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Recent trends in osteoporosis among postmenopausal women

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Abstract

Osteoporosis is considered by reduced bone mineral density and deteriorated bone microarchitecture, addressing the risk of fractures. Studies indicate that loss of estrogen can accelerate bone turnover, with one epidemiological study reflecting a more than two-fold increase in osteoporosis prevalence around menopausal period. Fractures associated with osteoporosis typically occur in the hip, spine, and wrist, significantly affecting mobility and quality of life. Additionally, the concept of osteoimmunology explains the reciprocal relationship between the immune system and bone health, showcasing how immune cells influence bone remodeling processes. It has been shown that inflammation-mediated pathways can lead to enhanced osteoclastogenesis as the process through which bone-resorbing cells named as osteoclasts are formed and culminating in the loss of bone mass.

Introduction

Osteoporosis, a condition defined by reduced bone mineral density and altered bone microarchitecture (1). Osteoporosis is a widespread health concern that particularly affects postmenopausal women, leading to increased bone fragility and susceptibility to fractures (2). Women in this state, experience significant hormone-related bone loss primarily due to declining estrogen levels (3). Several risk factors attributed to the increased prevalence of osteoporosis amongst women in the postmenopausal time (4). Some factors like low-dietary calcium intake, sedentary lifestyles, smoking, and genetic predispositions have been associated with strengthened fracture risks (2,5). In particular, studies have shown that women with lower body mass indexes are at a greater risk for developing osteoporosis, with a direct correlation between weight loss and decreased bone mineral density (6,7). Moreover, the onset of menopause not only affects hormonal levels but also shifts dietary and lifestyle patterns, that further exacerbates osteoporosis risks (8). Additionally, postmenopausal women have inadequate knowledge regarding their bone health, leading to diminished engagement in preventive behaviors such as exercise and healthy nutrition (9). Other studies also highlighted a concerning rise in the prevalence of osteoporosis among postmenopausal women in the last decades (10,11). The overall prevalence of osteoporotic fractures in this group has been reported as high as 82.2%, generally (12). Additionally, the CDC reports that the prevalence of osteoporosis among women increased from 14.0% in 2007-2008 to 19.6% in 2017-2018, revealing a troubling trend of escalating risk in recent years (13). The influence of osteoporosis on daily life is profound, as women with this disease experience a higher incidence of fractures, leading to severe morbidity and increased medical costs (14). It should remember that, osteoporotic fractures, particularly of the hip, vertebrae, and wrist, significantly diminish quality of life and are associated with up to 15% mortality within the first year post-fracture (15). Recently much attention has been directed toward the role of the immune system in the development and management of osteoporosis, since the term immunoporosis further highlights having immunological insight into its treatment (16). This narrative review sought to study the current and emerging therapeutic strategies for osteoporosis that are intricately linked to immune function, emphasizing the need for an interdisciplinary approach in addressing this debilitating condition.

Key point

Osteoporosis is increasingly recognized as a significant health concern affecting postmenopausal women, characterized by low-bone mineral density and heightened fracture risk. The transition into menopausal state initiates with a decline in estrogen levels, which plays a crucial role in maintaining bone consistency.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords like; osteoporosis, estrogen, bone mineral density, osteoclasts and osteoimmunology.

A short look at prevalence of osteoporosis

Osteoporosis affects an estimated 200 million women across the world (1). Approximately 54 million adults in the U.S. have osteoporosis or low-bone mass (17). Among the 10.2 million adults with osteoporosis in the United States, more than 80% were women (18). In addition, the study by Reginster et al showed that, the prevalence of osteoporosis in Caucasian postmenopausal women is estimated to be 30% (19). In the Japanese female population aged 50-79 years, the prevalence of osteoporosis has been estimated at about 35% at the spine and 9.5% at the hip (20). A previous report by Abimanyi-Ochom et al, showed that, about 4.7 million Australians over 50 years old had osteoporosis or osteopenia (21). A recent comprehensive study by Zhang et al utilizing data from the National Health and Nutrition Examination Survey (NHANES) documented an overall prevalence of physician-diagnosed osteoporosis at 17.4% from 2005 to 2018, with bone marrow density (BMD) testing revealing a prevalence of osteoporosis at 9.2% during the same period (22). This finding indicates that a significant proportion of the population is affected by this debilitating condition, warranting urgent attention and care (22). Additionally, the study by Reyes Balaguer and Moreno Olmos on the postmenopausal women showed a 50.4% prevalence of osteoporosis (23).

Rising prevalence rate of osteoporosis in post-menopause females

Recent data highlights a concerning rise in the prevalence of osteoporosis among postmenopausal women. As mentioned above and in other studies, the global prevalence of osteoporosis in postmenopausal state detected to be approximately 30% (4,19). Similarly, the cross-sectional study by Imran et al in India noted that osteoporotic fractures were present in 37.5% of postmenopausal women, with osteopenia affecting an alarming 44.7% (12). These findings exemplify the high prevalence rate of this disease that characterize this vulnerable population across different geographical contexts (12 24). Notably, increasing age further exacerbates this situation, as the prevalence of osteoporosis in postmenopausal women aged 65 years and older is reported to be four times higher than in those younger than 65 years (25-27). This escalation in prevalence rates is further emphasized by reports from the International Osteoporosis Foundation, which estimates that osteoporosis affects one in three women globally, particularly those over the age of 50 years (24,28). Another study from China by Tian and colleagues showed that in Gansu province, the prevalence of osteoporosis in postmenopausal women was 9.65% (29).

Effects of estrogen deficiency on bone health

Estrogen deficiency leads to significant disruptions in bone metabolism, increasing the risk of osteoporosis and fractures (3). In fact, bone metabolism is a dynamic process across the continuous remodeling of bone tissue. This process is tightly regulated by the interplay between osteoclasts and osteoblasts (30). Estrogen contributes to this balance by inhibiting osteoclastogenesis, and the formation of osteoclasts, and also promoting osteoblast survival and function. This phenomenon proceeded by regulating the expression of various proteins and cytokines associated with the differentiation and activity of bone cells (31). When estrogen levels decline, particularly during menopause an up-regulation of pro-inflammatory cytokines, such as RANKL (receptor activator of nuclear factor kappa-B ligand), and a down-regulation of osteoprotegerin (OPG) were happened, leading to an increased receptor activator of nuclear factor kappa-B ligand (RANKL)/OPG ratio (32). This imbalance promotes the differentiation and activation of osteoclasts, resulting in enhanced bone resorption (32). Elevated bone resorption surpasses the rate of new bone formation, leading to a net loss of bone density (33). As mentioned above, the result of estrogen deficiency is evident in the increased prevalence of osteoporosis among postmenopausal women (2); However, estrogen deficiency not only affects the quantity of bone but also affects its quality (3). Therefore, it is crucial to consider the microarchitectural changes that occur due to hormonal shifts (3,34). Meanwhile, advanced imaging techniques have shown that estrogen-deficient individuals exhibit trabecular bone thinning, decreased trabecular connectivity, and alterations in the structure of bone microarchitecture (35). These microstructural changes further compromise the mechanical integrity of bones, making them more prone to fractures (36). Furthermore, the influence of estrogen extends beyond direct actions on osteoclasts and osteoblasts; while it also regulates immune signaling pathways that can affect bone health (37). Chronic inflammation is commonly observed in estrogen deficiency, resulting in increased levels of pro-inflammatory cytokines that further exacerbate bone loss (38). The immune response plays a pivotal role in osteoclast formation, and elevated cytokines, including interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), promote osteoclastogenesis during states of estrogen deficiency (39).

Immunologic features of osteoporosis in postmenopausal women

The immune system has a profound impact on bone homeostasis, particularly in postmenopausal women where estrogen deficiency disrupts the delicate balance between bone resorption and formation (3). Estrogen, a key regulator of bone health, significantly affects the activity of immune cells, particularly T cells and B cells, which play pivotal roles in bone remodeling (osteoimmunology) (40). During menopause, decreased estrogen levels lead to increased activation of T cells, resulting in the production of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 (41). These cytokines are implicated in enhancing osteoclastogenesis, the process by which osteoclasts, the cells responsible for bone resorption, are formed (42). Recent studies have demonstrated that activated T cells upregulate RANKL, a crucial factor in osteoclast differentiation, while simultaneously down-regulating OPG, a decoy receptor that inhibits RANKL activity (43). The resulting imbalance in the RANKL/OPG ratio promotes osteoclast activation and subsequent bone resorption, underscoring the role of T cells in the inflammatory bone loss characteristic of menopausal osteoporosis (44). Moreover, specific T cell subsets, such as Th17 cells, have been found to be particularly influential in the pathogenesis of osteoporotic changes observed post-menopause. In this regard, Th17 cells produce IL-17, a potent cytokine that not only drives inflammation but also promotes osteoclastogenesis, thereby exacerbating bone loss (45). In fact, the connection between the immune response and bone health underlines the concept that osteoporosis may be fundamentally linked to chronic low-grade inflammation, a common feature in aging populations (46). In addition to T cell involvement, B cells are gaining recognition for their role in osteoporosis. Under estrogen-deficient conditions, there is an expansion of B cell populations that contribute to increased bone resorption through the secretion of osteoclastogenic factors such as RANKL (47). Elevated levels of RANKL production by B cells have been shown to correlate with osteoporotic fracture risk (48). Additionally, regulatory B cells that typically produce anti-inflammatory mediators such as IL-10 may become dysfunctional, further intensifying the inflammatory milieu that promotes bone loss during menopause (49). Beyond their direct effects on bone cells, B cells can also modulate T cell activity. This interaction exemplifies the intricate network between the adaptive immune response and bone metabolism (50). Therefore, it seems that, the pathophysiology of postmenopausal osteoporosis plausibly reflects a shift in B cell and T cell dynamics, emphasizing the need for more understanding of immune signaling in osteoporosis(51). It should also remember that, inflammatory markers in postmenopausal women have also been interacted with BMD (52). Evidence suggests that women with higher systemic immune-inflammation index scores show decreased BMD and an increased risk of osteoporosis (53). These findings reinforce the hypothesis that chronic inflammation augments the local and systemic factors driving bone loss. In particular, cytokines derived from activated immune cells promote the normal physiological processes of bone remodeling but in excess can lead to pathologic bone resorption (33). Moreover, shifts in gut microbiota have been found to contribute to immune dysregulation that increases inflammation and osteoclast activity in postmenopausal women, providing a novel mechanism through which osteoporosis may be influenced by the immune system (54). Thus, addressing inflammation through targeted therapies could potentially mitigate bone loss in this population (55).

Therapeutic strategies for osteoporosis related to immune function

The modulation of the immune microenvironment in osteoporotic conditions, specifically targeting innate and adaptive immune cells, is a key area of focus (56). Several therapeutic strategies that target immune function are being explored for osteoporosis (39). Current treatments for osteoporosis, including bisphosphonates (57), denosumab (58), teriparatide (59), and vitamin D supplementation (60), can modulate immune mediators to maintain bone consistency by balancing inflammatory and immunosuppressive immune cells (61). Meanwhile, calcitriol as the active form of vitamin D, can also modulate immune responses and promote bone health (62). In addition bisphosphonates, a common osteoporosis medication, may boost immune response in the lungs (63), offering a potential added benefit against respiratory infections beyond treating the osteoporosis (63,64). These compounds stimulate lung macrophages, enhancing their response to immune challenges (65,66). Prior studies found that immunotherapeutic targets that inhibit the production of inflammatory cytokines show promise in inducing bone regeneration (67). It is also possible, therapies that exploit the potential of immune cells are being selected as novel therapeutic tools for osteoporotic conditions (16). A recent study suggests that exogenous interferon-λ1 (IFN-λ1) could be a therapeutic treatment for osteoclast-related diseases (68). In addition, targeting pro-inflammatory cytokines are new options to control this disease (69). These pro-inflammatory cytokines promote osteoclast activity, leading to bone resorption (70). As mentioned above, therapeutic agents like Denosumab, as a monoclonal antibody that inhibits RANKL, a key mediator of osteoclast formation (71). Similarly, TNF-α inhibitors, which is administered in autoimmune conditions like rheumatoid arthritis, may also benefit for osteoporosis by reducing bone loss (72). While, IL-17 and IL-23 cytokines are involved in Th17-mediated bone resorption, biologic targeting of these pathways may help reduce bone loss (73). One of the modalities on this regard is enhancing anti-inflammatory

cytokines. More recent studies showed that, IL-4 and IL-10 cytokines also inhibit osteoclastogenesis and promote bone formation (42). Modalities to enhance their activity or mimic their effects could be beneficial (42,74). Recent studies also focused on TGF-β (transforming growth factor beta), while it promotes bone formation and inhibits bone resorption (75). Therapies targeting TGF-β signaling may help restore bone balance as well (75). Romosozumab is another promising monoclonal antibody that inhibits sclerostin, a glycoprotein that suppresses bone formation (76). By blocking sclerostin, romosozumab enhances bone formation while simultaneously reducing resorption, showcasing a dual-action mechanism beneficial for osteoporosis treatment (76,77). Likewise, investigating the role of specific immune cells such as regulatory T cells (Tregs) in preserving bone mass has revealed that enhancing Treg function may inhibit osteoclast development, presenting an innovative approach to osteoporosis management (78,79). Besides, in conditions like rheumatoid arthritis, B cells contribute to bone loss (80). Therefore, therapies like rituximab (anti-CD20) by B cell depletion, may indirectly benefit bone health (81). Also, the advent of cellular therapies utilizing mesenchymal stem cells may prove effective; these cells have the potential to modulate immune responses and enhance BMD, signifying their dual role in bone regeneration and immune regulation (82,83). Continuing exploration of other pathways, such as targeting the Wnt signaling pathway through osteocyte signaling or investigating the effects of dietary anti-inflammatory agents, may provide complementary strategies to existing treatments (84). Recent investigations also talk on Dickkopf-related protein 1 inhibitors: since DKK-1 is a Wnt inhibitor, that blocking it may promote bone formation (85). One of the interesting points on the treatment of osteoporosis is gut microbiota modulation; whereas, the gut microbiome also influences immune function and bone health (86). Probiotics and prebiotics may reduce systemic inflammation and improve bone density (87). Consequently, dietary interventions, like high-fiber diets and fermented foods can modulate immune responses and support bone health (88). More recently, some investigators focused on cellular senescence which contributes to chronic inflammation and bone loss. For example, senolytics that clear senescent cells may reduce inflammation and improve bone health (89) or anti-aging therapies, while targeting aging-related immune dysfunction could indirectly benefit osteoporosis (90). Importantly, several investigations are now in charge of exploring immunomodulatory checkpoints and molecules that mediate communication among bone cells in osteoporosis as potential therapeutic targets (16,91). Finally, lifestyle and nutritional interventions like weight-bearing and resistance exercises improve bone density and modulate immune function (92,93). Likewise, anti-inflammatory diet, which is rich in omega-3 fatty acids, and antioxidants, and low-intake of processed foods to reduce systemic inflammation are also hopeful modalities on this subject (94).

Conclusion

Osteoporosis is a major public health concern characterized by reduced bone density and increased fracture risk, particularly affecting postmenopausal women and the elderly. Traditional treatments have focused on hormonal and mechanical factors; however, recent advances in the understanding of the interplay between the immune system and bone metabolism suggest that immunological pathways may represent promising targets for therapeutic approaches. By targeting immune components involved in bone remodeling, such as specific cytokines and immune cells, novel therapies are emerging agents that promise both efficacy and specificity in the management of osteoporosis.

Authors' contribution

Conceptualization: Samaneh Saghafian Larijani.
Data curation: Samaneh Saghafian Larijani.
Investigation: Maryam Niksolat, Samaneh Saghafian Larijani.
Resources: Maryam Niksolat.
Supervision: Samaneh Saghafian Larijani.
Visualization: Maryam Niksolat.
Writing-original draft: Maryam Niksolat.
Writing-review and editing: Samaneh Saghafian Larijani.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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