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SCIENCE BOX

OSTEOPOROSIS: A MODERN VIEW OF THE PROBLEM

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Resuem: *Who defines osteoporosis as a systemic skeletal disease characterized by a decrease in bone density and disruption of bone microarchitecture with a subsequent increase in bone fragility and an increased risk of fractures. This definition of osteoporosis at the international level was formulated at the Consensus Development Conference: Diagnosis, prophylaxis and treatment of osteoporosis (1993). The definition is not complete*

The International Classification of Diseases (ICD 10) classifies osteoporosis as a "disease of the musculoskeletal system and connective tissue," and in this regard, the definition clearly positions it as a skeletal disease. On the other hand, osteoporosis is classified as a metabolic disease, but this important point is not included in the definition. Reduced bone density, impaired microarchitecture and increased bone fragility are the result of an imbalance in bone tissue metabolism with a predominance of resorption processes over formation processes, in which both of them are equally important . The result of this is a decrease in the strength of bone tissue, and the same degree of osteoporosis can be achieved by different ratios of decreased density and fragility.

Thus, osteoporosis can be defined as a chronic systemic progressive metabolic disease of the skeleton or a clinical syndrome in other diseases characterized by a decrease in bone tissue density, a violation of microarchitecture and an increase in bone fragility due to an imbalance in bone tissue metabolism with a predominance of resorption processes over formation processes, a decrease in strength bones and an increasing risk of fractures [3,4]. Fractures are the main complication of osteoporosis. The most common location of fractures is presented in Table 1. Fractures, unfortunately, are not limited to these locations. They can affect any of the tubular bones, vertebral bodies, pelvic bones, etc. According to epidemiological, scientific, preventive and clinical significance, WHO today places osteoporosis in fourth place after infectious, cardiovascular, tumor and endocrine (diabetes mellitus in the first place) pathology [2].Osteoporosis spares no one. There is no race, no nationality, no country free from osteoporosis. Its prevalence is steadily increasing, one of the main reasons for which is the maturation and aging of the population. Of great importance is also the deterioration of the living environment, unhealthy lifestyle (low physical activity, excess body weight, etc.), which is associated with a general decline in health, immune, metabolic and other disorders. More than 80% of women over 50 and virtually all women and men over 75 have osteoporosis. And this is another reason for the figurative name of osteoporosis "silent epidemic" [2,3]. According to the most tentative estimates, at least 10 million Americans suffer from clinically manifested osteoporosis, 80% of them are women. Vertebral compression fractures, fractures of the femoral neck and distal radius are observed in 40% of women and 10% of men aged 50 years and older. In the USA alone, about 250 thousand cases of hip fractures are diagnosed annually [9]. The classification of osteoporosis is presented in Table 2. The disease is characterized by loss of bone mass, which occurs gradually, latently and is often diagnosed after fractures of the vertebral bodies, femoral neck, proximal humerus or fractures of other locations.

Currently, osteoporosis is one of the main causes of disability, decreased quality of life and premature death in older people. The most common form of the disease is postmenopausal osteoporosis (PMO), in which a progressive decrease in bone strength is associated with the onset of menopause. Patients experience high bone turnover with intense processes of resorption of trabecular bone tissue with normal or increased bone formation. As is known, bone tissue consists of type I collagen and a number of other non-collagenous proteins. During a person's life, two interrelated processes occur: resorption of old bone and formation of new bone, components of the bone tissue remodeling cycle. In this case, osteoblasts synthesize a protein matrix, which subsequently undergoes mineralization. Bone remodeling is a dynamic process that varies with age. Thus, in the pubertal and postpubertal period, bone mass actively increases, reaching its maximum value on average by 20–30 years. From the age of 35 in women and from 45 in men, physiological loss of bone mass begins, which in women increases sharply in the first 5–10 years after menopause. Later (by the age of 65–70), bone loss decreases, averaging 0.3–0.5% per year, and by the age of 80, bone tissue in women decreases by 30% or more [1,2,12]. Endogenous estrogens play an important role in modulating bone resorption processes after menopause. Against the background of hypoestrogenemia, there is an acceleration of bone resorption processes. Estrogens have direct and indirect effects on the skeleton. The latter is accomplished by reducing the activity of parathyroid hormone, which helps reduce the absorption of calcium in the intestine and its reabsorption by the kidneys. The presence of highly specific estrogen receptors in the culture of bone tissue cells has been established, which indicates a direct effect of estrogens on the bone. Consequently, bone tissue cells are unique target cells for sex hormones that affect the skeleton [3,6]. The level of bone metabolism can be judged by biochemical markers determined in blood serum and urine. Markers of bone tissue formation include bone isoenzyme alkaline phosphatase, osteocalcin, and C-terminal peptide of type I collagen. The main biochemical indicators characterizing bone tissue resorption include urinary calcium excretion, N-terminal peptide of type I collagen, and pyridine bonds of collagen [5]. indicating a direct effect of estrogen on bone. Consequently, bone tissue cells are unique target cells for sex hormones that affect the skeleton [3,6]. The level of bone metabolism can be judged by biochemical markers determined in blood serum and urine. Markers of bone tissue formation include bone isoenzyme alkaline phosphatase, osteocalcin, and C-terminal peptide of type I collagen. The main biochemical indicators characterizing bone tissue resorption include urinary calcium excretion, N-terminal peptide of type I collagen, and pyridine bonds of collagen [5]. indicating a direct effect of estrogen on bone. Consequently, bone tissue cells are unique target cells for sex hormones that affect the skeleton [3,6]. The level of bone metabolism can be judged by biochemical markers determined in blood serum and urine. Markers of bone tissue formation include bone isoenzyme alkaline phosphatase, osteocalcin, and C-terminal peptide of type I collagen. The main biochemical indicators characterizing bone tissue resorption include urinary calcium excretion, N-terminal peptide of type I collagen, and pyridine bonds of collagen [5].

Timely diagnosis of osteoporosis allows in many cases to correct calcium metabolism in the body and prevent the development of complications. The difficulty lies in the fact that in 50% of cases there is an asymptomatic course of the disease, while complications (fractures of the vertebrae and tubular bones - femoral neck, distal forearm, etc.) are also its first clinical manifestations. It is characteristic that fractures most often develop spontaneously or with minimal trauma (for example, a fall from a height no higher than one's own height, etc.) [5,6]. Often the first symptom of osteoporosis is pain in the back: thoracic spine, lumbar -sacral region or sacrum. In the absence of fractures, the cause of pain may be microfractures of the trabecular zone of the vertebral bodies, as well as irritation of the periosteum by the deformed porous mass. Characteristic symptoms of osteoporosis are a decrease in the height of patients, limitation of movements in the lumbar spine, the formation of skin folds on the lateral surface of the chest, etc. Methods for instrumental diagnosis of osteoporosis are presented in Table 4. X-rays can reveal fractures in the thoracic and lumbar spine, deformation of the vertebrae,

when examining the pelvic bones, evaluate changes in the hip joints, femoral neck, and pelvic bones. One of the disadvantages of radiography in diagnosing osteoporosis is its low sensitivity, which makes it possible to detect a decrease in bone mass when the degree of decrease in mineralization reaches 20–40%, therefore it is almost impossible to establish a diagnosis of osteopenia and the initial manifestations of osteoporosis. In contrast, X-ray densitometers are highly sensitive and can detect bone mineral density (BMD) loss as low as 2–3%. However, the main task of classical radiology is the differential diagnosis of osteoporosis with other diseases of bones and joints. Therefore, standard radiography and X-ray densitometry are complementary methods [7,8]. A common radiological sign for all forms of osteoporosis is a decrease in the density of the shadow of the studied parts of the skeleton. With osteoporosis, the normal trabecular pattern of the bone gradually disappears; in the vertebral bodies, the transverse striation partially or completely disappears and the vertical striation increases. Osteoporosis is characterized by increased biconcavity of the vertebral bodies and their wedge-shaped deformity. However, due to the fact that radiographic changes appear with the loss of at least 30–40% of the minerals contained in the bone tissue, other instrumental methods must be used for early diagnosis of osteopenia. To assess BMD, a study of the proximal femur and lumbar spine is most often performed . Bone mass is assessed by the mineral content per unit area of bone, as well as as a percentage of normative values for people of the same sex and age and of peak bone mass. Along with absolute indicators of bone density in the densitometry results, T- and Z-criteria are automatically calculated as percentages and standard deviation (SD) values [6]. The T-criterion represents the number of standard deviations from the average BMD value of healthy individuals aged 20–40 years, and the Z-criterion is assessed in comparison with the average values standard for a given age and gender. According to the WHO criteria, BMD values that deviate by T-criterion by less than –1 SD are regarded as normal, values from –1 SD to –2.5 SD – as osteopenia, and values exceeding –2.5 SD – as osteoporosis. It should be emphasized that BMD indicators for assessing the risk of fractures are of the same importance as, for example, blood pressure levels for assessing the risk of stroke. With osteopenia, the mechanical strength of the bone in many cases remains sufficient to withstand normal mechanical (physiological) loads. Therefore, with T-criterion values from –1 SD to –2.5 SD, the risk of fractures is significantly less than with T-criterion deviations of more than –2.5 SD. However, in some cases, when BMD decreases by less than –2.5 SD, fractures develop. The reasons for the increase in BMD in these cases may be calcification of the aorta, anterior longitudinal ligament of the spine, the presence of osteophytes, etc. [10,11]. To predict the risk of a femoral neck fracture in osteoporosis, the most informative assessment of bone mass is in the femoral neck, in to a lesser extent - in the lumbar vertebrae, heel bones. Determining BMD in non-load-bearing parts of the skeleton (forearm, hand), according to some researchers, is not so informative, because these segments are subject to less intense mechanical stress. To diagnose osteoporosis, indicators characterizing the processes of bone resorption and bone formation are also used. Among markers of bone resorption, the current gold standard is the level of pyridinoline or deoxypyridinoline in the urine. It is known that the stability of the collagen matrix is ensured by intermolecular irreversible bonds formed between the amino acids included in the polypeptide chain of collagen. Due to the presence of a pyridine ring, the cross-links are called pyridinoline and deoxypyridinoline. To determine the content of these markers, it is recommended to study the second morning portion of urine (from 7 to 11 a.m.). The study of pyridinoline and deoxypyridinoline in urine is indicated not only for diagnosis, but also for monitoring therapy - treatment is considered effective if the excretion of pyridinoline and especially deoxypyridinoline decreases by 25% or more within 3-6 months. after prescribing anti-osteoporotic therapy [5,10]. Informative and accessible markers of bone formation are the activity of alkaline phosphatase and its bone isoenzyme, as well as the level of osteocalcin. Osteocalcin is a vitamin K-dependent non-collagenous protein of bone tissue. which is localized predominantly in the extracellular matrix of bone and makes up about 25% of the non-collagenous matrix. More than 90% of osteocalcin synthesized by mature osteoblasts in young people and approximately 70% in mature

people is included in the bone matrix, and the rest enters the bloodstream. Changes in its concentration in the blood reflect the metabolic activity of bone tissue osteoblasts. Thus, a decrease in the content of osteocalcin in bone tissue and peripheral blood is observed with an increase in the concentration of parathyroid hormone due to the inhibitory effect of the latter on the activity of osteoblasts. Vitamin D3 stimulates the synthesis of osteocalcin in osteoblasts and increases its concentration in the blood. The concentration of osteocalcin also increases in diseases characterized by increased bone turnover (Paget's disease, primary hyperparathyroidism, renal osteodystrophy, diffuse toxic goiter, etc.). In postmenopausal osteoporosis, an increase in the content of resorption markers is observed with an increased or normal level of bone formation indicators [6]. The formulation of the diagnosis of osteoporosis is shown in Table 5.

Positive dynamics are established when BMD increases by more than 2–3% per year in the absence of new fractures. A condition can be considered stable when there are no new bone fractures, but there is no increase in BMD or its decrease (±2%). The progression of osteoporosis (negative dynamics) is determined when new fractures occur during the treatment period and/or when BMD decreases by more than 3% per year. Assessing the dynamics of the course of osteoporosis is important for making a decision on further therapy [8]. Currently, the main criteria for the effectiveness of drugs in the treatment of osteoporosis are a decrease in the incidence of new bone fractures during a 3-5 year follow-up and an increase in BMD, determined using bone X-ray densitometers, normalization markers of bone metabolism. The main goal of treating osteoporosis is to normalize the processes of bone remodeling, i.e. suppression of bone resorption and stimulation of bone formation, which leads to stabilization and increase in BMD, improvement of bone quality and reduction in the incidence of fractures. This is achieved through the use of non-drug (preventive) and pharmacological methods (pathogenetic therapy). Among non-drug methods, great importance is attached to educational programs, giving up bad habits (smoking, alcohol abuse, drinking strong coffee, heavy physical activity), physical education (therapeutic gymnastics, swimming). This also includes measures to prevent falls - the abolition of sleeping pills, sedatives and psychotropic drugs, vision correction, treatment of concomitant diseases of internal organs, and if there is a high risk of femoral neck fractures - wearing hip protectors. Prevention of osteoporosis also consists of adequate consumption of calcium and other macro- and microelements in food [13]. The basis of any regimen for the treatment and prevention of osteoporosis is the use of calcium and vitamin D [4,9,14]. Bone formation - organized in time and space the process by which inorganic substances are deposited into an organic matrix. The mineral phase of this process consists primarily of calcium and phosphorus; the rate of its formation, among other factors, is determined by the concentration of ions of these minerals in the plasma and extracellular fluid. In the bones of the skeleton, calcium is represented by phosphates - $Ca_3(PO_4)_2$ (85%), carbonates - $CaCO_3$ (10%) and salts of organic acids - citric and lactic (about 5%). Outside the skeletal bones, calcium is contained in the extracellular fluid and is practically absent in cells [6]. In calcium phosphate, a crystalline mineral compound close to hydroxyapatite - $Ca_{10}(PO_4)_6(OH)_2$, some of the Ca^{2+} ions are replaced by Mg^{2+} ions and an even smaller part OH ions – fluorine ions, which increase bone strength. The mineral components of bone tissue are in a state of chemical equilibrium with calcium and phosphate ions in the blood serum. Bone cells may accelerate deposition or, conversely, dissolution and leaching of mineral components with local changes in pH, concentration of Ca^{2+}, HPO_4^{2-} ions and chelating compounds. The adult human body contains 1–2 kg of calcium, 98% of which is contained in the skeleton, which is equal to approximately 2% of body weight (about 30 mol). In the blood, the level of calcium is 9–11 mg/100 ml (2.2–2.8 mmol/l), in the extracellular fluid – about 20 mg/100 ml. The regulation of calcium exchange between extra- and intracellular fluid is carried out by parathyroid-stimulating hormone, calcitonin, and 1,25-dioxycholecalciferol. A decrease in the concentration of calcium ions leads to an increase in the secretion of parathyroid hormone. As a reaction to this, osteoclasts increase the

dissolution of mineral compounds contained in the bones. At the same time, the reabsorption of Ca2+ ions in the renal tubules increases, and as a result, the level of calcium in the blood serum increases. With an increase in the content of calcium ions, on the contrary, calcitonin is secreted, which reduces the concentration of Ca2+ ions due to its deposition as a result of the activity of osteoblasts. Vitamin D takes an active part in the regulation of these processes. It is required for the synthesis of calcium-binding proteins that control the absorption of Ca2+ ions in the intestine and reabsorption - in the kidneys. For the normal course of calcification processes, a constant supply of vitamin D to the body is necessary [9]. Thyroxine and androgens increase, and glucocorticoids decrease the content of Ca2+ ions in the human body. Calcium enters the human body with food. Dietary calcium is absorbed in the small intestine by two mechanisms: saturable (transcellular) - regulated by vitamin D and occurs mainly in the initial part of the small intestine, and non-saturated - passive diffusion from the intestinal lumen into the blood and lymph. The amount of calcium absorbed is a function of many variables, one of the most important of which is age. In the first days after birth, almost all the calcium received is absorbed, and then during the growth period its absorption remains high. Subsequently, it decreases with a maximum rate of decrease by the age of 60. The next variable that affects calcium absorption is diet. Absorption is greater when consuming high-calorie protein foods and lower when eating plant foods. Calcium absorption slows down in many pathological conditions, such as thyrotoxicosis, kidney disease, intestinal disease, gastro- and enterectomy, etc. The adult body contains about 670 g of phosphorus (1% of body weight), which is used for the formation of bone tissue and cellular energy metabolism. About 90% of phosphorus, like calcium, is also found in the skeleton. Together with calcium, it forms the basis of the hard substance of bone. In bones, phosphorus is represented by sparingly soluble calcium phosphate (up to 2/3) and soluble compounds (up to 1/3). Most of the remaining amount of phosphorus is found inside cells, and only 1% is in the extracellular fluid. Therefore, the level of phosphorus in the blood serum does not reflect its total content in the body [12]. Absorption of 70–90% of the volume of phosphorus occurs in the small intestine, from where it enters the liver, where it participates in the process of phosphorylation and is partially deposited in the form of mineral salts, which then pass into the blood and are used by bone and muscle (creatine phosphate synthesis) tissue. The quality of the exchange of phosphates in blood and bone tissue determines the quality of ossification processes, maintaining normal bone structure in principle. The skeleton is a reservoir of inorganic phosphorus: when its content in the blood plasma decreases, it enters it from the skeleton and, conversely, is deposited in the skeleton when its concentration in the plasma increases. The processes of calcium and phosphorus metabolism are closely interrelated with each other. It is believed that the optimal ratio of phosphorus and calcium for absorption with food is 1:1–1.5. Hypercalcemia, reducing the secretion of parathyroid hormone, stimulates the reabsorption of phosphates, which, through a combination with calcium, lead to its deposition in tissues and hypocalcemia. Hypocalcemia stimulates the secretion of parathyroid hormone and increases the production of vitamin D. As a result, the mobilization from the bones and the supply of calcium and phosphates from the intestines increases. Excess phosphates are excreted in the urine (phosphaturic effect of parathyroid hormone), while the reabsorption of calcium in the renal tubules increases, which normalizes its concentration in blood.

Hypophosphatemia is accompanied by increased secretion of only vitamin D, which reduces secretion and, as a result, the concentration of parathyroid hormone in the blood plasma. Hypophosphatemia also leads to stimulation of the absorption of phosphate and calcium in the intestine. Excess calcium is excreted in the urine, because Vitamin D, in comparison with the action of parathyroid hormone, enhances its reabsorption to a small extent. As a result of the described phenomena, the physiological concentration of phosphate in the blood plasma is restored regardless of the concentration of calcium. Vitamin D plays an important role for the body as a whole. It, unlike other vitamins, enters it not only with food, but is also formed in the skin under the influence of ultraviolet rays [6,7,13]. Vitamin D3 -

cholecalciferol or vitamin D2 - ergocalciferol are hydroxylated in the liver, forming 25-hydroxyvitamin D, the content of which in the blood ranges from 20 to 50 ng/ml. The latter does not have any metabolic activity and only after subsequent hydroxylation in the kidneys under the influence of parathyroid hormone is converted into the active form of 1,25-dihydroxyvitamin D3 - calcitriol. It is the latter that is involved in ensuring calcium homeokinesis through its regulation in the intestines and bones. In the intestines, calcitriol regulates the absorption of calcium and phosphorus, and in the bones, the mineralization of newly formed bone tissue. Calcium transport through intestinal cells is an active process, while phosphorus absorption increases. At bone growth points, calcium combines with inorganic phosphates. Osteoblasts use calcium phosphate for new bone formation. In addition to enhancing the absorption of phosphorus, calcitriol inhibits its loss and promotes the absorption of magnesium as a partner of calcium in all biochemical reactions.

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