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REVIEW ARTICLE

BIOCOMPATIBILITY OF ZIRCONIA

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ABSTRACT:
Zirconia has a variety of clinical applications because of its mechanical, chemical and optical properties. However, it is because of its biocompatibility that it has gained immense popularity as well as the fact that fewer bacteria adhere to the zirconia surface. There are no adverse tissue reactions with the fibroblasts and blood cells. This illustrates zirconia's appropriate beneficial cellular or tissue response optimizing its clinically relevant performance. This article reviews zirconia's biocompatibility in vitro and in vivo. It also elaborates on its biological properties that make it a favorable choice for crowns and bridges, intramucosal inserts, implant abutment, and implants.
Key words: Implants, Biocompatibility, Zirconia.

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INTRODUCTION

"Biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any inflammatory, allergic, immune, toxic, mutagen, or carcinogenic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy".[1,2]

Zirconia has a variety of clinical applications because of its aesthetic, and mechanical properties, however it is because of its biocompatibility that it has gained immense popularity. Zirconia is now used for a variety of reasons such as crowns and bridges, implant abutments, intramucosal inserts, implants and most recently as a scaffold for bone grafting procedures. Partially stabilized zirconia, has more favourable mechanical properties than the fully stabilized zirconia. Pure zirconia in equilibrium state exists in three polymorphic forms: monoclinic- below ~1170ºC, tetragonal in the temperature range ~1170-2370ºC and cubic above ~2370ºC of which the Yttria stabilized Tetragonal Zirconia Polycrystals (Y-TZP) are most stable. Its high fracture resistance is attributed to its energy-absorption property during martensitic transformation of tetragonal to monoclinic crystals.

REDUCED BACTERIAL COLONIZATION

The mouth being a humid environment, with a practically constant temperature of 36.68ºC, offers a multitude of ecological niches for the bacterial microflora. This flora is composed of commensal microorganisms whose abundance and virulence are dependent upon different factors like composition of the saliva, the anaerobiosis, the diet (acting on pH variations), and the immune System. Thus, this flora should be considered as a dynamic equilibrium between adhesion capacity of microorganisms and the removal forces active in the mouth.

Teeth, crowns, fixed dental prostheses, or endosseous implants provide non shedding surfaces facilitating the formation of thick biofilms generally in equilibrium with the host. However, loss of control (accumulation/metabolism) of these biofilms on such surfaces is the main source of dental pathologies (i.e., gingivitis, periodontitis, peri-implantitis, or stomatitis) and ultimate failures in implantology and crown and bridge restorations. The adhesion process is regarded either as a biochemical or physicochemical point of view dependent on the material surface roughness wettability and chemical

composition of the biomaterial. The adhesion/colonization of bacteria on titanium is highly related to surface roughness and surface irregularities which facilitate plaque accumulation in vivo. Takamori et al investigated the adhesion and morphology of fibroblasts on roughened surfaces of partially stabilized zirconia, fully stabilized zirconia, titanium grade 2 and polysterene.[3] They concluded that partially stabilized zirconia promoted the best initial adhesion, indicating that surfaces with Ra values smaller than 0.1 µm could be more favourable to initial adhesion. Rimondini et al observed inhibition of growth and adhesion (slime production) of selected oral bacteria in vitro on zirconia (Y-TZP) and concluded that differences in adhesion between zirconia and titanium could be observed for some of the selected bacteria.[4] The SEM analysis enabled them to conclude that both zirconia tested surfaces accumulated significantly fewer bacteria than titanium surfaces. Moreover, the prevalence of cocci, few short rods, and no long rods on ZrO2 (Y-TZP) surfaces were suggestive of an immature plaque. Therefore, the early colonization on the surface of zirconia is reduced when compared with titanium and would be more conducive to immature plaque. It was finally suggested that this result probably lies in the superficial structure of zirconium oxide (i.e., its electric conductivity).[5]

IN VITRO TESTS

Biocompatibility Tests on Fibroblasts: Li and co-workerscompared powders and ceramics of Y-PSZ only on human oral fibroblasts by direct contact.[6] They concluded that zirconia powders were more toxic than ceramics. Finally, zirconia powders were tested for their single toxicity. Dion et alanalysed zirconia powders on human umbilical vein endothelial cells (HUVEC) and murine 3T3 fibroblasts via indirect contact.[7] The authors could raise the conclusion stating that zirconia powders (ZrO2/Y2O3) do not present toxicity on the fibroblasts. Different physical forms of zirconia and fibroblast cell lines were used. They contributed to distinct conclusions on the toxicity of zirconia but pointed out the evidence that wear products of zirconia could somehow present toxicity. However, it is also worthwhile to note that this in vitro data obtained could be partly dubious because of the material characteristics themselves (reactive surface, impurity content, chemical composition). Tateishi et al pointed out the importance of test conditions.[8] In their Round Robin test for standardization of biocompatibility test with cell lines, the authors observed significant differences between different labs performing the same test with the same materials and cells.

Biocompatibility Tests on Lymphocytes, Monocytes, and Macrophages: Powders and particles of zirconia in vitro tested on different cell lines (human and murine) of lymphocytes, monocytes, or macrophages do not induce high cytotoxicity or inflammation (TNF-α quantification).[9]

Biocompatibility Tests on Osteoblasts: Most of the published results on zirconia report the absence of toxic effects on connective, immunologic, or bone tissues.[10-15] However, biocompatibility of zirconia was assessed few years before the first in vitro tests by implanting different physical and structural forms of zirconia in animals, studies were conducted with different bones (tibia, femur, or maxilla) in rabbits, pigs, monkeys.

IN VIVO TESTS

Biocompatibility in Soft Tissues: Several studies in various animals (rabbits, rats, mice, dogs, monkeys) reported on the behaviour of zirconia ceramics implanted into soft tissues. These in vivo tests performed with different physical (pins, bars, wear particles) and structural forms (TZP, PSZ, or coatings) of zirconia, placed in different sites of implantation elicited the presence of systemic toxicity and/or adverse reactions in the implanted soft tissues. Whichever physical forms tested, does not induce cytotoxicity in soft tissues even if fibers[16] were found in lymph nodes after intra-peritoneal injection of rat and particles in some macrophages.

***Biocompatibility in Hard Tissues*:** It appeared that the various forms of zirconia tested in hard tissues did not induce any adverse reaction or local toxic effects. Moreover, in the light of these in vivo biocompatibility tests, it became evident that zirconia, whichever physical and structural forms tested, is a biocompatible material.

BIOLOGICAL PROPERTIES

Soft tissue: Fewer bacteria adhere to the zirconia abutment surface. No adverse tissue reactions with the fibroblasts and blood cells were seen. S. Sanguis has more affitnity towards titanium surface as compared to Zirconia. A pellicle is usually seen at the titanium abutment surface which predominantly consists of rods and cocci.[5,17,18]

Hard tissue: increased proliferation of SAOS2 osteoblasts. The Bone Implant Contact is greater in Zirconia as in comparison to Titanium as seen in tests on rats the mean mineralized bone-to-implant contact showed the highest values after 14 and 28 days for the rough surfaces (titanium: 36/45%; zirconia: 45/59%).[13,19] Greater bone stability seen in zirconia implants.

CROWNS AND BRIDGES

Zirconia restorations require lesser amount of tooth reduction thus preserving more tooth structure and improving the resistance form of the tooth.[20] They prevent discoloration of the gingiva most commonly caused by porcelain fused to metal crowns because of the interaction of the metals with chromogenic bacteria in the dental plaque to produce surface stains.[21] They possess superior aesthetics by virtue of it being metal free and possessing better light reflection properties. They are indicated for masking of dischromic abutment teeth.

INTRAMUCOSAL INSERTS

The use of intramucosal inserts leads to a marked increase in the retention of the maxillary denture, thus providing comfort and confidence to patients.[22] They are placed usually along the ridge or on the palatal aspect of the ridge as the mucosa is thicker in that region. This technique was suggested by Hans Nordgren and developed by Gustav Dahl at the end of the first half of the 20th century.[23] They reported that the clinically, the insertion site was healthy without oedema or other signs of inflammation, showing pink mucosa of normal appearance.

Polished zirconia ceramic is very well tolerated by the mucosal tissue, leading to the accumulation of collagen fibers in the area around the insert, maintaining mild inflammatory response, and allowing reepithelialization, which is expressed by parakeratosis, epithelial hyperplasia and presenting granular layer. No granulomatous reaction or important inflammatory foci was observed.

Histopathological Evaluation of mucosal inserts placed in a period of one year revealed mucosa fragments showing central hole lined with white mucosa. The microscopic analysis revealed two patterns in the analyzed slides: (a) oral mucosa of the surgical margin: mild keratinization, moderate epithelial hyperplasia, keratinocytes with perinuclear halos, moderate spongiose, and mononuclear exocytosis; and (b) periorificial oral mucosa (in contact with the insert): parakeratosis, mild to severe epithelial hyperplasia, minimal to extensive granular layer; lamina propria with dense collagen bands, fading of the loose subepithelial connective tissue, few mononuclear leukocytes.[24] The focal mononuclear infiltrate, which was composed predominantly of T-lymphocytes, was confirmed by anti-CD3. Sparse new formed vessels, well evidenced by anti-CD31.

ABUTMENTS

Zirconia restorations give a good emergence profile and protects tissues by giving the gingiva a barrier from the final prosthesis. In case of mild recession esthetics are not compromised. Ease of preparation of the abutment as it is easily milled.

The attachment of the gingiva to dental implants/or natural teeth is mediated by the junctional epithelium. Cells of this tissue attach to tooth by means of hemidesmosomes, which are specialized in adhesion structures. In culture, most cells adhere by focal adhesion contacts (FACs) that are present at the basal membrane and the substrate. The localization, organization of FAC, and hemidesmosomes are good indicators of cell adhesion. Zirconium Nitride coatings, particularly favour the attachment of human gingival fibroblasts and been shown to reduce bacterial adhesion.[17] Initial inflammatory process after implantation may influence the degree of thickness of the fibrous encapsulation. Chemically stable ceramic materials are expected to be encapsulated by a thinner fibrous membrane compared with metals, which may dissolve.[25] The inflammatory response analysis on peri-implant soft tissues around titanium and zirconium oxide healing caps (Y-TZP) in human beings was observed.[26] The authors could highlight with biopsy of soft tissue from patients receiving Zirconia oxide healing caps that:

(1) The inflammatory infiltrate present in the peri-implant soft tissues (sub-mucosa mainly) around zirconium oxide gingival former was lower than that present around titanium one;
(2) The microvessel density was significantly lower than that with titanium caps; and
(3) Both NOS1 and NOS3 expression intensities, indicative of the activity of NO synthetases, were also significantly lower in tissue surrounding zirconium oxide healing caps

The authors finally concluded that zirconium healing caps seemed to actively interact with soft tissues by inducing different cellular pathways aiming at periointegration process. However, the physical and

chemical surface treatments of the implant abutment appeared to be of paramount importance in cell growth, cell adhesion, inflammation process, and bacterial colonization underwent a lower rate of inflammation-associated processes mostly related to a lower inflammation.

IMPLANTS

Zirconia has been used as non-dental implants since 1988 (total hip replacements).[27] It has proven to be biologically inert to acids and bases.[28] It can be used in patients who have shown allergic reactions to titanium. The orientation of peri-implant tissue is different from that of periodontal tissue because of periodontal ligament fibres, whose absence makes the implant–bone interface weaker than that of natural dentition. The implant biomaterial itself, its characteristic surface treatments (i.e., roughness[29], surface free energy, coating methods), controlled surgical procedures, quality of the bone where the implant is installed, the bacterial ecosystem, health of the peri-implant gingiva and functional loading are paramount factors influencing the healing and success of the implant. Yasumasa Akagawa et al histologically observed, the bone-implant interface was generally achieved in both unloaded and loaded implants.[30] Loss of marginal bone height was quite evident around loaded implants, but no significant difference of bone contact ratio was obtained in either type of implant. In 2004, Glauser and co-workers evaluated in humans an experimental self-made zirconia abutment with an objective of studying the peri-implant hard and soft tissue reaction as well as fracture resistance over time (four years).[31] While observing that no fractures occurred, a mean index plaque, bleeding on probing, and measures of mucosal sulcus depth around implant via clinical and radioscopic analysis revealed near identical outcomes to that of teeth and a reduced marginal bone loss was reported (1.2 mm).

CONCLUSION

Titanium, as a biomaterial of choice, has been and is still largely employed in dental restoration. However, its corrosion products and individual sensitivities to it are still controversial.[32] A huge amount of researches involving biocompatibility, improvement by coatings for osseointegration, bacterial adhesion, or infectious diseases in implantology with titanium has also been engaged in the last two decades.

In brief, zirconia has been proved to be biocompatible in vitro and in vivo; it has very interesting microstructural properties; and it is osseoconductive. Physical and chemical treatments of zirconia were shown to largely influence its soft tissue interactions (mainly fibroblastic ones). Few studies highlighted that zirconia and its derivatives (ZrN) have the capacity to reduce plaque on implant and surrounding tissues and consequently should be important in soft tissue healing and implant success at bone level. Its use as an intramucosal insert as a replacement to metal did not produce noticeable changes in the cellular response to the inserts, however it is preferred because of its safety, biocompatibility, stability and the lack of mutagenic and carcinogenic effects.[33]

A futurist strategy of dope osseointegration or periointegration would be grafting of extracellular matrix proteins or growth factors, which could accelerate the healing and anchoring of these biomaterials Finally, new zirconia-based composite bioceramics are under investigation, that is, hydroxyapatite-zirconia[34] or titania-Y-TZP[35] graded for their biocompatibility.

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