

ASSESSMENT OF BIOCOMPATIBILITY AND BIOINERTNESS OF DENTAL IMPLANTS MADE OF ZIRCONIUM DIOXIDE *IN VIVO*

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ABSTRACT

This article presents a method of mechanical processing of structural material for the manufacture of individual transcendental implants used to restore the biomechanical characteristics of teeth with a resected root. The technique is reproduced utilizing in-line exposure to zirconium dioxide stabilized with yttrium, aluminum oxide powder of a certain dispersion and particle diameter, under a pressure of 2 atmospheres. Additionally, the influence of structural material and artificially created surface roughness of individual transcendental zirconium dioxide implants on the formation of bone tissue in the jawbones of experimental animals was studied. Samples of individual transcendental implants were fixed in artificially created critical defects of the mandible of laboratory rabbits. Histological preparations were prepared in dynamics, at the time of withdrawal of animals from the experiment 1, 3, 6, and 9 months after surgery. The obtained results indicated the formation of mature bone tissue in the intraoperative defect around analogs of transcendental implants and the absence of inflammatory and macrophage reactions in dynamics. This indicates the biocompatibility, bioinertness, and effectiveness of zirconium dioxide as material for dental implants.

Key words: Transcendental implant, Zirconium dioxide, Osseointegration of dental implants, Biocompatibility.

Introduction

The development and application of new digital technologies in medicine, and in particular in dentistry, has led to the emergence of new structural materials used both for the manufacture of dentures and for the manufacture of artificial supports for these prostheses [1-3]. One of these materials is zirconium dioxide. It has found wide application in medicine due to its mechanical properties, low corrosion potential, low cytotoxicity, and minimal bacterial adhesion [4-6]. Currently, there is evidence of the use of zirconium for the manufacture of intraosseous implants, abutments, and ceramic crowns [7-9]. The advantages of ceramic implants over standard widespread titanium implants are a significantly reduced likelihood of allergic reactions, lower weight, and better aesthetic properties [10-12]. *In vitro* studies have shown that zirconium dioxide does not have a cytotoxic effect on osteoblasts and contributes to the manifestation of moderate proliferation [13-15]. Like a titanium implant, the surface of a zirconium intraosseous implant is important for the process of osseointegration [16-18]. Artificial roughening of the surface and other forms of modification of its topography improve the process of osseointegration and create a stronger connection of the implant with bone tissue [19-21]. At the same time, the development and selection of a technique for creating a special surface of zirconium dioxide implants in order to improve the strength of its connection with bone tissue is an urgent task of dentistry [22-34].

Therefore, this study aimed to evaluate the effectiveness of the proposed surface treatment technique for individual milled transcendental zirconium dioxide implants based on the results of their osseointegration in an experiment on laboratory animals *in vivo*.

Materials and Methods

Analogues of individual milled transcendental implants made of zirconium dioxide with yttrium additives were processed by a sandblasting machine under a pressure of 2 atmospheres with aluminum oxide powder with a grain size of 110 µm [35]. In this case, the treatment was performed in one direction, longitudinally along the axis of the implant. Further, these analogues, after sterilization treatment, were introduced into artificially created critical bone cavities of the jaws of 12 laboratory Chinchilla rabbits (**Figure 1**) [34-42]. Bone defects were created with a diameter of 10 mm and a depth of 3 mm using a drill and a milling cutter, in the projection of 2-3 teeth [43]. Osteoplastic material BioOss (Geistlich, Switzerland) was injected into the defects on both sides [44-48]. The perimeter of the defect was covered with a collagen membrane BioGide (Geistlich, Switzerland). After filling the bone cavities with these implants, the soft tissues above them were sutured tightly in layers [49]. In the postoperative period, clinical observation was carried out, with the use of antibiotics Baitril 0.5 ml intramuscularly for 7 days [50-54]. Animals were removed from the experiment for 1, 3, 6, 9 months: 3 animals for each period in each group by intraperitoneal administration of calypsol at a dose of 750

mg/kg and one at a dose of 200 mg/kg of the experimental animal's weight. Next, the skeletonization of the jaws and the manufacture of preparations for microscopy were carried out [55, 56].



Figure 1. Introduction of an analog of an individual milled transcendental implant made of zirconium dioxide into the defect

Results and Discussion

According to the results of the study, 1 month after implantation of an analog of an individual transcendental zirconium implant treated with aluminum oxide powder according to the proposed technology with the BioOss (Geistlich, Switzerland) glass-conductive preparation, numerous fragments of the BioOss material (Geistlich, Switzerland), devoid of cellular elements, were visible in the mandible cavity. Loose connective tissue was formed around these fragments, consisting of numerous cellular elements, such as fibroblasts with a slight admixture of macrophages and lymphocytes [57, 58]. The walls of the cavity of the bone defect were formed from maternal bone tissue [59]. There are practically no inflammatory phenomena and destruction of the defect walls (**Figure 2**). Phase contrast microscopy showed the disordered fibrillar structure of bone fragments of BioOss (Geistlich, Switzerland) and the fibrous structure of connective tissue (collagen fibers) [60, 61]. Polarization microscopy showed a weaker anisotropy (double refraction) than in normal bone tissue [62]. Notably, there was no obvious and characteristic outline of the implant, since the contents of the defect cavity are loose [22, 63-72].

As a result of the control study at the same time, i.e., a defect formed in the same animal on the opposite side of the rabbit jaw, filled with the BioOss osteoconductive drug (Geistlich, Switzerland) and blocked by the resorbable membrane of BioGuade (Geistlich, Switzerland), but without the introduced analog of an individual transcendental implant, the histological picture of the preparations of the three rabbits was similar. The bone defect was filled with small fragments of BioOss material (Geistlich, Switzerland) with the identification of a fibrillar structure, significantly different from the structures of healthy bone tissue, which were completely devoid of cells and stained with

hematoxylin and eosin with varying degrees of intensity with a slight macrophage reaction [73, 74]. During polarization microscopy, bone fragments of the bone replacement drug Bio Oss (Geistlich, Switzerland) were devoid of double refraction, unlike healthy bone tissue, that is, they were anisotropic [75, 76].

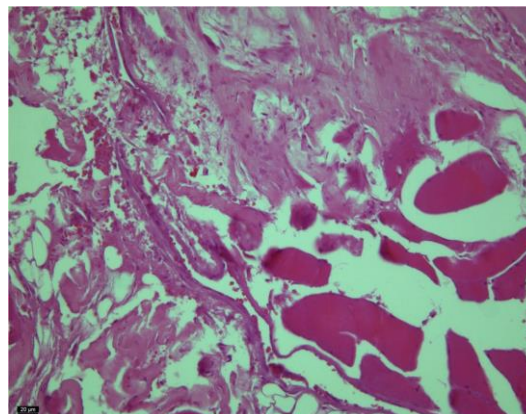


Figure 2. Histological examination. The withdrawal period is 1 month (experiment). There are numerous fragments of Bio-oss bone tissue and connective tissue in the cavity of the defect. Stain: hematoxylin and eosin, $\times 200$

When studying the drugs of the experimental group at the time of withdrawal from the experiment after 3 months, the histological picture is similar in all 3 animals. The wall of the bone cavity formed as a result of the removal of an analog of an individual transcendental implant made of zirconium dioxide is made up of mature fibrous connective tissue represented by intertwined strands of fusiform fibroblasts and collagen fibers (**Figure 3**).

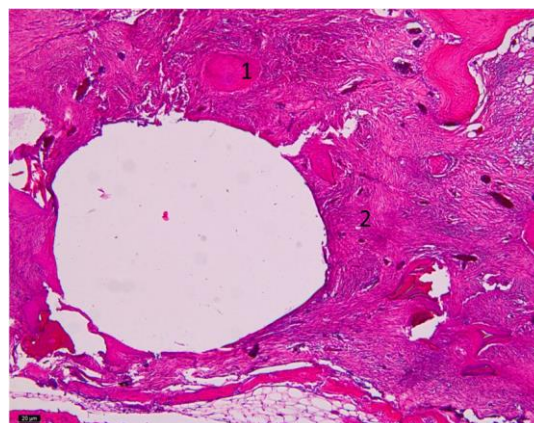


Figure 3. Histological examination. The withdrawal period is 3 months (experiment). The defect is filled with dense connective tissue. A rounded cavity is visible in it, from which the implant has been removed. Small fragments of Bio-Oss material are visible in the tissue (1), as well as elements of newly formed bone tissue (2). Stain: hematoxylin and eosin, $\times 200$

Separate small trabeculae of the newly formed bone are visible in this tissue [77]. The same trabeculae are also visible at a distance from the implant, where the bulk of the osteoconductive drug BioOss (Geistlich, Switzerland) was located. Connective tissue is well vascularized. The macrophage reaction along the boundaries of the location of the analog of the transdental implant is minimal. The inflammatory reaction, characterized by edema, neutrophil infiltration, is completely absent. This indicates the high biocompatibility of the structural material of the analog of the transdental implant. All of the above applies to the wide belt of connective tissue around the cavity from the implant. This fabric fills the entire area of the defect. At the very border between the cavity from the implant and the connective tissue, there is a very thin strip 20-30 μm thick, where the fibers and one or two layers of fibroblasts are located longitudinally. There are also a few macrophages. Hypothetically, it can be assumed that this strip is the implant's connective tissue capsule [78].

In the study of the control group, after 3 months, the cavity of the intraoperative defect was filled with connective tissue of various types. Basically, this connective tissue was represented by a relatively loose connective tissue of the fibroreticular type. However, there was a dense, mature tissue consisting of strands of fibroblasts and collagen fibers with single areas of osteogenesis [79, 80].

After 6 months in the experimental groups after implantation of analogs of individual transcendental implants made of zirconium dioxide and osteoconductive drug BioOss (Geistlich, Switzerland), the defect was filled with connective tissue, mainly this tissue has a dense fibrous character and is represented by coarse fibrous tissue. Minor fragments of Bio Oss material (Geistlich, Switzerland) remain in it and beams of newly formed bone tissue are visible, which grows from the walls of the maternal bone and often surrounds fragments of the glass-conductive material [81]. The wall of the cavity around the extracted implant analog, as well as in the previous period, consists of mature fibrous connective tissue with a high degree of vascularization, represented by intertwined strands of fusiform fibroblasts and, to a greater extent, collagen fibers. In this tissue, individual small trabeculae of the newly formed bone of the experimental animal are visible [82, 83].

Similarly to the preparations of experimental animals withdrawn from the experiment for 3 months, in the preparations after 6 months, there is a very thin strip of one or two layers of fibroblasts located longitudinally, but with a smaller thickness, 15-20 μm , at the boundary between the cavity from the implant and connective tissue. There are also no signs of an inflammatory reaction around the implant analogs (**Figure 4**).

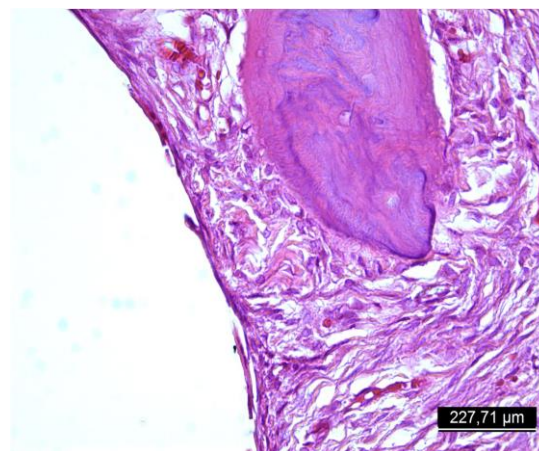


Figure 4. Histological examination. The withdrawal period is 6 months (experiment). Bone defect after removal of a transcendental implant made of zirconium dioxide. The wall of the cavity is made up of mature fibrous connective tissue, represented by intertwined strands of fusiform fibroblasts and collagen fibers. Separate small trabeculae of the newly formed bone are visible in this tissue. Stain: hematoxylin and eosin, $\times 400$

In the control group, after 6 months, the defect cavity, where Bio Oss material was implanted (Geistlich, Switzerland), but without an analog of an individual transcendental implant, was filled with fibrous and fibroreticular tissue without inflammatory infiltration. In this tissue, a few fragments of osteoconductive material BioOss (Geistlich, Switzerland) are visible, surrounded by newly formed bone tissue. Phase contrast and dark-field microscopy clearly show the fibrillarity of the connective tissue and the organized microstructure of the newly formed bone [84, 85].

When studying the preparations of the experimental group, after 9 months, a cavity is found in the bone tissue of the rabbit jaw, in which particles of the BioOss glass-conductive material remain reduced compared to the 6 months (Geistlich, Switzerland). The material has an amorphous granular structure. However, at high magnification, osteons with a fuzzy structure appear in places in it: a central vessel from which the rays radiate [86]. With phase contrast microscopy, osteons are more clearly visible, but mostly the material has a granular structure that differs sharply from the bone structure [87, 88]. However, fragments with preserved bone structure are found among this material.

Under dark field microscopy, the Bio-Oss material (Geistlich, Switzerland) differs sharply from the surrounding bone except for the fragments described above. During polarization microscopy, the bone walls of the cavity give anisotropy (double refraction). The destroyed Bio-Oss material (Geistlich, Switzerland), except for the fragments described above, does not give anisotropy [89]. It should be noted that the wall of the cavity consists of healthy mature bone tissue (**Figure 5**).

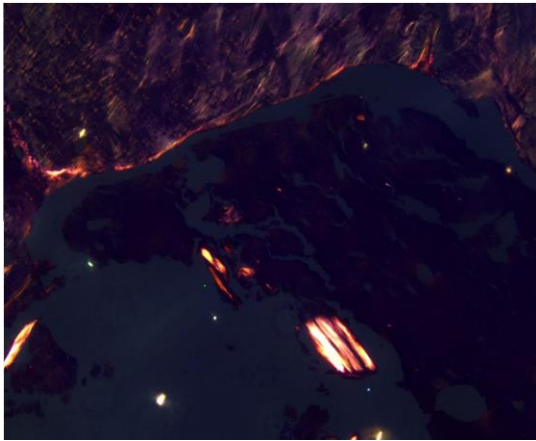


Figure 5. Histological examination. The withdrawal period is 9 months (experiment). During polarization microscopy, the bone walls of the cavity give anisotropy (double refraction). Stain: hematoxylin and eosin, $\times 400$

There are no connective tissue gaps between the cavity wall and the material in it. There are no signs of an inflammatory or dystrophic process in the bone tissue of the cavity walls. This indicates that zirconium dioxide (the structural material from which the transcendental implant is made) does not have any toxic effect on the hard and soft tissues of the animal [63, 90, 91]. Notably, when examining the drugs of the control group after 9 months, the histological picture of all 3 animals was similar. Namely, the defect cavity was filled with mature bone tissue with formed single osteons and a circulatory system. Small granules of Bio-Oss osteoplastic material were observed in places, located in a loose connective tissue capsule.

Conclusion

Thus, by analyzing the results obtained, namely, the formation of mature bone tissue in an intraoperative defect around analogs of transcendental implants and the absence of inflammatory and macrophage reactions in dynamics, it is possible to conclude biocompatibility, bioinertness, as well as confirmation of the effectiveness of the proposed methodology for modeling a special surface of a transcendental implant made by computer modeling and milling from zirconium dioxide.

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Ethics statement: The protocol for experiments with laboratory animals complied with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Protocol 3 dated by Aug 3, 2024).

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