TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 15
Number 1 *Fall 2021*

34-38

2021

Osteoporosis: A Comprehensive Review

Eliyahu Greenberg

Osteoporosis: A Comprehensive Review

Eliyahu Greenberg

Eliyahu Greenberg will graduate with a Bachelor of Science degree in Biology in May 2022.

Abstract

Osteoporosis is a disease of the skeleton that becomes more common with advanced age, especially in postmenopausal women. Osteoporosis increases the risk of fractures, thereby reducing the quality of life for those who suffer from it. Due to the aging population, direct costs resulting from osteoporosis are projected to reach upward of $25 billion per year by 2025. The main pharmaceuticals primarily target osteoclasts. Exercise may be an effective method of preventing osteoporosis, although more research needs to be done. More research should be conducted to explore potential ways to enhance osteoblastic activity as a method to treat and/or reverse osteoporosis. This review compares the pros and cons of major methods to treat osteoporosis.

Introduction:

Osteoporosis is a disease of the skeleton that becomes more common with advanced age, especially in postmenopausal women. The CDC reported based on the data from the NHANES (National Health and Nutrition Examination Survey) that 10.2 million adults had osteoporosis and 43.4 million had low bone mass, as of 2010 (Looker, 2015). Osteoporosis leads to an increased risk of fractures, reducing quality of life for those who suffer from it. Due to the aging population, direct costs resulting from osteoporosis are projected to swell upward of $25 billion by the year 2025 (Dempster, 2011). The goal of this review is to present the causes of osteoporosis, explain the current treatments, and weigh the pros and cons of the various therapeutics. Can osteoporosis be prevented, treated, or perhaps even reversed?

Bones are not inanimate objects that the body produces, rather bone is living tissue that continually undergoes a process called remodeling, i.e. the continuous degradation and rebuilding of the bone tissue.

Bones are composed of cells connected through a large extracellular matrix, which is comprised of 15 percent water, 20 percent collagen fibers, and 55 percent mineralized salts. The main salt is calcium phosphate, which combines with calcium hydroxide to form crystals of hydroxyapatite. These crystals continue to combine with other mineral salts to form a hardened tissue. This process, referred to as calcification, is initiated by cells called osteoblasts. Mineral salts crystallize in between and then around collagen fibers. The mixture of stiff crystalized minerals and flexible collagen provides bones with both strength and flexibility. Bone tissue is often compared to reinforced concrete. Collagen is analogous to flexible metal rods that provide support for the concrete-like mineral component (Totora & Derrickson, 2014).

There are many reasons for remodeling. Bones can buffer the amount of calcium in the blood by building more bone mass to use up excess calcium or degrade existing bone to release calcium when needed. The proper concentration of calcium must be maintained in the body, as too much calcium can cause a heart attack while too little can cause breathing to stop. There are two hormones regulating this process. PTH promotes the degradation of bone, releasing calcium, while Calcitonin promotes the deposition of bone, storing calcium.

Other factors that may affect remodeling and the rate of bone deposition include the availability of minerals that make up the bone, especially calcium and phosphorus. Vitamins, particularly Vitamin A which stimulate osteoblasts (the cells that build new bone), and Vitamin C, used in collagen production, are needed as well. Thyroid hormones (T3 and T4) from the thyroid gland promote bone growth by stimulating osteoblasts. In addition, the hormone insulin from the pancreas promotes bone growth by increasing the synthesis of bone proteins (Totora & Derrickson, 2014).

Sex hormones, including estrogen and testosterone, also affect bone growth. They are responsible for increased osteoblast activity, which is why post puberty, many teenagers experience growth spurts. As the level of sex hormones diminishes during middle age, especially estrogen in women after menopause, a decrease in bone mass occurs because bone resorption by osteoclasts outpaces bone deposition by osteoblasts. Estrogen can contribute to bone growth by promoting the death of osteoclasts. In addition, women who have smaller bones with less mass than those of men run a high risk of developing osteoporosis (Totora & Derrickson, 2014).

Bone remodeling happens in two stages. First, old bone tissue is broken down and reabsorbed into the blood via cells called osteoclasts. Then, bone deposition occurs, whereby osteoblasts deposit collagen fibers and minerals. Aside from calcium concentrations, remodeling may also be triggered by factors such as exercise, sedentary lifestyle, and changes in diet. Remodeling helps to fix injured bone and strengthen areas of bone subject to high stress. Newer bone is also more fracture-resistant than older bone (Totora & Derrickson, 2014). If the rate of degradation is higher than the rate of deposition, loss of bone mass will occur and result in osteoporosis.

Methods

The Touro library's database and Google were used to find peer-reviewed articles and papers. Search terms used included "prevention of osteoporosis", "treatment of osteoporosis", "adverse effects of osteoporosis treatments", etc. The Principles of Anatomy and Physiology 14th edition was used as well.

Discussion

Prevention

Although there are several pharmaceuticals that treat osteoporosis, treatments regimens are often poorly followed. A study of 178 patients on a course of treatment for osteoporosis found that 23% of patients did not stick to the prescribed treatment and dropped out. The study reported a number of reasons for noncompliance, ranging from expense, inconvenience of use, and fear of side effects (Segal, Tamir, & al, 2003). A large review of 24 studies on osteoporosis treatments found that "One-third to half of patients do not take their medication as directed. Nonadherence occurs shortly after treatment initiation" (Kothawala, Badamgarav, & al, 2007). As mentioned, bone is living tissue which respond to stress by strengthening itself. Therefore, applying stress through weight-bearing exercises could help to stimulate bone strengthening. A study showed that postmenopausal women who underwent back-muscle training for two years had a higher bone density than that of a control group. Interestingly, the effects were not immediately apparent, and were only evident when measured 8 years after the exercise regimen stopped. Apparently, exercise has long term, but not immediate effects (M. Sinaki, 2002). Aside from increased bone health, the impact of stronger muscles results in enhanced balance, which contributes to fewer falls and fractures. Conversely, an experiment was conducted to determine bone loss due to lack of physical stress. Ninety healthy men were placed on bed rest for 36 weeks and urine calcium concentration was measured to determine bone loss. The study found that urine calcium concentrations became elevated to 100 mg a day, showing demineralization of bone. This elevated excretion of calcium in urine continued for 36 weeks (Schneider, 1984).

How do bones react to physical stress? Bones react to physical stress through biochemical reaction resulting from mechanical stimulus. Bones contain cells called osteocytes, osteoblasts that have matured and reside within bone. Osteocytes are positioned in a way that the deformation of bone tissue is amplified by 20-100 times on its cell membrane. The deformation on the cell membrane signals that the bone is undergoing stress. This is thought to trigger a host of processes within the cell, resulting in osteogenesis. The process by which osteocytes signal is extremely complex and still not fully understood (Gusmão & Belangero, 2015). One way osteocytes can signal is through a chemical known as sclerostin, which promotes bone degradation and is coded for by the gene SOST. Mice with SOST gene deletion and humans with mutations on this gene have higher bone density. Mechanical loading has been reported to reduce sclerostin expression as well. New research is being conducted for an antibody against sclerostin to treat osteoporosis (Bonewald, 2011).

Treatments

The first line of treatment for osteoporosis is currently Bisphosphonates (BP), which disrupts osteoclastic activity. Because osteoclast are the cells responsible for bone degradation, many treatments seek to inhibit osteoclast activity. Osteoclasts degrade bone by releasing hydrogen ions, thereby creating a acidic environment. They use a ruffled border that attaches to the bone's surface. The ruffled border has crevices created by its protrusions which act as containers for the acid secreted by the osteoclast. The acid remains in these crevices, which form small pockets known as sub-osteoclastic compartments when sealing onto bone. The acidic environment causes the mineral component of bone to become more soluble, allowing bone's minerals to be absorbed by the osteoclasts.

BP has a strong affinity for calcium ions, which are found in bone, due to the presence of two phosphate groups, this results in the rapid localization of BP to bone material. Experiments using radio labeled BP has shown that BP are taken up and adsorbed in to bone primarily (Xiao-Long Xu, 2013).

When osteoclasts attach to bone that contains BP the acidic environment protonates the BP. Protonated BP has a lowered affinity for calcium ions, allowing for the release of BP into the sub osteoclastic compartment where BP is taken up by the osteoclast.

BP disrupts cell functions in the osteoclast, BP have a similar chemical structure to that of pyrophosphate. Pyrophosphate is involved in many cell processes in the osteoclast. Due to its similarity to pyrophosphate, BP is likely to interfere with any of the processes that involve pyrophosphate. It is thought that the BP inhibits prenylation of protein to the cell membrane, the lack of these proteins at the membrane results in loss of the ruffled border and prevents the osteoclast from being able to degrade the bone. This is shown as bisphosphonate-treated osteoclasts lack a ruffled border (Russell & Rogers, 1999).

Side Effects of BP

Doctors I have spoken with report that patients reported gastrointestinal (GI) discomfort while taking oral BP, and an NCBI continuing education paper for doctors states " All oral bisphosphonates have correlations with upper gastrointestinal adverse effects, including gastrointestinal reflux, esophagitis, esophageal/gastric ulcers, and

gastritis. Gastrointestinal side effects are the most common reason for discontinuation of oral bisphosphonates." The article recommends avoiding BP in patient that are at a higher risk of gastrointestinal distress (Ganesan K, 2021). A study conducted to determine the compliance of patient to osteoporosis treatment found that the major reason reported by patients for discontinuation of alendronate (a BP) was indeed GI side effects. Counter to this, a study conducted to determine if there is any correlation between alendronate (a BP) use and GI problems found no correlation of BP use and GI issues. The experiment was a randomized, double-blind, placebo-controlled trial with a mean follow-up of 3.8 years. Women were initially randomized to receive alendronate sodium, 5 mg/d, or placebo. After 2 years, the alendronate sodium dose was increased to 10 mg/d. The study did not find any significant correlation between BP use and GI problems. "The overall incidence of upper GI tract events was similar in the alendronate and placebo groups". The study goes on to suggest that GI side effects reported may be due to the higher age of osteoporotic patients (Bauer DC, 2000). The study that found that noncompliance in BP-taking patients also tracked patient adherence to Raloxifene (a different class of treatment known as a SERM), none of the Raloxifene-taking patients attributed the reason of their discontinuation of treatment due to gastrointestinal issues (Segal, Tamir, & al, 2003). This would call into question the suggestion that the gastrointestinal affects attributed to BP are really age related and not resultant of BP. Both groups were of the same population yet only the BP-taking group reported gastrointestinal issues. The study cited as well as other studies I came across that showed no correlation with oral BP use and upper GI issues were sponsored by pharmaceutical companies that produce oral BPs. These conflicting reports of gastrointestinal distress due raise eyebrows as to the potential biases in studies. Patients given intravenous BP do not report GI issues and the intravenous BPs need to be administered far less often. (Papapetrou, 2009) Both reasons make it more likely that a patient will maintain their intravenous treatment over an oral one and seem to make intravenous BP optimal.

Another method of treatment for osteoporosis is monoclonal antibodies. Osteoclasts originate from macrophages. The macrophage precursor cells have a receptor called RANK which binds to RANK ligand (RANKL) to differentiate into osteoclastic cells. Antibodies can bind to a ligand to prevent it from binding to its receptor. The antibodies bind to RANKL inhibiting their ability to bind with the RANK receptor on the macrophage precursor cells. As a result of the rate at which osteoclasts differentiate is decreases resulting in less osteoclastic cells that break up bone. (D. A. Hanley, 2012)

Antibody treatment, which circulate in the blood, can reach all skeletal sites. However, unlike BP which bind to bones and can have affects after cessation of treatment, antibodies lose their affect soon after cessation of treatment. Adverse events are rarely associated with denosumab. (Harshika Awasthi, 2018)

Calcium concentration is regulated by hormones PTH, and calcitonin. Calcitonin is produced in the thyroid gland and causes lower serum calcium concentration by acting on the renal tubules, causing them to excrete more calcium, and on osteoclasts, causing them to contract (temporarily), reducing their motility and ability to resorb bone. It also causes inhibition of carbonic anhydrase II, which disrupts the acidic environment that is optimal for osteoclast activity. Calcitonin also prevents osteoclast precursors from differentiating into their mature form. The ultimobranchial gland of salmon produces calcitonin with a different makeup of amino acids. Salmon calcitonin is a 32 amino acid, alpha-helical polypeptide that differs significantly from human calcitonin along amino acids 10-27. Salmon calcitonin is more potent then endogenous calcitonin due its difference in amino acids (Felsenfeld AJ, 2015)

Adverse Side Effects of Calcitonin

Adverse effects of calcitonin can include hypocalcemia, a dangerous condition. Since the calcitonin used to treat osteoporosis is sourced from salmon, patients who are allergic to fish can have an allergic reaction. Ten percent of patients taking calcitonin experience mild nausea that subsides as therapy continues. A meta-analysis of 21 randomized, controlled clinical trials with calcitonin-salmon (nasal spray and investigational oral forms) suggests an increased risk of malignancies in calcitonin-salmon-treated patients (4.1%) compared to placebo-treated patients (2.9%). A definitive causal relationship between the calcitonin-salmon use and malignancies cannot be established from this meta-analysis, the benefits for the individual patient should be carefully evaluated against all possible risks. (F. Cosman, 2014)

Further studies point to the questionable efficacy of calcitonin overall and show a definitive lack of efficacy in nonvertebrate fractures. This contrasts with both bisphosphonates and denosumab which both demonstrated a lowered fracture risk in vertebral, hip, and other nonvertebral fractures. (Overman RA, 2013)

Calcitonin has been shown to reduce fracture pain. The exact mechanism for its analgesic effects, is not known. There is a hypothesis that calcitonin may act on the central nervous system, and it has been used with some

success in patients with migraine pain, phantom limb pain, malignancy, Paget's disease, and other pathologies. It, however, has not been compared directly to NSAIDs in terms of effectiveness of pain relief. Regardless, Calcitonin may be helpful for pain in patients that cannot tolerate NSAIDS. (Linsey A Blau, 2016)

Post-menopausal women have low levels of estrogen, an essential hormone for bone remodeling. Osteoporosis is attributed to the diminished estrogen levels of post-menopausal women. Estrogen can inhibit osteoclasts from forming, cause osteoclastic apoptosis, as well as increase osteoblasts by inhibiting osteoblastic apoptosis (Sundeep Khosla, 2012) . An obvious therapeutic approach would be to provide hormone replacement therapy. However, hormone therapy is found to increase the risk of breast cancer (Beral, 2003) , and is therefore not widely used . Raloxifene, a drug that is an estrogen antagonist and agonist is promising drug, in bone, it behaves as an estrogen antagonist, increasing bone density, in reproductive and breast tissue it acts as an estrogen agonist. Thus, raloxifene both increases bone density and reduces risk of cancer. Raloxifene has not been shown to reduce non-vertebrate fractions and more research is necessary to determine its efficacy in non-vertebrate fractures. A meta-analysis found that "In comparison to other osteoporosis therapies, raloxifene has a lesser impact on bone mineral density, a similar effect on the occurrence of vertebral fractures, but no effect on the frequency of non-vertebral fractures. Raloxifene can be recommended for the prevention of vertebral fractures in women with osteopenia/osteoporosis who are not at high risk of non-vertebral fractures and who do not have a past history of venous thromboembolism" (Ann Cranney, 2005)

Conclusion

The most effective current method of treatment are bisphosphonates, which accumulate in bone and inhibit osteoclasts from functioning. However, many patients suffer gastrointestinal pain as a side effect. For those patients an antibody (denosumab) that prevent RANKL from signaling the osteoclastic precursor cells to mature, has also proven to be relatively effective. Other methods of treatment such as calcitonin and raloxifene while in theory look promising, proved to not be very effective in clinical trials. Calcitonin, while not necessarily very effective at reducing bone loss, may still play an important role in treating pain, especially in patients where NSAIDS aren't well tolerated. More research is needed to determine how effective exercise can be in the prevention of osteoporosis and what specific exercises, if any, would be most effective. Regardless, patients should be advised to exercise, as there is some evidence that links mechanical stress on bones to lasting improved bone mass., and stronger muscles can improve balance to further help reduce the risk of falls and fractures. Further research should be conducted to determine how it might be possible to enhance bone-building osteoblasts.

References

Ann Cranney, J. D. (2005). Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. drug safety . Retrieved from https://pubmed.ncbi.nlm.nih.gov/16048357/

Bauer DC, B. D. (2000). Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. Archives of internal medicine. doi:https://doi.org/10.1001/archinte.160.4.517

Beral, V. (2003). Breast cancer and hormone-replacement therapy in the Million Women Study. Retrieved from https://pubmed.ncbi.nlm.nih.gov/12927427/

Bonewald, L. F. (2011). The Amazing Osteocyte. JBMR. Retrieved from https://asbmr.onlinelibrary.wiley.com/doi/full/10.1002/jbmr.320

D. A. Hanley, J. D. (2012). Denosumab: mechanism of action and clinical outcomes. doi:https://dx.doi.org/10.1111%2Fijcp.12022

Dempster, D.W. (2011). Osteoporosis and the Burden of Osteoporosis-Related Fractures. The American Journal of Managed Care . Retrieved from https://www.ajmc.com/view/a357_11ma7__dempster_s164to169

F. Cosman, S. J. (2014). Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoperosis Internantional. doi:https://dx.doi.org/10.1007%2Fs00198-014-2794-2

Felsenfeld AJ, L. B. (2015). Calcitonin, the forgotten hormone: does it deserve to be forgotten? clinical kidney journal , 8. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4370311/

Ganesan K, B. P. (2021). Bisphosphonate. StatPearls Publishing LLC. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK470248/

Gusmão, C. V., & Belangero, W. D. (2015). HOW DO BONE CELLS SENSE MECHANICAL LOADING? (Revista brasileira de ortopedia). Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4799046/

Harshika Awasthi, D. M. (2018). The underlying pathophysiology and therapeutic approaches for osteoporosis. Medicinal research reviews. doi:doi:10.1002/med.21504

Kothawala, Badamgarav, & al, e. (2007). Sytematic reveiw

and meta-analysis of real-world adherance todrug therapy for osteoperosis.

Linsey A Blau, J. D. (2016). Analgesic Efficacy of Calcitonin for Vertebral Fracture Pain. Annals of Pharmacotherapy. Retrieved from https://journals.sagepub.com/doi/full/10.1345/aph.1C350?utm_source=summon&utm_medium=discovery-provider

Looker, A. C. (2015). Percentage of Adults Aged 65 and Over With Osteoporosis or Low Bone Mass at the Femur Neck or Lumbar Spine: United States, 2005–2010. Hyattsville, MD: national center for health statistics. Retrieved from https://www.cdc.gov/nchs/data/hestat/osteoporsis/osteoporosis2005_2010.htm).

M. Sinaki, E. I. (2002). Stronger back muscles reduce the incidence of vertebral fractures: a prospective 10 year follow-up of postmenopausal women. Bone. Retrieved from https://www.sciencedirect.com/science/article/pii/S8756328202007391

Overman RA, B. M. (2013). Salmon Calcitonin Use and Associated Cancer Risk. Annals of Pharmacotherapy. Retrieved from https://journals.sagepub.com/doi/full/10.1177/1060028013509233?utm_source=summon&utm_medium=discovery-provider

Papapetrou, P. (2009). Bisphosphonate-associated adverse events. Retrieved from https://link.springer.com/article/10.14310/horm.2002.1226#

Russell, R. G., & Rogers, P. I. (1999). Bisphosphonates: Pharmacology, Mechanisms of Action and Clinical. Osteoporosis.

Schneider, V. M. (1984). Skeletal calcium homeostasis and countermeasures to prevent disuse osteoporosis. Calcif Tissue Int. doi:https://doi.org/10.1007/BF02406149

Segal, E., Tamir, A., & al, e. (2003). Compliance of Osteoporotic Patients with Different. IMAJ. Retrieved from https://www.ima.org.il/FilesUploadPublic/IMAJ/0/54/27422.pdf

Sundeep Khosla, M. J. (2012). Estrogen and the skeleton. trends in Endocrinology and Metabolism. Retrieved from https://reader.elsevier.com/reader/sd/pii/S1043276012000525?token=63908E45D5D4576F15F33667D4F448A4B83328807CC51F274A7CF523C0055715A505995513A7A45EC41E20BE9F9EBAD&originRegion=us-east-1&originCreation=20210615063943

Totora, G. j., & Derrickson, B. (2014). Principles of Anatomy and Physiology 14th edition. Wiley.

Xiao-Long Xu, W.-L. G.-Y.-Y.-B. (2013). Basic research and clinical applications of bisphosphonates in bone disease: what have we learned over the last 40 years? Journal of Translational Medicine . Retrieved from https://translational-medicine.biomedcentral.com/articles/10.1186/1479-5876-11-303#citeas