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Osteoporosis - A Complication or Symptom of Axial Spondyloarthritis?

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Abstract According to the experts of the World Health Organization (WHO), OP is one of the most common diseases today, and it ranks fourth in the structure of population morbidity after myocardial infarction, sudden death, and death from oncological pathologies. In recent years, osteoporosis (OP) has been considered as one of the urgent problems of modern rheumatology. The study of secondary OP in rheumatic diseases is of theoretical and practical interest in various areas of medicine. The observation of OP in severe chronic inflammatory pathology in the human body, inflammatory rheumatic diseases, is proof of the role of immune mediators in its pathogenesis. The inflammatory process underlying most chronic rheumatic diseases increases the risk of developing various comorbidities, including OP.

Keywords Axial spondyloarthritis, Osteoporosis, Diagnosis

The term axial spondyloarthritis, known with both non-radiographic and radiographic axial spondyloarthritis, which is also called ankylosing spondylitis. The disease usually begins in the first ten years of life with a male to female ratio of two to one for radiographic axial spondyloarthritis and one to one for non-radiographic axial spondyloarthritis. More than 90% heritability has been identified, the highest genetic prevalence of the HLA-B27. The pathogenic role of HLA-B27 is still not clear, although there are various assumptions [4]. The mechanisms of interaction between inflammation and new bone formation are still not fully understood, but clarification will be important to prevent long-term structural bone damage.

Axial spondyloarthritis (AxS) is a chronic inflammatory disease belonging to the group of spondyloarthritis, which is characterized by damage to the hip joints and/or the spine and is accompanied by ankylosis of these joints [2]. Also, damage to most entheses and peripheral joints, and in some cases damage to the aortic valve and eyes are also observed in ACS. In this case, the prognosis of the disease can be determined by damage not only to the musculoskeletal system, but also to other organs - extraskeletal manifestations (EM) [1,3]. It is believed that, due to the inflammatory process underlying the pathogenesis of many rheumatic diseases, including axSpA, the disturbance of bone metabolism increases the risk of developing osteoporosis (OP) and can be considered as a specific indicator of the "severity" of the disease and the activity of inflammation [4,5]. These data allow us to consider OP as one of the manifestations of the disease in AS. In recent years, with the introduction of instrumental methods for determining bone mineral density (BMD), information on the frequent detection of OP in patients with axSpA has appeared [6].

In axSpA, two opposing bone remodeling processes occur simultaneously in the spine, i.e., new bone formation in the cortical part of the spine, facet joints, and ligamentous apparatus, and bone loss in the center of the vertebral body, which leads to OP. Accordingly, OP and osteopenia in patients with axSpA have specific diagnostic features. OP causes compression fractures of the spine, the risk of which is significantly higher in patients with axSpA not only compared to a group of healthy people comparable in terms of gender and age, but also to patients with rheumatoid arthritis. The COMOSPA study, which included 3984 axSpA patients from 23 countries, evaluated the association between age at axSpA diagnosis and the risk of low-energy fractures and OP [12-15]. The authors showed that in a group of patients with peripheral arthritis, the diagnosis of axSpA was associated with an increased risk of vertebral fracture when diagnosed at a young age (OR = 1.26, p=0.014), with a 26% increase for each younger patient. In addition, among the entire cohort, an association with a higher risk of OP in the femoral neck was shown in patients with a diagnosis of young axSpA (OR = 1.34, r=0.004). The authors recommend that fracture screening among axSpA patients should be carried out from the early stages of the disease. Early detection and treatment of fractures can reduce disability and mortality. If we dwell on the problem of osteoporosis, Osteoporosis is a systemic disease of the human skeleton that belongs to the group of metabolic osteopathies and is a nosological unit characterized by a decrease in the mass of bone tissue and a violation of its microarchitecture, resulting

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in a decrease in bone strength and its fractures [6,8,10,22].

The prevalence of osteoporosis, its serious consequences, high mortality rate, bone injuries, fractures of the proximal part of the femoral neck, often limiting the ability to provide self-service and reducing the quality of life make this pathology one of the most important among all human diseases [12,16,17]. According to experts of the World Health Organization (WHO), today osteoporosis is one of the most common diseases, and it ranks fourth in the structure of population morbidity after myocardial infarction, sudden death, and death caused by oncological pathologies [3,27]. Osteoporosis is not only a cause of disability, premature death and reduced quality of life among the elderly, but also a significant socio-economic problem [4,15,9,14,23].

The social importance of OP is determined by its complications and consequences, which cause a lot of costs in the health sector - fractures in the vertebral and tubular bones. One of the most serious complications of OP is a fracture of the proximal femoral head [5].

Modern views on OP were developed in the 40s of the 20th century by the American endocrinologist F. Owned by Albright. He mentioned that the disease in women is associated with estrogen deficiency during postmenopause. In the 70s and 80s, another scientist - B. Riggs proved the change in bone mineral density in different sex and age groups of the disease and brought the initial classification.

Accordingly, OP is classified as follows: morphologically, depending on the location of the process in the bone structure - trabecular, cortical and mixed, according to etiopathogenesis - primary (postmenopausal OP, senile OP, idiopathic and juvenile OP) and secondary OP (after various diseases or due to iatrogenic factors developed).

Studies have shown that fractures of the proximal part of the femur are associated with OP in 90% of elderly women and up to 80% of men [19]. According to the literature, the risk of bone fractures in people over 50 years old occurs in the following ratio between men and women: wrist bone fractures in women - 15%, men - 2.5%, hip bone fractures in women - 16%, men - 6%, spine fractures in women - 32 %, in men - 5%. According to the age indicator, the first peak of bone fractures is recorded before the age of 15, and the second peak after the age of 50. This age distribution is related to trauma-injury in the first age group, and OP in the second age group.

One of the important complications of OP is a fracture of the proximal femoral neck. Because this complication has higher medical costs, disability, and mortality than other osteoporotic fractures. Fractures in this localization are 2-3 times more common in women than in men, 3-4 times more common in whites than in blacks, and decrease from north to south and from west to east [23].

Vertebral fractures are one of the relatively common types of osteoporotic fractures. In OP, changes in the spine are long-term, and osteoporotic changes accumulate gradually. A decrease in bone mineral density (BMD) and microarchitectonic disturbances lead to the formation of deformations in the body of the vertebral bones. In several examination groups, visual assessment of lateral X-rays of the spine revealed three forms of compression, compression and wedge-shaped deformations in the bodies of the thoracic and lumbar vertebrae. In recent years, multidisciplinary studies in Europe have shown that vertebral fractures are often overlooked by health care providers and are incidentally detected on radiographs for other reasons [8]. When diagnostic fractures were morphometrically analyzed (in the analysis of 15,570 radiographs), the average number of vertebral fractures was 20.2% [14].

OP clinic may be asymptomatic or mildly symptomatic, and may even be diagnosed for the first time when a bone fracture is found. Such fractures can cause a progressive decrease in height, kyphosis, distortion of stature, constant pain in the lower back that interferes with daily activities [1,9].

In any form of OP pathogenesis lies the disturbance of the balance between the following two processes, i.e., bone formation and its resorption, resulting in both quantitative and qualitative changes in bone tissue [5,10,18]. The strength of bone tissue depends not only on its quantity, but also on its quality. The quantitative unit of bone tissue consists of its mass, that is, BMD, and its qualitative unit is made up of the organic matrix - microarchitectonics.

During the last 30 years, the rapid development of special non-invasive diagnostic methods makes it possible to measure the condition of bone tissue in the whole body or in its individual parts with high accuracy.

BMD is measured in special equipment - photon absorptiometry, or mono- and dual-energy x-ray absorptiometry, or densitometers based on measuring the speed of ultrasound waves passing through bone, as well as determined by computer tomography, isotope method and, if necessary, bone tissue biopsy [11,23]. Among the methods mentioned above, ultrasound densitometry has been actively developing in recent years and occupies one of the main places in the diagnosis of OP. In this method, the speed of ultrasound waves passing through the bone (SOS) and the amount of absorption of these waves in the bone (BUA) are determined. The obtained results are compared with the data on age indicators in the reference database, where the T-criterion decreases with increasing age of the subject, corresponding to the decrease in bone mass. According to the recommendation of WHO, OP is determined by evaluating the T-criterion [12]. Studies have shown that a one standard deviation decrease in BMD (according to the T-criterion) increases the risk of hip fracture by 2-3 times [6].

Despite the fact that the bone tissue has a stable appearance from the outside, it is an active metabolic system that is constantly renewed, the process of remodeling occurs continuously during human life. Bone turnover includes two opposite processes - old bone resorption (loss of mineral matter and organic matrix) involving osteoclasts (OC) and new bone formation (synthesis of new bone matrix and its subsequent mineralization) involving osteoblasts (OB). These processes are controlled by various hormones, humoral and tissue factors, and bone remodeling is continuous and

dynamic [7].

Disturbance of the balance between the processes of bone remodeling and the dominance of resorption gradually leads to a decrease in bone mass and the development of OP [13]. Nowadays, biochemical markers are widely used to evaluate the exchange process in bone tissue. Two types of biochemical markers of bone metabolism are distinguished: characterizing OB activity (alkaline phosphatase and osteocalcin), representing OK activity (acid phosphatase, sialprotein, Cross Laps).

The risk factors influencing the development of OP can be combined into the following groups [7,14,29]. They include: genetic, anthropometric and constitutional factors (older age, low body mass, family predisposition to OP, polymorphism of protein and non-protein genes involved in the remodeling process), hormonal factors (female sex, early menopause or ovariectomy), lifestyle, especially diet, low or excessive physical activity, lack of products containing calcium and vitamin D, smoking, alcohol and caffeine abuse, consumption of excess meat and drinks containing a large amount of phosphate, concomitant diseases, iatrogenic factors [15].

Smoking increases the risk of osteoporotic fractures because, along with many negative health factors, smoking supports the development of osteoporosis. Smoking narrows the smallest blood vessels (capillaries) and this impairs the access of nutrients to the bones.

Studies show that smoking increases the risk of pelvic fracture. Although the risk increases with age, cigarette smoking has an early effect on bones: studies have shown that young smokers experience a decrease in bone mineral density over the years and an increased risk of osteoporosis [15].

Alcohol disrupts the activation of vitamin D, increases the production of parathyroid hormone, which leads to calcium leaching [15].

Studies have shown that BMD in monozygotic twins is less different than in dizygotic or heterozygous twins [30].

According to the results of many epidemiological studies, low body mass is a risk factor for bone fractures. It was found that men with a body weight of less than 70 kg were associated with a lower BMD and a higher risk of bone fractures. According to European multidisciplinary studies, bone density increases by 0.52% per kg of body mass in men. Lack of physical activity has been proven in various studies to be one of the risk factors for OP, simple physical activities such as housework, walking, climbing stairs have a protective effect against hip fractures.

Peak bone mass occurs around age 30. Therefore, after the age of thirty, it is necessary to maintain muscle tone and stimulate bone tissue regeneration by strength exercises. Physical activity should be at least 2-3 times a week for 45-50 minutes.

In recent years, OP has been considered as one of the urgent problems of modern rheumatology. The study of secondary OP in rheumatic diseases (RD) is of theoretical and practical interest in various areas of medicine [27]. The observation of OP in severe chronic inflammatory pathology in the human body, inflammatory rheumatic diseases, is proof of the role of immune mediators in its pathogenesis [28]. The inflammatory process underlying most chronic rheumatic diseases increases the risk of developing various comorbidities, including OP. Anti-inflammatory therapy - glucocorticoids (GCs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are no exception [6].

According to the literature, it was found that some NSAIDs reduce the mineral density of the spine and femur [9,6]. Such a side effect is related to the mechanism of action of NSAIDs, which inhibits the activity of the cyclooxygenase enzyme complex (TsOG), catalyzes the cyclization reaction of arachidonic acid, and as a result, the production of prostaglandin (PG) stops from it [29].

Many studies show that the relationship between treatment with BMD and GCs agents and its cumulative dose increases the risk of OP development of these agents [6].

GCs affect the development of OP as follows: these drugs directly reduce bone formation by reducing the absorption of calcium and phosphorus from the intestines [17], and also increase calcium excretion with urine due to the effect of GKS on the channel reabsorption process [24]. A decrease in calcium absorption and an increase in excretion leads to a negative calcium balance, as a result of which secondary hyperparathyroidism develops and bone tissue resorption increases. [26,30].

It should be noted that GCs causes hypogonadism by reducing the secretion of sex hormones or pituitary gonadotropin, as well as reducing the concentration of testosterone in men and estrogen in women due to the reduction of luteinizing hormone, slowing down the process of bone marrow formation by inhibiting the anabolic properties of these hormones [12,30], inhibiting OB proliferation and reduces their interaction with the bone matrix, causes the development of OP by reducing the synthesis of type I collagen and non-collagen proteins [12,30].

We are particularly interested in the study of OP in patients with AxSpA. According to the literature, OP is one of the most common complications of this disease [2,12]. The fact that AxSpA develops at a working age and causes early disability is a sign of the significant social importance of this disease. According to many authors, the development of OP in AxSpA is related to the inflammatory process in the disease [15,27]. At the same time, disability and limitation of physical activity in patients with AxSpA also lead to OP, besides, pharmacotherapy in this disease does not affect bone marrow in turn [6,31]. The high frequency of OP in patients with AxSpA has not been fully studied pathomorphologically.

It is known that AxSpA belongs to the group of seronegative spondyloarthropathies based on genetic factors (HLA-B27). According to the literature, HLA-B27 peptide molecule consists of 13 amino acids and activates T-lymphocytes in peripheral blood [20]. Inflammation consists of biochemical and immunological processes controlled by many humoral mediators. Among these

mediators, cytokines with small protein molecules, which ensure intercellular interaction, are especially important [39,22]. The basis of the immune response disorder is the activation of a subpopulation of T-lymphocytes (especially CD4+ cells) and the synthesis of different types of cytokines from them. Normally, T-lymphocytes do not affect bone turnover, but pathological activation of these cells, resulting in an imbalance between inflammatory and anti-inflammatory cytokines, can affect bone turnover [13], with inflammatory cytokines stimulating bone resorption and anti-inflammatory cytokines inhibiting bone resorption. is related to.

T-lymphocytes are conditionally divided into 2 subpopulations: Th1- and Th2-cells. Th1 type cytokines include interleukin (IL)-2, IL-12, interferon (IFN)-u, IL-17 and, to some extent, tumor necrosis factor (TNF)-, and Th2 type cytokines - IL-4, IL-5, IL -8, IL-10, IL-13 are included. Cytokines of the Th1 type participate in cellular immune reactions (delayed hypersensitivity, inflammation, cellular cytotoxicity) and are defined as inflammatory cytokines. Th2 type cytokines act as a helper signal for antibody (or autoantibody) synthesis and show anti-inflammatory activity [30].

C-reactive protein (CRP) is a sensitive marker of inflammatory activity in AS, it is synthesized in the liver and plays an important role in the pathogenesis of AS (in the control of inflammatory cytokines, primarily IL-6, as well as IL-1, TNF) [26,30], resulting in bone mineral has a negative effect on density [30]. As mentioned above, two main types of cells - OK and OB - occupy the main place in the process of bone tissue remodeling. TNF, IL-6, IL-1 cytokines involved in local and systemic inflammatory processes participate in the process of bone remodeling, take part in the formation of OKs and enhance bone resorption. Similar to OBs in bone marrow, stromal cells themselves also synthesize cytokines. This indicates the participation of OBs not only in the process of bone remodeling, but also in myelopoiesis.

Thus, on the basis of the modern concept of the pathogenesis of OP, individual and external environmental factors affecting a person's life - age and gender, genetic predisposition, lifestyle, disease or iatrogenic factors identified in secondary osteoporosis are important. The inflammatory process, which is the pathogenetic basis of rheumatological diseases, and the treatment measures against it cause the development of OP in these patients.

In osteoporosis, a fracture (most commonly of the wrist, hip, spine) can occur from even minor trauma, and after a fracture, a person may experience long-term (chronic) pain. Often, fractures of the femoral neck or spine lead to disability and even death (within the first year). Therefore, the goal of osteoporosis treatment is to prevent fractures in the first place.

As mentioned above, various pathogenetic mechanisms of the development of osteoporosis in rheumatological diseases, including axSpA, have been cited and are causing controversy. This shows that scientific research should be carried out in this direction.

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