Histological study on structural changes in articular capsule with growth in rats

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Abstract:

This study was aimed to morphologically investigate, using normal rats in various growing stages, structural changes in an articular capsule of knee joint with growth as a basic study that examined a functional mechanism of an effect of electrical stimulation on the decrease in range of motion of the knee joint by an immobilization.Eight male Wistar rats aged 1, 3, 7 and 13 weeks were used as materials. After they were brought in, they were euthanized to remove the knee joints to prepare various specimens. The posterior part of the joint capsule was observed macroscopically and histologically. Synovial folds in the posterior capsule showed increases in thickness and length with age. In addition, the joint capsule at that site was composed of only several layers of synovial cells at 1 week of age. But at 3 weeks of age, an adipose tissue layer appeared behind the synovial cell layer. After 7 weeks, the thickness of the joint capsule increased due to the appearance of a layer

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of densely accumulated thick bundles of collagen fibers behind the adipose tissue layer and a layer of sparse fibers behind it. The posterior part of the joint capsule was composed only of synovial cells at 1 week of age, but as it grew, layers with dense adipocytes and collagen fibers appeared, which played the role in enhancing the joint capsule flexibility and strength. It was found that the rat joint capsule adapts to increased activity with development and changes in thickness and composition.
Keywords: joint capsule, growth, synovium

1. Introduction

A prevalence of knee osteoarthritis (OA) has been increased with aging, and today, is considered one of the most osteoarthritis in the elderly. This is due to the progression of degenerative changes in the joint components, and causes to restricted activity and bedridden conditions.

The knee capsule attaches to the femur, tibia, and patella and wraps the entire knee joint in a cylindrical shape[7], but among the joint capsules of such shape, the central responsible lesion for joint mobility limitation caused by OA is thought to be the posterior surface of the joint capsule [2–4]. According to Koizumi [1], the responsible lesion for contracture up to 2 weeks after the start of immobility is a muscle factor, but after that, the muscle factor decreases sharply and changes to a joint factor.

In order to understand the various pathological changes in joints, it is necessary to know the structure and function of the joint capsule. However, until now, most of the research on OA has been on articular cartilage, but only few on the joint capsule. In addition, in order to know the response of the joint capsule to the increase or decrease of mechanical stimulation, observation of structural changes associated with development provides effective suggestions, but there are few reports on the developmental changes of the joint capsule. Based on these findings, in this study, we morphologically investigated the structural changes in the synovium and connective tissue structure of the posterior capsule of the joint capsule during development using rats at various stages of development.

2. Matreials and Methods

2.1 Materials

Thirty-two Wister male rats from 1 to 13 weeks of age were used. Male Wistar rats (8 each) aged 1, 3, 7 and 13 weeks were brought in and euthanized to remove the knee joint. Using them, decalcified paraffin sections and non-decalcified resin-embedded polished

specimens were prepared, stained, and observed with an optical microscope. Furthermore, for some specimens, specimens for scanning electron microscope observation were prepared and observed.

2.2 Methods

2.2.1 Sampling and Fixation

Rats were inhaled with carbon dioxide and deeply anesthetized and euthanized. After peeling the skin of the hind limbs of the rat confirmed to be dead, soft tissues other than the joint capsule are removed from the knee joint. Using a dental hand motor, the femur and lower leg bone were cut at a height of about 1 cm above and below the knee joint, and further cut outward from the medial-lateral central part of the specimen in the sagittal direction. Then, it was immediately immersed in a 4% aqueous paraformaldehyde solution (PFA) or a Karnobski solution (KAR) and fixed. PFA-fixed specimens were used for Rigolac resin-embedded specimens and Paracline specimens, and KAR-fixed specimens were used to prepare scanning electron microscope (SEM) observation specimens. Specimens were immersed in KAR overnight (4 ℃.), then placed in stock solution (6.8 g saccharose dissolved in 0.1 M phosphate buffer) and stored in the refrigerator until embedding work began.

2.2.2 Sectioning of paraffine block

Specimens fixed with 4% paraformaldehyde were decalcified by immersing them in 8% EDTA (pH 7.2 to 7.4, 4 ℃) and Morse's solution. Following washing with water, vacuum dehydration was performed in a desiccator with 70, 95 and 100% (twice) ethanol (25 minutes each). Further, the mixture was evacuated with xylene (twice for 30 minutes) and immersed with xylene and paraffin (15 minutes). Then, it was immersed in paraffins I to III (1 day each) for permeation, and then embedded, and a sagittal continuous section having a thickness of 4 um was prepared by a microtome. The sections were stained with Masson trichrome and observed with an optical microscope.

2.2.3 Ground section of resin-embedded-block

PFA-fixed sagittal split specimens were dehydrated by immersion in 70, 90 and 100% ethanol in vacuum (20 minutes each). After that, it is immersed in acetone (30 minutes, twice) for permeation, and further, a mixed solution of acetone and rigorac resin 1: 1 (2 to 3 hours), 1: 3 (1 day), 1: 7 (1). Sun) and Rigolac resin stock solutions I and II (1 day each).

In the Rigolac resin stock solution, Rigolac resin 2004 and Rigolac resin 70F were mixed

at a ratio of 9: 1, and benzoyl peroxide was added to the solution at a ratio of 1/100 as a polymerization accelerator, and the mixture was sufficiently stirred. A specimen fully impregnated with resin was placed in a resin stock solution placed in an embedding cup and embedded, and the sample was further placed in a closed container and heated and polymerized in a constant temperature bath (38 ℃, 45 ℃, 55 ℃, 60 ℃: 1 day each).

After the polymerization was completed, the block was trimmed into small pieces with a dental hand motor and attached to an acrylic plate. It was carefully polished using a grindstone and a three-step polishing film until the final thickness was about 100 microns and the surface of the specimen was not scratched. When the polishing was completed, the mixture was etched with 0.1N hydrochloric acid (1 minute), stained with Tragin Blue (TB), and observed with an optical microscope.

2.2.4 Specimen of Scanning electron microscope

The sample surface was lightly removed of organic matter by immersing it in a 30% aqueous sodium hypochlorite solution for 10 seconds. Further, as post-fixation, the mixture was immersed in a 0.1 M phosphate buffer buffered 1% osmium solution (4 hours). Next, it was immersed in 70, 90 and 100% ethanol (30 minutes each) to dehydrate it, then immersed in t-butyl alcohol and directly placed in a freeze dryer (ES-2000 manufactured by Hitachi, Ltd.) for freeze-drying. Furthermore, carbon was vacuum-deposited using a carbon coater (VC-100 manufactured by Vacuum Device Co., Ltd.). After that, platinum coating was applied using ion sputter (E-1010 / E-1-2 manufactured by Hitachi, Ltd.), and the structure of the sagittal split-polished surface of the joint capsule was observed by SEM (S-3400, manufactured by Hitachi, Ltd.).

3.Results

The lateral side of the meniscus is thick, the medial side is thin, and the upper part is concave and joins the medial and lateral condyles of the femur. When observing the Rigo resin specimen and the paraffin specimen, the 1-week-old rat already had a meniscus（Fig.1 Fig.2）.

The knee capsule has four main layers, which are divided into synovial layer, fat layer, dense fibrous layer and sparse fiber in order from the inside. Abundant blood vessels, nerves and lymph vessels are distributed in the fibrous layer. The posterior part of the knee capsule is thicker than the medial and lateral surfaces. There are sparse fibers in the superficial layer behind the knee capsule, but when they were peeled off and observed in the deep layer, the fibers were densely gathered there. In addition, the synovial layer of

rats at 7 and 13 weeks was observed on the inner surface of the joint(Fig.1).

As the age of the week increases, the thickness of the joint capsule increases. A synovial layer and a sparse fibrous layer were observed from the first week of age. The meniscus and synovial folds are also visible in the joint cavity. From the third week, the joint capsule becomes thicker, and fat cells appear just below the synovial layer, forming the fat layer. In addition, blood vessels also appeared from the third week. At seven weeks, a dense fiber layer of collagen fibers appeared on the outside of the fat layer. At thirteen weeks, the fibrous layer thickens(Fig.1).

Adipose tissue decreases with the age of weeks. That is, miniaturization of adipocytes appears and the density decreases. On the other hand, the synovial layer does not change between 2 and 3 layers at any age. At 7 and 13 weeks of age, the arrangement of the fibrous layers becomes interlaced. Blood vessels were observed between the fibrous layers. From one week of age, a few blood vessels penetrate the knee capsule. The number of blood vessels that penetrated increases with age. The posterior cruciate ligament lies between the synovial and fibrous layers. The synovial layer covers the outside of the posterior cruciate ligament(Fig.1).

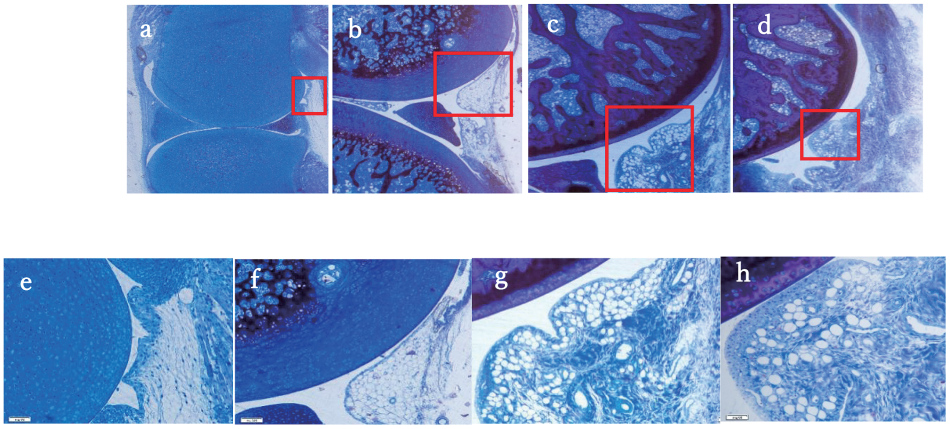

Fig.1. Sagital cross-sectional images of rat's knee joints
Undecalcified resin-embedded ground sections, TB staining
Figures of a, b, c, d indicate cross-sectional images of knee joints of 1, 3, 7 and 13 weeks old,respectively.
e, f, g, h : magnified images of square parts of a, b, c, d
Scale bar : Fig.a-c＝200μm, Fig.d＝1mm, Fig.e,h＝50μm, Fig.f,g＝100μm.

1-week-old resin-embedded polished specimen, decalcified paraffin section, and scanning electron microscope specimen from the left, with the red triangle being the posterior part of the joint capsule （Fig.2）

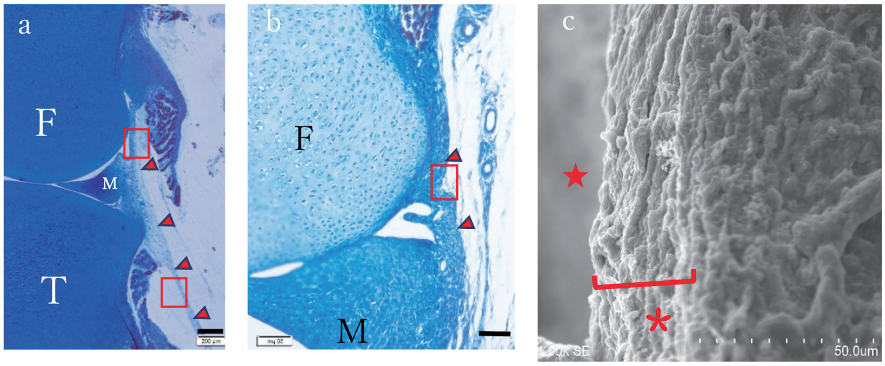

Fig. 2 A: Sagittal section of 1-week-old rat knee joint (non-decalcified resin-embedded polished specimen, TB staining)
B: Sagittal section of 1-week-old rat knee joint (decalcified paraffin section)
C: Sagittal section of 1-week-old rat knee joint (scanning electron microscope specimen)
F: Femur T: Tibia M: Joint meniscus
The red triangle is the posterior part of the joint capsule, and the square is the enlarged image of the synovium.
Scale bar: Fig.a = 200 μm, Fig.b, c = 50 μm.

At 1 weeks, there was no tissue further posterior to the posterior capsule. At 3 weeks of age, adipose tissue appeared posterior to the posterior capsule and was present until 13 weeks of age. However, the adipocytes in the adipose tissue became smaller as the age of the week progressed, the density decreased, and the atrophy of the adipose tissue was observed. Furthermore, the thickness of the joint capsule continues to increase at 7 and 13 weeks of age, which is the second half of the developmental period(Fig. 3).

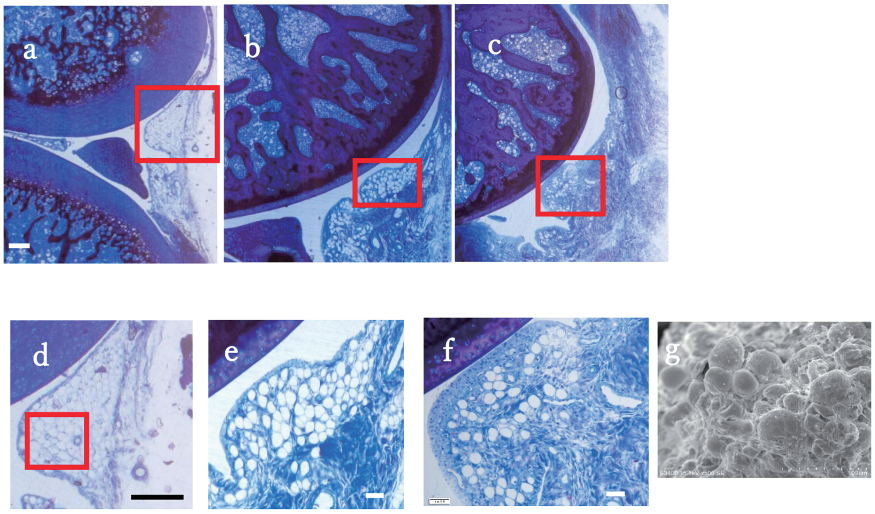

Fig. 3 a-f: Sagittal section of knee joint of rat (undecalcified resin-embedded polished specimen, TB staining)
g: Sagittal section of knee joint of 3-week-old rat (scanning electron microscope specimen)
a: 3 weeks old, b: 7 weeks old, c: 13 weeks old
d, e, f: square magnified image of a, b, c g: square magnified image of d
Scale bar: Fig.a-d = 200 μm, Fig.e, g = 100 μm, Fig.f = 50 μm

For rats at 13 weeks of age, their synovial layers are relatively thick and have two- or three-layer structures near the joint cavity. Along the top, the synovial layers become thinner and thinner, and there are no fat cells. The lower synovial cells appear in cube shape and gradually flatten in the upper direction(Fig.4).

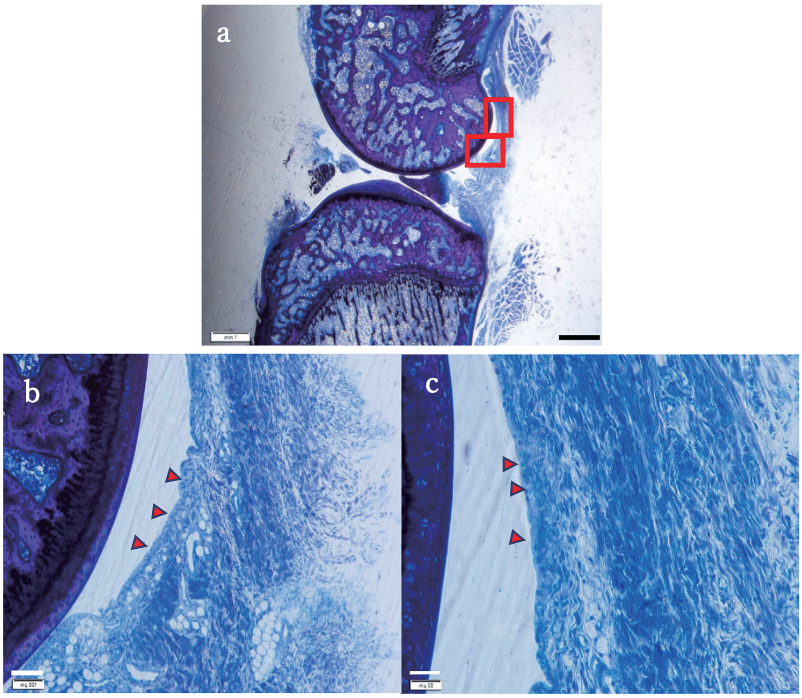

Fig. 4 a: Sagittal section of knee joint of 13-week-old rat (undecalcified resin-embedded polished specimen, TB staining)
b, c: Enlarged image of the square part Red triangle: Synovial cell
scale bar: Fig.a = 1mm, Fig.b = 100 μm, Fig.c = 50 μm

Fine fibers were not visible between the dense fibers at 7 weeks, but reticular fibers were observed between the dense fibers at 13 weeks. The dense fibers are mainly aligned in the axial direction, while the reticular fibers are connected between the dense fiber bundles (Fig. 5).

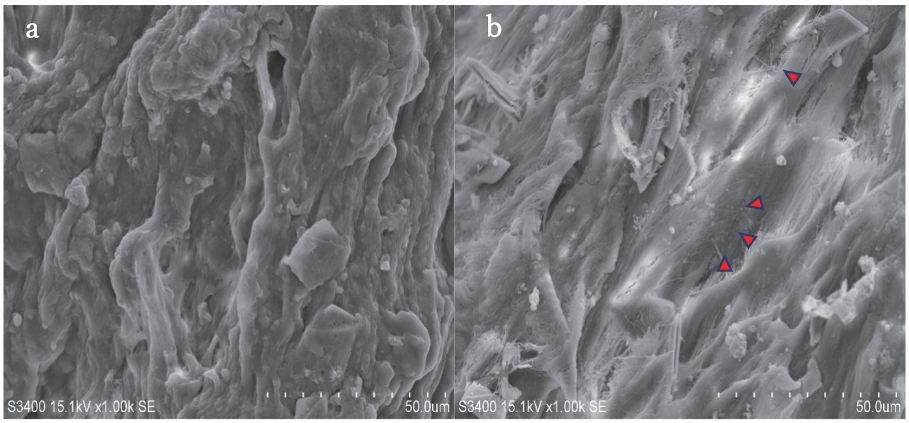

Fig. 5 a: Sagittal section of knee joint of 7-week-old rat rat (scanning electron microscope specimen)
b: Sagittal section of knee joint of 13-week-old rat rat (scanning electron microscope specimen)
Triangular part: thin fiber
scale bar: Fig.a, b = 50 μm

4. Discussion

The knee capsule is a structure that begins from the periosteum and continues to cover the entire joint. The outer part is composed of the fibrous layer and the inner part is composed of the synovial layer.The knee capsule attached to the femur, tibia and patella, and the entire knee joint had a cylindrical shape to enclose the knee joint. The posterior part of the joint capsule is recessed anteriorly, and the anterior-posterior cruciate ligament is attached there. The anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) are located in the knee capsule. The patellar ligament is the most anterior part of the knee capsule. The anterior cruciate ligament extends from the posterior part of the femur to the anterior part of the tibia. Conversely, the posterior cruciate ligament (PCL) is a ligament that connects the posterior part of the tibia to the lateral surface of the medial femur. It is wrapped by a capsule on the outside of the anterior-posterior cruciate ligament. This capsule joins the synovium of the knee capsule, by which it functions as protection and relaxation from the frictional force.

The articular meniscus is an important part of the knee capsule. It acts as a buffer, maintains stability, lubricates and supports loads. The articular meniscus shares 40% to 70% of the load on the knee joint. The remaining 30% to 60% of the force is directly transmitted to the articular cartilage [5].

In this study, a meniscus has been observed in a 1-week-old rat specimen. The process

of meniscus formation is still unclear. According to a report by Smillie, the meniscus during the embryonic period shows an oval structure, and the meniscus is formed by gradually cracking in the central part [18].

By the age of 13 weeks, their own weight and activity have increased, and it is believed that bones and joint capsules have acquired structures that can resist it.

4.1 Synovium

According to a study by Tanaka, the synovial surface of young rabbits is relatively flat and consists of one layer of cells, and the number of surface cells is relatively small [19]. However, in this study, although the 1-week-old synovium has the same thin membranous structure, a magnified observation shows that the synovium is composed of several layers of cells. The synovial joint of the knee is a connective tissue rich in blood vessels. It is composed of the intima of the synovium and the subsynovial layer. The endometrium was formed by combining approximately 1 to 4 layers of synovial cells [9].

The synovial layer separates the joint space from the joint capsule and prevents adhesion between the cartilage and the joint capsule. Not only does it have the function of nourishing cartilage and lubricating joints, but it also maintains joint mobility by producing hyaluronic acid and plasminogen activators [10]. On the other hand, hyaluronic acid secures a certain amount of synovial fluid in the joints during exercise [11].

There are two types of cells that mainly exist in the synovial intima: macrophage-like cells (A cells) and synovial fibroblasts (B cells). A cells swallow endogenous and exogenous foreign bodies in joints and are involved in intra-articular cleansing action. In contrast, B cells are involved in hyaluronic acid secretion or protein synthesis, as well as in the secretion of inflammatory cytokines and collagen degrading enzymes. Substances such as hyaluronic acid, glycoproteins, and collagen fibers are released between synovial cells [8]. According to a report by Mishari, MLS is derived from embryonic progenitor cells and bone marrow [20]. The origin of FLS is not yet clear.

4.2 Fat layer

Adipocytes, dense fiber bundles and sparse fiber bundles were observed in the subsynovial layer. Atsumi divided the joint capsule of a 6-week-old rat into four strata, synovial cell layer, adipocyte layer, dense fiber layer, and sparse fiber layer from the joint cavity side [8]. Suzuki divided the joint capsule of 8-week-old rats into three areas: a dense fiber area, an adipocyte-containing area, and a sparse fiber area[21].

These results are consistent with the results of this study. At 1 week of age, the joint capsule was composed of only several layers of synovial cells, but at 3 weeks of age, which corresponds to the weaning period, adipose tissue appears behind the joint capsule, and it seems to be useful for the buffering action between the femur and tibia. A clear four-layer structure was observed from the age of 7 weeks, which corresponds to puberty. On the other hand, 1-week-old rats have only a synovial layer and a sparse fibrous layer, and at 3 weeks of age, a fat layer appears in the subsynovial layer and becomes a three-layer structure. These structural changes correlate with biomechanical changes.

The first week after birth is still in the lactation period, and it is thought that the amount of activity is reduced because the mother supplies nutrition. Three weeks corresponds to the weaning period, so it is necessary to feed by yourself. Therefore, in order to support the body, a structure that can withstand pressure is required. Adipose tissue is ubiquitous around the knee joint, and the fat cells in the joint are elastic, enhancing joint stability and reducing friction.

Kling classified the adipose tissue of the knee joint as follows. ① Infrapatellar pad of fat posterior to the patellar ligament ② posterior suprapatellar fat pad covering the anterior periosteum of the femoral condyle ③ anterior suprapatellar fat pad between the quadriceps tendon and the anterior wall of the suprapatellar pouch ④ Popliteal fat pad on the back of knee [12].

The adipose tissue has a filling and lubricating action, and as the quadriceps muscle contracts, the pressure of the adipose tissue in the joint also increases, filling the extra space in the joint. This prevents hyperextension of the knee joint, supports excessive friction and pressure, and absorbs vibrations. The subpatellar fat pad is composed of adipose tissue containing adipocytes and collagen fibers. Collagen fibers are located between the amorphous matrices of glycosaminoglycans. The fat body is divided into two parts. The inner layer is the nucleus of the fat pad and has a function of relaxing because of the presence of hard adipose tissue. The outer tissue is a flexible adipose tissue that surrounds the inner tissue [13-14]. The inner layer structure withstands compressive forces and the outer layer structure withstands tensile forces.

On the other hand, capillaries and lymph vessels are also rich in the subsynovial layer, and nerve endings are also present. From a biomechanical point of view, the subpatellar fat pad can move smoothly between the femoral condyle and the joint capsule when activating the knee joint. In addition, the shape, position, and volume of the fat pad change depending on the situation when exercising the knee joint [15-16]. The subpatellar fat pad relieves the

frictional forces generated during exercise by increasing the area of the synovium.

4.3 Fiber layer

From 7 weeks, collagen fibers appear and become thick fibers, resulting in the gradual increase thickness of the joint capsule. Osaki reported that the orientation of collagen fibers greatly affects the function of living tissues, and that the arrangement of collagen fibers is also closely related to motor function[21] . At 7 weeks, the second half of the developmental period, rat activity increases and traction from muscles and bones increases. Collagen fibers are thought to strongly fix the femur and tibia and seek stability.

Ohno made observation on the medial and lateral collateral ligaments using the human knee joint, and found fine fibers orthogonal to the dense fibers [17]. Atsumi found that thin fibers were connected between thick fibers on the outermost layer of the anterior surface of the rat joint capsule [8].

In this study, thin fibers were clearly observed between the thick fiber bundles from 13 weeks. This is because the fibers are arranged horizontally to prevent the femur and tibia from slipping. Fine fibers connect to each other between dense fibers. These are considered to have the same structure as the bone lamellae. It means that it has a function to strengthen the fixation between fibers.

5.Conclusion

The posterior part of the knee capsule of immature rats is composed of only several layers of synovial cells, but adipose tissue appears behind it during the weaning period, and then the adipose tissue atrophies during the more vigorous period, resulting in forming a dense layer of collagen fibers.

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発育に伴うラット膝関節包の構造変化に関する組織学的研究

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要旨

本研究は、不動化に伴う膝関節の可動域低下に及ぼす通電刺激の作用機序を究明する基礎的研究として、種々の成熟段階にある正常なラットを用いて、膝関節包後方部の発育変化の過程を形態学的に検討することを目的とした。材料として１、3、７および13週齢のウィスター系雄性ラット、各8匹を用いた。それらを搬入後、安楽死させて膝関節を摘出し、それらの種々な標本を作成し、関節包の後方部を肉眼的および組織学的に観察した。関節包後方部における滑膜ヒダは１週齢では乏しかったが、週齢が進むに従って厚さと長さが増し、滑膜細胞層の厚さも増した。関節包内のコラーゲン線維は1週齢では疎であったが、増齢に伴って密度が増加した。また、7週齢以降では関節包の深部に太い束のコラーゲン線維が密に集積した層が出現し、それより前方には脂肪細胞が多い層が存在し、逆にそれより後方には線維の疎な層が認められた。関節包後方部には、発育に伴ってコラーゲン線維と脂肪細胞の密度の異なる3層が出現するが、この部位ではそれらを合わせ持つことが、関節包の強度および柔軟性の維持に影響していると思われる。発育に伴って関節包後方部では線維密度が増すのみならず、構造的に異なる３層構造が出現し、それらが関節の加重抵抗性更新に関わるであろうことが示唆された。

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