Zirconia Based Dental Biomaterials: Structure, Mechanical Properties, Biocompatibility, Surface Modification, and Applications as Implant

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Zirconia, with its excellent mechanical properties, chemical stability, biocompatibility, and negligible thermal conductivity, is ideal for dental and orthopedic applications. In addition, the biocompatibility of zirconia has been studied in vivo, and no adverse reactions were observed when zirconia samples were inserted into bone. However, their use is controversial among dentists and researchers, especially when compared with mature implants made of titanium alloy. The advantages and limitations of zirconia as biomaterials, such as implant materials, need to be carefully studied, and the design, manufacture, and clinical operation guidelines are urgently required. In this review, the special components, microstructure, mechanical strength, biocompatibility, and the application of zirconia ceramics in biomaterials are detailly introduced. The review highlights discussions on how to implement innovative strategies to design the physical and chemical properties of zirconia so that the treated zirconia can provide better osteointegration after implantation.

Keywords: zirconia, dentistry, biocompatibility, mechanical properties, surface modification, osteointegration, implant

INTRODUCTION

The word “pottery” comes from the Greek word “keramos” (1), which means pottery or burned objects. Ceramics are usually inorganic, non-metallic, and are cooled by proper heat treatment, and are subjected to subsequent treatment to synthesize solids. Zirconium dioxide (ZrO2) nanoparticles are one of the nanomaterials mainly used in the synthesis of refractories, foundry sand, and ceramics (2–4).

Zirconium dioxide, a bioceramic, was first proposed in 1789 by German chemist Martin Heinrich Klapropse (5). ZrO2 began to play a role as a biomaterial in 1969 when researchers described its use in biomedical sciences. The application of ZrO2 in dental prostheses has been underway since 1995 (6). The strongest dental ceramics on the market are 3 mol% yttria-stabilized quadrilateral zirconia polycrystals (3Y-TZPs), known simply as ZrO2. Because ZrO2 has high strength, hardness, wear resistance, corrosion resistance, similar to the elastic modulus of steel and iron, similar thermal expansion coefficient, and high fracture toughness and chemical properties,
ZrO₂ has been widely used in biomedical fields, such as used in biosensors, cancer treatment, and hip replacement. ZrO₂ can also be used for dental crowns, post and implant (7, 8). The biocompatibility of ZrO₂ has been widely evaluated, and there has been a significant increase in the number of ZrO₂ based ceramics used as biomaterials in dentistry, which has been confirmed in both in vivo and in vitro studies (9).

At present, ZrO₂ is widely used in dentistry. ZrO₂ is used in dental implants, abutments, crown prostheses, and post (10, 11). One of the trends in dental implants is the development of new ceramic-based implants to enhance the ability of periodontal integration and long-term firm adhesion with the surrounding tissues, such as osseointegration (12–14). ZrO₂ surface characteristics determine implant success and survival after implantation. These characteristics include implant microstructure, surface composition and properties, and design factors (15). The antimicrobial ability of ZrO₂, or the ability of its surface to reduce plaque accumulation, is an important property to improve the quality and volume of soft tissues and is considered as an alternative to titanium implants. Compared with other types of ceramic materials, yttrium stabilized tetragonal zirconia (Y-TZP) has better fracture toughness and bending strength, as well as excellent wear resistance, corrosion resistance, high-temperature resistance, oxidation resistance, and hydrophilic properties (16–20). These properties can solve the problems of strength and toughness deficiency of traditional ceramic materials. The seven aspects of introducing the application of zirconia as implants: (1) the zirconium oxide as the biological safety of the implants, (2) improve the osteogenesis effect after zirconium oxide within the bone graft, (3) improve the zirconia affinity with the surrounding soft tissues, (4) a new type of molding technology of zirconium oxide, (5) the methods of surface modification of zirconium oxide to improve biological safety, (6) zirconium oxide application prospect as an implant, and (7) the disadvantages of the application of ZrO₂ in the dental field.

**BIOSAFETY OF ZrO₂**

The surface morphology of biomaterials plays an important role in determining cellular response. Different surface treatment methods are used (21).

The surface morphology and chemical composition of ZrO₂ can be improved to enhance osseointegration (22–24). ZrO₂ toughened alumina (ZTA) is a kind of material combining the unique characteristics of ZrO₂ and alumina (Al₂O₃), which has been widely used. The advantage of ZTA is that it eliminates the individual limitation of ZrO₂ and Al₂O₃, and has rich biocompatibility and aging resistance. In addition, the results of in vitro cytotoxicity test proved that the Tb³⁺ doped ZTA composites had better biocompatibility. Some studies have shown that the quality and quantity of plaque adhesion to the surface of ZrO₂ is a key factor in maintaining the health of the surrounding tissues and determining the success of ZrO₂ cultivation (25–28). The presence of a micro space between the implant fixation and the abutment has been considered as a possible etiology. According to in vitro and in vivo models, this microleakage may play a role in bacterial growth and pathogenesis around zirconia. Recent studies have shown that fewer bacteria accumulate around yttrium zirconium ceramics (Y-TZP), reducing the incidence of peri-implantitis and increasing the long-term outcome of implants (25, 29).

Some scholars have measured the steady wear rate of several ceramics in the abrasive slurry test (30–33). The wear rate of the test cylinder was measured by turning it over in a variety of water-borne abrasive slurries. Mg-PSZ is the most wear-resistant material tested, only 0.05–0.2 of the wear rate of alumina. The impressive wear resistance of PSZ discussed above is the result of the surface strengthening phenomenon in which the tetragonal ZrO₂ precipitates are converted to a monoclinic structure through a specific wear process (34–37). The area of wear is, therefore, in a state of compression, and this compression tends to inhibit further removal of the material. The study aims to report the biocompatibility of PSZ based on preliminary results from in vitro and in vivo trials (38).

**EXPLORATION OF ENHANCING THE OSTEOGENIC ABILITY OF ZrO₂**

In dentistry, there are several types of bone graft materials that can be used directly for bone grafting (39, 40). An ideal feature of bone scaffolds is their ability to resist the functional load. Allergic reactions caused by some metal alloys are a disadvantage of metal prostheses, which have prompted the research and application of more biocompatible ceramic prostheses (41). ZrO₂ has high bending strength (900–1,200 MPa), excellent hardness (1,200 Vickers), low thermal conductivity, strong corrosion-resistance and biocompatibility, reducing platelet aggregation, surface wettability, surface energy, and surface morphology (42).

In general, ZrO₂ based ceramics are chemically inert and have no adverse reactions to general tissues, and have been designed for clinical use in recent years. Partially stable ZrO₂ is used in dental implants for its osseointegration, good biocompatibility, high strength, compressive resistance, and crack growth resistance. The biosafety and biocompatibility of ZrO₂ and the interaction of bone/zirconia have been studied. The long-term success of the implant is largely dependent on the ability of the material to blend with its surroundings. ZrO₂ dental implants are a better alternative to conventional immediate implants because they can use CAD/CAM technology into the shape of the root. In hard tissue engineering, calcium phosphate (CAP) ceramics, such as hydroxyapatite and tricalcium phosphate, have attracted wide attention due to their excellent biocompatibility and bone conductivity (43). Most clinical reports indicate that their poor mechanical properties, such as low strength and fracture toughness, limit their widespread use in hard tissue implants. Among all kinds of zirconia, Y-TZP is the main component of ZrO₂ implants and is considered as an orthopedic biomaterial. Studies from cell cultures to full-scale animal models have shown that the osseointegration observed on the optimized ZrO₂ surface is as good as, or better than, different materials (i.e., titanium alloys). Porous zirconia scaffolds can also be used as drug delivery
carriers to enhance bone response. Biological responses to dental implants are determined by several physical and chemical characteristics of the implant surface, including mechanical and physicochemical properties (44). ZrO₂ coating can induce the accumulation of apatite in the simulated body fluids, which can promote the adhesion and proliferation of osteoblasts. ZrO₂ as hydroxyapatite (HAP)/ZrO₂ composite material can improve the low bond strength caused by the mismatch of thermal expansion coefficient between porous HAP and main alloy components, thus promoting bone regeneration. Several studies have evaluated the reaction of bone with optimized zirconia scaffold surfaces. A recent study attributed the increase in cell survival to the internal structure of the scaffold, rather than the types of coating material used (45).

Some scholars prepared nHA/PA66/YTZ bone screws, implanted them into the joints of rabbits, and studied their biocompatibility and bioactivity in vivo. For aesthetic reasons, zirconia has been used as implant material in clinics. The high elastic and thermal modulus, low plaque affinity, and high biocompatibility of ZrO₂ ceramics may make them an alternative to titanium in implant dentistry. In addition, ZrO₂ had an inhibitory effect on bacterial colonization.

**EFFECTS OF ZrO₂ ON SOFT TISSUE**

Because ceramic implants are made with a polished surface at a very high temperature, they can reach the gingival tissue and help with the maintenance of gingival structures (46). Several studies in various animals have reported zirconium peroxide as a ceramic material for soft tissue implantation, followed by the analysis of systemic toxicity and adverse reactions in soft tissues (47, 48). After implantation, the zirconia material was wrapped in a thin layer of fibrous tissue for 12 weeks, regardless of the time of implantation. In all cases, ZrO₂ did not produce any form of adverse tissue reactions, indicating that ZrO₂ is a biocompatible ceramic material. In conclusion, zirconia do not cause cytotoxicity in soft tissues, even if it is intraperitoneally injected and fibers are found in the lymph nodes. ZrO₂ and titanium were used as soft tissue implants. Compared with ZrO₂, the inflammatory infiltration, microvessel density, and vascular endothelial growth factor expression around titanium implants were higher. In addition, cell proliferation on the surface of ZrO₂ was also higher than that on the surface of titanium (39).

ZrO₂ powders of 87 kinds were tested with different cell lines and extracts were extracted by different methods (cell viability and MTT analysis) (49). When the fibrous cells were co-cultured with ZrO₂, ZrO₂ had no cytotoxic effect. The 3T3 fibroblasts were more adhesive and diffusive on the ZrO₂ material observed by using scanning electron microscopy. The cytotoxic effects of ZrO₂- Yttrium oxide (Y₂O₃) on human lymphocyte mitogen were compared with those observed in the culture (50). It was confirmed that the cytotoxic effects of alumina and ZrO₂ were similar and lower than those of TiO₂. In the study on the colonization of bacteria in ZrO₂, some scholars have observed many ectopic epithelial cells on the surface of ZrO₂, suggesting that ZrO₂ may be a promising material that can enhance the adhesion of epithelial cells (51–53).

**ZIRCONIUM DIOXIDE FORMING TECHNOLOGY TO IMPROVE BIOCOMPATIBILITY**

Traditional ceramic molding methods, such as dry pressing, isostatic pressing, sliding casting, strip casting, and injection molding, have been used to prepare ceramics (54–56). However, these traditional ceramic forming techniques have some limitations, such as they cannot be used for parts with complex shapes (with inner holes, sharp corners, etc.) and parts requiring high precision. The traditional ceramic molding process needs mold manufacturing and post-treatment, and it is time-consuming and expensive (57, 58). The last decade has also witnessed the development of new processing technologies for producing zirconia, such as CAD, CAM, and rapid prototyping. In addition, some researchers have used the water system of sol-gel, powder pulp, and bionic solution to form the uniform coating on the surface of zirconia through the complex shape of implants and porous bone scaffolds.

Some scholars have prepared the cap ceramic and glass composite coatings on ZrO₂ substrate. ZrO₂ ceramics are widely used as substrates in hard structures due to their excellent strength and fracture toughness. Cap-ZrO₂ composite materials and Cap-coated porous ZrO₂ scaffolds have proved their excellent mechanical properties and cellular responses (59).

Due to its rapid prototyping technology, stereolithographic 3D (SLA-3D) printing technology has been widely used in the preparation of complex Al₂O₃, ZrO₂, and HAP ceramic parts (60).

Zirconia toughened alumina ceramics (ZTA) have high hardness, high strength, high toughness, and good thermal shock resistance (61). However, 3D rapid prototyping technologies including fused deposition modeling (FDM), selective laser sintering (SLS), stereolithography (SLA) can save time and allow the manufacture of any given shape and size model compared with the traditional part forming techniques. It has obvious advantages in the complex parts formation. At present, some important conclusions and achievements have been made in the preparation of ZTA components by SLA-3D printing technology (62–64).

Aluminum oxide is a highly biocompatible ceramic material that has good aesthetic properties but is associated with a high risk of fracture (65). Because of this key weakness, ZrO₂ was introduced as a substitute for titanium. Zirconia is divided into monoclinic (M), cubic (C), and tetragonal (T) phases according to different temperatures. The M-phase is fragile at room temperature and therefore requires stabilization in technical applications to prevent the transition from the tetragonal (T) to the monoclinal (M) phase. Y₂O₃ is a common stabilizer for maintaining the ZrO₂ phase. Y₂O₃-stabilized quadrangular polycrystalline zirconia (Y-TZP) has high strength, toughness, and biocompatibility, which can cause a biological reaction similar to that of titanium. Therefore, Y-TZP is considered a
potential substitute for titanium (66–68). However, ZrO₂ exhibits structural instability when degraded at low temperatures due to the tetragonal (T) to the monoclinic (M) phase transition under wet or stress conditions. On this basis, some scholars developed 3Y-TZP of co-doped Nb₂O₅ and Ta₂O₅ and (Y, Nb)-TZP and (Y, Ta)-TZP. These (Y, Nb)-TZP and (Y, Ta)-TZP biomaterials have a good ability to support osteogenesis, and can be used as substitutes for existing titanium dental implant materials (69–71).

INFLUENCE OF SURFACE MORPHOLOGY OF ZIRCONIA ON BONE INTEGRATION

Surface modification strategies can be generalized into three broad categories: physical (sandblasting, plasma spraying, ion implantation, laser treatment, and pulsed magnetron sputtering), chemical (acid etching, anodizing, and micro-arc oxidation), and biological (protein absorption and ion interaction) (12).

Zhao et al. (72) found that the tensile strength increased from 116 ± 13 to 274 ± 61 MPa when 0.1 wt.% of Li was added to Zn. Dai et al. (73) also found that the tensile strength and elongation were significantly improved compared with pure Zn when 0.5wt.% Li alloy was added. A ZrO₂ nano-film was constructed on the surface of Zn-0.1Li alloy (ZL) to control the corrosion rate of the matrix (72, 73).

Kawashima et al. investigated the surface characteristics of the annealed HAP/zirconia composite. They concluded that the HAP/zirconia has mechanical compatibility and a potential for good biocompatibility with bone tissue (74). ZrO₂ has also shown a superior ability to induce bone formation in biological environments. In final, silver inhibits bacterial growth, thus reducing the likelihood of infection during surgery, but may also improve mineral deposition and the expression of osteogenic markers. Bone integration was studied by biochemical analysis as well as bone histomorphometry and computed tomography (75).

So far, sandblasting or acid erosion blasting (SLA), dipping and plasma spraying have been the main methods for surface modification of titanium implants with ZrO₂ (76). Plasma spraying is a powerful surface modification tool with a wide selection of coating materials, such as metals, ceramics, and composites. Plasma spray coating can significantly improve the physical and chemical properties of the substrate material. By controlling the relevant parameters, the surface morphology, roughness, porosity, elemental composition, and crystallization degree can be easily controlled (77).

It has been reported that ZrO₂ nanoparticle has better biocompatibility compared with other nanomaterials such as iron oxide, TiO₂, and zinc oxide (ZnO). Consistent with these results, other studies have reported that nanoparticles of ZrO₂ can induce mild or no cytotoxic effects, and only few studies have shown mild cytotoxic potential (78, 79). Some researchers used TiO₂ as a control group, which is a traditional nanomaterial with similar physical and chemical properties. TiO₂ and ZrO₂ nanoparticles were cultured with MC3T3-E1 to observe osteoblast activity, oxidative stress and cell morphology, and the reaction of osteogenesis. If TiO₂ and ZrO₂ nanoparticles are in high concentrations, the toxicity will produce a large number of ROS, and ROS in the cytotoxicity induced by TiO₂ and ZrO₂ nanoparticles plays a key role including the cell vitality, apoptosis and necrosis, and the changes in cell morphology of MC3T3-E1 cells (80, 81).

APPLICATION OF ZrO₂ IN IMPLANT ABUTMENT

The white color of ZrO₂ is also aesthetically beneficial, as it can overcome the problems of penetration and staining that cover the gums. Similarly, the non-metallic appearance of ZrO₂ appeals to patients who require metal-free implants for aesthetic and other reasons. Among the metal-free implants, ZrO₂ abutments are often chosen as the first choice, especially in the growing number of patients with thin gingival soft tissue.

THE SHORTCOMINGS OF ZrO₂ AS DENTAL BIOMATERIALS

Due to its excellent mechanical properties, high-temperature stability, biological safety, and low thermal conductivity, zirconia ceramics have been widely used in clinical applications, especially in the restoration of posterior crowns and fixed bridges. However, under a relatively low temperature and humid environment, zirconia changes from a partially stable tetragonal phase to a monoclinic phase, that is, the phenomenon of low-temperature aging, which affects its mechanical properties (82, 83).

CONCLUSION

In this review, the application prospect and research status of ZrO₂ in the dental clinic have prospected, and the ZrO₂ based ceramics are reviewed. ZrO₂ has wide application prospects in implant, post-core, tooth crown, and so on. Extensive in vitro and in vivo studies have demonstrated high fracture resistance and can be used in stress-bearing areas. The characteristics of the ZrO₂ surface, such as the lack of plaque adhesion to the ZrO₂ and the absence of micro gaps between the fixtures, also discourage bacterial invasion. ZrO₂ platform restoration is a promising alternative to metal platform restoration. The bio-safety of ZrO₂ due to aging and wear of ZrO₂ restorations should be further evaluated to guide the safe use of ZrO₂ materials. The biocompatibility of ZrO₂ has been well-proved. The experiments of Y-TZP in vitro and in vivo show that it has good biocompatibility and has no adverse reactions to cells and tissues. With the improvement of the technology in preparing ZrO₂ and the modification of the surface of ZrO₂, the bio-safety of ZrO₂ will be affected, which is beneficial to the application of ZrO₂ as an implant in dentistry.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.
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