EXPERIMENTAL RESEARCHES

RESTORATION OF X-RAY BONE DENSITY WHEN REPLACING CORTICAL PLATE DEFECTS WITH A TISSUE-ENGINEERED CONSTRUCT IN THE EXPERIMENT

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ABSTRACT

Over the past decade, in global practice, the frequency of using high-resolution multi-layer spiral computed tomography (MSCT) for assessing the state of cancellous and cortical bone tissue has significantly increased. Using high-resolution MSCT makes it possible to assess X-ray bone density at various times after replacement of cortical plate defects with osteoplastic materials.

The aim of the research. *To study the restoration of cortical bone density in the area of osteoplasty using tissue-engineered construct in the experiment.*

Materials and methods. *In an in vivo experiment on New Zeland White (NZW) rabbits, perforation defects of cortical bone were formed in the femoral diaphysis. Three study groups were set up: group 1 – without bone defect replacement; group 2 – with bone defect replacement with deproteinized cancellous bone; group 3 – with bone defect replacement with tissue-engineered construct based on deproteinized cancellous bone with stromal vascular fraction of adipose tissue. Follow-up periods were 2, 4 and 6 weeks after the surgery. The X-ray density of cortical bone tissue was measured in Hounsfield units (HU). Fragments of deproteinized human cancellous bone were used alone and in combination with the stromal vascular fraction of NZW rabbit adipose tissue as a bone-replacing material for bone defect replacement.*

Results. *Cortical plate density the in the area of the defect in the group 3 by the week 6 is on average 1.3 times lower than that of the intact cortical plate and corresponds to D1 according to Misch classification. Cortical plate density in the area of the defect on the side of medullary canal by the week 6 in the group 3 corresponds to D1 according to Misch classification and is equal to 1351.25 ± 221.18 HU (1052; 1805), which is 1.5 times higher than in group 2 (D2 according to Misch classification; $p < 0.05$). The obtained results indicate an earlier restoration of X-ray bone density when using a tissue-engineered construct (group 3) compared to the same indicators in groups 1 and 2.*

Key words: *X-ray density, tissue-engineered construct, MSCT, stromal vascular fraction of adipose tissue, bone defect, deproteinized cancellous bone*

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ВОССТАНОВЛЕНИЕ РЕНТГЕНОВСКОЙ ПЛОТНОСТИ КОСТИ ПРИ ЗАМЕЩЕНИИ ДЕФЕКТОВ КОРТИКАЛЬНОЙ ПЛАСТИНЫ ТКАНЕИНЖЕНЕРНОЙ КОНСТРУКЦИЕЙ В ЭКСПЕРИМЕНТЕ

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РЕЗЮМЕ

За последнее десятилетие в общемировой практике для оценки состояния губчатой и кортикальной кости значительно возросла частота применения мультиспиральной компьютерной томографии (МСКТ) с высоким разрешением, позволяющим оценивать рентгеновскую плотность кости в различные сроки после замещения дефектов кортикальной пластины остеопластическими материалами.

Цель исследования. *Изучить восстановление плотности кортикальной кости в области остеопластики тканеинженерной конструкцией в эксперименте.*

Материалы и методы. *В эксперименте in vivo на кроликах линии New Zeland White (NZW) в диафизарной части бедренной кости сформированы перфорационные дефекты кортикальной пластины. Сформированы три группы исследования: 1-я группа – без заполнения дефекта; 2-я группа – с заполнением дефекта депротеинизированной губчатой костью; 3-я группа – с заполнением тканеинженерной конструкцией на основе депротеинизированной губчатой кости с стромально-васкулярной фракцией жировой ткани. Сроки наблюдения составили 2, 4 и 6 недель после операции. Плотность кортикальной пластины измеряли в единицах Хаунсфилда (HU). В качестве костно-замещающего материала для заполнения костных дефектов использовали фрагменты депротеинизированной губчатой кости человека изолированно и в сочетании со стромально-васкулярной фракцией жировой ткани кролика линии NZW.*

Результаты. *Плотность кортикальной пластины в области дефекта в 3-й группе к 6-й неделе в среднем в 1,3 раза ниже аналогичного показателя интактной кортикальной пластины и при этом соответствует D1 по классификации Misch. Плотность кортикальной пластины в области дефекта со стороны костномозгового канала к 6-й неделе в 3-й группе соответствует D1 по Misch и составляет 1351,25 ± 221,18 HU (1052; 1805), что в 1,5 раза выше, чем во 2-й группе (D2 по Misch; $p < 0,05$). Полученные результаты свидетельствуют о более раннем восстановлении рентгеновской плотности костной ткани при использовании тканеинженерной конструкции (3-я группа) по сравнению с показателями 1-й и 2-й групп.*

Ключевые слова: *рентгеновская плотность, тканеинженерная конструкция, МСКТ, стромально-васкулярная фракция жировой ткани, костный дефект, депротеинизированная губчатая кость*

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INTRODUCTION

In replacing bone tissue defects, in case of restrictions associated with the use of autografts, practical specialists (orthopaedic traumatologists, maxillofacial surgeons and others) prefer materials made of allogeneic and xenogeneic bone since they are widely available and have distinctive properties [1, 2]. This is why the development of new materials and tissue-engineered constructions (TECs) for bone tissue repair is a promising area of activity [2–4]. To assess the changes in X-ray density of bone tissue when using TEC from allogenic bone tissue, the main method of investigation is morphological. However, it has limitations with regard to "vital" macro- and microscopic assessment of bone tissue [1].

Over the last decade, the frequency of high-resolution MSCT application for the assessment of cancellous and cortical bone tissue has increased significantly in the global practice [1, 5, 6]. Multi-spiral computed tomography (MSCT) method together with specialised software allows not only quantitative assessment of bone density, but also obtaining a spatial image with the possibility of 3D-modelling [1]. The ability to visualise changes in X-ray density of bone tissue and assess bone and surrounding soft tissue allows for a 'vital' bone assessment. Therefore, it is relevant to study these parameters at different times after bone defects replacement by obtaining the necessary number of tissue contrast gradations [7–9].

THE AIM OF THE STUDY

To study the restoration of cortical bone density in the area of osteoplasty using tissue-engineered construct in the experiment.

MATERIALS AND METHODS

The study was performed on 24 sexually mature male rabbits of the New Zealand White (NZW) line weighing 2500-2800 g. The animals had a veterinary quality certificate of health status and were kept under identical standard drinking and feeding conditions (GOST R ISO 10993-2-2009). Fragments of deproteinized cancellous bone of human isolated and in combination with stromal vascular fraction of adipose tissue of rabbit NZW line were used as bone replacement material for filling bone defects.

According to the current standards, 3 perforation defects of the cortical bone were formed in the diaphyseal part of the femur of both hind legs of each animal under general combined anaesthesia in sterile conditions using sterile surgical instruments. Three study groups were formed:

- Group 1 – perforation defect of the cortical plate in sections of the diaphysis of the femur without replacement;
- Group 2 – perforation defect of the cortical bone plate in sections of femur diaphysis being filled with fragments of deproteinized cancellous bone (DPCB);
- Group 3 – perforation defect of the cortical bone plate in sections of the femoral shaft with being filled with tissue-engineered construction based on deproteinized cancellous bone with stromal vascular fraction (SVF) of adipose tissue (Patent US10512659B2).

Animals were removed from the experiment by overdose of ether anesthesia at 2, 4, and 6 weeks after surgery.

X-ray density of compact bone in the osteoplasty area at all follow-up periods was assessed by MSCT with an Aquilion Prime 2018 tomograph (Toshiba, Sapon Medical Systems, Japan). Sagittal slices of the bone regenerate area were processed in the multiplanar reconstruction mode (MPR, multiplanar reconstruction); slice parameters – 120 kV, 50 mA, Bone filter, slice thickness 0.5 mm. During the MSCT examination of the distal tibia of rabbits, the bone density from the medullary canal and periosteum sides, as well as the intact cortical plate density, were assessed. Cortical plate density was measured in Hounsfield units (HU, Hounsfield unit). Using the K-Pacs v. 1.6.0 software package designed for work with DICOM, ROI (Region of Interest) tool, the cortical plate density was measured by statistical evaluation of averaged values for each study group in three areas: the 1st corresponded to the area of bone defect on the periosteum side; the 2nd – to the area on the medullary canal side; the 3rd – to the area of intact cortical plate. According to the HU values, bone tissue was classified according to Misch [10].

Descriptive statistics of continuous defect measures were calculated as median [first quartile; third quartile] (M [Q1; Q3]), mean ± standard deviation (MEAN ± SD), minimum and maximum value (min-max). The nonparametric Wilcoxon test was used to compare the parameters of the defect areas with those of the intact cortical plate; differences at $p < 0.05$ were considered statistically significant. Statistical calculations were performed in the RStudio IDE (version 2022.07.2, build 576; RStudio PBC, USA) in the R language (version 4.1.3, https://www.R-project.org; Austria).

RESULTS

In the 1st study group 2 weeks after surgery, bone defects with signs of poorly expressed filling with bone tissue corresponding to the D4 type according to Misch classification were detected (Table 1).

At the same time, the mean X-ray density of bone in the area of bone defect on the medullary canal side was 27 ± 6.32 HU (14; 40) and on the periosteum side was 202.92 ± 65.35 HU (66; 296). In the area of intact bone plate, X-ray bone density measured 1880.88 ± 475.65 HU (1258; 3200) and was greater compared to other areas of measurement ($p < 0.001$).

At 4 weeks after surgery, the X-ray density of the bone tissue was found to correspond to the Misch D3 values

TABLE 1

BONE DENSITY INDICES ACCORDING TO MSCT DATA IN THE 1ST STUDY GROUP (BONE DEFECT WITHOUT REPLACEMENT)

Parameter name	Follow-up period: 2 weeks M [Q1; Q3] MEAN ± SD (min–max)	Follow-up period: 4 weeks M [Q1; Q3] MEAN ± SD (min–max)	Follow-up period: 6 weeks M [Q1; Q3] MEAN ± SD (min–max)
Areas (measurement points)			
on the side of the medullary canal (area 1), HU	26.5 [24.75; 29.25] 27 ± 6.32 (14–40)	14 [2.97; 27] 15.18 ± 17.21 (–12–47)	29 [–46.25; 81.25] 30.5 ± 78.01 (–84–197)
on the periosteum side (area 2), HU	225 [155; 253.25] 202.92 ± 65.35 (66–296)	907 [628; 983] 824.92 ± 252.64 (349–1242)	1302.5 [696; 1459] 1103.25 ± 440.15 (421–1678)
Intact cortical plate (area 3), HU	**1792 [1417.5; 2083]** **1850.88 ± 475.65** **(1258–3200)**	**2182.5 [2073.5; 2444]** **2220.33 ± 311.95** **(1508–2850)**	**2184.5 [2069; 2252]** **2178.67 ± 268.51** **(1726–2791)**
According to Misch (area 1 / area 2 / area 3)	4 / 4 / **1**	4 / 3 / **1**	4 / 2 / **1**
Comparison of measurement points (*p*)			
area 1 – area 2	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*
area 1 – area 3	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*
area 2 – area 3	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*

Note. * – statistically significant differences ($p < 0.05$).

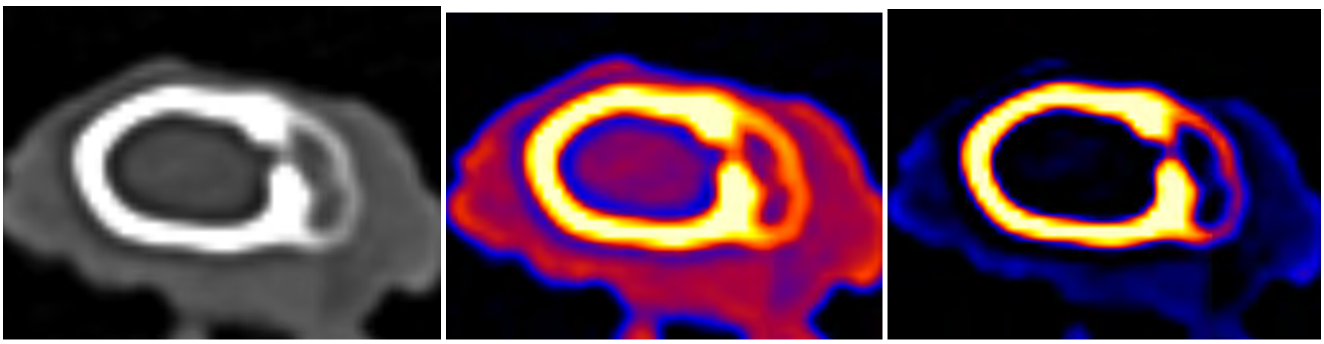

FIG. 1.
MSCT data at week 6 in the group 1 without bone defect replacement (processed in K-Pacs software v. 1.6.0, magnification ×10)

in the defect zone on the periosteum side and to the D4 values on the medullary canal side. Herewith, the mean X-ray density value on the medullary canal side (15.18 ± 17.21 HU (–12; 47)) was not significantly different from that noted at the previous study period. The X-ray density value for the defect area from the periosteal side was

824.92 ± 252.64 HU (349; 1242), which was 4.1 fold higher than the one obtained after 2 weeks.

After 6 weeks, bone density corresponded to D2 in the area of the bone defect from the periosteum side

TABLE 2

BONE DENSITY INDICES ACCORDING TO MSCT DATA IN THE 2ND STUDY GROUP (BONE DEFECT WITH DEPROTEINIZED CANCELLOUS BONE REPLACEMENT)

Parameter name	Follow-up period		
	2 weeks (*n* = 8) M [Q1; Q3] MEAN ± SD (min–max)	**4 weeks (*n* = 8) M [Q1; Q3] MEAN ± SD (min–max)**	**6 weeks (*n* = 8) M [Q1; Q3] MEAN ± SD (min–max)**
Areas (measurement points)			
on the side of the medullary canal (area 1), HU	580.5 [492; 639.25] 575.25 ± 130.04 (383–759)	519.5 [352.5; 660] 529 ± 244.42 (195–958)	777 [683.5; 1032.5] 874.38 ± 283.51 (575–1336)
on the periosteum side (area 2), HU	406.5 [37.25; 601] 322.38 ± 370.1 (–188–727)	1399 [1368; 1409.75] 1388.75 ± 32.73 (1329–1430)	1490.5 [1351.75; 1609.5] 1426.25 ± 326.81 (742–1774)
Intact cortical plate (area 3), HU	**1749.5 [1678; 1870.25] 1826.25 ± 255.89 (1558–2344)**	**2143.5 [2094; 2339.75] 2183.5 ± 226.68 (1770–2462)**	**2269 [2078; 2672.5] 2329.12 ± 414.44 (1659–2852)**
According to Misch (area 1 / area 2 / area 3)	3 / 3 / **1**	3 / 2 / **1**	2 / 1 / **1**
Comparison of measurement points (*p*)			
area 1 – area 2	$p = 0.195$	$p = 0.008$*	$p = 0.008$*
area 1 – area 3	$p = 0.012$*	$p = 0.008$*	$p = 0.008$*
area 2 – area 3	$p = 0.012$*	$p = 0.008$*	$p = 0.008$*

Note. * – statistically significant differences ($p < 0.05$)

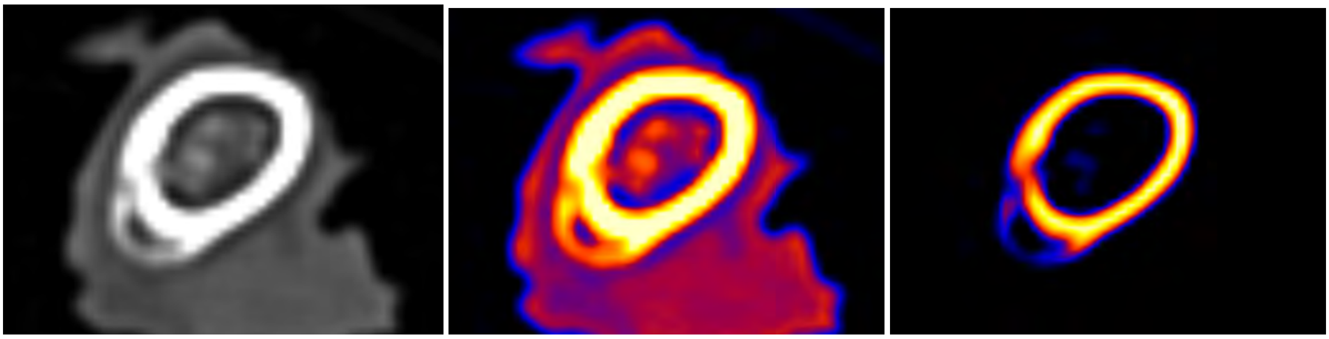

FIG. 2.

MSCT data at week 6 in the group 2 with bone defect replacement by deproteinized cancellous bone (processed by K-Pacs v. 1.6.0 software, magnification ×10) and D4 from the medullary canal side. As the follow-up period extended, a 1.3-fold increase in the X-ray density of bone in the defect area from the periosteum side and a slight increase from the medullary canal side were noted (Fig. 1). The density of the intact bone plate measured as 2178.67 ± 268.51 HU (1726; 2791) and had differ-

TABLE 3

BONE DENSITY INDICES ACCORDING TO MSCT DATA IN THE 3RD STUDY GROUP (BONE DEFECT WITH REPLACEMENT BY DEPROTEINIZED CANCELLOUS BONE WITH STROMAL VASCULAR FRACTION OF ADIPOSE TISSUE)

Parameter name	Follow-up period		
	2 weeks (*n* = 8) M [Q1; Q3] MEAN ± SD (min–max)	**4 weeks (*n* = 8) M [Q1; Q3] MEAN ± SD (min–max)**	**6 weeks (*n* = 8) M [Q1; Q3] MEAN ± SD (min–max)**
Areas (measurement points)			
on the side of the medullary canal (area 1), HU	560 [480.5; 664.25] 572.38 ± 178.07 (322–834)	1028 [897.5; 1204.25] 1043.62 ± 194.32 (789–1271)	1363 [1235; 1391.25] 1351.25 ± 221.18 (1052–1805)
on the periosteum side (area 2), HU	435.5 [347.25; 467] 413.38 ± 145.55 (158–649)	1260 [1220; 1393.5] 1294.12 ± 110.38 (1149–1442)	1330.5 [1294.75; 1383.25] 1360.75 ± 120.82 (1235–1580)
Intact cortical plate (area 3), HU	**1437 [1412.75; 1701.25] 1613.38 ± 344.39 (1353–2172)**	**2303 [2155; 2542] 2341.12 ± 213.97 (2113–2622)**	**1773 [1669; 1847.25] 1773.62 ± 149.36 (1548–1992)**
According to Misch (area 1 / area 2 / area 3)	3 / 3 / **1**	2 / 2 / **1**	1 / 1 / **1**
Comparison of measurement points (*p*)			
area 1 – area 2	$p = 0.148$	$p = 0.039$*	$p = 0.547$
area 1 – area 3	$p = 0.012$*	$p = 0.021$*	$p = 0.045$*
area 2 – area 3	$p = 0.012$*	$p = 0.021$*	$p = 0.023$*

Note. * – statistically significant differences ($p < 0.05$)

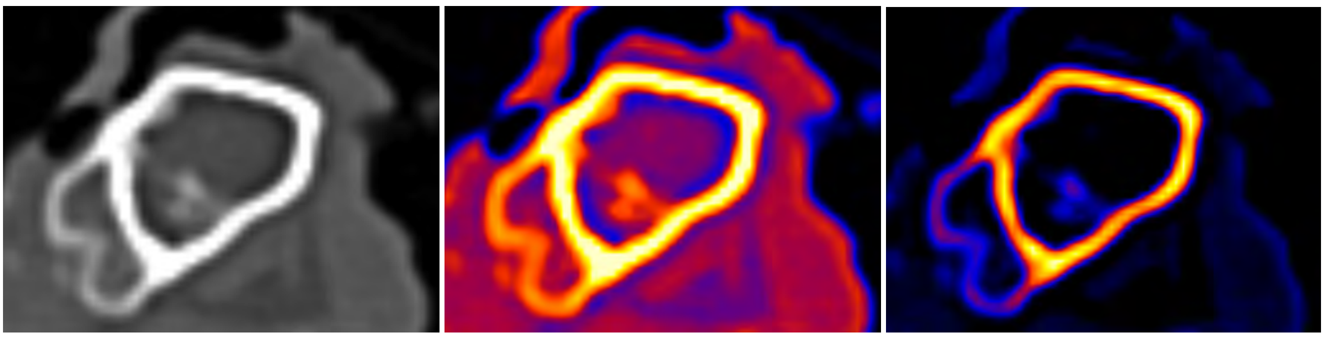

FIG. 3.
MSCT data at week 6 in the group 3 with bone defect replacement using tissue-engineered construction based on deproteinized cancellous bone with autologous stromal-vascular fraction as cellular material (processed by K-Pacs v. 1.6.0 software, magnification ×10)

ences with respect to the rest of the measurement areas ($p < 0.001$). The dynamics of X-ray bone density indices in the studied areas of the bone defect in group 1, demonstrates a gradual increase and approaching to the intact bone density indices.

The X-ray density of bone on both the periosteal and medullary canal sides was consistent with D3 in the 2nd study group 2 weeks after surgery (Table 2).

After 4 weeks, an increase in bone density indices was observed in all areas of measurement. After 6 weeks, X-ray density in the defect filling areas along the medullary canal side corresponded to the D3–D2 type and increased 1.6-fold from week 4 to week 6 (Table 2; Fig. 2). For the area of defect replacement from the periosteum side, a slight increase in X-ray density was observed from week 4 to week 6 of the study.

In the 3rd group 2 weeks after surgery, the X-ray density of bone in the area of bone defect replacement corresponded to the D3 type and the indices in the 2nd group during the similar study period. The mean bone density from the medullary canal side measured as 572.38 ± 178.07 HU (322; 834) and from the periosteum side as 413.38 ± 145.55 HU (158; 649) (Table 3).

At 4 weeks after surgery, X-ray density of the bone corresponded to D2 in the defect filling area on both the periosteal side (1294.12 ± 110.38 HU (1149; 1442)) and the medullary canal side (1043.62 ± 194.32 HU (789; 1271)). Besides, an increase in these indices was observed compared to the indices after 2 weeks by 3.1 and 1.8 times, respectively (Table 3). In the area of intact cortical bone plate, the mean X-ray density was slightly lower as compared to the indices at other follow-up periods and corresponded to the D1 type. This may be caused by the individual bone density characteristics of the selected line of animals. The difference between the values of the studied parameters in the area of bone defect replacement and the X-ray bone density of the intact cortical plate area was statistically significant ($p = 0.021$).

After 6 weeks, X-ray bone density in the area of bone defect replacement (Fig. 3) corresponded to D1 with evenly distributed compact and cancellous bone substance. The mean X-ray bone density indices in the area of TEC bone defect filling were: from the periosteum side, 1360.75 ± 120.82 HU (1235; 1580), and from the medullary canal side, 1351.25 ± 221.18 HU (1052; 1805) (Table 3). There was a 3.3-fold and 2.3-fold increase in these indices from week 2 to week 6, respectively.

The X-ray density indices of the intact cortical bone plate after 6 weeks measured as 1773.62 ± 149.36 HU (1548; 1992), corresponded to D1 (Table 3; Fig. 3), and were not significantly different from the X-ray bone density indices in the defect replacement area from the medullary canal side and the periosteum side ($p = 0.045$ and $p = 0.023$, respectively). This may indicate an earlier recovery of X-ray bone density in the defect replacement area if TEC is applied.

DISCUSSION OF RESULTS

According to the literature, three main factors influence the rate of bone remodelling and regeneration. The first factor – replacement of the bone defect with bone-replacement material – reduces the time of bone regeneration in the defect area. If bone-replacement material obtained from the head of the human femur bone was used, according to the MSCT findings, the rearrangement of the implanted material was already observed by the day 45 [1, 11]. However, these findings have not been confirmed morphologically.

The second factor having an influence on the rate of bone tissue regeneration may be the proregenerative effect of periosteum, which has a pronounced osteogenic potential induced by cellular elements [12].

The third factor affecting the rate of bone repair is the presence of cellular elements in the bone replacement material or tissue-engineered construction [6, 7, 12].

According to the conducted study, the variability of values of radiological density of intact cortical plate in rabbits of NZW line was revealed, which corresponds to the data of literature describing the variability of values of X-ray density of intact cortical plate ranging from 1080 ± 439 to 2890.0 ± 63.1 HU [8, 9, 13, 14].

As the follow-up period increased in all groups, the indices of X-ray bone density in the area of bone defect replacement both on the side of the medullary canal and on the side of the periosteum approached the indices of X-ray bone density of the intact cortical plate.

In group 3 at week 6 of the study, X-ray bone density in the defect replacement area corresponded to type D1 – thick compact bone. Meanwhile, the X-ray bone density index in the area of bone defect replacement from the medullary canal side was 1351.25 ± 221.18 HU (1052; 1805) and was 1.5 times higher than in the group 2, where the X-ray bone density index remained comparable to that of D2–D3 ($p < 0.05$).

CONCLUSION

Replacement of the perforation defect of the cortical plate density of the rabbit femur with tissue-engineered construction made of deproteinized cancellous bone in combination with stromal vascular fraction of adipose tissue leads to faster restoration of bone density in comparison with the unfilled defect and isolated use of deproteinized cancellous bone, as evidenced by the indices of radiological bone density at MSCT examination.

Ethical review

Extract No. 016/23 from the minutes of the meeting of the local Ethics Committee of the Novosibirsk Research Institute of Traumatology and Orthopedics named after Ya.L. Tsivyan No. 006/23 dated 31.07.2023.

Conflict of interest

The authors of this article report the absence of obvious and potential conflict of interests related to the publication of materials.

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