TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 15
Number 2 *Spring 2022*

54-60

2022

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Abstract

Osteoporosis affects tens of millions of people in America and is the most common disease of the bones. New treatments are constantly sought, as existing ones have documented side effects. This review seeks to pinpoint the most effective and safe treatment for osteoporosis by looking at head-to-head trials and research regarding combination therapies. This review also looks at the effectiveness of non-pharmacologic treatments and whether any options are beneficial. The importance of an open patient/provider relationship proves itself, as many medications and treatment plans depend on personal factors that need to be measured and weighed by a medical professional together with the patient.

Introduction

Osteoporosis is a condition in which the density of bones decreases and their overall quality deteriorates. Mainly affecting postmenopausal women and men over the age of 50, osteoporosis puts people at risk for fractures, disability, and in the case of hip fractures, even mortality (Panula et al., 2011).

Bones are dynamic and are constantly being remodeled. The remodeling process accomplishes two objectives: it repairs micro-cracks in bone that result from everyday use, and it also re-aligns and reshapes bone to better handle the stress put on it. The two main cells involved in this process are osteoblasts, responsible for building bone, and osteoclasts, responsible for removing old bone and the resorption of Ca2+ back into the bloodstream. Bones are extremely important for maintaining homeostasis because they are reservoirs of calcium. Muscles and the nervous system also use calcium ions in their basic functions, and when there is a shortage of calcium in the bloodstream, bone resorption is triggered. The thyroid and parathyroid glands control release of calcium from bone into the blood through endocrine signaling.

As we age, different factors increase the risk of osteoporosis. Vitamin and mineral deficiency, more commonly seen in those over 65 years old, contributes to bone loss as vitamin D3 and calcium are necessary for bone health. Stem cells differentiate into osteoblasts at a slower rate over time. Additionally, menopause leads to the decrease of estrogen, the sex hormone responsible for inhibiting osteoclast activity, thereby increasing the risk of osteoporosis in women over 45 years old.

There are numerous pharmacologic treatments approved by the FDA for both prevention and treatment of osteoporosis. These drugs vary greatly in their mechanisms and pathways but fall into two general categories. Some are anti-resorptive, preventing osteoclast activity, and others are anabolic, causing osteoblast activity. Unfortunately, these drugs come with side effects and health risks. The National Osteoporosis Foundation recommends clinicians to use the pharmacological approach only after attempting treatment through diet, exercise, physical therapy and fall prevention guidance. However, once a patient presents with a fracture, drugs are recommended immediately (Cosman et al., 2014).

The first line of treatment recommended are bisphosphonates, such as alendronate and zoledronic acid, which are anti-resorptive drugs that cause osteoclast apoptosis. A more expensive and effective drug is teriparatide (TPTD), the first anabolic drug for osteoporosis. It encourages osteoblast activity and results in greater bone density. Each of these treatments present with their own risks and cannot be used indefinitely, therefore there is a need to maximize the benefit of each treatment. This review is aimed at determining the best treatment of osteoporosis to date.

Methods

Articles were obtained using Touro College's online library and PubMed database using keywords such as "osteoporosis," "bisphosphonates," "teriparatide," and other key terms.

Diagnosis

There are a few major predictors of osteoporosis. The age of a patient is a factor, as most of those with osteoporosis are above the age of 50. A history of fractures and maternal history of fractures also provides a glimpse of future bone-related problems. The OFELY study identified left hand grip strength as an indicator, along with low physical activity and low bone mineral density (Albrand et al., 2003). Patients who have experienced a fracture or who are considered at risk for fracture are advised to have a dual energy x-ray absorptiometry (DEXA) test performed to measure their bone mineral density (BMD). A score is given based on comparison to DEXA results of 30-year-olds of the same race and gender. This frame of reference allows the clinician to assess whether medication is the correct approach to manage a patient's osteoporosis. A BMD T-score of ≤-1.0 in standard deviation indicates osteopenia, the stage of bone density decline that precedes osteoporosis. A score of ≤-2.5 is considered osteoporosis. Measures of the hip, femoral neck, and the vertebral column are taken, and their scores may be independent of each other. Using these numbers alone is not an appropriate way to gauge whether medication is correct. Patient lifestyle and diet should be considered,

as a sedentary individual or a patient who smokes is at risk for a sharper decline in bone density (Krall, Dawson-Hughes, 1999) and should be monitored more often than a physically active or non-smoking patient.

Pharmacologic Treatment

In the event medication is deemed appropriate, the numerous options available are both a blessing and a hurdle. No single medicine has proven completely effective or safe for long term use. As such, new remedies are constantly being sought and extensive research has been done to assess the efficacy of each drug and drug combination as well as the appropriate duration of treatment.

The drugs currently available fall into two main categories: anabolic and anti-resorptive. The anabolic drugs increase osteoblast activity, thereby directly building bone. The anti-resorptive drugs stop osteoclasts from destroying older bone by inducing apoptosis in osteoclasts.

In the category of anti-resorptive drugs are bisphosphonates. These drugs disrupt the resorptive action of osteoclasts by inducing osteoclast apoptosis. The osteoblasts will continue to build bone and that results in greater BMD. Alendronate (Fosamax) is usually the first medication given to an osteoporotic patient, and as Black et al. (2006) found, its effects continue even after discontinuation. Patients who took Alendronate for five years continued to have decreased markers for bone turnover for another five years. Taking bisphosphonates together with an anabolic drug, such as teriparatide (TPTD), a PTH analog, does not show any synergistic benefit, and using a bisphosphonate might even limit the anabolic effect of teriparatide (Black et al., 2003). However, Cosman et al. (2011) asserts that the combination of teriparatide and zoledronic acid (Reclast, a bisphosphonate) is better than either one alone. In a study done by Finkelstein et al. (2003), one group took only alendronate, and another group was given teriparatide 6 six months after starting alendronate. The results were in favor of alendronate monotherapy. Finkelstein comments that the study did not explore whether combination therapy would be better if the two drugs were started at the same time. Muschitz and colleagues researched what would happen if alendronate were given in conjunction with TPTD a few months after TPTD therapy was started, as opposed to TPTD monotherapy. The results showed that combination therapy was more effective (Muschitz et al., 2013). This would indicate that TPTD needs time to start building bone and only then will the combination of an anti-resorptive have an effect greater than TPTD alone. In Cosman's research the drug combination was started at the same time. One may explain such results by conjecturing that distribution of zoledronic acid inside the body works differently than alendronate and allows the TPTD to start building bone before the anti-resorptive starts working. However, this is not true because research has shown that zoledronic acid affects the body faster than alendronate does (Saag et al., 2007). It would seem that there is a benefit to taking zoledronic acid together with TPTD but not alendronate with TPTD.

The anabolic drugs available include teriparatide (Forteo) and abaloparatide (Tymlos). These drugs are recombinant parathyroid hormone, which stimulates the process of bone remodeling. Though continuous release of PTH in the body releases calcium from the bones, weakening them, spaced doses of these PTH analogs stimulate the entire bone remodeling unit. The result is increased bone formation. This is the basis for the hypothesis that bisphosphonates do not work together with anabolic drugs. Bisphosphonates inhibit osteoclasts, and anabolics might rely on osteoclasts as a part of the remodeling unit to result in a net gain of bone. Hagino et al. (2021) found a discrepancy between once-daily administered teriparatide and once-weekly administration. Hagino discovered that although once-daily increases bone formation, once-weekly also decreases bone resorption. We know that the amount of the drug given plays an important role, and a higher dose will result in greater bone formation but also greater bone resorption; at times leading to a net loss of bone density (Neer et al., 2001). The results of Hagino et al. indicate that even at high doses, a once weekly injection of teriparatide prevents bone resorption besides for increasing bone formation. Whether once daily or once weekly injections are more effective is a source of dispute between the results of different trials. The trial led by Hagino, called the JOINT-05 trial, indicated that once weekly is more effective as compared to the once daily VERO trial, led by Kendler. However, the VERO trial considered a patient who took 75% of the injections over the course of the study to be compliant (Kendler et al., 2017). In that case, once-daily administration may indeed be more effective if taken correctly. Additionally, only 29% of participants followed through in the JOINT-05 trial, and therefore the data is less reliable for comparison. In both trials teriparatide was proven to be more effective than bisphosphonates at preventing fractures. Both trials ended the treatment before 24 months because trials in animal models show a risk of osteosarcoma if teriparatide is taken for more than two years. No serious adverse effects were reported, making another case for the use of teriparatide over bisphosphonates.

Recently, Romosozumab (Evenity), a newcomer to the market, appeared to accomplish both goals of anabolism and anti-resorption. Romosozumab is a monoclonal

antibody that binds sclerostin, a protein produced by osteoclasts that inhibits bone growth. It too, was compared head-to-head with alendronate and increased bone mass more than alendronate (Saag, et al. 2017). In a study comparing it to teriparatide, Romosozumab performed better at increasing BMD and bone mineral content (Genant et al., 2017). That study was very small, so it is hard to consider the results as a final judgement. The authors attempt to justify their small numbers with the use of quantitative computed tomography (QCT) which is a more accurate way of imaging and might reflect the results of a larger trial. Romosozumab is administered once monthly as an injection and is to be used for only 12 months due to risk of cardiovascular issues.

Denosumab (Prolia), another monoclonal antibody, functions as an anti-resorptive by binding to receptor activator of nuclear factor-kappa B ligand (RANKL). This receptor normally activates its counter-protein RANK which in turn activates osteoclasts. By binding to RANKL, denosumab stops resorption and increases BMD at a rate similar to zoledronic acid. The two were compared head-to-head in a large trial by Choi et al. (2017). Both showed equal safety and positive effect on BMD and very few cardiovascular events. However, the mean age in the study was 63, and therefore would not reflect the safety of those substantially older and taking these drugs.

Denosumab can cause hypocalcemia and therefore must be taken with calcium and vitamin D3 supplements. Patients who discontinue denosumab lose BMD quickly and are at great risk for a rebound fracture. It is for this reason that those who stop taking denosumab are given a different osteoporotic drug (Cosman et al., 2014).

Denosumab and zoledronic acid are compared because of the frequency and route of administration: subcutaneous injection once or twice a year. Frequency and route of administration are important factors in treating osteoporosis because patient adherence is lower with oral bisphosphonates. They are not absorbed well and so must be taken on an empty stomach and the patient must not lie down for a period of time after taking them. They can cause esophageal ulcers and other GI ailments (Cosman et al, 2014). Denosumab and zoledronic acid are both injections which are absorbed much more efficiently. Their doses are spaced widely, so although they may cause a certain amount of discomfort, they are tolerated better than daily oral or subcutaneous administration.

One concern for all anti-resorptives is the risk for atypical femoral fractures (Shane et al., 2014). These fractures are caused by the decrease in bone remodeling. When osteoclasts are inhibited, they do not clear away old bone and the infrastructure upon which new bone is built can fracture even without trauma. However, these fractures are rare and the benefits of taking bisphosphonates or denosumab and preventing an osteoporotic related fracture outweighs the risk of an atypical femoral fracture. A summary of these drugs, their use, duration, and side effects is presented in Table 1.

Though the possible side effects for each drug might dissuade patients, most are relatively rare. It is notable that in every clinical trial there were those who discontinued the treatment simply due to the discomfort of taking the drug. Indeed, a drug such as zoledronic acid

Drug	Brand Name	Prevention or Treatment	Route of Administration/ Frequency	Type of Drug	Recommended Duration	Main Outcome	Side Effects
Alendronate	Fosamax	Prevention (lower dose) and treatment	Oral (IV not FDA approved) / Daily and weekly dosages available	Bisphosphonate	5-10 years	Anti-resorptive. Induces osteoclast apoptosis	GI perforation, ulcers, esophageal ulcers Rare: osteonecrosis of jaw, atypical femoral fracture
Teriparatide	Forteo	Treatment only	Subcutaneous / daily	Recombinant PTH analog	2 years	Builds bone by stimulating entire remodeling unit.	Hypercalcemia, nausea, pain Rare: osteosarcoma
Denosumab	Prolia	Treatment only	Subcutaneous / once every 6 months	Monoclonal antibody	Up to 10 years	Anti-resorptive, binds to RANKL, stops osteoclast formation	Hypocalcemia, Muscle and joint pain Rare: osteonecrosis of jaw
Romosozumab	Evenity	Treatment only	Subcutaneous / once a month	Monoclonal antibody	1 year	Binds sclerostin, anti-resorptive and anabolic.	Rare: cardiovascular events
Zoledronic Acid	Reclast	Prevention (lower dose) and treatment	IV / one time or once yearly (lower dose)	Bisphosphonate	2 years	Same as alendronate	Flu-like symptoms, muscle and joint pain

Table 1. Information based on National Osteoporosis Foundation's Clinician's Guide to Prevention and Treatment of Osteoporosis (Cosman et al., 2014). Denosumab was found to be safe for up to 10 years (Bone et al., 2017).

causes flu-like symptoms. To judge which drug is the best way to treat osteoporosis one might need to consider side effects that make it difficult to take the drug. The clinician should discuss the side effects with the patient and explain how the benefits outweigh the short-term discomfort.

Non-Pharmacologic Treatment

Osteocytes act as mechanoreceptors and signal bone modeling in areas of high stress. This greatly contributes to the thickness of cortical bone and the unique formation of trabecular bone each person may have. Exercise activates the osteocytes and builds bone. However, as a treatment for osteoporosis, it is difficult to prescribe exercise because of the numerous factors surrounding it. The intensity, type, and amount of each exercise and constitution of each individual plays a role in determining the efficacy of the exercise in building bone.

The LIFTMOR trial sought to demonstrate the effectiveness of high resistance training (HiRT) over a more aerobic, balance-focused exercise program. Using DEXA and a 3D imaging program, the authors verified that a high resistance training program, marked by higher loading and power lifting, will increase BMD significantly more than aerobic training (Watson et al., 2018). The LIFTMOR trial proved that with correct supervision, exercise could provide an increase in BMD and prevent fractures. However, the trial did not include those with cardiovascular problems, and the mean age was 65 ±5, leaving a large population for whom exercise may not be a solution. Additionally, the need for careful supervision during the program may explain why medicine is the first line of treatment for osteoporosis. It is of note that regarding the safety of this program only one out of a hundred and one participants suffered a minor injury that required only a week of rest from the program. Only 7 participants experienced a fall during the 8-month period; none of the falls resulted in a fracture. All the participants had low bone mass, so this indicates that all forms of exercise performed, both balance and HiRT, had a positive effect on fracture occurrences.

Besides for the benefit of high resistance exercise, a trial was done to ascertain whether the rate of mechanical loading also affected bone density. The participants were approximately 4.5 years post-menopause and were all accustomed to high resistance training. Two groups were formed: one performing exercise with a slower rate of loading and unloading, and another group performing the contraction part of each exercise as quickly as possible. Though an increase in BMD was noted in the second group, referred to as the power training (PT) group, it was only noted during the first year of the two-year trial, and only at the spine (von Stengel et al. 2007). Von Stengel hints that such results can be explained by the bones and muscles becoming accustomed to the rapid rate and the osteocytes no longer activating bone growth in response. If there had been a rest period and the exercise subsequently continued, it is possible there would have been an increase in BMD.

Fall prevention and balance training are always recommended (Cosman et al. 2014) and will have a positive effect for those with osteopenia and osteoporosis. Exercise as performed in the above trials is not an appropriate treatment for those with advanced osteoporosis or those who will not have supervision. But there remains an option for the elderly that does not involve medication – whole body vibration (WBV). Research into this technology shows that even the elderly can reap the benefits of mechanical stimulation using WBV. WBV involves a platform with a vibrating plate that delivers a low magnitude vibration that is barely felt yet causes anabolic growth via stimulating the bones (Rubin et al. 2001). A three-year study, however, did not show any benefit to using the WBV platform. The authors of that study conjecture that the large age range, a mean of 82.5 +/-8.1, might have interfered with their results. They also hypothesized that though the technology showed a benefit for younger patients at the same magnitude (Rajapakse et al, 2021), older individuals may require higher intensity (Kiel 2015). It seems that the study by Kiel et al. (2015) was done in a way to ensure safety, but the magnitude was much lower than the standard allowed. In addition, the participants only used the platform for ten minutes a day, whereas from a safety standpoint they could have used it for longer. Also, those who exercise spend more than ten minutes daily doing so, so if WBV can serve as a replacement it should be prescribed for longer durations. The study done by Rajapakse et al. (2021) holds a certain amount of weight over similar studies that did not show as much benefit in WBV because of the adherence level. In Rajapakse's study, the devices were fitted with a sensor that measured usage, supplying more accurate information than self-reporting.

Vitamins

The use of vitamins alone to prevent fractures serves the benefit, like exercise, of avoiding side effects from medication. Vitamin D3 is necessary for bone growth and is often given together with calcium, also a component of bone growth. In a three-year study in Denmark, where most people do not produce enough Vitamin D3 from sunlight alone, Vitamin D3 and calcium together showed

a 16% reduction in fractures (Larsen et al., 2004). In this study, and in another two that showed similar results, there was no use of BMD measurement. Instead, the researchers sent out questionnaires or followed patients through hospital registries to find out who suffered from a fracture. In one of those studies, it was demonstrated that daily administration of 800 IU cholecalciferol, an effective form of vitamin D3, together with calcium, significantly reduced fractures by 30% compared to a placebo (Chapuy et al., 1994). The participants all lived in nursing homes, so adherence was probably very high. The large group (over 870 participants per arm) and similar environment also gives weight to Chapuy's study. Trivedi et al. (2003) studied the effects of vitamin D3 given in large, spaced doses on fracture reduction. They gave a 100,000 IU pill once every four months over a five-year period. Adherence and collection of data was determined through a questionnaire sent with each pill. A 20% reduction in all fractures and 30% at major osteoporotic sites was found in the active group. These three studies imply that preventing fractures can be achieved in an economic fashion with vitamin D3. A difficulty with using fall data, as these three studies did (some via questionnaire), is the need to specify the type of fall, for example low or high impact, and which body parts were affected and whether there was a follow up by a doctor to see if the fall resulted in a fracture. Chapuy specifies whether there was a hip fracture or not and Larsen obtained fracture information from the Danish Hospital Registration Database. No sample of the questionnaires given out were provided, and there may have been cases of fractures that the patients did not report. In short, there is still a very strong case for prescribing medication and not relying on vitamins alone. Though the results are impressive at 30%, the remaining 70% (or a large portion) of participants who experienced fractures would have benefited from medication.

Conclusion

Though osteoporosis affects millions of Americans, there are many options to treat this disease. However, to ensure proper treatment, each case requires a thorough review of the patient's circumstances. This includes the progression of bone loss, patient's diet and lifestyle, and tolerance to drugs. For those with osteopenia or just meeting the threshold for osteoporosis it might be enough to engage in supervised resistance exercise and to take vitamin D3 and calcium. Those with fractures or advanced osteoporosis will require drugs in addition to balance therapy. Most clinicians will agree that the benefits of the current drugs available outweigh the risks of adverse effects. It is important to understand the risks of each drug to ensure that the more serious side effects, such as cardiovascular issues, will not be a concern with a particular patient. It is upon the clinician to have clear knowledge of the patient's health status and know which drug is most suitable. For example, though romosozumab causes the greatest bone growth, it is not suitable for a patient at risk for cardiovascular disease. Monitoring the progress of a treatment and discussing any side effects experienced will help the clinician further tailor the patient's regimen. As technology advances, we can look forward to new remedies in forms such as stem cell infusions and targeted gene therapy. Until then, treating osteoporosis is a lifelong process and patients can benefit from a combination of pharmacologic and non-pharmacologic treatments.

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