Current Treatment Approaches to Osteoporosis—2013

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Abstract
The clinical diagnosis of osteoporosis has evolved over the past 20 years to emphasize the relationship between compromised bone strength and fracture susceptibility. The goal of treatment of osteoporosis is fracture prevention. The aging of the American population will place additional burdens on our healthcare system among which will be the need to treat and prevent the estimated increase in fracture rates projected over the next 10 years. There is a significant number of currently available bone strengthening medications used in the treatment of osteoporosis, and this report highlights the effects of these drugs on bone mineral density values and on the relative rates of fragility fractures when these drugs are compared to placebo in clinical trials of subjects with osteoporosis. Identifying those individuals most in need of immediate treatment to prevent fractures remains a challenge despite the use of fracture risk assessment tools, which assess bone mineral density and clinical parameters in order to define an individual’s risk of fracture over a finite period of time. Newer tools that may help better define bone strength (resistance to fracture) include high resolution MRI and finite element analysis of the MRI generated images, and this technology and our experience with it is briefly reviewed in this report. There are a number of new classes of drugs in development for the treatment of osteoporosis, and the clinician is likely to have additional antiresorptive and anabolic agents as treatment options for this condition over the next few years.

The definition of osteoporosis has evolved over the past two decades in order to more accurately reflect the importance of decreased bone strength and its relationship to fracture susceptibility. Prior to 1994, osteoporosis was defined as a clinical syndrome of low trauma fracture in an elderly patient. In 1994, the WHO introduced an epidemiologic definition of osteoporosis based on a bone density test. The bone density diagnosis of osteoporosis was defined as a bone mineral density (BMD) value equal to or more than two and one-half standard deviations (-2.5) below the BMD values of a reference group of 30 year old women. In 2001, an NIH consensus conference defined osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Clinically, osteoporosis is a condition characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures. It is a condition most commonly seen among postmenopausal women mainly as a consequence of the accelerated bone loss that results from estrogen deprivation. According to the National Osteoporosis Foundation, 10 million individuals in the USA are estimated to have osteoporosis, 80% of whom are women. An additional 34 million people are estimated to have some degree of osteopenia. About 4% to 6% of men over the age of 50 have osteoporosis, and it is estimated that the lifetime fracture risk in men ranges from 13% to 25%, a prevalence significantly lower than women whose lifetime risk of fracture is about 50%. One out of every six women aged 50 and older have bone mineral density evidence of...
osteoporosis of the hip, a value similar to the lifetime risk of hip fracture in women. The US population aged 50 or older is predicted to increase by 60% from 2000 to 2025, eventually reaching 121.3 million people. This increase in aging of the population is also predicted to result in a significant increase in fractures among both men and women with the number and costs projected to increase by almost 50% by 2025. The goal of treatment for low bone mass is the prevention of fragility or osteoporotic related fractures. Identifying those individuals at increased fracture risk and establishing cost effective fracture prevention treatment strategies will be a major healthcare focus over the next decade. A review of population based bone density screening programs, the changing approaches to long-term bone strengthening treatment, and the use of fracture risk assessment tools to identify individuals at increased fracture is beyond the scope of this report but will likely be important components in the development of these strategies. Similarly, a discussion of the adverse effects of bone strengthening treatments including atypical femur fractures and osteonecrosis of the jaw, both associated with the use of bisphosphonates, will not be addressed in this report. Advances in imaging techniques and new tools that help to quantify bone strength will likely provide additional insights into identifying individuals at increased fracture risk. This review will focus on the therapeutic options available to prevent osteoporotic fractures once a decision has been made to initiate bone strengthening treatment and briefly introduce how we are using high resolution MRI and finite element analysis to help identify those individuals in need of such treatment.

Pharmacologic Therapy of Osteoporosis

All patients with low bone mass should have an adequate daily intake of calcium and vitamin D in addition to whatever bone strengthening medication they may be using. We generally recommend a daily calcium intake of 1,200 mg with most of the calcium derived from dietary sources if possible. There have been a number of studies questioning the cardiovascular safety of calcium supplementation, but a recent analysis of the Women’s Health Initiative data involving over 93,000 postmenopausal women failed to find evidence for an adverse influence of calcium and vitamin D supplementation on the risk for myocardial infarction, coronary heart disease, total heart disease, stroke, or total cardiovascular disease. While there are a number of different recommendations for daily vitamin D intake, we adjust the daily vitamin D dose to a level that provides an adequate serum level (30 ng/ml and above), a goal that is usually met with daily vitamin D intake of 1,000 to 2,000 IU.

The prescription drugs approved for the treatment of fracture prevention are often classified by whether they reduce bone loss (antiresorptive) or promote bone growth (Table 1). All of the approved drugs have been shown to improve bone mineral density and to prevent some fragility or osteoporosis related fractures. The approach to treatment is tailored to the clinical needs of each individual patient. Fracture risk and the need to initiate treatment is inversely related to bone mineral density and increases with age and a history of a previous osteoporotic fracture. Once a decision to begin treatment has been made, the clinician has a number of effective medications that can be recommended. Treatment decisions should be individualized according the patient’s age, bone density values, prior fracture history, underlying general health, and concomitant medications. Following below is a brief description and an accompanying table listing currently available drugs that have been shown to reduce the relative risk of fractures.

### Bisphosphonates

Alendronate, the first of the newer bisphosphonates to gain FDA approval (1995), has been the most widely prescribed agent of this class of drugs. It is used for the treatment of osteoporosis in men and women and for patients with glucocorticoid-induced osteoporosis (GIO). It increases spine and hip bone mineral density and reduces the relative risk of fracture of the spine, hip, and wrist by about 50%. It is available in a generic form although there have been published reports suggesting decreased efficacy of the generic versions when compared to the branded form of this bisphosphonate.

### Table 1 Bone Density Increases and Relative Fracture Rate Reduction Data for Drugs Used in the Treatment of Osteoporosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>BMD Increase</th>
<th>Fracture Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lumbar Spine</td>
<td>Hip</td>
</tr>
<tr>
<td>Alendronate</td>
<td>8%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Risedronate</td>
<td>5.4%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>5.7-6.5%</td>
<td>2.4% - 2.8%</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>4.3-5.1%</td>
<td>3.1% - 3.5%</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>9-13%</td>
<td>3% - 6%</td>
</tr>
<tr>
<td>Denosumab</td>
<td>8.8%</td>
<td>5.2% - 6.4%</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>1.1%</td>
<td>30% - 55%</td>
</tr>
</tbody>
</table>

All Data are Based on 36-Month Studies Except for Teriparatide which is Based on an 18-month Study; see text for references.
Risedronate was introduced several years after alendronate and is a widely used oral bisphosphonate. It is approved for use of osteoporosis in men and women with osteoporosis and GIO. It is available in once weekly and once monthly dosing options. Risedronate has been shown to reduce vertebral fractures by 41% and nonvertebral fractures by 39% over 3 years. A delayed release form of risedronate (Atelvia) has been approved for the treatment of postmenopausal osteoporosis. It is the only oral bisphosphonate that can be taken immediately after eating breakfast.

Ibandronate is approved for the treatment of postmenopausal osteoporosis. It is available as an oral medication administered on a monthly schedule and by an intravenous injection administered quarterly. It reduces the incidence of vertebral fractures by about 50%. It is also available in a generic version.

Zoledronic acid is given intravenously on an annual basis and has been shown to increase bone mineral density at the spine and hip as well as to reduce the relative incidence of spine fractures by 70%, hip fractures by 41%, and nonvertebral fractures by 25%. It is approved for the treatment of postmenopausal osteoporosis, osteoporosis in men, and for patients with GIO. Based on its fracture prevention data, zoledronic acid is the most potent of the bisphosphonates.

Other Antiresorptive Drugs
Raloxifene is the only selective estrogen receptor modulator (SERM) available in the USA. It is approved for the treatment and prevention of osteoporosis in postmenopausal women and also is indicated for the prevention of invasive breast cancer. It has been shown to increase bone mineral density at the spine and hip and reduce the relative risk of vertebral fractures by 30% (60 mg daily) to 50% (120 mg daily) compared to placebo in the Multiple Outcomes of Raloxifene (MORE) study.

Denosumab is a humanized monoclonal antibody that binds to the receptor activator of the nuclear factor kappa B ligand (RANKL). It rapidly reduces bone resorption by reducing osteoclast activation and function. It is indicated for the treatment of osteoporosis in postmenopausal women and for male osteoporosis. It is administered subcutaneously on an every 6 month dosing schedule. It increases bone mineral density at the spine and hip and reduces the relative risk of vertebral fracture by 68%, hip fractures by 40%, and nonvertebral fractures by 20%. In the 2 year extension phase of the original 3 year FREEDOM trial, denosumab continued to result in significant gains in bone mineral density at the spine and hip.

Calcitonin-salmon is available as an injection and as an intranasal spray. It reduces the incidence of vertebral fractures by 33%. It is usually reserved for the treatment of postmenopausal osteoporosis in women who are not able to tolerate other osteoporosis medications. It was recently determined by the FDA that the potential risks of calcitonin outweigh its benefits as an osteoporosis drug and its use for this indication is discouraged.

Figure 1 High-resolution 3T MR images of proximal femur microarchitecture in: (A) a postmenopausal female with a history of fragility fractures (hip BMD T-score = -2.4) and (B) a postmenopausal female without fracture (BMD T-score = -2.4). In both subjects, individual trabeculae are visible as dark or hypointense linear structures (arrows). In the subject with a history of fragility fractures, there is microarchitectural deterioration within the femoral neck with fewer trabeculae visualized (circles). Finite element analysis of the MR images revealed lower elastic modulus in the femoral neck of the fragility fracture patient (0.86 GPa) compared to the control (3.82 GPa).
Anabolic Drugs
Teriparatide is a human recombinant parathyroid hormone (PTH 1-34) and is the only currently available anabolic agent used in the treatment of osteoporosis. It is indicated for use in men with osteoporosis, women with postmenopausal osteoporosis, and for patients with GIO. It is administered by daily injection and is approved for a maximum of 24 months. It has been shown to increase bone mineral density at the spine and hip and to reduce the relative risk of vertebral fractures by 65% and nonvertebral fractures by 55% over 18 months compared to placebo.20 There have been a number of recent studies suggesting additive effects on bone mineral density when teriparatide is used with antiresorptive drugs.21,22 Such an approach could potentially be beneficial for patients with recurrent fractures as a result of severe osteoporosis.

The Use of High Resolution MRI and Finite Element Analysis in Osteoporosis
As indicated above, the goal of osteoporosis treatment is fracture prevention. While bone density testing is the most reliable tool to help in fracture prediction, many fractures occur in individuals who do not meet the bone density criteria for osteoporosis, whereas half of all women who do have osteoporosis never have a fracture. We have been using high resolution MRI and finite element analysis as methods to analyze the microarchitecture of bone and better define bone strength. After converting a stack of images of bone microarchitecture into a 3-D model made up of millions of small “finite elements,” FEA programs perform simulated loading or stress testing of bones in order to compute metrics of bone mechanical competence, such as elastic modulus or load-to-strength ratio. At NYU, we have developed a method to image bone microarchitecture within the proximal femur, the site of the most devastating fragility fractures.23,24 Preliminary results show that it is possible to detect lower proximal femur strength (elastic modulus) in subjects with fragility fractures compared to controls without fracture, even when these two groups do not differ by BMD T-scores (Fig. 1). We are hopeful that FEA will be a useful tool in studying the effects of bone microarchitecture on bone strength and can help identify patients with compromised bone strength who would most benefit from osteoporosis treatment.

Conclusion
Osteoporosis is a condition of compromised bone strength and increased fracture susceptibility. Identifying patients at increased fracture risk who require immediate bone strengthening medication for fracture prevention remains a challenge. There are a number of very effective drug treatments that have been shown to reduce fracture rates when used for up to 10 years. This review highlights the effects of these drugs on bone mineral density values and fracture rates from published data of placebo controlled clinical trials. This report also briefly described how new imaging techniques and computer modeling is being used to try to better define bone strength. In the future, newer treatment approaches using currently available agents are likely to be more widely used including cycling bisphosphonate treatment with periods of active treatment interrupted by drug holidays particularly for individuals at lower relative fracture risk. Additionally, combining antiresorptive agents with teriparatide may be an option for the most severe cases of osteoporosis with frequent fractures although the cost of such treatment will likely significantly limit its use. There are also new bone strengthening agents in development including cathepsin K inhibitors and anti-sclerostin antibody treatments, which may be clinically available in the years ahead. The aging of the American population will increase the number of people who will need fracture prevention treatment in the near future and identifying those at increased fracture risk who will require such treatment will be an increasing challenge to our healthcare system.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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11. Ringe JD, Moller G. Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis.


