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# Cellular mechanisms of age-dependent bone remodeling

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## ABSTRACT

The structural integrity of the skeleton is ensured by the constant remodeling of bone tissue, which is based on the functioning and interaction of osteolytic cells (osteoclasts) and bone tissue forming cells (osteoblasts/osteocytes). Despite the general understanding that the degree of mineralization of the bone matrix determines the fragility of the skeleton, there is currently insufficient information about its age-related changes associated with the functioning of these cells. The purpose of the review is to evaluate existing data on age-related bone changes associated with the functional state of mesenchymal stem cells, osteoblasts/osteocytes and osteoclasts. Inclusion criteria: randomized or non-randomized controlled studies examining age-related bone change. A search for studies in the field of bone tissue condition was carried out in electronic scientific databases Google Scholar, Medline, PubMed, Scopus, Web of Science and Cochrane Library by keywords and their combinations using the AMSTAR 2 program. The selection of publications (59 out of 680 included) was carried out randomly, after which three authors independently assessed their methodological quality. The main pathogenetic mechanism involved in bone loss with age is a decrease in the formation of osteoblasts with impairment of their ability to osteogenic differentiation. Osteocytes in old age are subject to excessive and prolonged stress, which causes unbalanced autophagy and apoptosis, which leads to changes in their ability to deposit and mineralize extracellular organic matrix. With age, accelerated osteoclastogenesis occurs, mediated by osteoblasts, which leads to increased expression of certain receptors at the level of bone stromal cells and osteoblasts. The presented literature data demonstrate convincing evidence that an increase in bone resorption due to complex metabolic processes with age occurs against the background of an increase in the number and activity of osteoclasts, apoptosis of osteoblasts with a decrease in their metabolic activity, as well as a redistribution of osteogenic differentiation of mesenchymal stem cells towards adipocytes. The results presented in the review can be used as a basis for developing diagnostic criteria for identifying senile osteoporosis and the risk of fractures.

**Keywords**: bone remodeling; aging; osteoblasts/osteocytes; osteoclasts; osteoarthritis; chemokines; cytokines.

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# Клеточные механизмы возраст-зависимого ремоделирования костной ткани

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**АННОТАЦИЯ**

Структурная целостность скелета обеспечена постоянным ремоделированием костной ткани, которое основано на функционировании и взаимодействии клеток остеолитических (остеокласты) и формирующих костную ткань (остеобласты/остеоциты). Несмотря на общее понимание, что степень минерализации костного матрикса определяет хрупкость скелета, на настоящий момент недостаточно информации о его возрастных изменениях, связанных с функционированием данных клеток. Цель обзора — оценка существующих данных о возрастных изменениях кости, связанных с функциональным состоянием мезенхимных стволовых клеток, остеобластов/остеоцитов и остеокластов. Критерии включения: рандомизированные или нерандомизированные контролируемые исследования, изучающие возраст-зависимое изменение кости. Поиск исследований в области состояния костной ткани осуществляли в электронных научных базах Google Scholar, Medline, PubMed, Scopus, Web of Science и Cochrane Library по ключевым словам и их сочетаниям, используя программу AMSTAR 2. Отбор публикаций (из 680 включено 59) производили случайным образом, после чего независимо три автора давали оценку их методологического качества. Основной патогенетический механизм, участвующий в потере костной массы с возрастом, — снижение образования остеобластов с нарушением их способности к остеогенной дифференцировке. Остеоциты в пожилом возрасте подвергаются чрезмерному и продолжительному стрессу, который вызывает несбалансированную аутофагию и апоптоз, что ведёт к изменению их способности к депонированию и минерализации внеклеточного органического матрикса. С возрастом происходит ускоренный остеокластогенез, опосредованный остеобластами, что приводит к усилению экспрессии определённых рецепторов на уровне костных стромальных клеток и остеобластов. Приведённые литературные данные демонстрируют убедительные доказательства того, что усиление резорбции кости вследствие сложных метаболических процессов с возрастом происходит на фоне повышения количества и активности остеокластов, апоптоза остеобластов при снижении их метаболической активности, а также перераспределения остеогенной дифференцировки мезенхимных стволовых клеток в направлении адипоцитов. Изложенные в обзоре результаты могут быть использованы в качестве основы разработки диагностических критериев для выявления сенильного остеопороза и риска переломов.

**Ключевые слова**: ремоделирование кости; старение; остеобласты/остеоциты; остеокласты; остеоартрит; хемокины; цитокины.

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ЭКО•ВЕКТОР

The World Health Organization defines healthy human aging as a continuous process of maintaining the functional viability of the body [1]. Depending on the physiological age and short-, medium-, and long-term influence of various factors, bone tissue is constantly changing [2].

According to the Julius Wolff law, bones adapt to the degree of mechanical load, and with its increase, the structure of the inner spongy part is strengthened with subsequent remodeling of the cortical layer. Moreover, their integrity is determined by the duration, magnitude, and speed of the forces applied to it [2].

Bone tissue remodeling maintains the balance of calcium, phosphorus, and other active components in the body, thus ensuring the structural integrity of the skeleton. This process is regulated by mechanical factors (e.g., physical activity) and endocrine (such as parathyroid hormone, growth hormone, estrogens, and calcitriol) and paracrine (insulin-like growth factor) signals and mediators, such as transforming growth factor, prostaglandins, nitric oxide, interleukin-1, interleukin-6, tumor necrosis factor [3].

Remodeling is based on the functioning and interaction of bone-forming (osteoblasts/osteocytes) and osteolytic (osteoclasts) cells. The activity of these cells is also under constant control of both local and systemic regulatory factors [2]. Deviation from the balance between the ratio of osteoblasts and osteoclasts can lead to the loss of bone density, tendency to fractures or, conversely, to its increase (osteopetrosis), and development of compression syndromes [2].

## AGE-RELATED CHANGES IN BONE MATRIX PROPERTIES AND POTENTIAL

Despite the general understanding that the degree of bone matrix mineralization determines skeletal fragility, current information on its age-related changes is insufficient [4, 5].

Bone matrix properties (tissue modulus, yield strength, ultimate stress/strain, strain-to-fracture, workability to fractures, and impact toughness) are assessed by testing, and aging does not significantly degrade the elastic modulus of bones [6]. However, in cortical bones of a person aged >30 years, the yield and tensile strengths decrease by approximately 1% and 2% per decade, respectively [7, 8], whereas impact toughness, energy dissipation, and ultimate strain decrease by approximately 10%–15% per decade [7, 9].

Fatigue life capability decreases exponentially with age, and bone exhibits reduced modulus and degradation profiles [7, 9]. Under fatigue loading, if diffuse damage is formed and local tissue rigidity is lost on the tensile side in young bones, then linear microcracks are formed, and rigidity is disrupted on the compressive side in old bones [7]. The tendency of aging bones to form linear microcracks, rather than diffuse ones, makes a significant contribution to the bone matrix quality and age-related fragility of the skeleton [7].

Type I collagen, the most common protein in the human body, is modified in the reaction of nonenzymatic glycation (Maillard reaction) with the formation of cross-links between reducing carbohydrates (glucose, fructose, etc.) and free amino groups. Such bonds within and between molecules contain pentosidine, carboxymethyl lysine, carboxyethyl lysine, crossline, and vesperlysine.

With age, advanced glycation end products accumulate as a result of the long half-life of collagen, which affects bone fragility [7, 10]. This accumulation also affects bone fracture resistance and disrupts the nanoscale mechanisms of collagen deformation and energy dissipation. In addition, the main pattern of increasing bone fragility is an increase in fibrillar collagen stiffness and a loss of its induced plasticity with the accumulation of advanced glycation end products [5].

Because bone mass decreases significantly in older people, particularly after menopause in women, it becomes a decisive factor in skeletal fragility and bone fractures [11]. Currently, many genetic studies have focused on deciphering the relationship between genes and bone mass or microarchitecture [12]. Without cellular components, bone tissue is deemed a biomaterial that consists of minerals, collagen, water, and a small amount of noncollagen proteins [11]. Bone minerals consist of weakly crystallized carbonate apatite and become longer and stiffer with age, which affects the reduction of the ultimate bone deformation and strength [13–15].

With age, the content of the bone matrix and degree and/or nature of cross-links between and within collagen fibers change, resulting in a loose tissue structure. Moreover, the amount of water, which constitutes 10%–20% of the cortical bone volume at a young age, decreases by 40% at 80 years [11, 16].

Moreover, a fracture at any site increases the risk of a subsequent fracture at any other site, which emphasizes the importance of non-mass factors, including the disruption of the bone architecture, changes in the bone mineral and matrix, delayed recovery of fatigue microdamage and excessive metabolism, but most importantly, the loss of osteocyte viability with age [16].

Conversely, noncollagen proteins such as osteocalcin and osteopontin also affect the properties of the bone matrix, regulating the size, shape, and orientation of crystals, replacing carbonate in the crystal lattice or changing mineral formation on the collagen framework [17].

The properties of the bone matrix are regulated by osteoblasts, osteocytes, and osteoclasts; however, their role is very specific because they participate to varying degrees in aging and age-related bone destruction [18]. Osteoblasts initiate bone matrix formation, and their reduced counts caused by decreased differentiation of bone marrow mesenchymal stem cells (MSCs) in them or increased apoptosis, or impaired adhesion to the bone surface with decreased mineralization can disrupt tissue formation [19].

Compared with osteoblasts and osteoclasts, osteocytes embedded in the bone matrix directly interact with it, forming a dendritic network of extensive area, and it is modified in response to endocrine, paracrine, and mechanical stimuli [18].

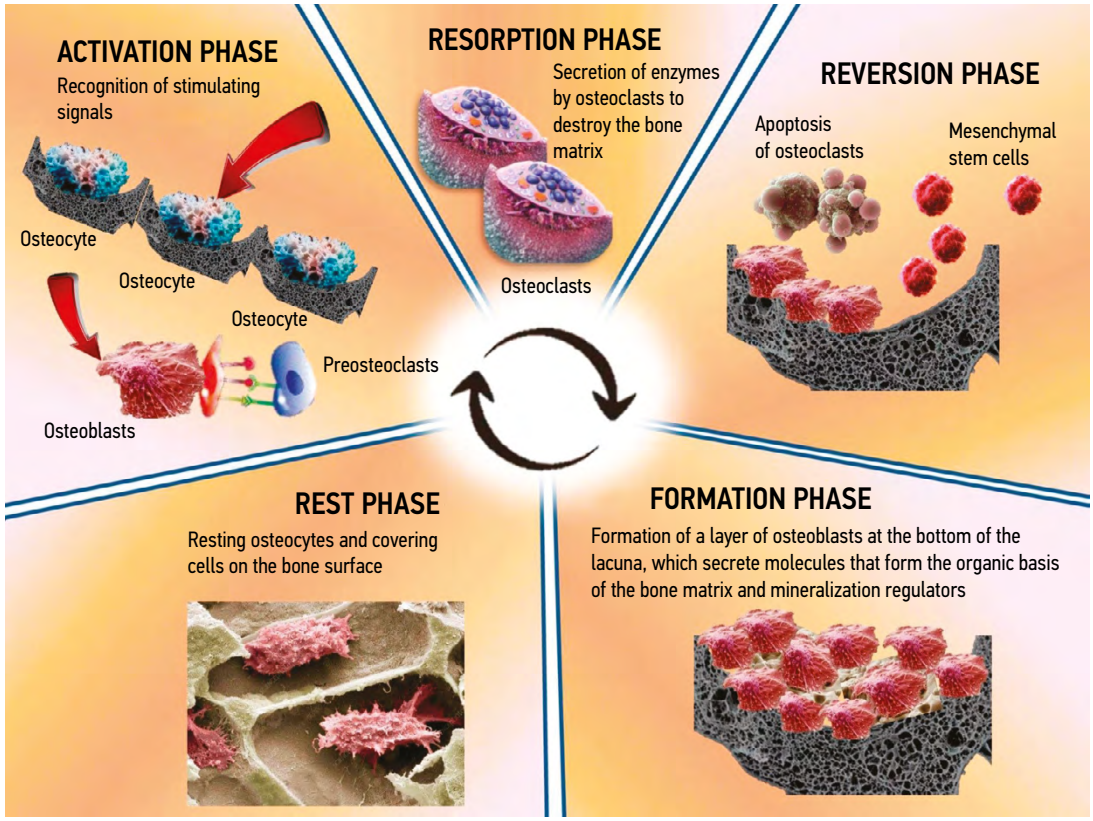


**Fig. 1**. Phases of the bone remodeling cycle

A study of age-related bone tissue aging using ribonucleic acid sequencing revealed transcriptomic changes associated with genes encoding extracellular matrix organizer proteins—collagen fibrils [20].

## CELLS IN BONE TISSUE REMODELING

The bone remodeling cycle includes activation, resorption, reversion, bone formation (mineralization), and rest [20]. In stage 1 of activation, stimulating signals (bone load, parathyroid hormone, calcitriol, interleukin-1, interleukin-6, and prostaglandins) are recognized by osteocytes located in the bone matrix, followed by signal transmission to osteoblasts covering the bone tissue surface (Fig. 1).

In response to biologically active components synthesized by osteoblasts (signaling proteins, monocyte colony-stimulating factor, and nuclear factor-κB ligand activator), cells of the monocyte–macrophage lineage migrate to the bone surface and then proliferate and differentiate into multinucleated osteoclasts. Hormonal signals directly or indirectly influence the activity and interaction of osteoblasts and osteoclast precursor cells, which can be a prerequisite for various pathophysiological consequences [21].

Osteoblasts also produce metalloproteinase enzymes that destroy the surface protein layer and noncollagenous proteins of osteoblasts (osteocalcin, sialoprotein, osteopontin, and Gla-protein matrix), which prepares the bone surface for osteoclast attachment. In the resorption stage up to 30–40 days, osteoclasts secrete enzymes that destroy the bone matrix, resulting in lacuna formation with a depth of 60 μm in young people, whereas in older people, its size is reduced to 40 μm while calcium and phosphates enter the bloodstream [22].

In the reversion stage, osteoclasts undergo apoptosis and are replaced by mesenchymal germ cells, preosteoblasts. Subsequently, bone formation is characterized by the formation of a layer of differentiated osteoblasts at the bottom of the lacuna, which secrete molecules that make up the organic basis of the bone matrix and mineralization regulators, namely, collagen type I, osteocalcin, osteonectin, and osteopontin. Matrix mineralization is implemented by the precipitation of calcium and phosphate from the bloodstream [23].

At the final stage, osteoblasts transform into resting osteocytes and covering cells on the bone surface until the next remodeling cycle [21]. In general, the bone tissue remodeling cycle normally takes approximately 150 days and ends with the filling of the resorptive lacuna with a new matrix [23]. Under pathological conditions, for example, in osteoporosis, the resorptive lacuna is not completely filled, which leads to a loss of bone mass with each remodeling cycle [24].

In the compact bone, remodeling occurs in tunnels (Haversian canals) formed by the resorptive cone of osteoclasts that remove old bone tissue, followed by the formation of a closing cone consisting of osteoblasts and the filling of the space with a new matrix [25].

Normally, the remodeling cycle on the trabeculae surface lasts for approximately 200 days, and that in compact bone

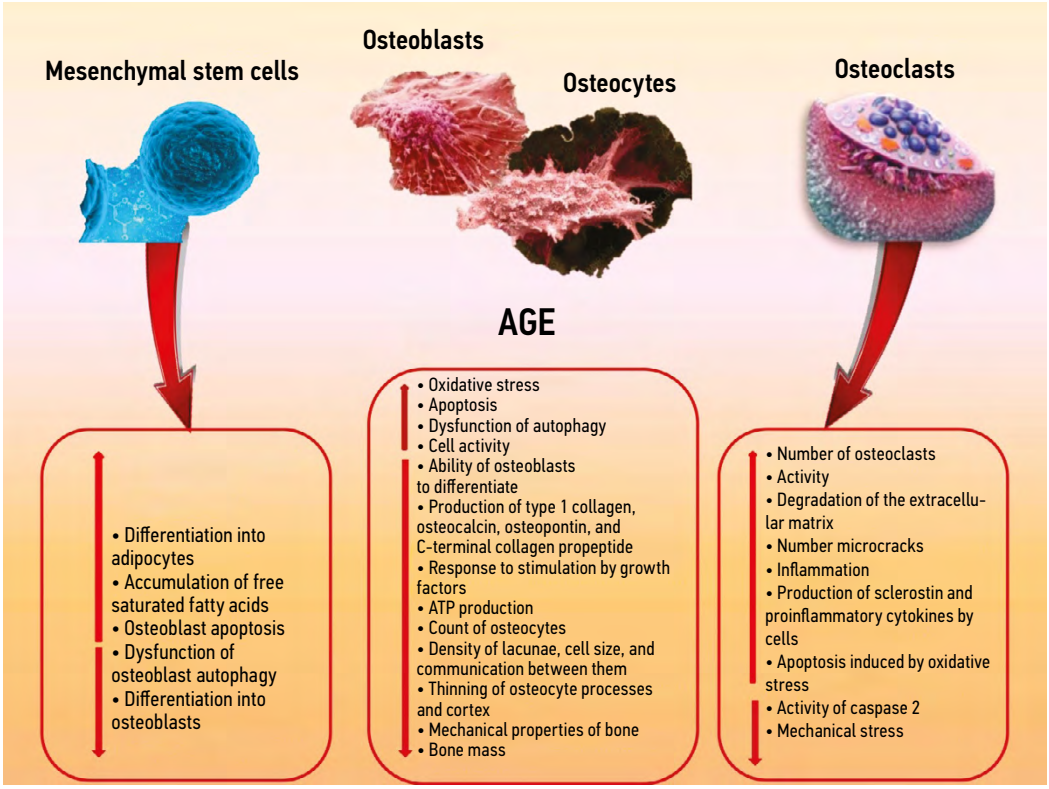


**Fig. 2**. The main changes in bone cells that occur in old age; ATP — adenosine triphosphate

for 120 days [26]. On average, approximately 30% of trabecular and 3% of compact bone undergo remodeling in the human body annually [27]. In childhood and adolescence, osteogenesis prevails, and bone mass increases by 8% annually. In adults, the remodeling stages are balanced, which allows maintaining the constancy of the structure [27]. After the age of 40 years, resorption begins to prevail over bone formation, which results in a gradual decrease in bone mass and strength.

On the periosteum surface, a positive balance between the remodeling stages is maintained throughout life. They are balanced on the surface of the Haversian canals, and a negative balance dominates on the endo-osseous surface. This causes thinning of the cortical layer and rarefaction of the spongy bone. With an increase in age by 20 years, with the same bone mineral density, the risk of fractures increases four times [27].

## MSCs

The bone remodeling cycle begins early in embryonic life and depends on the interaction between two cell lines: mesenchymal and hematopoietic. Stromal non-hematopoietic MSCs are localized in the bone marrow, periosteum, vascular wall, adipose tissue, muscle, tendon, peripheral circulation, skin, and dental tissues. They can self-reproduce and differentiate into various types of cells, such as chondrocytes, myocytes, adipocytes, and osteoblasts, participating in the regeneration of mesenchymal tissues, such as the bones, cartilages, ligaments, tendons, muscles, and adipose tissues [2].

Long-lived MSCs are those from which osteoblasts (little-known periosteal cells) and syncytium-lining resident terminally differentiated cells (osteocytes) originate. These cells are located in the bone marrow and spongy bones and are crucial in maintaining the dynamic balance of bone tissue, its resorption, and formation. Osterix, Runt-protein-related transcription factor 2 (RUNX2), and transcription factor P (FOXP) are the main factors involved in the differentiation of MSCs into osteoblasts [2].

A study proposed the identification of self-renewing multipotent human skeletal MSCs by the presence of expression of receptors for the integral membrane protein podoplanin type I and differentiation clusters CD73 and CD164 in the absence of CD146 molecules [28]. These cells are isolated from the adipose stroma of fetuses and adults when treated with bone morphogenetic protein 2 and can expand locally at the site of bone damage [28].

With age and in degenerative musculoskeletal (joints and bones) diseases, the regenerative capacity of MSCs is lost or redirected to the formation of other nonfunctional cell types, such as adipocytes and fibroblasts (Fig. 2) [29].

Increased differentiation of MSCs into adipocytes and decreased count and functionality of osteoblasts are the main factor involved in the pathogenesis of osteoporosis [30, 31]. Bone marrow fat cells have a special metabolism that depends on the lipolysis of their lipids inside them, and by releasing free saturated fatty acids, they negatively affect

the bone marrow. Palmitate is one of the most toxic and intensively secreted free fatty acids, and it is directly involved in bone destruction during aging by toxic effects on both osteoblasts and osteocytes [32].

With age, the expression levels of RUNX2 and erythroid nuclear factor 2 (NRF2) receptors on the surface of MSCs decrease, whereas conversely, the content of the differentiation-stimulating peroxisome proliferator-activated receptor-γ coactivator 1-α increases [33]. The latter serves as a major regulatory factor for the adipogenic differentiation of MSCs and can inhibit osteoblast activity by blocking the expression of nuclear binding factor $\alpha_1$ [33].

On the contrary, a decrease in FOXP levels directly affects MSCs, leading to increased adipogenesis, decreased osteoblast formation, and finally bone structure degradation. Other metabolic changes in MSCs in old age include a decreased response to bone morphogenic protein and a decrease in the levels of alkaline phosphatase, osteocalcin, and type I collagen secretion (Fig. 2).

Finally, yet importantly, osteoblast inactivation and stimulation of medullary adipose tissue formation are influenced by the Wnt signaling pathway, which is downregulated in old age (Wnt10b pathway), and MSC telomere dysfunction, which induces apoptosis by stimulating the proapoptotic protein P53/P21 ratio. In this case, the expression of the osteoblastic transcription factor Runx 2 is suppressed, which inhibits the transformation and differentiation of MSCs into osteoblasts, leads to a decrease in bone mass, and may be one of the causes of senile osteoporosis [34].

Thus, MSCs have therapeutic potential for the development of new clinical strategies to combat effectively congenital and age-related musculoskeletal disorders. Unfortunately, despite the use of these cells in clinical practice as injections for the treatment of some degenerative diseases, most of their anti-aging and regenerative potential is still unconfirmed [35].

## OSTEOBLASTS/OSTEOCYTES

MSCs differentiated into osteoblasts that fill the Howship lacunae, producing new collagen and minerals. These specialized bone-forming cells express parathyroid hormone receptors and synthesize osteoclastogenic factors, bone matrix proteins, and bone mineralization elements [36].

Osteoblasts include immature, intermediate differentiation, and mature cells, with maturation stages influencing their functional contribution to bone remodeling. Immature osteoblasts are thought to direct osteoclastogenesis, whereas mature osteoblasts perform matrix production and mineralization functions [37].

After performing their required functions, osteoblasts become either osteocytes (bone surface lining cells) or undergo apoptosis, which is important in age-related bone loss and osteoporosis [37]. Osteoblast apoptosis via the intracytosolic mechanism is induced by reactive oxygen species (ROS), derivatives of nicotinamide adenine dinucleotide phosphate oxidase, with depolarization of the mitochondrial membrane potential under the influence of oxidized proteins, which ultimately leads to osteopenia and bone microstructure destruction [37].

Thus, the main pathogenetic mechanisms involved in bone loss are a decrease in osteoblast formation with a disruption of their ability to deposit and mineralize extracellular organic matrix, as well as increased apoptosis and dysfunctional autophagy (Fig. 2).

During bone formation, a subpopulation of osteoblasts undergoes terminal differentiation and is absorbed by unmineralized osteoid, and after its mineralization, differentiates into osteocytes. The latter constitute 90%–95% of all bone tissue cells, are enclosed in fluid-filled lacunae, and have long dendritic processes that extend along tunnels within the mineralized matrix, forming a network [38].

The lacuna–canalicular system is necessary for the normal flow of tubular fluid, which, in addition to its important role in bone nutrition, at times of mechanical loading, is a stimulus for osteocytes mediating mechanotransduction. As the functional syncytium of osteocytes with cells of the vascular surfaces of bones (osteoblasts or bone shell cells), stromal and endothelial cells is the main cellular system.

Within the system, the interactions of osteocytes depend on the type of signals (metabolic or mechanical) through volume and/or conductive transmission. These cells are connected to each other by various connections, among which gap junctions within the matrix allow them to act in a neuronal-like manner. The maintenance of skeletal and mineral homeostasis as mechanosensors is attributed their ability to convert a mechanical stress signal into a biochemical one, triggering/modulating the response of the bone matrix through effector cells (osteoblasts and osteoclasts) [39].

The osteocyte-secreted regulator of skeletal metabolism protein sclerostin, which is a bone formation inhibitor by stimulating cell apoptosis, is also involved. These cells are critically involved in bone remodeling and mineral homeostasis both inside and outside the matrix microenvironment and are currently considered from the standpoint of endocrine function [40].

In addition to collagen and sclerostin, osteocytes secrete an important endocrine fibroblast growth factor-23, influencing phosphate metabolism regulation. Normally, osteocytes modulate osteoblast activity via the Wnt signaling pathway by secreting this protein, whereas osteoclast activation is achieved by secreting the activator of nuclear factor-κB ligand and monocyte colony-stimulating factor. Nitric oxide (NO), bone morphogenic proteins, and prostaglandin E2 are molecules produced by osteocytes and involved in bone homeostasis [41].

Osteocytes participate in bone mineralization and calcium phosphate metabolism by secreting proteins such as dentin matrix acidic phosphoprotein 1, bone sialoprotein, and fibroblast growth factor-23. These cells also express

the phosphate-regulating gene with homology to endopeptidases on the X chromosome and matrix extracellular phosphoglycoprotein [42].

During normal skeletal loading and age-related fatigue, the osteocyte network is integral to the transmission of mechanical stress and associated microdamage to mineralized bone (microscopic cracks or internal fractures) [43]. They can remove perilacunar matrix (osteolysis) and influence systemic mineral homeostasis with the release of calcium into the systemic circulation. Through receptors for parathyroid hormone, its soluble ligands, related peptides, sclerostin, and dentin matrix protein, these cells induce perilacunar osteoclast resorption [44].

Under certain circumstances, such as during exposure to calcium-requiring conditions, osteocytes express osteoclast markers such as tartrate-resistant acid phosphatase, cathepsin K, and carbonic anhydrase 2, triggering local demineralization and proteolysis of the lacunar and pericanalicular matrix [45]. Genetic studies of the dynamics of collagen gene expression in osteocytes during incorporation and mineralization into the bone matrix have demonstrated their involvement in changes in aging-related bone properties [46].

With age and in some pathologies, such as osteoporosis, when replacing old or damaged bones with new bones, an imbalance toward resorption is determined, which leads to a loss of mass, and in this case, osteocytes acquire osteoclast functions that atypical for them. Unlike short-lived osteoclasts (several days or weeks) and osteoblasts (several months), osteocytes live up to 50 years, and their death depends on the skeletal age [16]. Moreover, osteocyte apoptosis is the main factor in the decrease in bone strength with age (Fig. 2). Increased osteocyte death is associated with pathological conditions, such as aging, excessive mechanical stimulation, bone fatigue/microdamage, unloading/nonuse, estrogen and androgen deficiency, and inflammation [47].

In turn, accelerated apoptosis is induced by high levels of cortisol, intracytosolic increase in the formation of ROS and nitric oxide with the accumulation of molecular structures associated with damage, release of large amounts of adenosine triphosphate, and impaired autophagy [47]. Because of accelerated apoptosis of osteocytes, empty lacunae are filled with minerals (micropetrosis, which presumably serves as a compensatory mechanism for bone aging) [48].

The characteristic reduction of osteocytes and their network during aging leads to a sharp reduction in the cell surface, which is crucial for the efficient metabolism of nutrients, oxygen and viability of cells that provide mechanosensitivity and mechanotransduction of bones [40].

Oxidative stress is an independent risk factor for the development of dysfunction of bone homeostasis. It affects osteoblast-induced osteogenesis and osteoclast-induced osteoclastogenesis, thereby inducing bone diseases, namely, osteoporosis [32].

Osteocyte autophagy is a mechanism by which cellular debris is transported to lysosomes for degradation. It is aimed at eliminating damaged organelles and proteins, and has a critical effect on the differentiation, apoptosis, and survival of bone cells, including bone marrow stem cells, osteoblasts, osteoclasts, and osteocytes. High levels of ROS due to oxidative stress induce autophagy to protect cells from damage or apoptosis, but unfortunately, this cellular function declines with age [49].

Pathways, such as ROS/FOXO3, ROS/AMPK, ROS/Akt/mTOR, and ROS/JNK/c-Jun, are also involved in the regulation of osteoblast, osteocyte, and osteoclast autophagy. Conversely, the initiation of excessive oxidative stress with activation of the *p53* gene, mitochondrial membrane disruption, damage to deoxyribonucleic acid, and release of cytochrome C leads to the induction of intrinsic apoptotic mechanisms. Loss of dendrites triggers osteocyte death, resulting in the formation of dead or osteonecrotic bone. This damage does not heal through corrective remodeling and stops responding to mechanical loading [50]. Thus, osteocytes in old age are considered exposed to excessive and prolonged stress, which causes unbalanced autophagy and apoptosis.

## OSTEOCLASTS

The precursors of osteoclasts are mononuclear hematopoietic cells of myeloid origin, with predominant formation in the bone marrow. During injury and resorption, they are attracted to the bone surface by chemokines and other factors, including sphingosine-1-phosphate (Fig. 1) [16].

RAF6 factor, which binds to the tumor necrosis factor receptor, plays an important role in activating signaling pathways for the formation of multinucleated cells, osteoclasts, from myeloid precursors. Subsequent differentiation of osteoclasts depends on four main signaling pathways, namely, through the activation of proto-oncogenic tyrosine protein kinase, protein kinase inhibitor IkB kinase, extracellular signal-regulated kinase, and c-Jun-N-terminal kinase [51]. In addition, osteoclast-specific transcription factors such as Fos, p50, or nuclear factor of activated cytoplasmic T cells 1 may function as stimuli [29, 51].

Monocyte colony-stimulating factor, receptor for transcription nuclear factor-κB ligand, and cytokines produced by various cell types, including the osteoblast lineage, is another important pathway of osteoclast differentiation and activation [52]. Binding of monocyte colony-stimulating factor to c-Fms receptors on the surface of preosteoclasts increases RANK expression.

Multinucleated osteoclasts are short-lived cells (2–4 weeks). Upon attaching to the bone surface, they begin to function (Fig. 1). These cells contain lysosomal enzymes and hydrogen ions that can degrade the bone matrix, which consists of inorganic (calcium phosphate crystals, and hydroxyapatite) and organic (collagen, proteoglycans, and glycoproteins) parts. During resorption, areas of bone matrix "exhausted" by osteoclasts (Howship lacunae) remain. As cells of the mononuclear macrophage lineage, osteoclasts

can enter the "reverse" phase, during which the decomposition and processing of organic material of the bone matrix continues with the simultaneous release of growth factors to initiate its new generation [16].

Osteoclasts and their precursors regulate immune responses, formation and functions of osteoblasts through direct intercellular contact via receptors for ligands of ephrin proteins (eph receptors), plexins (receptors for semaphorins), and through clastokine expression [51, 53]. Thus, osteoclasts serve as immune cells that are not only significant in bone tissue resorption but also function as regulators of the body's defense [54, 55].

Old age is characterized by increased bone metabolism, with increased counts and activity of osteoclasts. Accelerated osteoclastogenesis mediated by osteoblasts occurs, which increases the expression of monocyte colony-stimulating factor and activator of nuclear factor-κB ligand at the level of bone stromal cells and osteoblasts [29]. Other important factors associated with aging that contribute to osteoclastogenesis and bone resorption and loss include extracellular matrix changes, microfractures, decreased mechanical loading, increased inflammation, sclerostin production, decreased testosterone and estrogen levels, secondary hyperparathyroidism and increased expression of c-Fms receptors, RANK, and activator of nuclear factor-κB ligand [56].

The deficiency of estrogen causes an increase in the secretion of proinflammatory cytokines such as interleukin-1β, tumor necrosis factor-α, interleukin-6, and transforming growth factor-β, which modulate the RANK signaling pathway, thereby stimulating the formation and activation of osteoclasts [57, 58]. Such cells are involved in extracellular matrix degradation in older people, who experience a significant increase, up to 300%, in the β-isomerization of C-telopeptide of type I collagen [59, 60]. Osteoclasts also produce sclerostin, which may contribute to impaired bone formation in old bones [45].

Among the major bone cell types, osteoclasts require very low ROS levels for differentiation and function. In the older people, osteoclast apoptosis decreased because of the loss of caspase 2 enzyme activity caused by oxidative stress [25, 60].

## CONCLUSION

With age, bone tissue remodeling is disrupted, its resorption increases, and osteogeneration decreases. Osteoporosis and risk of fractures are the most important clinical manifestations, with old age considered an independent risk factor [2]. Increased bone resorption caused by complex metabolic processes secondary to aging occurs in presence of an increase in the counts and activity of osteoclasts, apoptosis of osteoblasts with a decrease in their metabolic activity, and redistribution of osteogenic differentiation of MSCs toward adipocytes. The anabolic response of the bone to mechanical stress decreases because of the dysfunctional interaction of osteocytes through dendrites with a violation of the density of lacunae. Finally, increased oxidative stress correlates with rapid cellular apoptosis, which also leads to bone loss [50].

## ADDITIONAL INFORMATION

**Authors' contribution**. N.G.P. — conceptualization, formal analysis, writing — review and editing, supervision; P.A.K. — methodology, translation of articles; I.N.Ch. — writing — review and editing.

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**Competing interests**. The authors declare that there is no conflict of interest in the presented article.

## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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