Review article
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Current state and perspectives on the use of zirconium ceramic implants in traumatology and orthopaedics

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Abstract

Background Ceramic materials are currently in wide demand in various fields of medicine. Zirconium ceramics demonstrate exceptional mechanical properties and biocompatibility and do not cause cytotoxic effects or allergic reactions in surrounding tissues.

The objective was to present an analysis of current literature data on the use of zirconium ceramics as a bone replacement material in traumatology and orthopaedics.

Materials and methods The search for publications was conducted using the databases of Scopus, PubMed and the electronic scientific library eLIBRARY in the Russian and English languages using the keywords: bioceramics, bone, bone defect, zirconate, zirconium ceramics, bone tissue engineering, implant, scaffold, augment, biointegration, bioactivity. Depth of search for scientific papers was from 2000 to 2023.

Results and discussion Zirconium dioxide is the main ceramic bioinert material. The study presents the characteristics of ZrO_2 as a bone replacement material and its comparison with titanium implants. Data are presented on various strategies for improving zirconium bioceramics: improving the surface of the material by physical and chemical methods, obtaining volumetric porosity, including using additive technologies, creating composite materials, and developing bioactive coatings. New methods of creating zirconium ceramics compatible with living tissues containing bioactive ions that promote both osseointegration and bone tissue regeneration have been actively studied.

Conclusions Zirconium dioxide ceramics appear to be a promising alternative to titanium implants in terms of mechanical strength, biological functionality, chemical stability, osseointegration, and antibacterial properties. Future experimental and clinical studies will further improve zirconium ceramics.

Keywords: bioceramics, zirconate, bone defect, implant, biointegration

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INTRODUCTION

Annually, about 130 million fractures happen worldwide. A significant part of them develops bone defects that must be filled in [1]. Moreover, the problem of bone defect compensation exists in degenerative diseases of the musculoskeletal system, osteomyelitis, and oncological diseases that require surgical intervention using bone grafts [2]. Patients of older age groups, patients with complex comminuted fractures, patients with metabolic disorders are at risk for fracture nonunion due to impaired bone tissue repair [3]. Unfortunately, there are currently no complete solutions to this problem, since the ideal one would be to achieve a biocompatible scaffold similar to natural bone. One of the most important properties that a graft must have is osteoconduction, that is, the ability to function as a scaffold for mesenchymal stem cells (MSCs), osteoblasts and osteoclasts [4]. This property of the material is directly related to the quality of the surface, which should resemble the structure of cancellous bone [5]. Another required feature is osteoinduction or the ability of the graft to stimulate bone formation, ensure the recruitment, proliferation and subsequent differentiation of MSCs into chondro- and osteoblasts under the influence of growth factors, cytokines, and adhesion molecules. It is also worth noting that an important function of growth factors is induction of angiogenesis for the delivery of nutrient substrates to the developing bone tissue [6]. Osseointegration is a direct contact of the implant with the bone through newly formed bone tissue that should exclude the growth of fibrous tissue at the bone-implant interface. One of the determining factors for successful osseointegration is the geometry and size of pores on the surface and inside the structure of the material [7, 8]. Moreover, the osteosubstitution material must meet the mechanical characteristics of the bone, requirements of biocompatibility, strength, infectious safety and availability.

Autografting is considered the "gold standard" in the clinical practice due to a number of advantages: good osteoconduction, osteoinduction and stimulation of osteogenesis. However, we must not forget about possible complications both at the site of donor bone collection and at the site of bone defect [9, 10]. The use of allografts also has significant shortcomings: possible immune rejection, transmission of infection, and a high failure rate. The use of xenografts is limited by the presence of immunogenic interspecies barriers [11]. The shortage of natural sources due to growing demand for implants stimulated the search and development of artificial materials for osteoplasty.

The effectiveness of the interaction between the recipient bone bed and the implant depends not only on the regenerative potential of the bone tissue and the area of interaction between the implant and the bone in the defect area, but also on the compatibility of the osteosubstitution material with the body tissue in terms of physicochemical, biological and mechanical properties. Artificial materials that are developed specifically for medical purposes are biocompatible and are classified as biomaterials. Among such materials, a special place is occupied by bioceramics, which has a unique combination of properties versus metals or polymers. The biocompatibility of bioceramics ranges from oxides, which are inert in the body, to resorbable materials, which eventually decompose in the body. High internal strength, wear resistance, and low coefficient of friction allow the use of bioceramics under high loads. The compatibility of bioceramics with human tissue reduces the risk of adverse reactions or inflammation. Moreover, some types of bioceramics, in particular hydroxyapatite or bioactive glasses, exhibit properties that promote tissue regeneration and osseointegration. Bioceramics have the inherent versatility: the material can be molded into precise shapes and its composition can be tailored to improve specific properties. All these features make bioceramics an adequate material for solving a wide range of medical problems [12-15]. Research on ceramic biomaterials has been developing rapidly, finding new areas of application in medicine, in particular in traumatology and orthopaedics. Moreover, the analysis of the contemporary market of bioceramics showed that there has been a steady tendency towards the change of other types of oxide ceramics by zirconium ceramics [16].

Purpose Based on literature data, determine the prospects for using zirconium ceramics as a bone substitution material in traumatology and orthopaedics

MATERIALS AND METHODS

The search for publications on the topic was carried out in the PubMed databases and the electronic scientific library eLIBRARY in two languages: Russian and English. Key words used were: bioceramics, bone, bone defect, zirconate, zirconium ceramics, bone tissue engineering, implant, scaffold, augment, biointegration, bioactivity. Depth of the search for scientific papers was from 2000 throughout 2023. The literature search using keywords and abstracts found 592 sources. Of these, 79 full-text articles were selected according to the specified criteria. The choice was determined by the fundamental nature, evidence, and relevance of the work on the use of zirconium ceramics in traumatology and orthopedics.

RESULTS AND DISCUSSION

The term "ceramics" comes from the Greek word κεραμικὸ (keramikò) which means "fired material". Ceramics include inorganic materials consisting of metallic and non-metallic components chemically bonded to each other. The properties of materials depend significantly on their microstructure [17]. The main characteristics of ceramic materials are high strength, resistance to corrosion and wear, and good compression resistance [12, 13]. However, fragility and relatively low tensile and bending strength are a serious problem for the use of ceramics as implants [18, 19]. For biomedical applications, such materials can be used as all-ceramic components, or they can contain particles of other materials [20]. Bioceramic scaffolds play a central role in the engineering of bone tissue substitutes as a support and modulator for cell attachment, proliferation and differentiation, and as a carrier of osteogenic substances. It is important to note that the morphology, microstructure, porosity, mechanical and physicochemical characteristics of the scaffold should be as close as possible to natural bone [21].

Depending on their activity in interacting with the human body, ceramic biomaterials can be divided into three groups: 1) inert; 2) having low or medium surface activity; 3) bioresorbable (adsorbable). The choice of the type of ceramic material (inert, bioactive or bioresorbable) in each specific case depends on what functions the implant performs.

Inert bioceramics do not promote connection with living tissues; connective tissue of varying thickness develops around the implant that holds the implant and, at the same time, isolates it from neighboring tissues. Possessing high biocompatibility and mechanical strength, such bioceramics are usually used for permanent implants. Materials with low and medium activity, in addition to their ability of binding to specific proteins, can also release ions, thereby facilitating the integration of implants into living tissues. Bioresorbable ceramics should remain in the target site until bone regeneration occurs [14, 22].

Inert bioceramics The first generation of biomaterials was developed in the 1960s. Those materials were bioinert, showed minimal interaction with surrounding tissues, and did not stimulate bone formation [23]. The most important bioceramic inert materials are zirconium dioxide (ZrO_2) and alumina (Al_2O_3). Their properties such as reduced wear rates and good long-term biocompatibility make these materials suitable for orthopaedic applications. The use of ceramic materials, compared to implants made of metal alloys, provides a lower rate of component wear and leads to a decrease in the release of metal ions. [24].

Al_2O_3 was the first oxide used in orthopaedics due to its biological safety, strength, and reduction in the rate of aseptic osteolysis in comparison with metal implants [25]. Polycrystalline aluminum oxide has a relatively low cost, due to which it is widely used in traumatology and orthopaedics as a component in friction pairs of endoprostheses [26].

Zirconium dioxide has more than double strength compared to aluminum oxide, due to which this material has been actively used in the production of implants [27]. Zirconium dioxide occurs in three main crystal phase structures: cubic, tetragonal and monoclinic. Microcracks in the crystalline-network structure of zirconium dioxide are self-limiting if the transition from tetragonal to monoclinic crystal structure is controlled [28]. To stabilize the structure of zirconium dioxide, various oxides are added to it, in particular, yttrium oxide [29]. Zirconium dioxide bioceramics, in particular yttria-stabilized tetragonal zirconia polycrystalline (Y-TZP) ceramics, exhibit exceptional mechanical properties and biocompatibility, and do not cause cytotoxic effects or allergic reactions in surrounding tissues. Although this biomaterial was claimed to be inert, the adsorption of blood proteins, platelets and the migration of osteogenic cells suggest biological interaction with zirconia dioxide-based surfaces [30, 31].

Ceramic implants appear to be a promising alternative to titanium implants in terms of mechanical strength, biological functionality, chemical stability and osseointegration. Scarano et al. examined bone response to zirconia implants in an experimental study in rabbits. It showed that newly formed bone was actively formed in close contact with the surfaces of zirconium ceramics, the bone-to-implant contact rate was 68.4 ± 2.4 %, mature bone and actively secreting osteoblasts were revealed in most parts of the implant, and no inflammation was detected [34]. Comparative studies *in vitro* and *in vivo* showed that zirconia implants have similar results with titanium-based implants in terms of osseointegration indices [32-35].

An advantage of zirconium dioxide, in comparison with titanium, was also found in terms of antibacterial properties. Scarano et al. showed that the percentage of the surface covered with bacteria on zirconium oxide disks was significantly lower than on similar titanium disks [36]. Roehling et al. compared experimental disks made of titanium and zirconium dioxide with three types of surface topography: after mechanical or sandblasting and acid etching. It was shown that zirconium dioxide has significantly lower bacterial adhesion compared to titanium [37].

The attractiveness of ZrO_2-based ceramics for medical use is due to its exceptional chemical inertness, high strength and good compatibility with the human body, but its inertness limits its use as a bone substitute material for filling bone tissue defects. Various strategies have been used to improve the integration of zirconia implants into bone tissue.

The ***surface properties of the implant*** are of great importance for the formation of peri-implant bone tissue. Various methods are used to improve the surface of zirconia. Airborne particle abrasion, or sandblasting of zirconia surfaces, significantly improves osteogenesis and osseointegration around implants compared to treated titanium surfaces [33, 38, 39]. To improve the surface properties of zirconium dioxide, chemical treatment (acid etching) is also used [40, 41]. However, the strength of zirconium dioxide can decrease in mechanical processing due to abrasion by particles and the formation of deep microcracks while thermal and acid treatments can reduce the bending strength of zirconium under the conditions of low-temperature degradation. Further research is expected to develop parameters for mechanical and chemical surface treatment of the material that do not affect its mechanical properties.

Ultraviolet radiation can induce electron excitation, increasing the surface energy of zirconium dioxide, which leads to a decrease in the contact angle of its surface with water from 51 to 9.4° and, accordingly, increases wettability [42]. This, in turn, makes the surface of the material biologically more attractive for protein adsorption, osteoblast proliferation and osseointegration. Treatment of the zirconia surface with ultraviolet radiation promotes the attachment, proliferation and differentiation of osteoblasts without affecting the mechanical properties of the material [43].

Laser radiation may also be a promising way to improve osseointegration of zirconia. Laser modification improves the wettability of the material and increases the adhesion of osteoblasts compared to untreated samples [44].

The ***development of methods for obtaining porosity*** in ceramics enables to produce materials with improved osseointegration properties. Based on their structure, the following types of ceramics are distinguished: fine (less than 5 % of pores), coarse (from 5 to 30 % of pores), highly porous (more than 30 % of pores). The necessary porosity characteristics – the number of pores and their morphology – are achieved by special technological methods, including the introduction of special pore-forming additives. In this case, the geometry of pores in ceramics depends on the configuration of pore-forming particles [45]. Kalinina et al. developed highly porous bioceramics based on stabilized ZrO_2. A synthesized ceramic implant material with an open porosity of 55 % and a pore size of 40-800 nm was placed into the body of laboratory animals. Vascular ingrowth into the pore space of ceramics was demonstrated. The authors suggest that porous ceramics based on zirconium dioxide can be used in the production of implants for orthopaedics and traumatology [46]. Porous zirconium ceramics have been especially actively developed for the production of small-sized implants [45].

Work is underway to create domestic ceramic materials based on zirconium dioxide from nanostructured powders [47]. A highly dispersed powder (9-10 nm) was synthesized based on a tetragonal solid solution of partially stabilized zirconium dioxide (t-ZrO_2). Based on this powder, nanocrystalline ceramics (grain size 60-70 nm) with high physicochemical and mechanical characteristics were obtained. *In vivo* studies showed the absence of a toxic effect of the ceramic implant on the tissues surrounding the implant and on laboratory animals. The research results allow us to state that the resulting nano-sized bioceramics can be used for medical purposes [48]. Buyakova et al. presented the results of studies on the structure and mechanical behavior of porous ceramics produced from nanocrystalline powder of partially stabilized zirconium dioxide intended for use in joint replacement. Ceramics with porosity capable of providing a biomechanical connection at the bone tissue–implant interface were obtained; it opens up new possibilities in the use of highly porous ceramics for bone tissue substitution [49].

Additive technologies are being actively developed in relation to ceramic materials. Their use would provide personalized components from porous bioceramics to fill in large bone defects [50-52].

Zirconium dioxide-based materials have been used in orthopedics since the 1980s, mainly due to their excellent mechanical properties resulting from phase transformations. However, the material has been found to undergo hydrothermal aging (low temperature degradation), whereby its mechanical properties gradually deteriorate over time in a humid environment, what can lead to increased surface roughness and microcracking, with slow crack growth that ultimately causes catastrophic destruction [53, 54]. Material degradation is of particular importance for medical implants [55]. Fully stabilized zirconium dioxide is not subject to hydrothermal aging, but its mechanical properties are not high enough.

Creation of composite materials has largely solved the problem of low-temperature degradation of aluminum zirconium (ATZ). Ceramic composites made from hardened zirconium oxide are universal 56]. Compounds of alumina and zirconia have received considerable attention, particularly hardened materials known for their exceptional mechanical properties, including high strength, fracture viscosity, elasticity, hardness and wear resistance, and resistance to hydrothermal aging.

[57]. In this case, not only the composition of the material is important, but also the method of its synthesis. It has been shown, varying resistance of the resulting ceramic materials to degradation is observed by different temperatures [58]. ATZ ceramics hold significant promise for biomedical applications due to their biocompatibility and remarkable ability to withstand mechanical stress. Implants made from such ceramics have excellent wear resistance and strength, ensuring long survival in the human body and reducing the risk of adverse reactions, making them the preferred choice for the restoration and replacement of damaged bone tissue and joints, in particular in total hip and knee arthroplasty [31, 58-61], although Pluschev et al. indicated that if there is even minimal doubt about the stability of the head in the acetabulum, the use of ceramic components should be viewed critically [62].

Development of bioactive coatings on the surface of zirconia has been undertaken to improve the biocompatibility, antibacterial potential and biological activity of the material. Various coating materials with good biological properties have been described in the literature. Hydroxyapatite has mineral composition similar to bone, exhibits biologically active properties, enhancing osseointegration. Hydroxyapatite coatings enhance the osteogenesis capacity of porous zirconia scaffolds [63]. Moreover, an increase in the hydroxyapatite content led to a decrease in the mechanical and chemical stability of the material with a simultaneous increase in biological activity [64]. Research is being conducted to obtain and evaluate the quality of bioceramic coatings from a composite material based on the co-precipitation of hydroxyapatite and hydrated zirconium dioxide [65]. Calcium phosphate is also bioactive, but coatings made from this material exhibit low stability and provide weak adhesion to the substrate. To overcome these shortcomings, tricalcium phosphate-reinforced hydroxyapatite coatings have been studied [66]. A study conducted by Silva et al. showed that modification of the surface of scaffolds made of aluminum-zirconium porous ceramics with calcium phosphate and strontium included in its structure might yield scaffolds with high porosity, three-dimensional structure and preferential adhesion and maturation of osteoblastic cells, which are necessary to stimulate bone tissue regeneration in vivo [67]. Coating with functionalized carbon nanotubes, which enhance the roughness, wettability and cell adhesion of zirconia, contributed to the osseointegrative properties of the material [68]. Attempts have been made to produce bioactive glass coatings on zirconia substrates, but with limited success. These coatings have poor adhesion to the substrate, as a result of which they are often subject to delamination and destruction. To overcome these problems, a strategy based on a functionally graded glass/zirconia system has been proposed [69]. To improve the mechanical characteristics and wear resistance of zirconia implants, the use of graphene as a coating has been studied [70].

Creation of bioactive ceramics compatible with living tissues has been currently developed. By synthesizing biomaterials with appropriate biophysical and biochemical characteristics, it is possible to modulate the cellular response of peri-implant tissues. This property of bioactive materials, such as the release of bioactive ions (Ca, Mg, Sr, Zn, Cr, Ag, La, etc.) can be used to induce phenotypic changes in cells or modulate the immune microenvironment to control tissue healing and regeneration [71]. It has been proven that the biophysical characteristics of biomaterials, such as topography, charge, size, electrostatic interactions and stiffness, can be modulated by the addition of inorganic micro- and nanoparticles [72]. Current research shows that inert ZrO_2 can be converted into a bioactive system comprising various molecules that can mimic the structural and compositional properties of bone tissue at the macro-, micro- and nanoscale, improving implant osseointegration [73]. Considerable efforts have been made by researchers to modify zirconia in terms of morphology and improve biological activity for better cell attachment, proliferation and differentiation during the formation of peri-implant bone [74, 75]. Pardun et al. added magnesium oxide or magnesium fluoride to yttrium-stabilized zirconium dioxide. The presence of Mg^{2+} ions improved the proliferation and differentiation of osteoblast cells [75]. Mushahary et al. also showed that the introduction of magnesium promotes the proliferation of osteoblasts, increasing the biological activity of zirconium dioxide [76].

It is known that the crystal lattice of lanthanum zirconate ($La_2Zr_2O_7$) is tolerant to various types of substitutions, in particular, calcium and strontium ions. During the process of osseointegration, the release of lanthanum, zirconium, calcium, and strontium cations is possible. The interaction of free cations with bone tissue can have a beneficial effect on the process of osseointegration and promote cell adhesion and proliferation on the surface of zirconium implants. An in vivo experimental study of the newly synthesized material $La_{1.95}Ca_{0.05}Zr_2O_7$ as an implant showed that fully featured bone tissue is formed in the peri-implant area, the architectonics of which can effectively resist the action of mechanical stresses, which may indicate the compatibility of the material and bone tissue in terms of physicochemical and structural characteristics. A new material based on lanthanum zirconate seems promising for use in traumatology and orthopaedics [77]. The synthesis and properties of complex oxides based on lanthanum zirconate were studied ($La_2Zr_2O_7$, $La_{0.9}Ca_{0.1}Zr_2O_{6.95}$ and $La_{0.9}Sr_{0.1}Zr_2O_{6.95}$). It has been proven that the method of materials synthesis has an impact on the density and porosity of the samples. Determination of the cytocompatibility of ceramics based on undoped and doped lanthanum zirconate showed that during the interaction of human fibroblasts with the studied ceramic materials, cell viability changes within acceptable values and is sufficient to maintain their recovery potential. However, additional research is needed to optimize the integration of implants made of this material into bone tissue [78, 79].

CONCLUSION

Ceramic materials based on zirconium dioxide with exceptional mechanical properties and biocompatibility, which do not cause cytotoxic effects and allergic reactions in surrounding tissues, feature perspectives for being used as bone substitute materials in traumatology and orthopaedics. Such materials appear to be a promising alternative to titanium implants in terms of mechanical strength, biological functionality, chemical stability, osseointegration, and antibacterial properties.

Various strategies have been used in order to improve the integration of zirconia implants into bone tissue: improving the surface of the material using physical and chemical methods, obtaining volumetric porosity, including using additive technologies; various composite materials and bioactive coatings have been also developed. New methods of creating zirconium ceramics compatible with living tissues containing bioactive ions that promote both osseointegration and bone tissue regeneration have been actively studied.

Further in vitro and in vivo studies and long-term clinical trials should evaluate ceramic implants in terms of stability, risks of inflammation, infection and mechanical complications. It will provide a clearer picture of recommendations for improving zirconia ceramics.

Conflict of interests *The authors declare that there are no obvious or potential conflicts of interest related to the publication of this study.*

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