# PREDISPOSITION OF OSTEOPOROSIS COMPREHENSSIVE ACCOUNT ON POSSIBLE LIFESTYLE MODIFICATION

Corresponding author: Dr.Mohammad Khushtar\* Shabana Khatoon<sup>1</sup>

Department of Pharmacology, Faculty of Pharmacy, Integral University, Lucknow, India <u>skhatoon@iul.ac.in</u>

**Mohammad Khushtar\*** 

Department of Pharmacology, Faculty of Pharmacy, Integral University, Lucknow, India <u>mohdkhushtar@gmail.com</u>

Dr. Shazia usmani<sup>1</sup>

Department of Pharmacognosy, Faculty of Pharmacy, Integral University, Lucknow, India shazia@iul.ac.in

Dr. Shadma Wahab

Department of Pharmacognosy, College of Pharmacy, King Khalid University <u>sabdulwahab@kku.edu.sa</u>

Sivakumar Annadurai Department of Pharmacognosy, College of Pharmacy, King Khalid University <u>sannadurai@kku.edu.sa</u>

# Abstract

Osteoporosis and other chronic conditions have been increasing in prevalence. Menopausal transition years can put women at high risk for osteoporosis. There is a reduction in the population of females in India. Older women have weakened bones and a decrease in bone mineral density. Weakening results in a woman's life and leads to reduced quality of life along with a greater incidence of broken bones. There is a link between osteoporosis and the cessation of the function of the ovaries as you get older. Estrogen plays a part in both the formation of bone and the prevention of the resorption of bone. The treatment options are determined by the severity and rate of progression of the patient. Postmenopausal women should be made aware of this disorder and encouraged to cultivate a healthy lifestyle through the implementation of a proper diet and regular exercise. Smoking and drinking alcohol should be limited in order to prevent osteoporosis in women with or without osteoporosis. It is possible for all postmenopausal women to take the necessary steps to keep their bones strong.

**Keywords:** Bone function, Epidemiology, Bone Loss at Menopause, Nonpharmacologic treatments and lifestyle modifications

# Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural degradation of bone tissue, with an increase in bone fragility and susceptibility to break. A tool that could be used in epidemiological studies to quantify the prevalence of osteoporosis was provided by the diagnostic criteria [1]. The architecture of bone provides maximum strength for the smallest weight. The cortex and the central medullary or cancellous side of thin narrow bone trabecular are found in most bones. The cells are embedded in a hard intercellular material. The bone from other hard tissues is categorized by the two types of components of this material. The skeleton of the human is made of bone tissue[2].

# The functions of bone include

Structural support for the mechanical action of soft tissues, such as the contraction of muscles and the development of lungs. Soft organs and tissues are protected by the skull. The endocrine system regulates the level of calcium andphosphate in the circulating body fluids.

There are four cell types in bone: osteoblasts, osteocytes, osteoclasts, and undifferentiated bone mesenchymal stem cells. The synthesis and deposition of the new intercellular material is done by the osteoblasts. The cell lies within the bone. They are located within lacunae and are surrounded by a bone matrix that regulates mineral deposition and chemistry. The major local orchestrator of bone's functions is the osteocytes. Osteocytes do not play a major role in bone development and may only play a secondary role in growth and development. Cells that degrade bone can initiate normal bone remodeling and mediation of bone loss [3]. New bone is laid down during skeletal development and remodeling. osteoblasts interact with other cell types within bone [4]. osteoclasts are the cells that degrade bone to initiate normal bone remodeling and mediation of bone matrix they circulate in the blood [5]. The balance of bone metabolism is maintained by the cooperation of osteoclasts and osteoblasts [6].

# Epidemiology

Thirty percent of postmenopausal women suffer from osteoporosis according to the World Health Organization [7]. According to a report, 61 million people in India have osteoporosis [8].

Another work according to World health organization osteoporosis predisposes to fragility fractures and development of such fractures is associated with high rates of morbidity and mortality especially in elderly [9].

WHO scientific group on the assessment of osteoporosis at primary health care level. World Health Organization 2007.

Globally, nearly 200 million people suffer from osteoporosis each year.3 India, reported prevalence of osteoporosis affect the women 8 to 62%.5 [10].

This shows wide variation in prevalence across India. Further, the risk of osteoporosis is higher in women than men and in elderly than young adults. India is the second largest populated country in the world. By 2050, suggests that nearly 20% of population will be over age of 60 years. Globally, osteoporosis affects more than 200 million in population. According to Khadilkar et al; reported that the osteoporosis affect from 8% to 62% [11]. The estimate suggest that economic burden associated with osteoporotic hip and vertebral fractures, and shows the significant proportion of osteoporotic fracture costs that are due specifically to (NHNV) non-hip, non-vertebral fractures. The first-year healthcare costs of fractures were highest hip fracture in patients, followed by vertebral and (NHNV) non-hip, non-vertebral fractures. However, the overall cost impact of non-hip, non-vertebral fractures same or increase that of hip 12,13 Hip fractures, occurs symptoms of pain and an inability to bear weight, almost always require surgical fixation and are associated with more reduction in functional status and quality of life than all other types of fracture, with a high risk so its occurs mortality. Hip fractures is generally occurs in age (most occurring after age 80 years), and in women (only about a quarter of hip fractures occur in men), and marked geographical variation (>10 times differences in incidence). Currently most estimated 2.7 million hip fractures in 2010 worldwide, of which shows result 1 364 717 (51%) potentially preventable (264 162 in men, and 1 100555 in women).10 Vertebral fractures are much more variable in their presentation, ranging from those causing severe pain that requires admit to hospital, to those that produce few symptoms and are diagnosed on the basis of imaging.14–16 The majority of studies show that most vertebral fractures are not clinically recognised but importance as markers of skeletal fragility that signify increased risk for other fractures, including those affecting the hip.17-19 vertebral fractures have high fracture risk and result in mortality and adverse effect 20

#### **Bone Loss at Menopause**

In this study, OC, CTX-1(C-terminal telopeptide of type 1 collagen), and P1NP (procollagen type 1 N propeptide) were increased in the osteopenia group compared with the control group, but they were decreased in the osteoporosis group compared with the osteopenia group and again bone turnover rate decreases again 10 years after menopause [21]

Derivatives of anthocyanins, like resveratrol, lycopene, oleuropein, some vitamins, and thiol antioxidants, shows protective and therapeutic anti-osteoporotic effects. The natural antioxidants has been used to prevent oxidative stress bone damage, with a particular supportive role in anti fracture therapies. [22].

Ovariectomy has been shown to alter the antioxidant defense system of the cell, resulting in oxidative stress caused by accumulation of reactive oxygen species [23].

According to another study, lipid peroxidation caused a decrease in the femur antioxidant effect following OVX. Antioxidant activity protects cells and tissues from damage caused by free radicals. They convert free radicals into products that are not harmful. These compounds include in glutathione subordinate proteins, osteoporosis related with oxidative pressure, so because of reactive oxygen species (ROS) can make oxidative harm the cells and cells have a safeguard systems to shield themselves from the toxicity of reactive oxygen species (ROS) 24. Grassi et al; reported that bone loss was caused by oxidative stress in estrogen-deficiency ovariectomized mice, and antioxidant treatment could prevent bone loss [25]. Several investigations have also revealed that the diet based on antioxidants could be beneficial and helpful in preventing and treating postmenopausal osteoporosis [26, 27, 28]. Therefore, the reduction of lipid peroxidation and the increase in antioxidant enzyme activities in OVX rats were experimentally proved, and the strong antioxidant ability of Super Jami rice bran extract may have contributed to partially improving bone metabolism by reducing bone loss in OVX

rats. This pigmented rice bran extract can be potentially useful in preventing oxidative damage and bone loss in estrogen-deficiency in women. [29]

Other work reported that more than one-third of the osteoporosis occurs in women ages 60 to 70 years. The most common fractures are of the spine, hip, forearm and proximal humerus in the elderly. Hip fractures are the most common cause of morbidity and mortality. Osteoporosis is a silent disease that causes low bone density, which can leads to fractures [30]. In this study Esen et al; reported that the aged 50 to 74 years, in accordance with the approach used in a study by. With increasing age, bone balance becomes negative, such that bone resorption is more active than bone formation [31].

Vitamin D deficiency was common in all postmenopausal women but especially in those with lower education level and the veiled. Postmenopausal women should be screened for vitamin D deficiency and encouraged to benefit more from sunlight. Also, enriching foods in the markets with vitamin D may be helpful for decreasing hyperparathyroidism in this population. [32, 33].

After bone mass reaches its peak, bone turnover occurs more slowly, such that bone remodeling primarily comprises bone resorption, rather than bone formation. After menopause, there is increased bone resorption due to estrogen deficiency, thus accelerating bone loss. The extended duration of menopause tends to reduce bone mineral density and bone resorption [33, 34]. Nurunal et al; demonstrated that increased the time of menopause and more age reduce bone mineral density [35].

Serum calcium is elevated in postmenopausal due to the increase age in women. If decrease estrogen level in postmenopausal women so increased serum levels of PTH, which leads to the release of calcium ions from bones, thus increasing serum calcium levels and starting in menopause in women so increase levels of serum calcium; however, these levels decrease with age, due to increased intestinal calcium absorption [3, 5].

Increased calcium and phosphate levels begin at the beginning of the increase in PTH levels because phosphorus and calcium are regulated by PTH hormone and vitamin D. Excessive effect of the parathyroid gland will cause the absorption of calcium salts in the bone to increase in hypercalcemia [36, 37]. Serum calcium is elevated in postmenopausal due to the increase age in women. If decrease estrogen level in postmenopausal women so increased serum levels of PTH, which leads to the release of calcium ions from bones, thus increasing serum calcium levels and starting in menopause in women so increase levels of serum calcium; however, these levels decrease with age, due to increased intestinal calcium absorption [38, 39].Parathyroid hormone increases calcium reabsorption in the kidney, and calcitriol production increases calcium absorption in the intestine. Parathyroid hormones and calcitriol are the main regulators of calcium balance. PTH is largely responsible for serum calcium, while calcitriol maintains serum calcium concentrations. Calcitriol together with PTH plays a role in stimulating osteoclasts in bone resorption.Calcitriol is used for osteoclast differentiation from precursor mononuclear cells. as it happens, of the presence of PTH, calcium release from the bone is reduced, thus decreasing serum calcium levels [40].

Increase in bone remodeling shows high levels of alkaline phosphatase have been observed in both postmenopausal women and ovariectomized rats [41].

The proportion of trabecular and cortical bone can affect fracture resistance, while imbalance of remodeling and increased bone resorption cause more porosity in both trabecular and cortical areas, which effect to increase the risk of fracture [42].

Bone-specific alkaline phosphatase, amino-terminal procollagen and osteocalcin are the common biomarkers used to study bone remodeling. Mineralization is the formation of hydroxyapatite crystals in the superficial membrane of the osteoblasts, followed by the propagation of hydroxyapatite and its deposition between the collagen fibrils [43, 47].

The levels of this biochemical marker of bone remodeling, both in postmenopausal women and in adult ovariectomized Wistar rats, are high. Reference values in healthy adult rats are 1.0 mg/mL [44, 45]. In the case of rats from the OVX, NI and FI groups, osteocalcin serum values were above 2.0 mg/mL. These results further confirmed that rats had experienced bone resorption, and therefore, it was necessary to activate osteoblasts to initiate bone remodeling in such a way that bone mineralization is "increased", in order to recover bone lost by the action of osteoclasts. On the contrary, Ctrl, SH, FS groups showed values below 2.0 mg/mL, indicating that a marked osteoblastic activation was not necessary as in the case of rats from the OVX, NI and FI groups. Collagen is a heterodimer that contributes to the integrity and strength of bone matrix. Serum values of this marker increase during growth and in situations of augmented bone formation [46].

Our results who found that menopause results in elevated bone turnover, an imbalance between bone formation and bone resorption and net bone loss, and this is attributed to the cessation of ovarian function and tapering off of estrogen secretion [48].

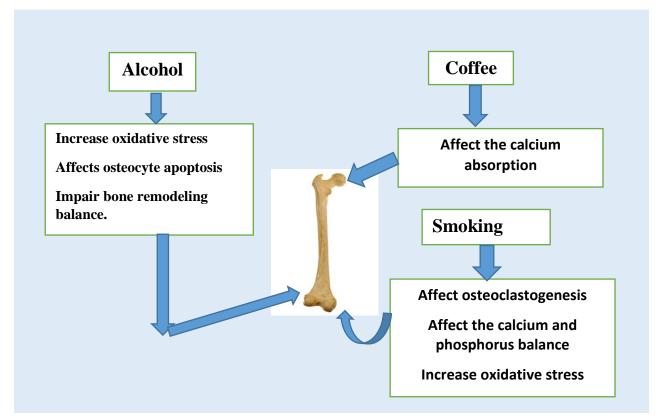
other risk factors for osteoporosis, such as premature ovarian insufficiency (POI) before 40 years of age or early menopause (40–44 years of age) due to genetic, autoimmune, surgical or cancer treatment sequelae. Other risk factors include Chinese ethnicity. (49)

The aim of this study was to examine the characteristics of 25-year changes in femoral BMD after menopause. We investigated associations between the rate of bone loss and selected risk factors (BMI and BMI change, number of diseases, bone-affecting diseases, use of HRT and corticosteroids, use of vitamin D and calcium supplementation, alcohol use, smoking, age, rheumatoid arthritis, and postmenopausal status at baseline) [50].

Recent study showed that the peak a BMD and the rate of bone loss during early postmenopause assessed by DXA at lumbar spine are independent risk factors for subsequent fractures.

Albert Shieh AK, Mei-Hua Huang, Weijuan Han, Gail Greendale. The associations of peak bone mineral density and rate of bone mineral density loss during the menopause transition and early postmenopause with subsequent fracture: results from the Study of Women's Health across the Nation (SWAN). In *American Society of Bone and Mineral Research Annual Meeting*. 2020.

Therefore, stress management is particularly important for the elderly to improve their health promotion performance. Consistent with the results of this study, in another study, the results indicate a relationship between psychological stress and low BMD in postmenopausal women [51]



#### NONPHARMACOLOGIC TREATMENTS AND LIFESTYLE MODIFICATIONS

#### Figure 1

clinical studies have found that COPD patients with OSA (Obstructive sleep apnea) have lower bone mineral density than patients with COPD alone. It may be associated with the increase of systemic inflammation and the decrease of exercise ability in COPD-OSA(Obstructive sleep apnea) overlap syndrome patients. Oxygen desaturation index is an independent factor related to bone mineral density in patients with COPD [52]. But our study is the first to observe osteoporosis in cigarette smoke and intermittent hypoxia overlapping exposed animal models [53].

Animal models have also confirmed that chronic smoke exposure is associated with osteoporosis.

53.

#### Avoiding harmful lifestyle factors

Cessation of smoking and limiting alcohol intake are important general health measures. The AEs of smoking on bone health appear to reverse when smoking is stopped [55].

The objective of treating osteoporosis is to reduce the likelihood of fragility fractures by strengthening the skeleton or decreasing fall frequency, or both. General measures (good nutrition, regular physical activity, avoiding harmful lifestyle habits) are recommended for all patients at risk of osteoporosis [56–58].

Most the studies that have investigated to remove the ovaries before menstruation periods stopped naturally, Poor dietary habits, including insufficient amounts of calcium and/or vitamin D or protein, Physical inactivity or prolonged periods of bed rest, cigarettes, Heavy

use of alcohol, Long-term use of certain medications, such as corticosteroids, proton pump inhibitors, and antiepileptic medications, Altered levels of hormones, such as too much thyroid hormone, too little estrogen in women, or too little testosterone in male. Low body mass index or underweight [59].

Prevention of osteoporosis consists of several aspects, including nutrition, exercise, lifestyle, and initial screening. The World Health Organization believes that, for the prevention of osteoporosis, women should follow a balanced diet, take Vitamin D and calcium tablets, and perform regular exercises [60].

In addition to taking calcium and performing regular exercise, an optimal amount of Vitamin D should be consumed for the prevention of osteoporosis [61,62]

There are several options for the reduction of osteoporosis risk. Lifestyle is pivotal, as the use of anti-osteoporotic drugs and physical activity and nutrition are two crucial lifestyle measures aimed at reducing osteoporosis risk [63].

Results of studies of relationships between protein intake and either BMD or fracture risk have also been inconsistent [64].

Environmental factors were more commonly described to affect the risk of falling for people with osteoporosis. Recently fell, she does recognize that there were environmental modifications she could have made, by adding ice picks to her boots to reduce the risk of falling on ice. Other participants have mentioned improving their footwear choices to reduce the risk of falling during the winter season. Always adhere to the exercise recommendations or modify their lifestyle to reduce the risk of falls, or consider which nutritional needs they might need to better manage their osteoporosis [65].

Physical activity may also be a preventive measure against Crohn's disease [66].

On the other hand, Yang et al. reported that the frequency of osteoporosis was greater among women who did not drink coffee [67].

Whereas according to the study by Hallström et al., high coffee consumption was associated with a slightly decreased BMD, but it did not increase the risk of fracture [68].

Cheraghi et al. reported the association between alcohol consumption and osteoporosis: subjects who consumed one to two and two or more portions of alcohol had a higher risk of osteoporosis by 1.34 and 1.63, respectively, when compared to non-drinkers [69]

Healthy nutrition is one of the several important components of lifestyle to maintain good bone health, but it is difficult to perceive the importance of healthy nutrition because its effects are subtle over long time periods [70].

Mental stress and osteoporosis occur through different mechanisms in the body, numerous studies suggest that there are many potential ways of linking the pathological response to stress and the development of bone disease. These pathways can include impairment of the hypothalamic–pituitary–adrenal axis; dysregulation of the inflammatory pathway, Insulin-like growth factor signaling, estrogen, serotonin, and gamma-amino butyric acid [71].

**Discussion:** Ovariectomized rats and mice are well-established models for the study of the pathogenesis of postmenopausal osteoporosis and are widely used for evaluation and development of new drugs for treatment of postmenopausal osteoporosis [71–73].

Previous studies have shown that osteoporosis-related bone loss in postmenopausal rat was partially prevented by moderate exercise [74–77].

Bone formation rate at the endosteal surface of cortical bones in the EX-OVX group was lower than that in the OVX group, suggesting that exercise may differentially regulate bone formation in trabecular and cortical bones. It seems that exercise can partially prevent estrogen deficiency-induced bone loss by suppressing bone resorption and increasing bone formation. While it is still debated whether decreased bone resorption or increased bone formation is the main reason behind exercise-induced bone mass elevation [78, 79].

# Conclusion

Postmenopausal osteoporosis is a silent disease that is very prevalent worldwide, as well as in India. It is a chronic condition that is asymptomatic, and its progression is slow. After years of research, we have finally discerned its pathogenesis and etiology. It is also evident what its risk factors. Postmenopausal women in India are made aware of the lifestyle modifications that need to be made during the perimenopause and postmenopause periods to help prevent this disorder, and treatment options should be made available to all patients at a minimal cost. Though it can be debilitating for those who suffer from it, can be managed by pharmacological and non-pharmacological intervention. the results of the most included studies showed that non pharmacological strategies are considered as the appropriate actions to prevention of the osteoporosis among the menopausal women so implementing these strategies. It can be a good alternative for contraindication of hormone therapy or therapeutic management in women. Furthermore, due to the other positive effects of exercise and also the uncomplicated nature of most the physical exercises, it is recommended that postmenopausal women follow a regular physical activity program after consulting with their physicians. The mechanism of bone resorption, so knowing the role of each factor is expected to reduce the effects of alveolar bone resorption that occurs in postmenopause. Postmenopausal osteoporosis can be managed by bringing about small but significant changes in one's lifestyle. Exercise, yoga, consumption of milk and its products, and stopping smoking and alcohol consumption can be very beneficial.

# **Reference:**

- Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993; 94: 646–50.
- 2. Mohamed AM. An overview of bone cells and their regulating factors of differentiation. Malays J Med Sci. 2008 Jan; 15(1):4-12. PMID: 22589609; PMCID: PMC3341892.
- Boyce BF, Yao Z, Xing L. Osteoclasts have multiple roles in bone in addition to bone resorption. Crit Rev Eukaryot Gene Expr. 2009; 19(3):171-80. doi: 10.1615/critreveukargeneexpr.v19.i3.10. PMID: 19883363; PMCID: PMC2856465.
- 4. Heaney, Robert Proulx and Whedon, G. Donald. "bone". Encyclopedia Britannica, 15 Feb. 2023, https://www.britannica.com/science/bone-anatomy. Accessed 27 March 2023.
- Boyce BF, Yao Z, Xing L. Osteoclasts have multiple roles in bone in addition to bone resorption. Crit Rev Eukaryot Gene Expr. 2009;19(3):171-80.doi: 10.1615/critreveukargeneexpr.v19.i3.10. PMID: 19883363; PMCID: PMC2856465.

- Haidi Bi 1<sup>+</sup>, Xing Chen 2<sup>+</sup>, Song Gao1<sup>+</sup>, Xiaolong Yu1, Jun Xiao1, Bin Zhang1, Xuqiang Liu1 \* and Min Dai1 Key Triggers of Osteoclast-Related Diseases and Available Strategies for Targeted Therapies: Frontiers in Medicine.4 Frontiers in Medicine Vol,20 December 2017,
- 7. Kanis J.A. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report. Osteoporos. Int. 1994;4:368–381.
- Joshi V.R., Mangat G., Balakrishnan C., Mittal G. Osteoporosis—Approach in Indian scenario. J. Assoc. Physicians India. 1998;46:965–967.
- 9. https://www.who.int/chp/topics/Osteoporosis.pdf.Accessed on 12-June-2020
- 10. Khadilkar AV, Mandlik RM. Epidemiology and treatment of osteoporosis in women: an Indian perspective. Int J Womens Health. 2015; 7:841-50.
- 11. International Orthopedics Foundation. Facts and Statistics. Available from: https://www.iofbonehealth.org/facts-statistics#category-26.Accessed on 12-June-2020.
- 12. Shi N, Foley K, Lenhart G, Badamgarav E. Direct healthcare costs of hip, vertebral, and nonhip, non-vertebral fractures. Bone 2009; 45: 1084–90.
- 13. Leslie WD, Metge CJ, Azimaee M, et al. Direct costs of fractures in Canada and trends 1996–2006: a population-based cost-of-illness analysis. J Bone Miner Res 2011; 26: 2419–29.
- 14. Oden A, McCloskey EV, Johansson H, Kanis JA. Assessing the impact of osteoporosis on the burden of hip fractures. Calcif Tissue Int 2013; 92: 42–49.
- Ensrud KE, Blackwell TL, Fink HA, et al. What proportion of incident radiographic vertebral fractures in older men is clinically diagnosed and vice versa: a prospective study. J Bone Miner Res 2016; 31: 1500–03.
- 16. Ensrud KE, Schousboe JT. Clinical practice. Vertebral fractures. N Engl J Med 2011; 364: 1634–42.
- 17. Schousboe JT. Epidemiology of vertebral fractures. J Clin Densitom 2016; 19: 8–22.
- 18. Naves M, Diaz-Lopez JB, Gomez C, Rodriguez-Rebollar A, Rodriguez-Garcia M, Cannata-Andia JB. The effect of vertebral fracture as a risk factor for osteoporotic fracture and mortality in a Spanish population. Osteoporos Int 2003; 14: 520–24.
- 19. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1999; 14: 821–28.
- McCloskey EV, Vasireddy S, Threlkeld J, et al. Vertebral fracture assessment (VFA) with a densitometer predicts future fractures in elderly women unselected for osteoporosis. J Bone Miner Res 2008; 23: 1561–68.
- Marcucci, G.; Domazetovic, V.; Nediani, C.; Ruzzolini, J.; Favre, C.; Brandi, M.L. Oxidative Stress and Natural Antioxidants in Osteoporosis: Novel Preventive and Therapeutic Approaches. *Antioxidants* 2023, *12*, 373. https://doi.org/10.3390/antiox12020373
- Sanchez-Rodriguez, M.A.; Zacarias-Flores, M.; Arronte-Rosales, A.; Correa-Muñoz, E.; Mendoza Nuñez, V.M. Menopause as risk factor for oxidative stress. *Menopause* 2012, *19*, 361–367.
- 23. Chung SI, Ryu SN, Kang MY. Changes in Bone Metabolism and Antioxidant Defense Systems in Menopause-Induced Rats Fed Bran Extract from Dark Purple Rice (Oryza sativa L. Cv. Superjami). Nutrients. 2021 Aug 24;13(9):2926.

- 24. Muthusami S, Ramachandran I, Muthusamy B, Vasudevan G, Prabhu V, Subramaniam V, Jagadeesan A, Narasimhan S. Ovariectomy induces oxidative stress and impairs bone antioxidant system in adult rats. Clin Chim Acta. 2005 Oct; 360(1-2):81-6.
- 25. 25.Grassi, F.; Tell, G.; Robbie-Ryan, M.; Gao, Y.; Terauchi, M.; Yang, X.; Romanello, M.; Jones, D.P.; Weitzmann, M.N.; Pacifici, R. Oxidative stress causes bone loss in estrogendeficient mice through enhanced bone marrow dendritic cell activation. *Proc. Natl. Acad. Sci. USA* 2007, *104*, 15087–15092.
- 26. De Franca, N.A.; Camargo, M.B.; Lazaretti-Castro, M.; Martini, L.A. Antioxidant intake and bone status in a cross-sectional study of Brazilian women with osteoporosis. Nutr. Health 2013, 22, 133–142. [Google Scholar] [CrossRef]
- 27. Muhammad, N.; Luke, D.A.; Shuid, A.N.; Mohamed, N.; Soelaiman, I.N. Tocotrienol supplementation in postmenopausal osteoporosis: Evidence from a laboratory study. Clinics 2013, 68, 1338–1343.
- 28. Sheweita, S.A.; Khoshhal, K.I. Calcium metabolism and oxidative stress in bone fractures: Role of antioxidants. *Curr. Drug. Metab.* 2007, *8*, 519–525
- 29. Słupski W, Jawień P, Nowak B. Botanicals in Postmenopausal Osteoporosis. Nutrients. 2021; 13(5):1609.
- 30. Marya CM, Dhingra C. Effect of osteoporosis on oral health. Arch Med 2015; 8(21): 1-8
- 31. Esen I, Akturk Esen S, Cander S, Oz Gul O, Ocakoglu G, Erturk E. Causes of elevated parathyroid hormone levels in postmenopausal women. Eur Res J 2017 May; 1-10.
- 32. Puspitadewi SR, et al. The relation of follicle stimulating hormone and estrogen to mandibular alveolar bone resorption in postmenopausal women. J Int Dent Med Res 2017; 10(3): 1-7.
- 33. Puspitadewi SR, Wulandari P, Kusdhany LS, Masulili SLC, Bachtiar H. Relationship of age, body mass index, bone density, and menopause duration with alveolar bone resorption in postmenopausal women 2019; 19(1): 1-10.
- 34. Sowers MR, Zheng H, Greendale GA, et al. Changes in bone resorption across the menopause transition: Effects of reproductive hormones, body size, and ethnicity. J Clin Endocrinol Metab 2013; 98(7): 2854-63
- 35. Nurumal MS, et al. Bone health status among postmenopausal women in malaysia. Int J Women's Health Reprod Sci 2019; 7(2): 169-73.
- 36. De Brito Galvao JF, Nagode LA, Schenck PA, Chew DJ. Calcitriol, calcidiol, parathyroid hormone, and fibroblast growth factor-23 interactions in chronic kidney disease. J Vet Emerg Crit Care (San Antonio) 2013; 23(2): 134-62.
- 37. Shoback D. Clinical practice. Hypoparathyroidism. N Engl J Med 2008; 359(4): 391-403
- 38. Choudhary RK. Evaluation of parathyroid hormones, serum calcium and risk of fracture in premenopausal and postmenopausal women : A hospital based study. Ann Int Med Dent Res 2019; 5(3): 9-12. [http://dx.doi.org/10.21276/aimdr.2019.5.3.OR3]
- 39. Usoro CAO, Onyeukwu CU, Nsonwu AC. Biochemical bone turnover markers in postmenopausal women in calabar municipality. Asian J Biochem 2007; 2: 130-5
- 40. Sharma S, Hashmi MF, Castro D. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Sep 12, 2022. Hypophosphatemia.
- 41. Martin, B.R.; Mohammad, S.; Legette, L. Diet calcium level but not calcium supplement particle size affects bone density and mechanical properties in ovariectomized rats. Nutr. J. 2009.

- 42. Martin, B.R.; Mohammad, S.; Legette, L. Diet calcium level but not calcium supplement particle size affects bone density and mechanical properties in ovariectomized rats. Nutr. J. 2009.
- 43. Beto, J.A. The role of calcium in human aging. Clin. Nutr. Res. 2015, 4, 1-8.
- 44. Patti, A.; Gennari, L.; Merlotti, D.; Dotta, F. Endocrine actions of osteocalcin. Int. J. Endocrinol. 2013. [CrossRef] [PubMed]
- 45. Ce, C.; Zhou, L.; Yu, D.; Zhao, Y.; Yang, N. Serum osteocalcin levels and bone mineral density in ovariectomized rats. Int. J. Innov. Sci. Eng. Technol. 2014, 5, 1–8.
- 46. Usha, K.; Nandeesh, B.N. Physiology of Bone Formation Remodeling, and Metabolism; Springer: Berlin/Heidelberg, Germany, 2012.
- 47. Bala, Y.; Bui, Q.M.; Wang, X.F.; Luliano, S.; Wang, Q.; Ghasem-Zadeh, A.; Rozental, T.D.; Bouxsein, M.L.; Zebaze, R.M.; Seeman, E. Trabecular and cortical microstructure and fragility of the distal radius women. J. Bone Miner. Res. 2015, 30, 21–629.
- 48. El Wakf AM, Hassan HA, Gharib NS. Osteoprotective effect of soybean and sesame oils in ovariectomized rats via estrogen-like mechanism. Cytotechnology. 2014;66(2):335–343.
- 49. Thu WPP, Logan SJS, Cauley JA, Kramer MS, Yong EL. Ethnic differences in bone mineral density among midlife women in a multi-ethnic Southeast Asian cohort. *Arch Osteoporos.* 2019; 14:80.
- Moilanen A, Kopra J, Kröger H, Sund R, Rikkonen T, Sirola J. Characteristics of Long-Term Femoral Neck Bone Loss in Postmenopausal Women: A 25-Year Follow-Up. J Bone Miner Res. 2022 Feb;37(2):173-178. doi: 10.1002/jbmr.4444. Epub 2021 Oct 19. PMID: 34668233; PMCID: PMC9298425.
- 51. Follis SL, Bea J, Klimentidis Y, Hu C, Crandall CJ, Garcia DO, et al. Psychosocial stress and bone loss among postmenopausal women: Results from the Women's Health Initiative. *J Epidemiol Community Health.* 2019;73:888–92.
- 52. Wang T-Y, Yu-Lun L, Chou P-C, et al. Associated bone mineral density and obstructive sleep apnea in Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis. 2015; 10:231–237.
- Sasaki M, Chubachi S, Kameyama N, et al. Effects of long-term cigarette smoke exposure on bone metabolism, structure, and quality in a mouse model of emphysema. *PLoS One*. 2018; 13(1):e191611.
- 54. Xiong J, Tian J, Zhou Lu, Le Yanqing, Sun Yongchang. Interleukin-17A deficiency attenuated emphysema and bone loss in mice exposed to cigarette smoke. Int J Chron Obstruct Pulmon Dis. 2020; 15:301–310.
- 55. Thorin MH, Wihlborg A, A° kesson K, Gerdhem P. Smoking, smoking cessation, and fracture risk in elderly women followed for 10 years. Osteoporos Int 2016; 27:249-255
- 56. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. Eur J Rheumatol. 2017 Mar;4(1):46-56. doi: 10.5152/eurjrheum.2016.048. Epub 2016 Dec 30. PMID: 28293453; PMCID: PMC5335887.
- 57. Body JJ, Bergmann P, Boonen S, Boutsen Y, Bruyere O, Devogelaer JP, Goemaere S, Hollevoet N, Kaufman JM, Milisen K, Rozenberg S, Reginster JY. Non-pharmacological management of osteoporosis: a consensus of the Belgian Bone Club. Osteoporos Int. 2011 Nov;22(11):2769-88. doi: 10.1007/s00198-011-1545-x. Epub 2011 Mar 1. PMID: 21360219; PMCID: PMC3186889.

- 58. LeBoff, M., Greenspan, S., Insogna, K. et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 33, 2049–2102 (2022).
- 59. Osteoporosis | National Institute on Aging (nih.gov) November 15, 2022
- 60. Michiko F. Osteoporosis prevention education for young women. Bachelor's Thesis: Degree Programme in Nursing Tampereen Ammattikorkeakoulu. Tampere University of Applied Sciences; 2011. p. 1-31. Available from: http://www.urn.fi/URN:NBN: fi:amk-2011120417097. [Last accessed on 2018 Sep 04].
- 61. Kamran M, Iftikhar A, Awan AA. Knowledge and behavior regarding osteoporosis in women. Pak Armed Forces Med J 2016; 66:927-32.
- 62. Osman AA. Assessment of osteoporosis KAP among women in Assir region, Saudi Arabia. J Med Med Sci 2013; 4:50-5.
- 63. N. Mendoza, C. De Teresa, A. Cano, D. Godoy, F. Hita-Contreras, M. Lapotka, et al.Benefits of physical exercise in postmenopausal women Maturitas, 93 (2016), pp. 83-88
- 64. Shams-White MM, Chung M, Du M, et al. Dietary protein and bone health: a systematic review and meta-analysis from the National Osteoporosis Foundation. Am J Clin Nutr 2017; 105: 1528–43.
- 65. christina ziebarta, joy macdermidb,c, rochelle furtadoa, tatiana pontesd, mike szekeresc, nina suhe and aliya khan, an interpretive descriptive approach of patients with osteoporosis and integrating osteoporosis management advice into their lifestyle. international journal of qualitative studies on health and well-being,2022, vol. 17
- 66. Wang, Q.; Xu, K.-Q.; Qin, X.-R.; Lu, W.; Liu, Y.; Wang, X.-Y. Association between Physical Activity and Inflammatory Bowel Disease Risk: A Meta-Analysis. Dig. Liver Dis. Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver 2016, 48, 1425–1431.
- Yang, P.; Zhang, X.-Z.; Zhang, K.; Tang, Z. Associations between Frequency of Coffee Consumption and Osteoporosis in Chinese Postmenopausal Women. Int. J. Clin. Exp. Med. 2015, 8, 15958–15966.
- Hallström, H.; Byberg, L.; Glynn, A.; Lemming, E.W.; Wolk, A.; Michaëlsson, K. Long-Term Coffee Consumption in Relation to Fracture Risk and Bone Mineral Density in Women. Am. J. Epidemiol. 2013, 178, 898–909.
- Cheraghi, Z.; Doosti-Irani, A.; Almasi-Hashiani, A.; Baigi, V.; Mansournia, N.; Etminan, M.; Mansournia, M.A. The Effect of Alcohol on Osteoporosis: A Systematic Review and Meta-Analysis. Drug Alcohol Depend. 2019, 197, 197–202.
- 70. Weaver CM. Nutrition and bone health. Oral Dis. 2017; 23:412-5.
- Kelly RR, McDonald LT, Jensen NR, Sidles SJ, LaRue AC. Impacts of psychological stress on osteoporosis: Clinical implications and treatment interactions. Front Psychiatry. 2019; 10:200.
- 72. Saville PD (1969) Changes in skeletal mass and fragility with castration in the rat; a model of osteoporosis. J Am Geriatr Soc 17: 155–166.
- 73. Inada M, Matsumoto C, Miyaura C (2011) [Animal models for bone and joint disease. Ovariectomized and orchidectomized animals]. Clin Calcium 21: 164–170.
- 74. Chachra D, Lee JM, Kasra M, Grynpas MD (2000) Differential effects of ovariectomy on the mechanical properties of cortical and cancellous bone in rat femora and vertebrae. Biomed Sci Instrum 36: 123–128.

- Barengolts EI, Curry DJ, Bapna MS, Kukreja SC (1993) Effects of endurance exercise on bone mass and mechanical properties in intact and ovariectomized rats. J Bone Miner Res 8: 937– 942.
- 76. Chen Y, Wang S, Bu S, Wang Y, Duan Y, et al. (2011) Treadmill training prevents bone loss by inhibition of PPARgamma expression but not promoting of Runx2 expression in ovariectomized rats. Eur J Appl Physiol 111: 1759–1767.
- 77. Winters-Stone KM, Dobek J, Nail LM, Bennett JA, Leo MC, et al. (2013) Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. Osteoporos Int 24: 1637–1646.
- 78. Iwamoto J, Takeda T, Ichimura S (1998) Effects of moderate intensity exercise on tibial bone mass in mature ovariectomized rats: bone histomorphometry study. Keio J Med 47: 162–167.
- 79. Barengolts EI, Lathon PV, Curry DJ, Kukreja SC (1994) Effects of endurance exercise on bone histomorphometric parameters in intact and ovariectomized rats. Bone Miner 26: 133–140.