An introduction of biological performance of zirconia with different surface characteristics: A review

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Zirconia (ZrO₂) ceramic is widely used in dentistry as a clinical dental biomaterial. In this review, we are focusing on and summarizing the biological performance of zirconia under different surface characteristics. We have included an initial tissue cell attachment study on zirconia and bacterial adhesion on zirconia. Our results suggest that surface modifications applied on zirconia may change the interfacial surface characteristics e.g. surface roughness, surface free energy, and chemistry of zirconia. The modifications also result in advanced biological performance of zirconia, including enhanced tissue cell attachment and reduction of bacterial adhesion. The recent laboratory research has provided many interesting modification methods and showed clinically interesting and promising outcomes. A few of the outcomes are validated and have been applied in clinical dentistry.

Keywords: Zirconia, Surface characteristics, Interface, Biological performance, Bacteria

INTRODUCTION

Zirconium dioxide (ZrO₂), zirconia, has been widely applied in contemporary dentistry due to its good mechanical properties, aesthetic appearance, and outstanding biocompatibility. It has been used as the major ceramic dental material applied in indirect restorations, dental implant abutments and also as a major ceramic dental material applied in indirect restorations, dental implant abutments and as full dental implants. A variety of surface modification treatments on zirconia have been scientifically assessed for the purpose of improving its adhesion. The biological interfacial aspects will be affected after these surface treatments. The definition of “an interface” is “a surface forming a common boundary of two bodies, spaces, or phases” by Merriam-Webster Dictionary. The surfaces between two matters would form an interface, which is a boundary between the two bodies. As such, a surface treatment will result in the change of interfacial surface characteristics, which play an important role also in the biological performance of zirconia.

The concept of “race for the surface” which is related to biological interfacial aspects of implant surface is defined. It describes the competition between tissue cells and bacterial adhesion on the implant surface (be it metallic or ceramic). On the one hand, if the tissue cell prevails over bacteria, the soft tissue can form an implant neck (abutment) seal preventing the invasion of oral microbial. That said, osseointegration will take place on the interphase between the zirconia implant surface and bone. On the other hand, if the colonization of bacteria overcomes the cell attachment, the soft tissue around the implant neck may break, resulting in subsequent peri-implant mucositis and peri-implantitis.

Peri-implant mucositis is considered as the precursor of peri-implantitis. When the inflammatory resorption of the surrounding alveolar bone takes place, peri-implantitis will follow clinically. A meta-analysis review reported that the prevalence for peri-implant mucositis was estimated to be 43% and for peri-implantitis of 22%. Peri-implant mucositis and peri-implantitis are caused by the bacteria adhesion and subsequent biofilm formation on the implant surface, and are considered as the underlying reason for lower success rate. Dental implants may have high rates of long-term survival. However, when considering their success rate instead of survival, the rates decrease significantly. The implants and restorations on them (crowns) may be compromised by mechanical and biological complications and result in a low success rate.

A systematic review evaluated the survival and success rates of osseointegrated implants in longitudinal studies, which were conducted in a follow-up period of more than 10 years. The survival rates in all of the studies have been reported with the cumulative mean values of 94.6%. The success rates were ranging from 34.9% to 100% in fourteen studies, due to the variation in the success criteria used. Seven studies (50%) among them used the same criteria proposed by Albrektsson et al. demonstrating a cumulative mean success rate of 89.7%.

CELL ADHESION ON ZIRCONIA

Cell adhesion is closely connected with the subsequent process of cell proliferation and cell differentiation. It has a great influence on the biomaterial and tissue integration. Protein adsorption is considered as the first step of cell attachment on a material surface. Surface characteristics are vital factors for the interaction between cell and material, which may regulate various intracellular signal connection associated with cell
attachment, proliferation, and differentiation\textsuperscript{26-28}). That said, the influence of surface characteristics on cell attachment and proliferation, \textit{e.g.} surface roughness, surface free energy (SFE), and surface chemistry have been widely investigated in dental research\textsuperscript{29-31}. We shall discuss this in details below.

\textit{Surface roughness}

The exploration of how roughness affects cell response is essential to understand and improve the performance of implant materials. It is widely accepted that a material with a relatively high surface roughness can accelerate initial cell attachment on roughened implant surfaces compared to smooth surfaces\textsuperscript{32-35}. The underlying reason may be that the roughness gradient can induce significant changes in the cell area, aspect ratio, and solidity. Nano-roughness parameters were reported to be correlated with cell solidity linearly, while micro-roughness parameters appeared to correlate to cell area nonlinearly, highlighting the importance of multiscale optimization of implant surface roughness and topography to induce the desired cell response\textsuperscript{36}. It has been demonstrated that microgrooves created on rough zirconia surface could modify the morphology and guide the size and alignment of human fetal osteoblasts. Zirconia surfaces with microgrooves of 30 µm (width) and 70 µm separation between grooves can enhance alkaline phosphatase (ALP) and alizarin red (ALZ) expression of human fetal osteoblasts\textsuperscript{37}. Another phenomenon reported was that the nano-patterned zirconia surface with arrays of nano-scale islets can improve the bioactivity of human fetal osteoblast-like cell line (hFOB), including cell proliferation and ALP activity, compared to the control substrates\textsuperscript{38}.

1. Grit blasting

Several surface modifications have been conducted on zirconia to modify surface roughness to promote cell attachment, \textit{e.g.} grit blasting ("sand blasting")\textsuperscript{39-40}, sterilization\textsuperscript{41}, and hydrofluoric acid etching\textsuperscript{39,42,43}. It was found that grit blasting can improve the mechanical properties of bioactive glass infiltrated zirconia with better osteoblast cell response\textsuperscript{44}. However, it was observed that grit blasting after sintered zirconia will damage the surface structure and result in unsatisfied mechanical properties of zirconia. That said, the method of roughening zirconia surface by grit blasting before the final sintering step was employed. The novel method was showed to increase the surface roughness of zirconia and enhance the osteoblast cell adhesion without impairing the original mechanical strength and phase transformation of zirconia\textsuperscript{45}.

2. Hydrofluoric acid (HF) etching

The surface roughness of zirconia can be increased, indeed, by grit blasting or unconditional HF etching\textsuperscript{39,42}. Grit blasting and HF etching can improve the initial attachment of osteoblast-like cells: the response of MC3T3-E1 osteoblast cells to the rough glass-infiltrated zirconia created by HF etching treatment was enhanced\textsuperscript{46}. The time of HF etching can also influence the surface roughness, and flexural strength. However, a drawback of this method was that severe HF etching (\textit{i.e.} too long a time, too concentrated acids) can compromise the mechanical strength of zirconia, which in turn affects the long term clinical performance\textsuperscript{47}.

3. Laser irradiation

Laser (light amplification by stimulated emission of radiation) irradiation has been also applied to increase the surface roughness\textsuperscript{48} and improve the bioactivity of zirconia\textsuperscript{49,50}. It was shown that cell proliferation, ALP activity, osteocalcin mRNA levels, and ALZ staining of MC3T3-E1 were all more effective on the rough surface created by irradiation with a fiber laser than on a polished smooth surface. Moreover, under laser treatment, the bone-implant contact ratio and removal torque on zirconia implants placed in rat tibiae were increased. It was suggested that laser irradiation produced adequate surface roughening of zirconia to support osseointegration\textsuperscript{51}. It is noteworthy that another study showed that laser surface treatment showed positive effect on the viability of L929 cells\textsuperscript{52}. Recently, micro-structured and nano-structured zirconia surfaces with higher surface roughness fabricated by solid-state laser sculpting were investigated. It was reported that this unique meso-/micro-/nano-scale rough zirconia after laser sculpting showed a remarkable increase in osseointegration compared to machine-smooth zirconia associated with accelerated differentiation of osteoblasts\textsuperscript{53}.

Nevertheless, although it is widely recognized that a relatively rough surface is favorable for cell adhesion, the cell type is considered to be another factor that may have an influence. Rough surfaces have provided favorable properties in terms of cellular adhesion of fibroblasts but not of epithelial cells. That said, there may exist complex soft tissue cell-substrate interactions between zirconia and cell attachment. The fibroblast and epithelial cell response have been investigated and it was concluded that they were influenced by both the material and surface topography\textsuperscript{54}.

\textit{SFE}

SFE, surface free energy, is considered to be a crucial factor of protein adsorption on zirconia, which is followed by the process of cell attachment and cell spreading\textsuperscript{28,55}. Given that, SFE appears to be an essential property interfering not only on the quality of osseointegration of implant but also on the soft tissue surrounding dental implants\textsuperscript{49}. SFE is determined by static measurement of the water contact angle. Generally, if the water contact angle is less than 90°, the solid surface is considered hydrophilic with high SFE (and low surface tension). If the water contact angle is larger than 90°, the solid surface is considered hydrophobic with low SFE (and high surface tension)\textsuperscript{49}. The correlation between the water contact angle and cell attachment on the implant material was reported: when the surface roughness value was below 0.2 µm, the water contact angle was
the only factor that showed a correlation in a third order manner implying its significance.

1. Dielectric barrier discharge treatment
It was reported that zirconia surface with high SFE is favorable to the osteoblast bioactivity. An in vitro study applied the treatment of atmospheric pressure argon (Ar) dielectric barrier discharge on different implant surfaces of machined, plasma-sprayed titanium, and blasted and acid-etched zirconia. All of the surfaces treated by argon showed a lower contact angle and increased osteoblast cell attachment.

Except for the osteoblast cells, the influence on gingival fibroblast cells was also investigated. It had been concluded that an early, effective tissue barrier around dental implants to avoid bacterial penetration is extremely important. The zirconia surface after dielectric-barrier-discharge plasma treatment was found to decrease the surface C/O (carbon to oxygen) ratio. The method also created a hydrophilic surface without affecting the surface morphology and roughness. Interestingly, the biological behavior of human gingival fibroblasts on zirconia was enhanced and cell density was promoted after the plasma treatment.

2. Ultraviolet (UV)
The surface treatment with UV irradiation has been observed to have the ability to reduce the atomic percentage of surface carbon content (i.e., hydrocarbon impurities) and introduce hydroxyl groups on zirconia. These groups can transform zirconia surfaces from hydrophobic to hydrophilic and favor cell proliferation of osteoblasts or fibroblast on zirconia. The article also described the attachment and proliferation of MC3T3-E1 osteoblast cells were higher on Ca-P (calcium phosphate) spots on modified zirconia, though its initial ALP activity was not significantly high. In addition, calcium phosphate coatings were deposited on zirconia substrates by radiofrequency magnetron sputtering previously. The tribasic calcium phosphate coating exhibited better mesenchymal stem cells adherence than the uncoated zirconia substrate.

In addition to calcium and phosphate, magnesium ions have also been applied to modify the biological properties of zirconia. A previous study was about magnesia-stabilized porous zirconia: although the cell number of MC3T3-E1 pre-osteoblasts, the ALP activity and collagen deposition after 14 days on zirconia were significantly higher in comparison to magnesia-stabilized porous zirconia, the mineralized calcium content was similar on both ceramics after 21 days. It was illustrated that magnesia-stabilized porous zirconia could direct the pre-osteoblasts toward a mature state capable of mineralizing the extracellular matrix. The influence of magnesium addition to zirconia-calcium phosphate coatings was also investigated. It was observed that the Mg-containing coatings exhibited better human osteoblast cell proliferation and differentiation than pure zirconia-calcium phosphate coatings.

It was also concluded that zirconia-based composite stabilized with ceria (CeO₂) is a promising biomaterial to facilitate periodontal tissue integration. Ceria-stabilized zirconia was shown to have the biological activity comparable to titanium and has the potential as a fixture for dental implants.

2. Hydroxyapatite (HA)
A HA thin film was applied on zirconia for the purpose of improving its biological properties. It was reported that the ALP activity and bone formation area of osteoblast cell on the HA films modified zirconia were increased. In another study, the osteoblast cell attachment and proliferation on the hydroxyapatite-based plasma electrolytic oxide coatings were better than the zirconia without coating. Recently, an investigation was published, aiming at developing micro-patterned silica (SiO₂) thin films (MSTFs) containing nano-hydroxyapatite (nano-HA) micro-aggregates that could directly interact with the surrounding cells. Zirconia specimens coated with MSTF and nano-HA were reported to show a higher cell metabolic activity and proliferation after 7 days of culture when compared with uncoated zirconia.

3. Bioactive glass
To combine the mechanical properties of a high-strength inert zirconia with the specific properties of bioactive glasses, composite materials of zirconia substrates coated with bioactive glasses were developed. An apatite layer was formed on the surface of the bioactive glass coated zirconia after immersion in simulated body fluid (SBF). The culture of fibroblasts and osteoblast-like cells on bioactive glass coated zirconia demonstrated a higher proliferation rate, higher cell density, and higher expression of ALP activity compared to (control) untreated zirconia substrate. In addition, the bioactive
BACTERIAL ADHESION ON ZIRCONIA

The above has made a brief overview on some effects of surface characteristics on the cell attachment on zirconia. That said, and not surprisingly, adhesion of microbial colonizers on dental materials is also associated with both physical and chemical characteristics of the material surface. Surface characteristics are understood to have a significant influence on bacteria adhesion. This applies in particular surface roughness, SFE, and surface chemistry.

Surface roughness

It has been concluded that biofilm formation and maturation are increasing on the dental implant surface with higher surface roughness, regardless of the implant material. It is noteworthy that 0.2 µm was supposed to be “the threshold R,” because the biofilms did not decrease significantly as the roughness reduced, i.e. when the R value was lower than 0.2 µm.

A recent study explored the effect of surface roughness on the adhesion and biofilm formation of Streptococcus mutans. It was found that the surface roughness (R) in nano-scale could affect the adhesion force and early attachment of S. mutans on the zirconia. However, it did not influence the development of biofilm in later stages (6, 8, 12, and 24 h). Nevertheless, there exists some debate on the influence of surface roughness on the bacteria performance on zirconia. In a previous study, variations in surface roughness of zirconia did not result in any difference in the adhesion of Staphylococcus epidermidis. That said, a surface with higher R, showed increased Streptococcus sanguinis adhesion, by and large. It was concluded that although the surface roughness may have an influence on the adhesion performance of bacteria to zirconia, the bacterial species were considered to be the predominant influencing factor. As it has been discussed, the roughness measurement and criteria “are very confusing and lack of unity”, i.e. there is no general consensus about the standardization of surface roughness in the variety of implant studies. Given that, the surface roughness values can be used as a relative guideline but not an absolutely exact value for ultimate comparison in osseointegration. It is necessary to investigate the relationship between surface roughness and adhesion, accumulation, and maturation of bacteria in the future studies.

SFE

SFE appears to be the most important factor that determines initial bacterial adhesion to smooth surface. Electrostatic interactions, indeed, affect the initial adhesion phase. The presence of polar and nonpolar components affect the number of bacteria that adhere onto material surfaces. In general, SFE has been considered to be directly related to the amount of biofilm formed on the implant abutment surface. In a previous study, the implant material with lower SFE, e.g. polished, partially stabilized zirconia, and titanium blasted with zirconia particles, demonstrated a lower percentage of bacterial adhesion compared with control, polished titanium surface.

Chemistry aspects

The ability of bacteria to adhere to surfaces and develop a biofilm is directly influenced by electrostatic interactions between the bacteria and the chemical composition of material surfaces. Given this, the chemical properties of zirconia have also modified to improve its biological interfacial performance.

Silver (Ag) has been widely investigated for preventing bacterial adhesion and biofilm formation on zirconia. It was reported that zirconia with nanocrystalline silver coating can release both Ag+ and free silver, Ag0, and lead to diminished postoperative infections. Zirconia coated with glass ceramic powder (containing Ag and F) was found to reduce the adhesion of S. mutans. Silver nanoparticles (AgNano) immobilized on zirconia has exhibited strong bactericidal properties by killing retained bacteria. The understood underlying mechanism of antimicrobial activity of Ag-nanoparticle-coated zirconia was that the bactericidal action of Ag-nanoparticle-coated zirconia is not mediated by the released Ag+ ions, but rather corresponds to contact killing.

The antimicrobial activity of synthesized zirconia nanoparticles (ZrO2NPs) has been investigated. It was shown that ZrO2NPs had an inhibitory effect...
against gram-negative bacteria such as *E. coli* and *Pseudomonas aeruginosa*, and on the other hand, the gram-positive *S. aureus*. Nevertheless, there was no effect against the gram-positive *Bacillus subtilis*. The values of inhibition zone increased linearly with the increase of the nanoparticle concentration. This better antibacterial effect against gram-negative bacteria may be due to the negatively charged cell wall of the gram-negative bacteria. It can be ruptured by the positively charged zirconium ions (Zr⁴⁺) released from ZrO₂NPs and lead to cell necrosis. In another study, the antibacterial function of ZrO₂NPs was ascribed to the atomic arrangements of different exposed surfaces, ZrO₂NPs with the same surface areas but with different shapes. This suggests that different active facets can show different antimicrobial activity.

**IN SUMMARY**

Zirconia as a dental biomaterial has firmly established its indications and is a gold standard. No contraindications are reported. Zirconia in dentistry has gained a vast amount interest in the last decade, having found its applications in prosthetic and implant dentistry. Laboratory studies have been focusing on modification of physico-chemical surface properties of zirconia for cementation, zirconia porcelain bonding and also to improve the biological performance of zirconia materials. The results above have showed that many proposed surface treatment methods might improve the biological performance of zirconia used as a dental restoration or implant fixture. So far, only few treatment methods of zirconia have been widely applied in clinical work. No new surface treatment has yet matured as a technique to apply as the routine zirconia modification method. Understanding the chemical, physical and biological nature of zirconia after the interfacial surface modifications is vital. With the help of this, the clinician may be able to choose the appropriate modification method and conduct a high quality treatment to satisfy the patient’s dental needs.

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