Osteoporosis: An Endocrinologist’s Perspective

Michael T. McDermott, MD
Professor of Medicine and Clinical Pharmacy
University of Colorado Denver Health Sciences Center
Director, Endocrinology and Diabetes Practice
University of Colorado Hospital
Corresponding author E-mail: Michael.mcdermott@ucdenver.edu

Conflict of Interest

Speaker’s Bureau (Honoraria):
  Eli Lilly
  Novartis
  Sanofi Aventis
  Procter and Gamble
Advisory Board
  Amgen

Introduction

Osteoporosis is defined as impaired bone strength that predisposes to the development of fragility fractures.\textsuperscript{1-4} Fragility fractures are bone fractures that occur with low trauma (a fall from a standing height or less).

\textbf{Figure 1:} Vertebral compression fracture at T6 (Lateral Chest X-ray).

\textbf{Figure 2:} Vertebral compression fracture at T6 (MRI).

\textbf{Figures 1 and 2} illustrate a vertebral fracture as imaged by a lateral chest X-ray and MRI, respectively. Bone mineral density (BMD) measurement is best used to identify osteoporosis in patients who have not yet had a fragility fracture. Osteoporosis is diagnosed by bone densitometry criteria when the lowest T-score (number of standard deviations the patient is below the average BMD for young normal adults) is \textless{} -2.5 and osteopenia is diagnosed when the lowest T-score is -1.0 to -2.4, whereas BMD is normal when T-scores at all sites are \textgreater{} -1.0. \textbf{Figure 3} shows a typical bone densitometry report. Osteoporosis is the most common cause but other conditions may contribute to or be the sole cause of low bone mass and fragility fractures (\textit{Table 1}). Once osteoporosis is diagnosed, an assessment for other bone disorders and secondary bone loss\textsuperscript{5,6} should be undertaken by a cost effective evaluation such as that outlined in \textit{Table 2}.
Determining which patients should receive active osteoporosis therapy is the first issue to settle. Treatment should be initiated for anyone who has sustained a vertebral or hip fragility fracture and for any patient who has a T-score < -2.5. For patients with osteopenia (T-score: -1.0 to -2.4) and no previous fragility fractures, the FRAX tool (URL: www.shef.ac.uk/FRAX; or Google: FRAX) is a valuable adjunct to assist in making treatment decisions (Table 3). Developed by the World Health Organization (WHO) and easily accessed online, this tool utilizes a weighted risk factor equation to estimate the 10 year probability of a fragility fracture.

Effective treatment must include both non-pharmacologic and pharmacologic measures. Non-pharmacologic interventions consist of adequate calcium intake (1200-1500 mg daily) and vitamin D intake (800-1200 units daily), regular exercise, and fall prevention. Dairy products are the best calcium source (~ 300 mg per serving: cup of milk, ounce of...
cheese, 6 ounces of yogurt) because dairy products contain both calcium and phosphorus, the two major mineral components of bone. When adequate calcium intake cannot be achieved by dairy products, calcium supplements should be added in amounts sufficient to achieve the goal calcium intake (diet plus supplements = 1200-1500 mg/day).

Table 4 lists some common calcium supplements that are available over the counter. Calcium carbonate and calcium citrate are equally well absorbed with meals if gastric acid is present. However, calcium carbonate absorption is significantly reduced in patients who have deficient gastric acid production (atrophic gastritis). There is ongoing controversy about the potentially adverse skeletal effects of proton pump inhibitors (PPIs). Three large epidemiologic studies have reported an increased risk of hip fractures in patients on PPIs, although the risk is clearly rather small. The mechanism of this effect is not completely clear. Some, but not all, studies have reported that PPIs significantly reduce intestinal calcium absorption. However, because the existing data are not conclusive...
and since PPIs are effective medications that provide significant relief to legions of patients, changes in the indications for PPI use and monitoring are not warranted at this time. Furthermore, any purported PPI effects on calcium absorption can be countered by increasing calcium carbonate doses or switching to calcium citrate supplements.

Vitamin D comes naturally in two major forms: Vitamin D3 (cholecalciferol) and Vitamin D2 (ergocalciferol)\(^1\). Vitamin D3 is synthesized from the 7-dehydrocholesterol precursor in the skin in response to sunlight exposure. Fatty fish are rich in Vitamin D3 and several foods (milk, cereals) are fortified with either Vitamin D2 or D3. Vitamin D2 and D3 supplements are available over the counter in multiple doses and 50,000 unit Vitamin D2 supplements can be given by prescription. Since sunlight exposure is often limited for many reasons, oral vitamin D is the major source for most people. The optimal vitamin D intake is 800-1200 units daily. Vitamin D supplements should be recommended to patients with serum 25 OH Vitamin D levels < 30 ng/ml\(^7,14,15\). Patients with malabsorption syndromes may need higher Vitamin D doses for prolonged periods or permanently\(^16\).

Exercise should be done at least 3-5 times weekly and should consist of both aerobic and resistance work. This improves both bone and muscle strength and can reduce the risk of falling. Fall frequency and risks should be assessed at each visit and measures instituted to correct or mitigate any identified fall risk factors, such the use of sedatives, visual impairment, musculoskeletal impairment and obstacles to ambulation in the home environment.

Pharmacologic therapy consists of medications that can alter bone remodeling. Remodeling is a natural process by which older, more fragile bone is replaced with newer, stronger bone. Osteoclasts bind to the surface of older bone and secrete chemicals that dissolve the underlying (bone resorption) creating resorption pits. Osteoblasts then migrate into these pits and secrete osteoid (bone specific collagen) which subsequently become mineralized with calcium-phosphate (hydroxyapatite) crystals to form strong new bone. Osteoblasts then become imbedded in the newly formed bone and transform into osteocytes, which serve as mechanoreceptors that sense areas

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Elemental Calcium per Tablet (mg)</th>
<th>Vitamin D Content per Tablet (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Carbonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caltrate</td>
<td>600 mg</td>
<td>200 IU</td>
</tr>
<tr>
<td>Oscal</td>
<td>500 mg</td>
<td>200 IU</td>
</tr>
<tr>
<td>Viactive</td>
<td>500 mg</td>
<td>100 IU</td>
</tr>
<tr>
<td>Tums</td>
<td>200 mg</td>
<td>0</td>
</tr>
<tr>
<td>Tums EX</td>
<td>300 mg</td>
<td>0</td>
</tr>
<tr>
<td>Tums Ultra</td>
<td>400 mg</td>
<td>0</td>
</tr>
<tr>
<td>Tums 500</td>
<td>500 mg</td>
<td>0</td>
</tr>
<tr>
<td>Nature Made</td>
<td>500 mg</td>
<td>200 IU</td>
</tr>
<tr>
<td>Nature Made</td>
<td>600 mg</td>
<td>200 IU</td>
</tr>
<tr>
<td>Maalox</td>
<td>222 mg</td>
<td>0</td>
</tr>
<tr>
<td>Rolaid</td>
<td>250 mg</td>
<td>0</td>
</tr>
<tr>
<td>Calcium Citrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citracal</td>
<td>200 mg</td>
<td>0</td>
</tr>
<tr>
<td>Citracal</td>
<td>250 mg</td>
<td>62.5 IU</td>
</tr>
<tr>
<td>Citracal</td>
<td>315 mg</td>
<td>200 IU</td>
</tr>
<tr>
<td>Multiple Vitamins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women’s One a Day</td>
<td>450 mg</td>
<td>400 IU</td>
</tr>
<tr>
<td>Centrum Silver</td>
<td>200 mg</td>
<td>400 IU</td>
</tr>
</tbody>
</table>

Table 4: Over the Counter Calcium Supplements
of skeletal stress and send signals to orchestrate the process of bone remodeling in areas of bone that need renewal. Bone loss occurs when the balance between bone resorption and bone formation is altered such that bone resorption exceeds bone formation.

Pharmacologic agents (Table 5) are classified into two main categories: anti-resorptive medications and anabolic medications. Anti-resorptive medications inhibit osteoclastic bone resorption and allow natural bone formation to continue for a variable period of time, resulting in a net gain of bone mass. Anabolic agents stimulate osteoblastic new bone formation, increasing bone mass by progressive bone accrual in up to 10% of patients, are heartburn and upper gastrointestinal pain, which in some cases is due to esophageal erosions and ulceration. Intravenous bisphosphonates are particularly useful in patients with upper GI side effects to the oral agents or prior poor adherence to the prescribed oral dosing regimen.

Pharmacologic agents (Table 5) are classified into two main categories: anti-resorptive medications and anabolic medications. Anti-resorptive medications inhibit osteoclastic bone resorption and allow natural bone formation to continue for a variable period of time, resulting in a net gain of bone mass. Anabolic agents stimulate osteoblastic new bone formation, increasing bone mass by progressive bone accrual in up to 10% of patients, are heartburn and upper gastrointestinal pain, which in some cases is due to esophageal erosions and ulceration. Intravenous bisphosphonates are particularly useful in patients with upper GI side effects to the oral agents or prior poor adherence to the prescribed oral dosing regimen.

Table 5: Osteoporosis Medications

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-Resorptive Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>Oral</td>
<td>10 mg</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70 mg</td>
<td>Weekly</td>
</tr>
<tr>
<td>Risedronate (Actonel)</td>
<td>Oral</td>
<td>5 mg</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 mg</td>
<td>Weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ibandronate (Boniva)</td>
<td>Oral</td>
<td>150 mg</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>3 mg</td>
<td>3 Months</td>
</tr>
<tr>
<td>Zoledronic Acid (Reclast)</td>
<td>IV</td>
<td>5 mg</td>
<td>Yearly</td>
</tr>
<tr>
<td><strong>Non-Bisphosphonates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene (Evista)</td>
<td>Oral</td>
<td>60 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Calcitonin (Miacalcin)</td>
<td>Nasal</td>
<td>200 U</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>SQ</td>
<td>100 U</td>
<td>Daily</td>
</tr>
<tr>
<td>Denosumab</td>
<td>SQ</td>
<td>60 mg</td>
<td>6 Months</td>
</tr>
<tr>
<td><strong>Anabolic Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide (Forteo)</td>
<td>SQ</td>
<td>20 mcg</td>
<td>Daily</td>
</tr>
</tbody>
</table>

Bisphosphonates are the most widely used anti-resorptive medications for osteoporosis management. The FDA approved bisphosphonates (Alendronate, Risedronate, Ibandronate, and Zoledronic Acid) have all been documented to significantly increase BMD and reduce the risk of vertebral fractures; Alendronate, Risedronate, and Zoledronic Acid have also been shown to reduce the risk of hip fractures. Side effects with the oral bisphosphonates, seen

The non-bisphosphonate anti-resorptive medications currently available are estrogen replacement therapy, Raloxifene (Evista) and salmon calcitonin. Estrogen replacement therapy (ERT) and estrogen plus progesterone replacement therapy (HRT) were commonly used in the past to prevent and treat postmenopausal osteoporosis. The Women’s Health Initiative (WHI) study report in 2002 confirmed the efficacy of ERT and HRT for prevention of fractures but also confirmed a previously reported increased risk of breast cancer and cardiovascular events; following this report, the use of ERT and HRT significantly decreased. Currently ERT (women without an intact uterus) and HRT (women with an intact uterus) are recommended mainly for limited use for up to 3 years to treat postmenopausal hot flashes. Women receiving these therapies should have regular mammograms and
gynecology visits to monitor for the development of breast and uterine cancers. It should be recognized, however, ERT and HRT are effective anti-resorptive regimens with anti-fracture efficacy and most women being treated with these regimens do not need to take concomitant osteoporosis medication.

Raloxifene is a synthetic Selective Estrogen Receptor Modulator (SERM) that binds specifically to estrogen receptors and selectively acts as an estrogen agonist in some tissues (bone) and an estrogen antagonist in other tissues (breast). Raloxifene has been demonstrated in increase BMD moderately and to reduce the risk of vertebral but not hip fractures. This medication also significantly reduces the risk of invasive breast cancer. Reported side effects include hot flashes, edema, and increased risk for venous thromboembolic events (VTEs) and fatal strokes.

Calcitonin is a less potent anti-resorptive medication that produces modest increases in BMD but has been shown to significantly reduce the risk of vertebral fractures. It is usually administered as a daily intranasal spray. Rhinitis, epistaxis and nasal ulcerations may occur, especially after prolonged use. When these side effects occur, one can switch to the subcutaneous preparation of this medication.

Denosumab is a monoclonal antibody that inhibits bone resorption by binding to Rank Ligand, a major regulator of osteoclastic bone resorption. It has been shown to significantly increase BMD and reduce the risk of vertebral, hip and non-vertebral fractures. The drug is administered by subcutaneous injection 60 mg once every 6 months.

Teriparatide (Forteo) is the only anabolic bone agent currently approved in the United States. The anabolic action of this 34 amino acid fragment of intact PTH results from once daily pulse exposure, since continuous exposure to PTH is known to stimulate bone resorption and bone loss. Teriparatide has been shown to increase BMD 2-3 times more than the anti-resorptive medications and to reduce the risk of both vertebral and non-vertebral fractures. Teriparatide should not be used in patients who have hypercalcemia. Osteogenic sarcomas were reported in preclinical research in rats given 3-60 times the equivalent human dose of Teriparatide but an increased incidence of this tumor has not been demonstrated in humans. Nonetheless, it is recommended that Teriparatide be avoided in patients who are at increased risk of developing bone cancer, including patients with open epiphyses, unexplained alkaline phosphatase elevations, Paget’s disease, primary or metastatic bone cancer, and a history of prior radiation therapy involving or significantly exposing the skeleton. Teriparatide treatment is currently limited to a single two year course of therapy. Following Teriparatide therapy, treatment with an anti-resorptive agent should be instituted to preserve the improvement in bone mass and strength achieved with Teriparatide.

Concern about over-suppression of bone remodeling is an issue that has recently arisen in the context of prolonged use of potent anti-resorptive medications like bisphosphonates. This has been fueled by the description of two rare conditions: osteonecrosis of the jaw (ONJ) and atypical femoral fractures. ONJ is defined as prolonged (> 8 weeks) non-healing bone and gums following invasive dental procedures (tooth extractions or implants). An example of ONJ is shown in Figure 4. It has been reported most commonly

There have now been over 100 reported cases of atypical transverse femoral fractures, often bilateral,
in patients on long term bisphosphonate therapy (> 5 years)\textsuperscript{38-40}. \textbf{Figure 5} shows an example of a transverse femoral fracture. Since all reported patients have had underlying osteoporosis, it is not clear whether the risk for these fractures results from prolonged bisphosphonate use or the underlying osteoporosis\textsuperscript{41}. Nonetheless, while no data exists regarding the benefits and risks of discontinuing therapy, many providers now consider a 1-2 year bisphosphonate drug holiday for patients who have osteopenia (T-score: -1.0 to -2.4) and are otherwise at a low risk of fractures. For patients who remain at high risk for fractures (previous fractures or T-score < -2.5), it is more common to either continue bisphosphonates, switch to anabolic therapy (Teriparatide), or change to a more quickly reversible non-bisphosphonate anti-resorptive therapy for 1-2 years with subsequent resumption of bisphosphonate therapy.

Repeat DEXA testing to monitor BMD responses to treatment should be repeated in 1-2 years for patients on active osteoporosis therapy and should be considered in 2 years for patients on preventive measures\textsuperscript{42,43}. In order to accurately interpret BMD changes to therapy, the least significant change (LSC) for the specific bone densitometry instrument must be known. The LSC is a precision estimate that informs the user about the minimum BMD change that should be considered significant. This is an internal quality assessment that must be done on every instrument at least every 6-12 months by the individual operators; standard procedures for completing this assessment are available on the International Society for Clinical Densitometry website, www.iscd.org. Potential BMD responses to therapy are shown in \textbf{Table 6}. BMD increases that exceed the LSC are the best responses and confer the maximum protection against future fractures; therapy should be continued in these patients. Stable BMD, with no change or changes that do not exceed the LSC, are considered an adequate response, since up to a 25% reduction in fracture risk has been demonstrated in treated patients whose BMD remains stable; therapy should be continued in these patients also. When the BMD decreases by more than the LSC, this is considered a treatment failure.

The most common reason for treatment failure is

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{BMD Change} & \textbf{Interpretation} & \textbf{Recommended Action} \\
\hline
Increase $\geq$ LSC* & Good Response & Continue Therapy \\
Change $<$ LSC* & Adequate Response & Continue Therapy \\
Decrease $\geq$ LSC* & Treatment Failure & Re-evaluate Cause, Consider Therapy Change \\
\hline
\end{tabular}
\caption{Bone Mineral Density Monitoring on Therapy}
\end{table}

*LSC = Least Significant Change (established for each bone density instrument)
non-adherence to the prescribed therapy. Other contributors include inadequate calcium and vitamin D nutrition and secondary bone loss from other illnesses or high risk medications (Table 1). Actual failure to respond to the medication itself is the least likely explanation for declining BMD. The management of treatment failures is outlined in Table 7. The importance of proper adherence to the prescribed medication regimen must be strongly emphasized. Adequate calcium and vitamin D intake should be encouraged. Illnesses that cause secondary bone loss should be treated and high risk medications should be reduced or discontinued if possible. If none of these factors are present and the provider concludes that the patient is just not responding to the specific medication, a change of therapy is warranted. For those taking an oral bisphosphonate, changing to an intravenous bisphosphonate (ibandronate, zoledronic acid) or anabolic therapy (teriparatide) are reasonable solutions. Those who do not respond to an intravenous bisphosphonate should be switched to teriparatide for two years with subsequent resumption of bisphosphonate therapy.

Gastroenterologists encounter many patients with conditions that predispose to bone loss and osteoporosis, including malabsorption disorders (Crohn’s disease, Celiac disease, bariatric surgery); biliary disorders (primary biliary cirrhosis, primary sclerosing cholangitis), liver failure and liver transplantation. In addition to regular BMD testing, other tools are available to assist providers identify specific disorders or issues that may need therapeutic attention. Assessing vitamin D status (serum 25 OH Vitamin D), calcium absorption (24 hour urine calcium, sodium and creatinine; not accurate if on a thiazide diuretic) will often provide useful information in these patients. Calcium and vitamin D malabsorption in those with Celiac disease often responds well to simple gluten avoidance. In contrast, patients with less manageable forms of malabsorption may require very large dose of vitamin D (50,000-100,000 units daily in some cases) to restore and maintain serum 25 OH Vitamin D levels above 30 ng/ml. Low urinary calcium levels (< 100 mg/day) in the presence of normal 25 OH Vitamin D levels should prompt an increase in dairy product or calcium supplement intake or a change to a different calcium supplement (replacing calcium carbonate with calcium citrate in PPI users and patients with achlorhydria); urinary calcium measurement can then be repeated and calcium intake titrated to reach a goal urinary calcium excretion of 150-300 mg/day. Once calcium and Vitamin D nutrition are assured, anti-resorptive or anabolic osteoporosis medications should utilized according to the fragility fracture and BMD guidelines discussed. Patients who are treated or will be treated with glucocorticoid therapy should be evaluated and treated more aggressively.

Glucocorticoids taken in supraphysiological amounts cause bone loss by adversely affecting both bone formation and bone resorption. These drugs directly suppress bone formation by inhibiting osteoblast activity through reduced osteoblastogenesis and increased osteoblast apoptosis. They also indirectly stimulate bone resorption through inhibition of osteoprotegerin, an endogenous anti-resorptive cytokine, and centrally mediated suppression of gonadal steroid production. Steroids also appear to enhance apoptosis of osteocytes, which normally function as mechanoreceptors within the bone matrix. As a result of these multiple effects, bone is lost faster with glucocorticoid therapy than in any other situation. Current guidelines from the American College of Rheumatology are to measure BMD in all patients who have been or will be on supraphysiological doses of glucocorticoids.
(prednisone > 5 mg daily or equivalent doses of other glucocorticoids) for > 3 months. Active treatment with osteoporosis medications should then be considered for anyone who has been or will be on these doses for > 3 months when the lowest BMD T-score for men and premenopausal women is < -1.0 and for all postmenopausal women. Three bisphosphonates (Alendronate, Risedronate and Zoledronic Acid) and teriparatide have been demonstrated to have efficacy in improving or stabilizing bone mass in patients with glucocorticoid induced osteoporosis and are FDA approved for use in this condition.

Figure 6: Osteoporosis Management Algorithm.

Figure 6 illustrates an approach the author employs for the general management of patients presenting with new or untreated osteoporosis. All people interested in prevention or treatment of osteoporosis should have adequate intake of calcium and vitamin D and should engage in regular exercise. Patients who have had a fragility fracture should have baseline bone densitometry testing and should be advised to start active medical therapy; based on fracture reduction data, the bisphosphonates and teriparatide are the best choices for patients with current or prior fractures. Bone densitometry testing should be ordered in postmenopausal women with 2 other risk factors, all women age 65 and over, all men age 70 and over and those on high risk medications. Treatment should be recommended for those with a T-score < -2.5; based on fracture reduction data, the bisphosphonates, teriparatide and raloxifene are all good choices for these patients. The FRAX tool should be used to assist in treatment decisions for those with osteopenia (T-scores of -1.0 to -2.4), with treatment recommended for those whose 10 year fracture risk is > 3% for hip fractures and > 20% for other major osteoporosis fractures; based on fracture reduction data, the bisphosphonates and raloxifene are good choices for these patients. For osteopenic patients with lower 10 year fracture risks and for subjects with T-scores > -1.0, preventive measures (calcium, vitamin D, and exercise) should be recommended.
References:


