was not found to correlate with avascular necrosis. Total glucocorticoid dosage was virtually identical in both groups.

Alcohol, antiphospholipid antibodies, SLE, sickle cell hemoglobinopathies, renal transplantation, gout, HIV infection, hypercoagulable states, and trauma have been also associated with increased risk of avascular necrosis.

Subjects with avascular necrosis typically present with pain in the affected joint and mostly late in the disease course.

Initial physical findings are largely nonspecific and may include tenderness around the affected bone and limitation of the range of motion. Physical findings depend on the location of the affected bone. Patients with advanced avascular necrosis of the hip may present with a limp [53]. A small proportion of patients with avascular necrosis may be asymptomatic.

Plain film radiographs, bone scanning, and magnetic resonance imaging (MRI) are helpful means of diagnosing avascular necrosis. MRI is much more sensitive than conventional radiographs and bone scanning.

Initial treatment includes bed rest or partial weight bearing activities. Nonsteroidal or other analgesics can also be used to relieve pain. If conservative management fails, additional

therapeutic options can be used that include core decompression, joint replacement, and osteotomy.

Because early diagnosis of avascular necrosis and appropriate intervention can prevent or delay progression of the disease and the need for joint replacement, a high index of suspicion is necessary particularly for those subjects with risk factors including high dose glucocorticoid use. It's recommended that patients be evaluated for joint pain and decreased range of motion at each visit and also be instructed to report these findings.

Endocrine and metabolic

Serum lipids—Serum lipids may increase during glucocorticoid therapy. The mechanism behind this hyperlipidemia is not known in detail. One study concluded that hyperlipidemia in glucocorticoid-treated patients may be partly due to glucocorticoid-induced reduction in ACTH release [54]. In this study, administration of ACTH for three weeks in nine hyperlipidemic glucocorticoid-treated patients with kidney disease led to a 20 to 50% reduction in the serum concentrations of triglycerides, total and LDL cholesterol and a 10 to 25% increase in HDL cholesterol.

However, results of some prospective studies have suggested that glucocorticoids may not have an adverse effect on serum lipids. In one study, for example, prednisone therapy (20 mg/day tapered to 5 mg/day during three months) had no significant adverse effect on serum lipids after adjustment for other risk factors [55]. Another study examining the relationship between glucocorticoid use and lipid profile, using the data from 15004 participants in the Third National Health and Nutrition Examination Survey, suggests that glucocorticoid therapy may be associated with a favorable lipid profile in patients ages 60 years and older [56]. It was noted that steroid therapy was associated with a higher serum HDL cholesterol level and a lower ratio of total-to-HDL cholesterol in those ages 60 years or older (multivariate difference 9 mg/dl [95% CI 3.9, 14.1] and −0.6 mg/dl [95% CI −0.9, −0.3], respectively).

Serum glucose—Glucocorticoids decrease glucose utilization and increase hepatic glucose production, leading to hyperglycemia. Although hyperglycemia is a known side effect of glucocorticoids, development of frank diabetes in a previously normal patient is uncommon [57]. Hyperglycemia is exacerbated in patients with pre-existing diabetes or glucose intolerance while taking glucocorticoids and the degree of exacerbation is proportional to the pre-existing status of glucose tolerance.

In a case-control study quantifying the risk of developing hyperglycemia requiring hypoglycemic therapy after oral glucocorticoid use, the estimated relative risk in patients taking glucocorticoids was 2.23 (95% CI, 1.92 to 2.59) in comparison with nonusers [58]. The risk increased proportionally with increasing glucocorticoid dose. Diabetes syndrome occurring after glucocorticoid therapy may be improved by the reduction of glucocorticoid dosage and may be reversed by stopping glucocorticoid treatment over many months [59].

Cardiovascular

Use of oral glucocorticoids is associated with adverse systemic effects; including hypertension, hyperglycemia, and obesity that may increase the risk of ischemic heart disease and heart failure. In a population based case-control study, 50656 patients with ischemic heart disease, ischemic stroke or transient ischemic attack, or heart failure were matched to an equal number of controls by sex, age, general practice, underlying disease, and calendar time [60]. There was a significant association between current glucocorticoid use and an increased risk of heart failure (adjusted OR 2.66, 95% CI 2.46–2.87) and a

smaller increased risk of ischemic heart disease (OR 1.20, 95% CI 1.11–1.29), but not ischemic stroke or transient ischemic attack. The association was stronger for current compared to recent or past use. Among current users, the association was stronger at higher doses, although the dose-response relation was not continuous.

Similar findings were noted in another population-based study that investigated the association between glucocorticoid therapy and the increased rate of subsequent cardiovascular disease [61]. After adjustment for known covariates, the rate of cardiovascular events was significantly higher in patients receiving high-dose glucocorticoids compared to nonusers (absolute risk difference 6.9 events per1000 person-years [CI, 6.0 to 7.7]; adjusted relative risk for a cardiovascular event in patients who were prescribed high doses of glucocorticoids 2.56 [CI, 2.18 to 2.99]). However, because the data used in this study was observational, extracted from a computerized database, residual confounding (e.g. smoking) is a potential issue that can't be excluded.

Pulse glucocorticoid therapy has been used in dermatology to treat severe inflammatory disorders. Serious adverse cardiovascular events, including sudden death, have been occasionally reported. In a literature review regarding serious adverse effects of pulse glucocorticoid therapy, it was noticed that these events were rare and have been mainly reported in patients with underlying kidney or heart disease [62]. These acute cardiovascular complications are believed to result from electrolyte shifts during a rapid rate of infusion. In addition, it was not clear whether these adverse events were due to glucocorticoid therapy or the underlying condition. Continuous cardiac monitoring is therefore indicated in patients with significant cardiac or kidney disease but a clear recommendation for other patients cannot be made without a prospective trial. To minimize the risk of acute cardiovascular complications, long infusion time (2–3 hours) is recommended [63].

Central nervous system

Behavioral and cognitive changes—Many psychiatric side effects have been noted with glucocorticoid administration such as alterations of mood, memory deficit, or even psychosis. Taking a comprehensive medical history before starting glucocorticoids is crucial, since glucocorticoids may also exacerbate pre-existing psychiatric disorders.

In a prospective study, 50 ophthalmologic patients receiving high doses of glucocorticoids had their psychopathology assessed before and after therapy [64]. About 30% of the patients experienced hypomania, and about 10% of them experienced depression. Those symptoms began on average one week following the initiation of therapy. Lithium has been successfully used for both prophylaxis and management of prednisone-related affective disorders [65]. Family history of depression or alcoholism has been reported as risk factors for developing affective disorders in patients taking glucocorticoids [66].

Daily split-dose therapy interferes with the normal diurnal production of cortisol, and may cause sleep disturbances such as insomnia and unpleasant dreams [67]. Glucocorticoid related insomnia may be relieved by the administration of glucocorticoids as a single morning dose, or regular night-time administration of sedative-hypnotics or drugs with sedative side effects.

In a study investigating the effects of glucocorticoid treatment on memory, hippocampal-dependent explicit memory tests were performed in 25 patients with systemic disease without CNS involvement taking prednisone doses of 5 to 40 mg daily for at least one year and 25 matched controls [68]. The glucocorticoid treated patients performed worse than the control group on explicit memory tests. Multiple regression analyses showed that elderly

patients are more prone to memory disturbance with less protracted treatment. Memory disturbances began about three months following the initiation of treatment.

Psychosis has been reported with doses of 20 mg/day for a prolonged period [69]. In 90% of patients, symptoms are reversible with reduction of glucocorticoid dose; 10% require antipsychotic drug treatment. Lithium carbonate has been reported to be successful in the prophylaxis of glucocorticoid-related psychosis. A prospective cohort study of patients with systemic lupus erythematosus suggested that low serum levels of albumin are predictive of glucocorticoid-induced psychosis [70].

Gastrointestinal

The use of systemic glucocorticoids is associated with gastrointestinal side effects including gastritis, peptic ulceration, and gastrointestinal hemorrhage. Although glucocorticoids have been shown to increase the risk of peptic ulceration and GI bleeding, the shown effect could in part due to concomitant use of non-steroidal anti-inflammatory drugs [71–73]. The synergistic increase in the incidence of peptic ulcer disease associated with combined use of glucocorticoids and NSAIDs suggests that physicians need to be cautious when prescribing this drug combination. Additional risk factors including advanced age and previous history of gastrointestinal events should also be considered.

Acute pancreatitis is another GI complication that has been occurred in glucocorticoid users [74]. However, a recent study suggested that glucocorticoid use does not appear to be the etiological agent in causing acute pancreatitis [75].

Conclusion

Systemic glucocorticoids are widely used to treat autoimmune and inflammatory skin diseases. The prolonged use of glucocorticoids, however, is associated with potentially serious adverse effects. Many of these side effects are potentially minimized by careful monitoring and using appropriate preventive strategies. As dermatologists, we can make patients aware of these data and help them decide which prevention/treatment options are best for them. In this article we have discussed the existing knowledge in the prevention and treatment of some of the major glucocorticoid-induced side effects involving musculoskeletal apparatus, endocrine system, cardiovascular system, central nervous system, and gastrointestinal tract. Glucocorticoid-induced bone loss is one of the most serious side effects associated with prolonged high-dose glucocorticoid therapy. The prophylaxis of osteoporosis should be started early during glucocorticoid therapy. Calcium and vitamin D supplementation is the most appropriate initial strategy to prevent bone loss in all patients. Bisphosphonates are a class of drugs that are approved by the FDA for preventing and treating glucocorticoid-induced osteoporosis. Treatment with these agents could be warranted if bone mineral density studies reveal a T-score of less than −1 or in patients on long-term therapy with high-dose glucocorticoids. Table 1 provides useful information regarding dose and administration of the most commonly used bisphosphonates.

Questions

1. Which is not true regarding the glucocorticoid-induced osteoporosis?
    a. The glucocorticoid-induced bone loss is dose-dependent and patients taking higher doses have significantly increased risk
    b. Low-dose glucocorticoid replacement therapy does not decrease bone mineral density
    c. Alternate-day glucocorticoid therapy can produce osteoporosis

d. In all individuals on glucocorticoid therapy, general principles include avoiding smoking and excess alcohol, and weight-bearing exercises

2. Which are reported side effects associated with intravenous bisphosphonates?

a. Dry mouth, blurred vision

b. Sexual dysfunction, weight changes

c. Flu-like symptoms, hypocalcemia

d. Anxiety/agitation, darkening of the skin color

3. A 36-year-old African-American woman presents to your office with chronic discoid skin lesions. She has been recently diagnosed with systemic lupus erythematosus and started on long-term glucocorticoid therapy. Which of the following is the most appropriate initial strategy to prevent bone loss in this patient?

a. Risedronate

b. Calcium and vitamin D

c. Calcitriol

d. Calcitonin

4. Which of the following agents can be considered in postmenopausal patients who have pain-causing fractures due to its ability to reduce bone pain?

a. Risedronate

b. Calcium and vitamin D

c. Calcitriol

d. Calcitonin

5. Glucocorticoids use has been associated with all of the following items except for?

a. Hypocalciuria

b. Reduction in bone formation

c. Increase in bone resorption

d. Reduction in serum sex hormone levels

e. Hypertension

6. Glucocorticoid-induced avascular necrosis most commonly occurs on which body site?

a. Knee

b. Hip

c. Elbow

d. Wrist

7. Which of the following psychiatric side effects has been noted with glucocorticoid use?

a. Hypomania

b. Memory disturbance

c. Depression

d. Psychosis

e. All of the above

8. Choose the answer that best describes the approach to a patient with glucocorticoid-induced myopathy.

a. MRI is the definitive diagnostic test for glucocorticoid myopathy.

b. EMG is the definitive diagnostic test for glucocorticoid myopathy.

c. Muscle biopsy is the definitive diagnostic test for glucocorticoid myopathy.

d. The diagnosis of glucocorticoid myopathy is one of exclusion

9. A 59-year-old Caucasian woman comes to your office with localized discoid skin lesions on her face. She had her menopause six years ago. She has been on 10mg/day prednisone for lupus arthritis for the past year. Which of the following therapeutic regimens is preferred to prevent bone loss in this patient?

a. Calcium and vitamin D plus risedronate, 150 mg once monthly (oral)

b. Calcium and vitamin D plus alfacalcidiol, 1 mg once monthly (oral)

c. Calcium and vitamin D plus risedronate, 5 mg once daily (oral)

d. Calcium and vitamin D alone

10. Which is true regarding the acute cardiovascular complications associated with pulse glucocorticoid therapy?

a. The acute cardiovascular complications are believed to result from electrolyte shifts during a rapid rate of glucocorticoid infusion

b. Continuous cardiac monitoring is indicated in patients with significant cardiac or kidney disease

c. To minimize the risk of acute cardiovascular complications, long infusion time (2–3 hours) is recommended

d. All of the above

Answers

1 b; 2 c; 3 b; 4 d; 5 a; 6 b; 7 e; 8 d; 9 a; 10 d

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Table 1

Bisphosphonates: Dosing, administration

Drug Name	Dosing: Prevention	Dosing: Treatment
Alendronate	5 mg/day (oral) 35 mg once weekly (oral)	5 or 10 mg/day (oral) 35 or 70 mg once weekly (oral)
Risedronate	5 mg/day (oral) 35 mg once weekly (oral) 150 mg once monthly (oral)	5 mg/day (oral) 35 mg once weekly (oral) 150 mg once monthly (oral)
Ibandronate	2.5 mg/day (oral) 150 mg once a month (oral)	2.5 mg/day (oral) 150 mg once a month (oral) 2–3 mg every three months (IV)
Pamidronate	Single doses should not exceed 90 mg (IV)	Single doses should not exceed 90 mg (IV)
Zoledronic acid	5 mg every 12 months (IV)	5 mg every 12 months (IV)