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Opinion Article

Pathophysiology of Osteoporosis: Bone Remodeling Imbalance and Cellular Mechanisms Explained

Qiang Xu*

Department of Orthopedics, the First Affiliated Hospital of Nanchang University, Nanchang, China

DESCRIPTION

Osteoporosis is a skeletal disorder characterized by low bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and a higher risk of fractures. The pathophysiology of osteoporosis is rooted in an imbalance between bone resorption and bone formation, processes that are normally tightly coupled in the dynamic system of bone remodeling. This imbalance results in the loss of bone density and disruption of the structural integrity of bone tissue, particularly affecting the trabecular (spongy) bone found in areas such as the vertebrae, hips, and wrists. Understanding the pathophysiological mechanisms underlying osteoporosis involves examining the role of bone cells, hormonal regulation, and systemic and local factors that influence bone metabolism.

Bone remodeling is a lifelong process through which old or damaged bone is replaced by new bone. This process is carried out by two primary cell types osteoclasts, which break down bone (resorption), and osteoblasts, which build new bone (formation). Under normal physiological conditions, the activities of osteoclasts and osteoblasts are balanced, maintaining bone mass and strength. In osteoporosis, this balance is disturbed, most commonly with increased osteoclastic activity and/or insufficient osteoblastic response, resulting in net bone loss over time.

A key factor in the development of osteoporosis is age-related decline in bone formation and increased bone resorption. With aging, the population of osteoblasts becomes less active and fewer in number, while osteoclasts continue to function, often at an enhanced rate. Additionally, the lifespan of osteoblasts shortens, while the lifespan of osteoclasts may increase, further tipping the balance toward bone resorption. This process is particularly accelerated in postmenopausal women due to the sharp decline in estrogen levels, a hormone crucial in regulating bone metabolism.

Estrogen plays a protective role in bone health by inhibiting osteoclast formation and activity, promoting osteoclast apoptosis, and supporting osteoblast survival and function. The reduction of estrogen during menopause leads to unchecked osteoclastic activity, increasing bone turnover and causing a rapid phase of bone loss. The result is thinning of the trabecular bone and increased porosity of cortical bone, both of which weaken the skeletal framework and make bones more susceptible to fractures.

The RANK/RANKL/OPG signaling pathway is central to the regulation of osteoclastogenesis and bone remodeling. RANKL (receptor activator of nuclear factor Kappa-B ligand) is produced by osteoblasts and bone marrow stromal cells and binds to RANK receptors on osteoclast precursors, stimulating their differentiation into mature, bone-resorbing osteoclasts. Osteoprotegerin (OPG), also produced by osteoblasts, acts as a decoy receptor that binds RANKL, preventing it from activating RANK and thus inhibiting osteoclastogenesis. In osteoporosis, the balance between RANKL and OPG is disrupted-either due to increased RANKL or decreased OPG levels-resulting in excessive osteoclast activity and bone resorption.

Inflammatory cytokines also play a significant role in the pathophysiology of osteoporosis. Interleukin-1 (IL-1), interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α) enhance RANKL expression and osteoclast differentiation, further contributing to bone resorption. Chronic inflammation, as seen in diseases like rheumatoid arthritis or other systemic inflammatory disorders, can exacerbate bone loss through these cytokine-mediated pathways.

Other hormonal factors influence bone metabolism and contribute to osteoporosis. Parathyroid Hormone (PTH), which regulates calcium homeostasis, has a dual effect depending on its pattern of secretion. Continuous elevation of PTH, as seen in primary hyperparathyroidism, promotes bone resorption, while intermittent exposure, used therapeutically, can stimulate bone formation. Thyroid hormone excess increases bone turnover and favors resorption. Glucocorticoids, whether endogenous or from chronic corticosteroid therapy, impair osteoblast function and enhance osteoclast survival, leading to secondary osteoporosis.

Mechanical loading and physical activity also regulate bone remodeling. Weight-bearing exercise stimulates bone formation through mechanotransduction pathways that activate osteoblasts.

Correspondence to: Qiang Xu, Department of Orthopedics, the First Affiliated Hospital of Nanchang University, Nanchang, China, E-mail: 170710787@stu.edu.cn

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Conversely, disuse or immobilization leads to bone resorption due to the lack of mechanical stress. This phenomenon is particularly observed in individuals on prolonged bed rest, astronauts in microgravity, or patients with neuromuscular disorders.

Nutritional deficiencies can also contribute to osteoporosis. Calcium and vitamin D are essential for bone mineralization. A deficiency in calcium leads to secondary hyperparathyroidism and increased bone resorption, while vitamin D deficiency impairs calcium absorption and bone matrix mineralization. Other nutrients, such as protein, magnesium, and vitamin K, also support bone health, and their absence may affect bone metabolism adversely.

The structural consequences of osteoporosis are most evident in trabecular bone, where the interconnected network of bone struts becomes thin and disconnected, significantly compromising mechanical strength. Cortical bone also becomes thinner and more porous. These structural changes not only reduce bone mass but also diminish bone quality, further increasing fracture risk. Vertebral compression fractures, hip fractures, and distal radius fractures are the most common clinical manifestations of osteoporotic fragility fractures.

CONCLUSION

The pathophysiology of osteoporosis is driven by an imbalance between bone resorption and formation, mediated by cellular, hormonal, and mechanical factors. Estrogen deficiency, RANKL-mediated osteoclast activation, inflammatory cytokines, hormonal disturbances, and lack of mechanical stimulation all contribute to increased bone turnover and net bone loss. Understanding these mechanisms is essential for developing effective prevention and treatment strategies, which aim to restore bone remodeling balance, preserve bone mass, and reduce the risk of fractures in affected individuals.