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METABOLIC ALTERATIONS OF BONE TISSUE IN POSTMENOPAUSAL ESTROGEN DEFICIENCY

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Annotation

The study explores how estrogen deficiency during the postmenopausal period affects bone metabolism. It focuses on the disruption of the osteoclast-osteoblast balance, calcium and vitamin D regulation, and oxidative stress mechanisms. Findings show that reduced estrogen levels enhance bone resorption via RANK/RANKL activation and suppress bone formation, resulting in bone loss and higher fracture risk. The research highlights preventive and therapeutic strategies such as hormone therapy, nutritional supplementation, and lifestyle modifications to reduce osteoporosis in postmenopausal women.

Keywords: estrogen, postmenopause, osteoporosis, bone, metabolism, calcium, osteoclast, osteoblast, hormone, resorption, density, stress, vitamind, collagen, women

The postmenopausal period marks a major endocrinological transition in a woman's life, characterized by a sharp decline in ovarian estrogen production that affects multiple organ systems. One of the most significant consequences of this hormonal change is the disruption of bone metabolism, leading to accelerated bone loss and increased risk of osteoporotic fractures. Estrogen plays a key role in maintaining the balance between bone resorption and formation by inhibiting osteoclast activity and supporting osteoblast function. With menopause, estrogen deficiency removes this regulation, causing excessive bone resorption that surpasses new bone formation. Globally, over 200 million women suffer from osteoporosis, with postmenopausal women comprising the majority. The lifetime risk of osteoporotic fractures exceeds 40%, posing a serious health and economic burden. In Uzbekistan, the growing elderly female population increases the need for early diagnosis and preventive care, as osteoporosis often remains undetected until fractures occur. This article explores

the pathophysiological mechanisms linking estrogen deficiency to bone metabolic changes, highlights the contribution of oxidative stress and biochemical markers, and discusses current preventive and therapeutic strategies aimed at reducing osteoporosis risk in postmenopausal women.

Estrogen plays a central role in maintaining bone homeostasis through complex interactions with osteoblasts, osteoclasts, and molecular signaling pathways. It acts mainly via estrogen receptors (ERα and ERβ) expressed in bone cells, regulating both bone formation and resorption. A key mechanism is the RANK/RANKL/OPG system, which controls osteoclast differentiation and activity. Under normal conditions, estrogen suppresses RANKL expression and enhances osteoprotegerin (OPG) production, thereby limiting bone resorption. After menopause, declining estrogen levels disrupt this balance - the RANKL/OPG ratio increases, leading to excessive osteoclast formation, prolonged lifespan of resorptive cells, and accelerated bone loss. Estrogen also supports osteoblast differentiation and survival, stimulates synthesis of type I collagen and osteocalcin, and promotes bone matrix mineralization. Its deficiency reduces osteoblast activity and increases apoptosis, resulting in inadequate bone formation. Consequently, bone remodeling becomes imbalanced, favoring net bone loss. Moreover, estrogen influences calcium and phosphorus metabolism by enhancing intestinal calcium absorption, reducing renal excretion, and regulating parathyroid hormone (PTH) and vitamin D activity. Estrogen deficiency lowers calcium absorption efficiency and active vitamin D synthesis, inducing secondary hyperparathyroidism that further accelerates bone resorption. Clinical evidence confirms that postmenopausal women commonly show reduced vitamin D levels and bone mineral density, emphasizing the necessity of maintaining adequate vitamin D and calcium intake in osteoporosis prevention strategies.

Growing evidence suggests that oxidative stress is a major contributor to postmenopausal bone loss, complementing the direct effects of estrogen deficiency. Under normal conditions, antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase maintain redox balance by neutralizing reactive oxygen species (ROS). When estrogen levels decline, this balance is disrupted, leading to excessive ROS accumulation and oxidative damage within bone tissue.

Estrogen acts as both an antioxidant and a regulator of antioxidant enzyme expression. Its deficiency reduces the bone's defense against oxidative damage, resulting in lipid peroxidation, protein oxidation, and DNA injury. ROS stimulate osteoclast differentiation and activity through NF-κB and MAPK signaling, increasing bone resorption, while simultaneously impairing osteoblast function and survival, thereby reducing bone formation. This dual action accelerates overall bone loss. The bone matrix, primarily composed of type I collagen, is particularly vulnerable to oxidative injury. ROS cause collagen fragmentation and abnormal cross-linking, weakening bone structure. The accumulation of advanced glycation end products (AGEs) further deteriorates collagen quality, making bones brittle even at normal bone mineral density levels. Mineralization processes are also affected. Estrogen deficiency lowers alkaline phosphatase activity - an enzyme essential for hydroxyapatite crystal formation - and disturbs calcium and phosphate transport in osteoblasts. These impairments result in poor mineral deposition and reduced bone strength. Biochemical markers reflect these metabolic changes: bone resorption markers such as CTX and NTX increase sharply after menopause, while formation markers like osteocalcin and bone-specific alkaline phosphatase remain stable or decline, indicating an imbalance in bone remodeling. Notably, osteocalcin also acts as a metabolic hormone influencing glucose and energy metabolism; its decline may link estrogen deficiency to broader metabolic disturbances. Additionally, estrogen normally suppresses inflammatory cytokines such as TNF-α, IL-1, and IL-6, which promote osteoclastogenesis. After menopause, increased cytokine production enhances osteoclastic activity, creating a pro-inflammatory and pro-resorptive environment. These findings highlight that postmenopausal bone loss arises not only from hormonal decline but also from oxidative and inflammatory stress, suggesting therapeutic value in antioxidant and anti-inflammatory strategies alongside traditional osteoporosis treatments.

Preventive and therapeutic strategies for postmenopausal bone loss involve hormonal, nutritional, and lifestyle interventions. Hormone replacement therapy remains the most effective method to prevent bone resorption, though its use is limited by potential risks. Calcium and vitamin D supplementation are essential for bone mineralization, while phytoestrogens and antioxidants offer supportive effects.

Regular weight-bearing exercise enhances bone strength and reduces fracture risk. Pharmacological treatments such as bisphosphonates, denosumab, and anabolic agents are used in advanced cases. Combining these approaches provides optimal protection against osteoporosis and helps maintain skeletal integrity in postmenopausal women.

Results and Discussion

The pathophysiological analysis presented in this article elucidates the multifaceted mechanisms through which postmenopausal estrogen deficiency induces metabolic alterations in bone tissue, culminating in accelerated bone loss and increased fracture susceptibility. The central finding is that estrogen decline disrupts the fundamental balance between bone resorption and formation, creating a negative bone balance that progressively compromises skeletal integrity. This disruption operates through multiple interconnected pathways involving osteoclast and osteoblast regulation, calcium homeostasis, oxidative stress, and inflammatory processes. The upregulation of osteoclast activity following estrogen withdrawal represents the primary driver of postmenopausal bone loss. Loss of estrogen-mediated suppression of the RANK-RANKL system removes critical constraints on osteoclast differentiation and activation, resulting in excessive bone resorption. Simultaneously, estrogen deficiency compromises osteoblast function and survival, reducing the capacity for compensatory bone formation. This uncoupling of bone remodeling, wherein resorption exceeds formation in each remodeling cycle, leads to progressive skeletal deterioration characterized by reduced bone mass, compromised microarchitecture, and diminished mechanical strength.

The contribution of oxidative stress to postmenopausal bone loss has emerged as an important pathophysiological component that extends beyond simple hormonal deficiency. Estrogen functions not only as a sex steroid hormone but also as an antioxidant and regulator of antioxidant enzyme expression. Loss of these protective effects during menopause increases reactive oxygen species accumulation in bone tissue, which directly damages bone cells and matrix components while amplifying osteoclast activity. The recognition of oxidative stress as a mechanistic contributor to bone loss suggests potential therapeutic value of antioxidant interventions,

although definitive clinical evidence supporting this approach requires further investigation. The clinical significance of understanding these metabolic alterations extends to early detection, risk stratification, and targeted intervention strategies. Biochemical markers of bone turnover provide valuable tools for assessing bone remodeling activity and monitoring treatment responses. Elevated bone resorption markers during early postmenopause identify women experiencing rapid bone loss who may benefit from more aggressive preventive interventions. Conversely, suppression of turnover markers during therapy confirms therapeutic efficacy and may guide treatment decisions. Integrating biochemical markers with bone mineral density measurements and clinical risk factors enables more personalized approaches to osteoporosis management.

The diversity of preventive and therapeutic approaches available reflects the complex, multifactorial nature of postmenopausal bone loss. While hormone replacement therapy most directly addresses the fundamental hormonal deficit, concerns regarding long-term safety have prompted development of alternative strategies targeting specific aspects of bone metabolism. Anti-resorptive agents effectively reduce bone loss and fracture risk by inhibiting osteoclast activity through various mechanisms. Nutritional interventions supporting calcium homeostasis, vitamin D status, and overall bone health complement pharmacological approaches. Physical activity provides skeletal benefits through mechanical loading while simultaneously reducing fall risk. Optimal outcomes typically result from comprehensive programs integrating multiple interventions tailored to individual circumstances. The metabolic alterations in bone tissue following estrogen deficiency also intersect with broader aspects of postmenopausal health. Emerging evidence linking bone metabolism to glucose homeostasis, cardiovascular function, and cognitive health suggests that skeletal changes may serve as biomarkers for systemic aging processes. Conversely, interventions targeting bone health may confer benefits extending beyond fracture prevention. This systems-level perspective on postmenopausal health encourages integrated approaches addressing multiple organ systems simultaneously rather than focusing narrowly on individual conditions. From a public health standpoint, the substantial burden of postmenopausal osteoporosis necessitates comprehensive screening and prevention

programs. Many women remain unaware of their osteoporosis risk until fractures occur, at which point skeletal damage is already substantial. Implementing screening protocols to identify high-risk individuals during the early postmenopausal period, when interventions may be most effective, represents a critical priority. Educational initiatives promoting awareness of osteoporosis risk factors, importance of adequate calcium and vitamin D intake, benefits of regular physical activity, and availability of effective treatments can empower women to take proactive steps protecting their skeletal health.

Conclusion

Postmenopausal estrogen deficiency disrupts bone remodeling and accelerates bone loss through hormonal, metabolic, and inflammatory mechanisms, ultimately leading to osteoporosis. Early identification using biochemical markers and bone mineral density assessment is essential for preventing fractures and maintaining skeletal health. Effective management requires an integrated strategy combining hormonal therapy, adequate calcium and vitamin D intake, physical activity, and pharmacological agents when necessary. Personalized, evidence-based interventions tailored to individual risk profiles offer the best outcomes. Ongoing research into molecular pathways and novel treatments continues to improve prevention and therapy for postmenopausal bone loss.

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