



Management of patients on chronic glucocorticoid therapy: an endocrine perspective

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In the 1930s, Henry Mason with others, isolated several steroid hormones from the adrenal cortex, with particular interest focused on one identified as “compound E,” later named *cortisol*. Within 10 years, Hensch et al [1] began to use cortisol as a treatment for patients with severely debilitating rheumatoid arthritis. Patients who had been incapacitated because of their disease experienced dramatic improvements, often within days. Newsreels dramatically depicted crutches being tossed away. As this information rapidly gained worldwide attention, just 1 year after the investigators published their results, Hensch, along with Kendall and Reichstein, was awarded the Nobel Prize for “discoveries relating to the hormones of the adrenal cortex, their structure and biological effects.”

Unfortunately, the side effects of glucocorticoid treatment became only too apparent with long-term use. Despite this disadvantage, glucocorticoids remain a mainstay of therapy for many inflammatory conditions and immunomodulators requiring therapeutic protocols. As recently as 1998, a survey of patients in the American Rheumatism Association Medical Information System database showed that 50% of patients were on long-term glucocorticoid therapy [1], so the challenge of how best to treat or to prevent the side effects of glucocorticoids continues.

The side effects of glucocorticoids can be divided into three categories [2]: immediate, gradual, and idiosyncratic. To what degree these side effects occur varies from one individual to the next but also varies by dose, duration of therapy, and to some extent, the particular type of glucocorticoid

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being used. The more immediate effects include fluid retention; blurriness of vision (likely related to pressure changes in the anterior chamber); mood changes, such as euphoria; insomnia; weight gain; and immune response modulation. More gradual effects are those specific to endocrine metabolism, specifically hyperglycemia, often referred to as *steroid diabetes*; osteopenia, leading rapidly to osteoporosis; dyslipidemia (particularly hypertriglyceridemia), with a proatherogenic effect not entirely explainable by the changes in low-density or high-density cholesterol or triglycerides; central obesity; and adrenal suppression. Additionally, acne, skin thinning with easy bruisability, and dyspepsia are typically gradual in onset. More idiosyncratic side effects include avascular necrosis, cataract formation, open angle glaucoma and psychosis.

Case management

A 54-year-old postmenopausal woman presents for evaluation of a rash, myalgias, and arthralgias. Medical evaluation reveals a diagnosis of systemic lupus erythematosus, and glucocorticoid therapy is indicated owing to renal involvement. Glucocorticoid therapy is started at 1 to 2 mg/kg/d, and the patient's condition improves. Whenever the practitioner begins to taper the dose, however, the lupus flares. Suspecting that the patient needs long-term glucocorticoid therapy, the practitioner considers how to monitor the potential implications of this therapy. In questioning the patient further, she reports a family history of type 2 diabetes mellitus in her mother and maternal grandmother. The practitioner reviews her last glucose result, which was obtained on a random draw before glucocorticoid therapy was started, and it was 150 mg/dL. The practitioner begins monitoring randomly drawn glucose levels with each month's chemistry tests.

Hyperglycemia

Glucocorticoids are the most common cause of drug-induced diabetes mellitus [3]. Not everyone treated with glucocorticoids develops diabetes, however. Predictors of development of diabetes are age, weight, family history of diabetes mellitus, or a personal history of gestational diabetes. There is evidence that patients with decreased insulin secretory reserve are much more likely to develop diabetes [4]. Abnormal glucose tolerance occurs in up to 90% of patients with Cushing's syndrome, but only 10% to 29% of these patients develop frank diabetes mellitus [5], suggesting that the dose of glucocorticoid may be another factor in the development of steroid diabetes. Diabetes from topical steroid use is uncommon, but high-dose steroids have been associated with significant hyperglycemia, including development of hyperglycemic hyperosmolar syndrome [6] and even diabetic ketoacidosis in patients with type 1 diabetes mellitus [7].

Several mechanisms contribute to the development of hyperglycemia and steroid-induced diabetes, including decreased peripheral insulin sensitivity, increased hepatic glucose production, and inhibition of pancreatic insulin

production and secretion [8–10]. As the glucocorticoid dose is tapered and these effects return to a more typical baseline, steroid-induced diabetes can be expected to resolve. This outcome does not always occur, however, so all patients taking high-dose glucocorticoids should be monitored throughout their therapy for the development and persistence of hyperglycemia.

Routine blood glucose monitoring should be initiated when a random glucose level of more than 180 mg/dL is noted on more than one blood chemistry check in the presence or absence of symptoms associated with hyperglycemia. As a tool, self-monitoring of blood glucose (SMBG) continues to be increasingly easier, and many glucose meters are small, allowing them to be easily carried to work or to any location outside the home. Other improvements make current meters much more usable for any individual, despite barriers of dexterity, mechanical ability, or comfort. Some meters contain internal strips used for blood processing and lancing devices to facilitate use. New meters on the market require as little as 1 μ L of blood, because an amount similar to the area of the head of a pin and alternative sites to finger tips for blood now are used widely. Expense still can be a barrier, however. Yet SMBG should be encouraged for all patients with hyperglycemia, because they need to know their glucose level to be able to follow, and potentially adjust, an implemented treatment plan. When considering treatment, keeping glucose levels less than 180 mg/dL minimizes glycosuria, polyuria, polydipsia, and electrolyte imbalance. In turn, this level of control should prevent volume depletion and calorie loss and diminish the infection risk associated with hyperglycemia [11].

The treatment of glucocorticoid-induced diabetes typically requires insulin. Diet alone has been recommended, as have oral agents, although published data regarding efficacy remain elusive. Although smaller doses of glucocorticoid potentially could allow for a therapeutic response to oral agents, the doses required for most current therapeutic uses induce more potent insulin resistance than is amenable to noninsulin therapy. The typical pattern of hyperglycemia is a minimal increase in fasting glucose but an exaggeration of postprandial glucose, with insensitivity to exogenous insulin. One- to two-hour postprandial glucose levels, drawn initially on a weekly basis, can be used as a screening tool. This frequency can be decreased as the steroid dose is tapered.

Insulin therapy is directed primarily to prandial coverage. It should be based on the patient's weight, calories consumed at mealtime, and meal pattern. Compared with patients who have type 1 or type 2 diabetes mellitus, patients who have steroid-induced diabetes often require only prandial insulin [8,12]. With higher doses of steroids or in the patient with pre-existing diabetes, basal insulin is needed, but typically this amount is only 30% of the total daily insulin need (versus 50% for usual diabetes dosing). Glucose toxicity or hyperglycemia-induced resistance to insulin also might result in higher insulin dosing needs at the onset of therapy; once glucose levels are controlled, patients often need less insulin [13].

The shorter-acting insulins are the prandial insulins of choice, and of these insulins, regular insulin is the recommended short-acting insulin when initiating prandial therapy. Once a blood glucose pattern and a meal regimen have been established for an individual, the provider can re-evaluate the optimal insulin type for a particular patient. Regular insulin generally is recommended for people consuming between-meal snacks, high-protein or high-fat meals, or those who may have delayed gastric emptying. Regular insulin should be given 20 to 30 minutes before meals. The rapid-acting insulin analogues (currently, lispro and aspart) are more appropriate for the person who does not snack between meals and consumes more carbohydrate-based meals. Lispro or aspart should be injected 10 to 15 minutes before a meal. An additional dose might be required for a between-meal snack. These insulins are particularly useful for children, in whom food intake is not always predictable. In such situations, rapid insulin may be administered immediately after the meal is finished.

At the author's institution, it has been found that a practical initial insulin dose is 0.1 U/kg/meal. For high doses of steroid (ie, >60–80 mg of prednisone per day), this amount might underestimate insulin need, but the dose base can be adjusted rapidly, if needed, after a review of glycemic response and the amount of supplemental insulin needed during the first several days of insulin therapy. Supplemental insulin is a correction dose of insulin that is used to correct for pre-meal hyperglycemia. Initially, the recommendation is that for every 50 mg/dL of glucose level greater than 200, an additional 0.04 U/kg/meal of insulin is added to the base. If the patient consistently has to correct for pre-meal hyperglycemia, however, then the dose for the preceding meal should be increased. As an example, if the patient consistently is using a dose of 6 U of regular insulin as a base for meals, yet also is supplementing consistently with an additional 2 U of insulin at lunch, then a new base of 8 U should be considered for breakfast.

Supplemental insulin given for the correction of pre-meal glucose should be given as 0.04 U/kg/meal for glucose levels of 200 to 300 mg/dL and 0.08 U/kg/meal for levels greater than 300 mg/dL, but if glucose levels higher than 300 mg/dL recur, the patient should be instructed to notify his or her designated provider. For example, if a 70-kg person finds his or her pre-supper glucose level to be 259 mg/dL, the calculated dose of prandial insulin is 7 U (0.1 U/kg) + 3 U (70 kg × 0.04 U/kg/meal) = 10 U total.

In some patients, fasting glucose levels also become abnormal. This effect can be seen if the corticosteroid is dosed twice daily, the patient's dose (even on a once-daily regimen) is a high one, or the patient has diminished pancreatic insulin reserve. If the fasting glucose level is greater than 200 mg/dL on at least two consecutive mornings, neutral protamine Hagedorn (NPH) insulin should be initiated at bedtime, at a dose of 0.1 U/kg. The patient should be instructed to check his or her glucose level between 2 to 3 AM to evaluate for hypoglycemia. Insulin glargine can be used as an alternative to NPH insulin, particularly if nocturnal hypoglycemia is present, although

this method might require readjustment of prandial dosing. Patients with inconsistent oral caloric intake may not be appropriate candidates for intermediate-acting insulin, because the risk of hypoglycemia is significant.

The use of bedtime intermediate-acting insulin is preferred to pre-dinner dosing due to a lower risk of nocturnal hypoglycemia [15,16]; however, if a glucose level greater than 300 mg/dL persists that is not amenable to an increase in pre-dinner insulin dosing, a supplement dose of 0.04 U/kg can be recommended for glucose levels of 300 to 400 mg/dL, and a dose of 0.08 U/kg can be recommended for levels greater than 400 mg/dL. The patient should notify his or her provider of this level, however, if a repeat glucose test remains elevated 2 hours later or if hypoglycemia is noted.

Morning NPH insulin typically is not indicated, because high pre-dinner glucose levels should be treated through an increase in base regular insulin at lunch. Exceptions to this rule are children, in whom NPH insulin divided into AM and PM doses might reduce the need for supplemental insulin (and therefore decrease the overall injection frequency). Also, in those patients using the very fast-acting analogues, such as lispro and aspart, morning NPH insulin might provide a better basal level of insulin during the day. Premixed insulins, such as 70% NPH/30% regular, 75% NPL/25% lispro or 70% NP/30% aspart might be alternative insulins for the patient receiving low-dose steroid treatment. These insulins, when used twice a day, frequently do not provide optimal glycemic control in the post-lunch period without pre-meal supplement [14].

Hypoglycemia may be defined as a glucose level less than 70 mg/dL in the typical corticosteroid-treated patient. The target level for the definition of hypoglycemia depends on the patient's overall well-being, his or her current medical status, and age. Recommended treatments for hypoglycemia are 4 to 6 oz of fruit juice, six to seven hard candy pieces, one cup of milk, or three to four glucose tablets. Blood glucose level should be checked 15 to 20 minutes later, with re-treatment as needed. If the next meal is more than an hour away, then a small combined carbohydrate-protein snack should be ingested after the above-described treatment; for example, one half of a meat sandwich and six crackers with 1 oz cheese. Subcutaneous glucagon rarely is needed, although its administration should be taught routinely to patients and their caregivers whenever insulin therapy is initiated.

Just as insulin might need to be added, its amount typically needs to be decreased as steroid doses are tapered, with intermediate insulin being the first that should be discontinued, then prandial. Alternate-day steroid regimens can be challenging with regard to insulin dosing needs, because the "off" days require a significant decrease in dose, if not frank cessation of insulin, to prevent hypoglycemia.

Although nutritional therapy needs to be individualized for each patient, encouragement of limitation of oral carbohydrate intake to 45 to 50 g per meal can provide a target of carbohydrate intake that allows for less variability in glucose response to the insulin dose given from 1 day to the

next day. The appetite stimulus and increased intake from glucocorticoid therapy, particularly in the evening hours, may necessitate intermittent evening-insulin supplements.

In further assessing the risks of long-term glucocorticoid therapy this reveals that her mother sustained a hip fracture at age 65 that resulted in the need for nursing-home placement. The patient also underwent a surgically induced menopause at age 48, after which she declined estrogen therapy. The practitioner orders a bone densitometry test.

Osteoporosis

Bone loss resulting in fractures is the most incapacitating problem of long-term glucocorticoid therapy [17,18]. It is suspected that long-term steroid therapy may cause or exacerbate osteoporosis and lead to excess fractures in up to 50% of patients [19,20], although the true incidence is unknown. Few studies have compared bone loss in patients who have received glucocorticoid therapy with patients having the same underlying disease process but no glucocorticoid therapy. Cross-sectional studies in patients with rheumatoid arthritis, sarcoidosis, vasculitides (such as giant cell arteritis, systemic lupus erythematosus), or asthma, and in patients undergoing organ transplant, however, show lower bone mass in patients treated with glucocorticoids than those who did not receive this therapy [21–28].

Longitudinal studies show that the most rapid bone loss occurs in the first 6 months after initiation of glucocorticoid therapy [24], with subsequent loss being slower but continual. Also, a relationship has been demonstrated between the rate of bone loss and the dose of glucocorticoid used for treatment [22,29]. Doses as low as 7.5 mg/d have been associated with bone loss. It is unclear whether cumulative steroid dose correlates to more bone loss, with one study suggesting this relationship at doses of more than 12.5 mg/d [30], whereas another study did not describe this relationship [31]. Even inhaled steroids have an effect on bone, because they decrease serum levels of osteocalcin, a marker of bone formation [32,33], and a single dose of 2.5 mg of prednisone prevents the nocturnal rise in osteocalcin [34], suggesting that even small doses of steroids have metabolic bone effects.

The osteoporosis of glucocorticoid therapy is attributable to several metabolic changes. Gonadal hormone function is altered through inhibition of pituitary gonadotrophin secretion and therefore inhibition of estrogen and testosterone production. Suppression of adrenal androstenedione further contributes to decreased circulating gonadal hormone levels [25]. Mineral metabolism is affected through a classic model of decreased intestinal calcium absorption, with then-increased compensatory secretion of parathyroid hormone. Although not all studies support this calcium model, when glucocorticoids are given acutely [35,36], with dosages greater than 20 mg/d over 14 days, there is decreased intestinal calcium absorption, increased renal calcium excretion, increased parathyroid hormone secretion,

increased bone resorption, and decreased bone formation [25,37]. Glucocorticoids can exert a direct effect on bone, with inhibition of osteoclast cell numbers, lifespan, and function [38,39]. Overall, the primary effect is inhibition of bone formation.

The risk factors for osteoporosis with glucocorticoid therapy are not the same as those typically associated with osteoporosis. Men and women of all ethnic backgrounds and ages are at risk for glucocorticoid osteoporosis; however, some evidence exists that young adult men lose bone more rapidly than older men, or premenopausal or postmenopausal women. Regardless, fracture risk remains highest in postmenopausal women, presumably owing to lower bone mass at initiation of therapy [40]. A cross-sectional study in postmenopausal women found that the risk factors for steroid-induced osteoporosis included duration of steroid use but also age and body mass index [41].

Assessment of bone density is typically through the use of dual-energy x-ray absorptiometry (DEXA). Although DEXA measures a combination of trabecular and cortical bone, and trabecular bone is lost more rapidly than cortical bone in glucocorticoid-induced bone loss, it is more easily accessible than quantitative CT (which does measure trabecular bone more directly); it is less expensive; and it is associated with less radiation exposure [25]. If only one site can be measured, it should be the lumbar spine in women and men younger than 60 years but the femoral neck in older individuals to minimize the potential effect of osteophyte formation at vertebral bodies affecting density readings. DEXA of the spine in the lateral position may be a more sensitive indicator of glucocorticoid-induced bone loss than the anteroposterior position [30,42]. Ideally, DEXA should be performed before the initiation of glucocorticoid therapy or soon thereafter. The optimal interval for follow-up DEXAs remains unclear; most recommend repeating them at yearly intervals [42]. Additional recommendations include measuring initial urinary calcium to assess risk for secondary hyperparathyroidism, measuring vitamin D levels to assess for deficiencies of this vitamin before treatment, and measuring serum osteocalcin levels for the assessment of osteoblast activity [25,33]; however, more data are needed before routine measurements can be justified.

The prevention and treatment of glucocorticoid-induced bone loss include nonpharmacologic and pharmacologic approaches. Clearly, the lowest dose for the shortest interval of therapy should be used. Alternate-day steroid administration does not protect against bone loss [43]. Weight-bearing exercise, fall prevention (including improvement of balance in the debilitated or elderly), smoking cessation, and limitation of alcohol intake should be recommended. Calcium and vitamin D supplementation recommendations include 400 IU/d of vitamin D (as 25-hydroxyvitamin D) and approximately 1500 mg of calcium (dietary or supplement) as can be titrated to acceptable levels of urinary calcium [42]. Sodium restriction can decrease urinary calcium excretion. Thiazide diuretics, with sodium restriction, can

improve intestinal absorption of calcium and further decrease urinary calcium loss [44].

The mainstays of glucocorticoid-induced bone loss prevention and treatment are the bisphosphonates. Cyclic etidronate, 400 mg/d for 2 weeks every 3 months, has been shown to prevent bone loss at initiation of glucocorticoid therapy, increase bone density over time, and decrease fracture incidence [45,46]. Alendronate, 10 mg daily, increases bone mineral density, decreases fracture rate [47], and is well tolerated by glucocorticoid-treated individuals. If gastrointestinal side effects make oral bisphosphonates difficult to use, intravenous pamidronate also increases lumbar and, to a lesser extent, hip bone mineral density [48], and has the additional advantage of needing to be given only every 3 months. A typical dose is 60 mg as an intravenous infusion over 3 to 4 hours.

Gonadal hormones have been shown to be protective of bone density in glucocorticoid-treated men and women when initial gonadal deficiency is present. A small crossover study described 15 men with glucocorticoid-treated asthma and initial low serum testosterone who were treated with testosterone over a 12-month period. An 8% gain was noted in lumbar spine bone mineral density, although this effect was not seen at the hip [49]. Muscle mass also improved, potentially decreasing fracture risk independently. Similarly in women, hormone replacement therapy was beneficial, although results from various studies suggest that there may be, at best, no additional loss of bone density with hormone replacement therapy and glucocorticoid combined use (as compared with only hormone replacement therapy), but no actual increase in bone mineral density [50]. Anabolic steroids and medroxyprogesterone (the latter in men), also have been shown to be beneficial, but side effects may make these therapies impractical [51,52]. Calcitonin, whether given subcutaneously or nasally, can protect against glucocorticoid-induced bone loss. Whether this effect can be translated to decreased fracture risk remains unclear, because bone mass does not seem to increase [53].

The patient reports concerns regarding her cholesterol, because she just found out that her brother has had emergency coronary bypass surgery at age 52, and his cholesterol level has been reported as “high.” She also read on the Internet that her prescribed prednisone regimen can be associated with elevations in baseline cholesterol. How should the practitioner advise her?

Dyslipidemia

Healthy men given a dose of 0.35 mg/kg/d of prednisone for 15 to 28 days showed a 22% increase in high-density lipoprotein cholesterol (HDL-C) and a 40% increase in triglycerides, but no change in low-density lipoprotein cholesterol (LDL-C) [54]. A short study of the effects of 10 mg of prednisone

3 times daily for just a week showed a 27% increase in HDL-C and no change in triglycerides or LDL-C [55]. Such studies suggest that glucocorticoids have a dose and duration effect on lipid values; however, the effect on lipids in patients treated with glucocorticoids after transplant or for inflammatory disease can be variable. For example, 40% to 50% of patients after renal transplant have normal lipid values [56,57]. In glucocorticoid-treated patients with localized inflammatory disorders such as uveitis, pemphigoid, and exophthalmos, a 20% increase in LDL-C was seen, with an increase of up to 67% in HDL-C but an insignificant 10% to 20% increase in triglycerides, and this change was seen only in women [58]. Patients with systemic inflammatory disease such as systemic lupus erythematosus and patients taking prednisone showed triglyceride increases of up to 44%, with a total LDL-C increase of 20% [59,60].

Statin medications are the drugs of choice to lower LDL-C and have been shown to be effective in post-transplant patients on glucocorticoid therapy [61–63]. Fibrates and nicotinic acid can be used to target hypertriglyceridemia [64], although the latter remains controversial as to its effect on potentiating glucose intolerance in a patient population already on glucocorticoid therapy. Omega-3 fatty acids can be effective in lowering triglyceride levels and are safer in combination with a statin medication than fibrates or nicotinic acid [65].

The role that glucocorticoids play in proatherogenesis can be extrapolated best from patients with Cushing's syndrome, those who have lipid abnormalities, those with glucose intolerance or diabetes, and those with hypertension. In a 1952 review of hypercortisolemic patients, 5-year mortality was 50%, with 40% of deaths due to cardiovascular complications or renal insufficiency [66]. By 1961, the rate of cardiovascular deaths related more specifically to hypertension in Cushing's syndrome was down to 20% [67]. With improvements in the treatment of hypertension and atherosclerotic heart disease, the incidence of death for any reason in patients with treated Cushing's disease was 6% in 1979 [68].

Adrenal insufficiency

Suppression of the pituitary–adrenal axis occurs rapidly with exogenous glucocorticoid therapy. A single dose can be associated with a blunted response to a major stressor, such as surgery; however, this suppression is rarely evident for more than a few hours. When glucocorticoid therapy is continued for several days, the hypothalamic–pituitary–adrenal axis response is more impaired. Fifty milligrams of prednisone per day for 5 days has been associated with decreased responsiveness to insulin-induced hypoglycemia and adrenocorticotropin (ACTH) stimulation [69]. Generally, after 1 month of high-dose glucocorticoid therapy, steroid-withdrawal syndromes should be considered, and doses should be tapered. Longer-acting steroids such as dexamethasone result in more axis suppression than

shorter-acting steroids such as prednisone, cortisol, or prednisolone [70]. Symptoms of steroid withdrawal are adrenal insufficiency with lethargy, malaise, nausea, arthralgias, myalgias, headache, and fever. Postural hypotension may occur; vomiting is uncommon. The symptoms might be mild and resolve spontaneously in several days, or they may be disabling, requiring resumption of higher doses of glucocorticoid for several days before tapering at a slower rate.

Protocols for steroid taper should entail small, graduated dose decreases over increments of 1 to 2 weeks for those who have been on long-term therapy to prevent precipitating an exacerbation of the underlying disease process treated with glucocorticoid, for example, decreasing a prednisone dose by 1.0 to 2.5 mg per week. When a dose of 5 mg of prednisone or its equivalent is reached, an assessment of adrenal reserve is indicated. Sequential (monthly) basal morning cortisol levels can be helpful, with a level higher than 10 allowing rate discontinuation of glucocorticoid therapy [66]. Rapid ACTH testing (25 U of cortrosyn given by intravenous push followed by a cortisol check drawn 45 minutes later should yield a cortisol value >20 $\mu\text{g/dL}$) is a useful test of the pituitary–adrenal axis that is performed easily in an office setting [71].

Summary

Glucocorticoids continue to be a potent therapeutic tool for various medical conditions; however, their medication side effects pose challenges. Steroid diabetes is treated primarily with prandial insulin, either regular or the rapid insulins (lispro or aspart). Intermediate insulin is indicated less frequently, for fasting hyperglycemia. Osteoporosis is the most debilitating of potential glucocorticoid side effects, with bisphosphonates the mainstay of prevention and treatment. Dyslipidemia can range from mild to significant, but it responds to therapy similar to that of nonglucocorticoid-induced lipid disorders. Glucocorticoid-induced adrenal withdrawal syndrome can occur even with short courses of longer-acting glucocorticoid therapy, but it responds to adjustment of glucocorticoid dose. When tapering down to near-physiologic dose, pituitary–adrenal axis responsiveness should be checked before discontinuing steroid use.

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