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Bone defect management with tissue-engineered constructs based on deproteinized cancellous bone: an experimental study

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Abstract

Background Management of bone defects with autologous bone grafting has always been the "gold standard" but it is not always possible to use it for a number of reasons. Preprocessed materials of biological and non-biological origin were developed as an alternative. A new branch of these materials is tissue-engineered constructs that fully imitate autologous bone in required volume. **Aim** is to study *in vivo* the possibility of using deproteinized human cancellous bone tissue as a matrix for creating tissue-engineered constructs. **Methods** The study was carried out on 24 NZW line rabbits, since this line has a fully characterized stromal-vascular fraction formula (SVF). The study design included 3 groups. Fikst group (control) had surgical modeling of bone defects in the diaphysis of the contralateral femur without reconstruction; Group 2 had bone defect reconstruction using fragments of a deproteinized cancellous bone graft; group 3 underwent bone defect reconstruction using fragments of deproteinized cancellous bone matrix along with the autologous adipose tissue SVF (obtained according to ACP SVF technology). Animals were sacrificed with ether anesthesia at 2, 4 and 6 weeks after the operation and subsequent histological study followed. **Result** During all periods of the study, the newly formed bone tissue volume density in the 3rd group (reconstruction with deproteinized human cancellous bone + stromal-vascular fraction) was 1.78 times higher ($p < 0.001$) than in the first group (bone defect without reconstruction), 1.21 times higher ($p < 0.001$) than in the 2nd group (reconstruction with deproteinized cancellous bone alone). The dynamics of changes in the mature bone tissue volume density was similar to those of the newly formed bone tissue. **Discussion** The comparative analysis of reparative processes using a tissue engeneered construst based on deproteinized cancellous human bone with adipose tissue stromal vascular fraction revealed that the use of these bone substitute materials contributes not only to the early activation of reparative regeneration of the main structural elements of bone tissue at the site of bone defect, but also their timely differentiation. **Conclusion** The use of deproteinized cancellous bone matrix combined with stromal-vascular fraction to create a tissue-engineered construct could unleash several regeneration mechanisms and accelerate the process of bone defect site repair, compared with 1st and 2nd group of study.
Keywords: Bone defect; bone matrices; deproteinized cancellous bone; bone defect reconstruction; adipose tissue stromal-vascular fraction

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Научная статья

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Замещение костных дефектов тканеинженерной конструкцией на основе депротеинизированной губчатой кости: экспериментальное исследование

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Аннотация

Актуальность. Замещение дефектов кости при помощи аутологичной кости всегда было «золотым стандартом», однако по ряду причин ее использование не всегда возможно. В качестве альтернативы были разработаны материалы биологического и небиологического происхождения с их предварительной обработкой. Новым направлением таких материалов являются тканеинженерные конструкции, способные полностью имитировать аутологичную кость в необходимом объеме. **Цель**. Изучить *in vivo* возможность использования депротеинизированной губчатой костной ткани человека в качестве матрицы для создания тканеинженерных конструкций. **Материалы и методы**. Исследование проведено на 24 кроликах линии NZW, поскольку данная линия имеет полностью охарактеризованную формулу стромально-васкулярной фракции (СВФ). Дизайн исследования включает 3 группы: 1-я группа (контрольная) – хирургическое моделирование костных дефектов в областях диафиза контралатеральной бедренной кости без реконструкции; 2-я группа – замещение костного дефекта фрагментами депротеинизированной губчатой кости; 3-я группа – замещение костного дефекта с использованием фрагментов депротеинизированной губчатой кости совместно с аутологичной СВФ жировой ткани (полученную по технологии ACP SVF). Животных выводили из эксперимента под эфирным наркозом через 2, 4 и 6 недель после операции, с последующим гистологическим исследованием. **Результаты**. Во все сроки исследования объемная плотность новообразованной костной ткани в 3-й группе (реконструкция депротеинизированной губчатой костью человека со стромально-васкулярной фракцией) была в 1,78 раза выше ($p < 0,001$), чем в 1-й группе (дефект костной ткани без реконструкции), в 1,21 раза выше ($p < 0,001$), чем во 2-й группе (реконструкция депротеинизированной губчатой костью). Динамика изменения объемной плотности зрелой костной ткани была аналогична динамике изменения объемной плотности новообразованной костной ткани. **Обсуждение**. Сравнительный анализ репаративных процессов с использованием тканеинженерной конструкции на основе депротеинизированной губчатой кости совместно со стромально-васкулярной фракцией жировой ткани показал, что применение данного костнозамещающего материала способствует не только ранней активации репаративной регенерации основных структурных элементов костной ткани в области замещения дефекта, но и своевременной их дифференцировки. **Выводы**. Использование депротеинизированной губчатой кости совместно со стромально-васкулярной фракцией для создания тканеинженерной конструкции позволяет реализовать ряд процессов регенерации и ускорить процесс восстановления дефекта кости по сравнению с 1-ой и 2-ой группой исследования.
Ключевые слова: костный дефект, депротеинизированная губчатая кость, замещение костного дефекта, стромально-васкулярная фракция жировой ткани

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INTRODUCTION

Bone defect repair remains to be a difficult prom in the field of reconstructive surgery. Despite several trends under study, autogenous bone grafting still is a "gold standard" [1, 2, 3]. However, for a number of reasons, it is not always possible to completely fill in a bone defect with the graft [4, 5, 6]. As an alternative to autogenous bone graft, bone substitute materials have been used. They can have different origin: biological or non-biological one. One of the ways of bone reconstructive technologies development is the use of combined tissue engineered constructs together with the patient's own cell material. Such construct design is able to fully imitate autogenous bone tissue in the required volume [7]. Currently, according to literature data, the most suitable in terms of its properties as the basis (or matrix) for such constructs is bone allograft [3, 8, 9]. Nevertheless, allogeneic bone cannot unleash the stimulation of the osteogenesis processes [3]. That is why autologous non-immunogenic cell material is strongly needed [7].

Aim is to study in vivo the possibility of using deproteinized human cancellous bone tissue as a matrix for creating tissue-engineered constructs.

MATERIAL AND METHODS

The study was carried out on 24 NZW line rabbits, since this line has a fully characterized stromal-vascular fraction formula (SVF) [10, 11, 12, 13, 14, 15]. The study complies with international standards and ethical principles for laboratory research ISO 10993-2, ISO 10993-6-2021. The design of the study included 3 groups. The first group (control) had surgical modeling of bone defects in the areas of the diaphysis of the contralateral femur without reconstruction, similar to the study groups; 2nd group had surgical modelling of the femoral diaphysis defect with its reconstruction using fragments of a deproteinized cancellous human bone graft (matrix); 3rd group underwent surgical modeling of femoral diaphysis defect with its reconstruction using fragments of deproteinized cancellous human bone matrix together with the autologous adipose tissue stromal-vascular fraction. Stromal-vasular fraction was obtained according to ACP SVF technology (Patent US10512659B2). Animals were sacrificed with ether anesthesia at 2, 4 and 6 weeks after the operation. Under the standard conditions, the material was harvested for subsequent histological assessment to evaluate the bone substitute materials local effect on living tissues and the implementation of reparative osteogenesis in the bone defect reconstruction area.

Adipose tissue material was taken through the dorsal paravertebral approach during the main surgical procedure. It is for this localization in adult rabbits that the largest amount of beige adipose tissue is typical [11, 16]. After obtaining adipose tissue, fragments of cancellous deproteinized bone matrices, 5 × 5 mm in size, were installed paravertebral and subcutaneously to determine their impact on living tissues.

To assess the effectiveness of reparative osteogenesis in the bone reconstruction site, fragments of deproteinized cancellous bone were implanted into simulated bone defects according to the study design. To confirm the absence of variability in the morphological manifestations of bone tissue reparative regeneration in the conditions of each individual animal, an additional defect was formed in the femur diaphyseal part on each limb.

After the harvesting, study samples were fixed in 10 % neutral buffered formalin solution for 72 hours, followed by decalcification in the Richmann-Gelfand-Hill solution for 10 days at a temperature of 20 °C. After standard histological processing in a series of alcohols and xylene increasing concentration, bone tissue samples were embedded in paraffin blocks, followed by making serial sections 4-5 μm thick and staining them with hematoxylin and eosin. For differentiated quantitative assessment of "mature" and emerging connective tissue in the study samples, histological sections were stained according to Van Gieson and impregnated with silver. Light microscopy with obtaining overview micrographs was carried out on an OLYMPUS CX 43 laboratory microscope with an OLYMPUS UC 90 camera (Olympus Medical Systems Corp., Japan). Morphometric study of histological samples of matrices heterotopic and orthotopic implantation sites was performed using the ImageJ software (version 1.53o, 2022, Wayne Rasband and contributors National Institutes of Health, USA) at 200 magnification. The numerical density of the vessels (Nai), the percentage of implantation zone full-blooded vessels (%), the volume density of mature collagen fibers (Vv%), the volume density of argyrophilic connective tissue fibers (Vv%), the volume density of mature and newly formed bone tissue (Vv%) were evaluated in histological sections.

The obtained morphometric data were statistically processed using the RStudio program (version 2022.02.1 Build 461 – © 2009-2022 RStudio, Inc., USA) in the R language (version 4.1.3 (2022-03-10), Vienna, Austria). Comparison of continuous scores between the groups was performed by a non-parametric unpaired Mann – Whitney U-test. The distribution bias was calculated with the 95 % confidence interval. Categorical scores were compared by Fisher's exact two-sided test. Correction for multiple testing error when comparing categories was carried out using the Benjamini – Hochberg method, the difference was considered statistically significant if $p < 0.001$.

RESULTS

From the 2nd week of the study, light microscopy of the heterotopic implant fixation area histological skin samples revealed the formation of a thick-walled connective tissue capsule with weak infiltration of the walls by macrophages and mononuclear leukocytes between the dermis and the muscle. Between the fibers of the connective tissue, a large number of small thin-walled blood vessels without signs of hemocirculatory disorders were revealed. Fragments of mplanted deproteinized cancellous bone matrices were represented by mature bone tissue. In the tissues, perifocal to the area of implantation of bone matrices, the formation of a cellular inflammatory infiltrate was not detected. Visual examination of the experimental bone defects modeling tissues areas with orthotopic

reconstruction using bone-substituting materials showed no signs of a local inflammatory reaction in all animals.

The assessment of reparative osteogenesis according to hystological sections is presented at the Table 1.

From the 2nd week, a significant prevalence of indicators of the vessels numerical density of groups 2 and 3 relative the control group 1 ($p < 0.001$) was determined. There were no significant differences between group 2 and 3 at this stage ($p = 0.699$). A significant prevalence of the group 3 indicators over those in group 2 was noted from the 4th week of the study ($p < 0.001$) and persists by the 6th week ($p < 0.001$) (Fig. 1).

Table 1

Histological study results of reparative osteogenesis in orthotopical reconstruction of bone defects with different types of bone substitute material (M ± m)

Study parameters	Study groups								
	1st group (control)			2nd group (deproteinized cancellous bone graft)			3rd group (deproteinized cancellous bone matrix with SVF)		
	Timeline (week of study)								
	2	4	6	2	4	6	2	4	6
Vessels numerical density, Nai	5.61 ± 1.5	8.25 ± 1.5	16.66 ± 5.7	10.43* ± 3.5	18.73* ± 2.2	23.70* ± 6.8	10.40* ± 3.41	20.36*,** ± 4.5	26.31*,** ± 7.9
Full-blooded vessels percentage, %	54.44 ± 0.2	78.82 ± 0.2	96.58 ± 0.1	38.3* ± 0.2	75.49* ± 0.2	92.20* ± 0.1	81.19*,** ± 0.2	64.45* ± 0.2	97.37 ± 0.3
Mature collagen fibers volume density, Vv%	5.15 ± 0.6	7.08 ± 1.1	12.68 ± 2.5	6.35* ± 3.8	8.83* ± 2.53	9.26* ± 1.6	6.88* ± 1.5	9.30* ± 1.1	10.68*,** ± 1.6
Argyrophilic connective tissue fibers volume density, Vv%	7.33 ± 0.7	11.83 ± 1.1	14.19 ± 2.4	7.25 ± 1.8	9.95* ± 1.6	10.03* ± 2.2	9.66*,** ± 1.3	10.23* ± 1.9	10.65* ± 2.1
Mature bone tissue volume density, Vv%	2.88 ± 0.7	6.43 ± 0.8	8.98 ± 1.6	5.98* ± 2.8	8.81* ± 1.5	12.83* ± 1.5	8.63*,** ± 2.2	11.51*,** ± 2.5	14.58*,** ± 2.2
Newly formed bone tissue volume density, Vv%	3.81 ± 0.7	6.43 ± 0.8	9.26 ± 2.1	6.11* ± 3.2	9.81* ± 1.6	13.53* ± 2.7	9.51*,** ± 2.2	12.95*,** ± 2.71	16.43*,** ± 2.1

* – statistically significant differences from indicators in the control group, $p < 0.001$; ** – statistically significant differences from indicators in the 2nd group, $p < 0.001$

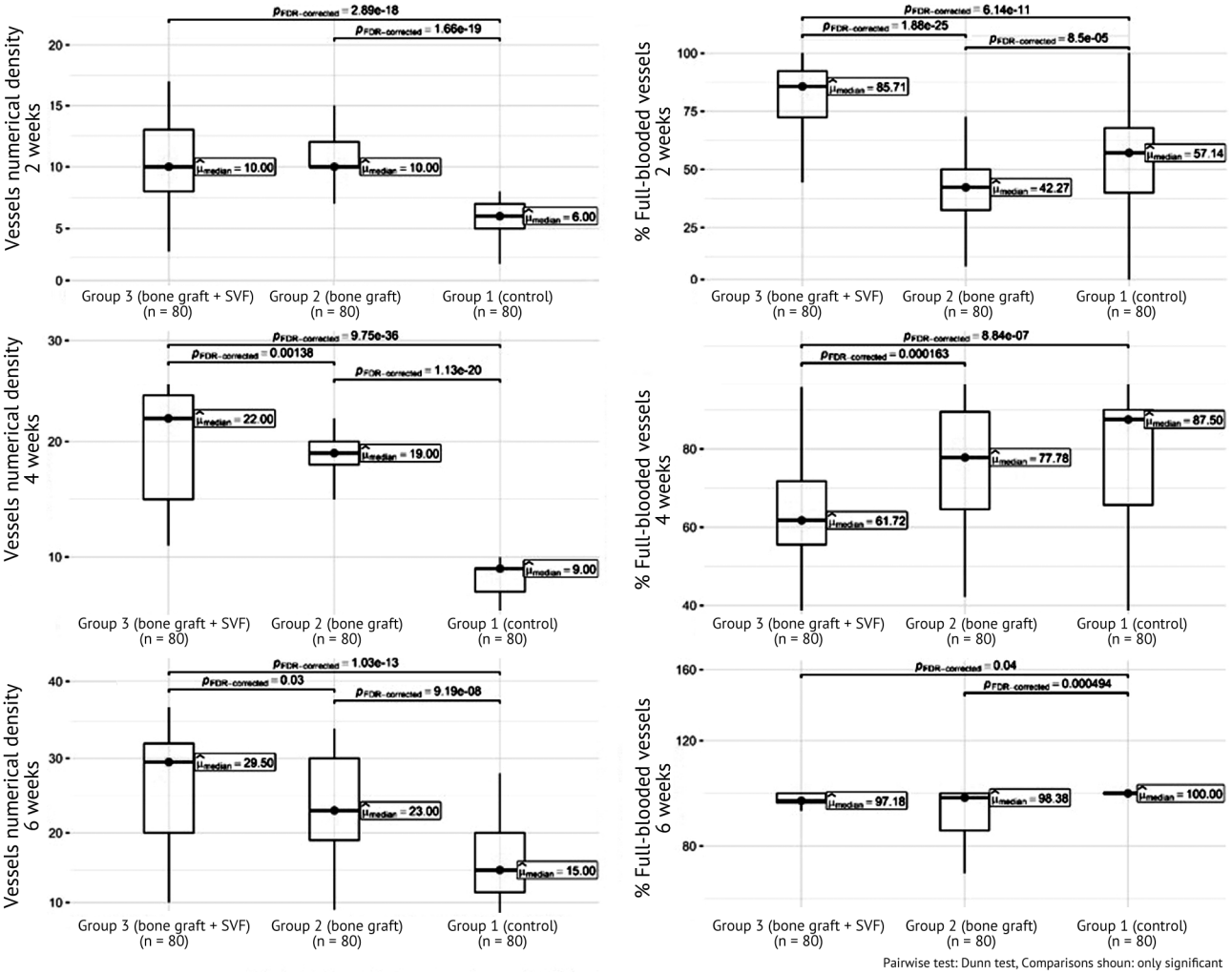

Fig. 1. Vessels numerical density and full-blooded vessels percentage for each group of the study at 2, 4 and 6 weeks

By 6 weeks, the percentage of full-blooded vessels progressively increases in all groups. Only a small decrease in this parameter in group 2 compared to the control group 1 was determined as statistically significant ($p < 0.001$) (Fig. 1 and 2).

The value of the newly formed bone tissue volume density progressively increased from the 2nd to the 6th week of the study in the 1st group – 1.6 times, in the 2nd group – 2.2 times and in the 3rd group – 1.7 times (Fig. 3 and 4). During all periods of observation, the newly formed bone volume density in the 3rd group was on average 2.1 times higher than in the 1st study group ($p < 0.001$), and on average 1.36 times higher than in the 2nd group ($p < 0.001$).

The mature bone tissue volume density in the study samples increased from the 2nd to the 6th week in all groups; in the 2nd and 3rd groups the indicators were greater than in the 1st group of the study during all period of study. The dynamics of changes in the mature bone tissue volume density was similar to those of the newly formed bone tissue. The studies indicated a more active process of differentiation of the newly formed bone tissue starting from the 4th week of the study.

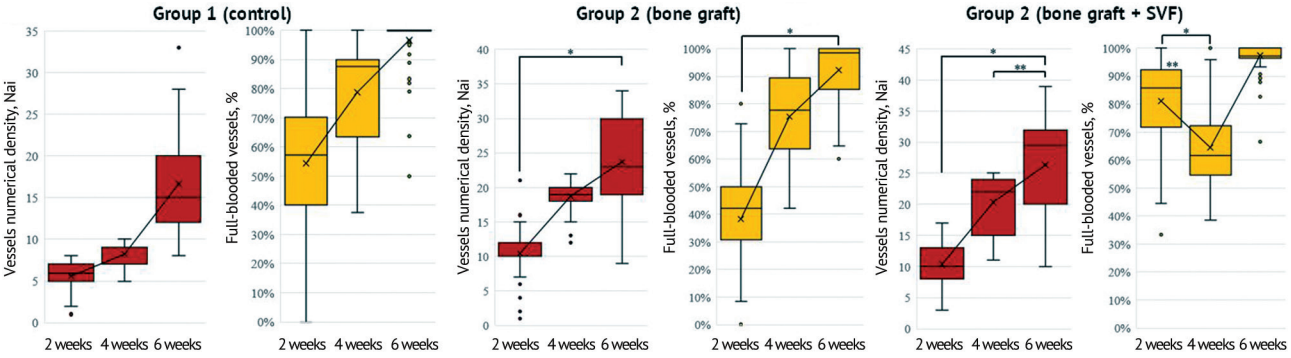

Fig. 2. Diagram showing vessels numerical density (left) and full-blooded vessels percentage (right) for each group of the study at 2, 4 and 6 weeks

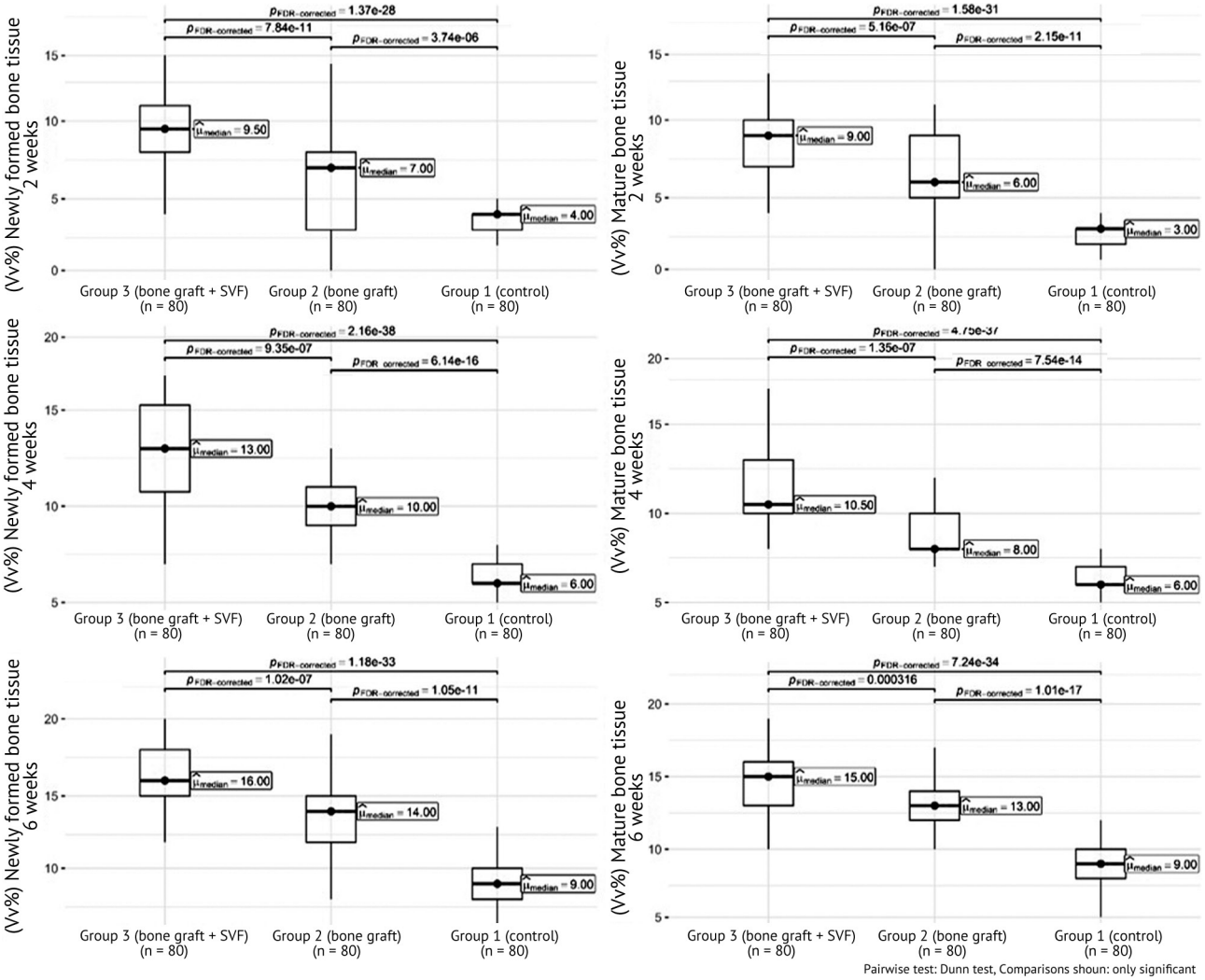

Fig. 3. Volume density of newly formed bone tissue (Vv%) and mature bone tissue (Vv%) for each group of the study at 2, 4 and 6 weeks

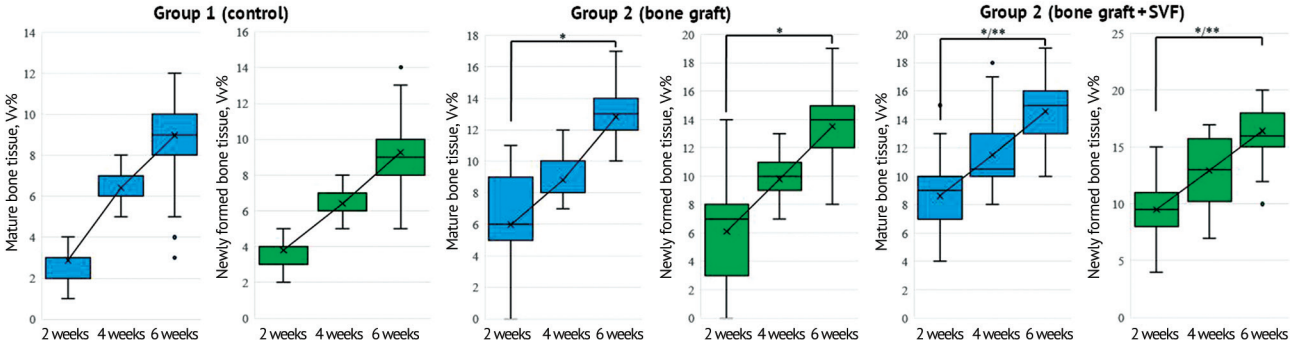

Fig. 4. Diagram showing volume density of newly formed bone tissue (right) and mature bone tissue (left) for each group of the study at 2, 4 and 6 weeks

DISCUSSION

The choice of the rabbit animal model for this study was justified by a similar type of reparative osteogenesis, the Haversian type in this species of mammals and humans [11, 17]. This allows the results of this study to be extrapolated to humans.

The choice of deproteinized cancellous human bone tissue as a bone matrix is justified by scientific literature data and the results of our previously conducted studies, which revealed the properties of this material, allowing it to be used as an independent bone-replacing material and considered as a bone matrix for creating efficient tissue engineering constructs [3, 18].

In the case of using a construct based on a deproteinized bone matrix containing an autologous material that can have impact on bone tissue regeneration, all four processes of bone tissue regeneration are switched on: osteoblastic, osteoinductive, osteoconductive, and stimulated osteogenesis (Fig. 5).

Despite the fact that in this study the bone matrices used are xenogenic for animals, starting from the 2nd week macro- and microscopic morphological signs of a local inflammatory reaction of soft tissues and rejection of bone matrices in areas of their heterotopic implantation were absent.

The adipose tissue stromal-vascular fraction, isolated and processed according to the standard method, was chosen as a biologically active component for creating a tissue-engineered construct based on a deproteinized cancellous bone matrix, enabling to exclude an additional experimental quantitative assessment of the cell composition of the obtained fraction [14, 15, 19].

This is justified by the cell composition of the fraction and the cells properties themselves - adipose tissue stem cells, endothelial and blood vessels smooth muscle cells and their precursors, fibroblasts, macrophages, T-lymphocytes, pericytes and other cells that cause a pronounced regenerative potential, anti-inflammatory effect and immunoregulatory activity. Also, the stromal-vascular fraction factors stimulate the formation of the vascular network, which contributes to the regeneration of bone tissue [2, 15, 20, 21, 22].

The comparative analysis of reparative processes using a deproteinized cancellous human bone tissue matrix and its combination with adipose tissue stromal vascular fraction revealed that the use of these bone substitute materials contributes not only to the early activation of reparative regeneration of the main structural elements of bone tissue at the site of bone defect, but also their timely differentiation.

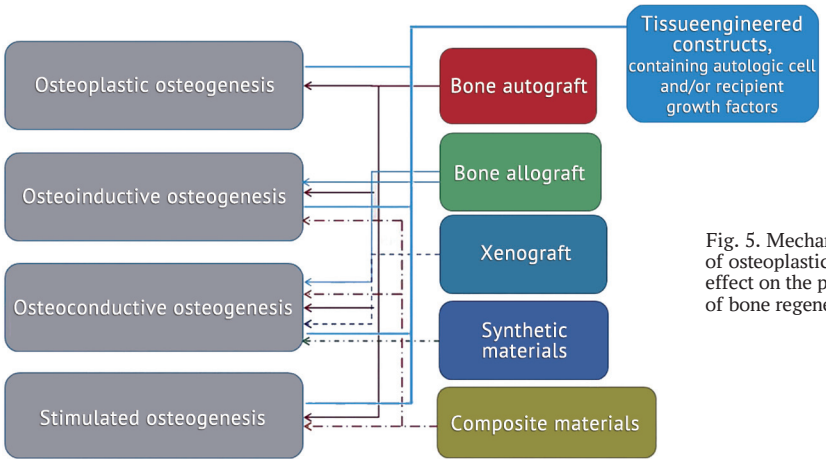

Fig. 5. Mechanisms of osteoplastic material effect on the processes of bone regeneration

CONCLUSION

According to the results of macro- and microscopic assessment at the deproteinized bone matrices heterotopic and orthotopic implantation sites, there were no signs of inflammation and destructive changes in the tissue. That fact is a sign of biological safety of deproteinized cancellous human bone tissue in relation to living tissues.

The use of deproteinized bone matrix in combination with stromal-vascular fraction to create a tissue-engineered construct may unleash several regeneration mechanisms and accelerate the process of bone defect site repair, compared to the situations with the use of a deproteinized bone matrix alone or without reconstruction of a bone defect.

Conflict of interest *The authors declare that they have no competing interests*

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Ethics approval *The study was approved by the institutional ethical committee at the FSBI Tsivyan Novosibirsk Research Institute of Traumatology and Orthopedics of the Ministry of Health of the Russian Federation, protocol №007/22 statement 029/22 dated 27.10.2022.*

REFERENCES

1. Gurazhev MB, Baitov VS, Gavrilov AA, et al. Methods of the Tibia Bone Defect Management in Primary Knee Arthroplasty: Systematic Review. *Traumatology and Orthopedics of Russia*. 2021;27(3):173-188. (In Russ.) doi: 10.21823/2311-2905-2021-27-3-173-188.
2. Stewart SK. Fracture Non-Union: A Review of Clinical Challenges and Future Research Needs. *Malays Orthop J*. 2019;13(2):1-10. doi: 10.5704/MOJ.1907.001
3. Kirilova IA, Podorozhnaya VT. Comparative characteristics of materials for bone grafting: composition and properties. In Kirilova IA ed. *Physicochemical and mechanical properties of the extracellular matrix as signals for controlling cell proliferation, differentiation, mobility and taxis*. Moscow: FIZMATLIT; 2021:27-54. (In Russ.)
4. Shastov AL, Kononovich NA, Gorbach EN. Management of posttraumatic long bone defects in the national and foreign orthopedic practice (literature review). *Genij Ortopedii*. 2018;24(2):252-257. doi: 10.18019/1028-4427-2018-24-2-252-257
5. Wang W, Yeung KWK. Bone grafts and biomaterials substitutes for bone defect repair: A review. *Bioact Mater*. 2017;2(4):224-247. doi: 10.1016/j.bioactmat.2017.05.007
6. Korytkin AA, Zakharova DV, Novikova YS, et al. Custom triflange acetabular components in revision hip replacement (experience review). *Traumatology and Orthopedics of Russia*. 2017;23(4):101-111. (In Russ.) doi: 10.21823/2311-2905-2017-23-4-101-111
7. Yu X, Tang X, Gohil SV, Laurencin CT. Biomaterials for Bone Regenerative Engineering. *Adv Healthc Mater*. 2015;4(9):1268-1285. doi: 10.1002/adhm.201400760
8. Vorobyov KA, Bozhkova SA, Tikhilov RM, Cherny AZ. Current Methods of Processing and Sterilization of Bone Allografts (Review of Literature). *Traumatology and Orthopedics of Russia*. 2017;23(3):134-147. (In Russ.) doi: 10.21823/2311-2905-2017-23-3-134-147
9. Khominets VV, Vorobev KA, Sokolova MO, et al. Allogeneic osteoplastic materials for reconstructive surgery of combat injuries. *Russian Military Medical Academy Reports*. 2022;41(3):309-314. (In Russ.) doi: 10.17816/rmmar109090
10. Hrapkiewicz K, Colby LA, Denison P. *Clinical laboratory animal medicine: an introduction*. John Wiley & Sons; 2013:431.
11. Liu E., Fan J. (ed.). *Fundamentals of Laboratory Animal Science*. CRC Press; 2017:352.
12. Yin N, Wang Y, Ding L, et al. Platelet-rich plasma enhances the repair capacity of muscle-derived mesenchymal stem cells to large humeral bone defect in rabbits. *Sci Rep*. 2020;10(1):6771. doi: 10.1038/s41598-020-63496-5
13. Luck J, Smith OJ, Mosahebi A. A Systematic Review of Autologous Platelet-Rich Plasma and Fat Graft Preparation Methods. *Plast Reconstr Surg Glob Open*. 2017;5(12):e1596. doi: 10.1097/GOX.0000000000001596
14. Oedayrajsingh-Varma MJ, van Ham SM, Knippenberg M, et al. Adipose tissue-derived mesenchymal stem cell yield and growth characteristics are affected by the tissue-harvesting procedure. *Cytotherapy*. 2006;8(2):166-177. doi: 10.1080/14653240600621125
15. Baer PC, Geiger H. Adipose-derived mesenchymal stromal/stem cells: tissue localization, characterization, and heterogeneity. *Stem Cells Int*. 2012;2012:812693. doi: 10.1155/2012/812693
16. Heuther S. Chapter 23. Obesity and disorders of nutrition. In: Brashers VL. et al. (ed.). *Pathophysiology: the biologic basis for disease in adults and children*. 8th edition. Elsevier; 2018:234-239.
17. Permuy M, López-Peña M, Muñoz F, González-Cantalapiedra A. Rabbit as model for osteoporosis research. *J Bone Miner Metab*. 2019;37(4):573-583. doi: 10.1007/s00774-019-01007-x
18. Cherdantseva LA, Anastasieva EA, Aleynik DY, et al. In Vitro Evaluation of the Allogeneic Bone Matrix Effect on the Adipose Mesenchymal Stromal Cells Characteristics in Combined Tissue Engineering. *Traumatology and Orthopedics of Russia*. 2021;27(1):53-65. (In Russ.) doi: 10.21823/2311-2905-2021-27-1-53-65
19. Sharun K, Pawde AM, Kumar R, et al. Standardization and characterization of adipose-derived stromal vascular fraction from New Zealand white rabbits for bone tissue engineering. *Vet World*. 2021;14(2):508-514. doi: 10.14202/vetworld.2021.508-514
20. Guo J, Nguyen A, Banyard DA, et al. Stromal vascular fraction: A regenerative reality? Part 2: Mechanisms of regenerative action. *J Plast Reconstr Aesthet Surg*. 2016;69(2):180-188. doi: 10.1016/j.bjps.2015.10.014
21. Bora P, Majumdar AS. Adipose tissue-derived stromal vascular fraction in regenerative medicine: a brief review on biology and translation. *Stem Cell Res Ther*. 2017;8(1):145. doi: 10.1186/s13287-017-0598-y
22. Gentile P, Sterodimas A, Pizzicannella J, et al. Systematic Review: Allogenic Use of Stromal Vascular Fraction (SVF) and Decellularized Extracellular Matrices (ECM) as Advanced Therapy Medicinal Products (ATMP) in Tissue Regeneration. *Int J Mol Sci*. 2020;21(14):4982. doi: 10.3390/ijms21144982

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