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Osteoporosis and reproductive health

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Abstract

Osteoporosis is a prevalent issue among menopausal women; however, the number of women with risk factors across all age groups is increasing. This trend can lead to the development of osteopenia or osteoporosis at a younger age, significantly impacting women's physical, emotional, and mental well-being. This review aims to evaluate the current literature on the prevalence of osteoporosis and its most common risk factors among women across all age groups. It serves as an updated reference for readers, helping to understand the fundamental pathophysiological mechanisms of the disease, diagnostic methods, and the role of medications and lifestyle in its prevention. Some authors suggest that the dominant mechanism of bone mass loss is slowed osteoblastic bone formation, while others highlight increased breakdown of the bone matrix as the more prominent mechanism of skeletal damage, depending on the underlying cause of osteoporosis. Increased bone fragility and a higher tendency towards pathological fractures significantly impact both the quality of life and life expectancy in women. Therefore, it is recommended that osteological screening and fracture risk assessment become a mandatory component of individualized care for women across all age groups. The focus of women's bone health care has shifted from postmenopausal treatment to preventative care.

Key words: osteoporosis, bone, menopause, prevention

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Introduction

Osteoporosis is a complex pathophysiological condition influenced by multiple factors, resulting in low bone mass and increased skeletal fragility. It is characterized by reduced bone density and the disruption of bone microarchitecture, making it a systemic skeletal disorder that significantly elevates the risk of fractures (1). The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) measurement more than 2.5 standard deviations (SD) below the average value for a young, healthy individual (a T-score of -2.5 or lower). T-scores are calculated as the difference between the individual's BMD and a reference population mean, divided by the standard deviation of the reference population. Bone density is compared to the average BMD of an adult of the same sex and race at the age of peak bone mass (approximately age 25 to 30) (2). The risk of bone fractures, particularly in the hip, spine, and wrist, increases as T-score values become more negative, a condition known as severe osteoporosis. A negative T-score between -1 and -2.5 SD is the key clinical indicator of osteopenia, a condition associated with a high risk of fractures and potential progression to osteoporosis (3). Many studies have shown differences in BMD values in various geographic regions, populations and ethnicities. It is believed that these differences may be due to several factors such as diet, nutritional status, physical exercise, vitamin D intake, and daily activities. Recent studies indicate that additional important factors that may influence BMD are annual sun exposure, lifestyle, demographic characteristics, education levels, and general health, which depends on age, disease, genetics, mechanical factors, nutrition and hormonal influences (4).

Osteoporosis can be classified into two categories: primary and secondary. Primary osteoporosis is the most common form. It is divided into juvenile and idiopathic osteoporosis, with idiopathic osteoporosis being subdivided into postmenopausal (type I) and age-related or senile (type II) osteoporosis. The development of primary osteoporosis is thought to be multifactorial, including diet, peak bone mass, heritable factors influencing bone fragility, physical activity, early menopause and estrogen status.

Primary osteoporosis is the result of the cumulative effect of bone loss and deterioration of bone structure that occurs as people age (5). It is a direct consequence of the lack of endogenous estrogen, imbalance in calcium and vitamin D intake, malabsorption of minerals in the intestines, and increased osteoclast and decreased osteoblast activity, which result in bone loss (5). Osteoporosis caused by certain medical conditions or medications is classified as secondary osteoporosis. The treatment of secondary osteoporosis is often more complex compared to that of primary osteoporosis, as it depends on managing the underlying condition (1). A bone fracture is often the initial sign of both primary and secondary osteoporosis (6). Estrogen plays an important role in the development of bone mass in women, and the subsequent loss of estrogen is one of the leading causes of osteoporosis (7). Estrogen inhibits bone resorption by inducing small but cumulative changes in multiple

estrogen-dependent regulatory factors. Estrogen reduces the levels of the proinflammatory cytokines interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), macrophage colony-stimulating factor (M-CSF), and prostaglandin-E2 (PGE2), which may lead to an increase in the pool size of pre-osteoclasts in the bone marrow. It has been found that estrogen upregulates tumor necrosis factor-beta (TGF-β), an inhibitor of bone resorption, and decreases osteoclast activity while increasing apoptosis. Although osteoporosis in women is often discussed primarily in the context of menopause, adolescence is considered to be a critical period for bone mineral accumulation, as 40 to 60% of adult bone mass develops during these years (9). However, recent research on osteoporosis has underscored the multifaceted nature of this disease, emphasizing the interplay between genetic predisposition, hormonal changes and environmental risk factors (10). It has been demonstrated that the decline in bone density is not solely caused by aging, but is also influenced by lifestyle factors, such as diet and physical activity (11).

The aim of this review article is to provide an updated perspective on the prevalence of osteoporosis and the risk of bone fractures in women, discussing the factors contributing to increased bone fragility, etiopathogenic mechanisms underlying bone quality decline, and the diagnosis and modern treatment of osteoporosis.

Epidemiology

Osteoporosis is a silent threat to health, marked by an increasing incidence with age and affecting over 200 million people worldwide. Each year, approximately 9 million fractures occur due to osteoporosis, affecting between 9% and 38% of women in developed societies (12, 13). Recent meta-analysis reviews based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA criteria) found that the prevalence of osteoporosis is 23.1% in women and 11.7% in men globally. PRISMA guidelines for meta-analysis are based on a four-step process including article identification, screening, review of article acceptance criteria, and review of articles that entered the meta-analysis process (15). The results of this meta-analysis indicate significant variability in osteoporosis prevalence across different continents, with the highest prevalence observed in Africa (14, 15). Globally, the prevalence of osteoporosis in women aged 50 to 70 is 5%, increasing to 20% for those aged 70 to 80, and exceeding 40% in women older than 80 (Figure 1) (16).

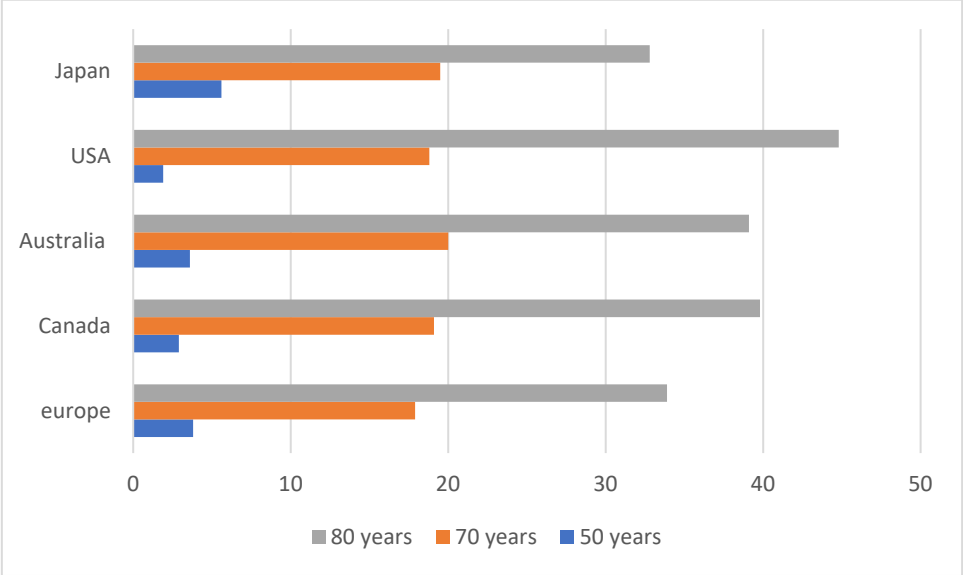

Figure 1. Prevalence of osteoporosis (%) in women in different world regions
Slika 1. Prevalencija osteoporoze (%) kod žena u različitim regionima sveta

Risk factors for osteoporosis

Osteoporosis is a complex condition influenced by multiple factors contributing to its onset. Genetic predisposition is a significant factor in the development of primary osteoporosis, as individuals with a family history of osteoporosis are at a higher risk due to inherited traits influencing bone density and quality. In addition to genetic factors, hormonal changes, particularly estrogen deficiency in postmenopausal women and those with premature ovarian failure, significantly accelerate bone loss, emphasizing the interplay between biological processes and disease onset. The risk is further exacerbated by lifestyle habits, such as inadequate dietary intake of calcium and vitamin D, which are essential for maintaining optimal bone health. Moreover, sedentary behavior and physical inactivity can weaken muscles, indirectly contributing to bone fragility (Figure 2). Factors that contribute to the development of secondary osteoporosis include the use of certain medications, most commonly antacids containing aluminum, heparin, anticonvulsants, thyroxine or steroid hormones (glucocorticoids), as well as excessive alcohol consumption and smoking (17, 18).

Primary osteoporosis	*Secondary osteoporosis*
Increased age	Long term glucocorticoid therapy
History of prior fracture	Long term thyroid replacement therapy
Estrogen deficiency	Some anticonvulsive therapies
Family history of osteoporosis	Malabsorption disorders
Premature menopause	Excessive alcohol intake
Poor nutrition	Excessive caffeine intake
Low calcium intake	Smoking

Figure 2. Main risk factors for osteoporosis
Slika 2. Najznačajniji faktori rizika za osteoporozu

Women engaged in professional sports should be considered a special risk group for osteoporosis due to the Relative Energy Deficiency in Sport syndrome, resulting from caloric imbalances, excessive energy expenditure, and menstrual irregularities (19).

Pathophysiology

The organic matrix of the bone primarily consists of two components: type I collagen and inorganic salt hydroxyapatite. The dynamic nature of bone tissue is reflected in the interactions between bone cells and other organs, as well as in the continuous cycles of bone modeling and remodeling (20). Bone resorption is initiated by osteoclasts, which are derived from macrophage polykaryons. These cells migrate to damaged areas of the bone and carry out the resorption process (20–22). Afterward, osteoclasts undergo apoptosis, leading to the formation of apoptotic bodies, which are believed to contribute to osteogenesis. Mesenchymal stem cells, produced by osteoblasts, migrate to the cavity and initiate bone formation. Osteoblasts become trapped within the bone matrix and differentiate into osteocytes. Osteocytes function as a mechanosensor and play an important role in the regulation of bone remodeling (20–23).

Through simultaneous resorption and formation at specific sites, the bone remodeling process maintains skeletal integrity by replacing old and damaged bone. In bone homeostasis, a constant balance is maintained between bone-forming osteoblasts and bone-resorbing osteoclasts (Figure 3).

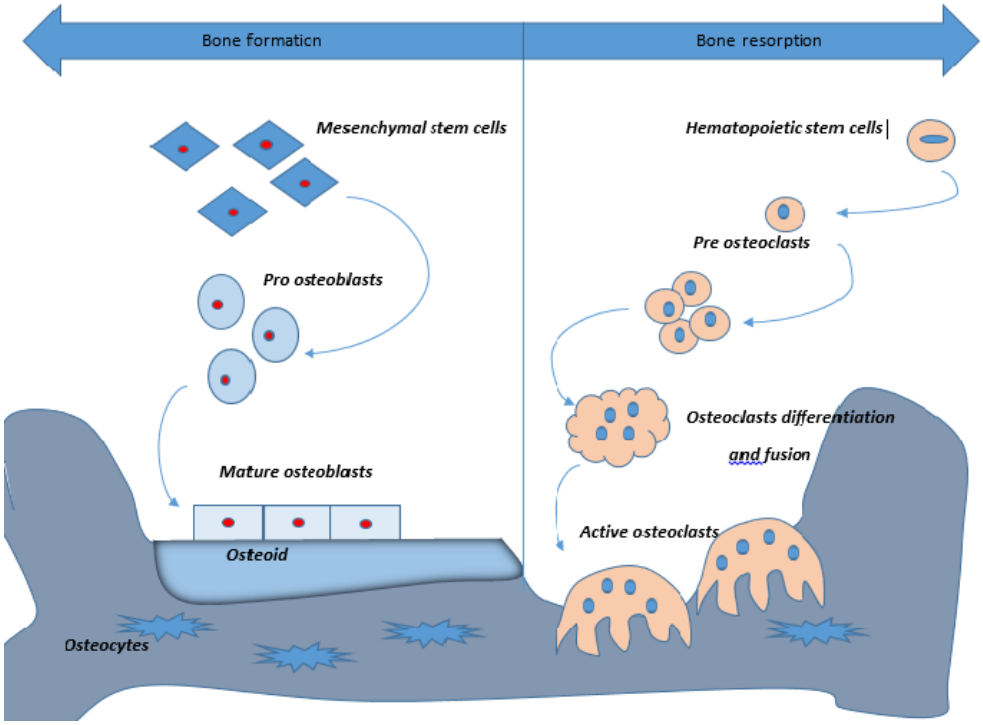

Figure 3. Bone remodeling under physiological conditions
Slika 3. Remodelovanje kostiju pod fiziološkim uslovima

The majority of the mechanosensitive bone cells in the body, osteocytes, are responsible for regulating this process. They reside in chambers within the porous hydroxyapatite bone matrix. This process is regulated by local factors including cytokines and growth factors, as well as systemic factors such as estrogen and calcitonin (CT) (20). CT is thought to exert its effects by binding to the calcitonin receptor (CTR) and the calcitonin receptor-like receptor expressed on osteoclasts. CT inhibits both basal and stimulated resorption by directly inducing the loss of the osteoclast wrinkled border and reducing osteoclast number over time. Evidence suggests that osteocytes may also express CTR and that its expression declines with age. CT mainly acts to complement the function of parathyroid hormone (PTH) by opposing the increased bone resorption induced by PTH (24). Estrogen inhibits bone resorption by directly inducing apoptosis of bone-resorbing osteoclasts. Estrogen has been shown to modulate the production of a number of bone-resorbing cytokines, including IL-1, IL-6, TNF-α (24, 25). The underlying pathophysiological mechanism of osteoporosis is an imbalance between bone resorption and bone formation due to impaired remodeling.

In recent years, it has become evident that the pathological mechanisms leading to osteoporosis are not solely due to hormonal changes, as previously believed. Numerous studies have highlighted the growing importance of osteoimmunology, the connection

between intestinal microbiota and bone health, as well as the pathophysiological mechanisms of cellular aging and their role in the onset of osteoporosis (26).

The bone remodeling process is influenced by both local and systemic molecular mediators whose expression, release and activity are tightly regulated. The physiological serum calcium level is controlled by CT, PTH, and vitamin D3, which are recognized as the primary hormonal regulators of osteoclastic bone resorption (21). CT and PTH are antagonistic hormones that regulate blood calcium levels. CT rapidly reduces circulating calcium levels by inhibiting osteoclasts through the CTR expressed only on osteoclasts (24, 25). PTH and the active form of vitamin D_3 ($1\alpha,25(OH)_2D_3$) affect the bone matrix by stimulating the formation of osteoclasts and increase serum calcium levels by activating osteoclasts (27). The primary cytokine facilitating communication between osteoblasts and osteoclasts is the Receptor Activator of Nuclear Factor κβ Ligand, also known as RANK Ligand (RANKL). RANKL is secreted by osteoblasts and its natural receptor is RANK. The interaction between RANKL and RANK activates signaling pathways responsible for the differentiation and activation of osteoclasts, leading to bone tissue resorption (20, 23). Osteoprotegerin (OPG), a cytokine receptor and a member of the TNF receptor superfamily, binds to RANKL, preventing its interaction with RANK. This mechanism helps maintain the balance of RANKL's effects on bone tissue. $1\alpha,25(OH)_2D_3$ and PTH exert their effects on osteoclast numbers indirectly by reducing RANKL expression in osteoblasts, while $1\alpha,25(OH)_2D_3$, through the vitamin D receptor expressed on osteoclasts, directly promotes their differentiation in the presence of M-CSF and RANKL. PTH and $1\alpha,25(OH)_2D_3$ form a tightly controlled feedback cycle, PTH being a major stimulator of $1\alpha,25(OH)_2D_3$ synthesis in the kidney, while $1\alpha,25(OH)_2D_3$ exerts negative feedback on PTH secretion (27, 28). Additionally, the bone remodeling process is affected by estrogen and androgens. By modulating osteoblast and osteoclast activities, these factors can inhibit bone remodeling, reduce bone resorption, and preserve bone formation. OPG-osteoblast expression is strongly regulated by estrogens, such as estradiol (E2). E2 regulates the expression of genes for OPG synthesis by binding to estrogen receptors (ER), predominantly ERα on the cell surfaces of osteoblasts.

The E2-ERα complex then translocates to the nucleus, where it binds to the estrogen response element in the promoter region of the OPG gene to upregulate OPG mRNA transcription (29). Estrogen suppresses osteoclastogenesis via increased OPG expression in cells of the osteoblast lineage. Androgens inhibit osteoclastogenesis by acting directly through androgen receptors (AR) on osteoclast precursor cells, without affecting the expression of OPG in osteoblasts. ERα, ERβ, and ARs have been detected in several cell types along the differentiation progression of mesenchymal and myeloid precursors to osteoblasts and osteoclasts, as well as in other cell types residing in the bone marrow, or even in tissues distant from the bone that may indirectly influence bone homeostasis (29, 30). ARs in the nucleus are responsible for the classic genomic transcription of the osteoblast's mRNA. Androgens freely diffuse through the plasma membrane, enter the nucleus, and bind to the AR. Modulated by various coactivators and corepressors, the AR, bound to the DNA, influences the transcription and translation of

the genes that govern the osteoblast function. There is an abundance of both ARs and ERs in osteoblasts, indicating the dual role of testosterone and E2 in normal bone physiology (29, 30). During bone remodeling, the bone matrix excavated by osteoclasts is replaced with the new matrix produced by osteoblasts. Both estrogens and androgens influence the generation and lifespan of osteoclasts and osteoblasts, as well as the lifespan of osteocytes.

In this way, osteoclast activity is stimulated by PTH, which simultaneously promotes the production of RANKL and inhibits OPG expression. Conversely, estrogen enhances OPG expression by inhibiting RANKL signaling, thereby reducing osteoclast activity and indirectly contributing to the preservation of skeletal mass. On the other hand, estrogen increases the expression of OPG by inhibiting RANKL signaling, which reduces the activity of osteoclasts and indirectly affects the preservation of skeletal mass (20, 23, 26). Low estrogen levels lead to increased production of RANKL, which enhances osteoclast-mediated bone resorption and contributes to the development of osteoporosis (Figure 4).

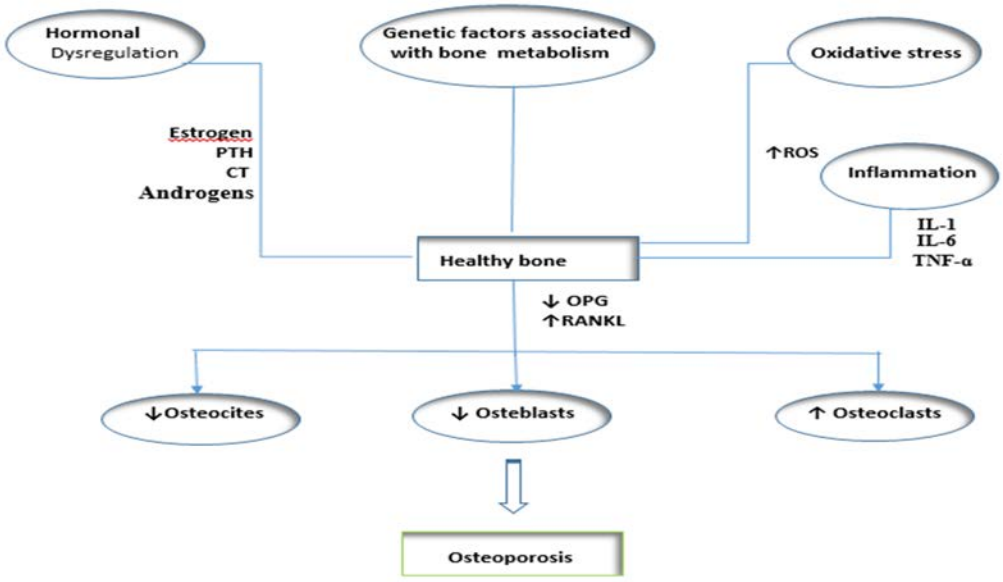

Figure 4. Mechanism of osteoporosis development
Slika 4. Mehanizam za razvoj osteoporoze

Over the past few decades, research has revealed exciting new insights into the mechanisms contributing to the onset of osteoporosis, extending beyond hormonal status to include interactions between bones and the immune system, the gut microbiome, and cellular senescence. The discovery that molecular cytokines, originally attributed to the immune system, have a significant impact on bone health and disease has led to a major shift in the understanding of bone pathologies such as osteoporosis (31).

The connection between the gut microbiome and bone health has become a major focus of biomedical research. Identifying specific bacterial strains, metabolites, and pathways involved in the gut–bone axis is essential for developing effective preventive and therapeutic strategies for bone-related conditions (32). The gut helps regulate the solubility and bioavailability of calcium, influencing its absorption, and it has been recognized as the essential supplier of vitamin B and vitamin K, which play important roles in skeletal homeostasis (33). The gut microbiota plays essential roles in the metabolism of vitamin D, whereby oral supplementation with probiotics significantly promotes circulating 25-hydroxyvitamin D levels, likely via an increase of intraluminal lactic acid production and 7-dehydrocholesterol synthesis.

Another important mechanism through which the gut microbiota contributes to bone remodeling is the diffusion of metabolites from the gut lumen into systemic circulation. The gut fermentation processes yield a variety of metabolites, such as short-chain fatty acids (SCFAs) acetate, butyrate, and propionate, which participate in modulating bone metabolism. These metabolites not only contribute to energy metabolism, but also affect bone cells, influencing the activity of osteoclasts and osteoblasts.

SCFAs not only promote the development of regulatory T cells (Tregs), but also inhibit the generation of T helper 17 (Th17) cells in the small intestine and reduce the production of inflammatory cytokines (IL-6, IL-17, IL-23) which maintain systemic immune homeostasis. In addition to the regulatory effect on the immune system, SCFAs directly affect the formation of osteoclasts and osteoblasts. Histone deacetylases (HDACs) are necessary for human osteoclastic bone development. Inhibition of the activity of HDACs has been shown to be one mechanism through which SCFAs suppress the differentiation of bone marrow cells into osteoclasts. SCFAs function by binding to G-protein-coupled receptors, and the free fatty acid G-protein-coupled receptors (GPR41 and GPR43) are involved in the SCFA-mediated suppression of osteoclast development. SCFAs play important roles in bone formation and mineralization by regulating OPG (33).

The primary mechanism of the interaction between bone metabolism and cellular senescence is that aging leads to the accumulation of senescent cells in the bone microenvironment, accompanied by their release of a proinflammatory Senescence-Associated Secretory Phenotype (SASP) (34). Despite extensive research in this area, the complete role of this mechanism remains to be fully elucidated.

Diagnosis

The National Osteoporosis Foundation of America recommends that indications for bone density testing should be determined only after an initial evaluation of risk factors in women (35).

Bone mineral density (BMD) testing should be considered for women over 65 years of age, regardless of clinical risk factors such as a parental history of hip fracture, body mass index (BMI) lower than 19, long-term use of high-dose steroid medication to treat

health conditions such as arthritis and asthma, and eating disorders, as well as for younger postmenopausal women aged 50 to 69 years with evident risk factors, and for women who have experienced fractures after the age of 50. Special monitoring is recommended for women with rheumatoid arthritis and those on glucocorticoid therapy, particularly if receiving a daily dose of over 5 mg of prednisone for more than 3 months. BMD testing is measured using dual-energy X-ray (DXA), single X-ray absorptiometry (SXA), quantitative computed tomography (QCT), and ultrasound (US) (35). Among these methods, DXA is considered the gold standard. It is a radiological test that evaluates BMD findings in relation to T and Z scores. The T score compares the patient's BMD to that of a young, healthy population, aiding in the assessment of fracture risk. The Z score measures bone density by comparing it to individuals of the same age group. The T score, however, is the standard metric used in most guidelines to assess fracture risk and guide therapy initiation. BMD values obtained from DXA scans are crucial for evaluating an individual's fracture risk and diagnosing osteoporosis (37). The use of QCT for BMD assessment is limited due to its higher radiation dose, cost, and lower predictive value for fracture risk compared to DXA. US can serve as an additional screening method in the diagnostic approach to osteoporosis. Complementary imaging techniques, and serum biomarkers such as vitamin D, calcium, and PTH offer critical insights into bone metabolism and overall health status. Low concentrations of vitamin D are associated with impaired calcium absorption, a negative calcium balance, and a compensatory rise in PTH, which results in excessive bone resorption. During the past decade, numerous clinical studies on osteoporosis have extensively investigated biochemical markers of bone turnover. Markers of bone formation include bone alkaline phosphatase (ALP) and osteocalcin (OC), while markers of bone degradation activity include beta "crosslaps" (CTx), pyridinoline, deoxypyridinoline, and N-telopeptides of type I collagen (PINP). It is generally accepted that these bone markers reflect bone remodeling in both physiological and pathological states. Glover et al. (38) established a reference interval for bone turnover markers in 637 healthy premenopausal women from different countries. The reported reference intervals were: PINP: 16.3–78.2 ng/mL, bone ALP: 5.15–15.32 mg/mL, CTX: 0.114–0.628 ng/mL. Hu et al. (39) calculated reference intervals of a healthy Shanghai population with similar results, where the reference interval for serum OC was 14.91 to 13.90 ng/mL. Saad et al. (40) showed that PINP at a cut-off value of $\leq$ 40.6 pg/ml had a sensitivity of 86.67% and specificity of 80% in predicting osteoporosis. Bone ALP at a cutoff value > 40.3 ng/ml had a sensitivity of 85% and specificity of 83.33% in predicting osteoporosis. Mobasseri et al. (41) showed that at the cut-off point of 16.28 ng/mL, where sensitivity and specificity were 70.3% and 70.9%, respectively, OC showed potential risk factors for developing low BMD in women after menopause. Reduced values of biochemical markers of bone formation combined with elevated values of markers of bone formation indicate a greater risk of osteoporosis. They have the potential to serve as valuable tools for monitoring osteoporosis therapy, identifying non-responders, and predicting bone fractures (42).

Osteoporosis represents a significant clinical challenge facing the global human population. Although DXA is the most commonly used quantitative radiological method for assessing BMD due to its non-invasiveness and cost-effectiveness, the future of diagnosing osteoporosis is likely to involve a combination of genetic, molecular, imaging, and artificial intelligence-based techniques (AI) (39). Recent advances in molecular diagnostics have shown remarkable potential in the field of BMD and diagnosing osteoporosis. Bone turnover marker (BTM) testing detects peptides produced during the formation and degradation of the bone matrix. These are substances found in the blood and urine that provide information about the rate at which bone tissue is resorbed and formed, in particular N-terminal propeptide and C-telopeptide procollagen type I. AI technologies have the potential to aid in the molecular diagnosis and genetic analysis of osteoporosis (43–45).

One potential future innovation is the assessment of BMD via QCT scanning, eliminating the need for DXA scanning. With the advent of AI, machine learning and deep learning models are being applied to the detection and classification of osteoporosis. In addition, the seamless integration of AI models into clinical workflows, as well as their interface with the existing radiology information systems and image archiving and communication systems, is crucial. The combination of AI with QCT diagnostic methods and molecular assessments has the potential to improve our understanding of osteoporosis, improve early detection, enable personalized treatment strategies, and ultimately reduce the burden of this disease on individuals and healthcare systems (42–45).

Treatment

Osteoporosis treatment aims to reduce the risk of fractures and bone loss, prevent disability, and manage pain (46). Two approaches can be implemented for osteoporosis treatment in women: one involves modification of lifestyle habits and the other involves use of medication. Lifestyle changes should focus on maintaining healthy habits, such as avoiding tobacco, alcohol, and excessive coffee consumption, as well as engaging in physical exercise for 30 minutes, 3 to 4 times per week. Before initiating medication, it is essential to incorporate supplemental calcium at a daily dose of approximately 1,200 mg per day and vitamin D at 400–800 IU. To prevent fractures and maintain health after menopause, it is important to engage in balance training, participate in muscle-strengthening physical activities, and exercise caution during daily activities (47). Following a diagnosis, treatment strategies should be individualized to address both fracture risk reduction and the optimization of bone health. Pharmacological interventions often include bisphosphonates, Selective Estrogen Receptor Modulators (SERMs), and hormone replacement therapy, which aim to inhibit bone resorption and promote bone formation. The use of bisphosphonates is associated with a reduction of bone resorption. They bind to hydroxyapatite crystals in the rapidly remodeling bone. Once internalized by osteoclasts, they induce apoptosis. The most commonly used bisphosphonates are alendronate, ibandronate, risedronate and zoledronic acid. Bisphosphonates should

generally be used for a maximum of five years, followed by a pause in medication during which vitamin D and calcium supplementation is recommended (48). Prolonged use of bisphosphonates can lead to atypical femoral fractures and jaw osteonecrosis (49). The use of recombinant PTH analogs, such as teriparatide and abaloparatide, represents a more contemporary approach to treating osteoporosis. Additionally, romosozumab, an antibody-targeting sclerostin, a glycoprotein that serves as a key negative regulator of bone formation, has emerged as a new treatment option for osteoporosis (50). Despite the availability of modern drugs for osteoporosis treatment, there are still many challenges that need to be overcome. One of these challenges is drug interference, as even seemingly harmless medications, such as proton pump inhibitors, can significantly contribute to decreased bone density (51).

The use of combination drug therapies has been shown to be more effective in reducing fracture rates among postmenopausal women (52). Finally, it is crucial to emphasize the importance of raising awareness about disease prevention and promoting preventive examinations in high-risk groups.

Conclusions

Osteoporosis is a common complication in menopausal women; however, given the lifestyle factors of young women and the presence of other chronic diseases and conditions, osteoporosis should be evaluated across all age groups of women. In recent years, numerous studies have enhanced our understanding of the etiopathogenetic mechanisms underlying skeletal damage caused by various diseases. Nonetheless, many uncertainties remain, highlighting the need for further research, particularly in young women. Due to the increasing prevalence of osteoporosis and increasing bone fragility, patient management must be highly individualized.

It is crucial to initiate preventive activities as early as possible, primarily in order to slow down bone demineralization. Developing specific clinical guidelines for the prevention, diagnosis and treatment of skeletal disorders in women throughout the reproductive period and menopause is essential. Considering the increasing aging of the population and the extension of life expectancy, the social and clinical burden of osteoporosis is expected to rise. Therefore, it is imperative to enhance preventive measures.

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Declaration of Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Danijela Ristovski Kornic - conceptualization, writing - original draft, review and editing. Mirela Matejić- writing - original draft.

References

1. Renfro J, Brown JB. Understanding and preventing osteoporosis. AAOHN J. 1998 Apr;46(4):181–91; quiz 192–3.
2. Hendrickson NR, Pickhardt PJ, Del Rio AM, Rosas HG, Anderson PA. Bone Mineral Density T-Scores Derived from CT Attenuation Numbers (Hounsfield Units): Clinical Utility and Correlation with Dual-energy X-ray Absorptiometry. Iowa Orthop J. 2018;38:25–31.
3. Cummings SR. Bone mass and bone loss in the elderly: a special case? Int J Fertil Menopausal Stud. 1993:38 Suppl 2:92–7.
4. Cossio-Bolanos M, Vidal-Espinoza R, Fuentes-Lopez J, Castelli Correia de Campos LF, Andruske CL, Urra-Albornoz C, et al. Reference values for bone density and bone mineral content from 5 to 80 years old in a province of Chile. PeerJ. 2022 Mar 23;10:e13092.
5. Meng-Xia J, Qi Y. Primary osteoporosis in postmenopausal women.Chronic Dis Transl Med Medicine. 2015; (1):9–13.
6. Dimić A. Osteoporoza, Nacionalni vodič za lekare 2008. Ministarstvo zdravlja, Republička stručna komisija za izradu i implementaciju. ISBN 86-7117-114-0. [Internet]. 2008 [cited 2024 Aug 18]. Available from: https://www.zdravlje.gov.rs/view_file.php?file_id=687&cache=sr.
7. Levin VA, Jiang X, Kagan R. Estrogen therapy for osteoporosis in the modern era. Osteoporos Int. 2018;29(5):1049–55.
8. Riggs BL. The mechanisms of estrogen regulation of bone resorption. J Clin Invest. 2000;106(10):1203–4.
9. Al-Ayyadhi N, Refaat LAE, Ibrahim MM, ElGalil HMA. Screening for bone mineral density and assessment knowledge level of low peak bone risk factors and preventive practices among Kuwaiti future mothers. J Multidiscip Healthc. 2020;13:1983.
10. Pouresmaeili F, Kamalidehghan B, Kamarehei M, Goh YM. A comprehensive overview on osteoporosis and its risk factors. Ther Clin Risk Manag. 2018;14:2029–49.
11. Liu X, Wu Y, Bennett S, Zou J, Xu J, Zhang L. The Effects of Different Dietary Patterns on Bone Health. Nutrients. 2024;16:2289.
12. Rachner TD, Hofbauer LC, Göbel A, Tsourdi E. Novel therapies in osteoporosis: PTH-related peptide analogs and inhibitors of sclerostin. J Mol Endocrinol. 2019;62(2):R145–R154.
13. Khadka B, Tiwari ML, Gautam R, Timalsina B, Pathak NP, Kharel K, et al. Correlates of Biochemical Markers of Bone turnover among Post-Menopausal Women. JNMA J Nepal Med Assoc. 2018;56(212):754–8.
14. Chew CK, Clarke BL. Causes of low pick bone mass in women. Maturitas. 2018;111:61–8.

15. Salari N, Ghasemi H, Loghman M, Behzadi MH, Rabieenia E, Shohaimi S, Mohammadi M. The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. J Orthop Surg Res. 2021;16:1983–91.
16. Kanis, J. Assessment of Osteoporosis at the Primary Health Care Level. Technical Report, World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield [Internet]. 2007 [cited 2024 Aug 12]. Available from: https://frax.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf.
17. Van Dort MJ, Driessen JHM, Geusens P, Romme EAPM, Smeenk FWJM, Wouters EFM, van den Bergh JPW. Vertebral bone attenuation in Hounsfield Units and prevalent vertebral fractures are associated with the short-term risk of vertebral fractures in current and ex-smokers with and without COPD: a 3-year chest CT follow-up study. Osteoporos Int. 2019;30(8):1561–71.
18. Thomasius F, Hadji P. Influence of hormone or hormone replacement therapy on bone healing. Unfallchirurg. 2019;122(7):512–7.
19. Ranson WA, Patterson DC, Colvin AC. Female athlete triad: Past, present, and future directions. Ann Joint. 2018;3:4.
20. Siddiqui JA, Partridge NC. Physiological Bone Remodeling: Systemic Regulation and Growth Factor Involvement. Physiology (Bethesda). 2016 May;31(3):233–45.
21. Samwald U, Dovjak P, Azizi-Semrad U, Kerschan-Schindl K, Pietschmann P. Osteoporosis: Pathophysiology and therapeutic options. EXCLI J. 2020;19:1017–37.
22. Longo N, editor. Harison's principles of internal medicine. 18th edition. Mc Graw Hill; 2012.
23. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys. 2008 May 15;473(2):139–46.
24. Chambers TJ, Athanasou NA, Fuller K. Effect of parathyroid hormone and calcitonin on the cytoplasmic spreading of isolated osteoclasts. J Endocrinol. 1984;102(3):281–6.
25. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. Biomed Res Int. 2015;2015:421746.
26. Silva de Sá MF. Premature Ovarian Insufficiency and Bone Health Care: A Concern of the Gynecologist. Rev Bras Ginecol Obstet. 2018;40(6):305–308.
27. Bikle DD. Vitamin D and bone. Curr Osteoporos Rep. 2012 Jun;10(2):151–9.
28. Crooks E, Bendall S. Parathyroid hormone and vitamin D: from bench to bedside. J Orthop Trauma. 2021;35(5):267–273.
29. Notelovitz M. Androgen effects on bone and muscle. Fertil Steril. 2002;77 (4):34–41.
30. Almeida M, Laurent MR, Dubois V, Claessens F, O'Brien CA, Bouillon R, et al. Estrogens and Androgens in Skeletal Physiology and Pathophysiology. Physiol Rev. 2017 Jan;97(1):135–87.
31. Guder C, Gravius S, Burger C, Wirtz DC, Schildberg FA. Osteoimmunology: A Current Update of the Interplay Between Bone and the Immune System. Front Immunol. 2020;11:58.
32. Inchingolo F, Inchingolo AM, Piras F, Ferrante L, Mancini A, Palermo A, et al. The interaction between gut microbiome and bone health. Curr Opin Endocrinol Diabetes Obes. 2024;31(3):122–30.
33. Tu Ye, Yang R, Xu X, Zhou X. The microbiota-gut-bone axis and bone health. J Leukoc Biol. 2021;110:525–37.

34. Khosla S, Farr JN, Monroe DG. Cellular senescence and the skeleton: pathophysiology and therapeutic implications. J Clin Invest. 2022;132(3):154888.
35. National osteoporosis foundation. Clinician's guide to prevention and treatment of osteoporosis [Internet]. 2008 [cited 2024 Nov 25]. Available from: https://www.natap.org/2008/HIV/NOF_Clinicians_Guide-1.pdf.
36. Löffler MT, Jacob A, Valentinitsch A, Rienmüller A, Zimmer C, Ryang YM, et al. Improved prediction of incident vertebral fractures using opportunistic QCT compared to DXA. Eur Radiol. 2019;29(9):4980–9.
37. Gutierrez-Buey G, Restituto P, Botella S, Monreal I, Colina I, Rodríguez-Fraile M, et al. Trabecular bone score and bone remodelling markers identify perimenopausal women at high risk of bone loss. Clin Endocrinol. 2019;91(3):391–9.
38. Glover SJ, Gall M, Schoenborn-Kellenberger O, Wagener M, Garnero P, Boonen S, et al. Establishing a Reference Interval for Bone Turnover Markers in 637 Healthy, Young, Premenopausal Women From the United Kingdom, France, Belgium, and the United States. J Bone Miner Res. 2009;24:389–97.
39. Hu W, Zeng H, Jin-Wei F, Wen-Zhen W, Chun Z, Hao Y, et al. Establishing Reference Intervals for Bone Turnover Markers in the Healthy Shanghai Population and the Relationship with Bone Mineral Density in Postmenopausal Women. Int J Endocrinol. 2013;2013:513925.
40. Saad MA, Aboelwafa RA, Elsayed EH. Could procollagen type I N-terminal propeptide (PINP) and bone alkaline phosphatase (B-ALP) be valid alternative diagnostic markers to dual X-ray absorptiometry (DEXA) in elderly females with osteoporosis? An Egyptian radiological and laboratory monocentric study. Egypt Rheumatol Rehabil. 2021;48:20.
41. Mobasseri M, Tarverdizadeh N, Mirghafourvand M, Salehi-Pourmehr H, Ostadrahimi A, Farshbaf-Khalili A. The role of bone turnover markers in screening low bone mineral density and their relationship with fracture risk in the postmenopausal period. J Res Med Sci. 2023;28:54.
42. Hlaing TT, Compston JE. Biochemical markers of bone turnover – uses and limitations. Ann Clin Biochem. 2014;52:189–202.
43. Liu Z, Wang S, Dong D, Wei J, Fang C, Zhou X, et al. The Applications of Radiomics in Precision Diagnosis and Treatment of Oncology: Opportunities and Challenges. Theranostics. 2019;9:1303–22.
44. Savage RH, van Assen M, Martin SS, Sahbaee P, Griffith LP, Giovagnoli D, et al. Utilizing Artificial Intelligence to Determine Bone Mineral Density Via Chest Computed Tomography. J Thorac Imaging. 2020;35(Suppl. S1):S35–S39.
45. Ong W, Liu RW, Makmur A, Low XZ, Sng WJ, Tan JH, et al. Artificial Intelligence Applications for Osteoporosis Classification Using Computed Tomography. Bioengineering (Basel). 2023 Nov 27;10(12):1364.
46. Spencer H. Osteoporosis: Goals of therapy. Hosp Pract. 1982;17(3):131–43.
47. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki KL, Saag KG, Singer AJ, Siris ES. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022;33(10):2049–102.
48. Hughes DE, Wright KR, Uy HL, Sasaki A, Yoneda T, Roodman GD, et al. Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. J Bone Miner Res. 1995;10:1478–87.

49. Mucke T, Krestan CR, Mitchell DA, Kirschke JS, Wutzl A. Bisphosphonate and medication-related osteonecrosis of the jaw: A review. Semin Musculoskelet Radiol. 2016;20:305–14.
50. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–41.
51. Chen Y, Zhu LL, Zhou Q. Effects of drug pharmacokinetic/pharmacodynamic properties, characteristics of medication use, and relevant pharmacological interventions on fall risk in elderly patients. Ther Clin Risk Manag. 2014;10:437–48.
52. Eastell R, Rosen CJ, Black D, Cheung A, Hassan M, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2019 May 1;104(5):1595–622.

Osteoporoza i reproduktivno zdravlje

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Kratak sadržaj

Osteoporoza je rasprostranjen problem među ženama u menopauzi; međutim, broj žena sa faktorima rizika u svim starosnim grupama raste. Ovaj trend može dovesti do razvoja osteopenije ili osteoporoze u mlađem dobu, značajno utičući na fizičko, emocionalno i mentalno blagostanje žena. Ovaj rezime ima za cilj da proceni trenutnu literaturu o prevalenciji osteoporoze i njenim najčešćim faktorima rizika među ženama svih starosnih grupa. Služi kao ažurirana referenca za čitaoce kako bi razumeli osnovne patofiziološke mehanizme bolesti, dijagnostičke metode i ulogu lekova i načina života u njenoj prevenciji. Neki autori sugerišu da je dominantni mehanizam gubitka koštane mase usporeno osteoblastno formiranje kosti, dok drugi ističu povećano razgrađivanje koštanog matriksa kao izraženiji mehanizam oštećenja skeleta, u zavisnosti od osnovnog uzroka osteoporoze. Povećana krhkost kostiju i veća sklonost ka patološkim prelomima značajno utiču i na životni vek i na kvalitet života žena. Stoga se preporučuje da osteološki skrining i procena rizika od preloma postanu obavezan deo individualizovanog pristupa ženama svih starosnih grupa. Fokus brige o zdravlju kostiju kod žena pomeren je sa postmenopauzalnog lečenja na preventivnu negu.

Ključne reči: osteoporoza, kosti, menopauza, prevencija