Volume 4, Issue 6, June 2026 ISSN (E): 2938-3765

THE ROLE OF HORMONAL FACTORS IN THE DEVELOPMENT OF OSTEOPOROSIS

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Abstract
Osteoporosis is a common systemic skeletal disease characterized by decreased bone mineral density and impaired bone quality, resulting in increased bone fragility and a higher risk of fractures. The maintenance of skeletal integrity depends on a complex network of hormonal regulators that coordinate bone formation and resorption throughout life. Among these, sex steroids, parathyroid hormone, vitamin D, glucocorticoids, growth hormone, insulin-like growth factor-1 (IGF-1), calcitonin, and thyroid hormones play key roles in preserving normal bone remodeling. Hormonal influences on bone health are particularly evident during ageing. In women, menopause-related estrogen deficiency is the major factor driving accelerated bone loss, largely through increased osteoclast activity and disruption of the regulatory pathways that maintain the balance between bone resorption and bone formation. In men, age-associated declines in testosterone and IGF-1 also contribute to progressive deterioration of both cortical and trabecular bone. This review examines the major hormonal mechanisms involved in the pathogenesis of osteoporosis and highlights recent advances in our understanding of endocrine regulation of bone metabolism. Particular attention is given to the clinical implications of these hormonal interactions for the diagnosis, prevention, and treatment of osteoporosis.

Keywords: Osteoporosis, bone mineral density, estrogen deficiency, parathyroid hormone, vitamin D, testosterone, glucocorticoids, bone remodelling, hormonal factors.

Introduction

Osteoporosis is defined by the World Health Organization as a bone mineral density (BMD) value 2.5 standard deviations or more below the mean for young healthy adults, expressed as a T-score of -2.5 or lower, and is associated with a substantially increased risk of fragility fractures at the spine, hip, and wrist. The condition represents a major global public health burden, with the lifetime risk of a fragility fracture in a postmenopausal woman estimated to exceed 40% in high-income countries. Bone mass is the product of two competing processes bone formation by osteoblasts and bone resorption by osteoclasts and their coordinated balance during the remodelling cycle is regulated by a complex network of systemic hormones, local paracrine signals, and mechanical stimuli [1,2].

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The hormonal contribution to bone metabolism encompasses virtually the entire endocrine system. Estrogen and testosterone are the principal regulators of peak bone mass accrual during adolescence and of bone maintenance in adulthood, while parathyroid hormone and the active form of vitamin D govern calcium homeostasis and directly modulate osteoclast and osteoblast activity. Growth hormone and insulin-like growth factor-1 stimulate bone formation, glucocorticoids in excess suppress it, and calcitonin and thyroid-stimulating hormone exert additional regulatory influences. Understanding the specific contribution of each hormonal axis is essential not only for elucidating the pathophysiology of primary and secondary osteoporosis, but also for identifying rational therapeutic targets [3,4].

Bone remodelling and hormonal regulation

Bone remodelling is a lifelong process that proceeds in discrete cycles through five sequential phases: quiescence, resorption, reversal, formation, and mineralisation. The activation of remodelling is initiated when osteocytes, the principal mechanosensory cells of bone, detect microdamage or changes in mechanical loading and transmit signals that recruit osteoclast precursors to remodelling sites. Osteoclast differentiation and activation are critically dependent on the interaction between receptor activator of nuclear factor kappa-B ligand (RANKL), expressed on osteoblasts and stromal cells, and its receptor RANK on osteoclast precursors. Osteoprotegerin (OPG), also secreted by osteoblasts, functions as a decoy receptor that competitively inhibits RANKL-RANK binding and thereby restrains osteoclastogenesis. The RANKL/OPG ratio is the central determinant of net bone resorptive activity and is modulated by virtually all hormones that influence bone metabolism [1,5].
A comprehensive review published in Biomedicines in 2024 summarised the roles of hormones and cytokines in osteoporosis, confirming that estrogen, parathyroid hormone, testosterone, and calcitonin influence bone density through shared and distinct effects on the RANKL/RANK/OPG axis, osteoblast proliferation and apoptosis, and osteoclast lifespan, while inflammatory cytokines including interleukins and tumour necrosis factor-α amplify resorptive signalling, particularly in the context of estrogen deficiency [2].

Estrogen and Postmenopausal Bone Loss

Sex steroids play a fundamental role in maintaining skeletal health, with both estrogens and androgens contributing to the regulation of bone remodeling and preservation of bone mass. Among these hormones, estrogen is particularly important because of its ability to suppress bone resorption and maintain the balance between osteoclastic and osteoblastic activity. Estrogen deficiency disrupts this balance, resulting in accelerated bone turnover and progressive bone loss affecting both trabecular and cortical compartments. Although much of the early research on osteoporosis focused on trabecular bone, increasing evidence suggests that cortical bone is also significantly affected by estrogen deficiency. Experimental studies have demonstrated that reduced estrogen levels are associated with alterations in cortical bone structure and mechanical properties, potentially compromising skeletal strength and increasing fracture susceptibility. In addition, estrogen deficiency may promote osteocyte apoptosis, further contributing to deterioration of bone quality [3].
The clinical consequences of estrogen deficiency are most evident during menopause, when the rapid decline in ovarian hormone production leads to accelerated bone loss and a marked increase in

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fracture risk. At the molecular level, estrogens exert their anti-resorptive effects through modulation of the RANK/RANKL/osteoprotegerin signaling pathway. By reducing RANKL expression and enhancing osteoprotegerin production, estrogens inhibit osteoclast differentiation and activity, thereby limiting bone resorption. Menopausal hormone therapy remains one of the most effective strategies for preventing bone loss in recently postmenopausal women, particularly those younger than 60 years of age. In addition, selective estrogen receptor modulators (SERMs), such as raloxifene and bazedoxifene, provide anti-resorptive benefits by mimicking the protective skeletal effects of estrogen and have been approved for the prevention and treatment of osteoporosis [4].

Parathyroid Hormone and Calcium Homeostasis

Parathyroid hormone (PTH) is a key regulator of calcium and phosphate metabolism and plays an essential role in maintaining skeletal homeostasis. It is secreted by the parathyroid glands and acts through a complex network of cellular and molecular pathways to regulate bone remodeling and mineral balance. The biological effects of PTH are mediated by specific receptors expressed in target tissues, particularly bone and kidney. Within the skeleton, PTH exerts its effects primarily through osteoblast-lineage cells, indirectly influencing osteoclast activity and bone resorption. Sustained elevations in PTH levels increase bone turnover and may lead to progressive bone loss, whereas intermittent exposure can stimulate bone formation. PTH promotes osteoblast proliferation and survival, enhances matrix production, and supports the activation of bone-forming cells, highlighting its dual role in skeletal metabolism [6].

Beyond its actions on bone, PTH contributes to calcium homeostasis through its renal effects. It increases calcium reabsorption in the distal nephron, reduces phosphate reabsorption, and stimulates renal 1α-hydroxylase activity, thereby enhancing the synthesis of active vitamin D. This coordinated regulation of calcium, phosphate, and vitamin D is critical for maintaining normal bone mineralization and skeletal integrity. The importance of PTH in bone biology is further reflected in its therapeutic applications. Recombinant forms of parathyroid hormone are used as anabolic agents in the treatment of osteoporosis, particularly in postmenopausal women and individuals at high risk of fracture. Experimental studies have also demonstrated interactions between PTH and insulin-like growth factor-1 (IGF-1), suggesting that PTH may partially counteract mechanisms responsible for impaired bone formation in glucocorticoid-induced osteoporosis [7].

Vitamin D

Vitamin D plays a fundamental role in skeletal health and calcium homeostasis, and its deficiency remains a major public health concern worldwide. It is estimated that approximately one-third of the global population has suboptimal serum 25-hydroxyvitamin D [25(OH)D] concentrations. In addition to its direct effects on bone metabolism, adequate vitamin D status appears to enhance the response to anti-resorptive therapies used in the treatment of osteoporosis [5]. The principal source of vitamin D in humans is cholecalciferol, which is synthesized in the skin following exposure to ultraviolet B (UVB) radiation. After undergoing hepatic and renal hydroxylation, vitamin D is converted into its biologically active form, which plays a critical role in regulating intestinal calcium and phosphate absorption. Insufficient vitamin D levels impair mineral absorption, resulting in a decline in serum ionized calcium concentrations and subsequent stimulation of parathyroid hormone secretion.

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The resulting secondary hyperparathyroidism promotes osteoclast activation and increases bone resorption in an attempt to maintain calcium homeostasis. Over time, this process contributes to loss of bone mineral density, deterioration of bone microarchitecture, and an increased risk of osteoporosis and fragility fractures. Epidemiological studies have consistently demonstrated an association between vitamin D deficiency and fracture risk, particularly among older adults, with the highest risk observed in individuals with markedly reduced serum 25(OH)D concentrations.

Androgens and Male Osteoporosis

Although osteoporosis is more prevalent in women, it represents a clinically important and underdiagnosed condition in men, in whom androgen deficiency plays a role analogous to estrogen deficiency in women. Testosterone exerts direct anabolic effects on bone through androgen receptors on osteoblasts and also contributes to bone maintenance indirectly through its aromatisation to oestradiol, which acts on estrogen receptors expressed in both osteoblasts and osteoclasts. Declining testosterone levels in ageing men whether due to hypogonadism or the gradual age-related decrease in Leydig cell function are associated with accelerated bone loss, particularly at cortical sites [3].

A review of osteoporosis from an endocrine perspective confirmed that the decline of both testosterone and insulin-like growth factor-1 (IGF-1) negatively impacts bone formation in elderly men, with the reduction in IGF-1 diminishing osteoblast proliferation and reducing periosteal bone apposition. The same review noted that follicle-stimulating hormone (FSH), whose levels rise with declining gonadal function in both sexes, may exert direct pro-resorptive effects on bone independently of sex steroid deficiency, representing a novel hormonal pathway contributing to age-related bone loss [5].

Glucocorticoids and Secondary Osteoporosis

Osteoporosis and osteoporotic fractures represent some of the most frequent adverse outcomes associated with long-term glucocorticoid therapy. Individuals receiving glucocorticoids have a substantially elevated risk of progressive bone loss. Furthermore, the underlying diseases requiring glucocorticoid treatment may independently contribute to reductions in bone mineral density. Additional risk factors, including advanced age, female sex, and low baseline bone mass, further increase susceptibility to skeletal complications. Recent studies have identified more than one hundred KEGG signaling pathways linked to genes expressed in individuals with osteoporosis. Glucocorticoid-induced osteoporosis (GIOP) is recognized as the most common form of secondary osteoporosis in adults, second only to postmenopausal osteoporosis in overall prevalence. The mechanisms underlying GIOP are multifaceted and involve numerous systemic and cellular processes. A marked decline in bone mass is frequently observed during the first year of glucocorticoid therapy, particularly within the lumbar spine [8]. The development of GIOP is associated with suppression of both the somatotropic and gonadotropic hormonal axes, decreased intestinal calcium absorption, glucocorticoid-related myopathy, ocular complications such as cataracts, and alterations in the survival and function of bone cells. At the cellular level, glucocorticoids promote osteoclast formation and activity, thereby shifting bone remodeling toward increased resorption.

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One of the key molecular mechanisms involves disruption of the Wnt/β-catenin signaling pathway. Glucocorticoids reduce the expression of Wnt agonists while simultaneously increasing the production of Wnt pathway inhibitors. Since Wnt/β-catenin signaling plays a pivotal role in osteoblast differentiation and bone formation, its suppression leads to impaired osteoblastogenesis and reduced bone-building capacity. Despite these detrimental skeletal effects, glucocorticoids exert potent anti-inflammatory actions by suppressing the synthesis of proinflammatory cytokines, including interleukin-1 (IL-1) and interleukin-6 (IL-6), which are known to stimulate bone resorption and inhibit bone formation. Through this mechanism, glucocorticoids may provide a degree of protection against inflammation-mediated bone damage. In addition, their influence extends beyond the skeleton, affecting various extraskeletal pathways that contribute to the overall pathophysiology of GIOP [1,8].

Growth Hormone, IGF-1, and Thyroid Hormones

Growth hormone and its principal mediator IGF-1 are important anabolic regulators of bone metabolism, stimulating osteoblast proliferation, differentiation, and collagen synthesis, as well as promoting periosteal bone apposition and increasing peak bone mass during skeletal development. Growth hormone deficiency in adults is associated with reduced BMD and increased fracture risk, and recombinant growth hormone replacement has been shown to partially reverse these deficits. The age-related decline in growth hormone and IGF-1 secretion (somatopause) contributes to the progressive bone loss observed in both men and women beyond the fifth decade of life [5].

Thyroid hormones exert complex effects on bone. At physiological concentrations, triiodothyronine (T3) stimulates both osteoblast and osteoclast activity and is required for normal skeletal development, whereas hyperthyroidism leads to accelerated bone turnover with net resorption and significantly reduced BMD. A review examining hormonal changes in the elderly noted that while elevated thyroid-stimulating hormone (TSH) appears to have a direct protective effect on bone mass through TSH receptors on bone cells, the decline of protective hormones and the relative rise of resorptive signals-particularly cortisol, PTH, and FSH collectively create a pro-resorptive hormonal environment in the ageing skeleton [5].

Conclusion

The evidence reviewed highlights the central role of hormonal regulation in the development and progression of osteoporosis. Bone health is maintained through a complex interplay of endocrine factors, and disturbances in hormonal balance can profoundly affect bone remodeling and skeletal integrity. Among the hormones involved, estrogen, testosterone, and glucocorticoids have particularly important effects on bone metabolism and are major contributors to both primary and secondary forms of osteoporosis. Estrogen and testosterone generally exert protective effects by preserving bone mass and limiting excessive bone resorption, whereas chronic glucocorticoid excess accelerates bone loss and increases fracture risk. These observations emphasize that osteoporosis should not be viewed solely as a disorder of bone mineral density but rather as a condition influenced by multiple interconnected physiological systems. A better understanding of the hormonal mechanisms underlying osteoporosis has important clinical and public health implications. Future research should continue to explore the complex interactions between endocrine pathways and

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skeletal health in order to improve risk assessment, prevention strategies, and therapeutic approaches. From a public health perspective, osteoporosis prevention programs should place greater emphasis on hormonal health alongside established measures such as adequate calcium and vitamin D intake, regular physical activity, and lifestyle modification. Integrating endocrine evaluation into osteoporosis screening and management may contribute to earlier identification of at-risk individuals and improved long-term skeletal outcomes.

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