DOI: 10.5281/zenodo.18475495
UDC: 616.71-007.234

REMODELAREA OSOASĂ ÎN OSTEOPOROZĂ: ASPECTE TEORETICE
BONE REMODELING IN OSTEOPOROSIS: THEORETICAL ASPECTS

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Rezumat
Introducere. Osteoporoza este considerată o problemă globală, silențioasă din punct de vedere clinic, ce este inclusă în lista bolilor asociate cu îmbătrânirea populației de către Organizația Mondială a Sănătății. Conform estimărilor efectuate în 27 de țări europene, prevalența osteoporozei la persoanele cu vârsta mai mare de 50 de ani a fost de 6,6% la bărbați și 22,1% la femei. La nivel mondial, prevalența osteoporozei la femei a fost raportată a fi de 23,1%, iar la bărbați – 11,7%. Un risc mai mare de a dezvolta boala îl au femeile albe și asiatice, în speciale femeile în perioada menopauzei din cauza modificărilor hormonale specifice acestei perioade.
Material și metode. Pentru acest studiu au fost utilizate bazele de date PubMed, Hinari, Google Scholar. Căutarea s-a axat pe articole de cercetare, rapoarte, ghiduri și liste de referințe. Au fost analizate doar publicațiile complete și în acces deschis. Cuvintele cheie au fost introduse în limba română, engleză, franceză și rusă: „osteoporoză”,„remodelare osoasă”,„densitate minerală osoasă”. Perioada de referință – ultimii zece ani.
Rezultate. Osul este un țesut complex organizat să ofere organismului o multitudine de funcții, dintre care două mai importante. Prima funcție este cea metabolică, de rezervă umorală pentru calciu, fosfor și magneziu, cealaltă funcție este structurală, de formare a scheletului antrenat în locomoție și protecție a organelor vitale. Sistemul osos se remodelează și se reînnoiește în mod continuu datorită proceselor de formare osoasă și resorbție osoasă. Remodelarea osoasă are loc permanent în orice moment și în orice loc a scheletului în centrele multicelulare de bază. Un ciclu ce are loc într-un centru multicelular de bază este egal cu 0,05 mm3 de țesut osos nou înlocuit. Homeostazia scheletului este menținută în condiții fiziologice printr-un echilibru al producției și resorbției osoase. Această ajustare este alterată în circumstanțe patologice sau fiziologice de timp în favoarea resorbției osoase mediate de osteoclaste. Ca urmare, la persoanele în vârstă există o scădere generală a osului în timp. Bilanțul negativ de calciu rezultat din scăderea aportului alimentar, reducerea absorbției și compromiterea funcției renale reduce activarea vitaminei D și absorbția calciului din intestin. Deficitul de estrogen este desigur, un alt factor critic responsabil pentru creșterea resorbției osului atât la bărbați, cât și la femei. Pentru ambele sexe, apare pierderea osoasă imediat după atingerea masei osoase maxime; cu toate acestea, acest proces accelerează după menopauză la femei și după vârsta de 70 de ani bărbați. Organizația Mondială a Sănătății definește osteoporoza bazându-se pe măsurarea densității minerale osoase (DMO). Această măsurare este exprimată ca un scor T, care compară DMO a unei persoane cu media DMO de vârf a unui adult tânăr sănătos de același sex. Conform OMS, osteoporoza este diagnosticată atunci când scorul T este -2.5 sau mai mic. Aceasta înseamnă că DMO a persoanei este cu 2.5 deviații standard sub media unui adult tânăr.
Concluzii. Studierea procesului de remodelare osoasă, a mecanismelor fiziopatologice favorizează o percepere mai amplă a osteoporozei, astfel metodele de prevenție și diagnosticare precoce pot contribui la ameliorarea acestei probleme globale cu impact economic.
Cuvinte-cheie: osteoporoză, remodelare osoasă, densitate minerală osoasă

Summary
Introduction. The World Health Organization has listed osteoporosis as a disease that is associated with population ageing and is considered a global, clinically silent problem. According to estimates from 27 European countries, the prevalence of osteoporosis in people over 50 was 6.6% in men and 22.1% in women. Worldwide, the prevalence of osteoporosis in women was reported to be 23.1% and 11.7% in men. White and Asian women are at higher risk of developing the disease, especially women in menopause due to hormonal changes.
Material and methods. PubMed, Hinari, Google Scholar databases were used for this study. The search focused on research articles, reports, guidelines and reference lists. Only complete and open access publications were analyzed. Keywords were entered in Romanian, English, French and Russian: "osteoporosis", "bone remodeling", "bone mineral density". Reference period - last ten years.
Results. Bone is a complex tissue organized to provide the body with a multitude of functions, two of which are particularly significant. The first function is metabolic, as a humoral reserve for calcium, phosphorus and magnesium; the other is structural, forming the skeleton for locomotion and protecting vital organs. The osseous system is continuously remodeled and renewed by the processes of bone formation and bone resorption. Bone remodeling takes place permanently at any time and at any place of the skeleton in the basic multicellular centers. One cycle occurring in a multicellular core center is equal to 0.05 mm3 of newly replaced bone tissue. Skeletal homeostasis is maintained under physiological conditions by a balance of bone production and resorption. This adjustment is altered under pathological or physiological circumstances over time in favor of osteoclast-mediated bone resorption. As a result, in the elderly there is a general decrease of bone over time. The negative calcium balance resulting from decreased dietary intake, reduced absorption and compromised renal function reduces vitamin D activation and calcium absorption from the gut. Estrogen deficiency is of course another critical factor responsible for increased bone resorption in both men and women. For both sexes, bone loss occurs immediately after reaching maximum bone mass; however, this process accelerates after the menopause in women and after the age of 70 in men. The World Health Organization (WHO) defines osteoporosis based on the measurement of bone mineral density (BMD). This measurement is expressed as a T-score, which compares an individual's BMD to the average peak BMD of a healthy young adult of the same sex. According to the WHO, osteoporosis is diagnosed when the T-score is -2.5 or lower. This means that the individual's BMD is 2.5 standard deviations below the young adult mean.
Conclusions. The study of bone remodeling process and pathophysiological mechanisms can lead to a more comprehensive understanding of osteoporosis, which can lead to improvements in this global problem with economic impact through prevention and early diagnosis.
Keywords: osteoporosis, bone remodeling, bone mineral density

Introduction

According to the classification of osteoporosis there are 2 major categories: primary - deterioration of bone mass is related to aging or decreased gonadal function. Usually seen in women in postmenopausal women or men after the age of 70. Secondary osteoporosis - results as complications of chronic conditions or medication: pathologies of the endocrine system, endogenous hypocorticism (Itsenko-Cushing syndrome), thyrotoxicosis, hypogonadism, hypoparathyroidism, diabetes (insulin-dependent), hypopituitarism, polyglandular endocrine insufficiency [1, 2, 3].

Another important aspect of this disease is its prevalence, in the world it constitutes 10.82% [4, 5, 6, 7]. In particular, this pathology affects females, but it is also found the opposite sex. According to estimates from 27 European countries, the prevalence of osteoporosis in over 50 years of age was 6.6% in men and 22.1% in women. At worldwide, the prevalence of osteoporosis in women was reported to be 23.1% and in men – 11.7% [7]. White and Asian women are at higher risk of developing the disease, particularly women in menopausal periods because of the hormonal changes specific to this period [8, 9].

In Europe, osteoporosis has a higher rate of disability and years of life lost compared to rheumatoid arthritis, but a lower rate compared to osteoarthritis. In terms of neoplastic diseases, disability from osteoporosis is higher than disability from all cancers except lung cancer. These statistics can be extrapolated for the Republic of Moldova, probably with a more severe impact. Osteoporosis is a problem of global importance and has been placed on the WHO list of diseases related to aging. Osteoporosis is the principal cause of bone fractures in the elderly, making it a substantial public health problem with a large impact on health systems. The social importance of osteoporosis is highlighted by its consequences: fractures of the vertebral and peripheral skeletal bones, which contribute to increased sickness, disability, and mortality in old age, and an increase in maintenance costs. Osteoporotic fractures also occur in many other areas, including the pelvis, ribs, distal femur, and tibia. In total, all osteoporotic fractures account for 2.7 million fractures in men and women in Europe [1]. Osteoporotic fractures increase the relative risk of mortality, particularly for femur fractures: it is 5-8 times higher in the first 3 months after onset, decreases over the next 2 years, but remains high even after a 10-year follow-up. The economic burden of such a widespread pathology is therefore very high [10, 11].

Material and methods

PubMed, Hinari and Google Scholar databases were used to conduct this study. These platforms were selected due to their extensive accessibility to a wide variety of scientific publications, allowing access to full-text and open access articles.

The main objective of the search was to identify research articles, reports, guidelines, and reference lists relevant to the topic under study, namely osteoporosis and bone remodeling. The search was performed using specific keywords in four languages: Romanian and English. The keywords used were "osteoporosis", "bone remodeling" and "bone mineral density". This multilingual approach was chosen to cover as wide a range of literature as possible and to include publications from different geographical and linguistic regions, thus ensuring the most comprehensive perspective on the topic. The reference period for the literature searches was limited to the last ten years. This strategy aims to ensure the relevance and timeliness of the data, focusing on the most recent findings and developments in the study of osteoporosis and bone remodeling. Searches were carried out systematically in each database, using the specific search interfaces and entering the set keywords. Search results were then filtered to exclude articles that did not correspond to open access criteria and to eliminate duplicates. Each article was initially evaluated based on its title and abstract to determine its relevance. Articles that appeared relevant were downloaded and read in full to ensure their quality and suitability for the study.

Results and discussion

According to the definition, osteoporosis is a pathology of the skeletal system characterized by a compromised mechanical strength of the bone, which increases the risk of fracture. The ability of bone to cope with fractures and other types of injuries is known as bone strength, which in turn depends on bone mass, quality, and density [1]. The elements of bone architecture that are responsible for bone quality are the number, thickness, separation, and connectivity of trabeculae, as well as the volume and porosity of the cortical layer of bone. Bone mass refers to the total amount of bone in the human skeletal structure. An important indicator of bone strength is bone density, which refers to the amount of minerals that are present in the bone.

Bone is a complex tissue organized to provide the body with multiple functions, two of which are more important. The first function is metabolic, serving as a humoral reserve for calcium, phosphorus, and magnesium. The other function is structural, forming the skeleton involved in locomotion and protecting vital organs. Structural bone mass consists of about 8% water and 92% solid substance, of which 35% is bone matrix or organic component, and 65% is inorganic or mineral component containing approximately: 99% of total body calcium, 85% phosphorus, 66% magnesium, and 60% sodium [2].

The bone system is continuously remodeling and renewing itself through the processes of bone formation and bone resorption. Bone remodeling takes place permanently at any time and place in the skeleton in the basic multicellular centers. One cycle occurring in a multicellular core center is equal to 0.05 mm^3 of newly replaced bone tissue. The basic multicellular unit (MCU) of bone remodeling comprises osteoclasts and osteoblasts whose activities are regulated by osteocytes [12].

The process of bone remodeling consists of a multitude of cellular activities structured into five phases. The first is the activation phase, which starts with the migration of partially differentiated mononuclear cells, or preosteoclasts, to the bone surface and the maturation of preosteoclasts

into osteoclasts, which are large, multinucleated cells. In the bone resorption phase, mature osteoclasts attach to the bone surface and cause limited resorption of minerals and bone matrix from the trabecular surface or into the cortex of the bone. Next is the reversal phase, where mononuclear cells linearly arrange themselves at the bone surface over the resorbed area, forming a layer called the 'cement line' to which osteoblasts will adhere, thus preparing an area for the formation of new bone tissue by osteoblasts. This is followed by the formation phase, where osteoblasts are deposited in successive rows on top of each other until the resorbed bone surface is completely replaced. Finally, there is a resting phase, which sets in at the end of the formation phase and lasts until a new remodeling cycle begins. During this phase, the bone surface is covered by a new layer of flattened, less active osteoblasts.

Bone remodeling adjusts bone architecture to meet changing mechanical needs and helps repair micro-damage in the bone matrix, preventing the accumulation of old bone. In osteoporosis, the resorption phase prevails over the bone-forming phase, thus compromising bone mechanical strength, increasing bone fragility, and raising the risk of fractures [3]. There are several key components of the remodeling cycle that are susceptible to systemic and local changes, and when disrupted, can lead to harmful changes in bone mass [13]. External signals such as the well-known parathyroid hormone (PTH), calcitonin, thyroid hormones, growth hormone, sex steroids, and estrogen deprivation, directed to resting osteoblasts and stromal cells, cause the release of cytokines such as interleukin IL-1, -6, -11, macrophage colony-stimulating factor (M-CSF), and tumor necrosis factor (TNF), which enhance the recruitment and differentiation of multinucleated giant cells destined to become bone-resorbing cells.

One could consider macrophages to play an important role in remodeling because these cells are present in the bone marrow niche and respond to injury via inflammatory cytokines and immune modulators [14]. With the activation of resting osteoblasts and lining cells, osteoblasts also synthesize more types of collagen, thus elaborating a series of growth factors such as IGF-I, IGF-II, and TGF-β. In addition, osteoblasts deposit growth factors in the skeletal matrix, where they are stocked in latent forms and released during cycles of subsequent remodeling. Bone cells and the skeletal matrix itself also produce and contain many signals that influence bone growth; in addition, muscle and adipose tissue in neighboring areas exert significant interactions, contributing to the quality of the final adult bone density. In particular, as shown by recent studies, larger muscle is associated with mass and volume of adipose tissue and with higher density and cortical bone thickness [12, 15]. The initiation of the bone remodeling cycle occurs through the activation of resting osteoblasts on the surface of bone stromal cells and bone marrow that start the process. Another possibility is that osteocytes that are embedded deep in the skeletal matrix can sense fluid shifts and are able to induce the remodeling sequence by paracrine signaling to the osteoblast. Thus, osteocytes are considered the "command and control" system for remodeling. The nature of the osteocyte-osteoblast-osteoclast interaction presents one of the most active areas of recent investigation in rheumatology. However, one of the most critical pathways in the osteoblast-osteoclast interaction scheme is RANKL-osteoprotogerin (OPG). OPG is a soluble peptide originally described as a factor that inhibits bone resorption and osteoclast differentiation in vitro. This protein is a member of the tumor necrosis factor receptor superfamily, and its role in bone remodeling is to act as a decoy receptor for RANKL. In fact, RANKL is just a surface peptide that, when expressed on osteoblasts, binds to the true receptor, also called the activator of the RANK receptor on osteoclasts, and initiates the cell-cell contact necessary for osteoclast activation and subsequent bone resorption. More recently, it has been shown that RANKL is produced by osteocytes and can lead to osteolysis during states of high calcium demand, such as lactation, estrogen deficiency, and even very heavy physical exertion. This led to the synthesis of RANKL antibodies. Denosumab was the first monoclonal antibody approved against RANKL for the treatment of postmenopausal osteoporosis due to its potent efficacy in reducing spine and hip fractures. It is given once every six months and suppresses bone resorption by 80–90%. The anti-resorptive effect diminishes rapidly, so there are concerns about post-treatment recurrence of fractures, particularly of the spine. The other monoclonal antibodies that bind to sclerostin have also been studied, for example, romosozumab, which has also been approved for the treatment of postmenopausal osteoporosis. This antibody monoclonal improved bone formation, increased bone mineral density by 13–15% at one year, suppressed bone resorption mediated by RANKL, and reduced overall spine fractures [16]. More recently, researchers believe that receptor activator of nuclear factor-kappa B ligand (RANKL), released from osteocytes as well as stromal cells, drives osteoclast differentiation, starting the process of active resorption before osteoblast differentiation. Osteoclasts, once differentiated, can elaborate growth factors like Wnt to send signals back to the osteoblast progenitors. Wnt are secreted factors that regulate growth cells, motility, and differentiation. They act as a group of signal transduction pathways and utilize either nearby cell-cell communication (paracrine) or communication with the same cell (autocrine). Wnt signaling is often involved in stem cell control, providing proliferative and self-renewal signals. After osteoclast-induced bone resorption, components of the matrix, such as (TGF-β) tumor suppressor beta and (IGF-I) growth inhibitory factor, as well as collagen, osteocalcin, and other protein and mineral components, are released into the bone niche microenvironment. Growth factors released by resorption contribute to the recruitment of new osteoblasts to the bone surface, which begin the process of collagen synthesis and mineralization. At this point, calcium stores play a crucial role. In healthy adults, up to two million remodeling sites may be active at any one time, and it is estimated that nearly one-quarter of all trabecular bone is remodeled each year. Generally, bone resorption lasts only 10–13 days, while bone formation is much more deliberate

and can take up to three months. The cessation of bone formation almost certainly occurs through osteocytes that produce sclerostin, which is a protein that inhibits osteoblast activity by antagonizing and blocking Wnt signaling pathways. Skeletal homeostasis is maintained in physiologic conditions by a balance of bone production and resorption. This adjustment is altered under pathological or physiological circumstances over time in favor of bone resorption mediated by osteoclasts. As a result, in the elderly, there is a general decrease in bone over time. Negative calcium balance resulting from decreased dietary intake, reduced absorption, and compromised kidney function reduces vitamin D activation and calcium absorption from the gut. Estrogen deficiency is, of course, another critical factor responsible for increased bone resorption in both men and women. For both sexes, bone loss occurs immediately after reaching maximum bone mass; however, this process accelerates after menopause in women and after the age of 70 in men. Estrogens are well known for regulating bone synthesis, having a bone-protective role by limiting resorption, and supporting bone formation [10, 12, 13, 17]. Of particular importance between the characteristics of estrogen deficiency and those of age-related osteoporosis is the development of an increased adipose mass in the bone marrow. Indeed, the presence of excess fat in the bone marrow may be a risk factor for osteoporotic fractures. One of the most important components that drive osteogenesis is Runx2, a gene that provides instructions for the manufacture of a protein that is involved in the development and maintenance of teeth, bone, and cartilage and is essential in the pathway of early osteoprogenitor differentiation [17]. The regulation of Runx2 has become a major target in bone formation and the reduction of marrow adipogenesis. As a result, estrogen deprivation causes osteoporosis, which is associated with increased bone resorption due to increased numbers and osteoclast activity, as well as osteocyte death. Osteoporosis related to the loss of estrogen is also due to increased oxidative stress and changes in the immune system, the inflammatory pathways, which are accentuated by the aging process [17]. Osteocyte apoptosis may contribute to age-related osteoporosis, either directly or through systemic peptide elaboration. The remodeling process starts at the surface of trabecular and cortical bone through multiple pathways and signals from osteocytes, probably starting with osteoclast differentiation and then signaling back to osteoblasts and vice versa [13, 17]. The evolution of bone mass goes through many stages. The ossification process starts as early as weeks 6–7 of intrauterine development, when ossification centers appear in fetal bones to coordinate accelerated growth. To adapt to this rapid process, a fetus needs a large amount of protein and minerals, and any maternal condition and placental deficiency can jeopardize this demand and lead to abnormal or poor skeletal growth, e.g., mineral deficiency or vitamin D deficiency [18]. During childhood and adolescence, linear bone growth and the accumulation of bone minerals proceed in different ways and at different rates at different skeletal sites. In particular, growth of the appendicular skeleton is widespread in childhood, while that of the spine often occurs later in adolescence [12]. In the peri-pubertal period, the bone mineral area content and bone mineral density in the lumbar spine and proximal femur increase by 4 to 6 times, and at the same time, the diaphysis of the long bones increases by two times [19]. Puberty is a period with major gender differences in bone growth, particularly in bone size and bone mass. It is usually at this stage that the rate of bone mass accrual suffers due to the speed of rapid growth in height. Therefore, relatively undermineralized bones and a higher risk of fractures characterize this period up to peak bone mass. Approximately peak bone mass is considered to occur around the age of 30. In fact, the increase in mass and density continues several years after the end of linear growth. The exact time at which bone accrual ceases is unknown [12]. Adult bone mineral density represents the end result of two processes: the acquisition of maximum bone mass during adolescence and the maintenance of bone mass in middle age and later years. Changes in bone mass result from physiological and pathophysiological processes in the bone remodeling cycle. This may occur during the accelerated linear growth phase in adolescence or much later in life, usually after the age of 50 [13]. The natural loss of bone mass that occurs through physiological mechanisms but also results in osteoporosis begins at the age of skeletal maturation between 35 and 40 years of age and continues, more or less markedly, throughout life as "physiological osteopenia." The two sexes lose bone mass differently: men lose bone mass almost linearly, with a single increase after the age of 70, and women with two, one at the age of menopause between 50 and 55 and the other after the age of 70 years. Over their lifetime, men lose 30% of their spongy bone and 10% of their cortical bone, while women lose 50% of their spongy bone and 30% of their cortical bone [2, 3]. The diagnosis of osteoporosis is based on the determination of bone mineral density (BMD), which is the equivalent of the amount of bone mineral, and a physical examination that involves pain on palpation along the spine, decreased height, and, in the absence of osteoporotic fractures, the physical examination may not reveal any particularities. Because bone hardness and resistance to fracture depend on BMD, its assessment is also important for prognosis. Analysis of prospective cohort studies has established a direct link between decreased BMD and increased fracture risk. In addition, there is a strict correlation between increased BMD during antiosteoporotic treatment and a decrease in the frequency of subsequent fractures. For assessment of the state of bone tissue, the following is currently used: dual-beam X-ray absorptiometry (DXA), ultrasonometry, spinal radiography, and quantitative computed tomography. DXA is the standard for the diagnosis of osteoporosis. Several studies have demonstrated its effectiveness in assessing fracture risk, particularly in Caucasian women in the postmenopausal period. Basic indicators of bone tissue mineralization by DXA (dual X-ray absorptiometry) are: bone mineral content (BMC), which shows the amount of mineralized tissue (g) by bone scan, usually determined by the surface length scanned (g/cm); and BMD, which determines the density of mineralized bone

tissue in the scanned area. BMD is currently estimated using T and Z scores. The T score represents the number of standard deviations of BMD from the peak value in young women. The T-score decreases in parallel with the gradual loss of bone mass with increasing age. The Z score is the number of standard deviations of BMD measured relative to healthy subjects of the same age and sex. The World Health Organization relies on the determination of BMD by T-score at any point of investigation and defines osteoporosis as the presence of a bone mineral density (BMD) of 2.5 standard deviations below the mean for young white adult women. Interpretation of BMD indices: a T score -1 standard deviation from the mean is considered to be within the norm; osteopenia T score from -1 to -2,5 standard deviation; osteoporosis T score -2,5 and above; severe osteoporosis T score -2.5 and more; plus the presence of at least one fracture. Indications for DXA testing for women and men over 40 years of age: o DXA is recommended according to fracture risk calculated by FRAX (light orange area mandatory, dark orange area on treatment fundus for assessment of treatment effectiveness). Under 40 years of age: non-traumatic vertebral fracture and non-tumorous vertebral fracture; peripheral fracture without major trauma; history of secondary osteoporotic risk; body mass index greater than 19 kg/m2; history of corticosteroid therapy for more than 3 months; and dose ≥7.5 mg/day of prednisone equivalent. At any age: any patient who is planned to receive antiresorptive therapy; any patient receiving antiosteoporotic therapy for monitoring the efficacy of treatment [1, 2]. Prior to the widespread application of DXA, osteoporosis was rarely diagnosed, only in women with symptomatic vertebral fractures or osteopenia observed by radiography for other reasons. BMD measurements by DXA changed everything, especially when it became clear that a single BMD measurement at any skeletal level is a very strong predictor of future spine fractures and hip fractures. The definition of osteoporosis has also started to evolve, and estimates of the number of people affected have changed since the WHO established DXA as a standard method [13, 20, 21]. Laboratory investigations important for establishing and monitoring treatment include: complete blood count (CBC) and erythrocyte sedimentation rate (ESR) to exclude an inflammatory process, urinalysis to rule out kidney damage as a cause of the aggravation of low back pain, serum biochemistry (including serum calcium, alkaline phosphatase, ionogram, ALAT, ASAT, total bilirubin and its fractions, urea, and creatinine) to determine biochemical indices of bone mass loss and monitor treatment safety, C-reactive protein (CRP) and fibrinogen to exclude an inflammatory process, and hormone level testing (including parathormone, FSH, LH, estradiol, progesterone, cortisol, testosterone, TSH, free T3, and free T4) to assess the hormonal status, determine the causes of secondary osteoporosis, and correct them. The laboratory investigations in the diagnosis of osteoporosis have an adjuvant role; the standard is the DXA method [1, 2, 22].

Conclusions

1. A detailed study of the process of bone remodeling and the pathophysiological mechanisms provides a deeper understanding of osteoporosis. This expanded understanding is essential for the development of effective prevention and early diagnosis strategies, which, in turn, can significantly contribute to the amelioration of this global problem with considerable economic impact.
2. The economic impact of osteoporosis is significant, and the costs associated with treatment, fractures, and rehabilitation of patients are very high. By implementing effective prevention and early diagnosis strategies, we can reduce the economic burden on health systems and society as a whole.

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Received – 18.07.2024, accepted for publication – 28.08.2024
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Conflict of interest Statement: The author reports no conflicts of interest in this work.
Citation: Bologan V. Remodelarea osoasă în osteoporoză: aspecte teoretice [Bone remodeling in osteoporosis: theoretical aspects]. Arta Medica. 2026;98(1):80-85.