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CHONDROCYTES. THEIR STRUCTURE, FUNCTIONS, CHANGES IN OSTEOARTHRITIS, THE INFLUENCE OF DRUGS

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The study has shown that osteoarthritis is caused by the action of biomechanical and biological factors. It manifests itself as destabilization of normal correlation between the processes of synthesis and degradation of chondrocytes, cartilage extracellular matrix components and subchondral bone. Chondrocytes are mature cell forms that have lost the mitosis ability, but have high rates of functional biosynthetic activity. Anti-osteoarthritis drugs action is based on activation of biosynthetic processes (synthesis of proteoglycans, glycosaminoglycans), inhibition of proteolytic enzymes and cytokines production by chondrocytes, that stimulate degradation of articular cartilage.
Key words: chondrocytes, structure, function, osteoarthritis

Introduction

Today, one of the most common joint disease is osteoarthritis (OA) - a chronic, noninflammatory, progressive disease of synovial joints, characterized by degeneration of articular cartilage, subchondral bone structural changes and existing or hidden synovitis [1,7,8,16,17]. According to population-based studies, its prevalence ranges from 4.2 to 22.6%. In the structure of rheumatic diseases the incidence of OA is 40-50%. According to prognosis by the World Health Organization (WHO) OA in the next 10-15 years will be the fourth main cause of disability among women, and eighth – among men [9]. According to the results of epidemiological studies, the prevalence of OA in different regions of the globe reaches 30% [14], and among people aged 60 y.o. – 97% [27]. In Australia, OA affects 15% of the population [27], in Saudi Arabia the only clinically symptomatic gonarthrosis is diagnosed in 13% of people [27]. The prevalence of OA in Ukraine is 240 per 10 000 of population, and these rates grow year-to-year [7,8]. Primary disability due to OA in Ukraine is almost 1 per 10 000 of population [7]. In the U.S. economic costs associated with OA, exceed $ 60 billion per year [17], and in Hong Kong, only one patient, on average, spends more than 40 thousand dollars a year [28]. In France, the annual costs increase by 8%, accounting to EUR 1.8 billion [26].

The problem is of a special importance due to increasing human longevity. Degenerative changes in the joints are detected in almost 50% of people over 40 years, and at age of 70 y.o. the disease is found in 90% of the population. The rate of OA in general morbidity of the population is about 12% and ranked first in the joint pathology [10].

By definition of American College of Rheumatology (ACR), OA is a disease caused by the action of biological and mechanical factors destabilizing the normal correlation between the processes of degradation and synthesis of chondrocytes, extracellular matrix of articular cartilage and subchondral bone. In this regard, chondrocytes are one of the main targets of destruction in OA. In research of OA the perspective is the study of the structure, functions of chondrocytes, their changes in OA and actions of various groups of drugs.

Objectives.

Survey of the structure and function of chondrocytes in normal condition and analysis of biochemical and histological changes in OA.

Chondrocytes structure. Morphological study in the age-group of 23-49 y.o. determined that the number of chondrocytes in the cubic millimetre of articular cartilage is 9626, the average diameter of the cells is 13 microns, and their density is 1.65% [22].

In the articular cartilage of various joints, there is considerable variation in the density of chondrocytes. The highest density of cells is in the surface layer, the lowest is in the calcified one. Furthermore, even within the same joint, the cell density is uneven: the highest density is at sites of mechanical load, the lower is in areas with low load. Chondrocytes are phenotypically heterogeneous populations of cells having specific vertically oriented position and various metabolic features [5]. Chondrocytes are located in capsules which protect the cells from pressure that affects the cartilage tissue in different functional states. Chondrocytes are spaced with matrix, which has a complex macromolecular organization [1,9].

Thus, human articular cartilage is composed of hydrogenated extracellular matrix and cells immersed in it, which make up 2-3% of the total tissue. Because cartilage has no blood and lymph vessels, the interaction between the cells, delivery of nutrients, removal of metabolic products are carried out by diffusion through the extracellular matrix. Despite the fact that chondrocytes are extremely active metabolically, normally in adults they are not fissionable. Chondrocytes exist in oxygen-free environment, their metabolism is predominantly anaerobical.

Each chondrocyte is considered as a separate metabolic unit of cartilage, isolated from other cells by extracellular matrix, and responsible for the production and maintenance of its components [24].

The contact of chondrocytes with capsular matrix is made by numerous cytoplasmic appendices rich with microfilaments, and by specific matrix molecules like ankorin and CD44-like receptors. Chondrocytes of mature cartilage tissue perform the active metabolic control over their pericellular and territorial matrix, the inter-territorial matrix is less actively controlled, and it can be metabolically inactive [22,31].

Between the structures of chondrocytes in different zones of articular cartilage, there are significant differences. At its surface zone chondrocytes are arranged in 1-2 layers, have an elongated shape and oval nuclei surrounded by a thin layer of cytoplasm. The axis of cells runs parallel to the surface of articular cartilage and corresponds to the direction of collagen fibers. The cells of this zone usually don’t form capsules, they resemble fibroblasts by its shape, have a nucleus with a compact arrangement of chromatin, and their cytoplasm contains a well-developed endoplasmic reticulum (EPR). Unlike chondrocytes in intermediate and deep zones, in cytoplasm of these cells the glycogen granules are not defined, which is one of the factors of cytodifferentiation of chondrocytes. Chondrocytes synthesize a small amount of aggrecan [18]. They are dominated by the synthesis of hyaluronic acid and collagen type I, which does not exclude the influence of synovial fluid hyaluronate on the cellular metabolism. Chondrocytes produce a larger amount of non-aggregating small proteoglycans and metalloproteinases in response to stimulation by cytokines. The affinity of receptors on the membrane of surface zone chondrocytes to the cytokines is 6 times higher than in chondrocytes of other zones [9].

Intermediate zone occupies 40-60% of the total depth of articular cartilage. The most active chondrocytes are located there. The number of cells prevails in the areas adjacent to the surface zone, deeper they form isogeneic groups and columns of chondrocytes. Architectonics of the extracellular matrix in this zone is characterized by the presence of collagen fibers of different orientation, forming a grid that permeates the entire depth of the articular cartilage and pericellular perilacunar areas. Such structural composition of extracellular matrix structure provides virtually complete suppresion of the action of high pressure and conservation of cellular elements in the "capsules" [12]. The cell nuclei are mainly represented by euchromatin. Heterochromatin is concentrated only at the inner surface of the nuclear membrane.

Determination of chondrocytes with developed granular EPR indicates a high level of protein biosynthesis, mainly collagen. Other cells contain developed granular (smooth) EPR, composit organized Golgi complex, and a large number of secretory vesicles with granules, indicating the intensification of synthesis of carbohydrate compounds. Chondrocytes typically specialize in biosynthesis of collagen and glycosaminoglycans, even within one isogenic group. Mitochondrias in cells are sporadic and usually small. Glycogen is determined virtually in all cells as small, diffusely located granules in the cytoplasm [9,12].

Deep zone chondrocytes have mainly ellipsoidal shape and are combined in the radial chains of 2-6 cells. There are hypertrophied cells and chondrocytes with degenerative and necrotic changes (pyknotic nuclei, karyorhexis, evident stringiness in cytoplasm, etc). This is also indicated by the increased expression of alkaline phosphatase, the presence of matrix vesicles and type X collagen synthesis. In the deep zone of articular cartilage the concentration of sulfated glycosaminoglycans is increased, and the amount of collagen is reduced. Synthesis of collagens and proteoglycans, as well as regulation and remodulation of the system as a whole, are made by chondrocytes having probably the longest term of life [12]. Generally chondrocytes have a complex organized cytoplasm with developed EPR, Golgi complex, large amount of mitochondria and lysosomes. Their distinct difference from other layers cells are large clusters of glycogen granules, which is a signal to the ossification.

Chondrocytes in the calcination area are located at a significant distance from each other and have a sizable capsule. The cell nuclei are dense, cytoplasm is poorly organized with many impurities as glycogen granules and lipids. In this zone, the hypertrophied cells are common, which is indicated by increased secretion of alkaline phosphatase and type X collagen. Chondrocytes in the calcination area decree large quantities of collagen type II [26].

If we consider the cellular organization of articular cartilage as a whole, the complexity of the ultrastructural organization of cells is observed in the direction from the surface to the deep zone [9,12].

Function of chondrocytes. In cartilage, as well as in other types of connective tissue, there is a strong correlation between cellular and extracellular components. I.e. chondrocytes synthesize and secrete collagen molecules, noncollagenous proteins, glycoprotein, proteoglycan, and the molecules, in turn, form the matrix – the environment for chondrocytes – and affect the process of cell differentiation. Quantitative characterization and metabolic balance between matrix molecules determine the functioning peculiarities of cartilages in various joints. Matrix is divided into territorial, which is distributed around the cells, and inter-territorial - the bulk of the cartilage tissue [8,9].

Specific function of chondrocytes is biosynthesis of collagen type II. In different areas of articular cartilage, this process is dissimilar. Chondrocytes of surface zone, degenerating chondrocytes and chondroblasts synthesize collagen type I. Pericelular collagens are determined in the intracellular matrix, forming cytoskeleton-type support for cells. It is known that cytoskeleton of chondrocytes plays a role of physical interface between chondrocytes and extracellular membrane, and induces the formation of biosynthetic response, counteracting the mechanical irritant [19]. Tubulin is a structural element of microtubules, determined predominantly in superficial zones of cartilage, compared with the deeper zones, and in the chondrocytes located on the periphery [29]. Actin is a soluble globular protein found in thin filaments. One of the main functions of this protein in chondrocytes is supporting the stability of its shape, which allows to maintain and align to the norm the mechanical strength of cell [29]. Elaboration of exoskeleton of cells runs involving collagen type V, which is approximately 1% of all collagen types, and appears in the extracellular matrix [19].

Collagen type VI is concentrated mainly in the territorial matrix and it forms microfibrils that are capable of aggregation. The fibrils have a periodicity which is 110 nm, and are formed of 3 chains: α_1 (VI), α_2 (VI), α_3 (VI) [31]. This type of collagen plays a major role in the process of attachment of cells to fibrils [22]. Collagen type X is one of the main markers of chondrocyte

hypertrophy and mineralization processes. This type of collagen dominates in the calcified areas of cartilage [17].

Important component of the extracellular matrix are glycoproteins which should include fibronectin and chondronectin. Chondronectin molecules mediate binding of chondrocytes to collagen type II. There are also transmembrane glycoproteins CD44, which are expressed by chondrocytes and bind to collagen types I and IV. Extracellular matrix (ECM) contains another type of molecule – proteoglycans (PG), which constitute 10-20% of the molecular weight. Proteoglycan molecules are synthesized by chondrocytes, and decreed into the extracellular matrix. The major proteoglycan of articular cartilage is aggrecan, which is about 90% of the total weight of proteoglycans. In the ECM it is stabilized by glycosaminoglycans and N- and C-terminal oligosaccharides [25].

Two types of aggrecan are identified in articular cartilage [23]. The average size of the first type aggrecan is 60 S, and second type - 120 S. Last one differs by large number of binding protein molecules [23]. Presence of these superagents may play an important role in the functioning of tissues: after the limb immobilization during the recovery of tissue, in the middle layers of articular cartilage their higher concentrations is found in joints affected with OA, in the early stages of the disease their size significantly reduce [23].

Aggrecan molecules, after secretion into the extracellular matrix through binding protein and hyaluronic acid threads, form stable aggregates. Up to 200 aggrecan molecules can bind to one molecule of hyaluronic acid. Formed aggregates maintain connection with chondrocytes through interaction with receptors on the cell membrane [6]. Besides aggrecan, the articular cartilage contains smaller proteoglycans. Ankorin, protein weighing 34 kDa, is localized on the surface of chondrocytes and in the cell membrane, it provides the interaction between cell and matrix. Due to its high affinity to the collagen type II, aggrecan can serve as mechanoreceptor, it transmits a signal of change in pressure on chondrocyte fibrils [22]. 36 kDa protein is produced by chondrocytes and is involved in cell-matrix communication, as well as cartilaginous tissue restructuring. 21 kDa protein is produced by hypertrophic chondrocytes, it interacts with collagen type X, and operates in the region of basophilic line. 39 kDa protein is synthesized by chondrocytes of intermediate and surface zone, its function has not been fully ascertained. Cartilage oligomeric protein (COMP 83 kDa) serves as a marker of normal cell differentiation, since its content in hypertrophic chondrocytes is very low [4].

Detected in matrix glycosaminoglycans are chondroitin-4-sulfate, chondroitin-6-sulfate and keratin sulfate. The main glycosaminoglycan of a cartilage is chondroitin-6-sulfate. Its amount in the ground substance of cartilage, as well as of keratin, increases with age, and the concentration of chondroitin-4-sulfate perceptibly reduces. Glycosaminoglycans are major component of the PG, which are presented in cartilage as complexes. PG monomer is built of about 60 keratan sulfate chains and about 100 chondroitin sulfate chains, which are joined by covalent bonds in a polypeptide chain, forming a molecule of PG. Further, 100-140 of such molecules with interval of 300 A, in turn, are joined by non-covalent bonds through the binding protein to long thread of hyaluronic acid. As to its structure it's very similar to dish-washing brush [26].

In addition, PG monomer can form a dimer in association with C-terminal areas of the acceptor protein. N-terminal areas of the acceptor proteins of dimer, in turn, interact with the binding glycoprotein molecules, and form primary aggregates. Further, the aggregates of higher order may be formed, where the dimers are simultaneously joined to two or more molecules of a higher order, in which the dimers are simultaneously connected to two or more molecules of binding protein [18]. Chondroitin sulfate chains of individual PG monomers intertwine and create a spatially dense network. This structure ensures the stability of the cartilage matrix to overloads and explains its known biological properties.

During the differentiation of cartilage cells the composition of glycosaminoglycans changes. It has been ascertained that high level of synthesis of hyaluronic acid is specific for precartilaginous cells, which plays a certain role in the migration and proliferation of

chondrocytes [21]. During cell differentiation, the synthesis of hyaluronic acid is reduced, and hyaluronidase content increases. That is, the process of differentiation of chondrocytes is in interaction of hyaluronic acid and hyaluronidase [20].

Hyaluronic acid exposure on the metabolism of cartilage tissue comes through specific receptors on chondrocyte membrane, as well as a secondary through interaction with glycoproteins [21].

Osteoarthritis-caused changes in chondrocytes. In inflammatory rheumatic disorders, the changes in the cartilage are usually secondary and associated with an inflammatory process which is of autoimmune and/or immunocomplement nature. Primarily synovial tissue metabolism changes, which has an impact on metabolism of articular cartilage. It is known that synovial layer of articular capsule, synovial fluid and hyaline articular cartilage form synovial environment of the joint [11,20].

The recent studies determined the role of biomechanical factors in occurrence of OA. Prolonged dynamic load on cartilage leads to chondrocyte hypertrophy, their proliferation, change in the qualitative composition of the extracellular matrix, thereby it increases adaptation to large loads. However, presence of other risk factors in different combinations leads to an imbalance between the process of synthesis and degradation of cartilage tissue to the degradation direction, that causes morphological changes of cartilage [1,12].

Histologically, early stages of OA cause degenerative and necrotic changes; emergence of signs of fibers separation in the surface zone of articular cartilage; events of osteosclerosis and subchondral bone osteonecrosis.

OA is characterized by qualitative and quantitative changes of the cartilage matrix macromolecules. Due to changes in chondrocyte phenotype, "short" collagen is synthesized (with increased degradation of collagen type II and increase in amount of collagen type VI, which is seen as a stimulating factor for the formation of isogenic groups of chondrocytes), it secretes non-glycolised forms of non-aggregable small proteoglycans. The size of both types of aggregates is significantly reduced in a joint affected with OA in the early stages [28].

Joint fluid of patients with OA contains high concentration of fibronectin fragments, so they may participate in pathogenesis of disease in the later stages. Fibronectin is a component of most of the cartilage tissues, slightly different from fibronectin of blood plasma [16]. Fibronectin contributes to matrix integration through interaction with cell membranes and other matrix components such as collagen type II and thrombospondin [16]. Fibronectin fragments negatively affect chondrocyte metabolism, inhibiting the synthesis of aggrecan and stimulating catabolic processes. Apparently, fragments of other matrix molecules possess the same effects, which bind to chondrocyte receptors [23].

Various isoforms of CD44V5 are determined in articular cartilage, which are synthesized already in the late stages of osteoarthritis [13,24]. The expression of this isoenzyme is clearly correlated with the histological stages of cartilage degradation [24].

TNF-α stimulates cartilage matrix degradation and inhibition of synthetic processes in chondrocytes. IL-1 is produced by chondrocytes and stimulates catabolism, inhibits synthesis of matrix macromolecules, contributes to synthesis of metalloproteinases, especially collagenases, and increases the level of nitric oxide [18].

It is believed that molecules that have lost their function, become strangers to the body. They, as well as decomposition products of collagen and chondrocytes, acquire antigenic properties and can induce autoimmune inflammation, contributing to progression of degenerative changes in articular cartilage and supporting synovial inflammation [13].

Destruction of chondrocytes. With the progression of degenerative and destructive processes in articular cartilage, chondrocytes density decreases due to their death. There are two ways of cell death: natural programmed death – apoptosis, which is caused by the action of the body's regulatory factors involving genetic mechanisms, and pathological (accidental) death as a

result of deep, incompatible with life, cell lesions caused by the action of pathological factors [6,13].

Nowadays it's proved that in OA chondrocytes die by apoptosis. Induction of apoptosis in certain extent is related to the action of tissue metabolite - nitric oxide (NO), whose production intensifies in OA. One of the mechanisms of nitric oxide influence on the cells is inhibition of biosynthesis of proteoglycans [21].

The main signs of chondrocyte apoptosis is DNA fragmentation and activation of cytosolic and mitochondrial cysteine-containing aspartat-specific proteins that act as mediators of cell membrane receptor binding with necrotizing growth factor (TNF-α) [13].

Antiapoptotic action may be carried by the hormone prolactin, which acts as a protector of chondrocytes. Lowering of prolactin level in synovial fluid contributes to the process of destruction of cells [28]. Study of the chondrocytes apoptosis mechanisms paves the way for development of pathogenic drug therapy [9].

Drugs influence on the chondrocyte function. One of the OA treatment methods is pharmacological one. It is based on the use of medicines of local and systemic action.

There are slow- and fast-acting drugs. Non-narcotic analgesics, or nonsteroidal anti-inflammatory drugs (NSAIDs), and long-acting glucocorticosteroids belong to quick symptomatic agents.

Non-narcotic analgesics are used as a first step therapy. Most studies show that paracetamol provides a powerful analgesic, anti-inflammatory and antipyretic activity. The mechanism of paracetamol action is based on reducing the activity of oxidized forms of cyclooxygenase (COX-1 and COX-2) in the CNS and spinal cord [15].

Next step of therapy is the use of other NSAIDs. In patients with an increased risk of gastrointestinal lesions, selective COX-2 inhibitors or nonselective NSAIDs should be used, in combination with effective gastroprotectives [9].

Several NSAIDs affect the synthesis of proteoglycans by chondrocytes in vitro [1,8,9]. J. T. Dinger and M. Parker (1997) have suggested the differentiation of NSAIDs based on drug action on the synthesis of extracellular matrix macromolecules of articular cartilage in OA: inhibiting (acetylsalicylic acid, indomethacin, etc), stimulating (aceclofenac, tenidap, etc), neutral (ibuprofen piroxicam, nabumetone, nimesulide, etc).

Optimal NSAID medication that is used in these patients is nimesulide. The drug was developed in 1980 and after 5 years was used in more than 50 countries around the world under different names. Nimesulide is a 4-nitro-2-sulfonamides fenoksimetan, and is a neutral anti-inflammatory drug (pKa is approximately 6.5), and belongs to a highly selective COX-2 inhibitors, providing anti-inflammatory, analgesic, antipyretic effects, and inhibiting the formation of free acid radicals without affecting the homeostasis and phagocytosis. Leukocyte cyclooxygenase-2 is inhibited by the drug for 8 hours, and in synovial fluid - within 12 hours after ingestion. Nimesulide is well tolerated by patients of different age groups.

Upon receiving, nimesulide is well absorbed in the gastrointestinal tract. The maximum concentration of active substance in plasma is determined in 1.5-2.5 hours, and analgesia comes at the same time. In synovial fluid, therapeutically maximum concentration is reached similarly to blood. In synovial fluid, nimesulide at low concentration inhibites collagenase and unlike the most of drugs do not exert an adverse effect on the cartilage. Binding with blood proteins is up to 99%. It is metabolized in liver. The main metabolite - hydroxynimesulide (25%) - is pharmacologically active. Effect of the drug is based on: inhibition of prostaglandin synthesis (COX-2), formation of toxic oxygen metabolites, liberation of cytokines, synthesis of IL-6 and urokinase while increasing formation of the inhibitor, which activates plasminogen-1; changing the expression of glucocorticoid target-genes that contribute to the reduction of appearance of the inflammatory process; prevention of cartilage degradation [1].

The average therapeutic dose is 100 mg twice a day, after meals, or in the form of suppositories - 200 mg once throughout the day.

The next step is application of opioid analgesics therapy – the use is rational in case of NSAIDs (including selective COX-2 inhibitors) are ineffective, contraindicated or cause significant difficulties.

Systemic enzyme therapy is indicated for the treatment of patients with OA in combination with NSAIDs and chondro-protective agents [7,8], which have proven efficacy, safety and high performance of combined therapy.

Modulation of the cytokines activity, growth factors (TGF-α) by means of enzymatic agents is useful due to the imbalance of the immune system that occurs in OA. Excess of IL-1 and tumor necrosis factor plays a significant role in the pathogenesis of synovitis and cartilage tissue damage, so the important property of macroglobulin activated by proteinase is to inactivate and withdraw these agents [3,18]. At the moment, among systemic enzymes, widely used are phlogenzym and vobenzim [3].

In the presence of severe pain and synovitis of the joint, glucocorticoids with prolonged action are indicated. Such therapy is indicated for the ineffectiveness of NSAIDs and/or opioid analgesics [9].

Slow-acting symptomatic agents, used to treat OA, or cartilage-protectors are drugs which have a beneficial effect on the metabolism of articular cartilage. This group include glucosamine sulfate and its derivatives, chondroitin sulfate, hyaluronic acid, diacerin and herbal preparations (ginger extract, unsaponified compounds of avocado and soybean).

Glucosamine sulphate is a glycosaminoglycan contained in the extracellular matrix, in vivo is synthesized by chondrocytes from glucose in presence of glutamine; it is used by cells for the synthesis of glycosaminoglycans, proteoglycans and hyaluronic acid. It inhibits activity of catabolic enzymes, such as collagenase, agrekinase, stromelysin, phospholipase A_2, reduces formation of superoxide radicals, inhibits nitric oxide synthesis and activity of the lysosomal enzymes, reduces content of IL-lβ in synovial fluid, and has anti-inflammatory activity [2, 19]. Prostaglandin synthesis is not suppressed by glucosamine sulfate. When administered p.o., it is well absorbed and found in high concentrations in the synovial fluid [25].

Hyaluronic acid and sodium hyaluronate is a polysaccharide that is a natural component of cartilage, it is actively involved in its trophic and effectively used for intra-articular treatment of osteoarthritis in the composition of many pharmacological agents (Hyalual® ARTRO, Hyalgan, Synhyal, Synocrom, Durolane etc). Hyaluronic acid normalizes viscoelastic, cushioning and lubricating properties of synovial fluid; affects nociceptors of synovium interlayer and reduces the induction of pain mediators that provides an analgesic effect; forms the basis for aggrecan, which is important for the maintenance of structural and functional integrity of articular cartilage; retains water molecules to provide the necessary physical properties of the synovial fluid; has a protective effect on the cells of cartilaginous tissue – chondrocytes; facilitates penetration of nutrients and substances necessary for construction of the cartilage matrix; interacts with specific cell receptors (CD-44, RHAMM, I-CAM), and reduces concentration of the inflammatory mediators in the synovial fluid, causing anti-inflammatory effect; inhibits the activity of enzymes that destroy articular cartilage. Exogenous HA stimulates the synthesis of endogenous HA and synthesis of extracellular matrix components of cartilage, suspends the process of proteoglycan loss in cartilage, reduces the level of apoptosis of chondrocytes. At the moment a large number of sodium hyaluronate based drugs are registered in Ukraine. Among them there is Hyalual® ARTRO, by pharmaceutical company "Yuria-Pharm Ltd". Effective combination of hyaluronic acid with sodium succinate in Hyalual® ARTRO determines the uniqueness of its effect on the metabolism of articular cartilage in osteoarthritis and other cartilage lesions. Sodium succinate in Hyalual® ARTRO provides normalization of intracellular metabolism and tissue respiration under hypoxic conditions, restoring NAD^+ through the mechanism of reverse electron transfer in the mitochondrial respiratory chain, and it is involved in the biotransformation of xenobiotics monooxygenase system of the endoplasmic reticulum, it normalizes physiological condition and a number of acid-alkaline balance indicants

in acidosis due to changes in hydrogen ion out of mitochondria, it is involved in the regulation of transport of K^+ and Ca^{2+}, and stabilizes the prooxidant-antioxidant balance [1,8,21].

Diacerein is an anthraquinone derivative that inhibits IL-1, IL-6, TNF-α, and leukemic inhibitory factor, inhibits the formation of nitric oxide, reduces the amount of plasminogen activator receptor on chondrocytes and synoviocytes. Due to these effects, the drug reduces the production of metalloproteinases of collagenase, stromelysin, inhibits the release of lysosomal enzymes, stimulates the synthesis of hyaluronic acid, proteoglycans and glycosaminoglycans.

Unsaponified compounds of avocado and soy stimulate collagen synthesis by chondrocytes, inhibit IL-1 and its induced production of stromelysin, IL-6, IL-8 and collagenase [15].

Ginger Extract restores normal metabolism of articular cartilage, by suppression of production by chondrocytes of TNF-α and IL-1β-cytokines that stimulate the degradation processes of articular cartilage [15].

Conclusion

Osteoarthritis is the most common form of joint disease. The disease is caused by the action of biomechanical and biological factors. It manifests itself by destabilization of the normal correlation between the processes of synthesis and degradation of chondrocytes, extracellular matrix components of cartilage and articular bone. Chondrocytes are mature cell forms that lost the ability to mitosis, but having high functional biosynthetic activity. The cell density varies depending upon the location area in the articular cartilage, it is proportional to the load that the joint during the life is exposed to, and its cartilage. In different areas of articular cartilage there are chondrocytes different in shape and electron-microscopic characteristics. In normal condition, chondrocytes produce macromolecules of matrix (collagen, proteoglycans, glycoproteins and non-collagenous proteins), and macromolecules, in turn, form the environment of the cell, and directly affect its functioning. In articular cartilage affected by OA, chondrocytes synthesize anti-inflammatory cytokines IL-1, IL-6, TNF-α, MMP. Cartilage-protective agents and NSAIDs are drugs that directly affect the metabolism of articular cartilage. Action of drugs is based on the activation of biosynthetic processes (synthesis of proteoglycans and glycosaminoglycans), inhibition of production by chondrocytes of proteolytic enzymes and cytokines that stimulate degradation of articular cartilage.

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