CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will anticipate an increased risk of fractures in patients taking certain drugs and will take appropriate steps to mitigate the risk

FAYE N. HANT, DO, MSCR
Associate Professor of Medicine, Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC

MARCY B. BOLSTER, MD
Associate Professor of Medicine, Harvard Medical School; Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Boston, MA

Drugs that may harm bone: Mitigating the risk

ABSTRACT

Glucocorticoids, proton pump inhibitors, selective serotonin reuptake inhibitors (SSRIs), certain antiepileptic drugs, and aromatase inhibitors have significant adverse effects on bone. Healthcare providers should monitor the bone health of patients on these agents, supplement their intake of calcium and vitamin D, encourage weight-bearing exercise, and initiate osteoporosis-prevention treatment as indicated.

KEY POINTS

Professional society guidelines advise initiating treatment for bone loss in patients starting glucocorticoid therapy expected to last at least 3 months and for women taking an aromatase inhibitor.

If patients taking a proton pump inhibitor take a calcium supplement, they should take calcium citrate.

Daily SSRI use nearly doubles the risk of hip fracture in people over age 50.

Many drugs for epilepsy are associated with increased fracture risk, but so are seizures (which may confound the issue).

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Drug-induced osteoporosis is common, and the list of drugs that can harm bone continues to grow. As part of routine health maintenance, practitioners should recognize the drugs that increase bone loss and take measures to mitigate these effects to help avoid osteopenia and osteoporosis.

Osteoporosis, a silent systemic disease defined by low bone mineral density and changes in skeletal microstructure, leads to a higher risk of fragility fractures. Some of the risk factors are well described, but less well known is the role of pharmacologic therapy. The implicated drugs (**Table 1**) have important therapeutic roles, so the benefits of using them must be weighed against their risks, including their potential effects on bone.

This review focuses on a few drugs known to increase fracture risk, their mechanisms of bone loss, and management considerations (**Table 2**).

GLUCOCORTICOIDS

Glucocorticoids are used to treat many medical conditions, including allergic, rheumatic, and other inflammatory diseases, and as immunosuppressive therapy after solid organ and bone marrow transplant. They are the most common cause of drug-induced bone loss and related secondary osteoporosis.

Multiple effects on bone

Glucocorticoids both increase bone resorption and decrease bone formation by a variety of mechanisms.[1] They reduce intestinal calcium absorption, increase urinary excretion of calcium, and enhance osteocyte apoptosis, leading to deterioration of the bone microarchitecture and bone mineral density.[2] They also

TABLE 1

Drugs that may harm bone

- Glucocorticoids
- Selective serotonin reuptake inhibitors
- Aromatase inhibitors
- Hypoglycemic agents (thiazolidinediones)
- Proton pump inhibitors
- Antiepileptics
- Anticoagulants (heparin and oral agents)
- Loop diuretics
- Antiretroviral agents
- Calcineurin inhibitors
- Androgen deprivation therapy
- Depot medroxyprogesterone acetate

affect sex hormones, decreasing testosterone production in men and estrogen in women, leading to increased bone resorption, altered bone architecture, and poorer bone quality.[3,4] The bone loss is greater in trabecular bone (eg, the femoral neck and vertebral bodies) than in cortical bone (eg, the forearm).[5]

The implicated medications have important roles, so weigh their risks and benefits

Glucocorticoids have other systemic effects that increase fracture risk. For example, they cause muscle weakness and atrophy, increasing the risk of falls.[4] Additionally, many of the inflammatory conditions for which they are prescribed (eg, rheumatoid arthritis) also increase the risk of osteoporosis by means of proinflammatory cytokine production, which may contribute to systemic and local effects on bone.[4,6]

Bone mineral density declines quickly

Bone mineral density declines within the first 3 months after starting oral glucocorticoids, with the rate of bone loss peaking at 6 months. Up to 12% of bone mass is lost in the first year. In subsequent years of continued use, bone loss progresses at a slower, steadier rate, averaging 2% to 3% annually.[5,7,8]

Oral therapy increases fracture risk

Kanis et al[9] performed a meta-analysis of seven prospective cohort studies in 40,000 patients and found that the current or previous use of an oral glucocorticoid increased the risk of fragility fractures, and that men and women were affected about equally.[9]

Van Staa et al[10,11] reported that daily doses of glucocorticoids equivalent to more than 2.5 mg of prednisone were associated with an increased risk of vertebral and hip fractures; fracture risk was related mainly to daily dosage rather than cumulative dose.

Van Staa et al,[12] in a retrospective cohort study, compared nearly 250,000 adult users of oral glucocorticoids from general medical practice settings with the same number of controls matched for sex, age, and medical practice. The relative risks for fractures and 95% confidence intervals (CIs) during oral glucocorticoid treatment were as follows:

- Forearm fracture 1.09 (1.01–1.17)
- Nonvertebral fracture 1.33 (1.29–1.38)
- Hip fracture 1.61 (1.47–1.76)
- Vertebral fracture 2.60 (2.31–2.92).

The risk was dose-dependent. For a low daily dose (< 2.5 mg/day of prednisolone), the relative risks were:

- Hip fracture 0.99 (0.82–1.20)
- Vertebral fracture 1.55 (1.20–2.01) .

For a medium daily dose (2.5–7.5 mg/day), the relative risks were:

- Hip fracture 1.77 (1.55–2.02)
- Vertebral fracture 2.59 (2.16–3.10) .

For a high daily dose (> 7.5 mg/day), the relative risks were:

- Hip fracture 2.27 (1.94–2.66)
- Vertebral fracture 5.18 (4.25–6.31).

Fracture risk rapidly declined toward baseline after the patients stopped taking oral glucocorticoids but did not return to baseline levels. The lessening of excess fracture risk occurred mainly within the first year after stopping therapy.

Other studies[5,9,13] have suggested that the increased fracture risk is mostly independent of bone mineral density, and that other mechanisms are at play. One study[14] found that oral glucocorticoid users with a prevalent vertebral fracture actually had higher bone mineral density than patients with a fracture not taking glucocorticoids, although this finding was not confirmed in a subsequent study.[15]

Inhaled glucocorticoids have less effect on bone

Inhaled glucocorticoids are commonly used to treat chronic obstructive pulmonary disease

and asthma. They do not have the same systemic bioavailability as oral glucocorticoids, so the risk of adverse effects is lower.

Data are inconsistent among several studies that evaluated the relationship between inhaled glucocorticoids, bone mineral density, osteoporosis, and fragility fracture. The inconsistencies may be due to heterogeneity of the study populations, self-reporting of fractures, and different methods of assessing chronic obstructive pulmonary disease severity.[16]

A Cochrane review[17] in 2002 evaluated seven randomized controlled trials that compared the use of inhaled glucocorticoids vs placebo in nearly 2,000 patients with mild asthma or chronic obstructive pulmonary disease and found no evidence for decreased bone mineral density, increased bone turnover, or increased vertebral fracture incidence in the glucocorticoid users at 2 to 3 years of follow-up (odds ratio for fracture 1.87, 95% CI 0.5–7.0).

The Evaluation of Obstructive Lung Disease and Osteoporosis study,[16] a multicenter Italian observational epidemiologic study, reported that patients taking the highest daily doses of inhaled glucocorticoids (> 1,500 µg of beclomethasone or its equivalent) had a significantly higher risk of vertebral fracture (odds ratio 1.4, 95% CI 1.04–1.89).[16]

A meta-analysis[18] of five case-control studies (43,783 cases and 259,936 controls) identified a possible dose-dependent relationship, with a relative risk for nonvertebral fracture of 1.12 (95% CI 1.0–1.26) for each 1,000-µg increase in beclomethasone-equivalent inhaled glucocorticoid per day.

In summary, the effects of inhaled glucocorticoids in adults are uncertain, although trends toward increased fracture risk and decreased bone mineral density are evident with chronic therapy at moderate to high dosages. The risks and benefits of treatment should be carefully considered in patients with osteoporosis and baseline elevated fracture risk.[19]

Managing the risk of glucocorticoid-induced osteoporosis

In 2010, the American College of Rheumatology published recommendations for preventing and treating glucocorticoid-induced osteoporosis, which were endorsed by the American Society for Bone and Mineral Research.[20] To lessen the risk of osteoporosis, the recommendations are as follows:

Limit exposure. Patients receiving glucocorticoids should be given the smallest dosage for the shortest duration possible.

Advise lifestyle changes. Patients should be counseled to limit their alcohol intake to no more than two drinks per day, to quit smoking, to engage in weight-bearing exercise, and to ingest enough calcium (1,200–1,500 mg/day, through diet and supplements) and vitamin D.

Monitor bone mineral density. Patients starting glucocorticoids at any dosage for an expected duration of at least 3 months should have their bone mineral density measured at baseline. The frequency of subsequent measurements should be based on the presence of other risk factors for fracture, results of

TABLE 2

How to manage drugs that affect bone health

General recommendations

Reassess need for medication

Use lowest dosage and shortest duration needed

Counsel patients on lifestyle changes: encourage weight-bearing exercise, cessation of tobacco use, and limiting alcohol use

Supplement calcium and vitamin D

Consider screening and monitoring bone density with dual-energy absorptiometry (DXA)

Initiate osteoporosis treatment if indicated

Oral glucocorticoids

Therapy anticipated for ≥ 3 months at any dose: get baseline DXA scan

Follow American College of Rheumatology recommendations for initiating osteoporosis prevention treatment

Proton pump inhibitors

Supplement calcium with calcium citrate

Consider alternative therapy such as a histamine-2 receptor blocker

Aromatase inhibitors

Consider bisphosphonate treatment for postmenopausal women with T scores < –2.0 or with other risk factors

previous bone density testing, glucocorticoid dosage, whether therapy for bone health has been initiated, and the rate of change in bone mineral density. If warranted and if the results would lead to a change in management, patients can undergo dual-energy x-ray absorptiometry more often than usual, ie, more often than every 2 years. Prevalent and incident fragility fractures, height measurements, fall risk assessments, laboratory measurements of 25-hydroxyvitamin D, and consideration of vertebral fracture assessment or other imaging of the spine, as necessary, should be part of counseling and monitoring.

Osteoporosis treatment. For patients who will be taking glucocorticoids for at least 3 months, alendronate, risedronate, zoledronic acid, or teriparatide can be initiated to prevent or treat osteoporosis in the following groups:

- Postmenopausal women and men over age 50 if the daily glucocorticoid dosage is at least 7.5 mg/day or if the World Health Organization Fracture Risk Assessment Tool (FRAX) score is more than 10% (the threshold for medium fracture risk)
- Premenopausal women and men younger than 50 if they have a history of fragility fracture, the FRAX score is more than 20% (the threshold for high fracture risk), or the T score is less than –2.5.

Use proton pump inhibitors only if there is a clear indication for them and their benefits likely outweigh the risks

Certain clinical factors can also put a patient into a higher-risk category. These include current tobacco use, low body mass index, parental history of hip fracture, consuming more than three alcoholic drinks daily, higher daily or cumulative glucocorticoid dosage, intravenous pulse glucocorticoid usage, or a decline in central bone mineral density that exceeds the least significant change according to the scanner used.[20]

The FRAX tool accounts for bone density only at the femoral neck, and while useful, it cannot replace clinical judgment in stratifying risk. Moreover, it does not apply to premenopausal women or men under age 40.

The long-term risks of medications to treat glucocorticoid-induced osteoporosis are not well defined for premenopausal women (or their unborn children) or in men younger than 40, so treatment is recommended in those groups only for those with prevalent fragility fractures who are clearly at higher risk of additional fractures.[20]

PROTON PUMP INHIBITORS

Proton pump inhibitors are available by prescription and over the counter for gastric acid-related conditions. Concerns have been raised that these highly effective drugs are overused.[21] Several of their adverse effects are self-limited and minor, but long-term use may entail serious risks, including propensity to bone fracture.[22]

Low acid leads to poor calcium absorption

Why fracture risk increases with proton pump inhibitors is controversial and may relate to their desired effect of suppressing gastric acid production: calcium salts, including carbonate and chloride, are poorly soluble and require an acidic environment to increase calcium ionization and thus absorption.[23] For this reason, if patients taking a proton pump inhibitor take a calcium supplement, it should be calcium citrate, which unlike calcium carbonate does not require an acid environment for absorption.

Higher risk in older patients, with longer use, and with higher dosage

Since the first reports on proton pump inhibitors and fracture risk were published in 2006,[24,25] a number of studies have reported this association, including several systematic reviews.

In 2011, the US Food and Drug Administration (FDA) updated a 2010 safety communication based on seven epidemiologic studies reporting an increased risk of fractures of the spine, hip, and wrist with proton pump inhibitors.[24–31] Time of exposure to a proton pump inhibitor in these studies varied from 1 to 12 years. Fracture risk was higher in older patients,[26] with higher doses,[24,29] and with longer duration of drug use.[24,27] On the other hand, one study that included only patients without other major fracture risk factors failed to find an association between the use of proton pump inhibitors and fractures.[28]

Is evidence sufficient for changing use?

The FDA report included a disclaimer that they had no access to study data or protocols and so could not verify the findings.[26] More-

over, the studies used claims data from computerized databases to evaluate the risk of fractures in patients treated with proton pump inhibitors compared with those not using these drugs.[24–31] Information was often incomplete regarding potentially important factors (eg, falls, family history of osteoporosis, calcium and vitamin D intake, smoking, alcohol use, reason for medication use), as well as the timing of drug use related to the onset or worsening of osteoporosis.[26]

Although 34 published studies evaluated the association of fracture risk and proton pump inhibitors, Leontiadis and Moayyedi[32] argued that insufficient evidence exists to change our prescribing habits for these drugs based on fracture risk, as the studies varied considerably in their designs and results, a clear dose-response relationship is lacking, and the modest association is likely related to multiple confounders.

Bottom line: Use with caution

Although the increased fracture risk associated with proton pump inhibitors is likely multifactorial and is not fully delineated, it appears to be real. These drugs should be used only if there is a clear indication for them and if their benefits likely outweigh their risks. The lowest effective dose should be used, and the need for continuing use should be frequently reassessed.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Depression affects 1 in 10 people in the United States, is especially common in the elderly, and leads to significant morbidity and reduced quality of life.[33] Selective serotonin reuptake inhibitors (SSRIs) are often prescribed and are generally considered first-line agents for treating depression.

Complex bone effects

SSRIs antagonize the serotonin transporter, which normally assists serotonin uptake from the extracellular space. The serotonin transporter is found in all main types of bone cells, including osteoclasts, osteoblasts, and osteocytes.[33] Serotonin is made by different genes in the brain than in the periphery, causing opposing effects on bone biology: when generated peripherally, it acts as a hormone to inhibit bone formation, while when generated in the brain, it acts as a neurotransmitter to create a major and positive effect on bone mass accrual by enhancing bone formation and limiting bone resorption.[34,35]

Potential confounders complicate the effect of SSRIs on bone health, as depression itself may be a risk factor for fracture. Patients with depression tend to have increased inflammation and cortisol, decreased gonadal steroids, more behavioral risk factors such as tobacco and increased alcohol use, and less physical activity, all of which can contribute to low bone density and risk of falls and fractures.[33]

Daily use of SSRIs increases fracture risk

A 2012 meta-analysis[36] of 12 studies (seven case-control and five cohort), showed that SSRI users had a higher overall risk of fracture (adjusted odds ratio 1.69, 95% CI 1.51–1.90). By anatomic site, pooled odds ratios and 95% CIs were:

- Vertebral fractures 1.34 (1.13–1.59)
- Wrist or forearm fractures 1.51 (1.26–1.82)
- Hip or femur fractures 2.06 (1.84–2.30).

A 2013 meta-analysis[37] of 34 studies with more than 1 million patients found that the random-effects pooled relative risk of all fracture types in users of antidepressants (including but not limited to SSRIs) was 1.39 (95% CI 1.32–1.47) compared with nonusers. Relative risks and 95% CIs in antidepressant users were:

- Vertebral fractures 1.38 (1.19–1.61)
- Nonvertebral fractures 1.42 (1.34–1.51)
- Hip fractures 1.47 (1.36–1.58).

Depression itself may be a risk factor for fracture

A population-based, prospective cohort study[38] of 5,008 community-dwelling adults age 50 and older, followed for 5 years, found that the daily use of SSRIs was associated with a twofold increased risk of clinical fragility fractures (defined as minimal trauma fractures that were clinically reported and radiographically confirmed) after adjusting for potential covariates. Daily SSRI use was also associated with an increased risk of falling (odds ratio 2.2, 95% CI 1.4–3.5), lower bone mineral density at the hip, and a trend toward lower bone mineral density at the spine. These effects were dose-dependent and were similar

for those who reported taking SSRIs at baseline and at 5 years.

Bottom line: Counsel bone health

Although no guidelines exist for preventing or treating SSRI-induced bone loss, providers should discuss with patients the potential effect of these medications on bone health, taking into account patient age, severity of depression, sex, duration of use, length of SSRI treatment, and other clinical risk factors for osteoporosis.[34] Given the widespread use of these medications for treating depression, more study into this association is needed to further guide providers.

ANTIEPILEPTIC DRUGS

Antiepileptic drugs are used to treat not only seizure disorders but also migraine headaches, neuropathy, and psychiatric and pain disorders. Many studies have linked their use to an increased risk of fractures.

The mechanism of this effect remains controversial. Early studies reported that inducers of cytochrome P450 enzymes (eg, phenobarbital, phenytoin) lead to increased vitamin D degradation, causing osteomalacia.[39] Another study suggested that changes in calcium metabolism and reduced bone mineral density occur without vitamin D deficiency and that drugs such as valproate that do not induce cytochrome P450 enzymes may also affect bone health.[40] Other bone effects may include direct inhibition of intestinal calcium absorption (seen in animal studies) and the induction of a high remodeling state leading to osteomalacia.[41,42]

The benefit of preventing seizures outweighs the risks of fractures

Epilepsy itself increases risk of fractures

Patients with seizure disorders may also have an increased risk of fractures because of falls, trauma, impaired balance, use of glucocorticoids and benzodiazepines, and comorbid conditions (eg, mental retardation, cerebral palsy, and brain neoplasm).[43]

A 2005 meta-analysis[43] of 11 studies of epilepsy and fracture risk and 12 studies of epilepsy and bone mineral density found that the risks of fractures were increased. The following relative risks and 95% CIs were noted:

- Any fracture 2.2 (1.9–2.5), in five studies
- Forearm 1.7 (1.2–2.3), in six studies
- Hip 5.3 (3.2–8.8), six studies
- Spine 6.2 (2.5–15.5), in three studies.

A large proportion of fractures (35%) seemed related to seizures.

Certain drugs increase risk

A large 2004 population-based, case-control, study[44] (124,655 fracture cases and 373,962 controls) found an association between the use of antiepileptic drugs and increased fracture risk. After adjusting for current or prior use of glucocorticoids, prior fracture, social variables, comorbid conditions, and epilepsy diagnosis, excess fracture risk was found to be associated with the following drugs (odds ratios and 95% CIs):

- Oxcarbazepine 1.14 (1.03–1.26)
- Valproate 1.15 (1.05–1.26)
- Carbamazepine 1.18 (1.10-1.26)
- Phenobarbital 1.79 (1.64–1.95).

The risk was higher with higher doses. Fracture risk was higher with cytochrome P450 enzyme-inducing drugs (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone; odds ratio 1.38, 95% CI 1.31–1.45) than for noninducing drugs (clonazepam, ethosuximide, lamotrigine, tiagabine, topiramate, valproate, and vigabatrin; odds ratio 1.19, 95% CI 1.11–1.27). No significant increased risk of fracture was found with use of phenytoin, tiagabine, topiramate, ethosuximide, lamotrigine, vigabatrin, or primidone after adjusting for confounders.

Bottom line: Monitor bone health

With antiepileptic drugs, the benefit of preventing seizures outweighs the risks of fractures. Patients on long-term antiepileptic drug therapy should be monitored for bone mineral density and vitamin D levels and receive counseling on lifestyle measures including tobacco cessation, alcohol moderation, and fall prevention.[45] As there are no evidence-based guidelines for bone health in patients on antiepileptic drugs, management should be based on current guidelines for treating osteoporosis.

AROMATASE INHIBITORS

Breast cancer is the most common cancer in women and is the second-leading cause of cancer-associated deaths in women after lung cancer. Aromatase inhibitors, such as anastro-

zole, letrozole, and exemestane, are the standard of care in adjuvant treatment for hormone-receptor-positive breast cancer, leading to longer disease-free survival.

However, aromatase inhibitors increase bone loss and fracture risk, and only partial recovery of bone mineral density occurs after treatment is stopped. The drugs deter the aromatization of androgens and their conversion to estrogens in peripheral tissue, leading to reduced estrogen levels and resulting bone loss.[46] Anastrozole and letrozole have been found to reduce bone mineral density, increase bone turnover, and increase the relative risk for nonvertebral and vertebral fractures in postmenopausal women by 40% compared with tamoxifen.[47,48]

Base osteoporosis treatment on risk

Several groups have issued guidelines for preventing and treating bone loss in postmenopausal women being treated with an aromatase inhibitor. When initiating treatment, women should be counseled about modifiable risk factors, exercise, and calcium and vitamin D supplementation.

Baseline bone mineral testing should also be obtained when starting treatment. Hadji et al,[49] in a review article, recommend starting bone-directed therapy if the patient's T score is less than –2.0 (using the lowest score from three sites) or if she has any of at least two of the following fracture risk factors:

- T score less than –1.5
- Age over 65
- Family history of hip fracture
- Personal history of fragility fracture after age 50
- Low body mass index (< 20 kg/m^2)
- Current or prior history of tobacco use
- Oral glucocorticoid use for longer than 6 months.

Patients with a T score at or above –2.0 and no risk factors should have bone mineral density reassessed after 1 to 2 years. Antiresorptive therapy with intravenous zoledronic acid and evaluation for other secondary causes of bone loss should be initiated for either:

- An annual decrease of at least 10% or
- An annual decrease of at least 4% in patients with osteopenia at baseline.[49]

In 2003, the American Society of Clinical Oncology updated its recommendations on the role of bisphosphonates and bone health in women with breast cancer.[50] They recommend the following:

- If the T score is –2.5 or less, prescribe a bisphosphonate (alendronate, risedronate, or zoledronic acid)
- If the T score is –1.0 to –2.5, tailor treatment individually and monitor bone mineral density annually
- If the T score is greater than –1.0, monitor bone mineral density annually.

All patients should receive lifestyle counseling, calcium and vitamin D supplementation, and monitoring of additional risk factors for osteoporosis as appropriate.[50]

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***ADDRESS**: Faye N. Hant, DO, MSCR, Associate Professor of Medicine, Division of Rheumatology and Immunology, Medical University of South Carolina, 96 Jonathan Lucas Street, Suite 816, Charleston, SC 29425; hant@musc.edu*