CLINICAL PRACTICE

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Glucocorticoid-Induced Osteoporosis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

For the past month, a 75-year-old woman with polymyalgia rheumatica has received prednisone at a dose of 20 mg daily. The treatment plan is to try to taper the dose to 5 mg daily within 6 months. Given typical durations of treatment, the expectation is that she will continue to receive prednisone for 2 years. She is otherwise healthy and has no personal or family history of fracture. She does not smoke or drink alcohol. Her height is 168 cm, and she weighs 68 kg. Her serum 25-hydroxyvitamin D level is 30 ng per milliliter (74 nmol per liter). Her bone mineral density T score is –1.2 at the femoral neck. What would you advise to prevent glucocorticoid-induced osteoporosis and fracture?

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THE CLINICAL PROBLEM

Approximately 1% of all adults and 3% of adults older than 50 years of age receive glucocorticoids for allergies, inflammatory conditions, or cancer.[1] Long-term use of glucocorticoids is associated with clinically significant toxic effects. Fracture is the most common serious and preventable adverse event associated with these agents.[2-4] The risk of fracture increases with age and with the dose and duration of glucocorticoid use[5-7] (Table 1).

Vertebral fractures are the most common fractures associated with glucocorticoids; the risk of vertebral fracture increases within 3 months after initiation of treatment and peaks at 12 months.[7,8] The relative risk of clinically diagnosed vertebral fracture doubles and the risk of hip fracture increases by approximately 50% among patients who receive 2.5 to 7.5 mg of prednisolone daily.[8] In a study with a follow-up of 6 months to 10 years, glucocorticoids taken at very high doses significantly increased the risk of vertebral fractures; among adults who received 30 mg of prednisolone per day with cumulative doses of at least 5 g, the risk of vertebral fracture increased by a factor of 14 and the risk of hip fracture increased by a factor of 3. The intermittent use of high-dose glucocorticoids with cumulative doses of 1 g or less had less effect on the risk of fracture,[8] whereas the use of high-dose inhaled glucocorticoids (≥1000-μg fluticasone dose equivalents) for more than 4 years increased the risk of fracture slightly (relative risk, 1.10; 95% confidence interval [CI], 1.02 to 1.19).[9]

Glucocorticoids have direct and indirect effects on bone remodeling (Fig. 1). Bone loss results from increases in expression of receptor activator of nuclear factor-κB ligand (RANKL), which lead to increases in the number of bone-resorbing osteoclasts.[4] Osteocyte apoptosis induces osteolysis, which results in an early

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KEY CLINICAL POINTS

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

- Risk factors for glucocorticoid-induced fractures include age (>55 years), female sex, white race, and long-term use of prednisone at a dose of more than 7.5 mg per day.
- Screening for fracture risk should be performed soon after the initiation of glucocorticoid treatment. The risk of fracture among patients who are 40 years of age or older can be estimated with the use of bone mineral density testing and the fracture risk assessment tool (FRAX).
- Patients who receive glucocorticoids should be counseled about adequate intake of calcium and vitamin D, weight-bearing exercise, and avoidance of smoking and excessive alcohol intake.
- Pharmacologic treatment is strongly recommended for anyone who has had a fracture and for patients who are at least 40 years of age if, according to the FRAX tool, the risk of major osteoporotic fracture is 20% or higher or the risk of hip fracture is at least 3%. Among patients who are receiving glucocorticoids and have a bone mineral density T score of –2.5 or less (indicating osteoporosis) at either the spine or the femoral neck, pharmacologic treatment is also recommended for men who are 50 years of age or older and for postmenopausal women.
- Bisphosphonates are recommended as first-line treatment of osteoporosis because of their low cost and safety.
- The risk of fracture decreases rapidly when glucocorticoids are discontinued. Exposure to glucocorticoids should be minimized as much as possible.

Table 1. Risk Factors for Fractures in Patients Receiving Glucocorticoids.*

Category of Risk	Risk Factors
Related to glucocorticoid use	High daily dose of glucocorticoid (e.g., >7.5 mg of prednisone daily), cumulative dose of glucocorticoid >5 g, current or recent (<3 mo) use of glucocorticoid, glucocorticoid-associated myopathy that increases the risk of falls, glucocorticoid-induced hypogonadism
Related to underlying condition	Rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, biliary cirrhosis
Related to risk of osteoporosis	Age >55 yr; white race; female sex; menopause; smoking; excess alcohol use (>2 units per day)†; bone mineral density T score below –1.5; increased fall risk; endocrine disorders: hypogonadism, hyperparathyroidism, or hypoparathyroidism; malabsorption; BMI <18.5; previous fracture

* The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
† According to the U.K. National Health Service, a standard glass of wine (175 ml) is 2.1 units (www.nhs.uk/live-well/alcohol-support/calculating-alcohol-units/).

increased risk of fracture even before bone mineral density decreases. Bone formation also decreases early in glucocorticoid treatment because of a decrease in osteoblast recruitment and accelerated apoptosis. Indirect glucocorticoid effects that also predispose patients to an increased risk of fracture include reduced muscle mass leading to an increased risk of falls, decreases in renal calcium resorption and levels of sex hormones, and alterations in parathyroid hormone pulsatility.[10]

The risk of fracture rapidly decreases when glucocorticoids are discontinued. A prospective study showed clinically significant improvement in bone mineral density at the lumbar spine within 6 months after discontinuation of glucocorticoids.[11] A large retrospective study showed an increased risk of a major osteoporotic fracture among patients with recent prolonged glucocorticoid use but not among those with intermittent or past use of these agents.[12]

Treatment of the underlying conditions for which glucocorticoids are prescribed often requires multiple medications, tests, and medical visits. The underlying condition (e.g., rheumatoid arthritis), as well as clinically evident glucocorticoid-associated adverse effects (e.g., muscle weakness and decreased skin integrity), are typically the focus of treating clinicians. Moreover, patients are frequently resistant to the ad-

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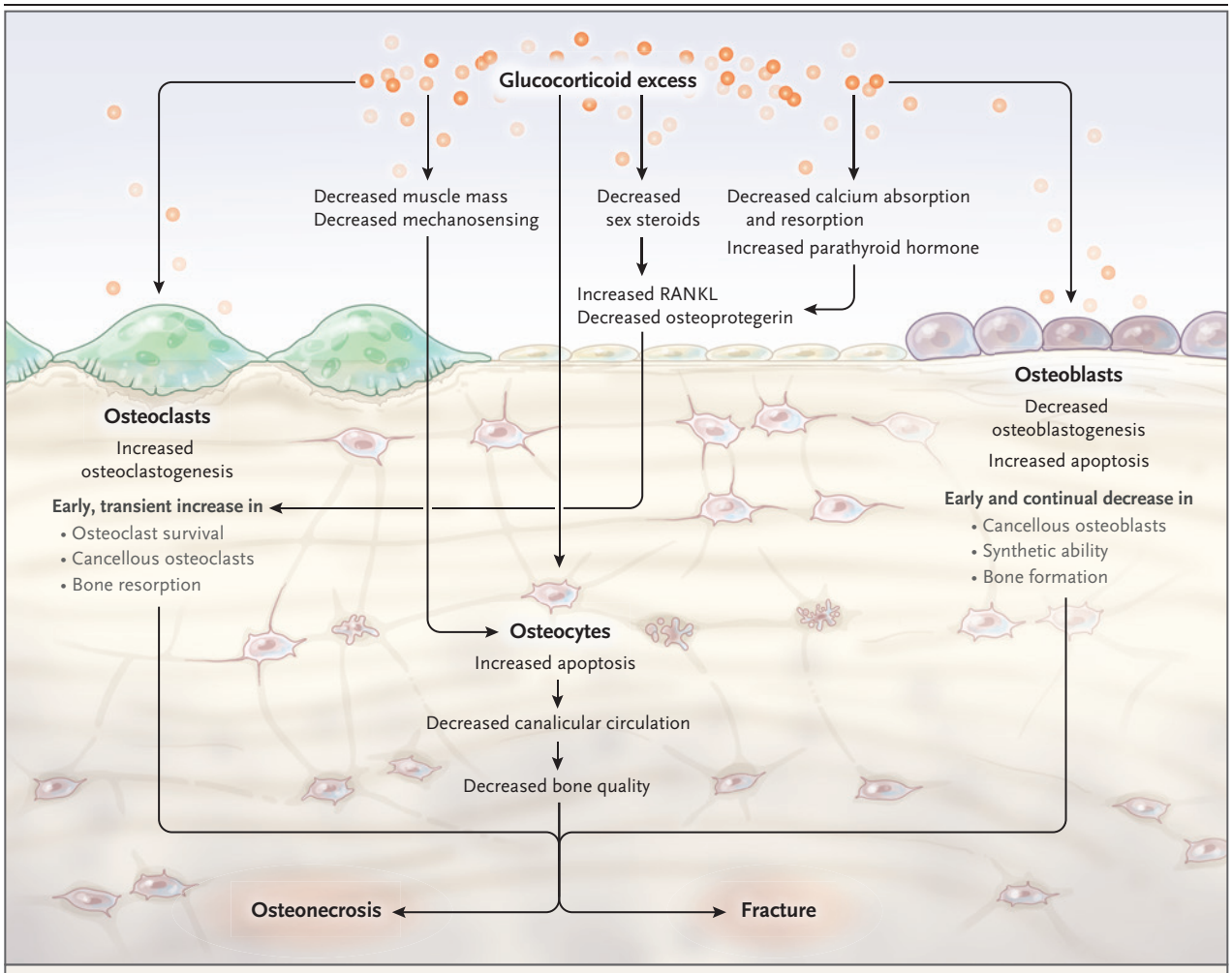

Figure 1. Mechanisms of Glucocorticoid-Induced Bone Loss.

Excessive amounts of systemic glucocorticoids lead to clinically significant adverse effects on the musculoskeletal system by inducing inappropriate bone remodeling through direct and indirect mechanisms and muscle atrophy that contributes to osteoporosis and fractures. Early bone loss is driven by changes in levels of estrogen and parathyroid hormone that stimulate receptor activator of nuclear factor-κB ligand (RANKL)–induced osteoclastogenesis. Osteocyte and osteoblast apoptosis prevents effective mechanosensing and new bone formation.

dition of medications to prevent osteoporosis, a condition that does not currently affect their quality of life, and many are concerned about rare potential adverse effects of antiosteoporosis medications. Thus, assessment and treatment of osteoporosis are frequently postponed or missed.

STRATEGIES AND EVIDENCE

Prevention of glucocorticoid-induced fractures requires identification of patients who should receive preventive treatment. The fracture risk assessment tool (FRAX) (www.shef.ac.uk/frax/) combines many risk factors for osteoporosis (including glucocorticoid use) with the bone mineral density to provide an estimate of the 10-year risk of major osteoporotic fracture and hip fracture among patients who are at least 40 years of age.[13] Although the risk of fracture can be calculated when the bone mineral density T score is not available, bone mineral density testing is recommended for people who receive glucocorticoids and are at least 40 years of age, since this testing improves the accuracy of FRAX

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estimates. When glucocorticoid use is added as a risk factor in the FRAX tool, the fracture estimates reflect the risk associated with prednisone at a dose of 2.5 to 7.5 mg per day; however, analysis of data from the U.K. General Practice Database suggests that among patients who receive more than 7.5 mg of prednisone daily, the FRAX-predicted risk of major osteoporotic fracture has to be increased by 15% and the risk of hip fracture has to be increased by 20%.[14] However, among patients who receive very high doses of prednisone (>30 mg per day or cumulative doses to >5 g per year), this adjustment may underestimate the risk of fracture. Another limitation of the FRAX score calculation is the use of bone mineral density at the hip instead of at the lumbar spine, since glucocorticoids have the greatest negative effect on trabecular bone in the spine.

Currently, tools to estimate the risk of fracture among patients who are younger than 40 years of age are lacking. The risk of fracture increases and the time to fracture decreases considerably with increasing age among patients who receive glucocorticoids.[15]

TREATMENT

NONPHARMACOLOGIC OPTIONS

Given the potential to recover bone mass, minimizing glucocorticoid use is the most important intervention to prevent fractures. For patients who receive glucocorticoids, routine lifestyle recommendations that are based on observational data largely from patients who have not received glucocorticoids include weight-bearing exercise, maintenance of normal weight, smoking cessation, limitation of alcohol consumption, and the assessment and management of fall risks.

CALCIUM AND VITAMIN D

Adequate dietary intake of calcium (1000 mg per day) and vitamin D (600 to 800 IU) is routinely encouraged in patients who receive glucocorticoids. Calcium and vitamin D may be more important for patients who receive glucocorticoids than for the general population because glucocorticoids increase the excretion of urinary calcium. A Cochrane meta-analysis estimated that the bone mineral density (measured in grams per square centimeter) at the lumbar spine was significantly higher among patients who received calcium and vitamin D supplementation than among those who received placebo (weighted mean difference, 2.6%; 95% CI, 0.7 to 4.5).[16] Randomized trials have shown that calcium and vitamin D supplementation prevented decreases in bone mineral density in the spine during long-term use of low-dose prednisone (mean dose, 5 mg per day)[17] but did not completely prevent bone loss in patients who were beginning to receive high-dose treatment (mean dose, 23 mg per day).[18] Calcium alone is not effective in preventing bone loss,[19] and studies of the effect of calcium and vitamin D on rates of fracture among patients who receive glucocorticoids are lacking.

PHARMACOLOGIC TREATMENT

The 2017 guidelines of the American College of Rheumatology[20] recommend pharmacologic treatment to prevent additional fractures in any patient with a previous osteoporotic fracture who is receiving glucocorticoids (prednisone dose >2.5 mg per day). Among patients who are receiving glucocorticoids and have a bone mineral density T score of –2.5 or less at either the spine or the femoral neck, pharmacologic treatment is also recommended for men who are 50 years of age or older and for postmenopausal women. Among adults who are 40 years of age or older and who do not meet the above criteria, pharmacologic treatment is recommended if the 10-year risk of major osteoporotic fracture is at least 20% or if the risk of hip fracture is at least 3% according to the FRAX tool (after increasing the risk by 15% and 20%, respectively, for a prednisone dose >7.5 mg daily). Table 2 lists these indications and other recommendations that should be considered for adults 40 years of age or older who are at moderate risk for fracture and for adults younger than 40 years of age.

Bisphosphonates

Numerous randomized trials have shown that bisphosphonates (alendronate, risedronate, zoledronate, and ibandronate) increase bone mineral density in patients who receive glucocorticoids.[24-29] In a 2016 Cochrane review that included 12 randomized trials and involved 1343 participants, participants who received bisphosphonates had a 43% (95% CI, 9 to 65) lower risk

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of new vertebral fractures than participants who received calcium, vitamin D, or both; the estimated number needed to treat to prevent one glucocorticoid-induced vertebral fracture was 31.[30] In patients who received bisphosphonate treatment for osteoporosis for 3 to 5 years, serious adverse events, including atypical femoral fractures and osteonecrosis of the jaw, have been reported to be rare (<0.01% and <0.001%, respectively).[31,32] Given their low cost and good safety profile, oral bisphosphonates are recommended as first-line agents to prevent glucocorticoid-induced fractures unless there are contraindications or unacceptable side effects. Intravenous bisphosphonates may be preferred in patients who are not adherent to oral bisphosphonates or in those who cannot safely take the oral formulation.

Other Recommended Agents

Teriparatide and abaloparatide are anabolic and increase bone formation.[33,34] In a trial involving 428 patients who were receiving glucocorticoids, patients received either teriparatide or alendronate for 36 months. Teriparatide was associated with greater increases in bone mineral density at the spine than alendronate (11% vs. 5.3%, P<0.001) and a lower rate of radiographic vertebral fractures (1.7% vs. 7.7%, P=0.007); however, there was no significant difference in rates of nonvertebral fracture between the two treatment groups.[33] Hypercalcemia occurred in 21% of patients in the teriparatide group, as compared with 7% of those in the alendronate group. In a smaller trial involving middle-aged men who were receiving glucocorticoids, the bone mineral density was higher and the rate of fracture was lower among patients who received teriparatide than among those who received risedronate.[35] However, bone loss and fractures occur rapidly after teriparatide is discontinued; therefore, after discontinuation, an antiresorptive agent such as bisphosphonate or denosumab should be initiated. Initial treatment with an anabolic agent such as teriparatide or abaloparatide, followed by an antiresorptive agent, may be considered for treatment of severe osteoporosis (bone mineral density T score below –2.5 in patients with a history of fracture).

Denosumab inhibits bone resorption by binding to RANKL and interfering with the development of osteoclasts. A noninferiority trial comparing denosumab with risedronate in patients who were beginning to receive glucocorticoids and in those who had received these agents long-term showed superiority of denosumab with respect to increases in bone mineral density at the spine at 12 months and noninferiority with respect to rates of fracture.[36] Some but not all studies have shown a higher risk of infection with denosumab than with bisphosphonates.[37,38] Given the limited available safety data, denosumab is generally not recommended as the first-line treatment in patients taking multiple immunosuppressive drugs or a biologic treatment.

At doses of denosumab that are used to treat osteoporosis, the risks of osteonecrosis of the jaw (0.001 to 0.15%) and atypical fractures are low.[32] However, rates of vertebral fracture increase rapidly after denosumab is discontinued, especially among patients with a previous vertebral fracture, and an alternative antiresorptive therapy is recommended after discontinuation.[39]

Third-Line Agents

Treatment either with raloxifene (a selective estrogen-receptor modulator) in postmenopausal women or with calcitonin, another antiresorptive agent, should be reserved for patients in whom other treatments are contraindicated or in whom such treatments have failed. Raloxifene is approved by the Food and Drug Administration for the prevention and treatment of glucocorticoid-induced osteoporosis in postmenopausal women. One trial showed that in postmenopausal women who received glucocorticoids, raloxifene significantly increased absolute bone mineral density (measured in grams per square centimeter) at the lumbar spine by 1.3% from the baseline measure, as compared with calcium and vitamin D supplementation, which decreased the absolute bone mineral density.[40] However, there was no difference in bone mineral density at the femoral neck between the treatment groups, and trials assessing rates of fracture among patients who have received both glucocorticoids and raloxifene are lacking. Although raloxifene has been shown to reduce the risk of estrogen-receptor–positive breast cancer,[41] potential adverse effects include hot flashes, leg cramps, venous thromboembolism, and fatal stroke.[42]

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Table 2. Recommendations from Recent Guidelines for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis.*

Variable	American College of Rheumatology[20]	European League Against Rheumatism[21]†	International Osteoporosis Foundation and European Calcified Tissue Society[22]‡	National Osteoporosis Guideline Group[23]‡
Patients warranting intervention on the basis of dose and duration of glucocorticoid treatment	All adults taking ≥2.5 mg of prednisone daily for >3 mo	All adults taking any dose of prednisone daily for >3 mo	Any adult with previous fracture, age ≥70 yr of age, or taking ≥7.5 mg of prednisone daily for 3 mo; dosages for all other adults are based on intervention thresholds that differ according to country	All adults taking any dose of prednisone daily for >3 mo
Whom to test and monitor for changes in BMD	All adults ≥40 yr of age and adults <40 yr with a history of fragility fracture or other risk factors; test within 6 mo after initiation of glucocorticoids; repeat testing every 2–3 yr and every 1–3 yr in adults ≥40 yr receiving glucocorticoids without treatment for osteoporosis	Premenopausal women or men <70 yr of age; not recommended for postmenopausal women and older men, since they will receive treatment for osteoporosis regardless of BMD	Patients without previous fracture, <70 yr of age, <7.5 mg of prednisone daily; monitor patients receiving glucocorticoids at appropriate intervals thereafter (not specified)	Not specified
Correction used with the FRAX tool to adjust risk estimate for prednisone dose >7.5 mg	Risk of major osteoporotic fracture is increased by 15% and risk of hip fracture is increased by 20%	None	Risk of major osteoporotic fracture is increased by 15% and risk of hip fracture is increased by 20%; if receiving <2.5 mg of prednisone daily, FRAX risk of major osteoporotic fracture is decreased by 20% and risk of hip fracture is decreased by 35%	Risk of major osteoporotic fracture is increased by 15% and risk of hip fracture is increased by 20%; if receiving <2.5 mg of prednisone daily, FRAX risk of major osteoporotic fracture is decreased by 20% and risk of hip fracture is decreased by 35%
Calcium and vitamin D supplementation	800–1000 mg of calcium daily and 600–800 IU of vitamin D daily	Supplement if receiving ≥7.5 mg of prednisone daily; no recommended dose of calcium and vitamin D	Supplement if receiving glucocorticoids for >3 mo; no recommended dose of calcium and vitamin D	Supplement if levels of dietary calcium and vitamin D are inadequate
Threshold for pharmacologic treatment	All adults with a previous fragility fracture; adults ≥40 yr with BMD T score of –2.5 or less or FRAX risk ≥20% for major osteoporotic fracture or ≥3% for hip fracture§; consider in adults ≥40 yr with FRAX risk 10 to 19% for major osteoporotic fracture or >1 to 2.9% for hip fracture, adults <40 yr with BMD T score below –3 and >7.5 mg of prednisone daily, adults with >10%/yr bone loss at hip or spine, and adults ≥30 yr taking very-high-dose glucocorticoids (≥30 mg daily) or high cumulative use (>5 g in 1 yr)	Adults with a previous fracture or taking >15 mg of prednisone daily; postmenopausal women and men >70 yr taking >7.5 to 15 mg of prednisone daily; premenopausal women and men <70 yr taking >7.5 to 15 mg of prednisone daily with a high-risk BMD T score (not specified); adults taking <7.5 mg of prednisone daily with risk factors and high-risk BMD T score (not specified)	Adults with previous fracture or age ≥70 yr or ≥taking 7.5 mg of prednisone daily; adults with no previous fracture, age <70 yr, or taking <7.5 mg of prednisone daily with a FRAX or BMD T score above treatment threshold (varies according to country)	Adults with a previous fragility fracture or taking ≥7.5 mg of prednisone daily; women and men ≥70 yr

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Pharmacologic interventions¶	First-line therapy: oral bisphosphonates; second-line therapies (in order of preference): intravenous bisphosphonates, teriparatide, denosumab, raloxifene (only in postmenopausal women when other listed second-line medications are not appropriate)	Bisphosphonates according to thresholds and risk factors (decreased BMD, female sex, age ≥70 yr, postmenopausal status, BMI below normal range, previous fracture)	First-line therapies: bisphosphonates or teriparatide	First-line therapies: oral bisphosphonates; second-line therapies: intravenous bisphosphonates or teriparatide
Duration of pharmacologic intervention	If continuing to receive glucocorticoids >5 yr, continue treatment if moderate to high risk; if glucocorticoids discontinued before 5 yr, continue treatment for osteoporosis for 5 yr if moderate to high risk; discontinue treatment for osteoporosis when glucocorticoids are discontinued if low risk	Not specified	For duration of glucocorticoid therapy	For duration of glucocorticoid therapy

* BMD denotes bone mineral density, and FRAX fracture risk assessment tool.
† This guideline predated approval of teriparatide and denosumab.
‡ This guideline predated approval of denosumab.
§ This is a conditional recommendation because of poor quality of data or lack of data about benefits, harms, or both.
¶ Alendronate, risedronate, zoledronic acid, teriparatide, and denosumab are approved by the Food and Drug Administration for the treatment of glucocorticoid-induced osteoporosis.

A meta-analysis of nine trials involving nearly 500 patients who were receiving glucocorticoids showed that the bone mineral density at the lumbar spine (but not hip) was higher among patients who were receiving calcitonin than among those who were receiving calcium and vitamin D supplementation alone (weighted mean difference, 2.8%), but there was no difference between the groups in the risk of vertebral fracture.[43] Calcitonin, which can be administered subcutaneously or by nasal spray (with less absorption), may cause nausea or vomiting.

TREATMENT IN WOMEN OF CHILDBEARING AGE

Pharmacologic treatment to prevent fractures is not recommended in pregnant women. A summary of 15 case reports and case series involving 65 women who received a bisphosphonate before or in the first few months of pregnancy showed no clinically significant adverse effects in the fetus,[44] but more data are needed. There has also been a reluctance to treat premenopausal women with bisphosphonates because of concerns that the long-term retention of these agents in bone may later affect the fetal skeleton. When treatment is needed in women of childbearing age (e.g., in those with previous fracture or a high risk of fracture while receiving glucocorticoids), agents such as risedronate and teriparatide that have a shorter half-life and less retention in bone are generally recommended. Studies in animals have shown that denosumab has teratogenic effects and should be used with caution and with birth control in women of childbearing potential.[45]

AREAS OF UNCERTAINTY

Long-term use of glucocorticoids is common after organ transplantation, and fractures are a known complication of transplantation, but many patients who receive transplants are not assessed for fracture or treated to prevent fracture. Although data on the effects of medications for osteoporosis on bone mineral density in transplant recipients are limited,[46-48] gains in bone density with bisphosphonates are similar to those seen in patients treated with glucocorticoids who have not received transplants. Larger studies are needed to elucidate the relative risks and benefits of various agents in these patients, especially those with chronic kidney disease.

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Data to guide assessment of the risk of glucocorticoid–associated fractures among adults who are younger than 40 years of age are lacking. Tools to estimate short-term and long-term risks of fracture are needed for this population.

The natural history of bone loss attributable to glucocorticoids differs from that related to menopause and aging. Glucocorticoid use is typically a time-limited risk factor, the rate of bone loss varies over the course of glucocorticoid treatment, and bone strength improves with the discontinuation of glucocorticoids. Despite these differences, patients who receive glucocorticoids often receive the same regimens used to treat osteoporosis in postmenopausal women. Data on the effectiveness and safety of alternative regimens that may be more acceptable to patients are lacking. Such regimens include targeting antiosteoporosis therapy to periods of higher-dose glucocorticoid use, followed by calcium and vitamin D supplementation alone during periods of low-dose glucocorticoid use.

GUIDELINES

Several professional societies have published guidelines for the prevention and management of glucocorticoid-induced osteoporosis.[20-22,47,48] Owing to limitations in high-quality data to inform screening and treatment, guidelines vary with respect to the glucocorticoid doses warranting intervention, the need for bone mineral density testing and calcium and vitamin D supplementation, recommendations for pharmacologic treatment, and the thresholds and duration of osteoporosis treatment (Table 2). The recommendations in this article are consistent with the guidelines of the American College of Rheumatology.

CONCLUSIONS AND RECOMMENDATIONS

The 75-year-old woman with polymyalgia rheumatica described in the vignette is currently receiving prednisone at a dose of more than 7.5 mg per day and is expected to receive a lower dose for the foreseeable future. On the basis of her bone mineral density T score and use of high-dose prednisone, the FRAX 10-year risk of major osteoporotic fracture is 18% and the risk of hip fracture is 3.8% (after increases of 15% and 20%, respectively, in the risk because of use of high-dose prednisone). This level of risk meets American College of Rheumatology guideline criteria for pharmacologic treatment (≥20% risk of major osteoporotic fracture or ≥3% risk of hip fracture). In keeping with these guidelines, we would recommend bisphosphonates (e.g., oral alendronate at a dose of 70 mg once weekly) as first-line treatment. The prednisone dose should be tapered as quickly as possible according to disease activity. We would continue to recommend bisphosphonate treatment for 5 years as long as the patient is taking prednisone at a dose of at least 2.5 mg per day. When the prednisone dose is reduced below 2.5 mg per day, we would reassess the risk of fracture and discontinue bisphosphonate treatment if the predicted risk no longer meets the criteria for pharmacologic treatment. Optimization of calcium and vitamin D intake, weight-bearing exercise, and strategies to prevent falls should be encouraged.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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