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Pathogenetic features of experimental osteoarthrosis induced by dexamethasone and talc

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Abstract

The aim of the study was to investigate the pathogenesis of experimental osteoarthrosis induced by dexamethasone and talc by examining the structure and defining the morphometric and metabolic features of knee joint skeletal connective tissues in rats.

Materials and methods. We performed a morphometric evaluation of articular cartilages (their thickness, extracellular matrix arrangement, spatial arrangement of the main components, distribution density, and main cellular indices of chondrocytes), as well as changes in subchondral bones (the presence of trabeculae in the basal layer of the articular cartilage and individual osteophytes) in 30 rats with a model of primary osteoarthrosis induced by sequential administration of 0.5 ml dexamethasone (2 mg) and 1 ml 10% sterile talc suspension mixed with normal saline into the joint cavity. We studied the histologic specimens of the knee joints stained with hematoxylin – eosin, Alcian blue (pH 1.0 and 2.5), as well as with Van Gieson's, Masson's, and Mallory's trichome stains. The metabolic features of the articular cartilage and bone tissues were investigated by determining the hyaluronan, osteocalcin, and type I collagen levels in the serum of the rats.

Results. In the rats with dexamethasone- and talc-induced osteoarthrosis, the thickness of cartilages in their weight-bearing areas decreased by 50%, the spatial arrangement of chondrocytes was impaired, and the nuclear – cytoplasmatic ratio ($p < 0.01$) decreased to 0.3. Besides, a rise in the serum levels of hyaluronan ($p < 0.001$) to 110.2 ng / ml, type I collagen fragments ($p < 0.001$) to 217.9 ng / ml, and osteocalcin ($p < 0.001$) to 231.1 ng / ml was detected.

Conclusion. The main pathogenetic features of experimental osteoarthrosis induced by dexamethasone and talc include impaired distribution density, morphological characteristics, and functional activity of chondrocytes, which results in inhibited synthesis of extracellular matrix components in the articular cartilage and activated destruction of proteoglycans containing unsulphated glycosaminoglycans. The subchondral bone remodeling in experimental osteoarthrosis induced by dexamethasone and talc is characterized by intensification of synthetic activity of osteoblasts.

Keywords: osteoarthrosis, rats, dexamethasone, articular cartilage, chondrocytes, osteocalcin, subchondral bone, hyaluronic acid, type I collagen

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Conformity with the principles of ethics. The study was approved by the local Ethics Committee at Saratov State Medical University named after V.I. Razumovsky (Protocol No. 2 of 02.10.2018).

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Патогенетические особенности экспериментального остеоартроза, индуцированного дексаметазоном и тальком

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РЕЗЮМЕ

Цель – изучение патогенеза экспериментального остеоартроза (ОА), индуцированного дексаметазоном и тальком, на основании исследования структуры, определения морфометрических характеристик и метаболических особенностей скелетных соединительных тканей коленных суставов у крыс.

Материалы и методы. Осуществлена морфометрическая оценка суставного хряща (толщина, организация внеклеточного матрикса, пространственное расположение основных компонентов, плотность распределения, основные клеточные индексы хондроцитов) и изменений субхондральной кости (наличие костных разрастаний в виде появления костных балок в базальном слое суставного хряща и наличия единичных остеофитов) у 30 крыс с моделью первичного ОА, индуцированного путем последовательного введения в полость сустава 0,5 мл дексаметазона (2 мг) и 1 мл 10%-й суспензии стерильного талька в изотоническом растворе натрия хлорида. Изучены гистологические препараты коленных суставов, окрашенные гематоксилином Майера и эозином, альциановым синим (pH 1,0 и 2,5) по Ван-Гизону, Массону и Маллори. Метаболические особенности хрящевой и костной тканей изучены путем определения в сыворотке крови лабораторных животных концентраций гиалуронана, остеокальцина и коллагена I типа.

Результаты. У крыс с ОА, индуцированным введением дексаметазона и талька, выявлено уменьшение на 50% толщины суставного хряща в его нагружаемых участках, нарушение пространственного распределения хондроцитов, снижение ($p < 0,01$) ядерно-цитоплазматического отношения хондроцитов до 0,3 и повышение в сыворотке крови концентраций гиалуронана ($p < 0,001$) до 110,2 нг/мл, фрагментов коллагена I типа ($p < 0,001$) до 217,9 нг/мл и остеокальцина ($p < 0,001$) до 231,1 нг/мл.

Заключение. Основными патогенетическими особенностями экспериментального остеоартроза, индуцированного дексаметазоном и тальком, являются нарушение плотности распределения, морфологических характеристик и функциональной активности хондроцитов, что приводит к угнетению синтеза компонентов внеклеточного матрикса суставного хряща, а также сопровождается активизацией деструкции протеогликанов, содержащих несульфатированные гликозаминогликаны. Особенностью ремоделирования субхондральной кости при экспериментальном ОА, индуцированном дексаметазоном и тальком, является интенсификация синтетической активности остеобластов.

Ключевые слова: остеоартроз, крысы, дексаметазон, суставной хрящ, хондроциты, остеокальцин, субхондральная кость, гиалуроновая кислота, коллаген I типа

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INTRODUCTION

Osteoarthrosis (OA) is a common group of polyetiologic musculoskeletal diseases that progress over time and cause permanent changes in skeletal connective tissues [1]. Studying the pathogenetic mechanisms of the progress of inflammatory and destructive changes in the joints on animal models is aimed at enhancing available diagnostic and treatment strategies and designing new ones for further implementation of the obtained results into clinical practice [2, 3].

Commonly recognized methodological approaches to the experimental modeling of chronic joint disorders closely approximated to human OA in their morphology and involving all joint components (subchondral bone, articular cartilage, articular capsule and ligaments, as well as skeletal muscles that affect the joint) are based on the following major trends: breeding of animals of the same species with genetically determined OA, surgical destabilization of the knee joint components by resection of the anterior cruciate ligament or dissection of the menisci; affecting lubrication properties of the synovial fluid by administering abrasive solutions into the joint cavity, direct invasive effect of physical factors [4].

Initiation of degenerative and dystrophic changes in the articular cartilage through local application of various chemical agents, such as steroid medications (intraarticular administration of hydrocortisone acetate at a dose of 500 mg /kg of body weight, weekly intramuscular injections of dexamethasone at various doses depending on the animal species and duration of the experiment: 3 mg / kg, 7 mg / kg, or 10 mg / kg of body weight) is also widespread. The administration of other biologically active substances (intraarticular injections of vitamin A, monoiodoacetic acid in isotonic natrium chloride solution, 1% papain solution) also causes irreversible degenerative and destructive changes in the articular cartilage and a metabolic imbalance in the subchondral bone [5].

The mentioned methods of OA modeling result in quick (within 4–6 weeks after the manipulation) progression of damage to the joint structures similar to OA manifestations in humans. However, in animals, the most feasible methods of OA remodeling are comprehensive complex techniques based on a simultaneous targeted effect of a few harmful factors on joint tissues, reproducing various pathogenetic links of this chronic musculoskeletal pathology. In particular, this experimental trend is represented by local administration of 0.5 ml dexamethasone (2 mg) followed by intraarticular administration of 10% aqueous suspension of sterile talc into the articular cavity of the knee joint. This causes changes similar to stage I–II deforming arthrosis in humans [6].

Although experimental OA can be modeled by various methods [7], the morphology and metabolic features of articular tissues are similar and characterized by changes in the normal multilayer structure of the articular cartilage and impaired synthetic activity of chondroblasts with respect to aggrecan and lubricin that ensures viscosity of the synovial fluid. Moreover, in experimental OA, signs of hypercellularity in the basal layer of the articular cartilage, as well as structural and functional disorders in the articular cartilage – subchondral bone system are revealed [8].

There are studies confirming that along with uneven distribution of chondrocytes in various topographic areas of the articular cartilage, there are significant morphologic changes in chondrocytes characterized by karyopyknosis, karyolysis, and dystrophy leading to profound general changes in the metabolic activity of chondrocytes with respect to the main components of the extracellular matrix (ECM) and synovial fluid [9]. It was established that hyaluronan functions as a key protector and structural framework in providing appropriate microarchitecture of the articular cartilage under physiologic conditions along with proteoglycans (PG). This hyaluronic acid (HA) derivative is directly involved in stabilization and spatial arrangement of carbohydrate – protein complexes in the articular cartilage ECM. Besides, HA and its derivatives to-

gether with lubricin participate in cartilage homeostasis by affecting the diffusion and loading mechanism of articular tropism, as well as regulation of cell proliferation and migration, which proves their key role in maintaining the redox balance in articular structures [6].

However, opinions on the features of HA metabolism and its role in skeletal connective tissue remodeling in OA, especially in its early stages, differ. According to some studies, one of the key pathogenetic mechanisms in progression of damage to articular structures in OA is inhibition of HA synthesis against the background of increased hyaluronidase activity [10]. Some authors suggest that accumulation of HA in organs and tissues in OA results from an imbalance of its metabolism characterized by activation of its synthesis, as well as by functional and structural inconsistency of unsulfated glycosaminoglycans (GAG) formed following metabolic disturbances [11]. Therefore, we initiated a study aimed at investigating the structural and metabolic features of chondral and bone tissue remodeling in early manifestations of simulated knee OA.

The aim of the study was to investigate the pathogenesis of experimental OA induced by dexamethasone and talc by examining the structure and defining the morphometric and metabolic features of knee joint skeletal connective tissues in rats.

MATERIALS AND METHODS

The study was carried out in compliance with the principles of humanity set out in the directives of the European Community (86 /609 / EC), the Declaration of Helsinki, and "Rules for carrying out work using experimental animals" (Appendix to the order of the Ministry of Health of the USSR No. 755 dated 12.08.1977) and approved by the local Ethics Committee at Saratov State Medical University named after V.I. Razumovsky (Protocol No. 2 of 02.10.2018).

The study included 30 white outbred male rats aged 18 months and weighing 180–210 g. The animals were fed with standard wet food with free access to water and food. The animals were randomly divided into 2 groups: the control group included 10 intact rats, while the treatment group encompassed 20 animals. The animals of the treatment group had primary OA simulated in their knee joints by sequential administration of 0.5 ml dexamethasone (2 mg) into the cavity of their right (experimental) knee joint followed by 1 ml of 10% aqueous suspension of sterile talc a day later. 0.5 ml of isotonic sodium chloride solution was administered into their left (control) knee joint. Four weeks after the administration, the experimental OA had formed in the right knee joint of the animals corresponding to stage II–III deforming arthrosis in humans [4].

The animals were kept under observation for 4 weeks. The free movement amplitude was regularly evaluated, and the local status of the knee was defined. Local temperature was measured with infrared LAICA SA5900 (Italy) thermometer. Serum concentrations of hyaluronan, the key structural unsulfated glycosaminoglycan in the articular hyaline cartilage ECM, were determined by the end of the experiment by enzyme-linked immunosorbent assay (ELISA) using Quantikine® Hyaluronan Immunoassay (American Diagnostic Inc., USA). The findings were interpreted on the EPOCH™ spectrophotometer (BioTek Instruments, USA). Bone metabolism was assessed with reference to serum concentrations of type I collagen fragments found by ELISA using RatLaps™ enzyme-immunoassay (EIA) kits (Immunodiagnostic Systems Holdings Ltd, UK), as well as osteocalcin as a marker of osteoblast activity using Rat-MID™ Osteocalcin EIA kits (Immunodiagnostic Systems Holdings Ltd, UK).

After the rats were sacrificed, their knee joints were isolated as single osseomuscular specimens to study the features of their structure. The osseomuscular specimens were placed in 10% formalin, processed routinely, and embedded in paraffin. The histologic sections were cut and stained with Mayer′s hematoxylin (BioVitrum, Russia) and eosin (BioVitrum, Russia). The sections were mounted in the Bio Mount medium (Bio-Optica, Italy). To reveal histologic signs of OA, 8–10 7–10 μm thick frontal sections of the knee joints were used, cut at about 200 μm intervals in the areas of interest (lateral and medial femoral condyles, medial and lateral tibial plateaus). To assess the histologic changes in the knee joints, a semiquantitative scale was used [12].

The morphometric assessment of the histologic specimens (changes in particular areas of the articular cartilage and calculation of the nuclear – cyto-

plasmic (N / C) ratio for the main types of chondrocytes) was performed considering the cell area (*Sc*, μm²) and the nucleus area (Sn, μm²) in both groups of the animals. The N / C ratio was calculated using the following formula: N / C = Sn /(Sc – Sn), the measurements were taken using the Axio Imager Z2 microscope (Carl Zeiss, Germany).

The morphometric data were analyzed using digital images of the articular cartilage and subchondral bone in the areas of interest corresponding to the research objectives. The average number of cell elements was calculated in 6 fields of view in no less than 6 knee joint specimens for each topography area, and then the mean value was calculated. The sections were additionally stained with Alcian blue to reveal GAGs in the histologic specimens. Highly sulfated (pH 1.0) and total (pH 2.5) GAGs, as well as collagen fibers, underwent van Gieson's and Masson's staining, and collagen fibers were identified by van Gieson's and Mallory's staining.

Histologic specimens of the knee joints obtained from intact animals were used as controls. The animals were anesthetized with a combination of 0.05 ml / kg Zoletil-100 (Virbac Sante Animale, France) and 1 ml / kg Xylazine (Interchemie, the Netherlands) according to the instructions ("Veterinary Medicines in Russia" Guidelines, 2015). The animals were sacrificed by a 200 mg / kg overdose of Zoletil-100.

The findings were statistically processed using Statistica 10.0 software (StatSoft Inc, USA). All variables were tested using the Kolmogorov – Smirnov and Shapiro – Wilk tests. The retrieved values for each criterion suggested non-normal distribution of the data. As the findings did not correspond to the normal distribution, they were evaluated using the nonparametric Mann – Whitney U-test. The findings were presented as the median and the interquartile range *Me* (Q_1; Q_3). The differences between the animals with OA and the controls were considered statistically significant at $p < 0.05$.

RESULTS

The thickness of the articular cartilage in the weight-bearing areas of the femoral condyles in the controls (Table 1) was on average 220–300 μm, the articular cartilage contained mostly oval chondrocytes 11–18 μm in diameter with centrally located, normochromal nucleus, N / C 0.64 – type I chondrocytes. These cells were arranged both separately and in isogenous groups of 3–4 to 6 chondrocytes (Fig. 1).

Table 1

Morphometric features of the articular cartilage of the knee in the rats of the treatment and control groups, *Me* (Q_1; Q_3)

Group	Measured parameter		
	The thickness of the articular cartilage in the non-weight-bearing areas of the tibiae, mm	The thickness of articular cartilage in the weight-bearing areas of the femoral condyles, mm	The difference in the thickness of articular cartilages in weight-bearing and non-weight-bearing topography areas, %
Control group, $n = 10$	0.234 (0.221; 0.297)	0.226 (0.196; 0.281)	4.0 (0.9; 7.1)
Treatment group, $n = 20$	0.185* (0.209; 0.273) $p < 0.05$	0.105* (0.095; 0.125) $p < 0.01$	54.2 (22.4;67.1) * $p < 0.001$

* here and in Table 2, the differences between the parameters of the treatment and control groups at $p < 0.05$

The number of isogenous groups within one field of view was close to 10–11. Type II chondrocytes were located mostly in the basal layer of the articular cartilage, they were 8–9 μm in diameter, had centrally located pyknotic nuclei, and their N / C ratio did not exceed 0.30. There were 39–47 cells in each of the selected fields of view in the areas of interest, 70% of them were type I chondrocytes. In the superficial layer of the articular cartilage, cells were flattened and spindle-shaped with normochromic, bean-shaped nuclei.

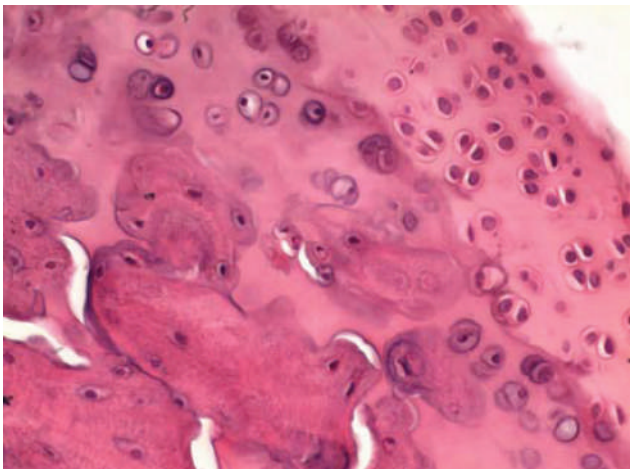

Fig. 1. The section of the articular cartilage in the knee of the intact control rat:hematoxylin – eosin staining, ×40

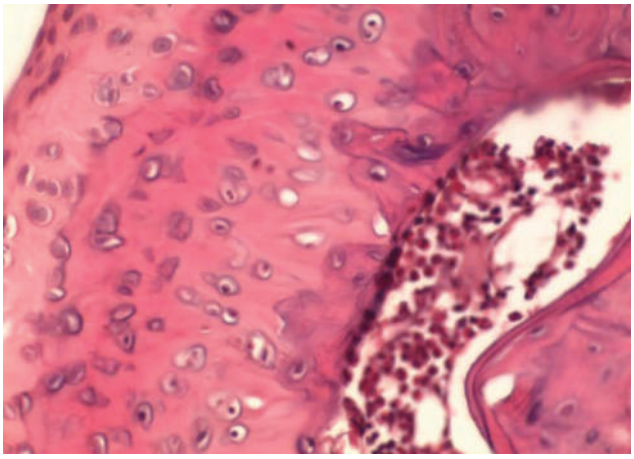

Fig. 2. The section of the articular cartilage in the knee of the rat from the treatment group: hematoxylin – eosin staining, ×40

4 weeks after the start of OA simulations, a decrease in the articular cartilage thickness ($p < 0.01$) in the weight-bearing areas was observed in the rats of the treatment group (Fig. 2). We also revealed changes in the proportion of chondrocytes, as well as in their morphology. The relative count of type I chondrocytes decreased and made about 40–50% of all articular cartilage cells. Their diameter did not exceed 10–13 μm, and their N / C ratio was close to 0.44. In some type I chondrocytes, the nuclei were heterochromatic and took an irregular bean shape, their arrangement was eccentric, and their cytoplasms had vague contours and triangular, spindle-like, or irregular bean-like shapes.

Type I chondrocytes formed a small number of isogenous groups (1–2 in the field of view), and each isogenous group comprised no more than 2–3 type I chondrocytes. About 22% of type II chondrocytes were characterized by pronounced karyopyknosis and eccentric arrangement of their nuclei, and 70% of all type II chondrocytes were characterized by microcytosis (4–6 μm in diameter). Enucleated forms of type II chondrocytes (karyolysis) made up about 40% of all chondrocytes. Individual acellular lacunae were found in the articular cartilage. Around 27–30 isolated or clustered chondrocytes were observed in each field of view. We also observed some individual trabeculae in the basal layer of the articular cartilage, which had a regular round shape in their cross-section.

Additional staining methods allowed to detect a decrease in the levels of all analyzed GAGs in the organic ECM of the articular cartilage in the animals of the treatment group. This indicated profound degenerative and dystrophic processes and was proven by biochemical findings. Thus, the study of the key cartilage and bone metabolites in the serum (Table 2) revealed a significant increase in the concentrations of type I collagen fragments ($p < 0.001$) and hyaluronan ($p < 0.001$) in the animals of the treatment group compared with the controls. Osteocalcin supply to the blood of OA rats ($p < 0.001$) decreased suggesting signs of inhibited synthetic activity in osteoblasts.

Table 2

Serum concentrations of hyaluronan, type I collagen fragments, and osteocalcin in the rats with simulated primary OA, *Me* (Q_1; Q_3)

Group	Serum concentrations		
	Hyaluronan, ng / ml	Type I collagen fragments, ng / ml	Osteocalcin, ng / ml
Controls, $n = 10$	66.5 (57.6; 69.9)	144.2 (99.3; 170.1)	231.5 (222.9; 258.4)
Treatment group, $n = 20$	110.2* (81.4; 142.9) $p < 0.001$	217.9* (200.5; 248.2) $p < 0.001$	176.9* (133.1; 194.4) $p < 0.001$

DISCUSSION

Under physiological conditions, the metabolism of skeletal connective tissues is characterized by the balance between catabolic and anabolic processes, which provides structural and functional integrity of the knee joint [13]. Cells, such as synoviocytes, mononucleotides that infiltrate the synovial membrane, osteocytes in the subchondral bone, and chondrocytes, play an essential role in healthy skeletal connective tissue remodeling [3].

The articular cartilage is a complex structural and functional system of cells and extracellular matrix (fibers and amorphous core). However, the major biomechanical features of the articular cartilage are determined by high aggrecan hydration, while degenerative and dystrophic changes in OA result from several unfavorable exogenous and endogenous effects leading to an evident decrease in cartilage congruence [1, 11].

The conducted morphology tests revealed the progression of irreversible degenerative and dystrophic changes in chondrocytes in simulated OA,

manifested through impaired cell ratios, proliferation, and death. The changes observed in simulated OA suggested that the imbalance of metabolic processes in the articular cartilage ECM resulted from its structural and functional modification (reduction of chondrocyte density, their rearrangement, changes in the N / C ratio, signs of cell death). This was confirmed by the increase in serum hyaluronan concentrations in the rats of the treatment group. These changes probably result from the prevalence of destructive changes aimed at disorganizing proteoglycan complexes of intercellular substance in the articular cartilage. The imbalance between catabolic and anabolic responses in the articular cartilage is confirmed by a significant decrease in its thickness in simulated OA.

Disorders in the subchondral bone are definitely some of the key factors in the OA pathogenesis. Under normal conditions, they ensure essential needs of the articular cartilage, including its densification, hardening, and osteophyte formation with changes in the general biomechanics of joints and active penetration of inflammatory mediators and growth factors in response to enhanced angiogenesis [14, 15]. Our findings revealed the activation of osteogenesis following the increase in osteoblast secretion and alteration of their metabolism, which was confirmed by the increase in serum osteocalcin levels in the rats of the treatment group in early signs of OA.

CONCLUSION

The main pathogenetic features of experimental OA induced by dexamethasone and talc include impaired distribution density, morphological characteristics, and functional activity of chondrocytes, which results in inhibited synthesis of extracellular matrix components in the articular cartilage and activated destruction in supramolecular complexes containing unsulfated GAGs. Disturbances of subchondral bone remodeling in experimental OA are characterized by intensification of synthetic activity in osteoblasts.

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