Drug-induced Osteoporosis: Mechanisms and Clinical Implications

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ABSTRACT

Drug-induced osteoporosis is common and has a significant impact on the prognosis of patients suffering from chronic debilitating diseases. Glucocorticoids are the drugs causing osteoporotic fractures most frequently, but osteoporosis with fractures is observed also in women treated with aromatase inhibitors for breast cancer, in men receiving anti-androgen therapy for prostate cancer, in postmenopausal women treated with high doses of thyroxine, and in men and women treated with thiazolidinediones for type 2 diabetes mellitus. Bone loss with fractures also occurs in patients treated with drugs targeting the immune system, such as calcineurin inhibitors, antiretroviral drugs, selective inhibitors of serotonin reuptake, anticonvulsants, loop diuretics, heparin, oral anticoagulants, and proton pump inhibitors.

Osteoporosis is a skeletal disorder characterized by a decrease in bone mineral density (BMD) and loss of structural and biomechanical properties of the skeleton, leading to an increased risk of fractures. Individual patients have genetic and acquired risks for osteoporosis. Among acquired risks, pharmacological interventions are important contributors to the bone loss observed in osteoporosis (Table 1). Drug-induced osteoporosis is common, and has a significant impact on the morbidity and mortality of patients suffering from chronic debilitating diseases for which drug intervention is necessary. Unfortunately, awareness of this form of secondary osteoporosis is limited. This article reviews the mechanisms and clinical implications of drug-induced osteoporosis (Tables 2 and 3).

We performed a formal search of the electronic literature (MEDLINE) from 1990 to 2009 using the following search terms: osteoporosis, bone fractures and glucocorticoids, thyroxine, aromatase inhibitors, ovarian suppressing agents, androgen deprivation therapy, thiazolidinediones, selective serotonin reuptake inhibitors, anticonvulsants, heparins, oral anticoagulants, loop diuretics, calcineurin inhibitors, antiretroviral therapy, proton pump inhibitors. One hundred and eighty-nine original articles, systematic reviews, and meta-analyses from studies in humans published in the English language were considered.

HORMONAL THERAPY

Glucocorticoids

Glucocorticoids are used in the treatment of inflammatory and autoimmune diseases, neoplasias, and following organ transplantation. Glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis. The central mechanism of action of glucocorticoids is decreased bone formation, secondary to impaired osteoblastic differentiation and function.1 However, during the initial phases of glucocorticoid exposure, bone resorption is increased, ex-
plaining an early bone loss. Glucocorticoids inhibit bone formation and have additional indirect effects on bone metabolism, explaining an increased risk of fractures (for a complete review, see ref. 1). The underlying disorder for which glucocorticoids are administered is often associated with bone loss as a consequence of chronic inflammation, malnutrition, and reduced physical activity.1

Glucocorticoid-induced osteoporosis is characterized by low bone turnover and fractures, which occur in 30%-50% of patients.2 Glucocorticoids affect predominantly cancellous bone, increasing the risk of vertebral fractures, which may be asymptomatic and occur early during the first months of glucocorticoid treatment.2,3 Published reports suggest that there is no dose of glucocorticoid therapy that is safe for the skeleton. Regimens of daily prednisone at doses as low as 2.5 mg have been associated with an increased risk of hip and vertebral fractures. The risk increases by 5-fold, with prednisone doses above 7.5 mg daily. A dramatic 17-fold increase in vertebral fracture incidence was observed in subjects who used prednisone continuously more than 10 mg per day for longer than 3 months. As expected, the greatest increase in fracture incidence was seen in postmenopausal females and elderly males. The risk of osteoporotic fractures remains increased in patients undergoing cyclic corticosteroid treatment at high doses. It is noteworthy that fracture risk decreases after discontinuation of oral corticosteroids, although the time it takes to reduce the risk appears to be variable.5 The risk of osteoporosis associated with inhaled glucocorticoids or with budesonide, a topical steroid used in inflammatory bowel disease, is small because their absorption is limited.

In glucocorticoid-induced osteoporosis, fractures occur at higher BMDs than in postmenopausal osteoporosis.5 Consequently, guidelines for the treatment of postmenopausal osteoporosis are not applicable to glucocorticoid-induced osteoporosis, and patients should be treated at BMD T-scores of ≤−1.0 to −1.5.5 Because vertebral fractures may be asymptomatic, a radiological evaluation is often necessary for their identification.

It is appropriate to treat individuals exposed to glucocorticoids (prednisone equivalents ≥5 mg/day) for 3-6 months. Vitamin D and calcium are recommended for the management of all patients treated with glucocorticoids. Bisphosphonates should be considered for the prevention and treatment of this disorder, because they can prevent the initial loss of bone mass in this disorder. Alendronate, risedronate, and zoledronic acid were shown to prevent and reverse the loss of BMD in glucocorticoid-induced osteoporosis with greater effects than those observed with vitamin D and calcium.7,8 In fact, bisphosphonates induce improvement of BMD that is 2-fold greater than that observed during vitamin D treatment (ie, 4.6% vs. 2.0%).9 Anabolic therapy appears to be ideal for the treatment of glucocorticoid-induced osteoporosis, and teriparatide causes a greater increase in BMD than alendronate and greater reduction in the risk of vertebral fractures.9

**Table 1**  **Drugs Associated with Osteoporosis**

<table>
<thead>
<tr>
<th>Hormonal therapy</th>
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<tbody>
<tr>
<td>Glucocorticoids</td>
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<tr>
<td>Thyroid hormone</td>
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<tr>
<td>Aromatase inhibitors</td>
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<tr>
<td>Ovarian suppressing agents</td>
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<tr>
<td>Androgen deprivation therapy</td>
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<tr>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Psychotropic and anticonvulsant therapy</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Drugs used for cardiovascular diseases</td>
</tr>
<tr>
<td>Heparins</td>
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<tr>
<td>Oral anticoagulants</td>
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<tr>
<td>Loop diuretics</td>
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<tr>
<td>Drugs targeting the immune system</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
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<tr>
<td>Anti-retroviral therapy</td>
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<tr>
<td>Drugs used for gastrointestinal diseases</td>
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<tr>
<td>Proton pump inhibitors</td>
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</tbody>
</table>

**CLINICAL SIGNIFICANCE**

- Hormonal and nonhormonal (psychotropic and cardiovascular) drugs may cause osteoporosis.
- Drug-induced osteoporosis occurs primarily in postmenopausal women, but premenopausal women and men are also significantly affected.
- Glucocorticoids are the most common cause of drug-induced osteoporosis.
- Diagnostic criteria for postmenopausal osteoporosis do not necessarily apply to drug-induced osteoporosis.
- Anti-osteoporotic treatments may be effective in drug-induced osteoporosis, if drug discontinuation is not feasible.

**Thyroxine**

Thyroxine is prescribed for the treatment of hypothyroidism, goiter, and thyroid carcinoma following thyroid ablation. Patients with thyroid carcinoma are treated with high doses of thyroxine to suppress endogenous thyrotropin (TSH). In hypothyroidism, thyroid replacement therapy is used to normalize serum thyroid hormone levels. However, about 25% of these patients are over-treated and display suppressed serum levels of TSH.10 Subclinical thyrotoxicosis causes atrial fibrillation, cardiac dysfunction, and bone loss in elderly subjects and postmenopausal women.11 Thyroid hormones increase bone resorption directly and indirectly by inducing the production of bone-resorbing cyto-
kines. Recently, TSH was reported to inhibit bone resorption directly, suggesting that the suppression of TSH itself may cause bone loss.\textsuperscript{13,14}

Thyrotoxicosis increases bone turnover, decreases BMD, and increases the risk of fractures. The impact of subclinical hyperthyroidism on the skeleton is dependent on the age and sex of patients, duration of thyroxine treatment, and the presence of additional factors predisposing them to bone loss.\textsuperscript{11,15} Thyroid suppression therapy causes bone loss in postmenopausal women, increasing the risk of vertebral and hip fractures by 3- to 4-fold.\textsuperscript{11,15,16} There are no specific guidelines for the prevention of bone loss when thyroid suppression is necessary. Supplemental calcium and vitamin D should be used, and patients with increased fracture risk should be treated with antiresorptive drugs. However, long-term TSH-suppressive therapy with thyroxine may reduce the beneficial effects of bisphosphonates on BMD.\textsuperscript{17}

### Aromatase Inhibitors

Aromatase inhibitors are more effective than tamoxifen as adjuvant therapy of estrogen-receptor-positive breast cancer, with longer disease-free survival and without the risk of endometrial hyperplasia and cancer, cerebrovascular and venous thromboembolic events. Whereas tamoxifen can have estrogen-like effects on bone, aromatase inhibitors induce bone loss. Aromatase inhibitors inhibit the aromatization of androgens and their conversion to estrogens in peripheral tissues. The substantial reduction in estrogen concentrations caused by the suppression of androgen aromatization causes bone loss. Anastrozole and letrozole are nonsteroidal aromatase inhibitors, and exemestane is a steroid similar to androstenedione that binds and irreversibly inhibits aromatase.

Letrozole and anastrozole increase bone turnover, decrease BMD, and increase the relative risk of vertebral and nonvertebral fractures by 40\%, when compared with tamoxifen.\textsuperscript{18,19} The skeletal effects observed are correlated inversely with baseline BMD and serum estradiol concentrations, and osteoporosis is more prevalent in women starting aromatase inhibitors early after menopause.\textsuperscript{19,20} There is only a partial recovery of BMD following the withdrawal of aromatase inhibitors. Bone loss with increased risk of fractures.

### Table 2 Mechanisms of Drug-induced Osteoporosis in Vivo

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Effects on Bone Remodeling</th>
<th>Effects on Calcium Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone Resorption</td>
<td>Bone Formation</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>↑↑</td>
<td>↑</td>
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<tr>
<td>Aromatase inhibitors</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Ovarian suppressing agents</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Androgen deprivation therapy</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Thiazolidinediones</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Not determined</td>
<td>↓</td>
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<tr>
<td>Anticonvulsants</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Heparin</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Oral anticoagulants</td>
<td>Not determined</td>
<td>↓</td>
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<tr>
<td>Loop diuretics</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Calcineurin inhibitors</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Anti-retroviral therapy</td>
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<td>↑</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

\textsuperscript{1} PTH = Parathyroid hormone.
\textsuperscript{2} ↑ = increased; ↓ = decreased; ↔ = unchanged.

### Table 3 Clinical Aspects of Drug-induced Osteoporosis: Impact on Bone Mineral Density and Fractures

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Bone Mineral Density</th>
<th>Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lumbar Spine</td>
<td>Hip</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>↓↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>↓↑</td>
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<td>↑↑</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Fractures were assessed by a clinical approach.

\textsuperscript{2} ↑ = increased; ↓ = decreased; ↔ = unchanged.
gility fractures also is observed in women receiving exemestane.21

Zoledronic acid and risedronate were shown to prevent and reverse aromatase inhibitor-induced bone loss, but data on fracture reduction efficacy are scanty.22,23 Zoledronic acid was more effective in preventing than in reversing bone loss, and as an additional benefit, it increased disease-free survival in subjects with carcinoma of the breast.22,24 Denosumab, a monoclonal antibody against receptor activator of nuclear factor–kappa B ligand, is effective in preventing aromatase inhibitor-induced bone loss in women with non-metastatic breast carcinoma.25 Patients should receive supplemental calcium and vitamin D. Bisphosphonates should be prescribed to individuals with fractures, established osteoporosis (T score ≤ −2.5) or osteopenia (T-score between −1 and −2.5 SD), and additional risk factors.26 Women with normal BMD and without osteoporosis risk factors should be monitored with dual-energy X-ray absorptiometry every 12 to 24 months, although fragility fractures may occur independently of BMD.

**Ovarian Suppressing Agents**

**Gonadotropin-releasing Hormone Agonists.** Gonadotropin-releasing hormone agonists are drugs with increased receptor affinity or prolonged half lives, leading to persistent activation of gonadotropin-releasing hormone receptors, causing an initial release of pituitary gonadotropins followed by a downregulation of gonadotropin-releasing hormone receptor and suppression of gonadotropin secretion. Consequently, ovarian sex-steroid production is suppressed. Gonadotropin-releasing hormone agonists are effective in the management of endometriosis and breast cancer in premenopausal women. They suppress estrogen levels and cause bone loss. A decrease of about 6%/year in BMD is observed in patients on gonadotropin-releasing hormone agonists with a recovery of bone mass after discontinuation. Gonadotropin-releasing hormone agonists may not increase the risk of fragility fractures in women with normal BMD.27

**Medroxyprogesterone Acetate.** Medroxyprogesterone acetate inhibits gonadotropin secretion, suppressing ovulation and production of estrogens by the ovary. It is effective in the treatment of endometriosis and as a contraceptive agent. Medroxyprogesterone acetate causes a decrease in BMD and increases the risk of fractures. Its discontinuation results in BMD restoration.28,29

**Androgen Deprivation Therapy**

Androgen deprivation therapy is used in the treatment of metastatic and locally advanced prostate carcinoma, and is effective in reducing tumor growth and improving survival of men affected by this tumor. Androgen deprivation therapy is achieved with gonadotropin-releasing hormone analogs alone or in combination with anti-androgenic therapy. Gonadotropin-releasing hormone analogs reduce serum testosterone and estradiol levels and increase bone turnover and bone loss.30 Decrease in lean body mass, increase in fat mass, and impaired muscular strength are observed and may contribute to increased risk of fractures.31

In men with carcinoma of the prostate, BMD at hip, ultradistal radius, and lumbar spine decreases by 2%-5% after 12 months of androgen deprivation therapy, and the relative risk of vertebral and hip fractures increases by 40%-50%.32,33 The risk of fractures correlates with the degree and rate of BMD decrease, patient age, and duration of therapy, but not with tumor stage.33,34

Treatment is recommended for patients with pre-existing osteoporotic fractures, T-scores ≤ −2.5 or between −1 and −2.5 with significant risk factors for fractures.35 Calcium and vitamin D are indicated. Bisphosphonates are effective in the prevention and reversal of androgen deprivation therapy-induced bone loss, but data on fracture reduction effects are scanty.36,37 Selective estrogen receptor modulators, such as raloxifene and toremifene, also have beneficial effects on BMD.38,39 Recently, denosumab was shown to prevent bone loss and the incidence of vertebral fractures in men receiving androgen deprivation therapy.40 An assessment of risk-benefit ratio of androgen deprivation therapy should be performed. Indeed, androgen deprivation therapy is frequently administered to patients with nonmetastatic prostate cancer, in whom effects on survival have not been documented. Alternatives to androgen deprivation therapy, such as the nonsteroidal anti-androgen bicalutamide, may be preferable in the management of prostate carcinoma in patients with osteoporosis because this drug has comparable effectiveness to gonadotropin-releasing hormone agonists without deleterious effects on bone.41

**Thiazolidinediones**

Thiazolidinediones are insulin-sensitizing drugs used for the treatment or prevention of type 2 diabetes mellitus. Thiazolidinediones may cause side effects on the cardiovascular system, liver and skeleton. Currently available thiazolidinediones, rosiglitazone and pioglitazone, are selective agonists of peroxisome proliferator-activated receptor-γ. In vitro and in vivo studies demonstrate that peroxisome proliferator-activated receptor-γ induction in mesenchymal cells leads to increased adipogenesis and decreased osteoblastogenesis.42 Thiazolidinediones also decrease the expression of insulin-like growth factor I, and this may contribute to decreased bone formation.43 In addition, thiazolidinediones promote osteoclast differentiation and bone resorption.44

Long-term treatment with thiazolidinediones increases the risk of fractures by up to 4-fold in postmenopausal women and in men.45,46 This risk correlates with the duration of treatment with thiazolidinediones and is significant after 12 to 18 months.47 Thiazolidinediones should be avoided in patients with established osteoporosis or at high risk for fractures.45,46 Patients on thiazolidinediones should be assessed by dual-energy X-ray absorptiometry and thiazolidinediones should be
discontinued if significant bone loss occurs, although reversibility of bone loss is unknown.\textsuperscript{45,46}

**PSYCHOTROPIC AND ANTICONVULSANT THERAPY**

Selected drugs with central nervous system effects may alter skeletal metabolism. This has clinical relevance because patients taking these drugs are often elderly and frail, with a propensity to fall and, consequently, to fracture.

**Selective Serotonin Reuptake Inhibitors**

Selective serotonin reuptake inhibitors, agents used for the treatment of depression, can cause bone loss. Functional serotonin receptors and transporters are present in osteoblasts and osteocytes, and serotonin can influence bone metabolism.\textsuperscript{48} Postmenopausal women on selective serotonin reuptake inhibitors exhibit bone loss and a 2-fold increase in the risk of nonvertebral fractures.\textsuperscript{49} There are no specific guidelines for the prevention of the bone loss observed with selective serotonin reuptake inhibitors, but screening of women on these drugs for osteoporosis and appropriate therapy should be considered.

**Anticonvulsants**

Anticonvulsants are used in epilepsy, psychiatric conditions and in chronic pain management. Anticonvulsants may cause bone loss, but the mechanisms are unclear. There is accelerated vitamin D metabolism, but anticonvulsants also may have direct inhibitory effects on osteoblast differentiation, and valproate and carbamazepine have anti-androgenic effects.\textsuperscript{50}

Low serum 25-hydroxyvitamin D levels, high bone turnover, and secondary hyperparathyroidism can occur in patients on anticonvulsants, decreasing BMD and increasing the risk of fractures by 2-fold.\textsuperscript{50} BMD loss correlates with treatment duration. Most of the fractures are nonvertebral and tend to occur in younger individuals, suggesting that epilepsy itself may contribute to an increased risk of osteoporosis and fractures. There is limited understanding of the pathogenesis of this skeletal disorder, so diagnostic and therapeutic guidelines have not been established. Calcium and vitamin D supplementation is recommended. Because anticonvulsants accelerate vitamin D metabolism, doses required to correct vitamin D deficiency may be greater than those required in the general population.

**DRUGS USED FOR CARDIOVASCULAR DISEASES**

**Heparin**

Heparin is effective in the prevention and treatment of venous thromboembolism. In vitro, heparin inhibits the differentiation and function of osteoblasts.\textsuperscript{51} In vivo, heparin decreases bone formation and increases bone resorption, the latter by inhibiting the expression of osteoprotegerin, a decoy receptor for receptor activator of nuclear factor–kappa B ligand.\textsuperscript{51}

In pregnant women, up to one third of patients placed on heparin have a significant decrease in BMD, with fractures occurring in only 2.2%-3.6% of all cases.\textsuperscript{52,53} In nonpregnant women, the incidence of fractures is higher, and \( \sim 15\% \) of patients experience vertebral fractures 3-6 months after starting heparin.\textsuperscript{54} Fragility fractures are less frequent in patients on low-weight heparin than unfractionated heparin.\textsuperscript{54} Moreover, the newly developed anticoagulant fondaparinux does not cause bone loss and may be considered as an alternative to heparin in osteoporotic patients.\textsuperscript{55}

**Oral Anticoagulant Therapy**

Oral anticoagulants are often used in older subjects to prevent or treat deep vein thrombosis; their effects on bone metabolism are controversial. Anticoagulants are vitamin K antagonists that interfere with gamma-carboxylglutamate formation, and consequently inhibit the accumulation of osteocalcin in the extracellular matrix.\textsuperscript{56} Although these are potentially negative effects, evidence that these drugs cause osteoporosis and fractures in the general population is insufficient.\textsuperscript{57,58}

**Loop Diuretics**

Loop diuretics are often used in the management of congestive heart failure, which itself is associated with an increased risk of fragility fractures.\textsuperscript{59} Loop diuretics inhibit sodium and chloride reabsorption and consequently inhibit calcium reabsorption, increasing its renal excretion and bone turnover.\textsuperscript{60} This results in decreased BMD and increased risk of fractures in men and postmenopausal women on long-term treatment with these drugs.\textsuperscript{61,62} Most of the fractures are nonvertebral.

**DRUGS TARGETING THE IMMUNE SYSTEM**

**Calcineurin Inhibitors**

Calcineurin inhibitors are immunosuppressants used in combination with glucocorticoids in patients undergoing organ transplantation. In vitro, cyclosporine and tacrolimus inhibit osteoclastogenesis and bone resorption.\textsuperscript{63} However, in vivo, these drugs cause bone loss due to markedly increased bone resorption.\textsuperscript{64} Changes in T-cell cytokine production and altered vitamin D metabolism with secondary hyperparathyroidism may contribute to the effects of calcineurin inhibitors. Furthermore, it is not possible to isolate the contribution of the underlying disease and glucocorticoids from their effects on BMD and fragility fractures.\textsuperscript{65} Fracture risk is related to the patient age and the underlying disease.\textsuperscript{65} Older age and lower BMD are predictors of vertebral fractures in patients with cardiac disease, but not in those with liver disease. In this condition, prevalent vertebral fractures are the only predictors of future vertebral fractures.\textsuperscript{66} BMD is of modest value in patients with end-stage renal disease because of renal osteodystrophy.

Because bone loss occurs in the initial months of immunosuppressive therapy, treatment should be instituted early.
Calcium and vitamin D supplementation, and antiresorptive agents should be considered for the prevention of bone loss occurring after transplantation with uncertain effects on fracture risk.67

Antiretroviral Therapy
The introduction of antiretroviral therapy significantly reduced morbidity and mortality in patients suffering from human immunodeficiency virus (HIV). Antiretroviral drugs cause bone loss by increasing osteoclastogenesis and bone resorption, and by causing mitochondrial damage, impairing osteoblastic function and bone formation. These effects lead to a decrease in BMD.68

Data on fracture incidence are limited, and studies on HIV patients do not discriminate between those receiving and not receiving antiretroviral therapy. The relative risk of vertebral and nonvertebral fractures increases by about 40% and 70%, in females and males with HIV infection, respectively.69 Currently, antiretroviral therapy-induced bone loss is managed with a reduction of risk factors, supplemental calcium and vitamin D, and physical exercise. Alendronate and zoledronic acid increase BMD in HIV patients, but their benefit on fracture reduction is not documented.70,71

DRUGS USED FOR GASTROINTESTINAL DISEASES
Proton Pump Inhibitors
Proton pump inhibitors are commonly used in the treatment of diseases of the upper gastrointestinal tract. In vitro, the inhibition of proton pumps on the osteoclast ruffled border may decrease bone resorption.72 However, proton pump inhibitors decrease intestinal calcium absorption, increasing bone resorption in vivo. Proton pump inhibitors decrease BMD at the lumbar spine and hip, and increase the risk of vertebral and nonvertebral fragility fractures, depending on drug dose and duration of therapy.73,74 Fracture risk is reversed 1 year after proton pump inhibitors withdrawal. Histamine-receptor 2 blockers do not cause bone loss.75

CONCLUSIONS
Drugs routinely used for treatment of multiple diseases have detrimental effects on the skeleton. Awareness of this clinical problem is limited, and consequently, preventive measures are often not undertaken. Adequate monitoring of bone health and therapeutic intervention are recommended when drugs with an adverse bone safety profile are used, particularly in patients with additional risk factors for osteoporosis.

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References


