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Bone Tissue Properties after Lanthanum Zirconate Ceramics Implantation: Experimental Study

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Abstract

Background. The ceramic based on lanthanum zirconate is characterized by optimal mechanical characteristics, low corrosion potential and the absence of cytotoxicity. Thus, the possibility of its use as bone substituting material is currently studied. ***The purpose of the study*** was to determine the mechanical, morphological and X-ray spectral characteristics of bone tissue after implantation of ceramic material based on lanthanum zirconate. ***Materials and Methods.*** The experiment was conducted on 27 female guinea pigs of a single line, divided into 3 groups of 9 animals. In the main group (LZ), lanthanum zirconate rods were implanted. In the comparison group (β-TCP), fixation was performed with β-tricalcium phosphate rods. In the native control group (NC) no surgical procedures were performed. A fracture was created in distal metadiaphysis area of femur using open osteoclasia. Animals were hatched 4, 10, and 25 weeks after the start of the experiment. Bone tissue features were studied in the perifocal region. The following methods were used: uniaxial compression, scanning electron microscopy (SEM), energy dispersive X-ray microanalysis (EDXMA). The statistical analysis was performed using the Mann-Whitney test. ***Results.*** The architectonics of the newly formed bone in the LZ group appeared as a developed lacunar tubular network. The structural components of the extracellular matrix were oriented along the bone functional load vectors. The Ca/P ratio in the periimplant region of the bone in the LZ group was significantly higher than in the β-TCP and NC groups. This may indicate a high strength of the newly formed bone. Mechanical testing showed that the strength and performance of the system of "lanthanum zirconate – bone" under uniaxial compression exceeded the similar indicators in the β-TCP group. ***Conclusion.*** The synthesized new material based on lanthanum zirconate seems promising for use in trauma and orthopedic surgery. Additional studies are needed to optimize these implants integration into bone tissue.

Keywords: bone tissue, augmentation, ceramics, lanthanum zirconate, bone mechanical properties.

The biological processes on the boundary line of the implant and bone is very difficult and depends on the vital functions of the bone in the defect zone, the area of implant contact with the bone, as well as on the compatibility of the bone-replacing material with the surrounding tissue in terms of physicochemical, biological and mechanical properties [1, 2, 3]. Today, zirconia ceramics been successfully used in modern dentistry as a coating and as a materials to build in medical implant manufacturing [4, 5]. Also,

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this type of ceramics is used in the friction pair in traumatology and orthopedics, demonstrating the best wear resistance by comparison with the other materials [6]. Zirconia is a ceramic material with adequate mechanical properties [7, 8], low corrosion potential [9], lack of cytotoxicity, and minimal potential to bacterial adhesion [10, 11, 12]. All of the above makes it possible to be considered as a bone replacement material.

The purpose of the study was to investigating the mechanical, morphological, X-ray spectral characteristics of bone tissue after implantation of ceramic material based on lanthanum zirconate.

Materials and Methods

Material

The synthesis of lanthanum zirconate ($La_{1.95}Ca_{0.05}Zr_2O_7$) was carried out in the Laboratory of solid oxide fuel cells of the Institute of High Temperature Electrochemistry, Ural Branch of the Russian Academy of Sciences, using the citrate-nitrate method. This material was used to make rods 25 mm long with a square (1.5 × 1.5 mm) cross section. The similar rods were made from *β-tricalcium phosphate* ($Ca_3(PO_4)_2$), β-TCP.

Animals

The study was carried out on 27 female linear guinea pigs. The animals were kept in the vivarium of the Institute of Immunology and Physiology, Ural Branch of the Russian Academy of Sciences, and had a veterinary certificate of quality and health. All guinea pigs were kept in identical feeding and housing conditions. The animals were kept and animal experiments were according to Requirements the Directive 2010/63/EU "on the protection of animals used for scientific purposes".

Study design

The animals were divided into 3 groups with 9 animals in each group:

– the animals of the *1 treatment group* (Tg1) underwent implantation of rods made of lanthanum zirconate;

– in the *2 treatment group* (Tg2), the fixation was performed with a similar rod from β-TCP;

– in the group of *control* (Cg), the animals did not any surgery.

In animals of the Tg1 and β-TCP groups, a fracture model was created by an original method (RF patent No. 2688944) that was open osteoclasia at the distal metadiaphysis of the femur. Then the osteosynthesis was performed using an intramedullary pin of osteoplastic material, depending on the different group. Clinical assessment was performed at 4, 10 and 25 weeks (three animals for each group at each time point).

Methods

To carry out the mechanical tests for uniaxial compression, samples with a height of 8 mm were made from the shaft of the femur (2 samples from each animal included in the experiment). The end faces of the samples were polished on a diamond disk to make their planes parallel. To prevent the organic components of the bone damage, polishing was carried out in an aqueous medium. The final specimen height was 6 mm. The mechanical testing of the specimens for uniaxial compression was carried out on a Shimadzu AG-X 50 kN testing machine (Shimadzu, Japan) at a loading rate of 1 mm/min. During the tests, two values were controlled: load in N and relative deformation in percent. The tests were stopped at a significant decrease in the load, which corresponded to a break (change in the path) on the deformation curve and the initiation of cracks in the sample. The morphological diagnostics by *scanning electron microscopy* (SEM) and X-ray spectral characteristics of the peri-implant bone (Ca, P and Ca to P ratio) by *energy dispersive X-ray microanalysis* (EDXMA) were carried out on the MIRA3 LMU scanning electron microscope (TESCAN, Czech Republic). The bone samples were taken from the area of the femoral distal epimetaphysis and diaphysis, degreased in acetone. Then they were poured into epoxy resin, followed by grinding and polishing the surface (RF patent No. 2684356).

Statistical analysis

The Mann-Whitney test was used to determine the significance of the differences between the study groups indicators. The $p < 0.05$ level was considered statistically significant. Data are presented as median [interquartile range].

Results

According to SEM data, lanthanum zirconate is a material with a closed type of porosity, the volume fraction of pores is about 15% (Fig. 1). The pores have a complex shape ranging in size from 1–2 to 30 μm. The composition of the material is dominated by four main elements: zirconium 19.92 ± 0.2 at. %, lanthanum 21.24 ± 0.16 at.%, oxygen 58.54 ± 0.33 at. %, calcium 0.3 ± 0.03 at.%.

During the entire observation period, both in the Tg1 and in the β-TCP group, the growth of bone tissue occurred only peri-implantly. The newly formed bone did not penetrate into the pores of the implants.

In 4 weeks after the surgery, the bone trabeculae in the Tg1 group were tightly attached to the implant (Fig. 2 a). In the β-TCP group, the trabeculae of the newly formed bone tissue were directly adjacent to the material. The separate foci of neoosteogenesis were visible in the perifocal zone (Fig. 2b).

In 10 weeks after the surgery, the islets of the newly formed bone were determined around the implant in Tg1 group (Fig. 3 a). The architectonics of the peri-implant area was determined as a developed lacunar-tubular network, the components of the structure of the extracellular matrix in the form of complexes of mineralized collagen in the layers of lamellae and bone trabeculae were oriented along the functional bone load vectors. This makes it possible to effectively resist the action of mechanical stress. In the β-TCP group, the implant was surrounded by young bone tissue along the entire perimeter (Fig. 3 b). The signs of material resorption were noted as the surface layer density decrease with irregularities of the implant contours.

In 25 weeks after the surgery, the bone tissue in Tg1 group had a mature hierarchical structure: osteocyte lacunae, lamellae layers were clearly visible, the Haversian systems could be seen in the large trabeculae (Fig. 4 a). In the β-TCP group, the implant was surrounded by neoplastic bone tissue along the entire perimeter, its contour was scalloped (Fig. 4 b). The bone tissue contained a greater number of osteocytes, the color of the bone was dark due to the higher content of the organic phase. The structure of the bone was heterogeneous, the individual Haversian systems were seen with well traced concentric layers of the lamellae inside them.

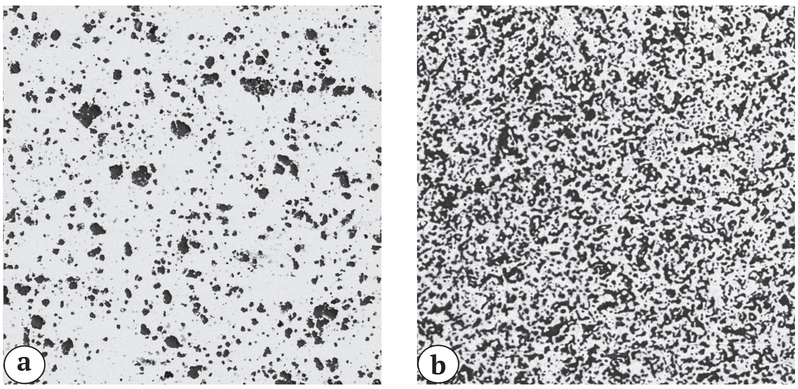

Figure 1. The structure of implantable materials: a – lanthanum zirconate; b – β-tricalcium phosphate. SEM, x 200.

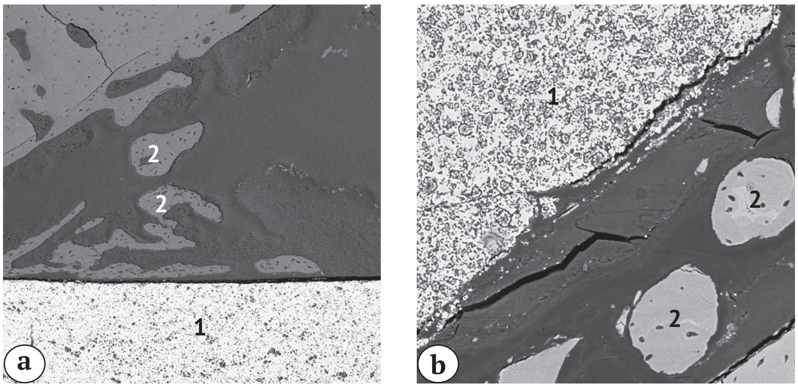

Figure 2. The structure of the material and newly formed bone in 4 weeks after the surgery:
a – Tg1 rod implanted in the femoral diaphysis;
b – β-TCP rod implanted in the femoral diaphysis.
The numbers denote:
1 – bone substituting material;
2 – newly formed bone**.** SEM, x 200.

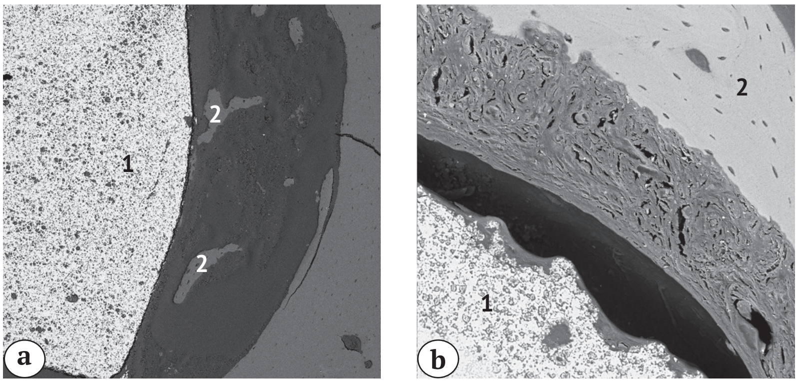

Figure 3. The structure of the material and newly formed bone in 10 weeks after the surgery:
a – Tg1 rod implanted in the femoral diaphysis;
b – β-TCP rod implanted in the femoral diaphysis.
The numbers denote:
1 – bone substituting material;
2 – newly formed bone. SEM, x 200.

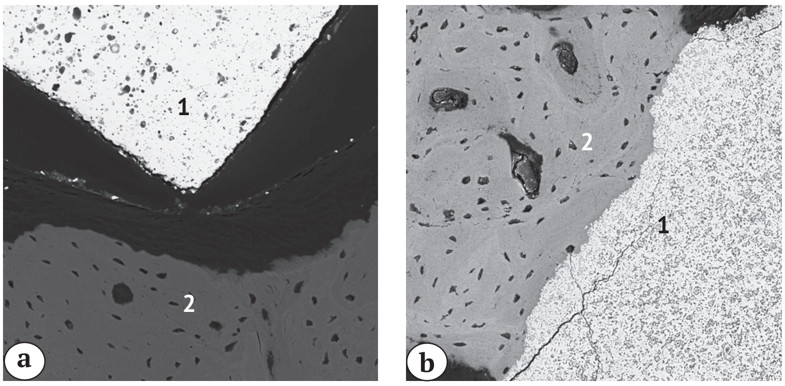

Figure 4. The structure of the material and newly formed bone in 25 weeks after the surgery:
a –Tg1 rod implanted in the femoral diaphysis;
b – β-TCP rod implanted in the femoral diaphysis.
The numbers denote:
1 – bone substituting material;
2 – newly formed bone. SEM, x 500.

The study of the Cg group bone tissue showed that it was light in the micrograph due to the high inorganic substances content (Fig. 5). The structure of the bone was homogeneous with a developed osteocytic network.

The results of Ca, P and the Ca to P ratio determination in the peri-implant bone by the EDXMA in the studied groups are shown in Table 1. The peri-implant area calcium content in the Tg1 and β-TCP groups in 4 weeks after the surgery was significantly lower than in the Cg group. However, by the 10^{th} week of the postoperative period, the Ca level in the both groups significantly exceeded this indicator in the Cg group. In 25 weeks after the surgery, the Ca content in the peri-implant zone in the Tg1 group was comparable to that in the Cg group. In the β-TCP group, the Ca content exceeded this indicator of the group, apparently due to the high Ca in the implanted β-TCP. By phosphorus content in the peri-implant zone in 4 weeks after the surgery, the Tg1 and β-TCP groups did not differ from each other and were significantly inferior to the Cg group. By the 10^{th} week after the surgery, significant differences appeared between the Tg1 and β-TCP groups: the phosphorus level in the Tg1 group became lower than in the Cg group, while in the β-TCP group, it was significantly increased relative to the Cg. These differences persisted until the end of the follow-up and are apparently associated with the high phosphorus content in the implant which composition was based on β-TCP.

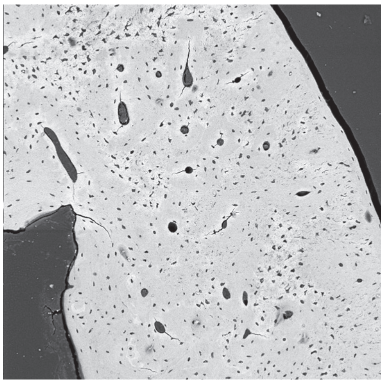

Figure 5. Native control (Cg). The diaphysis of the femur. SEM, ×200.

Table 1

The calcium and phosphorus content and the Ca/P ratio in peri-implant bone samples after the surgery

Time after the surgery	Calcium, %			Phosphorus, %			Ca to P ration		
	Tg1 group	β-TCP group	Cg group	Tg1 group	β-TCP group	NC Cg group	Tg1 group	β-TCP group	Cg group
4 weeks	18.82 [18.47; 19.09]§	18.,01 17.43§ 19.31§		10.71 [10.47; 11.02]§	10.19 [10.02; 11.16]§		1.77 [1.72; 1.78]§	1.76 [1.74§ 1.80]§	
10 weeks	20.87 [20.57; 21.41]§*	26.02 [25.91; 26.24]§	19,51 [19,40; 19,97]	10.92 [10.88§* 1.14§*	17.73 [17.50; 17.86]§	12.18 [11.98; 12.30]	1.90 [1.90; 1.91]§*	1.48 [1.47; 1.49]§	1.61 [1.59; 1.63]
25 weeks	19.23* 18.85; 19.89	26.67 [26.24; 27.06]§		11.12 [10.80§* 11.48§*	17.54 [17.31; 17.65]§		1.74 [1.73; 1.76]§*	1.52 [1.51; 1.55]§	

The results are presented as median [interquartile range];

* The differences between the groups Tg1 and β-TCP are statistically significant, $p < 0.05$;

§ The differences between the Cg group are statistically significant, $p < 0.05$.

The Ca to P ratio in 4 weeks after the surgery in the Tg1 and β-TCP groups had the similar values and was significantly higher than in the Cg group. In 10 weeks after the surgery, there were the significant differences between the Tg1 and β-TCP groups. In the Tg1 group, the Ca to P ratio increased relative to Cg. At the same time, the β-TCP group revealed its significant decrease. That meant, that calcium-deficient hydroxyapatite was formed with a Ca to P ratio below stoichiometric characteristic of the mature bone matrix. The same pattern took place in 25 weeks after the surgery.

Mechanical tests showed that in the process of uniaxial compression of bone tissue samples, a gradual decrease in the height of the sample occurred. The maximum load of the "bone tissue – lanthanum zirconate" system in the Tg1 group was comparable to that in the NC Cg group and was higher than in the β-TCP group. These differences became statistically significant in 10 weeks after the surgery (Table 2). There were no statistically significant differences between the groups in terms of deformity index during the follow-up (Table 3).

The changes in the samples under uniaxial compression in the experimental groups were different, reflected by the deformation curves presented in Figures 6, 7, 8.

The mechanical action on the “bone – implant” system in the Tg1 group first result-

Table 2

The maximum load of the system "bone tissue – lanthanum zirconate" after the implantation

Time after the surgery	Maximum load, N			p^1	p^2	p^3
	Tg1 group	β-TCP group	Cg group			
4 weeks	1064 [870; 1464]	978 [754; 1229]	1024 [670; 1187]	0.52	0.66	0.23
10 weeks	1138 [562; 1450]	781 [663; 846]		0.02	0.23	0.28
25 weeks	977 [773; 1700]	885 [865; 901]		0.63	0.32	0.91

The results are presented as median [interquartile range];

p^1 The statistical significance of the differences between the Tg1 and β-TCP groups.

p^2 The statistical significance of the differences between the Tg1 and NC Cg groups.

p^3 The statistical significance of the differences between the β-TCP and NC Cg groups.

Table 3

Deformation of the system "bone tissue – lanthanum zirconate" after the implantation

Time after the surgery	Maximum load, N			p^1	p^2	p^3
	Tg1 group	β-TCP group	NC Cg group			
4 weeks	3.7 [3.02;6.06]	2.9 [2.2; 4.5]	3.3 [2.4; 4.6]	0.52	0.59	0.45
10 weeks	3,7 [2.1; 5.09]	3.9 [2.9; 5.5]		0.33	0.45	0.52
25 weeks	4,0 [1.8; 4.7]	2.2 [2.0; 4.5]		0.62	1.00	0.45

The results are presented as median [interquartile range];

p^1 The statistical significance of the differences between theTg1 and β-TCP groups.

p^2 The statistical significance of the differences between theTg1 and NC Cg groups.

p^3 The statistical significance of the differences between the β-TCP and NC Cg groups.

ed in the appearance of many cracks on the lateral surfaces of the specimen, led to the separation of bone tissue into thin plates of various sizes (scaly dissection). In the bone tissue of the β-TCP group, a gradual accumulation of irreversible deformation was observed with no disintegration of the sample into parts. The deformation character of the Cg group samples was similar to that of the β-TCP group.

The above patterns were typical for all follow-up periods. According to the obtained deformation curves, the samples in the Tg1 group were broken down stepwisely (cyclical stress rises and falls on the graph). The longitudinal elasticity modulus of the "bone – lanthanum zirconate" system exceeded that in the β-TCP group (the angle of the deformation curve rise is sharper). The samples of the β-TCP group gradually decreased in height and lose in strength under uniaxial compression. There was no secondary increase in strength in this group. The samples of the Cg group were inferior in strength to the samples of the Tg1 group and also were broken down step-wisely, but they surpassed the β-TCP samples in mechanical characteristics.

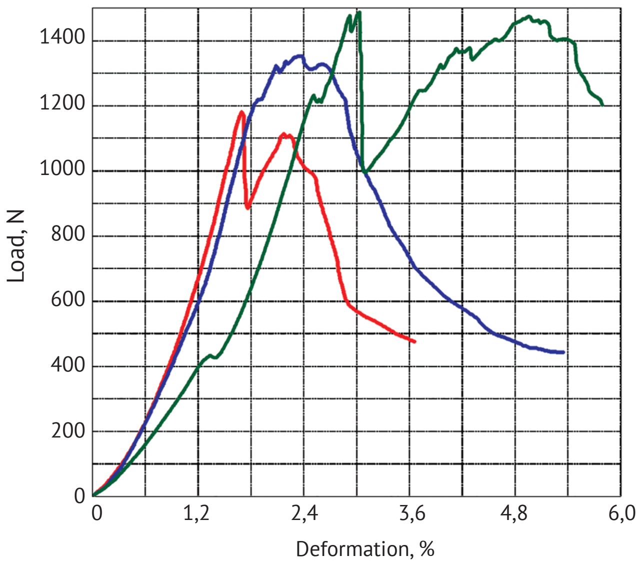

Figure 6. The deformation curves of a sample of the Tg1 group (green), β-TCP group (blue), NC Cg group (red), 4 weeks after the surgery.

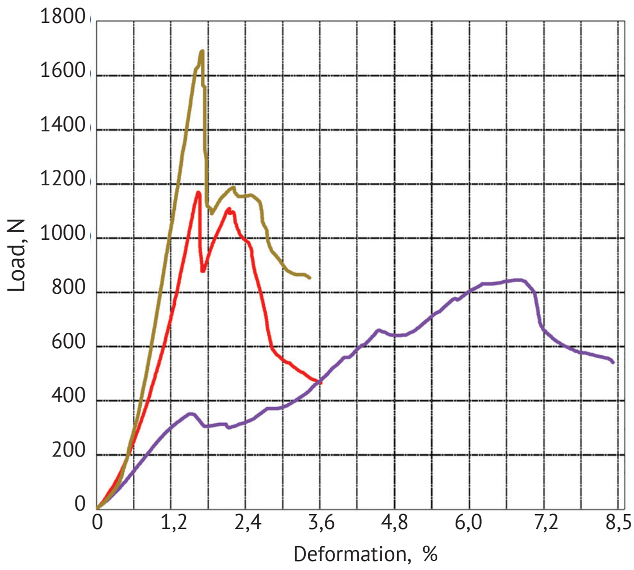

Figure 8. The deformation curves of a sample of the Tg1 group (green), β-TCP group (blue), NC Cg group (red), 25 weeks after the surgery.

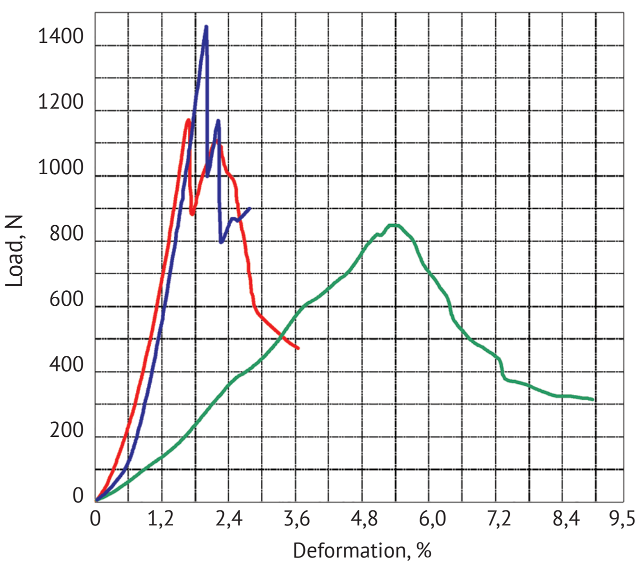

Figure 7. The deformation curves of a sample of the Tg1 group (green), β-TCP group (blue), NC Cg group (red), 6 weeks after the surgery.

Discussion

Zirconium ceramics, along with the absence of cytotoxicity [10], have good mechanical characteristics [8]. The latter make it attractive for use in traumatology and orthopedics. In this regard, attempts are made to modify the chemical structure of zirconium ceramics and obtain compounds with better mechanical characteristics [13]. Polycrystalline tetragonal zirconium, partially stabilized by yttrium, showed higher resistance to fracture in comparison with other ceramic materials [14, 15, 16]. In addition, cerium-stabilized polycrystalline nanocomposites based on zirconium oxide had the highest destruction viscosity and resistance during aging at low temperatures [17]. Another group of authors reported the development of a new material – hardened alumina doped with chromium zirconium oxide. This material exhibited mechanical properties suitable for implants subjected to significant axial loads [18]. Its X-ray examination showed no signs of implant loosening up to 12 months, and no long-term pathogenic effect *in vivo* and no long-term carcinogenic effect *in vitro* [18]. Also, zirconium dioxide *in vitro* studies demonstrated no toxic effect on osteoblasts even promoting their moderate proliferation [19].

We used in our study a newly synthesized material (La1.95Ca0.05Zr2O7). Four main elements (zirconium, lanthanum, oxygen and calcium) are dominated in its composition. This material has a closed type of porosity with a pore volume fraction of about 15%, pores of complex shape ranging in size from 1–2 to 30 μm.

The effectiveness of implantation depends not only on the chemical composition, but also, to a large extent, on the design of the implant [20]. The so-called "shape effect" is at work. This is the dependence of the mechanical characteristics on the longitudinal and transverse dimensions of the implant [21] and the influence of stress concentrators due to heterogeneous structure [22]. We used rods 25 mm long with a square (1.5 × 1.5 mm) section.

According to SEM data, active peri-implant (without invasion into the implant material) growth of newly formed bone tissue was observed both in the case of using the new material based on zirconium and in the case of using β-TCP. However, in case of using the lanthanum zirconate rod, no resorption of the reinforcing material was observed during the entire follow-up period, in case of a using the β-TCP rod the pronounced signs of implant resorption were observed already in 10 weeks after the surgery. Resorption of β-TCP led to an increase in the content of calcium and phosphorus in the peri-implant area. However, their Ca to P ratio was significantly lower than in the native mature bone tissue. That meant that calcium-deficient hydroxyapatite was probably formed. At the same time, the Ca to P ratio in the bone in the contact area with lanthanum zirconate showed a significant increase relative to the native bone up to the 25th week of follow-up. This could indicate the high strength of the newly formed bone.

Ceramics based on zirconium dioxide are prone to brittle while bone behaves like an elastic-plastic material and is destructed viscously [23, 24, 25]. The contact area of lanthanum zirconate with the bone is a vulnerable zone. A large difference in mechanical properties of these two materials leads to dangerous tensile stresses in the area of contact [26, 27].

Lanthanum zirconate alloy significantly increases the modulus of longitudinal elasticity of the system in comparison with the samples of the β-TCP group and makes the system more rigid and less susceptible to shock loads. Such a system is characterized by stepwise destruction. After a bone layer destruction, a secondary increase in the strength took place. Then bone tissue strength decreased again. Several cycles passed this way (some peaks on the deformation curve).

The surface structure of a zirconium intraosseous implant is important for the osseointegration process [28]. A large surface area, and high pore volume can improve the process of osseointegration and create a stronger connection between the implant and the bone tissue [29, 30, 31]. In addition, implantation of the augment based on zirconium dioxide together with the osteoconductive preparation Bio-Oss (Geistlich, Switzerland) and a collagen membrane led to the filling of the defect in the rabbit's mandible with connective tissue. About high-level of biocompatibility of zirconium augments tell us missing signs of acute local inflammationm [32]. Further research on the external design modification, as well as the microstructure of the implants, will increase their osseointegration and improve their mechanical properties. The creation of composite materials based on lanthanum zirconate it's a very promising area.

Study demonstrates clinical advantages of using the new material based on lanthanum zirconate as an implant in the reinforcement of bone injury:

1) a full-fledged bone tissue is formed in the peri-implant area, the architectonics of which makes it possible to effectively of resistance to mechanical stress. This indicates that the material and bone tissue in terms of physicochemical and structural characteristics are highly compatible;

2) new bone formation accompanied by highly strength characteristics in the peri-

implant area already in the early postoperative period, as evidenced by the high Ca to P ratio;

3) the system "lanthanum zirconate – bone" under uniaxial compression exceeds the strength of intact bone and is better in comparison to β-TCP to reinforce the injured area.

The synthesized new material based on lanthanum zirconate appears to be promising for use in traumatology and orthopedics; at the same time, further research is needed to optimize the integration of implants from this material into the bone tissue.

Competing interests: The authors declare no conflict of interest.

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Authors' contributions

M.Yu. Izmodenova – conduction of experiments, participation in data processing and analysis, participation in text preparation.

M.V. Gilev – research concept and design, participation in research conduction, data analysis, participation in text preparation.

M.V. Ananyev – research concept and design, validation of critically important intellectual content.

D.V. Zaytsev – experiment conduction, data analysis, participation in text preparation.

I.P. Antropova – experiment conduction, data processing, participation in text preparation.

E.S. Farlenkov – experiment conduction, validation of critically important intellectual content.

E.S. Tropin – experiment conduction, validation of critically important intellectual content.

E.A. Volokitina – research concept and design, validation of critically important intellectual content.

S.M. Kutepov – general research management, validation of critically important intellectual content.

B.G. Yushkov – general research management, research concept and design, validation of critically important intellectual content.

All authors made a significant contribution to the research and preparation of the article and read and approved the final version before its publication. They agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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