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MORPHOLOGICAL CHARACTERISTICS OF MANDIBULAR BONE REGENERATION IN AN EXPERIMENT USING NATURAL COLLAGEN

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The purpose of the study was to determine the dynamics of histoarchitectural reconstructions of bone-ceramic regeneration after augmentation of an experimental defect of the lower jaw of a rabbit with an osteoplastic material – natural collagen. Despite the already-known results of using osteoplastic materials in clinical practice, complete and high-quality regeneration of the bones of the maxillofacial area, its mechanisms, and dynamics remain incompletely understood and require clarification and detailing. Sexually mature male rabbits aged 6–7 months, weighing 2.5–3 kg, were used for the study. The control group included animals with a bone tissue defect that healed under a blood clot. The experimental group consisted of rabbits in which the bone defect was filled with natural collagen. Control of the post-traumatic state of bone tissue in the area of the defect was carried out for 84 days. Ultrastructural changes were studied by scanning electron microscopy. Three parameters were calculated to determine changes in the composition of the regenerate. The data were analyzed using Student's t-test. The difference at $p<0.05$ was defined as statistically significant. The study of the surface relief features of the experimental lower jaw bone defect after implantation with Col-C material in animals revealed numerous regenerative changes after injury. It differed from reparative osteogenesis in the control group. Most osteons that regenerate near the outer bone plate do not differ from the typical structure of the native bone. However, in contrast to the group of control animals, the bone plates between the neighboring osteons were weakly structured. A morphometric study of the relative volume of the osteoplastic material in the regenerate established a gradual decrease in the material's content until its almost complete bioresorption.

Key words: rabbits, mandible, maxillofacial apparatus, regeneration, osteoplastic materials, collagen, morphometry, scanning electron microscopy.

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МОРФОЛОГІЧНА ХАРАКТЕРИСТИКА РЕГЕНЕРАЦІЇ КІСТКИ НИЖНЬОЇ ЩЕЛЕПИ В ЕКСПЕРИМЕНТІ ПРИ ЗАСТОСУВАННІ НАТУРАЛЬНОГО КОЛАГЕНУ

Метою дослідження було визначити динаміку гістоархітектурних перебудов кістково-керамічного регенерату після аугментації експериментального дефекту нижньої щелепи кролика остеопластичним матеріалом – натуральним колагеном. Незважаючи на вже відомі результати застосування остеопластичних матеріалів у клінічній практиці, повна та якісна регенерація кісток щелепно-лицевої ділянки, її механізми та динаміка залишаються не до кінця вивченими, потребують уточнення і деталізації. Для дослідження використовували статевозрілих кроликів-самців віком 6–7 місяців, вагою 2,5–3 кг. До контрольної групи увійшли тварини з дефектом кісткової тканини, який загоювався під кров'яним згустком. Експериментальну групу складали кролики, у яких кістковий дефект заповнювали натуральним колагеном. Контроль посттравматичного стану кісткової тканини в ділянці дефекту здійснювали впродовж 84 діб. Ультраструктурні зміни вивчали методом скануючої електронної мікроскопії. Для визначення змін складу регенерату використовували підрахунок трьох параметрів. Дані проаналізували за допомогою t-критерію Стьюдента, різницю при $p<0,05$ визначили як статистично значущу. Дослідження особливостей рельєфу поверхні експериментального кісткового дефекту нижньої щелепи після імплантації тваринам матеріалу Кол-К дозволило виявити численні регенераційні зміни, що відбувалися після нанесення травми та відрізнялися від репаративного остеогенезу в контрольній групі. Більшість остеонів регенерату поблизу зовнішньої кісткової пластинки за своєю будовою не відрізнялась від типової будови материнської кістки, проте, на відміну від групи контрольних тварин, між сусідніми остеонами містилися слабо структуровані за геометрією кісткові пластинки. Морфометричне вивчення відносного об'єму остеопластичного матеріалу в регенераті встановило поступове зниження вмісту матеріалу до майже повної його біорезорбції.

Ключові слова: кролики, нижня щелепа, зубощелепний апарат, регенерація, остеопластичні матеріали, колаген, морфометрія, скануюча електронна мікроскопія.

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New technologies for restoring bone tissue are prioritized in dentistry and traumatology [14]. Defects of the jaws resulting from infections, trauma, tumors, or congenital abnormalities are common. The literature reviews show that surgical intervention using bone substitutes is necessary in such cases [5, 9]. The most abundant protein in the bone matrix is type I collagen, which forms a triple helix structure that provides structural support and mechanical strength [4], biocompatibility, cell adhesion, and osteoconductivity [7]. Despite its advantages, collagen has disadvantages, such as low mechanical strength, rapid decomposition, and lack of osteoinductivity, which significantly prevent its widespread use in clinical practice. [7, 8]. The process of collagen synthesis in bone tissue occurs mainly by fibroblasts and osteoblasts. Given that collagen itself is not osteoinductive [7], successful bone tissue replacement and the provision of necessary vascularization require collagen-based materials to be modified and combined with other bioactive substances, growth factors, mesenchymal stem cells, osteoblasts, osteoclasts, endothelial

cells, and others. Combining collagen with therapeutic agents, such as antibiotics, is also promising [13]. Thus, bone grafting remains one of the most common methods for treating bone defects. The choice of material for bone grafting depends on numerous factors, including availability, defect size, biomechanical properties, ease of processing, cost, ethical considerations, biological properties, and potential complications [3, 12].

The purpose of the study was to determine the dynamics of histoarchitectural rearrangements of bone-ceramic regeneration after transplantation of natural collagen into an experimental defect of the lower jaw of a rabbit.

Materials and methods. The study was performed on 45 male rabbits aged 6–7 months, weighing 2.5–3.0 kg. 5 animals were intact. 20 animals were in the control group, and 20 were in the experimental group. Animals of the control and experimental groups were given general anesthesia by intraperitoneal injection of Thiopenate (Bropharma, Ukraine) at the rate of 25 mg/kg of the animal's body weight at the level of the edentulous area of the alveolar part of the mandible. A 4x3 mm bone defect was created using a dental drill. The control group included animals with a bone tissue defect that healed under a blood clot. The experimental group consisted of rabbits with bone defects filled with natural collagen Collacone (Botiss Dental, Germany), Col-C. It is produced in the form of a collagen cone. The state of bone tissue in the area of the applied defect was examined 1, 7, 14, 21, 28, 35, 56, and 84 days after the injury.

The dynamics of histoarchitectural reconstructions of bone tissue in the area of the experimental defect of the lower jaw was studied by scanning electron microscopy, performed on a JEOL T220A scanning electron microscope at the laboratory of physical research methods in the geology of I. Franko LNU. To photograph the surface of the samples, magnification x 15-200 was used, and the accelerating voltage in all experiments was equal to 20 kV [6, 11].

The production of histological slides of mandibular bone fragments with osteotropic material was performed by a generally accepted method [1], visualized using a light microscope UlabXSP-137TLED (PRC) and photographed with an XCAM-1080 P camera (PRC). The calculation of the relative volume of bone tissue, osteoplastic material, and connective tissue in the regeneration determined changes in its composition. Morphometric parameters of bone tissue in the control group were compared with those in animals treated with Col-C.

Analysis of the distribution histogram, indicators of asymmetry and extinction coefficients, and the Shapiro-Wilk test were used to determine the subordination of the obtained data to the normal distribution law. The results of each group at different points in time were subject to the normal distribution law. They are presented in the form of M±m, where M is the arithmetic mean, and m is the standard deviation of the mean. The Student's t-test was used to determine the probable differences between the average values of parameters in different periods of the experiment and to compare the data of the control group with those of the experimental group during the same observation period. The difference between groups was considered significant at $p<0.05$.

All animals were kept in vivarium conditions, and the procedures related to housing, care, labeling, and all other manipulations were carried out in compliance with the provisions of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1985), “General ethical principles of animal experiments”, adopted by the First National Congress on Bioethics (Kyiv, 2001), Law of Ukraine No. 3447 – IV “On the Protection of Animals from Cruelty Treatment” by the EU Council Directive 2010/63/EU on compliance with regulations, laws, and administrative provisions of the EU States on the protection of animals used for scientific purposes.

Results of the study and their discussion. Using a scanning electron microscope, we studied the microrelief of the surface of the experimental lower jaw bone defect after the Col-C material was implanted in animals. We observed several significant features of the regeneration process, which differed from reparative osteogenesis in the control group. One day after the experimental injury, damaged blood microvessels with thrombi were identified on the smooth surface of the trepanation hole in the compact cortical plate. Around them, hemorrhages from different areas were found. Between the damaged trabeculae of cancellous (spongy) bone tissue at the edges of the defect of the native bone, a moderate number of small fragments of different shapes were found, along with perivascular accumulations of erythrocytes, leukocytes, and fibrin masses (Fig. 1). A significant accumulation of exudate was observed between the fibrous elements of the matrix of the Col-C implanted material. At the end of the first day of the post-traumatic period, the signs of perivascular and intracellular edema in those structures located near the experimental jaw defect were significantly pronounced.

One week after the application of the experimental defect and the implantation of the Col-C material, the formation of numerous osteoid tubercles and outgrowths, which varied in size and shape and

almost completely covered the surface of the trabeculae, occurred on the tissue surface of the damaged osteons and bone trabeculae of the native bone. Perivascular edema, leukocyte infiltration, and other signs of inflammation in the defect area during the first two weeks were intense and only partially reduced by the end of the third week after the intervention. Numerous small foci of desmal osteogenesis contained diffusely located fibroblast cells, and their number significantly exceeded that in the control group of animals. In the peripheral areas of the regenerate, the newly formed trabeculae between the fibrous fragments of the Col-C implanted material connected with the bumpy trabeculae of the native cancellous bone. In the vast majority of observations, there was a fairly clear demarcation between the surface of the fibrous implant, covered with newly formed osteoid trabeculae, and the native bone from the side of the wall of the experimental shaft. Deep areas of the regenerate contained a moderate number of bloods microvessels surrounded by active fibroblasts and dense spicule-like connective tissue outgrowths.

During the 4th to 5th weeks after the implantation of the Col-C material, moderate manifestations of inflammation remained in the area of the experimental defect – perivascular edema, leukocyte infiltration, and isolated diapedesis hemorrhages. By the end of the 5th week, the symptoms above were almost entirely reduced. On the periphery of the regenerate, osteoid trabeculae of various shapes and sizes, predominantly radial in orientation and with tight anastomosis, were visible. Covered with newly formed trabeculae, the surface of the regenerate closely adjoined the native bone. Individual small fibrous remains of osteotropic material were found in moderate quantities. In the deep zones of the experimental defect, areas of woven bone tissue varying in area were found, in the thickness of which primitive blood microvessels and individual fragments of resorbed Col-C material, integrated into newly formed trabeculae were densely located (Fig. 2).

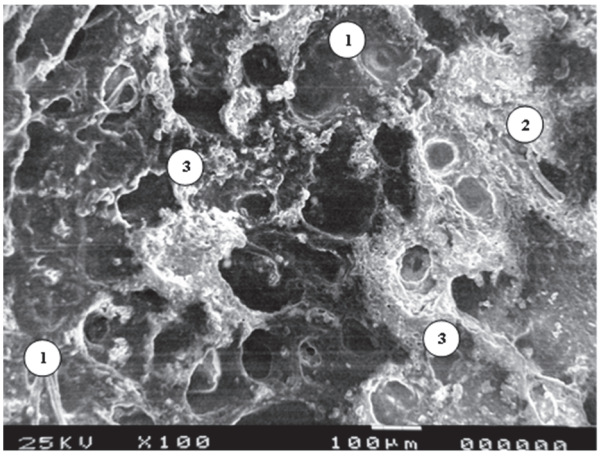

Fig. 1. Electronic scan of the bone defect zone of the lower jaw of a rabbit 1 day after injury and filling of the defect with Col-C material. ×100. 1 – damaged surface of cancellous bone of the side wall of the shaft, 2 – fibrin masses, 3 – damaged trabeculae.

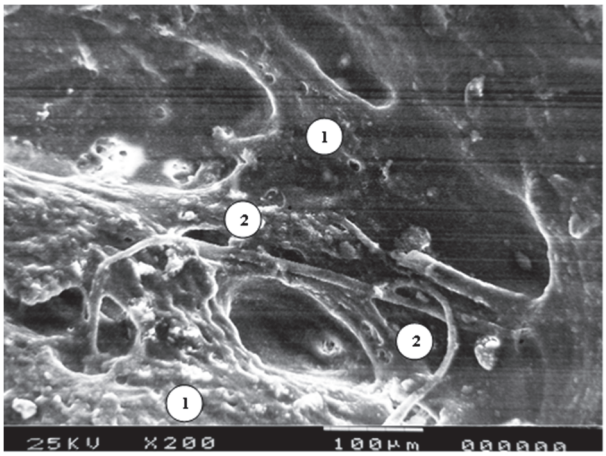

Fig. 2. Electronic scan of the bone defect zone of the mandible of a rabbit 5 weeks after injury and filling of the defect with Col-C material. ×200. 1 – newly formed trabeculae, 2 – remnants of the fibers of the implanted material.

A large number of osteoblasts formed numerous clusters between osteogenic islands and hemocapillary. Moderate in number and variable in size, areas of the deep zone of the regeneration, along with the remains of the implanted material, contained cells of desmal osteogenesis with a significant number of cells of the fibroblastic lineage. Osteoblasts predominated quantitatively in the peripheral newly formed trabeculae between the fragmented Col-C fibers. Still, a moderate number of primary osteocytes significantly exceeded the content of these cells observed in the study of control group samples. A distinct heteromorphic tuberosity was visualized on the surface of most of the newly formed trabeculae. A moderate number of osteoclasts were found at the border of the regenerative material, along with lamellar bone tissue on the cortical plate of the native bone. Unlike the control group, after 5 weeks of the experiment, signs of desmal osteogenesis remained in the surface localization of the regeneration. Also, on the border of tight adhesion of the woven bone tissue of the newly formed trabeculae to the osteons of the native bone, osteoclasts with different sizes and different degrees of activation were found near the bioresorption zones of the regenerate along with the fibrous remains of the Col-C implanted material.

After 8 weeks of the experiment, the trabeculae composition was dominated by woven bone tissue with a small percentage of primary osteoblasts at the depth of the applied bone defect on the regeneration zone's periphery. Osteoclasts were rarely detected near microvessels in the middle of desmal osteogenesis. The border between the newly formed trabeculae and the native cancellous bone had the appearance of a strip of varying width, which contained thin osteoid formations attached to the trabeculae (Fig. 3).

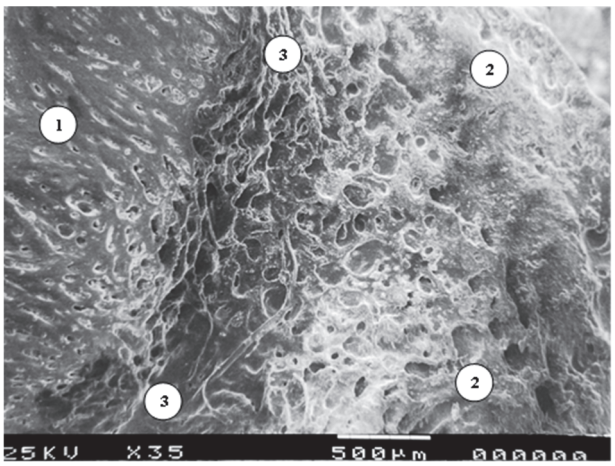

Fig. 3. Electronic scan of the bone defect zone of the mandible of a rabbit 3 weeks after injury and filling of the defect with Col-C material. ×35. 1 – native bone of the wall of the experimental shaft, 2 – relief of newly formed bone trabeculae on the regeneration surface, 3 – demarcation zone.

Inside the regenerate, a heteromorphic spongy structure was observed. It consisted partly of primitive bone plates and, to a large extent, of woven bone tissue, with a significant content of fibrous fragments of the implanted material. Connective tissue areas around microvessels were found more often than in animals of the control group in the form of layers enriched in randomly grouped collagen fibers. Osteoblasts predominated among osteogenic cells and were distributed diffusely, in a moderate amount. The newly formed immature osteons with initial signs of lacuna-tubular architecture were determined at the regeneration boundary with the native bone's outer bone plate. In contrast to the control group, a small number of osteoclasts was determined in areas of woven bone tissue in isolated regions of trabeculae remodeling.

Twelve weeks after the experimental defect and Col-C material implantation, the cancellous bone of the alveolar process contained trabeculae consisting mainly of lamellar tissue. In the inner zones of the regenerate, small cells of woven bone tissue and individual unresorbed fragments of the implanted material were present. The microrelief of the surface of the trabeculae near the native cancellous bone in the peripheral areas of the regenerate was smooth, without signs of intensive osteogenesis. Activated osteoclasts and osteogenic cells were found in fewer numbers and less densely than observed after 8 weeks of the experiment. In general, after applying the Col-C material, most osteons that regenerate near the outer bone plate did not differ from the typical structure of the native bone in terms of their structure. However, unlike the control animals' group, there were weakly structured bone plates between the neighboring osteons.

During the morphometric study of the dynamics of changes in the relative volume of bone tissue during the regeneration of the experimental defect in the control group, active growth of the parameter was determined from the first to the fifth week after the defect was applied (Table 1). In particular, the relative content of bone tissue in the regeneration after 2 weeks of the experiment was 2.75 times ($p<0.05$) higher than the value of the 1st week; after 3 weeks, the parameter increased by 60.4 % ($p<0.05$) relative to the level of the previous term; after 4 and 5 weeks – by 68.0 % ($p<0.05$) and 32.0 % ($p<0.05$), respectively. In the period from the 5th to the 8th week, the increase in the relative volume of bone tissue in the regenerate formed under the blood clot was 24.5 % ($p<0.05$). Later, until the 12th week of the experiment, changes in the parameter did not have statistical significance compared to the value of the 8th week, stabilizing at 70.3±4.8 %.

Table 1

Dynamics of changes in the relative volume of bone tissue, osteoplastic material, and connective tissue in the regenerate (%), M±m

Term	Bone tissue		Material	Connective tissue	
	Control	Col-C	Col-C	Control	Col-C
1 day	3.7±0.6	4.8±0.7	80.7±7.2	6.9±0.4	7.3±0.6
7 days	5.6±0.8#	7.9±0.9#	65.3±5.4#	14.7±1.1#	16.3±1.4*#
14 days	15.4±1.2#	21.3±2.4*#	34.9±3.8#	30.5±2.4#	44.8±3.8*#
21 days	24.7±1.8#	39.0±3.4*#	22.5±2.4#	56.1±3.5#	42.9±3.6*
28 days	41.5±3.4#	52.1±3.8*#	16.1±2.3#	41.8±3.1#	35.0±2.7*#
35 days	54.8±3.7#	64.7±4.0*#	10.5±1.4#	34.2±2.3#	26.3±2.1*#
56 days	68.2±4.5#	74.9±5.7#	5.8±0.7#	20.7±1.7#	18.4±1.6#
84 days	70.3±4.8	76.8±6.1	1.8±0.7#	24.5±2.0	16.1±1.5*

Note: * – the difference is statistically significant when compared with the control group; # – the difference is statistically significant when compared with the previous term of the experiment.

In the experimental group of animals, where the plastic defect was performed using Col-C material, a slow increase in the relative volume of bone tissue in the regeneration was observed in the first three weeks after implantation. In particular, 1 week after the injury, the parameter's value did not change significantly relative to the indicator of the first day and did not differ substantially from the control level.

Two weeks after the implantation of Col-C material, there was an increase in the parameter by 92.4 % ($p<0.05$) compared to the first week, but this increase was inferior to the control group by 33.8 % ($p<0.05$). After 3 weeks, a similar situation was observed: the increase in bone tissue content by 77.5 % ($p<0.05$) compared to the previous period was inferior in intensity to the reference indicator by 26.7 % ($p<0.05$). After 4 weeks of the experiment, the studied parameter sharply increased – 2.3 times relative to the value of the third week – reaching the level of the control group. From the 5th to the 8th week, the studied parameter continued to grow moderately and stabilized at a level that was not statistically significantly different from the parameters of the control group. After 12 weeks of the experiment, the relative volume of bone tissue in the regenerate formed after the implantation of Col-C material was 67.3±4.1 %, which was also not significantly different from the control level.

Quantification of the relative volume of osteoplastic material in the regenerate at the stages of augmentation of the experimental defect after the implantation of the Col-C material determined the general dynamics of changes, which consisted in a gradual decrease in the content of the material until its almost complete bioresorption. During the first week after implantation, the parameter did not change to a statistically significant degree relative to the value after 1 day. From the second week, the reduction of material content in the regenerate was 22.2 % ($p<0.05$) compared to the first week. After 3, 4, and 5 weeks of the experiment, the value of the parameter decreased by 20.9 % ($p<0.05$), 33.7 % ($p<0.05$), and 31.2 % ($p<0.05$), respectively, in comparison with an earlier term. 8 weeks after Col-C implantation, a two-fold reduction of the parameter was observed. After 12 weeks of the experiment, the regenerate's material content approached the minimum, only 2.5±0.4 % of its total volume.

A morphometric study of the relative volume of connective tissue in regenerating the experimental defect in the control group made it possible to establish the phase nature of the dynamics of parameter changes. In the first three weeks of the experiment, an active increase in the content of the connective tissue component in the regeneration was observed. In particular, 1 week after the injury, the parameter increased by 2.1 times ($p<0.05$) relative to the value after 1 day; after 2 weeks of the experiment – by 107.5 % ($p<0.05$) compared to the value of the 1st week; after 3 weeks, the parameter increased by 83.9 % ($p<0.05$) relative to the level of the previous term and reached the highest value of 56.1±3.5 %. In the further dynamics of changes in the content of connective tissue, a gradual decrease of the indicator was observed after 4 weeks – by 25.5 % ($p<0.05$) relative to the peak value of the 3rd week; after 5 and 8 weeks – by 18.2 % ($p<0.05$) and 39.5 % ($p<0.05$), respectively, compared to the previous period of the study. From the 8th to the 12th week, the relative volume of connective tissue in the regenerate formed under the blood clot did not change statistically significantly and stabilized at 24.5±2.0 %.

According to the results of determining the relative volume of the connective tissue in the regenerate, 1 week after the implantation of the Col-C material, a two-fold increase in the parameter was observed in comparison with the level of the first day of the experiment, but such an increase did not lead to its significant predominance over the control level. However, 2 weeks after the injury, after a sharp increase in the content of connective tissue in the regenerate by 116.8 % ($p<0.05$) compared to the first day of the experiment, the parameter reached a value that was 23.0 % ($p<0.05$) exceeded the value of the control group corresponding to the term. 3 weeks after the implantation of the Col-C material, the parameter did not change to a statistically significant degree compared to the previous period. At the same time, in the control group, the parameter increased to 56.1±3.5 %, which by 38.9 % ($p<0.05$) exceeded the parameter of the experimental group. During the fourth and fifth weeks of the experiment, the regenerate gradually reduced its connective tissue content. After 4 weeks, the parameter of the experimental group was inferior to the value of the 3rd week by 25.2 % ($p<0.05$), corresponding to the control value by 27.8 % ($p<0.05$). 5 weeks after implantation of the material, the parameter was inferior to the value of the 4th week by 26.8 % ($p<0.05$), corresponding to the control value by 35.4 % ($p<0.05$). In terms of 8–12 weeks after the Col-C material implantation, the connective tissue content in the regenerate did not change significantly compared to the indicator of the previous term and did not statistically significantly differ from the control level.

Bone grafting is a common procedure in dentistry, traumatology, and regenerative medicine, and it is widely used in various clinical situations [2, 4]. It is used both in periodontal surgery and during tooth implantation, as well as sinus lifting, cell preservation, and many other procedures [10, 12]. The use of collagen in the regeneration of bone tissue has taken a significant step forward. Thanks to improvements in production and purification methods, modern collagen products preserve the most natural structure and have the least ability to cause an immune reaction. The 100 % natural collagen product Collacon (Col-C) is a resorbable material that is widely used to stimulate wound healing and preserve the alveolar process. It promotes post-extraction and encourages blood clot formation with subsequent reorganization.

The studies showed that the data we obtained will complement the existing research results on using collagen-based osteoplastic materials and help create innovative approaches in regenerative medicine. This will ultimately benefit patients who need the treatment mentioned above.

Conclusions

1. In the experimental group of animals, where the plastic defect was performed using Col-C material, several significant features of the regeneration process were observed, which differed from reparative osteogenesis in the control group.

2. After applying the Col-C material, most osteons that regenerate near the outer bone plate did not differ from the typical structure of the native bone in terms of their structure. However, unlike the control animals' group, weakly structured bone plates existed between the neighboring osteons.

3. Morphometrically, it was determined that in the first three weeks after implantation, the Col-C material caused a slow increase in the relative volume of bone tissue in the regenerate, in contrast to the active growth of this parameter in the control group.

4. In the dynamics of changes in the relative volume of connective tissue, its content in the regenerate did not change significantly compared to the parameter of the previous period and did not differ statistically significantly from the control level.

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