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Glucocorticoid - Induced Osteoporosis: Considerations in Ophthalmology

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Ophthalmologists, on occasion, take the initiative and the responsibility for prescribing systemic steroids to patients with vision-threatening ocular inflammatory disorders. Examples of such disorders include orbital pseudotumor, scleritis, uveitis, giant cell arteritis and optic neuritis. Preoccupation with the challenge and goal of preservation of vision, coupled with the propensity for some cases to relapse with attempted steroid taper (with resultant need to raise the steroid dose again) can lead to prolonged steroid use without attention to bone preservation strategies.

It is well known that prolonged use of glucocorticoids (GC) has a 100% chance of adverse reactions¹, including: severe bone mineral loss, insulin resistance, myopathy, behavioral disorders, easy bruising, rise in blood pressure, cataract, glaucoma.² Cyclosporine A, which may also be used in combination with GC to obtain control of ocular inflammation, also can cause bone loss by inducing high intensity bone remodeling and resorption exceeding formation in animal models, indicating an increase of osteoclast activity^{3,4}.

Osteoporosis means “porous bone”. The Consensus Development Conference held in conjunction with the Fourth International Symposium on Osteoporosis defined osteoporosis as “a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture”. Osteoporosis is a serious public health concern that affects almost 28 million people in the United States, and the overall cost of acute and long-term health care associated with it will approach \$14 billion annually, or more than \$38 million per day by 2015 (National Osteoporosis Foundation, 1997).

The incidence of atraumatic fractures in patients who receive supraphysiologic glucocorticoid therapy is 30 to 50%.^{5,6} The chronic use of GC is associated with a lower bone mineral density (BMD) and a higher risk of bone fractures in a dose-response relationship. Most of the BMD loss occurs during the first 12 months, peaking at 6 months⁷.

Glucocorticoids cause bone loss by suppressing bone formation. If bone resorption is simultaneously increased (by other medications, by the illness for which the glucocorticoids are prescribed, or by concomitant circumstances such as estrogen lack), then bone loss is particularly rapid. Dosages of GC >5 mg /day are associated with accelerated bone loss in elderly men and women⁸. It has been estimated that 800 mcg/day of beclomethasone, budesonide or fluticasone can cause bone loss.^{9,10} It is also known that the use of alternating doses of GC does not prevent bone loss¹¹.

GC cause suppression of Insulin-like Growth Factor-1 (IGF-1) either because inhibition of its release or its production¹². IGF-1 plays an important role in the acquisition and maintenance of bone. Until now, however, the exact mechanism for this is unknown. Recombinant IGF-1 can prevent devastating effects of GC on bone. But this therapy has certain disadvantages: it is expensive; there are significant potential adverse effects (dermatologic and cardiac); and IGF therapy must be delivered by subcutaneous injections.

The effects of GC on bone and mineral are summarized in Table 1. GC also can induce androgen deficiency by pharmacological suppression of adrenal function¹³, and androgen deficiency increases

bone resorption. This is evident in postmenopausal women¹⁴ and in hypogonadal males. The adrenal glands are an important source of circulating androgens. In addition, high doses of GC decrease testicular responsiveness to gonadotropins, and thereby reduce serum testosterone even in normal males.

Strategies to prevent GC induced bone loss

Bone mineral density testing is the most reliable tool to assess fracture risk. Routine radiography used to be the only non-invasive method to evaluate BMD. Currently the most reliable method to assess BMD is dual energy x-ray absorptiometry (DEXA). It has proven to be a reliable indicator of risk for developing osteoporotic fracture, and an efficient tool to assess response to treatment of bone loss. DEXA is non-invasive, and has a precision of 1%. Two measures are of importance when interpreting DEXA results. Both measures are statistically compared in standard deviations (SD) from a normal distribution or along a "bell curve". They are the individual's T-score and Z-score. The T-score compares the patient's BMD to the mean score of a healthy adult. The Z-score compares the patient's BMD to the mean score of an age-matched control. The World Health Organization has established the following criteria for osteoporosis preventive and therapeutic decisions¹⁵:

- Normal: a value for BMD greater than -1 SD of a healthy young adult mean value.
- Osteopenia: a value for BMD more than -1 SD but less than -2.5 SD below that of a healthy young adult mean value.
- Osteoporosis: a BMD value -2.5 SD or greater below that of a healthy young adult mean value.
- Individuals who have sustained one or more low-impact fractures are considered to have osteoporosis regardless of their BMD score.

It is important for a physician not only to recognize the risk of osteoporosis induced by anti-inflammatory therapy but also to explain this to patients. The consequences of profound bone loss and fractures can be devastating from the standpoint of patients' well being, health care costs and legal issues.

We address medications used for the prevention of GC-induced bone loss.

Bisphosphonates

Bisphosphonates have been marketed since 1988, and are effective in the prevention of GC-related BMD loss¹⁶. The mechanism of action is the inhibition of osteoclast bone resorption once the drug adheres to the bone surface. Potential side effects include gastritis/esophagitis¹⁷, myalgia¹⁸, and altered hepatic function¹⁸. Since bone resorption is essential for healing of fractures and repair of microscopic fatigue cracks in bone, inappropriately high doses of bisphosphonates may interfere with repair of fractures and weaken bone strength by forcing bones to accumulate and propagate fatigue cracks. Bisphosphonates may also abolish the skeleton's adaptive powers¹⁹. But in general, bisphosphonates are well tolerated.

Several studies have shown that treatment with calcium and multivitamins plus alendronate (Fosamax) or risendronate (Actonel) prevents glucocorticoid-induced bone loss in the spine and hip, whereas treatment with calcium and multivitamins plus placebo does not.^{20,21,22}. The results are summarized in Table 2. Patients who were recently started on glucocorticoid therapy require higher bisphosphonate doses than patients who have been treated for prolonged periods with GC (Table 3). Patients who had less than 4 months of prior GC use or women with estrogen deficiency require 10mg of alendronate a day (as opposed to 5 mg) to have significant improvement on BMD. A risendronate (Actonel) placebo-controlled trial came to the same conclusions. The effect of both drugs is dose-dependent. Weekly doses are now available: 70 mg of alendronate or 35 mg of risendronate.

Human parathyroid hormone and Hormone Replacement Therapy (HRT)

Postmenopausal women on chronic GC are only partially protected from bone loss by HRT alone. Additionally, one must be aware of the possible side effects of chronic HRT, including increased risk of breast cancer, stroke, and myocardial infarction²⁴. One study

demonstrated that the use of human parathyroid hormone dramatically increased bone mass in the lumbar spine and in hip of postmenopausal women with glucocorticoid-induced osteoporosis who were already taking hormone replacement therapy. However, the maximum effect of this anabolic agent on BMD of the hip took place after 6 months of treatment²³. Human parathyroid hormone must be administered by daily subcutaneous injections, which are obviously inconvenient. Forteo, a breakthrough therapy derived from synthetically produced parathyroid hormone, is now FDA approved and available to patients with severe osteoporosis.

Selective estrogen receptor modulators

Raloxifene (Evista) was initially developed as a breast cancer preventive drug. It has the ability to increase BMD in spine and hip, but not as effectively as bisphosphonates, or estrogen. This drug acts on estrogen receptors and has the agonistic effect on bone and lipids. Raloxifen (Evista) alone does not prevent GC induced bone loss ^{25,26}.

Calcitonin

Salmon Calcitonin (SCT), delivered by nasal spray, can prevent BMD loss by suppressing osteoclast action. Luengo et al. found in patients with GC dependent asthma, that SCT given intranasally increased spinal BMD during the first year of treatment and maintained bone mass in a steady state during the second year ^{27,28}. Adachi et al. also report the effects of nasal SCT in patients with polymyalgia rheumatica with or without temporal arthritis who were on chronic high dose GC therapy ²⁹. Nasal SCT prevented loss of bone in the lumbar spine as measured by dual-energy X-ray absorptiometry. Both studies used 200 mcg of SCT and calcium supplement (800 – 1000 mg) daily. These studies share a small number of patients.

There is lack of large studies, which can give more reliable data about the benefit of SCT therapy in patients with chronic use of GC. ³⁰. SCT may be a good option for pregnant women on chronic GC therapy, because the use of bisphosphonates is contraindicated in pregnant women ^{31,32}.

Vitamin D

Patients over the age of 60 and patients with chronic diseases tend to have low levels of Vitamin D. Chronic use of GC may increase catabolism of vitamin D and may reduce serum levels of Vitamin D by 5-10%³³. Vitamin D, 25-OH vitamin D, and 1,25-(OH)₂ vitamin D were reported to increase BMD in GC-treated patients, but other studies failed to confirm such benefits ^{33,34,35}. Vitamin D and its metabolites have not improved bone mass in GC-treated patients if vitamin D deficiency was excluded³⁶. Vitamin D deficiency is surprisingly frequent in places with long deprivation of sunlight, such as northern climates in winter. But benefit of Vitamin D as a monotherapy in the treatment of BMD loss is questionable. Vitamin D supplementation should, however, be part of chronic GC therapy.

Systemic illness causing bone loss

Cushing's disease causes severe bone loss, but osteopenia can reverse completely after cure of Cushing's³⁷. Hyperparathyroidism is another well-known cause of bone loss. Successful surgical treatment results in improvement of bone density, with an 8 to 12% increase in bone mass observed during the first 2 to 4 years following surgery.³⁸

Gastrointestinal diseases associated with bone loss include celiac sprue, cystic fibrosis, chronic liver disease and inflammatory bowel disease. Osteopenia is explained by glucocorticoid use in many patients with inflammatory bowel disease. But it appears that inflammatory bowel disease may cause osteoporosis even in the absence of such therapy³⁹, with a 40% increase in fracture rate reported by some authors.⁴⁰

Summary:

These are the recommendations to stop GC-induced osteoporosis:

- Check axial BMD early, preferably in lateral and PA spine

- Assure 1000-1500 mg Ca and 800 units vitamin D in tablets daily
- Then check serum PTH and 25-OH vitamin D
- Refer to a specialist if there are multiple osteoporosis risk factors
- Prescribe a bisphosphonate as first line treatment, or PTH if the patient has had a fragility fracture or if the T-score is below - 2.5 SD
- Consider nasal spray calcitonin if T-score is borderline low, or if the patient is pregnant
- If androgen therapy would be safe: check serum testosterone in men over 60, and in men taking high-dose GC
- Other medications resulting in bone loss include anti-convulsants, heparin and supraphysiologic doses of levothyroxine (i.e. those used to treat thyroid tumors).
- Remember that risk factors, such as smoking, alcohol abuse and sedentary lifestyle contribute to increased rate of bone loss.

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