Treatment of Osteoporosis in Patients with Chronic Liver Disease and in Liver Transplant Recipients

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Opinion statement

The pathogenesis of osteoporosis in chronic liver disease and post-liver transplantation is complex and heterogeneous. The development of hepatic osteodystrophy may be related to both increased bone resorption and decreased bone formation. Available medical treatments can be broadly classified into antiresorptive and bone-stimulating agents. Most published studies on the treatment of osteoporosis in patients with liver disease have used the commonly prescribed antiosteoporosis drugs approved for postmenopausal osteoporosis. These studies have included a small number of subjects and used bone mineral density (BMD) changes rather than fracture occurrence as an endpoint because of the short follow-up. Although the increases in BMD are promising, no intervention is proven to have antifracture efficacy in hepatic osteodystrophy. The natural history of bone disease following liver transplantation has not been fully investigated, although studies suggest that bone mineral loss is transient and generally reverses within a year following transplantation. The approach to treatment in liver transplant recipients should be targeted at preventing the early bone loss without interfering with the later recovery. Based on the available data, no single available agent can be considered as first-line therapy. In our opinion, the best treatment approach involves the elucidation of modifiable risk factors and the selection of agents targeted at the underlying derangements.

Introduction

Osteoporosis and osteoporotic fractures occur commonly in patients with liver cirrhosis and following liver transplantation. The prevalence of osteoporosis and osteoporotic fractures in chronic liver disease has been reported to vary between 37% and 53% and 4% and 21%, respectively [1–3]. The fracture incidence following successful liver transplantation is relatively high and ranges between 10% and 43% [4,5]. The rationale for evaluating and treating osteoporosis in patients with liver disease is to prevent the morbidity associated with these osteoporotic fractures.

The pathogenetic mechanism of hepatic osteodystrophy is complex and may be due to defective osteoblastic bone formation, increased osteoclastic bone resorption, or both (Table 1). These changes may be secondary to genetic and/or acquired causes. Evidence for a genetic link includes a weak correlation between bone mineral density (BMD) in primary biliary cirrhosis (PBC) patients and certain polymorphisms in the genes for the vitamin D receptor and collagen type Iα1 [6]. Acquired causes include environmental factors such as diet (insufficient intake of calcium, vitamin D),

Table 1. Pathogenesis of osteoporosis in chronic liver disease and in patients post-liver transplantation

Increased bone resorption	
Contributor	Molecular mechanism
Gonodal hormone deficiency	Cytokine-mediated (IL-1, IL-6, others)
Vitamin D deficiency	PTH-mediated
Glucocorticoid treatment (early)	↑ RANKL/OPG ratio, secondary hyperparathyroidism
Immunosuppressive agents (eg, cyclosporine, tacrolimus)	Direct effects on bone, secondary hyperparathyroidism
Decreased bone formation	
Contributor	Molecular mechanism
Alcohol	Direct effects on osteoblast
Decreased hepatic IGF-1 production	Decreased osteoblastic proliferation and differentiation
Hyperbilirubinemia	Impaired osteoblastic proliferation
Glucocorticoid treatment (chronic)	Increased osteoblast and osteocyte apoptosis, impaired osteoblastic function

IGF-1—insulin-like growth factor-1; OPG—osteoprotegerin; PTH—parathyroid hormone; RANKL—receptor activator of nuclear factor-kappa-B ligand.

lifestyle factors (smoking, alcohol intake, and physical exercise), and medications (steroids, cholestyramine) [7•]. The dysregulation of vitamin D and sex hormone metabolism also is likely to contribute to the bone abnormalities of cirrhotic patients [8]. Furthermore, hyperbilirubinemia has been shown to impair the proliferation of human osteoblastic cell line [9]. Moreover, impaired hepatic synthesis of insulin-like growth factor-1 (IGF-1), a key regulator of osteoblastic proliferation and differentiation, occurs in patients with chronic liver disease [10].

Following liver transplantation, a rapid decline in BMD occurs in the first 3 to 6 months and is associated with a significant increase in the incidence of osteoporotic fractures [4]. These changes have been ascribed to the high doses of glucocorticoids and other immunosuppressive agents, such as cyclosporine-A and tacrolimus (FK-506), that increase bone resorption [11•]. Published studies suggest that the rapid fall in BMD in post-liver transplantation patients is transient, and in most patients, the BMD increases gradually starting 3 to 6 months after successful liver transplantation, regardless of the treatment [12,13]. Furthermore, the incidence of bone fractures (mostly spine and ribs) following liver transplantation parallels the early changes in BMD and declines after 1 year [5].

In our opinion, a thorough investigation must be initiated by reviewing the modifiable risk factors previously described. We also suggest measuring BMD and evaluating the biochemical profile, including parathyroid hormone (PTH), 25-hydroxyvitamin D, gonadal hormones, and markers of bone turnover. This evaluation will allow for individualization of the treatment approach, which should be targeted at the specific underlying abnormalities.

Treatment

- Most available treatments for osteoporosis have been extensively studied in patients with postmenopausal osteoporosis. Limited data are available on the heterogeneous population of patients with chronic liver disease. Similarly, our knowledge of prevention and treatment of osteoporosis in post-liver transplantation patients is limited by the small number of studied patients and the lack of availability of fracture data. Finally, although most of the available reports have used BMD as the primary endpoint, it has been argued that BMD changes post-liver transplantation are poor predictors of fractures in transplanted patients [14]. Despite these limitations, BMD remains the best available tool and surrogate marker to estimate bone strength.

Lifestyle

Exercise

- The skeletal effects of lifestyle modification in patients with chronic liver disease have not been reported. In patients with postmenopausal osteoporosis, an exercise regimen that includes supervised aerobic, weight-bearing, and weightlifting exercises increased femoral neck, trochanteric, and lumbar spine BMD by approximately 1% to 2%. Resistance training led to a faster recovery in the BMD post-cardiac transplantation when compared with no specific exercise regimen [15], but its effects have not been reported in liver transplant recipients.

Sun exposure

- Sun exposure is probably the single most important source of vitamin D [16]. Ten to 15 minutes of sun exposure without sunscreen to the face, hands, arms, or back at least twice weekly typically is sufficient to provide adequate vitamin D [17]. On the other hand, liver transplant recipients are at increased risk for skin cancer [18] and thus may need to receive vitamin D in the form of supplements.

Smoking

- Smoking has been shown to influence estrogen metabolism and may directly impair osteoblastic activity. In patients with chronic liver disease, one may assume that smoking cessation also may play an important role in fracture prevention, although specific data are lacking.

Pharmacologic treatment

- Adequate calcium and vitamin D intake should be ensured in all patients before other antiosteoporotic treatments are initiated. Aside from calcium and vitamin D, available pharmacologic treatments can be broadly classified into antiresorptive and bone-stimulating agents. Antiresorptive drugs include calcitonin, estrogen, selective estrogen receptor modulators, and bisphosphonates. These agents inhibit osteoclastic bone resorption through a variety of mechanisms and as a result transiently raise and then stabilize BMD. Bone-stimulating medications include PTH and fluoride. These drugs stimulate *de novo* osteoblastic bone formation, resulting in a more persistent rise in BMD. Head-to-head comparison of the antifracture efficacy of these agents has not been examined.

Calcium

Standard dosage	Recommended daily allowance: 1000 to 1500 mg elemental calcium in divided doses (two to three times daily).
Mode of action	Essential component of bone mineral, suppresses PTH (thus lowering bone resorption).
Contraindications	Hypercalcemia. Nephrolithiasis is a relative contraindication.
Main drug interactions	Concomitant oral intake of calcium may impair the absorption of bisphosphonates, thyroid supplements, and tetracycline.
Main side effects	Constipation, hypercalciuria/kidney stones. Calcium administered with meals may lower intestinal phosphorus absorption.
Special points	Bioavailability of calcium citrate is superior to that of other commercially available calcium salts [19]. Calcium supplements other than calcium citrate depend upon gastric acid secretion for optimal calcium absorption and therefore should be taken with meals. In patients taking proton-pump inhibitors, calcium citrate is the preferred calcium salt. Calcium supplementation alone may slightly increase BMD in patients

with chronic liver disease [20], but it does not prevent BMD loss post-liver transplantation [11•]. The antifracture efficacy of calcium supplementation alone in these patients has not been studied. On the other hand, most of the studies utilizing specific antiosteoporotic agents were conducted in combination with sufficient provision of calcium. Therefore, an optimal intake of 1000 to 1500 mg elemental calcium is recommended in patients with liver disease and those who are post-liver transplantation, as in the general population.

Cost Calcium supplements are available over the counter; most cost less than $0.30 per tablet.

Vitamin D

Standard dosage The physiologic requirement for vitamin D is 400 to 800 IU/d [16]. The major source of vitamin D is skin production from sunlight exposure. The main dietary sources are animal liver, cod liver oil, fish, vitamin D-fortified milk (100 IU/8-oz cup) and vitamin D-fortified orange juice (100 IU/8-oz cup) [16]. Standard multivitamin tablets and most calcium supplements provide 200 IU per tablet. Vitamins D_2 (ergocalciferol, plant source) and D_3 (cholecalciferol, animal source) can be used for vitamin D supplementation in vitamin D-deficient patients, although vitamin D_2 (ergocalciferol) is the only readily available preparation in the United States. In the body, vitamin D is hydroxylated to its active metabolite, 1,25-dihydroxyvitamin D (calcitriol), which is active in regulating calcium absorption from the gastrointestinal tract and its utilization in the body.

Mode of action Increases fractional intestinal calcium absorption.

Contraindications Ergocalciferol and calcitriol are contraindicated in patients with hypercalcemia, hypervitaminosis D, and/or abnormal sensitivity to the toxic effects of vitamin D.

Main drug interactions None known.

Main side effects Vitamin D toxicity, hypercalcemia. Measurement of serum 25-hydroxyvitamin D concentration should be considered in special cases.

Special points Patients with PBC due to cholestasis and those with associated celiac disease are susceptible to vitamin D deficiency and may require therapeutic doses of prescribed vitamin D (up to 50,000 U/wk). In patients with fat malabsorption and/or chronic diarrheal states, oral suspensions of vitamin D_2 (ergocalciferol), 1000 U/mL, can be used. Prospective studies have not shown a consistent increase in BMD in patients with hepatic osteodystrophy and post-liver transplantation treated with vitamin D [21–23] or calcitriol alone [24,25]. Nevertheless, an effort should be made to accommodate the daily physiologic requirement of vitamin D in this patient population.

Cost Ergocalciferol, 50,000-IU capsules: $75.80 for 50 capsules. Calcitriol, 0.25-μg capsules: $42.65 for 30 capsules.

Calcitonin

Standard dosage Salmon calcitonin: 200 IU intranasal daily.

Mode of action Interacts with the calcitonin receptor on osteoclasts and reduces bone resorption.

Contraindications Allergy to salmon calcitonin.

Main drug interactions No known major drug interactions.

Main side effects Nasal irritation, epistaxis, rhinitis.

Special points Efficacy in raising the bone density in patients with hepatic osteodystrophy is not clearly established [26]. Calcitonin is not effective in the prevention of bone loss in early post-liver transplantation patients [12,27], although it may have an effect on BMD late (> 1 year) post-transplantation [26]. Calcitonin is a safe alternative in patients who cannot tolerate other treatments.

Cost A 3.7-mL bottle, 200 IU/inhalation (30-day supply) costs $90.04.

Estrogen

Standard dosage A large number of preparations and various routes of administration are available. Most commonly prescribed preparations include the following:

Estradiol: 0.5 mg, 1 mg, 1.5 mg, and 2 mg orally; 0.025 to 0.1 mg/24 h weekly and twice-weekly transdermal patches.

	Conjugated estrogens: 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg orally. Historically, transdermal estrogen was thought to have an advantage over the oral route in patients with liver disease because of diminished risk of worsening cholestasis, although the two routes were shown to be equally safe in recent studies.
Mode of action	Inhibits osteoclastic bone resorption.
Contraindications	Undiagnosed abnormal genital bleeding. Known, suspected, or history of breast cancer. Known or suspected estrogen-dependent neoplasia. Active deep vein thrombosis, pulmonary embolism, or a history of these conditions. Active or recent (ie, within the past year) arterial thromboembolic disease (eg, stroke, myocardial infarction).
Main drug interactions	Estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma estrogen concentrations. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma estrogen concentration and may result in side effects.
Main side effects	Increased risk of endometrial and breast cancer. Increased risk of cardiovascular disease and thromboembolism.
Special points	Since the results of the Women's Health Initiative studies [28], estrogen replacement is no longer considered for the prevention and treatment of postmenopausal osteoporosis. Despite some reservation regarding estrogen use in patients with cholestatic liver disease, several studies reported no alteration in liver function tests following administration of oral, topical, and parenteral preparations of estrogen in these patients [29,30]. Nevertheless, we suggest following liver function tests in women with cholestatic disease receiving estrogen treatment. No prospective trial has shown that estrogen replacement therapy is effective against fractures in patients with chronic liver disease and in post-liver transplantation patients. However, in a few retrospective studies, estrogen treatment has been associated with higher BMD in PBC patients [29,30] and liver transplant recipients [31].
Cost	Different costs.

Selective estrogen receptor modulator

Standard dosage	Raloxifene, 60 mg/d.
Mode of action	Inhibits osteoclastic bone resorption.
Contraindications	Contraindicated in lactating women, in women who are or who may become pregnant, and in women with active or past history of venous thromboembolic events.
Main drug interactions	Coadministration of cholestyramine with raloxifene hydrochloride is not recommended.
Main side effects	Hot flashes and leg cramps. Venous thromboembolism.
Special points	Raloxifene has been shown to prevent vertebral but not hip fractures in postmenopausal osteoporosis. Its effectiveness in patients with chronic liver disease and in post-liver transplantation patients has not been studied in a systematic fashion [32].
Cost	$84.91 for 30-day supply of 60-mg tablets.

Testosterone

Standard dosage	Intramuscular: testosterone enanthate or cypionate, 100 to 200 mg intramuscularly every 2 weeks. Transdermal patch: 2.5 to 6.0 mg/d. Topical gel: 2.5 to 5.0 g/d. Oral transmucosal: 30 mg every 12 hours.
Mode of action	Increases bone formation and suppresses bone resorption (depending on dose).
Contraindications	Androgens are contraindicated in men with carcinomas of the breast, prostate, and, possibly, hepatocellular carcinoma.
Main drug interactions	No major drug interactions.
Main side effects	Polycythemia, prostate enlargement (benign prostatic hypertrophy and, possibly, prostate cancer), gynecomastia, skin reaction (depending on preparation), hepatotoxicity and alteration of lipid profile with oral androgens.
Special points	Androgens are indicated for replacement therapy in male hypogonadism, a common finding in men with chronic liver disease [8]. Because of alteration in sex hormone-binding globulin with liver disease, free testosterone rather than total testosterone

should be evaluated in patients with liver disease. Transdermal and topical preparations are preferred over intramuscular products in patients with liver disease. Testosterone replacement increased BMD in a small number of hypogonadal men with hemochromatosis [33]. Antifracture has not been proven. Testosterone levels normalize in the majority of liver transplant recipients.

Cost Intramuscular: $5 to $40/mo. Transdermal: $120/mo. Topical: $180/mo.

Bisphosphonates

Standard dosage Oral: alendronate, 10-mg daily tablets and 70-mg weekly tablets; risedronate, 5-mg daily and 35-mg weekly tablets; ibandronate, 2.5-mg daily and 150-mg monthly tablets. Intravenous: pamidronate, 30-, 60-, and 90-mg vials; zoledronic acid, 4-mg vials; ibandronate, 3-mg vials.

Mode of action Inhibits osteoclastic bone resorption.

Contraindications Oral and intravenous agents: not recommended for patients with renal insufficiency (serum creatinine > 3.0 mg/dL or creatinine clearance < 35 mL/min) or in patients with hypocalcemia or disorders of mineral metabolism, including vitamin D deficiency and hypoparathyroidism. Oral agents: abnormalities of the esophagus that delay esophageal emptying, such as stricture, achalasia, or varices. Inability to stand or sit upright for at least 30 minutes.

Main drug interactions No drug interactions.

Main side effects Oral and intravenous agents: hypocalcemia, especially in patients with vitamin D deficiency, hypoparathyroidism, and renal insufficiency. Avascular necrosis of the jaw (mostly with repeated intravenous dosing). Oral bisphosphonates may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer. Intravenous bisphosphonates may cause renal insufficiency, especially with repeated dosing.

Special points Bisphosphonates are the most potent antiresorptive agents available. Vitamin D deficiency should be corrected prior to initiation of bisphosphonates. Intestinal absorption of oral bisphosphonates is very limited (~ 1%); therefore, these agents must be administered on an empty stomach and with water only. Oral bisphosphonates are corrosive to the esophageal mucosa (hence the need for water intake and 30 to 60 minutes of upright posture after ingestion). Furthermore, this erosive property has limited the use of oral bisphosphonates in patients with varices from portal hypertension. Patients with chronic diarrhea and malabsorption are specifically at risk of developing bisphosphonate-induced hypocalcemia, due to concomitant vitamin D deficiency. The limited data available regarding the use of oral bisphosphonates in patients with chronic liver disease suggest a significant increase in BMD [34,35], although no antifracture efficacy data are available. Oral [36] and intravenous bisphosphonates [37,38] administered with calcium and vitamin D are effective in preventing BMD loss early after liver transplantation, although fracture prevention has not been demonstrated. The optimal dose, timing, frequency, and duration remain to be determined. In our opinion, liver transplant recipients, due to the transient nature of their bone loss, should receive a single intravenous dose of either pamidronate or zoledronic acid at the time of transplantation. This strategy was proven to be successful in kidney transplant recipients [39] but should be tested in controlled studies in liver transplantation.

Cost Alendronate: $70.37 for four 70-mg tablets, $75.40 for 30 10-mg tablets. Risedronate: $70.48 for four 35-mg tablets, $75.52 for 30 5-mg tablets. Ibandronate: $241.50 for three 150-mg tablets, cost unknown for 3 mg/3 mL prefilled syringe. Zoledronic acid: $999.39 for 4 mg/5 mL infusion. Pamidronate: $839.60 for 90 mg for infusion.

Fluoride

Standard dosage Slow-release fluoride, 25 mg twice daily.

Mode of action Stimulates bone formation.

Contraindications Gastric ulcers/irritation, renal insufficiency.

Main drug interactions None described.

Main side effects Fluorosis, gastric irritation.

Special points Not US Food and Drug Administration approved. Adequate calcium and vitamin D supplementation are required for optimal mineralization of newly laid-down bone collagen and avoidance of osteomalacia. Cyclic treatment is important to prevent high-fluoride skeletal burden. No commercially available preparation in the United States. In studies in limited numbers of patients with PBC [40] and following liver transplantation, fluoride showed promising BMD results, although antifracture efficacy was not shown.

Cost No commercially available preparation in the United States.

PTH

Standard dosage Teriparatide (PTH 1-34), 20 μg subcutaneously daily.

Mode of action Stimulates osteoblastic bone formation.

Contraindications Hypercalcemia, patients at risk for bone cancer. In rats, teriparatide caused an increase in the incidence of osteosarcoma that was dependent on dose and treatment duration. The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with teriparatide: Paget's disease of bone, pediatric patients, and patients who have received prior external beam or implant radiation therapy involving the skeleton. Teriparatide should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

Main drug interactions No known drug interactions.

Main side effects Dizziness and leg cramps.

Special points Despite its effectiveness in raising BMD at the lumbar spine and the hip, teriparatide may lower BMD at the radius bone [41]. Therapy should be limited to no more than 2 years. Efficacy may be attenuated if used simultaneously with bisphosphonate treatment. No studies published to date have shown the efficacy of teriparatide in patients with chronic liver disease or in post-liver transplantation patients. Teriparatide as a bone-forming agent may have a role in this patient population.

Cost $624.18 for 750-μg/3 mL vial (1-month supply).

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