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Review Article

### A REVIEW ON THE MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

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**Abstract:**

*Osteoporosis, derived from the Greek term "porous bone," means a systemic bone disease, characterized by micro architectural deterioration, bone loss and density. Decreased bone density is also associated with increased bone density and softening of the bones. This results in increased medical expenditures and morbidity with a decrease in the quality of life of patients. According to the World Health Organization, this is defined as a decrease in bone mass (BMD) of a normal deviation of 2.5 or more below the maximum BMD rate in adults with an equal number of x-ray absorptiometry. The main objective of this article is to guide the causes, risk factors, pathogenesis, prevention, diagnosis, and management of osteoporosis in postmenopausal women. Altering the current screening guidelines for bone density and suggestions for treatment is essential. The choice of treatment depends on the age, presence or absence of fractures, especially in the spine, and the level of mineral bones measured in the spine.*

*Osteoporosis is a bone disease characterized by bone loss, density, mass, and microarchitectural tissues that lead to bone fractures worldwide. Risk factors are associated with age, sex, hormone deficiency, underlying issues, previous fractures, and medications. The pathophysiology includes different pathways, such as classical, epigenetic, post-transcriptional, gut microbiotas, and stress-mediated signalling. Bone loss occurs without any symptoms. Screening includes both laboratory and instrumental tests such as FRAX score, thyroid dysfunctions, X-ray absorptiometry and ultrasonography. Management includes calcium/vitamin D, bisphosphonates, denosumab, estrogen replacement, and selective estrogen receptor modulators, calcitonin, odanacatib, lasofoxifene, parathyroid, and hormone-related protein analogs, strontium ranelate for a better treatment strategy approach to improve patient health.*

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## INTRODUCTION:

Osteoporosis, derived from the Greek term "porous bone," [1] means a systemic bone disease, characterized by micro architectural deterioration, bone loss and density. [2,3,4]

These bone fractures are injurious to patients, [5&6] as they weaken the bones, it increases the risk of sudden, unexpected fractures and affects people. It may often occur without any pain or symptoms [7] and increases with aging, affecting about 30% of postmenopausal women. [8, 9&10]

Decreased bone density is also associated with increased bone density and softening of the bones. This results in increased medical expenditures and morbidity with a decrease in the quality of life of patients. According to the World Health Organization, this is defined as a decrease in bone mass (BMD) of a normal deviation of 2.5 or more below the maximum BMD rate in adults with an equal number of x-ray absorptiometry. [1]

The main objective of this article is to guide the causes, risk factors, pathogenesis, prevention, diagnosis, and management of osteoporosis in postmenopausal women. [11,12] Altering the current screening guidelines for bone density and suggestions for treatment is essential. [13] The choice of treatment depends on the age, presence or absence of fractures, especially in the spine, and the level of mineral bones measured in the spine. [14]

Hence, pharmacological treatments can considerably decrease the rate of fractures. Identifying high-risk patients is the cornerstone of the management of osteoporosis. [15,16,17] Non-pharmacological treatments include adequate calcium and diet, exercise, reducing other risk factors for osteoporotic fractures, and the risk of falls in the elderly [14]

### Etiology and risk factors:

#### Primary Osteoporosis:

It is associated with age and gender. Age results from the deterioration of the trabeculae in bone continuously. In men, the inactivation of testosterone and estrogen occurs as aging by sex-hormone-binding globulin, which decreases in BMD with time. [18] **Bone loss:** Generally, it begins in the mid-'30s. In which bones lose calcium (minerals make them strong, hard, and fast) and the bone becomes thin. [19] Decreased estrogen production in postmenopausal women causes bone loss.

#### Secondary Osteoporosis:

It is associated with various co-morbid diseases or medications. Diseases include mechanisms related to calcium imbalance, Vitamin D and sex hormones. It can affect both sexes but is most common in women after menopause due to a decrease in estrogen levels. This levels protects against osteoporosis. **Men:** Use of excessive alcohol, glucocorticoid, and hypogonadism are more commonly associated. **E.g:** Androgen-deprivation therapy (ADT) in men with prostate cancer is at a high risk of osteoporosis. **Women:** Caused by hypercalciuria, calcium malabsorption, hyperparathyroidism, Vitamin-D deficiency, hyperthyroidism, Cushing's syndrome, and hypocalciuric hypercalcemia. [18]

#### Others:

**General**–Gender-female, older age, Race-Caucasian; **Fractures**-Previous fragility fracture; **underlying medical issues**-kidney diseases, organ transplantation, rheumatoid arthritis, multiple myeloma, HIV, diabetes, overactive thyroid/parathyroid, Cushing syndrome, malabsorption, celiac disease. [19, 20,21, 22]

**Body Habitus**-Kyphosis, low body weight (<57 kg), weight loss (recently-4.5 kg/more);

**Medications**-Chemotherapy, gonadotrophin-releasing hormone agonists, aromatase inhibitors, depo-medroxyprogesterone contraceptives, glucocorticoids, lithium, vitamin-A drugs, PPI's, and antiepileptics. [13,21,22]

**Genetic factors:** family members with hip fracture or osteoporosis diagnosis; **height and weight:** over 5 feet 7 inches tall or weighing under 125 pounds may develop osteoporosis; **Reduced sex hormones:** Decreased estrogen levels may make it harder to regenerate bone. [21 & 22] Obesity initiates mechanical outcomes with the aid of overloading, muscle weakening, and biomechanical modifications [23&24] and reasons damage to the knee joint to the metabolic outcomes. [23&25] E.g. lipids, humoral mediators. [23&26]

**Lifestyle factors:** cigarette smoking, alcohol consumption, poor diet, lack of physical activity. [17 & 22]

#### Pathophysiology of postmenopausal osteoporosis:

- The variations in osteoclastogenesis and osteoblastogenesis show a significant pathological basis for osteoporosis, affected by classical pathways, epigenetic and post-transcriptional regulations, oxidative stress-mediated signalling. [27]
- In the menopause condition, decreased estrogen levels impair the cycle by increasing osteoclastic reabsorption and causing a net loss of bone, termed as "uncoupling". Increased Tumour Necrotic factor (TNF) production, stromal cells/osteoblastic lineages are highly sensitive to Interleukin (IL-1).
- These factors, along with preosteoblasts, release several cytokines such as IL-6, IL-11, granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor (TGF), and macrophage colony-stimulating factor.
- Cytokines from the osteoblasts bind to RANKL (receptor activator of nuclear factor B ligand) on osteoclasts. RANKL has osteoprotegerin (OPG) secreted by stromal osteoblast lineage cells and stimulated by estrogen. Hence, the pool size of osteoclasts in the bone marrow increases reabsorption, down-regulated by estrogen (increases-OPG, Decreases-M-CSF, RANKL). [28]

#### How Osteoporosis relates to menopause:

There is a direct relationship between perimenopause, menopause, and osteoporosis, which developed due to the low levels. Hormone levels are low in early menopause (age-before 45) and prolonged period conditions. Menstrual periods that are absent/infrequent may cause loss of bone mass. [7]

#### Symptoms of Osteoporosis:

Osteoporosis is also called a "silent disease" because, initially, loss of bone occurs without any symptoms. Even patients don't know that they have OA, until their bones become too weak. A sudden bump, fall, or strain shows fractures and vertebral collapse. These collapsed vertebrae are initially seen as severe back pain, height loss, and spinal deformities where posture is stopped. [7]

#### Screening and diagnostic parameters:

Diagnostic parameters of osteoporosis require several laboratory and instrumental tests. [29] Patients/individuals should be pre-screened starting at 50 years of age to widen the benefits for the prevention of fractures. [30] Laboratory test

parameters are commonly used to eliminate secondary causes, such as thyroid dysfunction, parathyroid dysfunction, and hypomagnesemia. [31] The standard diagnostic technique is dual-energy x-ray absorptiometry, which provides a measure of BMD, as this x-ray absorption is directly related to the content of tissue-calcium. [32]

This is considered in patients with a T-score of -2.5 or less. [33] Limitations of dual-energy x-ray absorptiometry were generally reported in individuals with previous fractures, osteoarthritis, osteomalacia, and metal implants. Another limitation is the propensity for discrepancies in the collection and interpretation of results. [34]

Some limitations may be overcome by quantitative computed tomography by allowing measurement of bone density with a single diagnostic device. However, this method requires a higher dose of radiation, is expensive, and has poor quality control because it needs calibration for each measurement. [35] The combination of FRAX score and ultrasonography should be included in the diagnosis because of non-radiation exposure and cost-effectiveness. [36,37,38]

#### Management of postmenopausal osteoporosis:

Pharmacological treatment of osteoporosis is related to the severity of the pathology. Initially, prevention of fragility fractures is important with an effective lifestyle and appropriate nutritional supplements, including daily intake of calcium and vitamin D supplements, weight-bearing activities, avoiding smoking, and drinking alcohol. [39] Based on the density of bone, various treatments are used to increase bone mass and strength by inhibiting the resorption of supporting bone formation. [40] To relieve pain, surgical treatments like vertebroplasty and kyphoplasty are used (unclear benefits). Treatment should be given in patients with osteopenia, a history of hip/spine fragility fractures, a T-score of 2.5 or lower in the spine, femoral neck, hip, or 33% radius, and a T-score between -1.0 and -2.5 if the FRAX® 10-year probability of fracture is  $\geq 20\%$ . [41]

#### Calcium or Vitamin D:

These supplements play a crucial role in the management of osteoporosis, but are not sufficient to reduce the risk of fractures. A combination of these drugs is recommended, although some evidence shows their benefits in the prevention and treatment of glucocorticoid-induced osteoporosis. [42] daily intake

in postmenopausal osteoporotic women is recommended at up to 1200 mg (diet, supplements) or 800 IU, fixed before starting treatment for osteoporosis.

#### **Bisphosphonates:**

Considered as first-line drugs due to long-term safety, efficacy, and affordability for post-menopausal women who are at high risk of fracture. [43] It results in cellular toxicity by involving intracellular pathways in osteoclasts. It binds to hydroxyapatite by inhibiting osteoclastic resorption via several modalities: Cytotoxic injury of mature osteoclasts, inhibition of osteoclast bone attachment, differentiation, or recruitment, and interference with osteoclast features for bone resorption (that is the components of cytoskeleton) [32]

It consists of two subclasses, namely: nitrogen-containing bisphosphonates (NBP's) such as **alendronate, ibandronate, pamidronate, risedronate, and zoledronate**, and non-nitrogen-containing bisphosphonates (NNBP's) such as **etidronate**. NBPs inhibit the mevalonate pathway involved in osteoclast formation and function. NNBP's induce osteoclast apoptosis by the formation of toxic ATP analogs and metabolites. [34]

The drug of choice is usually an oral regimen of alendronate or risedronate taken once a week on an empty stomach in the morning with at least 240 ml of water. After drug administration, a patient needs to stand upright for at least 30–60 min to minimize assimilation and potential gastrointestinal adverse events. [32]

**Oral dose:** Alendronate-10 mg daily (70 mg once weekly); 5 mg daily (35 mg once weekly).

**Parenteral dose:** IV-Zoledronic acid (infused yearly for at least 15 min); Intravascular-Ibandronate (every 3 months for at least 15 to 30 sec) is advised for bisphosphonate contraindicated patients (low tolerance, gastrointestinal, or assimilation problems), started after 4–6 weeks due to delayed healing time.

Adverse events are Barrett's esophagus, gastrointestinal disturbances such as dyspepsia, esophagitis, and esophageal varices. Rarely, atrial fibrillation and renal failure have occurred. Hence, intravascular injections are not suggested for chronic renal failure patients. (GFR<30-35 ml/min) Due to

over-suppression of bone turnover, atypical femur fractures occur (subtrochanteric, diaphyseal). [43]

#### **Denosumab:**

It is the first human monoclonal antibody that binds to human RANKL and inhibits bone reabsorption by the formation and activation of osteoclasts. In fact, this can stop the progression of bone loss and erosion. Due to its efficacy in decreasing spine and hip fractures, this drug has been approved. Administered every 6 months, it suppresses bone resorption by 80-90%. [44&45]

It leads to toxicity by lack of renal clearance, and its anti-resorptive effects last only 4-6 months due to total suppression of remodeling. Hypocalcemia, vitamin D deficiency is managed with Denosumab therapy. [43] This is well-tolerated and does not cause symptomatic hypocalcemia, jaw osteonecrosis, or arterial fibrillation.

It is not recommended for premenopausal women, children, or preventive therapy for osteoporosis. Not used in combination, because it inhibits the binding of RANKL to RANK on T & B-lymphocytes and dendritic cells in addition to pre-osteoclasts. [46] In recurrent infections, antibiotic prophylaxis should be considered, and patients are instructed to report any signs of infection during treatment.

#### **Estrogen Replacement and Selective Estrogen Receptor Modulators:**

The use of hormone replacement therapy (estrogen-progestin, estrogen) with tibolone is potent for the prevention of osteoclast programmed cell death. This increased bone density at the lumbar spine and reduced bone turnover markers at 2 years of treatment. [47] Not used as first-line therapy, due to the risk of venous thromboembolic disorders, cardiac events, stroke, breast cancer, and endometrial cancer, and is administered at the lowest effective dose for a short period. [48] Women, who stopped hormone replacement therapy were at a greater risk of incurring osteoporotic fractures. [49]

The FDA-approved drugs for selective estrogen receptor modulators are raloxifene, lasofoxifene, and bazedoxifene, and they are used in combination with estrogens. [50] This reduces vertebral fractures by increasing trabecular bone mass in the axial skeleton. Raloxifene is effective in cortical porosity treatment. [51]

**Calcitonin:**

This increases osteoblast activity by inhibiting bone resorption. When first-line drugs are intolerable or do not show any therapeutic response, they are considered second-line therapy for osteoporosis. Available in formulations such as oral, and injections as intranasal, it shows an effect on BMD of other skeletal sites. [52] Women may experience lumbar spine BMD and a decrease in biomarkers of bone turnover by oral formulation. However, this does not prevent new vertebral, non-vertebral, or hip fractures. Some clinical trials failed to show efficacy in preventing fractures. [53]

**Odanacatib:**

This is a selective inhibitor of a protease called CatK, released by osteoclasts to promote collagen in bones degradation. [18]

**Lasofloxifene:**

Lasofloxifene (Sermonix) is a third-generation SERM. This treatment is associated with reductions in coronary heart disease, stroke, and breast cancer. [18]

**Parathyroid hormone & parathyroid hormone-related protein analogs: Teriparatide & Abaloparatide:**

Postmenopausal women with osteoporosis are at high risk of fractures (severe, multiple or vertebral). This therapy is recommended for up to 2 years for vertebral and nonvertebral fractures. After this treatment, antiresorptive osteoporosis therapy is recommended for bone density maintenance. [54]

**Strontium Ranelate:**

It is an anti-resorptive agent used for the severe osteoporosis in both men and post-menopausal women (intolerance to other drugs). But the results were inhibition of osteoclasts and promotion of osteoblast differentiation and proliferation through the calcium-sensing receptor (CaSR) along with increased BMD. [55] Adverse events such as cardiovascular events, venous thromboembolism, gastrointestinal discomfort, nervous system disorders, (headache, seizure, memory loss), rarely allergic reactions (rash with eosinophilia and systemic symptoms-DRESS syndrome) are noticed. [35,56,57] considered second-line therapy due to the risk of heart injuries. When used alone or in combination for a prolonged period, it has limitations due to adverse events. Hence, it represents

an option for treating osteoporosis in selected patients. [58]

**Summary:**

Osteoporosis is a bone disease characterized by bone loss, density, mass, and microarchitectural tissues that lead to bone fractures worldwide. Risk factors are associated with age, sex, hormone deficiency, underlying issues, previous fractures, and medications. The pathophysiology includes different pathways, such as classical, epigenetic, post-transcriptional, gut microbiotas, and stress-mediated signalling. Bone loss occurs without any symptoms. Screening includes both laboratory and instrumental tests such as FRAX score, thyroid dysfunctions, X-ray absorptiometry and ultrasonography. Management includes calcium/vitamin D, bisphosphonates, denosumab, estrogen replacement, and selective estrogen receptor modulators, calcitonin, Odanacatib, lasofloxifene, parathyroid, and hormone-related protein analogs, strontium ranelate for a better treatment strategy approach to improve patient health.

**Conflicts of Interests:**

Pravallika, Priyanka, Rahmath Nisha, Devaki, Kishore Babu, Ganesh Kumar and Jeevan Kumar declares that they have no conflict of interest. Human/Animal Rights: This article does not contain any studies with human or animal subjects performed by the any of the authors.

**REFERENCES:**

1. Pavone V, Testa G, Giardina SMC, Vescio A, Restivo DA, Sessa G. Pharmacological therapy of osteoporosis: A systematic current review of literature. *Front Pharmacol.* 2017;8:803.
2. Learn what osteoporosis is and what it's caused by [Internet]. *Nof.org.* 2015 [cited 2021 Sep 21]. Available from: <http://www.nof.org/patients/what-is-osteoporosis/>.
3. Mackenzie Moritz et al. Updates in the treatment of postmenopausal osteoporosis [Internet]. *Uspharmacist.com.* 2019 [cited 2021 Sep 21]. Available from: <https://www.uspharmacist.com/article/updates-in-the-treatment-of-postmenopausal-osteoporosis>
4. Mohamed AS, Khalifa AI, Abotaleb AA-M, Eldesoky NA-R. Comparative study between periostin and osteocalcin as biomarkers for osteoporosis and fracture risk in Egyptian postmenopausal women. *Int J Pharm Pharm Sci.* 2020;17–22.



5. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: An endocrine society\* clinical practice guideline. *J Clin Endocrinol Metab.* 2019;104(5):1595–622.
6. About NOF [Internet]. Nof.org. 2016 [cited 2021 Sep 21]. Available from: <http://www.nof.org/about-us/about-nof/>.
7. Osteoporosis and Menopause [Internet]. Webmd.com. [cited 2021 Sep 21]. Available from: <https://www.webmd.com/menopause/guide/osteoporosis-menopause>
8. Rossi LMM, Copes RM, Dal Osto LC, Flores C, Comim FV, Premaor MO. Factors related with osteoporosis treatment in postmenopausal women. *Medicine (Baltimore).* 2018;97(28):e11524.
9. Dawson-Hughes B, Looker AC, Tosteson ANA, Johansson H, Kanis JA, Melton LJ 3rd. The potential impact of the National Osteoporosis Foundation guidance on treatment eligibility in the USA: an update in NHANES 2005-2008. *Osteoporos Int.* 2012;23(3):811–20.
10. Morrison A, Fan T, Sen SS, Weisenfluh L. Epidemiology of falls and osteoporotic fractures: a systematic review. *Clinicoecon Outcomes Res.* 2013;5:9–18.
11. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society: 2010 Position statement of The North American Menopause Society. *Menopause.* 2010;17(1):25–54
12. Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res.* 1994;9(8):1137–41.
13. Amber R, Erin Z, Tamera P. Osteoporosis: Bisphosphonate therapy in postmenopausal women. *J Fam Med Dis Prev.* 2019 [cited 2021 Sep 21];5(4).
14. Delmas PD. Treatment of postmenopausal osteoporosis. *Lancet.* 2002;359(9322):2018–26.
15. Watts NB, Bilezikian JP, Camacho PM, Greenspan SL, Harris ST, Hodgson SF, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocr Pract.* 2010;16 Suppl 3:1–37.
16. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society: 2010 Position statement of The North American Menopause Society. *Menopause.* 2010;17(1):25–54; quiz 55–6.
17. Kwun S, Laufgraben MJ, Gopalakrishnan G. Prevention and treatment of postmenopausal osteoporosis. *Obstet Gynaecol.* 2012;14(4):251–6.
18. Kristie N, et al. Osteoporosis: A review of Treatment Options. *2018;43(2):92-104.*
19. WebMD - Better information. Better health [Internet]. Webmd.com. [cited 2021 Sep 21]. Available from: <https://www.webmd.com/osteoporosis/understanding-osteoporosis-basics>.
20. 19Jeremiah MP, Unwin BK, Greenawald MH, Casiano VE. Diagnosis and management of osteoporosis. *Am Fam Physician.* 2015;92(4):261–8.
21. Osteoporosis: Treatment, symptoms, causes, medications, exercise & diet [Internet]. Medicinenet.com. [cited 2021 Sep 21]. Available from: <https://www.medicinenet.com/osteoporosis/article.htm>
22. MacGill M. Osteoporosis: Risk factors, diagnosis, and treatment [Internet]. Medicalnewstoday.com. 2019 [cited 2021 Sep 21]. Available from: <https://www.medicalnewstoday.com/articles/155646>
23. Ateia YA, Al-edanni MS, Al-qurtas MI. Impact of metformin and serratiopeptidase in obese patients with knee osteoarthritis. *Int J Pharm Pharm Sci.* 2018;10(2):37.
24. Runhaar J, Koes BW, Clockaerts S, Bierma-Zeinstra SM. A systematic review on the changed biomechanics of lower extremities in obese individuals: a possible role in the development of osteoarthritis. *Obes Rev* 2011;12:1071–82.
25. Brooks PM. Impact of osteoarthritis on individuals and society: how much disability? Social consequences and health economic implications. *Curr Opin Rheumatol* 2002;14:573–7.
26. Velasquez MT, Katz JD. Osteoarthritis: another component of metabolic syndrome? *Metab Syndr Relat Disord* 2010;8:295–305
27. Matt. Postmenopausal osteoporosis: A mini review [Internet]. Emjreviews.com. 2019 [cited 2021 Sep 21]. Available from: <https://www.emjreviews.com/rheumatology/article/postmenopausal-osteoporosis-a-mini-review/>

28. Tella SH, Gallagher JC. Prevention and treatment of postmenopausal osteoporosis. *J Steroid Biochem Mol Biol.* 2014;142:155–70.
29. Schweser KM, Crist BD. Osteoporosis: a discussion on the past 5 years. *Curr Rev Musculoskelet Med.* 2017;10(2):265–74.
30. Gillespie CW, Morin PE. Trends and disparities in osteoporosis screening among women in the United States, 2008-2014. *Am J Med.* 2017;130(3):306–16.
31. Zheng J, Mao X, Ling J, He Q, Quan J, Jiang H. Association between serum level of magnesium and postmenopausal osteoporosis: a meta-analysis. *Biol Trace Elem Res.* 2014;159(1–3):8–14.
32. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos.* 2017;12(1):43.
33. Nayak S, Greenspan SL. Cost-effectiveness of osteoporosis screening strategies for men. *J Bone Miner Res.* 2016;31(6):1189–99.
34. Garg MK, Kharb S. Dual energy X-ray absorptiometry: Pitfalls in measurement and interpretation of bone mineral density. *Indian J Endocrinol Metab.* 2013;17(2):203–10.
35. Pisani P, Renna MD, Conversano F, Casciaro E, Muratore M, Quarta E, et al. Screening and early diagnosis of osteoporosis through X-ray and ultrasound based techniques. *World J Radiol.* 2013;5(11):398–410.
36. Kanis JA, Johansson H, Oden A, Cooper C, McCloskey EV, Epidemiology and Quality of Life Working Group of IOF. Worldwide uptake of FRAX. *Arch Osteoporos.* 2014;9(1):166.
37. Høiberg MP, Rubin KH, Hermann AP, Brixen K, Abrahamsen B. Diagnostic devices for osteoporosis in the general population: A systematic review. *Bone.* 2016;92:58–69.
38. Karjalainen JP, Riekkinen O, Töyräs J, Jurvelin JS, Kröger H. New method for point-of-care osteoporosis screening and diagnostics. *Osteoporos Int.* 2016;27(3):971–7.
39. Testa G PV, Lucenti L AF. The importance of a correct diet in preventing osteoporosis. *J Osteoporos Phys Act* [Internet]. 2015;03(03). Available from: <https://www.longdom.org/open-access/the-importance-of-a-correct-diet-in-preventing-osteoporosis-2329-9509-1000160.pdf>
40. Fukumoto S, Matsumoto T. Recent advances in the management of osteoporosis. *F1000Res.* 2017;6:625.
41. Watts NB, Bilezikian JP, Camacho PM, Greenspan SL, Harris ST, Hodgson SF, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocr Pract.* 2010;16 Suppl 3:1–37.
42. Hiligsmann M, Neuprez A, Buckinx F, Locquet M, Reginster J-Y. A scoping review of the public health impact of vitamin D-fortified dairy products for fracture prevention. *Arch Osteoporos.* 2017;12(1):57.
43. Pazianas M, Abrahamsen B. Osteoporosis treatment: bisphosphonates reign to continue for a few more years, at least? *Ann N Y Acad Sci.* 2016;1376(1):5–13.
44. Takeuchi T, Tanaka Y et al. Effect of denosumab on Japanese patients with rheumatoid arthritis: a dose-response study of AMG 162 (Denosumab) in patients with Rheumatoid arthritis on methotrexate to Validate inhibitory effect on bone Erosion (DRIVE)-a 12-month, multicentre, randomised, double-blind, placebo-controlled, phase II clinical trial. *Ann Rheum Dis.* 2016;75(6):983–90.
45. Suzuki T, Nakamura Y, Kato H. Changes of bone-related minerals during denosumab administration in post-menopausal osteoporotic patients. *Nutrients* [Internet]. 2017;9(8). Available from: <http://dx.doi.org/10.3390/nu9080871>
46. Bonani M, Frey D, de Rougemont O, Mueller NJ, Mueller TF, Graf N, et al. Infections in DE Novo kidney transplant recipients treated with the RANKL inhibitor denosumab. *Transplantation.* 2017;101(9):2139–45.
47. Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone replacement therapy versus the combined oral contraceptive pill in premature ovarian failure: A randomized controlled trial of the effects on bone mineral density. *J Clin Endocrinol Metab.* 2016;101(9):3497–505.
48. Tabatabaei-Malazy O, Salari P, Khashayar P, Larijani B. New horizons in treatment of osteoporosis. *Daru.* 2017;25(1):2.
49. Lobo RA, Pickar JH, Stevenson JC, Mack WJ, Hodis HN. Back to the future: Hormone replacement therapy as part of a prevention strategy for women at the onset of menopause. *Atherosclerosis.* 2016;254:282–90.
50. Qaseem A, Forciea MA, McLean RM, Denberg TD, Clinical Guidelines Committee of the American College of Physicians, Barry MJ, et al.

- Treatment of low bone density or osteoporosis to prevent fractures in men and women: A clinical practice guideline update from the American College of Physicians. *Ann Intern Med.* 2017;166(11):818–39.
51. Börjesson AE, Farman HH, Movérare-Skrtic S, Engdahl C, Antal MC, Koskela A, et al. SERMs have substance-specific effects on bone, and these effects are mediated via ER $\alpha$ AF-1 in female mice. *Am J Physiol Endocrinol Metab.* 2016;310(11):E912-8.
  52. Bandeira L, Lewiecki EM, Bilezikian JP. Pharmacodynamics and pharmacokinetics of oral salmon calcitonin in the treatment of osteoporosis. *Expert Opin Drug Metab Toxicol.* 2016;12(6):681–9.
  53. Henriksen K, Byrjalsen I, Andersen JR, Bihlet AR, Russo LA, Alexandersen P, et al. A randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy and safety of oral salmon calcitonin in the treatment of osteoporosis in postmenopausal women taking calcium and vitamin D. *Bone.* 2016;91:122–9.
  54. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: An endocrine society\* clinical practice guideline. *J Clin Endocrinol Metab.* 2019;104(5):1595–622.
  55. Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS), Italian Society of Rheumatology (SIR), Varenna M, Bertoldo F, Di Monaco M, Giusti A, et al. Safety profile of drugs used in the treatment of osteoporosis: a systematical review of the literature. *Reumatismo.* 2013;65(4):143–66.
  56. Das S, Crockett JC. Osteoporosis - a current view of pharmacological prevention and treatment. *Drug Des Devel Ther.* 2013;7:435–48.
  57. Komm BS, Morgenstern D, A Yamamoto L, Jenkins SN. The safety and tolerability profile of therapies for the prevention and treatment of osteoporosis in postmenopausal women. *Expert Rev Clin Pharmacol.* 2015;8(6):769–84.
  58. O'Donnell S, Cranney A, Wells GA, Adachi JD, Rejnster JY. Strontium ranelate for preventing and treating postmenopausal osteoporosis. *Cochrane Database Syst Rev.* 2006;(3):CD005326.