MORPHOLOGICAL FEATURES OF SYNOVIAL JOINT ELEMENTS FORMATION IN THE OFFSPRING DEVELOPED UNDER EXPERIMENTAL HYPOTHYROIDISM AND EXPOSED TO HYPODYNAMIA

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Abstract: *This study investigates the morphological features of synovial joint elements in the offspring developed under conditions of experimental hypothyroidism and exposed to hypodynamia. To perform a comparative scientific analysis, the morphological characteristics of joint capsules and their synovial structures in the offspring born to intact control rats were initially examined at all observation periods. The findings obtained from the control group served as baseline parameters for evaluating structural changes occurring under the combined influence of experimental hypothyroidism and hypodynamia.*

Keywords: *joint capsule, fibrous layer, tendons, synovial membrane, experimental hypothyroidism, musculoskeletal system, morphology.*

Background. Endocrine system disorders, particularly hypothyroidism associated with thyroid gland hypofunction, represent one of the major biomedical problems affecting growth, development, tissue differentiation, and regeneration. Current knowledge regarding the functional anatomy of synovial structures and their relationship with the ligamentous apparatus remains limited and, in some cases, contradictory. Therefore, identifying the morphological features of large joint structures, determining areas of reduced stability, age-related periods of increased vulnerability, and understanding the biomechanics of joint injuries are important scientific challenges. Worldwide, numerous studies are focused on age- and sex-related functional characteristics of the thyroid gland. Special attention is paid to maternal hypothyroidism and its adverse effects on fetal development, including pathological changes in the musculoskeletal system, which may lead to severe developmental abnormalities and disability. Consequently, investigation of the morphofunctional characteristics of large joints and prevention of injury-related and degenerative-dystrophic changes remain highly relevant.

Objective. To investigate the dynamics of morphological development of synovial structures in large joints of offspring developed under conditions of experimental hypothyroidism and hypodynamia during the early stages of postnatal ontogenesis.Materials and Methods. The study was conducted on 40 sexually mature female white rats. Experimental hypothyroidism was induced in 30 pregnant females by intragastric administration of mercazolil at a dose of 2.5 mg/100 g body weight, while 10 control animals received physiological saline. A total of 120 offspring (30 control and 90 experimental) maintained under identical environmental and nutritional conditions for 60 days of postnatal development were examined. Hypodynamia was induced by housing the animals in restricted cages measuring 15 × 15 cm. Pathomorphological and morphometric changes of the knee joint capsule were evaluated using macroscopic, histological, histochemical, morphometric, and statistical methods.

Results. It is well known that the fibrous layer of the synovial membrane consists of dense connective tissue rich in newly formed and mature blood vessels. In its deeper layers, scattered venules, arteries, and nerve trunks are observed, which frequently form neurovascular bundles.

During the initial observation period, no significant morphological differences were detected between the study groups. Microscopic examination of the synovial membrane revealed a small number of broad and short villi projecting into the joint cavity. These villi exhibited either slightly

undulating or smooth surfaces. In certain areas, a layer of varying thickness composed of a mildly basophilic substance was observed directly above the lining layer. In both smooth and villous regions of the synovial membrane, the lining layer consisted of densely arranged synoviocytes.Most villi were characterized by numerous synoviocytes, which in some areas formed several layers. These cells varied in size, and their nuclei were round, oval, rod-shaped, or spindle-shaped. Occasional mitotic figures were also observed among them. In both villous and non-villous regions, the lining layer gradually merged into the fibrous layer composed of delicate, loosely arranged collagen fibers accompanied by occasional fibroblast-like cells.

Blood vessels were distributed throughout most parts of the fibrous layer; however, elongated vascular bundles consisting of arterioles, venules, and capillaries were also identified in certain regions. In areas containing vascular bundles, developing adipose tissue pads were observed within the core of the villi. In some regions, the synovial membrane was found to transition directly into dense fibrous connective tissue, forming tendons that appeared in longitudinal, transverse, and oblique sections of the histological preparations.

The tendons consisted of primary and secondary bundles. A considerable number of young fibroblasts were present between the collagen fibers. Between the secondary collagen bundles, a loose layer of immature connective tissue was identified, representing the endotenon, which was rich in capillaries and connective tissue cells. In some microscopic fields, the peritenon of the tendons containing numerous arterioles and venules was also observed.

14-Day-Old Animals In 14-day-old animals, the synovial membrane was mainly composed of specialized differentiated flat or slightly undulating connective tissue structures. Only in areas located over loose fibrous (areolar-type) connective tissue did the membrane form relatively shallow and predominantly broad villi. At this stage, three types of synovial tissue were identified according to the structure of the subsynovial tissue: areolar, adipose, and fibrous types. The adipose type of the synovial membrane formed relatively large fat pads, whereas the fibrous type occupied a comparatively small area.

In some regions of the synovial lining layer, synoviocytes were sparsely distributed, while in other areas they formed multiple cell layers. The superficial layer consisted of cells with relatively scant cytoplasm and round, triangular, or irregularly shaped nuclei. These cells stained intensely, lacked distinct nucleoli, and were classified as phagocytic synoviocytes (type A). Among them and in the deeper portions of the lining layer, fibroblastic (secretory) synoviocytes (type B) were identified. These cells were oval or slightly elongated, possessed lightly stained nucleoplasm with one to three nucleoli, and exhibited moderately distinct cytoplasm.In regions where capillaries and small blood vessels were located superficially and closely adjacent to the lining layer, fibroblastic synoviocytes were observed to differentiate into vascular adventitial cells. A considerable portion of the lining layer consisted of intermediate synoviocytes (type S), which displayed morphological characteristics of both type A and type B cells.

At this age, small blood vessels with well-formed lumina and clearly defined walls frequently appeared within the fibrous connective tissue directly beneath the lining layer. In addition, developing vessels represented by clusters of endothelial cells were observed.

The adipose regions of the lining layer were formed by fat pads, which were either isolated or connected to deeper perivascular adipose tissue. Beneath the synovial membrane, dense regular fibrous connective tissue forming tendons was present. Tendon fibers were arranged in parallel bundles composed of collagen fibers that were relatively loosely packed.

These structures represented primary tendon bundles and consisted of relatively narrow collagenous bands composed of clearly distinguishable fibrils. The cellular composition of the endotenon was relatively sparse and included fibroblasts, histiocytes, and occasional fibrocytes. Vascular bundles consisted of small arterioles and venules surrounded by a small amount of connective tissue cells. One or two mast cells were occasionally observed in the perivascular

region.The peritenon filling the spaces between the collagen fibers of the secondary tendon bundles displayed a rich and diverse composition. This broad connective tissue layer was partially formed by loose irregular fibrous connective tissue. Along with medium-sized arteries and veins, lymphatic vessels were identified and were distinguished by their large size and wide lumina. The cellular composition of the peritenon was abundant and included fibroblasts, fibrocytes, histiocytes, macrophages, occasional lymphocytes, and mast cells.

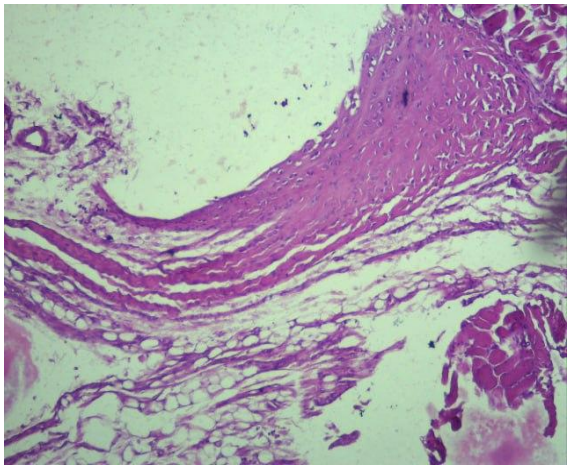


Figure 1. **Villi of the areolar type synovial membrane. Hematoxylin and eosin staining (H&E). Magnification ×400**

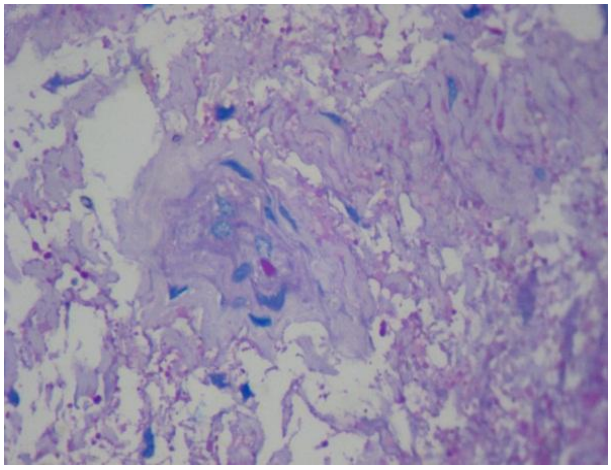


Figure 2. **Nodular and perivascular edema of the adipose type synovial membrane. H&E. Magnification ×400**

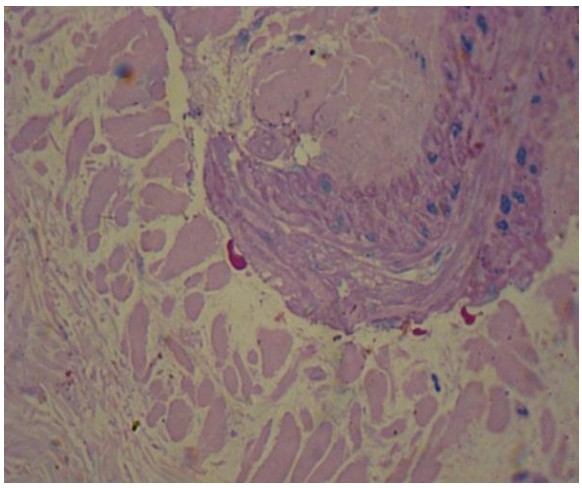


Figure 3. **Fibrous type synovial membrane; blood vessels are visible within the fibro-elastic layer. H&E. Magnification ×400**

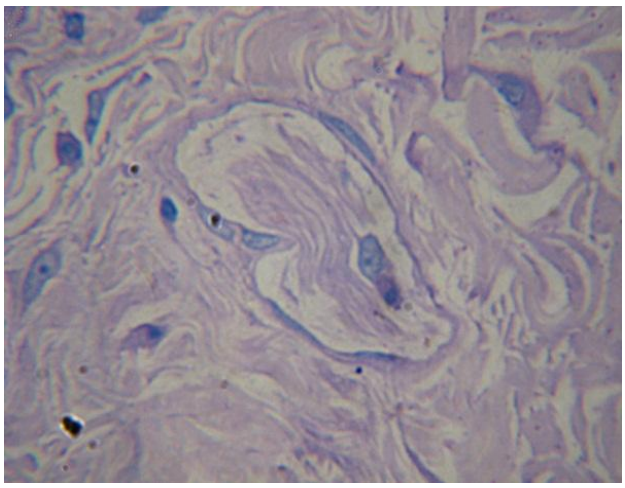


Figure 4. **Accumulation of poorly differentiated fibrolytic synoviocytes at the apices of the villi. H&E. Magnification ×400**

One-Month-Old Animals In the specimens obtained during the one-month observation period, the synovial membrane consisted predominantly of areolar and adipose types, with a smaller proportion represented by the fibrous type. In some areas, transitional forms were observed, in which one type gradually merged into another, resulting in mixed structural characteristics.

Regardless of the nature of the subsynovial tissue (loose connective, adipose, or dense fibrous tissue), the surface of the synovial membrane appeared smooth, slightly undulating, folded, or formed villi of varying height and thickness. In contrast to the previous age group, the superficial layer was

predominantly composed of closely packed synovial cells arranged in smooth rows, most of which belonged to the secretory (type B) synoviocyte population. A smaller number of macrophage-like (type A) synoviocytes were also present, together with occasional intermediate forms.

Alongside mature differentiated fibroblasts, less specialized cells with round or oval nuclei and well-developed basophilic cytoplasm were identified. These cells were most frequently concentrated at the apices of the synovial villi.In certain regions, the lining layer consisted of one or two layers of synoviocytes, whereas in other areas the cells formed multiple rows. The increased number of capillaries within the lining layer promoted the accumulation of synovial cells around the vascular structures. Blood vessels of various calibers became more numerous in both the superficial and deeper layers of the synovial membrane. At the same time, developing blood vessels were still observed and appeared as clusters of proliferating endothelial cells.

Cellular elements, including histiocytes, fibroblasts, macrophages, and smaller numbers of fibrocytes and lymphocytes, were mainly concentrated in perivascular regions. These cells were less frequently encountered between the fibrous structures, where the fibers remained loosely arranged within the extracellular matrix.

In the adipose type of synovial membrane, fully differentiated mature adipocytes were not yet observed. The few blood vessels supplying these regions were surrounded by delicate loose connective tissue of an immature structure. In the areolar type of synovial membrane, the subsynovial tissue contained numerous small- and medium-caliber blood vessels, while the collagen fibers were considerably thicker than those observed in younger animals.In some areas, the synovial membrane was directly attached to the tendons, with the intervening peritenon layer being almost absent. Regardless of the thickness and structure of the subsynovial tissue, it gradually transitioned into the fibrous connective tissue separating the secondary tendon bundles, known as the endotenon, which was rich in blood vessels.

The tendon bundles, separated by broad layers of extracellular matrix, were characterized by a high cellular density. In transverse sections, these tendon cells exhibited a wing-like appearance. Layers of extracellular matrix between the primary collagen bundles were observed only rarely.

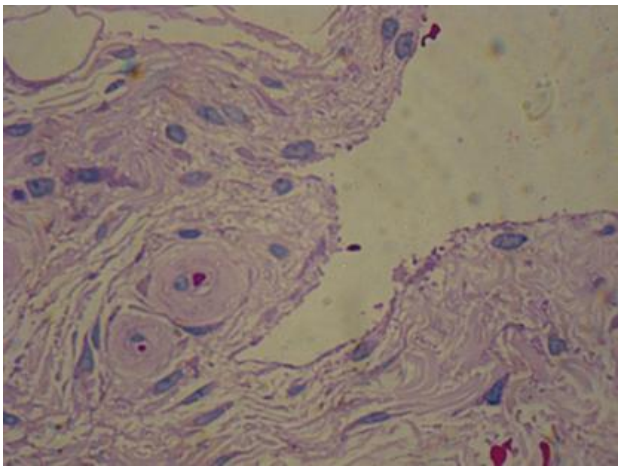


Figure 5. **Synovial structures of the joint capsule. Semi-thin section. Hematoxylin and eosin staining (H&E). Magnification ×400**

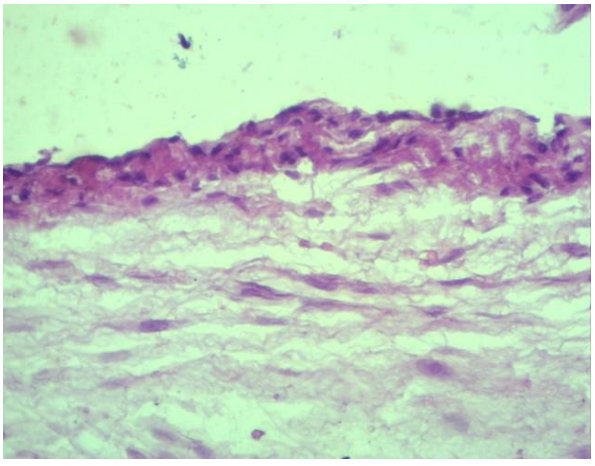


Figure 6. **Smoothing of the synovial membrane surface with edema of the interfibrous spaces in the fibrous layer. H&E. Magnification ×400**

Discussion. The fibrous structure of the collagen-elastic layer of the synovial membrane varies in both thickness and density. In the smooth areas of the synovial membrane facing the joint cavity, the collagen fibers are densely packed and exhibit intense staining properties. In the folded and villous

regions, the layers of the synovial membrane consist of loosely arranged fibers without a distinct supporting framework, and clear unstained areas of the extracellular matrix are visible between them.At this stage of development, the distribution of blood vessels within the fibrous layer and subsynovial tissue is uneven. Numerous longitudinally arranged small- and medium-caliber blood vessels are frequently observed between the fibrous structures of the inner layer of the synovial membrane. These vessels possess clearly defined lumina and are filled with blood. The endothelial cells contain hyperchromatic oval or elongated nuclei and are surrounded by pericytes and a small number of connective tissue cells.

A considerable number of developing blood vessels are also present. These vessels are characterized by dense aggregations of endothelial cells encircled by pericytes in a basket-like arrangement. In villous regions, blood vessels are located very superficially, almost directly beneath the synovial lining layer, whereas in smooth regions they are situated within the deeper fibroelastic layers of the synovial membrane. Within the subsynovial connective tissue, vascular bundles composed of medium-sized arteries and veins are surrounded by collagen fibers. The tunica media of these vessels contains well-developed smooth muscle cells. Larger muscular-type arteries are occasionally observed at some distance from these bundles, displaying a markedly thick muscular layer. Their adventitial layer is enclosed by cuff-like collagen fibers.

Compared with previous developmental stages, the lumina of these vessels are enlarged and their walls appear noticeably thinner. The composition of vascular bundles varies; in some cases, they consist exclusively of microcirculatory vessels, including arterioles, venules, and capillaries. Most vascular bundles contain small arteries, veins, and lymphatic vessels. Individually located vessels are surrounded by dense collagen fibers forming a protective sheath, whereas vessels within bundles are freely embedded in loose connective tissue and adipose tissue.

Conclusion. In the offspring born under conditions of experimental hypothyroidism and subsequently developed under hypodynamic conditions, disturbances in the differentiation of the synovial membrane of the knee joint were observed. The synovial villi of the joint capsule demonstrated vascular congestion, lymphocytic colonization, and mast cell activation. In addition, the fibrous layer exhibited disorganization and dispersion of collagen fibers, particularly involving type III collagen structures. These findings indicate that the combined effects of experimental hypothyroidism and hypodynamia adversely influence the normal morphogenesis and structural organization of synovial tissues during postnatal development.

REFERENCES

1. Adamova YaG, Chumachenko AN. Morphological features of various thyroid gland pathologies in populations living in technogenically polluted regions. Arkhiv Patologii. 2007;(2):24–27.

2. Balabolkin MI, Telnova ME, Antonova KV. Diagnosis and treatment of hypothyroidism in clinical practice. Endokrinologiya. 2008;(15):988–993.

3. Dedov II, Melnichenko GA, Fadeev VV, Morgunova TB. Thyroid diseases in regions with mild iodine deficiency. Vrach. 2008;(10):51–57.

4. Portyannikova OO, Tsvinger SM, Govorin AV, Romanova EN. Analysis of the prevalence and risk factors of osteoarthritis in a population. Modern Rheumatology Journal. 2019;13(2):105–111.

5. Jepsen S, Blanco J, Buchalla W, et al. Prevention and control of dental caries and periodontal diseases at individual and population level: Consensus report of Group 3 of the Joint EFP/ORCA Workshop on the Boundaries Between Caries and Periodontal Diseases. Journal of Clinical Periodontology. 2017;44(Suppl 18):S85–S93.

6. Duntas LH. Thyroid disease and lipid metabolism. Vascular Health and Risk Management. 2005;1(2):113–120.

7. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocrine Reviews. 2008;29(1):76–131.

8. Rasulov KhA, Isaeva NZ, Eshonkulova BD, Ibrokhimova LI. Morphological changes in para-articular tissues in children with congenital hip dislocation associated with hypothyroidism. Nazariy va Klinik Tibbiyot Jurnali. 2018;(2):124–125.

9. Rasulov KhA. Morphological and metabolic state of the apophyseal-tendon complex in rats with experimental hypothyroidism. Pediatriya. 2018;(4):263–266.

10. Rasulov HA, Maxmadaliev XJ, Temirova NT, Magribov ShG. Morphological characteristics of rat limb tendons in experimental hypothyroidism. Tibbiyotda Yangi Kun. 2018;3(23):225–228.

11. Rasulov KhA, Nuraliyev AA, Eshonkulova BD. Effects of hypodynamia on joints and synovial membranes in hypothyroidism syndrome and morphological features of synovial layers. Tibbiyotda Yangi Kun. 2025;12(86):780–783.

12. Rasulov KhA, Nuraliev AA. Influence of hypodynamia on joints and synovial membranes in hypothyroidism syndrome and morphological features of synovial layers. International Journal of Formal Education. 2025;4(12):383–386.

13. Rasulov KhA, Eshonkulova BD, Butaev ChJ, Nuraliyev AA. Influence of hypodynamia on joints and synovial membranes in hypothyroidism syndrome and morphological features of synovial membranes. American Journal of Biomedicine and Pharmacy. 2025;2(12):148–151.