An Overview of Treatment Options for Osteoporosis

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ABSTRACT

Background:
Many skeletal disorders cause long-term degeneration, such as osteoarthritis, osteopenia, and osteoporosis.[1] In the United States, approximately 19.6% of women and 4.4% of men in the United States are diagnosed as having osteoporosis.[2-4] An even more shocking statistic is that 51.5% of women and 33.5% of men, 50 or older, present with low bone mass density, a precursor to osteoporosis.[4] The recognition and treatment for osteoporosis is becoming more important due to the increasing life expectancy of both females and males.

Methods:
This study was performed with the intent of gathering information regarding the most modern methods of treatment, whether it is lifestyle, pharmacological, or surgical treatment options. The sources were gathered from different journals that publish works on the subject of different treatment modalities of osteoporosis.

Results:
The results showed that there are numerous treatment modalities that can be offered to patients in newly diagnosed or long standing osteoporosis.

Conclusion:
Due to the rising life expectancy of both genders the signs and symptoms of bone degenerative disorders and provide patients with a variety of management and treatment plans.

INTRODUCTION

Many skeletal disorders cause long-term degeneration, such as osteoarthritis, osteopenia, and osteoporosis.[1] In the United States, approximately 19.6% of women and 4.4% of men in the United States are diagnosed as having osteoporosis.[2-4] An even more shocking statistic is that 51.5% of women and 33.5% of men, 50 or older, present with low bone mass density, a precursor to osteoporosis.[4] The recognition and treatment for osteoporosis is becoming more important due to the increasing life expectancy of both females and males. Although both sexes are susceptible to bone degeneration, women are more affected and account for 70-80% of wrist, hip, and spine fractures exacerbated during the menopausal stage of life due to decreased estrogen levels. When estrogen levels are low bone mass loss increases.[3] Because the average age of people has increased over the past decades due to new medicines and technologies, it has become even more important to be aware of the signs and symptoms of bone degenerative disorders and provide patients with a variety of management and treatment plans.

Our skeletal system from a young age has been constantly growing larger, denser, and stronger. This improvement comes from the balanced remodeling of the skeleton; however this remodeling is not as well sustained in older patients and risks the development of osteoporosis.[5] Osteoblasts are cells that help to form bone and are derived from mesenchymal stem cells (MSCs). These MSCs can form many different cell types as they are stimulated, but specifically with osteoblasts taken from aged donors, when compared to young donors, presents a reduced capacity to expand, appeared flat and widespread versus the rapidly proliferating, spindle-shaped cells of the younger donors.[5] Aged MSCs also favor forming adipocytes which is why in older bones, there will be increased levels of fat in the bone marrow.[5] In postmenopausal women, the balance between bone formation and bone resorption is altered due to decreased estrogen levels. An additional effect estrogen has on the skeletal system is the increase of osteogenic differentiation of mesenchymal stem cells and osteoblast formation.[6] Estrogen also inhibits osteoclast formation and induces its apoptosis to help prevent bone resorption.

During menopause, women have decreased levels of estrogen leading to decreased osteoblasts activity and increased osteoclast activity, which leads to ongoing bone resorption. It is also known that under estrogen-deficient states, immune cells can produce TNFα, increasing osteoblast cell death and indirectly stimulating osteoclastogenesis resulting in bone resorption. Neutrophils, for example, play a part in bone formation and resorption homeostasis.[6] However, when estrogen levels are low, the neutrophils can become overactive, contributing to osteoblast apoptosis and increasing osteoclastogenesis.[6] Mast cells also have a role in the progression of osteoporosis due to their high levels of osteoclastic mediators, including IL-6 and RANKL, within their granules. These mediators are seen to be significantly increased in osteoporotic bone.[6] We can conclude, not only do aged MSCs have an effect on skeletal degeneration, but the immune system plays a big role in bone resorption leading to osteoporosis in postmenopausal women.

METHODS

This study was performed with the intent of gathering information regarding the most modern methods of treatment, whether it is lifestyle, pharmacological, or surgical treatment options. The sources were gathered from different journals that publish works on the subject of different treatment modalities of osteoporosis.

RESULTS

The results showed that there are numerous treatment modalities that can be offered patients in newly diagnosed or long-standing osteoporosis have been shown to either maintain bone density or even improve the bone density in the patient. It is shown that 80-90% of osteoporotic patients are not given appropriate osteoporosis management plans.[7] This result details the necessity of provider competency and appropriate screening for patients who are either a previously diagnosed or at risk of developing severe bone loss or osteoporosis.

DISCUSSION

Osteoporosis is a chronic condition that has no cure and is characterized by low bone mineral density (BMD) and degeneration of bone architecture.[7] Clinically, it is known to cause approximately 80% of all fractures, leading to decreased quality of life and an increase in premature mortality and disability. These are the major complications with osteoporotic individuals, especially when they are not given the necessary tools to help reduce the possibility of fractures. *The Endocrine Society Clinical Practice* has published guidelines for the treatment and management of osteoporotic patients. In postmenopausal women at high risk of fractures, bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) or denosumab are recommended as an initial treatment.[8] With patients already experiencing multiple vertebrae fractures, teriparatide is recommended for up to two years to reduce vertebral and nonvertebral fractures.[8] Finally, with postmenopausal women who are at high risk of fractures with either severe osteoporosis (i.e., low T-score <-2.5) or already have had vertebral fractures, romosozumab is recommended for up to one year of treatment to reduce vertebral, hip, and nonvertebral fractures.[8]

When comparing the drugs given, bone-forming agents such as teriparatide or romosozumab have demonstrated more significant results in reducing fractures in patients with a high risk of fractures.[9-10] These are recommended as the first option treatment rather than risedronate or alendronate, which are antiresorptive. However, once treatment with one of the bone-forming agents has finished, it should be followed by an antiresorptive to prevent the rapid loss of BMD.[11-12]

Over the past few decades, surgical techniques such as vertebroplasty and kyphoplasty have been used to treat painful acute vertebral bone compression fractures associated with osteoporosis.[13] In a retrospective report conducted in 2003, Evans et al. reported 245 patients with vertebral compression fractures who had a significantly decrease in pain after undergoing vertebroplasty.[14] In a separate study, 90% of 29 osteoporotic patients reported pain relief from vertebral compression fractures following a vertebroplasty procedure.[15] In a more recent study performed

in 2009, 131 patients with osteoporotic vertebral body fractures either received vertebroplasty or a sham procedure, where both groups reported improvements in disability and pain, and even at one month out, there was no significant difference between the two groups in terms of disability or pain as judged by the modified Roland-Morris questionnaire scores.[16] It should be noted that the placebo effect could be indicated with the sham procedure group. With that being said, the vertebroplasty group did present with improvements that validate the procedure as a reconable treatment option for patients who present with vertebral bone compression fractures.

A more non-interventionist way for possible management of bone degeneration as people age is resistance training, which is the act of using resistance to help gain strength. This can include weightlifting, swimming, and walking up steep inclines, among others. Weight-bearing physical training is thought to provide a mechanical stimulus that is important for maintaining and improving bone health.[33] In contrast, physical inactivity has been implicated in bone loss and associated health costs.[33] For patients with osteoporosis, guidelines will recommend moderate-intensity exercise rather than high-intensity exercise and it should also be noted that high-intensity exercise is not recommended for people with established osteoporosis because of the increased risk of fracture.[17-18-19] This prevailing thought has led to a more conservative approach to recommendations for these patients.

Strength training provides a distinct physiological reaction to osteogenesis.[23] Several studies have demonstrated that strength training has a unique ability to inhibit bone demineralization in older women and men.[24-25-26] A study performed by Bocalini et al.[24] evaluated the effects of strength training with postmenopausal women without hormone replacement therapy for 24 weeks. The women who were in the trained group were able to maintain their bone mineral density. However, the women in the untrained group exhibited a significant percentage decrease in bone mineral density at both the femoral neck and lumbar spine. During the 24 weeks, trained women did not significantly increase bone mineral density, and the untrained women demonstrated a significant loss in bone mineral density. The results did not demonstrate an increase in bone density with the trained group however, the significant result was that there was no decrease in bone mineral density which can be a reliable form of treatment for postmenopausal women and can be expanded to older men who are also experiencing bone mineral density loss.

Research has concluded that in the first few years after menopause, women can lose up to 5% of bone mass annually, followed by 2-3% annual loss after that.[20-21] Men, on the other hand, start at a higher baseline of bone density and will lose approximately 1-2% of bone mass density per year.[22] The commonalities between these studies are that exercise does have a positive effect in either minimizing or preventing the loss in bone mineral density. Furthermore, this can have a positive impact on decreasing fractures in people who have low bone density either for postmenopausal women or older men with are experiencing low bone density.

Although some studies support the idea of strength training for bone mineral density for postmenopausal women, a study done by Nikander et al.[27] found no significant effect to recommend any training program. Furthermore, Guadalupe-Grau et al.[28] have reported that studies performed in older adults only reported mild increases or just maintained bone mineral density. However, other studies agree that exercise benefits the femoral neck and lumbar spine in

postmenopausal women.[29-30] Moreover, systematic reviews and articles found that both impact and non-impact exercises positively affect maintaining bone mineral density. These exercises can include jogging combined with low-impact exercises, such as stair climbing, walking, and resistance training.[31-32] The majority of research concludes that strength training and physical exercise not only has a benefit in maintaining bone mass density, but also can be beneficial for patients experiencing osteoporosis.

Among new orthopedic, plastic, and cardiovascular surgical techniques, platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) are used as surgical adjuvants or regenerative medicine.[34-35] The basic idea is that within our blood, there are growth factors, healing proteins, cell signals, and immune cells, which are a part of the natural healing process that can usually be taken from the donor, concentrated, and applied or injected to a wound or surgical site to enhance healing.[34] Platelet-rich fibrin releases (PRFr) can also be used, containing rich amounts of growth factors, leukocytes, lipids, and proteins such as vitronectin and fibronectin.[36] Vitronectin actively stimulate a variety of cell and tissue functions, including cell proliferation.

In a clinical setting, both PRP and PRF have been used however, an in vitro study has demonstrated that growth factors released by PRF gradually expressed more substantial and more durable effects on the proliferation and differentiation of rat osteoblasts than PRP. A study performed by Shi-Yaun et al.[34] tested the effects of PRFr, ADSCs (adipose stem cells), and PRFr + ADSCs injections to observe the effects on bone mass density in osteoporotic mice. Each of the methods tested reported significantly higher bone regeneration, with PRFr averaging 42%, ADSCs averaging 58%, and PRFr + ADSCs averaging 64% improved bone mineral density. The researchers postulated that the positive effects of ADSCs on bone formation might be enhanced in the presence of PRFr. This could be due to the concentrated growth factors from the PRFr that can promote ADSCs' growth and osteogenic differentiation capacities in vitro. It is also hypothesised that PRFr can accelerate bone formation during skeletal repair by upregulating the proliferation and osteogenesis of ADSCs. They conclude by explaining that PRFr and ADSCs promote new bone formation but that the combination may be a promising novel therapeutic strategy in osteoporotic bone regeneration.

CONCLUSION

This paper presents the different treatment plans for patients already experiencing osteoporosis or at risk of developing low bone density. It is shown that 80-90% of osteoporotic patients are not given appropriate osteoporosis management plans.[7] The purpose of this paper is to shed light on the different treatment options that physicians can prescribe or recommend to their patients. Management plans are critical because fractures associated with osteoporosis, especially hip fractures, can have devastating effects on functional capacity, quality of life, and mortality of older individuals. Roughly 10% of patients become disabled due to hip fractures, and approximately 19% require institutionalization into nursing homes.[38] Postmenopausal women have roughly a 10% chance of developing vertebral deformities that cause chronic pain.[38]

The treatment and management of osteoporosis is crucial for patients experiencing low bone density. It is especially important for physicians to talk with their female patients who are approaching postmenopause to ensure that these patients have the correct understanding of the condition and treatment measures for either prevention or management of possible low bone

density conditions. Bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) or denosumab are recommended as an initial treatment.

We have presented classic treatment options including bone forming agents including teriparatide or romosozumab and antiresorptive such as risedronate or alendronate. We also have new age treatments such as PRP, and PRF(r) that can be a great way of managing osteoporosis. We have also presented non-medical ways to help manage bone loss and even manage osteoporosis such as exercise and resistance or strength training. Over the past few decades medicine has made many leaps in helping people live longer and as people have an increased life expectancy we should come to expect and be ready to treat low bone density and its progressive disorders such as osteoporosis.

REFERENCES

1. Li B, Chen D. Degenerative musculoskeletal diseases: Pathology and treatments. *Journal of Orthopaedic Translation*. 2019;17:1-2. doi:https://doi.org/10.1016/j.jot.2019.05.001

2. Thomas AC, Hubbard-Turner T, Wikstrom EA, Palmieri-Smith RM. Epidemiology of Posttraumatic Osteoarthritis. *Journal of Athletic Training*. 2017;52(6):491-496. doi:https://doi.org/10.4085/1062-6050-51.5.08

3. Khinda R, Valecha S, Kumar N, et al. Prevalence and Predictors of Osteoporosis and Osteopenia in Postmenopausal Women of Punjab, India. *International Journal of Environmental Research and Public Health*. 2022;19(5):2999. doi:https://doi.org/10.3390/ijerph19052999

4. CDC. Osteoporosis or Low Bone Mass in Older Adults: United States, 2017–2018. www.cdc.gov. Published March 26, 2021. https://www.cdc.gov/nchs/products/databriefs/db405.htm

5. Roberts S, Colombier P, Sowman A, et al. Ageing in the musculoskeletal system. *Acta Orthopaedica*. 2016;87(363):15-25. doi:https://doi.org/10.1080/17453674.2016.1244750

6. Fischer V, Haffner-Luntzer M. Interaction between bone and immune cells: Implications for postmenopausal osteoporosis. *Seminars in Cell & Developmental Biology*. 2022;123:14-21. doi:https://doi.org/10.1016/j.semcdb.2021.05.014

7. Brown JP. Long-Term Treatment of Postmenopausal Osteoporosis. *Endocrinology and Metabolism*. 2021;36(3). doi:https://doi.org/10.3803/enm.2021.301

8. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. *The Journal of Clinical Endocrinology & Metabolism*. 2020;105(3):587-594. doi:https://doi.org/10.1210/clinem/dgaa048

9. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet (London, England)*. 2018;391(10117):230-240. doi:https://doi.org/10.1016/S0140-6736(17)32137-2

10. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *New England Journal of Medicine*. 2017;377(15):1417-1427. doi:https://doi.org/10.1056/nejmoa1708322

11. Cosman F, Nieves JW, Dempster DW. Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis. *Journal of Bone and Mineral Research*. 2017;32(2):198-202. doi:https://doi.org/10.1002/jbmr.3051

12. McClung MR. Role of bone-forming agents in the management of osteoporosis. *Aging Clinical and Experimental Research*. 2021;33(4):775-791. doi:https://doi.org/10.1007/s40520-020-01708-8

13. Fung DA, Davis TT, Lee PC. Injections of the Cervical, Thoracic, and Lumbar Spine. *Springer eBooks*. Published online January 1, 2015:389-409. doi:https://doi.org/10.1007/978-1-4939-2465-3_54

14. Ding D, Jensen ME, Kip KE, et al. Vertebral Compression Fractures: Pain Reduction and Improvement in Functional Mobility after Percutaneous Polymethylmethacrylate Vertebroplasty—Retrospective Report of 245 Cases. *Radiology*. 2003;226(2):366-372. doi:https://doi.org/10.1148/radiol.2262010906

15. Jensen ME, Evans AJ, Mathis JM, Kallmes DF, Cloft HJ, Dion JE. Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects. *AJNR American journal of neuroradiology*. 1997;18(10):1897-1904. https://pubmed.ncbi.nlm.nih.gov/9403451/

16. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *The New England Journal of Medicine*. 2009;361(6):557-568. doi:https://doi.org/10.1056/NEJMoa0900429

17. Watson SL, Weeks BK, Weis LJ, Horan SA, Beck BR. Heavy resistance training is safe and improves bone, function, and stature in postmenopausal women with low to very low bone mass: novel early findings from the LIFTMOR trial. *Osteoporosis International*. 2015;26(12):2889-2894. doi:https://doi.org/10.1007/s00198-015-3263-2

18. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR. Physical Activity and Bone Health. *Medicine & Science in Sports & Exercise*. 2004;36(11):1985-1996. doi:https://doi.org/10.1249/01.mss.0000142662.21767.58

19. Giangregorio LM, Papaioannou A, MacIntyre NJ, et al. Too Fit To Fracture: exercise recommendations for individuals with osteoporosis or osteoporotic vertebral fracture. *Osteoporosis International*. 2013;25(3):821-835. doi:https://doi.org/10.1007/s00198-013-2523-2

20. Gómez-Cabello A, Ara I, González-Agüero A, Casajús JA, Vicente-Rodríguez G. Effects of Training on Bone Mass in Older Adults. *Sports Medicine*. 2012;42(4):301-325. doi:https://doi.org/10.2165/11597670-000000000-00000

21. Bellantoni MF, Blackman MB. The menopause. In: au Schneider EL, au Rowe JW, editors. Handbook of the biology of aging. 4thed. San Diego (CA): Academic Press, 1996: 415–30

22. Looker AC, Orwoll ES, Johnston CC, et al. Prevalence of Low Femoral Bone Density in Older U.S. Adults from NHANES III. *Journal of Bone and Mineral Research*. 1997;12(11):1761-1768. doi:https://doi.org/10.1359/jbmr.1997.12.11.1761

23. Nelson ME. Effects of High-Intensity Strength Training on Multiple Risk Factors for Osteoporotic Fractures. *JAMA*. 1994;272(24):1909. doi:https://doi.org/10.1001/jama.1994.03520240037038

24. Bocalini DS, Serra AJ, dos Santos L, Murad N, Levy RF. Strength Training Preserves the Bone Mineral Density of Postmenopausal Women Without Hormone Replacement Therapy. *Journal of Aging and Health*. 2009;21(3):519-527. doi:https://doi.org/10.1177/0898264309332839

25. de Matos O, Lopes da Silva DJ, Martinez de Oliveira J, Castelo-Branco C. Effect of specific exercise training on bone mineral density in women with postmenopausal osteopenia or osteoporosis. *Gynecological Endocrinology*. 2009;25(9):616-620. doi:https://doi.org/10.1080/09513590903015593

26. Daly RM, Dunstan DW, Owen N, Jolley D, Shaw JE, Zimmet PZ. Does high-intensity resistance training maintain bone mass during moderate weight loss in older overweight adults with type 2 diabetes? *Osteoporosis International*. 2005;16(12):1703-1712. doi:https://doi.org/10.1007/s00198-005-1906-4

27. Nikander R, Sievänen H, Heinonen A, Daly RM, Uusi-Rasi K, Kannus P. Targeted exercise against osteoporosis: A systematic review and meta-analysis for optimising bone strength throughout life. *BMC Medicine*. 2010;8(1). doi:https://doi.org/10.1186/1741-7015-8-47

28. Guadalupe-Grau A, Fuentes T, Guerra B, Calbet JAL. Exercise and Bone Mass in Adults. *Sports Medicine*. 2009;39(6):439-468. doi:https://doi.org/10.2165/00007256-200939060-00002

29. Kelley GA, Kelley KS, Tran ZV. Exercise and Lumbar Spine Bone Mineral Density in Postmenopausal Women: A Meta-Analysis of Individual Patient Data. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2002;57(9):M599-M604. doi:https://doi.org/10.1093/gerona/57.9.m599

30. Wolff I, van Croonenborg JJ, Kemper HCG, Kostense PJ, Twisk JWR. The Effect of Exercise Training Programs on Bone Mass: A Meta-analysis of Published Controlled Trials in Pre- and Postmenopausal Women. *Osteoporosis International*. 1999;9(1):1-12. doi:https://doi.org/10.1007/s001980050109

31. Wallace BA, Cumming RG. Systematic Review of Randomized Trials of the Effect of Exercise on Bone Mass in Pre- and Postmenopausal Women. *Calcified Tissue International*. 2000;67(1):10-18. doi:https://doi.org/10.1007/s00223001089

32. Martyn-St James M, Carroll S. A meta-analysis of impact exercise on postmenopausal bone loss: the case for mixed loading exercise programmes. *British Journal of Sports Medicine*. 2008;43(12):898-908. doi:https://doi.org/10.1136/bjsm.2008.052704

33. Layne JE, Nelson ME. The effects of progressive resistance training on bone density: a review. *Medicine & Science in Sports & Exercise*. 1999;31(1):25-30. doi:https://doi.org/10.1097/00005768-199901000-00006

34. Sheu SY, Hsu YK, Chuang MH, et al. Enhanced Bone Formation in Osteoporotic Mice by a Novel Transplant Combined with Adipose-derived Stem Cells and Platelet-rich Fibrin Releasates. *Cell Transplantation*. 2020;29:096368972092739-096368972092739. doi:https://doi.org/10.1177/0963689720927398

35. Dohan Ehrenfest DM, Andia I, Zumstein MA, Zhang CQ, Pinto NR, Bielecki T. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. *Muscles, Ligaments and Tendons Journal*. 2014;4(1):3-9. https://pubmed.ncbi.nlm.nih.gov/24932440/

36. Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part I: Technological concepts and evolution. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2006;101(3):e37-e44. doi:https://doi.org/10.1016/j.tripleo.2005.07.008

37. Melton LJ. Adverse Outcomes of Osteoporotic Fractures in the General Population. *Journal of Bone and Mineral Research*. 2003;18(6):1139-1141. doi:https://doi.org/10.1359/jbmr.2003.18.6.1139

38. Ciolac EG, Rodrigues-da-Silva JM. Resistance Training as a Tool for Preventing and Treating Musculoskeletal Disorders. *Sports Medicine*. 2016;46(9):1239-1248. doi:https://doi.org/10.1007/s40279-016-0507-z