Future prospects of zirconia for oral implants —A review

Masao YOSHINARI

Oral Health Science Center, Tokyo Dental College, 2-9-18 Kandamisaki-cho, Chiyoda-ku, Tokyo 101-0061, Japan
Corresponding author, Masao YOSHINARI; E-mail: yosinari@tdc.ac.jp

Zirconia have been applied to dental implants as well as fixed dental prostheses due to their mechanical, esthetic and biocompatible performance. Moreover, they offer an advantage over titanium (Ti) implants, in that there is no risk of discoloration or hypersensitive reaction with allergy. In this review, the durability and tissue-compatibility of zirconia for the oral implants was mainly discussed.

INTRODUCTION

Despite decades of titanium (Ti) as the gold standard in oral implantology, the search for alternatives has been growing, because of its disadvantages of discoloration of the peri-implant soft tissue, possible hypersensitivity, and the debated contribution to peri-implantitis development1-3). Zirconia, tetragonal zirconia polycrystal (TZP) in particular, gained increasing importance due to their mechanical, esthetic and biocompatible performance for dental implants. In the recent reviews, it is reported that zirconia implants are a promising alternative to Ti with comparable osseointegration, a superior soft-tissue response in short-term outcomes4-7). However, more evidence data are needed to confirm the presently evaluated outcomes. Table 1 shows the suitability of zirconia as implant materials compared with Ti (Ti alloy) and apatite-coated Ti. This review is focused on the durability and tissue-compatibility of zirconia, which should be mainly elucidated, for the oral implants.

DURABILITY (FATIGUE PROPERTIES)

Little information is available on the durability of zirconia implants with exposure to cyclic fatigue8-11). This is important, as Y-TZP may undergo low-temperature degradation in the aqueous solutions encountered in the oral environment, possibly resulting in a significant reduction in strength and toughness12,13).

Hot isostatic press (HIP) treatment and increased alumina content are some methods used to improve the strength of conventional zirconia. In general, fixed TZP prostheses are fabricated by pre-sintering compaction and post-sintering at around 1,350°C. HIP under high pressure in an inert atmosphere is considered to be suitable for application to the implant body, as oral implants are not fabricated for the individual patient. This means that high mechanical performance can be ensured by HIP processing without resort to a complicated fabricating procedure.

Surface roughening of Ti implants by gridblasting and acid-etching, for example, is usually used to enhance osteogenesis at the implant/bone interface. Such surface treatment, however, carries the risk of introducing flaws or microcracks into the zirconia surface that may accelerate failure during clinical use14). Few studies were reported about the cyclic fatigue properties of TZP implants with a roughened surface. Therefore, the influence of surface roughness on fatigue resistance in zirconia was evaluated in vitro study using Y-TZP (conventional Y-TZP), Y-TZP HIP (HIPed Y-TZP) and NanoZR (Ce-TZP/Al2O3) (Table 2)15,16). Biaxial flexural strength was determined by both static and cyclic fatigue testing (Fig. 1). Fracture strength in the cyclic fatigue test showed a remarkable 50–70% decrease in comparison with that in the static test under all conditions. Y-TZP HIP showed larger fatigue strength than other specimens. From the clinical point of view, Y-TZP HIP treated by gridblasting and acid-etching was much higher than 320 MPa, the required fatigue strength of Y-TZP in surgical implants as specified in ISO 13356.

The cyclic fatigue resistance of zirconia in a clinical situation was also investigated according to standardized implant fatigue testing protocol in ISO 1480117) using cylinder specimens with 3.0-mm diameter treated with gridblasting and acid-etching (Fig. 2). The results indicate that Y-TZP HIP has sufficient fatigue resistance for application to one-piece dental implants even though a 3.0-mm diameter. Two-piece implant with hollow-cylinder is desirable to have a requisite...
Table 1  Suitability of zirconia as implant materials compared with Ti (Ti alloy) and apatite-coated Ti

| Property                          | Zirconia | Ti (Ti alloy) | Apatite-coated Ti |
|-----------------------------------|----------|---------------|-------------------|
| Strength                          | ◎        | ○             | △                 |
| Ductility                         | ×        | ◎             | △                 |
| Durability (Fatigue)              | △        | ○             | △                 |
| Elastic modulus (Young’s modulus) | ×        | △             | △                 |
| Workability (Dimensional accuracy)| △        | △             | △                 |
| Esthetics (Translucency)          | ○△       | ×             | △                 |
| Corrosion, Tarnish                | ◎○△      | ◎             | ○                 |
| Allergy                           | ○        | △             | ○                 |
| Antagonistic tooth wear           | △        | ○             | ○                 |
| Osseointegration                  | ○△       | ◎             | ○                 |
| Tissue compatibility              | △○       | △             | ◎                 |
| Biofilm formation                 | △○       | ×△            | ×△                |

Table 2  Materials used and surface treatment for biaxial flexural testing under static and cyclic fatigue testing

| Code  | Composition (mass%) | Manufacturer                  | Sintering condition           |
|-------|---------------------|-------------------------------|------------------------------|
| Y-TZP | ZrO₂ balanced; Y₂O₃ 5.16; Al₂O₃ 0.25 | Tosoh                         | 1,350°C, 2 h, in Air          |
| Y-TZP HIP* | ZrO₂ balanced; Y₂O₃ 5.16; Al₂O₃ 0.25 | Panasonic healthcare         | 1,300°C, 1 h, 147 MPa in Ar   |
| NanoZR | ZrO₂ balanced; Al₂O₃ 21.5; CeO₂ 10.6 | Panasonic healthcare         | 1,450°C, 2 h, in Air          |

*HIP: hot isostatic press

| Code       | Treatment                                      |
|------------|------------------------------------------------|
| MS         | Mirror-polished finally with colloidal silica  |
| SB150      | Grid-blasted with 150 μm-alumina               |
| SB150E+HF  | Etched SB150 with HF (46%) for 15 min          |

minimum thickness in pipe wall of 0.6 mm (Data is not shown). These results suggest that the enhanced fatigue strength of HIPed Y-TZP make it a promising material for application to oral implant systems.

**TISSUE-COMPATIBILITY**

Since implant materials including zirconia contact many different tissues, those materials must have optimum surface compatibility with the host bone tissue and soft tissue, as well as anti-microbial properties on an exposed region of the mucosa. Such materials can be created under well-controlled conditions by modifying the surfaces of materials that contact those tissues. “Tissue-compatible zirconia implants”, which are compatible with all host tissues, should be developed by controlling the “surface topography” and “surface physico-chemistry” (Fig. 3).

Surface topography has marked effects on cell behavior. Generally, cell adhesion is greater on rough
Fig. 2 Cyclic fatigue resistance in a clinical situation using cylinder specimens with 3.0-mm diameter treated with grid-blasting and acid-etching. 
A: Schematic of test set-up for cyclic fatigue test. (a); HIPed Y-TZP specimen (white) and CP-Ti specimen, (b); cylinder specimen covered with hemispherical cap, (c); fixed in specimen holder. B: Fracture force (TZP) and yield force (Ti) under static loading (Static) and cyclic fatigue tests (Fatigue).

Fig. 3 Schematics of tissue-compatible zirconia implants.

Fig. 4 Isoelectric point (x-axis) and hydropathy index (y-axis) of amino acids.

Bone tissue/implant interface (osseointegration)
1) Influence of surface topography
The gridblasted with large grid and acid-etched (SLA), most of Ti implants currently in use[18], is expected to improve the osseointegration capability for zirconia implants. It is reported that modified zirconia surfaces clearly demonstrate faster osseointegration than that on untreated surfaces[19], and achieving good stability in bone and the histological results that no statistical differences showed between the zirconia and the Ti implants[20].

The behavior of human mesenchymal stem cells (hMSCs) on Y-TZP and CpTi with different surface topography including mirror-polished (MS), gridblasted with 150-µm alumina (SB150), and SB150+acid-etched
(SB150E), was investigated\textsuperscript{21}). Acid-etching with \%HF-RT-15min and 36\%HCl+96\%H\textsubscript{2}SO\textsubscript{4}-70°C-3min for TZP and Ti were carried out, respectively. The SEM showed that micro- and nano-topographies were created on both TZP and CpTi SB150E surfaces. The SB150E surface of TZP showed more fine texture with a comparatively large configuration compared to that of CpTi (Fig. 5). The proliferation ability, ALP activity, expression of Runx2 on the SB150E specimens was significantly higher than those on MS and SB150 specimens. Comparison in

**Fig. 5** SEM images of mirror-polished (MS), grid-blasted with 150-µm alumina (SB150), and grid-blasted with 150-µm alumina and acid-etched (SB150E) specimens for investigating the cell behavior.

**Fig. 6** Comparison of cell behavior between TZP and CpTi. (a), (b) cell proliferation, and (c), (d) ALP activity for MS and SB150E, respectively.
cell behavior between TZP and CpTi is shown in Fig. 6. In MS surfaces (Figs. 6-a, c), both cell proliferation and ALP activity on CpTi exhibited higher tendency than that on TZP. In contrast, in SB150E surfaces (Figs. 6-b, d), reverse tendencies were recognized, indicating that micro- and nano-topography on TZP might have more advantageous potential than CpTi on hMSCs. Furthermore, the effect of surface topography on osteoblast-like cells (MC3T3-E1) behavior on TZP showed the same results as on hMSCs. These results indicated that grid blasting and acid-etching on TZP may offer a promising method with synergetic effect of micro- and nano-topographies for enhancing the osteogenesis in clinical application.

2) Influence of surface physico-chemistry

As for surface physico-chemistry, surface modification with a thin calcium phosphate coating is useful in producing rapid osteogenesis and strong osseointegration. In particular, thin carbonate-containing hydroxyapatite (CHA) coatings using a molecular precursor method are useful for zirconia implants. The molecular precursor method with a solution composed of an EDTA-calcium complex is very simple, and the film thickness is less than 1 µm, and showed an excellent degree of adhesion to the substrates. As the CHA coatings deposited by molecular precursor method to TZP, initial cell adhesion of osteoblast like cell (MC3T3-E1) was enhanced, and marked progress of actin filaments was observed on TZP-CHA compared to on bare TZP. In addition, cell proliferation on TZP-CHA was significantly higher than that on bare TZP. Collagenous fibers with mineral precipitants accompanied by phosphorous and amino groups were also observed on TZP-CHA. In addition, animal experiments were performed using CHA coated TZP implants. Histomorphometrical evaluations showed a significantly higher bone-to-implant contact ratio and bone mass on CHA coated TZP after implantation into the femoral trabecular bone of rabbits. These results indicate that thin CHA coating with molecular precursor method offers promise as a means of enhancing cell response and osteogenesis in bone tissue.

The other strategy is a superhydrophilic treatment onto zirconia. Super-hydrophilic treatment comprised application of stored in distilled water immediately after blasting and acid-etching (Blast/Etch), oxygen plasma (Plasma) and ultraviolet light (UV). The Blast/Etch, Plasma and UV specimens showed the superhydrophilicity that is the water contact angle is almost zero. X-ray photoelectron spectroscopy elicited a marked decrease in carbon content and an increase in hydroxyl groups (Fig. 7). Superhydrophilic treatments enhanced initial attachment of osteoblast-like cells and a change in cell morphologies. Finally, Blast/Etch, Plasma, or UV treatment has potential in the creation and maintenance of superhydrophilic surfaces and enhancing initial attachment of osteoblast-like cells.

Soft tissue/implant interface (fibrointegration)

Dental implants lack the structures that maintain the continuity between the epithelium and connective tissues that are normally formed by hemidesmosomes and the basal lamina. Peri-implant epithelium has a reduced capacity to act as a proliferative defense mechanism than does the junctional epithelium. Therefore, to prevent the invasion of the bacteria and epithelium, a system of biological sealing is required. It is reported that behavior of the fibroblast and epithelial cell response on zirconia and Ti alloy is influenced by both the material and surface topography, and peri-implant soft tissue histomorphology composition in implant abutments were similar on zirconia and Ti.

On the surface topography, multi-grooves, a combination macro-grooves and micro-grooves, are considered to be useful for extracellular matrix (ECM) production with contact guidance (Fig. 1). These surface topographies may help in providing a biological seal around the zirconia implants.

As for the surface physico-chemistry, coating of Ti alloy with laminin-332 (laminin-5) is reported to promote cell attachment and hemidesmosome assembly in
gingival epithelial cells\textsuperscript{32}. In addition, tresyl chloride treatment is used to adhere the fibronectin onto Ti in contact with subepithelial connective tissues\textsuperscript{33}. Accordingly, modifying with cell-adhesive ECM such as fibronectin or laminin-332 on zirconia implant is considered to be effective for soft tissue/implant interface.

The surface wettability of an implant material is the important factors in the process of making a soft tissue barrier (Fibrointegration), possibly regulating protein adsorption and subsequent cell behavior\textsuperscript{34,35}. The fibronectin adsorbed much more on a hydrophilic surface while albumin dominated on a hydrophobic surface in a competing mode, suggesting that the importance of the surface wettability of biomaterials on initial cell attachment and spreading\textsuperscript{36}.

Surface modifications with ultraviolet light (UV) and oxygen plasma (Plasma) onto TZP were performed\textsuperscript{37}. The results of cell culture experiments using human oral keratinocytes showed expression of laminin 332-specific γ2 chain in and integrin β4 was promoted only in Plasma specimens even though superhydrophilicity was obtained in both UV and Plasma specimens (Fig. 8-A). The Integrin α6β4 is a cellular adhesion molecule that binds to laminin 332 in the extracellular matrix and nucleates the formation of hemidesmosomes. In the Plasma group, laminin γ2 was distributed with more pronounced features that completely covered the periphery of the cells. Immunofluorescence images of actin filaments showed that the cells were obviously larger on the Plasma-treated TZP surfaces than on the untreated and UV-treated surfaces after 24 h of incubation (Fig. 8-B). On the cell morphologies, lamellipodia were observed, and the cells spread even more, especially in the Plasma group, and became completely flat, with good attachment to the substrate (Fig. 8-C). TZP surface treated with oxygen plasma could accelerate the turnover of peri-implant epithelium (PIE) with the promotion of cell migration.

Photocatalytic activity was believed to be closely

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Confocal laser scanning microscope images and SEM images of human oral keratinocytes attached to TZP after 24 h of cultivation.\newline
control: untreated, UV: ultraviolet-light irradiation, Plasma: oxygen-plasma irradiation.\newline
(A) stained for nuclei using DAPI (blue), by antibody to laminin 332-specific γ2 chain (red), and by antibody to integrin β4 (green). (scale bars: 50 µm), (B) stained for nuclei using DAPI (blue), and for filamentous actin stress fibers using phalloidin (green). (scale bars: 50 µm), (C) SEM images (Cell morphology) (scale bars: 20 µm).}
\end{figure}
involved in the above-mentioned differences. In the case of Ti, UV light energy of greater than 3.2 eV, corresponding to a wavelength of less than 387 nm, is needed to induce the photocatalytic activity of TiO\(_2\) (anatase) to excite an electron from the valence band to the conduction band\(^{38}\). ZrO\(_2\) also shows photocatalytic activity similar to TiO\(_2\)\(^{39,40}\). The band gap of ZrO\(_2\) is 5.82 eV, which corresponds to a wavelength of approximately 213 nm. Therefore, in order to induce photocatalytic activity on ZrO\(_2\), larger energy is required than that for TiO\(_2\). Plasma generated energy of 5.0–13.1 eV, corresponding to a wavelength of 95–250 nm. Accordingly, Plasma enabled the induction of photocatalytic activity on ZrO\(_2\). In contrast, UV irradiation with a wavelength of around 250 nm such as UV-C has quite fewer energy to induce the photocatalytic activity on ZrO\(_2\), unless high-energy UV irradiation, that is, a wavelength of less than 213 nm, such as excimer UV, were used. Therefore, it is believed that the increase of basic hydroxyl groups and polar components on the Plasma specimen was greatly based on the photocatalytic activity, and that the initial attachment capability of human oral keratinocytes was promoted by the Plasma.

Thus, TZP surface treated with oxygen plasma promotes the initial attachment capability of human oral keratinocytes with enhancing the extracellular matrix such as laminin\(\gamma_2\), leading to an important consideration in the clinical application of this technology. In addition, atmospheric-pressure plasma is useful in chairside application to zirconia abutment due to the treating time of this method is quite few of about 10 s.

Oral fluid/implant interface
Microbial plaque accumulation surrounding dental implants may develop into peri-implantitis, which is defined as inflammation around an implant, with accompanying bone loss. Biofilm is primarily formed by early-colonizing bacteria (Streptococci), after that it is formed by late-colonizing pathogenic bacteria including periodontopathic bacteria\(^{41}\). It is therefore important to maintain the surface of dental implants exposed to the oral cavity (oral fluid/implant interface) free of biofilm to prevent peri-implantitis. Several studies have reported that there is less difference in biofilm formation between zirconia and Ti abutments\(^{42,43}\). There are at least two methods of inhibiting the formation of microbial plaque. The first is to inhibit the initial adhesion of oral bacteria. The adhesion of bacteria is greatly influenced by electric charges on the implant surface because bacteria have a large specific surface area. The second is to inhibit the colonization of oral bacteria, which involves surface antimicrobial activity.

1) Initial adhesion of oral bacteria
The in vitro adherence (initial attachment and colonization) of selected periodontopathic bacteria to two kinds of TZP (Y-TZP, NanoZR) was compared with that to Cp-Ti\(^{44}\). As a result, no significant differences among specimens were observed in the adherence, although a decrease was observed in the adherence to saliva-coated specimens (Fig. 9). These results indicated that the adherence of the periodontopathic bacteria on TZP was similar to that on Cp-Ti, suggesting that a strategy is required for inhibition of the bacterial adherence to TZP.

2) Antimicrobial activity
One possible strategy is surface modification to create antimicrobial activity is use of fluorides, which is widely used as a highly effective anticaries agent. The principal antibacterial mechanism is considered that a metal fluoride complex affects bacterial metabolism as an enzyme inhibitor. On the Ti specimens, it is reported that the adherence of S. mutans was significantly lower in the groups stored in fluoridated saliva\(^{45}\), and F-implanted specimens inhibited the growth of both P. gingivalis and A. actinomycetemcomitans\(^{46}\). Accordingly, surface modification with fluorides against zirconia may be useful.

Atmospheric-pressure plasma irradiation is also
considered to be effective for antimicrobial activity against zirconia as same as that against Ti. The oxygen-plasma enabled the induction of photocatalytic activity on ZrO2 as above mentioned in soft tissue/implant interface. Furthermore, surface modification with conjugated molecules consisting of zirconia-binding peptides and antimicrobial peptides is a possible candidate for reduction of biofilm formation on zirconia implants.

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