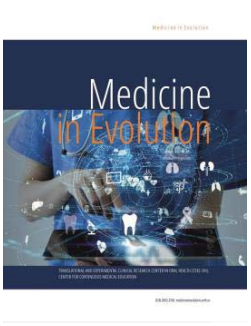
Bone remodelation pathogeny in postmenopausal osteoporosis



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Abstract

Osteoporosis is a progressive bone metabolic disorder with socioeconomic serious impact. Osteocytes are the most abundant bone cells. They keep the matrix calcified, and the rapid resorption of the matrix follows their death. While they share most matrix-related activities with osteoblasts, osteocytes also express many different proteins, including factors with paracrine and endocrine effects that help regulate bone remodelling. This article presents the mechanisms involved in the occurrence of postmenopausal osteoporosis based on literature review. Beyond classical mechanisms, molecular mechanisms involving Circ_0134944, pancreatic and duodenal homeobox 1 (PDX1) and S1P by sphingosine kinase 1 and 2 (SPHK1) are implicate in osteogenesis homeostasis.

Keywords: osteoporosis, menopause, bone resorption, bone density

INTRODUCTION

Osteoporosis is a quiet and progressive bone metabolic disorder that is often brought to the attention of patients or the doctor only after a fracture. The etiology of osteoporosis is multifactorial and is related to two main processes: the acquisition of maximum bone density at the end of the third decade and bone loss and bone resorption from menopause to old age. The cardinal features of osteoporosis are pain, fracture, and deformity [1]. Measurement of low bone mineral density is the most reliable diagnostic tool in the early stages of osteoporosis [2].

STRUCTURAL AND BONE RESORPTION IMPLICATIONS

The primary structural component of the bone matrix is types I collagen and, to a lesser extent, type V collagen. Traces of other types have also been found in the matrix, such as type III, XI, and XIII collagens. All collagen molecules make up about 90% of the total weight of the protein bone matrix [3].

The matrix also contains other proteins that are the primary substance of bone. Nearly a minor component of bone, making up only 10% of the total weight of bone matrix proteins, they are essential for bone development, growth, reshaping, and repair. Both collagen and the soil substance become mineralized and form bone tissue [4]. The four main groups of non-collagenous proteins found in the bone matrix are presented in Figure 1.

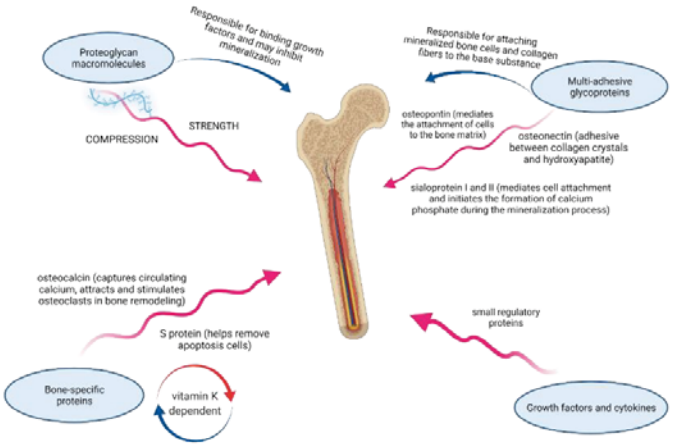

Figure 1. Four main groups of non-collagenous proteins found in the bone matrix

The bone matrix contains gaps connected by a network of canaliculi (Figure 2). There are spaces in the bone matrix called gaps, each containing a bone cell or osteocyte. During the transition from osteoblasts to osteocytes, cells extend many long dendritic processes surrounded by a calcified matrix [5].

Osteocytes are the most abundant bone cells. They keep the matrix calcified, and the rapid resorption of the matrix follows their death. While they share most matrix-related activities with osteoblasts, osteocytes also express many different proteins, including factors with paracrine and endocrine effects that help regulate bone remodeling [6].

The extensive lacunar-canalicular network of these cells and their communication with all other bone cells allows osteocytes to serve as sensitive detectors of stressors, microtraumas induced by bone fatigue and trigger the remedy by activating osteoblasts and osteoclasts. Bone tissue depends on osteocytes to maintain viability [4].

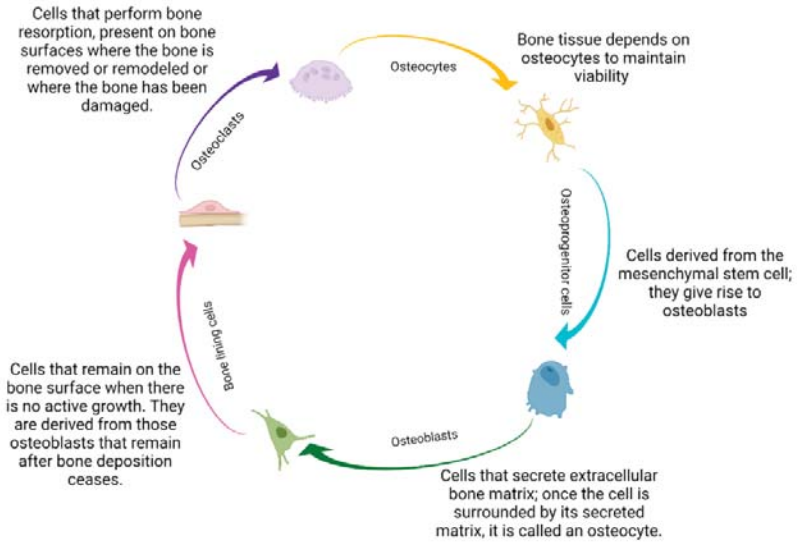

Figure 2. Extensive lacunar-canalicular network of these cells and their communication

Osteoblasts produce the organic components of the bone matrix, including type I collagen fibers, proteoglycans, and matrix cellular glycoproteins such as osteonectin. The deposition of inorganic bone components also depends on the activity of osteoblasts. Active osteoblasts are located exclusively at the surfaces of the matrix bone, to which integrins link them, usually forming a single layer of cuboidal cells joined by adherent and gap junctions [4]. When their synthesis activity is completed, some osteoblasts differentiate as osteocytes trapped in the matrix gaps, some flatten and cover the surface of the matrix as bone lining cells, and most undergo apoptosis [6]. During the matrix synthesis and calcification processes, osteoblasts are polarized cells with ultrastructural features designed for the synthesis and active secretion of proteins [5]. This process of bone growth in apposition is completed by the subsequent deposition of calcium salts in the newly formed matrix. The process of matrix mineralization is not entirely understood [5].

Endochondral ossification takes place inside the hyaline cartilage. This type of ossification forms most bones [5]. Enchondral ossification takes place in the hyaline cartilage, whose shape resembles a small-scale pattern of bone that will form. Most of the bones that make up the skeleton appear by chondral ossification, this model being studied mainly in the development of long bones. The chondral ossification of a long bone consists of a succession of processes. The first bone structure that forms is a bony sleeve that surrounds the diaphysis of the cartilaginous model. This bone sleeve is produced by the activity of osteoblasts in the local perichondrium [7]. The sleeve blocks the diffusion of oxygen and nutrients in the underlying cartilage, causing degenerative changes. Chondrocytes begin to produce alkaline phosphatase and enlarge (hypertrophy), widening the gaps in their location [5]. The changes lead to the compression of the matrix into narrow trabeculae and the calcification of these structures. Cell death of chondrocytes leads to the appearance of a porous structure composed of remaining calcified cartilaginous elements, over which a layer of osteoblasts is formed. The blood vessels in the perichondrium (which has become periosteal) penetrate through the bone sleeve, transporting osteoprogenitor cells into the central porous region. Subsequently, osteoblasts adhere to the structural remnants of the calcified cartilaginous matrix and begin to produce reticular bone tissue. At this stage, the cartilage is basophilic, while the newly formed bone tissue is acidophilic [8].

Through this process at the diaphysis level, the primary ossification center is formed, starting from the first trimester of intrauterine life. Secondary ossification centers appear later in the cartilaginous epiphyses and remodelling. Primary and secondary ossification centers

produce cavities gradually occupied by bone marrow and trabeculae belonging to spongy bone tissue [5].

The sum of the activities of osteoblasts and osteoclasts in a growing bone is osteogenesis, or the process of bone modelling, which maintains the general shape of each bone as it increases its mass. Bone growth involves the continuous resorption of earlier formed bone tissue and the simultaneous establishment of new bone at a rate exceeding that of removal [7]. The rate of bone fluctuation is very active in young children, where it can be 200 times faster than that of adults. In adults, the skeleton is also continuously renewed in bone remodelling involving coordinated cells, localized bone resorption, and bone formation activities [5].

The constant remodelling of the bone ensures that, despite its hardness, this tissue remains plastic and able to adapt its internal structure in the face of stress. A well-known example of bone plasticity is the ability of teeth to change their positions in the jaw bone, to be altered by lateral pressures produced by orthodontic appliances [8]. The bone typically has an excellent repair capacity because it contains osteoprogenitor stem cells in the periosteum, endorsed, and bone marrow and is very well vascularized. Bone repair after a fracture or other injury is performed using cells, signalling molecules, and processes already active in bone remodelling [4]. Surgically created gaps in the bone can be filled with new bone, especially when the periosteum is left in place. The significant phases that usually occur during bone fracture repair include the initial formation of fibrocartilage and its replacement with a temporary callus of bone tissue [5].

REGULATION OF BONE BIOLOGICAL ACTIVITY

Bone remodelling is the morphological basis of bone turnover and has two biological purposes: maintaining the biomechanical competence of the bone and contributing to mineral homeostasis [9,10].

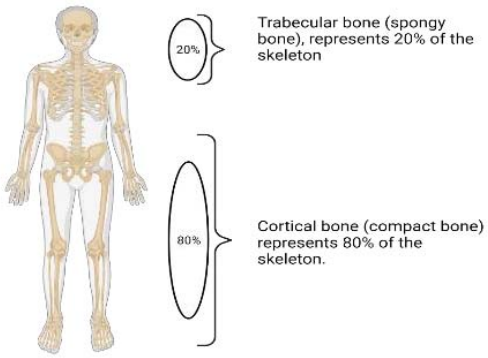

Figure 3. Trabecular and Cortical bone

The proportion between these two types of bone differs depending on the skeletal areas: the trabecular bone predominates in the vertebral bodies, while in the femoral neck, the cortical one predominates (Figure 3). Bone remodelling is a surface process, which makes bone turnover high in trabecular bone and low in cortical bone. Another feature of remodelling is its components' sequential and coupled character: resorption and bone formation occur sequentially, are limited in time, and are quantitatively equivalent, which is called being coupled. In this way, the end of the bone remodelling cycle is constant, and the

functioning of bone remodelling is based on the actions of a cell couple, represented by osteoblasts, which form bone and osteoclasts, which resorb [11].

Exercise under gravity is the most important exogenous factor in maintaining the balance of the bone remodelling process. Sedentary people, as well as prolonged immobilization due to suffering, are firmly at risk of osteoporosis. Also, the marked reduction of gravity (in the case of astronauts) leads to marked and rapid loss of muscle and bone mass [8].

The relationship between the kidneys and the bone is highly complex, and the kidney plays an important role in regulating bone development and metabolism. The kidney is the main organ involved in regulating the homeostasis of calcium and phosphate, which is essential for bone mineralization and development. Many substances synthesized by the kidneys are involved in various stages of bone formation, remodelling, and repair [12]. In addition, some cytokines that can affect the kidneys, such as osteoprotegerin, sclerostin, fibroblast growth factor, and parathyroid hormone, also play important roles in bone metabolism. Most of these cytokines can interact, forming a complex network between the kidneys and the bone. Therefore, the renal disease should be considered in patients with osteodystrophy and bone and mineral metabolism disorders, and treatment for renal dysfunction may accelerate their recovery [6].

The parathyroid hormone, whose production is stimulated by hypocalcemia, acts on three target organs. In bone, it stimulates the activity of osteoclasts and the maturation of proosteoclasts. In the kidneys, it acts directly, increasing calcium resorption, promoting phosphorus excretion, and indirectly inducing the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (the active form of vitamin D) due to the stimulation of the specific enzyme 1-α-hydroxylase. The action on the digestive tract is done indirectly through vitamin D, which strongly stimulates the intestinal absorption of calcium and phosphorus [13].

Vitamin D further stimulates tubular calcium resorption by direct action and accelerates osteoclastic bone resorption [14].

These hormonal and vitamin actions are ways to correct changes in serum calcium. Its decrease is compensated by mobilizing deposits (bone), increasing digestive absorption, and amplifying renal resorption. All these processes are mediated by parathyroid hormone and vitamin D [15]. Calcitonin has opposite effects, stopping bone resorption. Its secretion is stimulated by hypercalcemia [14].

Last decades, molecular mechanisms are studied, involving Circ_0134944, pancreatic and duodenal homeobox 1 (PDX1) and S1P by sphingosine kinase 1 and 2 (SPHK1) and their role in osterogenesis homeostasis [16-19].

A recent study on 115 women demonstrate that stress-related neurobiological activity were correlate with postmenopausal osteoporosis due to the suppression of the differentiation and proliferation of osteoblast, increasing the levels of glucocorticoid in systemic circulation [21-21].

CONCLUSIONS

In conclusion, these findings could support the proposed mechanistic relationship between loss bone and osteoporosis in postmenopausal women. Moreover, this study further highlights the multifactorial mechanism and raise the question of high risk assessment of postmenopausal women at risk for osteoporosis.

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