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Glucocorticoid-Induced Osteoporosis

The prescription of oral glucocorticoids (GCs) has increased in the past few decades to include approximately one-half percent of the total population.[1] GCs widespread use is secondary to their efficacy for treatment of autoimmune, pulmonary and gastrointestinal disorders, neoplastic diseases, and patients post-organ transplant.[2] In these chronic conditions, often long term (> 1 year) treatment with GCs is utilized.[3] GC therapy can have many adverse effects on skeletal integrity leading to bone loss and glucocorticoid-induced osteoporosis (GIO).[2] GIO occurs in 30-50% of patients receiving long-term GC therapy.[2, 3] Secondary to the extensive molecular damage GCs cause to skeletal cells, GIO is the second most prevalent form of osteoporosis second to postmenopausal osteoporosis.[4, 5]

Osteoporosis is diagnosed and treated after dual energy X ray absorptiometry (DXA) reveals a bone mineral density (BMD) value with T-score of -2.5 or less.[6] A -2.5 T-score indicates that BMD is 2.5 standard deviations less than young adult Caucasian women mean value.[6, 7] The operational definition of GIO has been proposed to include patients with BMD between a T-score of (-1) to (-1.5) because fractures often occur in patients on GC therapy with BMD levels above the conventional 2.5 standard deviation definition.[6]

Pathophysiology of Glucocorticoid-Induced Osteoporosis

GIO pathophysiology is complex, but it is generally accepted that it occurs in two phases in humans, both secondary to GCs direct effects on osteoblasts, osteocytes and osteoclasts.[2] There is a rapid initial phase of decreased BMD secondary to excessive bone resorption and a

second phase of decreased BMD attributed to impaired bone formation.[2] As depicted in Figure 1 in the Appendix, GC therapy has stimulatory effects on cell recruitment and differentiation of osteoclasts as well as anti-apoptotic effects on osteoclasts.[2,8] These effects lead to increased bone resorption during initial stage.[2,8] Further, GC damages the ability of osteoblasts to replicate, differentiate and function.[8] GC therapy also stimulates osteoblast and osteocyte apoptosis and inhibition of osteoblastic production of type 1 collagen.[2,3,8] These effects lead to decreased bone formation and decreased repair of damaged bone seen in the later stage of BMD loss.[2,3,8]

Initially, GCs preferentially affect trabecular bone integrity by thinning and perforating the bone leading to increased fragility.[1,8] For this reason, vertebral bodies which consist of mostly trabecular bone are a common site of GC induced fracture.[1] Decreases in number, thickness and connectivity of trabeculae are not captured by DXA scans but contribute to bone fragility, which may be a reason that fractures occur at higher BMD in patients on GCs.[9] In later stages of GIO, cortical porosity and endosteal thinning are observed increasing fracture risk in cortical bone.[8]

Additionally, GCs can indirectly affect bone health by affecting calcium metabolism through decreased renal absorption and increased urinary calcium excretion.[2,6] GCs cause decreased intestinal absorption of calcium and phosphate by blocking action of vitamin D.[2,3,8] GCs may also influence production and function of hormones such as gonadorophin, estrogen, and testosterone that regulate bone and calcium metabolism and resorption.[2,3,6] GCs can weaken and decrease mass of muscles and tendon soft tissues attached to bone reducing normal forces and tension of these attachments on bone and thereby reducing the stimulus for bone

formation.[3] With chronic administration of GCs, the direct and indirect negative effects previously described cumulate, further destroying skeletal integrity.[8]

The destruction the skeleton leaves it unable to sufficiently resist mechanical forces, provide mobility, prevent fractures and provide the body a source of calcium and other metabolites.[8] Fracture risk is related to bone strength, which is dependent on both the quality of boney architecture and the quantity of bone.[2] Osteoporosis affects the bones geometry and micro architecture, collagen matrix and mineralization, which all contribute to its fracture resistance and strength against mechanical forces.[8] Further, strength of bone depends on BMD, the quantity of bone, which is considered one of most important indicators of osteoporotic fracture risk.[8]

Increased Risk of Fracture

GIO is associated with increased risk of spinal and hip fracture, especially in older adult populations.[1] Daily and cumulative dose affects the incidence of fractures, but the rapid onset of negative effects suggest that fracture risk may be more related to daily doses than cumulative doses.[6, 10] A large cohort study revealed a dose-dependent relationship between GCs and relative fracture risk.[11, 12] The study revealed a 1.33 relative risk for non-vertebral fracture and 2.60 relative risk for vertebral fractures at doses at 5 mg or less.[11] At higher doses (>7.5mg/day) investigators found 2.27 and 5.18 relative risk, respectively.[11, 12] Even at doses less than 5mg there were increases in relative risks.[2] The incidence of fractures is also related to the duration of GC exposure. There is a rapid onset of fracture risk within first 3-6 months of oral GC therapy.[11, 12] This can be attributed in part due to rapid decrease of bone loss during this period, an average of 5% loss, over first year of GC therapy.[3] With continual long-term consumption of

GCs, bone loss and associated risk of fracture rate increases. Patients on chronic GC therapy experience a 30-50% fracture rate.[2]

Fractures occur at higher BMD values in patients on GC therapy than in other forms of osteoporosis, making early prevention critical.[6] GIO especially in early periods of GC therapy, may remain silent until a fracture occurs.[8] Seventy percent of vertebral fractures are asymptomatic.[1] Many physicians treating patients with GC therapy are unaware of the risks of GIO.[1,2] Fewer than 1 in 6 patients who take GCs long-term receive treatment to prevent osteoporosis.[3] This must be ramified because non-vertebral and vertebral factures are associated with increased morbidity and mortality and intervention could help avoid the negative complications of GC therapy.[6]

Risk Factors

Some populations are more at risk for negative effects of GCs than others. Risk factors for developing GIO can be categorized into major and minor. Major risk factors include: personal history of fracture in adult life, history of fracture in immediate family member, current tobacco consumption and low weight (<57 kg).[13] Minor risk factors include: advanced age, estrogen deficiency (menopause before age of 45), low calcium ingestion during life, malnutrition, sedentary lifestyle (defined as energy expenditure < 1,682 kcal/day), high alcohol consumption (>3 units of alcohol/day), recent falls, dementia, vision deficiency, and poor health.[13,14] A study performed in post-menopausal women demonstrated that low dietary calcium and physical activity are independent risk factors for low BMD.[15]

Further, patients with underlying inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and chronic obstructive pulmonary disease are more at risk of GIO because these conditions promote bone loss through release of destructive cytokines and

therefore are risk factors for osteoporosis. [3, 14] Transplant patients are also further at risk. [3] A study found that liver transplant patients on GC therapy had increased risk of developing osteoporosis because they are often treated with high-dose immunosuppressant therapy. [3] Patients with hepatic disorders such as biliary cirrhosis, have 2 fold higher incidence of osteoporosis than general population secondary to decreased bone formation and osteoblast activity and increased bone turnover rates. [3]

Further, general differences in individual susceptibility to GCs exist secondary to differences in gender, age, and peak bone mass prior to starting GC therapy. [6] There may be personal differences in physiologic absorption, distribution or metabolism of the steroid molecule and differences in the number and quality of GC receptors. [6, 14]

Prevention and Treatment

Bone mineral density peaks during early adulthood. [16] Therefore, a patient's maximum BMD is related to the amount accrued by this age. [16] Age-related bone loss begins in the fourth decade and is accelerated in women in early postmenopausal years. [16] Therefore during adulthood the primary goal is to maintain bone mass. Primary prevention of GIO is aimed at preventing rapid bone loss caused by GCs within the first 3 months of initial dose to decrease fracture risk. [6] Secondary prevention is designed to decrease fracture risk in patients who have been on long-term GCs and already have experienced some bone loss. [6]

In efforts to prevent fractures the American College of Rheumatology recommend increasing general health awareness of GIO and prevention, taking baseline height and DXA or other imaging, completing a falls risk assessment, administering calcium and vitamin D3, reducing the dose of GCs to the minimum, and when indicated prescribing pharmacological intervention with bisphosphonates and/or other agents. (Table 1, Appendix) [2, 6, 17] Intake of 1500

mg daily of calcium and 800 IU daily of vitamin D are recommended values for prevention, though this should be tailored to the patient based on their dose and duration of GCs and personal history.[2] Calcium and vitamin D supplementation should be considered the first line of therapy in absence of contraindications because they may reduce fracture risk and have low toxicity and cost.[11, 14] Richy et al completed a meta-analysis that found that calcium and vitamin D were more effective in preserving BMD than no therapy or calcium alone in patients on GC therapy.[18] Patients taking GCs should be encouraged to make lifestyle modifications such as cessation of smoking, reduced alcohol consumption if excessive, restriction of sodium intake in the presence of hypercalciuria, and increased physical activity.[11, 17]

Even for patients who reduce their modifiable risk factors and remain physically active, pharmacologic therapy may be recommended for prevention of osteoporosis, especially in at-risk populations, such as post-menopausal women.[7] Currently, bisphosphonates are the most studied and effective treatment option for GIO.[1] Homik et al found that bisphosphonates are effective in preventing bone mineral loss in lumbar spine and hip in patients taking GCs, but that the protection of BMD was of greater magnitude in lumbar spine than hip.[6, 19] Recently, studies show that teriparatide and zoledronic acid are effective in treating GIO and may improve BMD to a greater degree than alendronate and risedronate in some cases.[17] Further study is necessary before these medications are utilized to same degree as bisphosphonates.[17]

The ACR recommends that patients starting GC therapy at levels of ≥ 5 mg/day planned for ≥ 3 months take a bisphosphonate.[1, 11] Alendronate and risedronate are FDA approved bisphosphonates and are recommended by ACR as preventative treatment.[1, 11] Bisphosphonates are also recommended for patients who are on long-term doses of GC, have several of above GIO risk factors, or if their BMD is below at T score of (-1).[11] Bisphosphonates work by

inhibiting osteocyte and osteoblast apoptosis caused by GCs, thereby increasing BMD and decreasing fracture risk.[3, 11, 14] Duration of treatment using bisphosphonates is suggested to last as long a patient is taking GCs at a dose greater or equal to 5-7.5 mg daily.[6, 11] Laan et al found that the skeleton is capable of recovery after GCs have been stopped, which suggests that after GC therapy is finished, bisphosphonates are not necessary.[6, 20]

Controlled studies have demonstrated that estrogen replacement therapy increases lumbar spine bone mass in postmenopausal women on low doses of GCs.[11] Therefore hormone replacement therapy (HRT) may be considered for postmenopausal women, though there is some dispute to its use in patients secondary to HRT potentially increasing the risks of coronary heart disease, stroke and breast cancer.[3, 11] Men with low androgen levels may also benefit from testosterone replacement therapy. A randomized control trial by Crawford et al found that testosterone replacement therapy decreased bone and muscle atrophy in patients taking GCs after 1 year.[21]

Impact of Physical Exercise

Currently, the evidence of physical exercise in primary and secondary prevention of osteoporosis is inconsistent.[16] Specifically, studies performed studying exercise effects on patients taking GCs are limited. Therefore, some studies mentioned below describe patients with postmenopausal osteoporosis. The pathophysiology of bone loss is different between these two types of osteoporosis, so the impact of exercise on patients susceptible to GIO may vary.[16]

In general, high intensity weight-bearing endurance or resistance exercise has demonstrated ability to increase BMD in adulthood.[7] The dynamic and repetitive impact loading and muscular loading forces on bone during this type of exercise contributes to development and maintenance loading bearing and strength of bone.[22] Impact loading induces

high strain rates and high peak forces, which provide stimulus for bone growth.[22] Schmitt et al completed a review that found that BMD increases are site-specific with high intensity activity.[16] The review concluded that individualized exercise programs that combine intense and high impact exercise are most effective in prevention osteoporosis.[16] When weight-bearing exercise is safely tolerated by any underlying condition(s), then it can be utilized to maintain not only BMD but also prevent muscle atrophy often associated with GC therapy.[6]

Aerobic exercise may also play role in preservation of bone mass. A meta-analysis completed by Bonaiuti et al found that aerobics, weight bearing and resistance exercise, and walking were effective in increasing BMD of spine in postmenopausal women.[23] Feskaurch et al studied 61,200 postmenopausal women and found that performing moderate aerobic exercise at 9 MET (metabolic equivalent task) hour per week or higher significantly reduced hip fracture risk.[24] A study by Chien et al explains a rationale for this in their study suggesting that sub-maximal aerobic exercise may decrease the maximum systemic concentration of GC.[25] In this study men took a low dose (5 mg) of prednisone and then cycled at 70% VO2max.[25] Investigators hypothesized that the altered prednisone absorption pattern was due to changes in blow flow away from internal organs towards muscles during activity and decreased stomach-emptying rates during exercise.[25]

A RCT completed by de Jong et al provides further support of efficacy of aerobic activity and resistive muscle strengthening.[22] Investigators found that both types of activity are independently associated with increases in BMD at the hip in patients taking GCs with Rheumatoid Arthritis (RA).[16, 22] This protocol consisted of aerobic exercise in form of continuous vigorous bicycling (at 50-70 RPM) for a 5 minute duration that was progressed to 18 minutes by 6 months.[22] The bicycle load was kept at level that maintained the patient at 70-90%

of maximal heart rate (HR) and at rate of perceived exertion (RPE) between 4-5.[22] After aerobic component, an exercise circuit was performed consisting of 8-10 strengthening, joint mobility, endurance and activities of daily living exercises.[22] These were completed 8-15 times with rest between sets and progressed in intensity and frequency every 8 weeks.[22]

As previously noted, patients with inflammatory conditions such as RA have predisposition for BMD loss and therefore these results should be interpreted with caution in other patient populations on GC therapy.[16] Research of effects of aerobic activity and muscle strengthening in a lower risk population taking GCs is necessary for better generalizability.[16]

Some argue that high impact exercise is more important than endurance exercise in prevention of bone loss.[16] Additionally, several studies have demonstrated that group style aerobic classes, Tai Chi and walking programs that reduce risk of falls in general population, are less effective than individually tailored programs for patients taking GCs.[13,16] Further research is necessary to ascertain the benefits of endurance type exercise and use of group programs in prevention of osteoporosis. Group exercise programs are widely available and more cost effective, which would make them more accessible and likely to be utilized by patients taking GCs.[16] Adherence to a bone protecting form of physical activity is important because although physical activity has demonstrated ability to decrease fracture risk, it must be maintained for this affect and to preserve BMD.[16]

One study found that the combination of physical activity and pharmacologic management was an effective form of prevention. Braith et al studied the effect of utilizing exercise and alendronate (a bisphosphonate), alendronate alone, or control in heart transplant recipients taking GCs.[5] They concluded that resistance exercise and taking alendronate is more effective in than taking alendronate alone in improving bone mass at lumbar spine and femur.[5]

In this combination, the subject receives both benefits of the osteogenic stimulus (loading through exercise) and the anti-resorptive agent (bisphosphonate).[5] The subjects who only took aldenronate demonstrated stabilized BMD, while control continued to lose bone mass.[5]

Further, increased physical activity has additional benefits beyond slowing down rate of systemic bone loss, such as increased muscle strength, endurance, balance and posture, which can contribute to prevention of falls.[16] Exercise can also improve quality of life and prevent cardiovascular disease.[16] A recent review of literature states that investigators were unable to estimate the impact that physical activity has on GIO, but based on the positive whole body effects of resistive physical exercise in patients with osteoporosis, they recommended it conjunction with balance exercises for reduction of fall risk.[13]

Physical Therapy Considerations

Secondary to the low rate of preventative treatment of GIO, physical therapists may be first health care provider to serve patients at risk for GIO. Patients seeing a physical therapist for other reasons (besides osteoporosis or fracture attributed to this) may be taking GCs and present with several risk factors for GIO. A thorough patient history and physical examination including presence and history of fractures, kyphosis, back pain, height loss, balance and motor coordination and exposure to GCs should be completed to determine patient risk for GIO and fracture.[3] Making the appropriate referrals to a physician for determination of BMD and a detailed physical may provide useful information about state of bone health. Physicians are recommended to order a BMD score for patients initiating 22 months of GC treatment.[3] Monitoring of BMD is recommended even for patients on low doses of GCs that may not require pharmacologic treatment.[6]

An interdisciplinary plan for these patients should include education on proper nutrition, weight bearing exercise, assessment of need for vitamin D and calcium supplementation and pharmacologic prophylaxis against osteoporosis. [3] As with other conditions, patient's ability and willingness to participate in physical therapy will depend on various factors including general health (including underlying conditions), body mass index, and socioeconomic position.[16]

For patients with low BMD and risk factors of GIO, fracture prevention strategies can be utilized during therapy. For spinal fracture prevention, patients can be instructed on safe lifting and turning techniques and postural retraining focused on reducing biomechanical flexion forces placed on spine, strengthening of back extensors and improving postural awareness. Sinaki et al found that strengthening of back extensors decreased kyphosis and risk of sustaining vertebral compression fractures. [26] Further, physical therapy may include high-intensity weight bearing and aerobic exercise depending on patient's condition and contraindications. If appropriate, a fall risk assessment including balance and gait evaluation and education on fall prevention strategies for home, work and community can be provided. [9] Further details of physical therapy aimed to prevent bone loss and fractures at hip and other areas of body are not within contents of this discussion.

Conclusion

Fracture risk is related to bone strength, which is weakened by glucocorticoids direct and indirect affects on micro and macrostructure of bone, systemic absorption of calcium and hormones and integrity of surrounding tissue. Actual prevention and treatment of GIO is currently suboptimal; only 5-35% of patients taking GCs receive preventative or therapeutic interventions designed to decrease fracture risk. [4] Physicians and other health care professionals

often do not know the guidelines regarding GIO prevention and therefore do not recommend appropriate management of patients taking GCs.[1]

Early diagnosis of GIO is important as more effective treatment and prevention options have become available.[8] Encouraging patients to make changes in modifiable risk factors, improving calcium and vitamin D in diet, promoting physical exercise and use of bisphosphonate therapy with higher doses is recommended. Physical activity has been suggested to slow bone loss, which can help prevent osteoporotic fractures and associated morbidity and mortality.[16, 22] Further, regular exercise can increase muscle strength, balance and mobility reducing risk of falls that could lead to fracture in this population.[13] Physical therapists, as front line health care providers, should be aware of the negative effects of GCs and to be sure to conduct a comprehensive evaluation to determine patients at risk for GIO and then base referrals, treatment and plan of care accordingly.

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Appendix

Figure 1: Direct and indirect effects of glucocorticoids on bone leading to glucocorticoid-induced osteoporosis and increased risk of fractures.[9] Adapted with permission from *Glucocorticoid-induced osteoporosis: pathophysiology and therapy.*

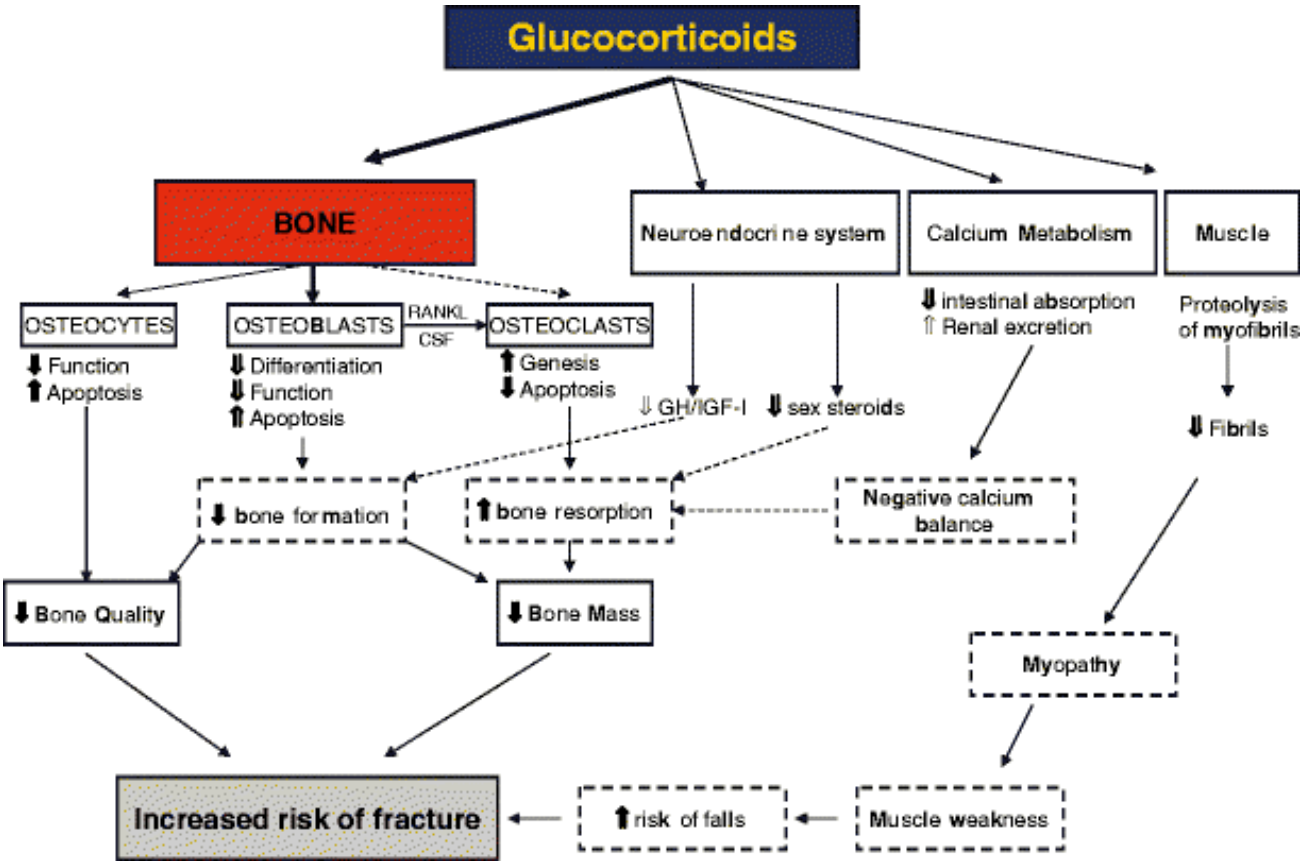

Table 1. Level of evidence for recommendations for assessment and lifestyle modifications for patients starting glucocorticoids at any dose with planned duration of ≥3 months. [17]

Adapted with permission from Table 2 of *American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis.*

Recommendation	**Level of Evidence**
Weight-bearing activities	C
Smoking cessation	C
Avoidance of excessive alcohol intake (>2 drinks per day)	C
Nutritional counseling on calcium and vitamin D intake	C
Fall risk assessment	C
Baseline dual x-ray absorptiometry	C
Baseline height	C
Assessment of prevalent fragility fractures	C
Consider radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone ≥5 mg/day or its equivalent	C
Calcium intake (supplement plus oral intake) 1,200–1,500 mg/day*	A
Vitamin D supplementation*	A