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Патогенетические и клинические аспекты остеоартроза и остеоартроз-ассоциированных дефектов хряща коленного сустава с позиций представлений о роли субхондральной кости

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АННОТАЦИЯ

В статье представлен аналитический обзор современных представлений о патогенезе остеоартроза, основанный на результатах изучения субхондральной кости и её значения в развитии этого заболевания. Показано, что данные многочисленных исследований последних лет выявляют всё больше и больше доказательств первостепенности патологических изменений именно в субхондральной кости при развитии остеоартроза и его прогрессировании. В подавляющем числе научных работ находит своё подтверждение факт того, что гиалиновый хрящ и субхондральная костная ткань представляют собой единый морфофункциональный биокомпозит со взаимозависимой системой биохимических связей и молекулярного сигналинга, а также коррелятивными реакциями на стрессовые механические нагрузки. Авторами детально проанализированы механизмы клеточного и молекулярного взаимодействия в системе «гиалиновый хрящ — субхондральная кость» при развитии остеоартроза, убедительно демонстрирующие активное и приоритетное участие субхондральной костной ткани в дебюте и поддержании деструктивно-дистрофического процесса. В дискуссионном аспекте обсуждаются необходимость ухода от хондроцентрической модели патогенеза остеоартроза и целесообразность пересмотра точек приложения лечебных мероприятий у пациентов с остеоартрозом коленного сустава. Проведён обзор применяющихся в настоящее время способов оперативного лечения остеоартроза коленного сустава с позиций их патогенетической направленности. Авторы обсуждают актуальность разработки концепции органосохраняющей хирургии деструктивно-дистрофических поражений суставов, которая должна быть основана на данных о роли и значимости субхондральной и метафизарной костной ткани в вышеуказанных патологических процессах.

Ключевые слова: остеоартроз; субхондральная кость; гиалиновый хрящ; дефект хряща; коленный сустав.

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Pathogenetic and clinical aspects of osteoarthritis and osteoarthritis-associated defects of the cartilage of the knee joint from the standpoint of understanding the role of the subchondral bone

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ABSTRACT

The article presents an analytical review on modern ideas about the osteoarthritis pathogenesis based on the findings regarding the subchondral bone and its importance in the development of this disease. It is shown that the data of numerous studies in recent years reveal more and more evidence demonstrating the primacy of pathological changes in the subchondral bone in the development of osteoarthritis and its progression. The vast majority of scientific papers confirm the fact that hyaline cartilage and subchondral bone tissue are a single morphofunctional biocomposite with an interdependent system of biochemical connections and molecular signaling, as well as correlative reactions to stressful mechanical loads. The authors analyzed in detail the mechanisms of cellular and molecular interaction in the system "hyaline cartilage — subchondral bone" in the development of osteoarthritis, vividly demonstrating the active and priority involvement of subchondral bone tissue in the debut and maintenance of the destructive-dystrophic process. The necessity to leave the chondrocentric model of osteoarthritis pathogenesis and the expediency to revise the points of application of therapeutic measures in patients with knee joint osteoarthritis are discussed. The current methods of surgical treatment of knee joint osteoarthritis are critically reviewed from the perspective of their pathogenetic orientation. The authors discuss the relevance in developing the concept of organ-preserving surgery in destructive-dystrophic joint lesions, which should be based on the findings describing the role and significance of subchondral and metaphyseal bone tissue in the above pathologic processes.

Keywords: osteoarthritis; subchondral bone; articular cartilage; articular cartilage defect; knee joint.

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INTRODUCTION

Among all joint pathologies in orthopedic and rheumatologic practice, destructive–dystrophic diseases, of which osteoarthritis (OA) [1] is the most widespread, lead to severe and persistent functional impairment and represent a major medical and social problem. Currently, OA is defined as a group of diseases that have different etiologies but have common pathogenetic mechanisms and similar morphologic and clinical manifestations. OA outcomes are attributed to the sequential involvement of all joint structures—hyaline cartilage, subchondral bone, synovial membrane, menisci, ligaments, capsule, and periarticular soft tissues—in the pathological process and is represented by the progressive development of gross anatomical and functional changes and a significant reduction in the quality of life [2].

To date, OA subtypes correlated with various risk factors, lesion localization, clinical manifestations, course, and prognosis, which not only determine the disease onset and progression rate but are also of key importance in the selection of planned treatment techniques. In this regard, knee OA occurs in 29.4%–35.2% of all disease localizations and represents not only the most urgent medical but also a highly significant socioeconomic problem. It causes progressive damage of the largest and one of the leading supporting joints of the lower limb, occurs in middle-aged, healthy, and most professionally and creatively matured people, leads to persistent statodynamic dysfunction and disability, and is accompanied by the development and aggravation of several economic consequences [1, 3].

SOURCING METHODOLOGY

NCBI, PubMed, eLIBRARY, and Cochrane Library databases were used for the literature search. The keywords for the search were “osteoarthritis,” “osteoarthritis,” “osteochondral defect,” “cartilage defect,” “subchondral bone,” “hyaline cartilage,” “pathogenesis of osteoarthritis,” and “bone remodeling” (in Russian and English). The selection criteria for journal articles and other materials were as follows: publication year not earlier than 2010, emphasis on pathologic anatomy, pathophysiology, and experimental medicine, and systematic reviews.

According to domestic and foreign data, 23%–37% of patients with knee OA develop defects of the articular surfaces of the femur and tibia, and in OA stages 2 and 3, they occur in 44%–60% of cases. The development of full-thickness chondral defects of the knee joint is associated with the most severe clinical picture of intra-articular damage and a negative prognosis of spontaneous repair [4].

The pathogenesis of OA has historically been viewed through the prism of primary and priority structural changes in articular cartilage. Therefore, OA was initially treated as a cartilage disease, and the vast majority of therapeutic and surgical correction methods, both historically and currently, are aimed specifically at damage to the hyaline cartilage. However, to date, several studies have convincingly demonstrated the primacy of bone changes in the pathogenesis of OA, and recent studies have proved that pathological processes in the subchondral bone tissue determine disease onset and progression [1, 3–5].

Data revealed that the periarticular bone transformations characterizing the process of OA development represent the adaptation to local biomechanical and biological signals. These processes are mediated by bone cells that modify bone architecture and properties [1, 2, 6]. In this case, bone remodeling not only affects bone tissues but also causes changes in the contour and shape of the subchondral bone. These changes create a biomechanical environment that adversely affects the articular cartilage and leads to its degradation and destruction.

In 1986, E.L. Radin and R.M. Rose emphasized skeletal changes as the initial effector of OA. They suggested that the pathogenesis of OA may be associated with the primary changes in the periarticular bone [1] and that the destructive–dystrophic process is initiated by an increase in the density, volume, and stiffness of subchondral bone with a subsequent increase in the load transfer to the overlying articular cartilage. This leads to chondrocyte dysfunction and subsequently causes cartilage matrix degradation and loss. At present, their hypothesis is supported by numerous studies demonstrating that changes in the subchondral bone in the presence of OA occur very early and, apparently, even before changes in the hyaline cartilage [7, 8].

The first direct evidence of the pathogenetic relationship between the primary changes in the subchondral bone and the subsequent OA development was obtained in 1993 by Dieppe et al. who used the scintigraphic method to initiate several similar studies. They conducted a prospective follow-up of 94 patients with knee OA for 5 years. All patients underwent radiographic and scintigraphic examinations of the joints. A positive correlation was found between OA progression, determined by joint gap narrowing, and scintigraphic data, namely, increased accumulation of technetium-99 in the subchondral bone tissue, indicating the intensification of its remodeling. In 34% of patients with significant radionuclide accumulation in the subchondral bone, narrowing of the X-ray articular gap by >2 mm was observed during the observation period. Conversely, no disease progression was observed in patients with unchanged scintigraphic picture. Based on their results, the authors concluded that increased technetium-99 accumulation can be a predictor of articular cartilage loss, which is a direct consequence of changes in bone tissue metabolism [8].

Studies have shown that both cortical and trabecular bones can change their architecture and structural properties at a much higher rate than the hyaline cartilage, whose chondrocytes modulate their morphological status and functional state in response to loading for a much longer period. Some authors actively studied the importance of

subchondral bone tissue and have demonstrated that with OA progression, its metabolism can increase 20 times compared with physiological bone metabolism [3, 4, 9, 10].

One of the key aspects of the relationship between the hyaline cartilage and the subchondral bone in OA development is the analysis of blood circulation in the latter, showing its crucial role in the regeneration and remodeling and providing trophic needs not only of the bone tissue but also of the overlying articular cartilage. Changes in the microcirculatory channel causing venous stasis, vessel occlusion, spasms, or others lead to the development of pathologies of the subchondral bone and hyaline cartilage [4, 5, 11].

Modern radiographic techniques, including magnetic resonance imaging (MRI) with dynamic contrast and positron emission tomography, show that venous outflow obstruction, which causes decreased perfusion, venous stasis, and subsequent ischemia, leads to trabecular bone remodeling and induces changes in the physicochemical properties of the subchondral bone similar to those in OA. Osteoblasts exposed to hypoxia changed their expression profile of cytokines, proteins, and growth factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor-2, and transforming growth factor β1 (TGF-β1). TGF-β1, hypoxia-induced factor 1α, type 1 collagen, and tissue inhibitor of matrix metalloproteinase (MMP)-1 are associated with accelerated bone remodeling and cartilage degeneration, which is a histopathologic feature of OA [12].

In addition, changes in the perfusion and pressure in osteoblasts result in the activation of cell signaling pathways, including transcription factors (c-Fos and Egr1), inflammatory mediators, intercellular secondary messengers (Cox2, prostaglandin E2, and nitric oxide) and enzymes, particularly MMP 1, 3, and 13. Under these conditions, osteoblasts also begin to express large amounts of cytokines associated with bone outgrowth, namely, osteocalcin, alkaline phosphatase, and insulin-like growth factor-1, and participate in the induction of remodeling of compact and cancellous subchondral bone tissue, also very similar to the structural changes observed in OA [4, 5, 8].

The close physical relationship between the cartilage and subchondral bone in joints has introduced the concept of "biochemical and molecular crosstalk"– biochemical and molecular cross-links in the affected area. Chondrocytes possess receptors that respond to biomechanical perturbations in the surrounding cartilage matrix and intrinsic and extrinsic growth factors, cytokines, and other inflammatory mediators. Several integrins, which serve as receptors for fibronectin fragments (FN) and type II collagen (COL2), when activated, can stimulate the production of matrix-degrading proteinases and inflammatory cytokines and chemokines in the chondrocytes. The significant phenotypic modulation of the chondrocytes through increased synthesis of FN, COL2, and aggrecan (AGG) immediately after disease onset suggests that articular chondrocytes are attempting to repair the damaged matrix. However, this repair process appears to be unsuccessful, leading to irreversible cartilage degeneration [3, 4, 6, 13].

Conversely, during the development of OA in the subchondral bone, the expression levels of certain genes are increased in conjunction with changes in cartilage and the production of various inflammatory mediators, biological factors, and cytokines, which are also biochemical markers of the disease. Subchondral bone explants from patients with OA secrete high levels of alkaline phosphatase, osteocalcin, osteopontin, interleukin-6, interleukin-8, ankylosis progression gene homolog, urokinase-type plasminogen activator, prostaglandins, and insulin-like growth factor-1 compared to bone explants from healthy individuals. In addition, subchondral bone osteoblasts from patients with OA express higher levels of alkaline phosphatase, osteopontin, matrix ribonucleic acid osteocalcin, collagen type 1 protein, and growth factors such as insulin-like growth factors 1 and 2, and TGF-β than normal subchondral bone osteoblasts. The increased secretion of biochemical factors that promote bone formation suggests increased bone anabolic activity of subchondral bone osteoblasts, exemplified by osteophyte formation [1, 2, 5].

Destruction and degradation of the hyaline cartilage and bone tissue are accompanied by the appearance and/or elevation of key biochemical markers, and the main ones are presented in Table 1.

All these data indicate that the subchondral bone and hyaline cartilage should be considered a single morphofunctional biocomposite with an integrated system of molecular signaling, unified metabolism, and equal mutual influence of cartilage and bone tissues on each other in daily living. They are dynamic support structures that simultaneously and interconnectedly perceive and distribute mechanical load, change their metabolism, and modulate their biomechanical characteristics to adapt to stress loads. The close anatomical relationship of cartilage and subchondral bone gives them ample opportunity to induce physical and functional changes in each other through molecular interactions. Recent studies support the view of the transduction of active molecules between the bone and cartilage. Biological factors and signaling molecules produced by both tissues can transfer from one area to another, affecting their homeostasis. Modern in vitro and in vivo studies convincingly prove the presence and uniqueness of a crosstalk between the cartilage and subchondral bone in synovial joints.

Increased vascularization and development of microfractures in the bone matrix in OA strongly suggest that mediators secreted from chondrocytes and subchondral bone cells directly interact with each other through these channels. In OA, regulatory factors secreted by chondrocytes in degenerated cartilage may play a definite role in osteoclastogenesis and thus contribute to subchondral bone mass loss [3, 5, 12]. During endochondral ossification, cartilage hypertrophy appears to be the result of signals

Table 1. Biomarkers of the cartilage and subchondral bone during the onset and progression of osteoarthritis

Biomarker	Function in the joint	Processes due to increased expression in osteoarthritis
Cartilage biomarkers		
Oligomeric cartilage matrix protein	It is synergistic with inflammatory synovial proliferation, regulation of fibril assembly, and maintenance of a mature collagen network	Cartilage degradation
C-terminal telopeptide of collagen type II	Provides strength and integrity and maintains the shape of the fabric	Remodeling of the calcified cartilage
Helix fragments (Helix II Coll 2-1, and Coll 2-1NO2)	Promote the inflammation and catabolism of the cartilage in the joint	Degradation of type II collagen
Amino-terminal propeptide of procollagen type II	One of two propeptides of type II procollagen and reflects the rate of type II collagen synthesis	Cartilage degradation
Carboxyterminal propeptide of procollagen type II	One of two propeptides of type II procollagen and reflects the rate of type II collagen synthesis	Cartilage degradation
YLK-40 glycoprotein: non-collagen proteins	Plays a vital role in the development or alteration of tissue inflammation, immunity, and/or remodeling	Cartilage degradation
Keratan sulfate	Acts as a cushion to absorb mechanical shock	Aggrecan and cartilage degradation
Epitope 846 chondroitin sulfate	Provides a hydrated gel structure (through the interaction with hyaluronic acid and binding protein) that provides the load-bearing properties of cartilage	Cartilage metabolism
Hyaluronic acid	Necessary for the viscosity and elasticity of the synovial fluid and cartilage	Cartilage degradation
Bone biomarkers		
N-terminal telopeptide of collagen type I	Supports the bone remodeling process	Degradation of type I collagen
C-terminal telopeptide of type I collagen (serum C-terminal telopeptide)	Collagen type I cross-linking peptide essential for immunoreactivity	Increased osteoclastogenesis and bone degradation
Amino-terminal propeptide of procollagen type I	One of the two propeptides of type I procollagen and reflects the rate of type I collagen synthesis	Bone degradation
Carboxyterminal propeptide of procollagen type I	One of the two propeptides of type I procollagen and reflects the rate of type I collagen synthesis	Bone degradation
Osteocalcin	Essential for bone mineralization and recruitment of osteoblasts and osteoclasts at the site of bone formation	Anabolic bone metabolism
Total pyridinoline in urine	Helps stabilize and strengthen the entire collagen tissue structure, both bone and cartilage tissues	Catabolic bone metabolism
Bone sialoprotein	Essential for mineralization in the interaction of the cartilage and bone tissue	Anabolic bone metabolism

derived from various cells such as osteoblasts and hematopoietic cells. On the contrary, an experiment showed that signals from hypertrophied chick cartilage chondrocytes stimulate osteoblast differentiation and subsequent bone matrix deposition.

To provide an idea of the nature, extent, and depth of cellular and molecular interactions in the hyaline cartilage–subchondral bone system that determines OA onset and progression, the factors involved in these processes can be classified into the following most important groups:

- Biological factors
- Wingless (Wnt)-type signaling pathways
- TGF-β/bone morphogenetic protein (BMP) signaling system
- mitogen-activated protein kinase/ERK kinase (MARK) signaling system

Biological factors

Despite ongoing discussions in the professional community regarding the significance of synovial inflammation in OA,

studies have emphasized verifiable synovitis, including the infiltration of activated B cells and T lymphocytes along with the overexpression of proinflammatory mediators in both early and late disease stages. Proinflammatory mediators present in the synovial fluid contribute to the catabolic activity of chondrocytes leading to the remodeling of the cartilage extracellular matrix [1, 2, 7, 9]. In vivo and in vitro studies have demonstrated that the amounts of chemokines and cytokines present in the synovial fluid are sufficient to activate chondrocytes and subsequently increase their synthesis of matrix molecules and promote their destruction through the synthesis of proinflammatory cytokines and proteases. Chondrocytes in OA secrete interleukin-1, interleukin-1β-converting enzyme (caspase-1), and interleukin-1 receptor. The concentration of interleukin-1 synthesized by chondrocytes can induce the expression of MMPs, aggrecanases, adisintegrin, metalloproteinases with thrombospondin motifs, and other catabolic genes in areas of OA-induced cartilage matrix depletion [3, 4]. Changes in cartilage remodeling lead to the loss of the components and structure of the extracellular matrix, affecting the characteristic phenotype of hyaline cartilage chondrocytes. Under these conditions, chondrocyte expression of molecules associated with chondrocyte hypertrophy and terminal differentiation, such as VEGF, Runt-related transcription factor 2 (RUNX2), and MMP-13, is stimulated. These events also lead to the calcification of the extracellular matrix around chondrocytes and contribute to the thinning of the articular surface. The secretion of angiogenic factors such as VEGF increases vascularization in the deep layers of the articular cartilage, facilitating molecular transport by the diffusion of molecules through calcified articular cartilage tissues from the subchondral bone [5, 8, 9].

Evidence shows that chemokines, cytokines, and proteases secreted from chondrocytes are involved in the alteration of the biochemical and functional capabilities of subchondral bone osteoblasts. For example, interleukin-6, in combination with other cytokines such as interleukin-1β, can switch osteoblasts from a normal phenotype to a sclerotic phenotype. Chondrocytes undergoing destruction also secrete large amounts of the receptor activator of nuclear factor κB ligand (RANKL), a factor that induces osteoclastogenesis. High RANKL expression is associated with increased metabolism of the subchondral bone tissue at early stages of OA [2, 7, 10].

Additionally, to the stimulatory role of chondrocytes with respect to the subchondral bone, the number of factors produced by the subchondral bone tissue and involved in both remodeling of the bone and modulation of cartilage catabolism increased. In vitro experiments have shown that subchondral osteoblasts in OA lead to a reduction in a specific cartilage phenotype (glycosaminoglycan, AGG, and COL2) when co-cultured with articular cartilage chondrocytes. In addition, cultured subchondral osteoblasts from patients with OA caused increased degradation of proteoglycans in the cartilage compared with control subjects containing healthy subchondral bone tissue osteoblasts. Researchers explain this effect by the increased production of MMP-2 by subchondral bone osteoblasts [3, 6, 11].

Wingless type signal paths (Wnt)

Joint homeostasis critically depends on the balance between various anabolic and catabolic molecular signaling pathways of bone and cartilage tissues [3, 12]. Signaling mechanisms in joints are essential for maintaining a stable phenotype of the articular cartilage and subchondral bone, sustained synthesis of the extracellular matrix, balancing of bone remodeling processes, efficient cleavage and clearance of macromolecules and dead cells, and functional and molecular adaptation to mechanical stress. Several signaling pathways between the bone and cartilage coexist in the joints, which are necessary to maintain homeostasis and ensure adequate joint function. However, the imbalance of the delicate balance between them that develops in destructive–dystrophic joint lesions leads to the gradual hypertrophy of the subchondral bone and deterioration of the quality of the hyaline cartilage, contributing to OA progression [1, 8].

Wnt pathways represent a large family of cysteine-rich morphogens. To date, 19 structurally related glycoproteins that can transduce their signal through various intracellular cascades have been identified. Classically, Wnt pathways have been classified into canonical and noncanonical pathways. Canonical pathways can inhibit GSK-3β phosphorylation of β-catenin and its subsequent degradation (e.g., Wnt 1, 3a, and 8), and noncanonical pathways do not affect the level of β-catenin (e.g., Wnt 4, 5a, and 11) [4, 7].

Studies on experimental animals (mice) have emphasized the importance of the canonical Wnt signaling system in maintaining the mature phenotype of the articular cartilage, which is characterized by prolonged cell survival and lack of differentiation toward hypertrophy [2, 3]. Several studies have demonstrated that the canonical Wnt signaling system acts as a survival signal by inhibiting chondrocyte apoptosis. Conversely, the overexpression of Wnt signals is harmful to the chondrocytes, leading to destructive and dystrophic changes in the cartilage [7].

The implementation of both canonical and noncanonical cascades of the Wnt signaling system in chondrocyte proliferation and differentiation indicates its importance in the regulation of cartilage homeostasis. In addition, to chondrogenesis, the Wnt signaling system is essential for bone development and its subsequent homeostasis. The positively regulating Wnt signaling system can induce sclerosis in bones [3, 5, 7].

TGF-β/BMP signaling system

BMPs perform many functions in the skeletal system, including the regulation of the cartilage extracellular matrix and bone remodeling. The BMP signaling system regulates the process of bone induction and is essential for enchondral

bone formation. As an intermediate stage of bone formation, BMPs are involved in all phases of chondrogenesis. BMPs 2, 4, and 5 are essential for chondrocyte proliferation and matrix synthesis [2, 3, 5, 6].

BPMs are crucial for cartilage protection and repair by regulating aggrecan and proteoglycan synthesis and are involved in various stages of chondrocyte terminal differentiation. This signaling system not only plays an important role in the early stages of chondrogenesis by stimulating the synthesis of matrix molecules such as COL2 but also actively participates in the terminal differentiation of chondrocytes by increasing the expression of MMP-13, which is observed in the hyaline cartilage in OA [3, 5, 9, 11]. Alternatively, BMPs are potent osteogenic stimulators and can regulate the activity of osteoblasts and osteoclasts in vitro and in vivo [2]. In particular, the reduced levels of BMP signaling stimulator, such as GDF5, affects the properties of the subchondral bone and its remodeling processes in destructive–dystrophic articular lesions [7].

Along with BMPs, TGF-β also plays an indispensable role in maintaining metabolic homeostasis and structural integrity of the articular cartilage [4, 9]. TGF-β is expressed at high levels in healthy cartilage, whereas it is nearly absent in OA cartilage. Since TGF-β is a potent inducer of cartilage extracellular matrix synthesis, a decrease in its level leads to proteoglycan loss and cartilage degradation. Moreover, the ablation of endogenous TGF-β1 activity suppresses osteophyte formation and synovial thickening in vivo [1, 3, 11, 13]. Along with its critical role in cartilage homeostasis, TGF-β1 regulates osteoclastic bone resorption and induces the migration of bone marrow mesenchymal stem cells into resorption pits to form new trabecular bone in long bones [2, 4, 12]. These studies have suggested that the TGF-β/BMP signaling system is one of the most important systems for the normal homeostasis of the cartilage–bone biochemical unit. The increased production of TGF-β in the deteriorating cartilage in OA affects the homeostasis not only of the cartilage but also of the subchondral bone, which once again proves the molecular level of the depth of the crosstalk between cartilage and bone tissues.

TGF-β1 inhibition restored the microarchitecture of the subchondral bone by arresting angiogenesis, reducing the population of bone marrow mesenchymal stem cells undergoing osteogenesis, as well as attenuating proteoglycan loss and increased calcification observed in mice with experimental OA [12].

Mitogen-activated protein kinase (MAPK) signaling system

MAPK includes three broad categories of kinases: extracellular signal-regulated kinases (ERK), stress-activated protein kinases/c-Jun N-terminal kinases, and p38 kinases. Recently, the MAPK family was found to be associated with the pathophysiology of OA. The activation of ERK and p38 is a key signaling event in the processes leading to articular cartilage degeneration. The activation of both ERK and p38 signaling is necessary for MMP expression and activity, whereas only ERK activation is necessary for aggrecanase-mediated cartilage degeneration [4, 5]. MMP-13 production from subchondral bone osteoblasts in response to mechanical stress may trigger the cartilage degradation observed during OA progression. The possibility of MAPK-mediated release of degradative enzymes from the subchondral bone affecting chondrocytes suggests the existence of intercellular communication between cartilage and bones affecting each other. In this case, articular cartilage chondrocytes in OA lead to the increased production of markers of their differentiation, such as RUNX2, alkaline phosphatase, osteopontin, and osteocalcin, by healthy subchondral osteoblasts, whereas normal articular chondrocytes inhibit this process [9, 11].

Secreted cytokines, growth factors, and signaling molecules that form the biochemical units of the cartilage and bone play a modulating role in altering joint pathophysiology in OA. The complexity of Wnt, BMPs, TGF-β, and MAPK signaling systems in the maintenance and control of joint homeostasis, their role in the crosstalk between cartilage and subchondral bone, and the observed alterations in OA change the views on the pathogenetic mechanisms of this disease [1].

In the analysis of the results of numerous studies aimed at objectivizing the assessment of OA pathogenesis processes, we should state that dogmatic attitudes regarding the understanding of the role and participation of bone and cartilage tissues, their interaction, and sequence of key events accompanying the debut and progression of this pathology have been revised. The close morphofunctional interrelation of the subchondral bone tissue and hyaline cartilage, complexity and proven absolute interdependence of molecular signaling pathways between them, emerging and accumulating data on the peculiarities of subchondral bone tissue metabolism and its importance in ensuring adequate vital activity of articular cartilage determine the departure from the chondrocentric model of OA pathogenesis, which postulated the primary role of articular cartilage in disease development. Today, increasing evidence shows that the subchondral bone is the initiator and key player in OA progression. OA first manifests as molecular disorganization and development of abnormal metabolism of the bone, cartilage tissue and their interface, followed by anatomophysiological abnormalities, manifesting with clinical manifestations and an extensive disease picture. At present, most researchers studying the pathophysiology of destructive–dystrophic joint diseases, with regard to OA, no longer adhere to the position of the parallelism of the start of pathological processes in bone and cartilage tissues but raise the question: “How early do changes in the subchondral bone begin in relation to hyaline cartilage”?

The formation of articular cartilage defects in OA is the final manifestation of the destructive and dystrophic changes in the cartilage and, of utmost importance, subchondral bone. Until recently, a certain stereotypical view of chondral

defects of the knee joint in OA was raised in the professional community owing to the lack of instrumental diagnostic capabilities in relation to the initial stages of the pathological process and the postulation of the primary changes in OA in the articular cartilage and, accordingly, the a priori impossibility to detect these changes clinically up to the terminal disease stages. A direct evidence of this is the continued use of two main classification systems of OA in the world: the exclusive radiologic classification of Kellgren and Lawrence (1957) with modifications, which distinguishes four disease stages, and the clinical and radiologic classification of N.S. Kosinskaya (1961), according to which three OA stages are verified. Neither the first nor the second of them assess changes in the articular cartilage, which, obviously, can be explained by the historical impossibility of detailing its condition at the development of these classifications. However, this argument loses its validity, because at present, even though a highly sensitive and highly specific diagnostic method such as MRI is widespread, no MRI classification of OA stages is universally accepted. The same should be said for our country: no MRI classification of OA is validated in the Russian Federation. This also applies to other instrumental methods of OA verification, which include computed tomography and ultrasonography. The MRI systems developed and currently used to assess the severity of pathologic changes in OA include the Boston Leeds osteoarthritis knee score, whole-organ magnetic resonance imaging score, MRI osteoarthritis score, and outcome measures in rheumatology – knee inflammation MRI scoring system (OMERACT-KIMRISS) – they have a very narrow focus of application, mainly in patients with combined traumatic injuries of the soft tissue structures of the knee joint.

The characteristics of the knee joint structures during the development of OA-associated articular surface defects generally correspond to the pathologic transformations characteristic of OA stages 2 and 3. In the articular surface, predominantly the medial femoral condyle, numerous deep cartilage erosions are formed, penetrating the calcified cartilage and subchondral bone, sometimes dividing the hyaline cartilage into isolated fragments. In some of the most stressed areas, the hyaline cartilage thins, sometimes exposing the subchondral bone, forming defects of the articular surface of irregular round shape with often indistinct boundaries. In the defect area, the subchondral bone appears as a smooth shiny surface, macroscopically hypertrophied, and not bleeding when damaged. The hyaline cartilage surrounding such a full-layer defect shows signs of moderate degeneration, corresponding to the degree of the destructive–dystrophic process in a particular clinical situation. Defects of the articular surfaces in primary OA, unlike aseptic osteonecrosis, never extend in depth below the subchondral bone plate, which is their bottom [5].

When considering the issues of articular hyaline cartilage repair in the development of degenerative–dystrophic joint diseases, the current lack of a complete understanding of the mechanisms of its realization should be also recognized. Our knowledge of the peculiarities of reparative chondrogenesis is based on either the analysis of acute traumatic injuries of the hyaline cartilage or the study of various experimental models of artificial chondrodestruction and can be extrapolated to the processes in OA and its treatment with a large degree of conventionality [6].

The possibilities of hyaline cartilage for reparative regeneration are limited by its avascularity and the peculiarities of its anatomy. The absence of blood vessels in the articular cartilage makes it impossible for the inflammatory phase to unfold and stem cells to migrate into the cartilage. Moreover, the extracellular matrix forms a physical barrier to the migration of existing chondrocytes into the damaged area. In damaged cartilage, the sources of its regeneration are the cartilage itself, synovial membrane of the joint, bone tissue cells transforming into cartilage cells, and bone marrow cells, which can serve as sources of regeneration in deep cartilage damage that affects the subchondral bone tissue [2, 7, 8]. However, to date, the participation of chondrocytes in the regeneration process is very insignificant and does not play an appreciable role [1, 3].

Although the subtle morphofunctional features of the hyaline cartilage, subchondral bone, and their tissue and molecular interactions do not allow us to fully determine the course of the spontaneous repair of lesions in the articular surfaces, recent studies have demonstrated the crucial role of the subchondral bone in these processes. In fact, the completeness of reparative processes in full-thickness and penetrating chondral defects in OA directly correlate with the quality of subchondral and metaphyseal bone tissue, adequacy of its metabolism, and restoration of bone morphofunctional sufficiency during treatment.

In the analysis of the medical care problem for patients with knee OA and associated local lesions of articular surfaces, two differently polar vectors of treatment strategy can be conditionally distinguished today. First, a wide, active and aggressive introduction of nonoperative methods of chondrogenesis stimulation into clinical practice continues, including various invasive methods aimed at direct stimulation of hyaline cartilage formation processes or the creation of favorable conditions for their course, such as intra-articular injection of hyaluronic acid-based preparations, PRP, and SVF therapy. These methods have gained and retained a kind of popularity niche in the professional environment because of, among other things, the possibility of their application in outpatient settings, absence of the need for constant long-term medical supervision of the patient, high patient compliance, and patient's psychologically more positive attitude to treatment, which does not require hospitalization.

Second, there is a clear trend toward an increase in the number of organ-substituting surgical interventions such as unicondylar and total joint endoprosthetics in the Russian Federation. The prospect of a one-stage and radical relief from suffering, high efficiency in the maximum and full

restoration of the joint and limb function after surgery, prognosis of rapid and significant improvement in the quality of life, material and technical capabilities of specialized trauma and orthopedic hospitals, widespread availability and accessibility of courses and training cycles for specialists, and to a certain extent the image component have led to the use of endoprosthesis.

However, joint endoprosthetics, which involves the mechanical removal of affected cartilage and bone tissues, the main but (and this is important) not the only source of the patient's suffering, cannot be considered a pathogenetic way of treating OA and is essentially an operation of partial replacement of the affected organ.

Furthermore, the risks of serious complications such as paraendoprosthesis infection, periprosthetic fractures of the femur and tibia, early aseptic instability of the endoprosthesis components, venous thrombosis, which in some cases are fatal for the joint and affects the quality of life of patients and often require long-term and economically expensive treatment, issues of patients' satisfaction with the mid-term and long-term results of the operation (which does not exceed 42%–65%,), dictate the need for a very careful and balanced approach when planning total endoprosthesis as the operation of choice in these patients.

CONCLUSIONS

An important factor that determines treatment effectiveness in patients with knee OA is the current understanding of the priority of the functional state of the joint: even against the background of significant morphological changes in intra- and para-articular structures, including hyaline cartilage, in certain cases, the joint function can be relatively compensated for a long time. This leads to the revision of views on the correlation approach to the choice of treatment techniques established in the professional orthopedic community, which for many years was defined by the formula "the more severe the degree of destructive–dystrophic lesions of the knee joint, the more radical the surgery should be."

Against this background and considering emerging data on the pathogenesis of OA and associated local lesions of the hyaline cartilage, the development and introduction into clinical practice of organ-preserving surgical interventions, minimally invasive surgical techniques of chondroplasty, methods of stimulation of reparative chondro- and osteogenesis and their combinations, which allow the restoration of the anatomical integrity of the joint structures and its functional sufficiency and thus improve the quality of life, are becoming increasingly important nowadays.

The effectiveness of the organ-preserving methods of surgical treatment in bone–cartilage defects of destructive–dystrophic genesis directly correlates with the state of subchondral and metaphyseal bone tissue; thus, the completeness and adequacy of the restoration of its anatomical integrity and provision of metabolic restitution are the most important tasks of surgical reconstructive and plastic correction. Attempts at the isolated treatment of hyaline cartilage lesions in the light of currently available new ideas about the pathogenetic mechanisms of the development of destructive–dystrophic knee joint diseases, are ineffective, and its results do not satisfy patients or doctors. Thus, a fundamentally important and difficult task in the treatment of these patients is a one-stage correction of both articular cartilage damage and pathologic changes in the subchondral bone and bone tissue of the femoral and tibial metaphyzes. Conditions and opportunities for the most complete regeneration of articular cartilage can be provided only in this case, which further determines the restoration of the functions of the knee joint and lower extremity.

Thus, the currently established similarity of the underlying pathogenetic mechanisms of knee joint OA and the emerging persistent trend toward the development and implementation of reconstructive surgical treatment in operative orthopedics, which allows the preservation of the anatomy and function of the joint, necessitate the development of organ-preserving surgery of destructive–dystrophic joint lesions, based on the modern techniques of reconstructive surgery of the knee joints.

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Вклад авторов. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией). Наибольший вклад распределён следующим образом: Г.П. Котельников — редактирование статьи; Ю.В. Ларцев — обзор литературных источников, редактирование статьи; Д.С. Кудашев — оперативное лечение пациентов, сбор и анализ литературных источников, подготовка и написание текста, редактирование статьи; С.Д. Зуев-Ратников — оперативное лечение пациентов, сбор и анализ литературных источников; В.Г. Асатрян — курация и хирургическое лечение пациентов; Н.Д. Щербатов — сбор и анализ литературных источников.

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ADDITIONAL INFO

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