

A Review on Zirconia As The Upcoming Material for Dental Implants

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Abstract : Titanium has been serving as satisfactory material for manufacturing of dental implants. Titanium dental implants have disadvantages like corrosion, radiating ions to the human body as well as having many separate parts to be assembled. Also the need for high esthetic material especially for maxillary anterior region has inspired us to be in constant search of a new material which is esthetic in nature and also possess ideal properties of a dental implant material. A review of literature on zirconia in this regard is presented in this article. New generation of patients demand metal free restorations. Ceramic implants are aptly indicated in such cases. However, ceramics are known to be sensitive to shear and tensile loading, and surface flaws may lead to early failure. Physical and mechanical properties of zirconia are discussed. Performance of zirconia as an implant material and as a coating for dental implants in terms of osseointegration is analysed with respect to various animal, human studies, and case studies in the literature. Response of the peri-implant soft tissue is also discussed. Zirconia certainly seems to have a potential to become material of choice for dental implant in coming days.

Keywords: Dental implants, esthetics, osseointegration, titanium, zirconia

I. Introduction

Surprising discovery by Branemark¹ in the form of osseointegration of titanium has changed the future of dentistry for good. Today replacement of missing tooth or teeth with dental implants has become a popular treatment option. An ideal implant material should possess various characteristics like biocompatibility, adequate toughness, strength, corrosion, wear and fracture resistance^{2,3}. Titanium is serving as satisfactory material for dental implants for past 30-40 years. But special situations like maxillary anterior region has lead us through a lot of experimentation in search of an esthetic material in the form of ceramic materials and/or zirconia. A review of literature on zirconia in this regard is presented in this article. The review is written under various headings to critically analyze zirconia as a dental implant material.

II. Drawbacks Of Titanium

Titanium dental implants have disadvantages like metallic hue, corrosion, radiating ions to the human body as well as having many separate parts to be assembled. Dark grayish color of titanium makes it difficult to suit in esthetic zone. In presence of thin gingival biotype it shows through impairing esthetic outcome. Unfavorable soft tissue conditions or recession of the gingiva may lead to compromised esthetics. This is of great concern when the maxillary incisors are involved. Recently, studies have shown that metals induce a nonspecific immunomodulation and autoimmunity.⁵ Galvanic side effects after contact with saliva and fluoride are also described.⁶ Titanium implants constantly release metal ions into the mouth. This chronic exposure can trigger hypersensitivity, inflammation and allergies, as well as autoimmune disease in people with high sensitivity. With a metal implant the patient's mouth can behave like a battery with another dissimilar metal in the form of fillings, crowns, partials, and orthodontic appliances and saliva as an electrolyte. This type of oral galvanism increases the rate of corrosion or dissolution of metal-based dental restorations. These ions can react with other components of body causing sensitivity and autoimmune disease. Although allergic reactions to titanium are very rare, cellular sensitization has been demonstrated.^{7,8} Increasing the corrosion rate, therefore, increases the chance of developing immunologic or toxic reactions to the metals.

A second concern is that some individuals are very susceptible to these internal electrical currents. Dissimilar metals in the mouth can cause unexplained pain, nerve shocks, ulcerations and inflammation. Many

people also experience a constant metallic or salty taste, a burning sensation in the mouth, and insomnia. New generation of patients demand metal free restorations. Ceramic implants are aptly indicated in such cases. Novel implant technologies that produce ceramic implants are being developed.⁹ However, ceramics are known to be sensitive to shear and tensile loading, and surface flaws may lead to early failure. These realities imply a high risk for fracture.¹⁰ In recent years, high strength zirconia ceramics have become attractive as new materials for dental implants. They are considered to be inert in the body and exhibit minimal ion release compared with metallic implants.

III. Discussion

Properties of zirconia

Chemist Martin Klaproth¹¹⁻¹³ in 1789 first discovered zirconium, a metal with the atomic number 40. The material has a density of 6.49 g/cm³, melting point of 1852 °C and a boiling point of 3580 °C. Zirconia is not found in a pure state in nature. It is possible to obtain it in conjunction with silicate oxide with the mineral name Zircon (ZrO₂ × SiO₂) or as a free oxide (ZrO₂) with the mineral name Baddeleyite¹⁴. Because of impurities of various metal elements that affect color and because of natural radionuclides like urania and thoria, which make them radioactive, these minerals cannot be used as primary materials in dentistry¹⁵. After a complicated procedure of these elements pure zirconia powder is produced. Zirconia occurs in three forms: monoclinic, tetragonal and cubic. The monoclinic phase is stable at room temperatures up to 1170 °C, the tetragonal at temperatures of 1170-2370 °C and the cubic at over 2370 °C^{18,19}. However, changes in volume are observed during these transformations. The monoclinic to tetragonal transformation shows a 5% decrease in volume when zirconium oxide is heated; conversely, a 3%-4% increase in volume can be seen during the cooling process^{14,20}.

Stabilized zirconia

Several different oxides like Magnesia (MgO), Yttria (Y₂O₃), Calcia (CaO), and Ceria (CeO), are added to zirconia to stabilize the tetragonal and/or cubic phases which allows the generation of multiphase materials known as Partially Stabilized Zirconia (PSZ). Its microstructure consists of cubic zirconia as the major phase, with monoclinic and tetragonal zirconia precipitates as the minor phase, at room temperature^{14,21,22}.

Zirconia ceramic systems in dentistry

Three zirconia-containing ceramic systems used in dentistry are

1. Yttrium-Stabilized Tetragonal Zirconia Polycrystals (3Y-TZP)
2. Glass-Infiltrated Zirconia-Toughened Alumina (ZTA)
3. Alumina Toughened Zirconia (ATZ)

Most commonly used material amongst all in manufacturing oral implants is yttria-stabilized tetragonal zirconia polycrystal (Y-TZP, short: zirconia) with or without addition of a small percentage of alumina. To improve material characteristics, HIP process (HIP: hot isostatic postcompaction) is used which give rise to highly compacted structures with fine grain size and high purity of Y-TZP. Y-TZP have higher fracture resilience and higher flexural strength as compared to aluminum oxide. Also, Zirconia has mechanical properties similar to those of stainless steel. Its resistance to traction can be as high as 900-1200 MPa and its compression resistance is about 2000 MPa. It can tolerate cyclical load stresses well. Cales and Stefani observed that some 50 billion cycles were necessary to break the samples, if an intermittent force of 28 kN is applied to zirconia substrates, but with a force in excess of 90 kN structural failure of the samples occurred after just 15 cycles. Physical properties of zirconia can be modified by surface treatments.

They have also been used successfully in orthopaedic surgery to manufacture ball heads for total hip replacements; this is still the current main application of this biomaterial. Zirconia seems to be a suitable dental implant material because of its tooth like color, mechanical properties, and biocompatibility. Commercially available zirconia dental implant systems are listed below. First ever zirconia dental implant system in the commercial market was Sigma implant (Sandhause, Incermed, Lausanne, Switzerland), developed in 1987. Other systems available are the Cera Root system (Oral Iceberg, Barcelona, Spain), the ReImplant system (ReImplant, Hagen, Germany), the White Sky system (Bredent Medical, Senden, Germany), the Goei system (Goei Inc, Akitsu-Hiroshima, Japan), the Konus system (Konus Dental, Bingen, Germany), the Z-systems (Z-systems, Konstanz, Germany), and the Ziterion system (Ziterion, Uffenheim, Germany).

Biocompatibility of zirconia

Osseointegration

Various articles have discussed osseous healing, histologic analyses, and BIC of zirconia dental implants. Zirconia is discussed as a dental implant material and as a coating material for dental implants in following sections.

Zirconia used as an implant

Al Qahtani WM²³ et al observed the Effect of surface modification of zirconia on cell adhesion, metabolic activity and proliferation of human osteoblasts. . The approach investigated here to roughen zirconia implants by sandblasting before sintering shows potential to improve the clinical performance of ceramic dental implants. In a research by Hirano T et al²⁴ titled Proliferation and osteogenic differentiation of human mesenchymal stem cells on zirconia and titanium with different surface topography, the results suggested that creation of micro- and nano-topographies on TZP and CpTi by blast and acid-etching may offer a promising method for enhancing the proliferation and differentiation of hMSCs in clinical application. Thoma DS et al²⁵ in a Histological analysis of loaded zirconia and titanium dental implants in the dog mandible inferred that One- and two-piece zirconia rendered similar peri-implant soft tissue dimensions and osseointegration compared to titanium implants that were placed at 6 months of loading. Zirconia implants, however, exhibited a relatively high fracture rate. In vitro study by Delgado-Ruíz RA²⁶ et al on human fetal osteoblast behavior on zirconia dental implants and zirconia disks with microstructured surfaces concluded that The roughness is increased and chemical composition enhanced on the surface of zirconia implants with microgrooves. The LSA of microgrooved zirconia implants is greater and provides more available surface compared with implants of the same dimensions without microgrooves. Microgrooves on zirconia implants 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 enhance ALP and ALZ expression by human fetal osteoblasts.

Dubruille et al²⁷ compared the BIC on 3 types of dental implants: titanium, alumina, and zirconia (Sigma, Lausanne, Switzerland) placed in dog mandible. At 10 months, BIC was found to be 68% for alumina, 64.6% for zirconia, and 54% for titanium with no statistically significant difference. Investigation by Schultze-Mosgau et al²⁸ about the osseointegration of Y-TZP cones and titanium cones with regard to their application for apicectomy revealed no differences in the morphology and dynamics of bone healing and a significantly higher ratio was found for Y-TZP (1.47 ± 1.12) than for titanium (0.97 ± 1.10) after 6 months. Scarano et al²⁹ found a great quantity of newly formed bone with zirconia implants at 4 weeks (68.4%). These studies concluded that zirconia implants are highly biocompatible and osteoconductive.

In a rabbit model, Sennerby et al³⁰ investigated histologically and biomechanically the bone tissue response to Y-TZP implants with 2 different surface modifications. Removal torque (RTQ) tests values after a period of 6 weeks were significantly higher for the surface modified zirconia implants and the titanium implants compared to the zirconia implants with the machined surface. Gahlert et al³¹ also found the same results. Alzubaydi et al³² found the interface reaction of bone toward coated implants was faster than toward uncoated ones. However, Ferguson et al³³ observed lower values for RTQ at 8 weeks with zirconia implants,

Langhoff et al³⁴ found out in a sheep pelvis model that the zirconia implants presented 20% more bone contact than the titanium implants at 2 weeks, improved toward 4 weeks, then were reduced at 8 weeks. Although statistically not significant, a clear tendency was noted for the chemically and pharmacologically modified implants to show better BIC values at 8 weeks compared with the anodic plasma treated-surface of zirconia implants. All titanium implants had similar BIC at 2 weeks (57%–61%); only zirconia was found to be better (77%). Deprich et al³⁵ compared 24 screw-type zirconia implants (Konus Dental, Bingen, Germany) with acid-etched surfaces with commercially pure titanium. At 12 weeks, ultrastructural evidence of successful osseointegration of both implant systems was found. The same researchers³⁶ found significantly higher cell growth on the zirconia surfaces than on the titanium surfaces on day three and five. Yet another animal study showed slightly better BIC on titanium than on zirconia surfaces at 1, 4, or 12 weeks with no significant difference. Studies with loaded implants in animal are available in literature. Akagawa et al³⁷ observed the initial implantbone interface with the 1-stage zirconia screw implant (Goei Industry, Akitsu-Hiroshima, Japan) with different occlusal loading conditions in beagle dogs. At 3 months, no significant difference was noted for BIC between the loaded (69.8%) and unloaded (81.9%) groups. They³⁸ also observed the role of osseointegration around the 1-stage zirconia screw implant (Goei) with various conditions for loading support after 2 years of function in monkeys. Histologically, the direct bone-implant interface was generally attained in all observed zirconia implants in all three groups, single freestanding implants, connected freestanding implants, and a combination of implant and tooth.

Kohal et al³⁹ observed mean mineralized BIC after 9 months of healing and 5 months of loading as 72.9% for titanium implants and 67.4% for zirconia implants (ReImplant, Hagen, Germany). Recently, Kohal RJ⁴⁰ et al reported histologic and histomorphometric evaluation of 22 cases. Peri-implant bone response to retrieved human zirconia oral implants after a 4-year loading period was observed. The

porous zirconia implants showed a sufficient BIC in the areas where bone still was attached. Although the implants had to be removed due to increased bone loss, it seems that the presented zirconia implant surface per se elicited appropriate osseointegration. In a study by Hoffmann et al.⁴¹ zirconia implants demonstrated a slightly higher degree of bone apposition (54%–55%) compared with the titanium implants (42%–52%) at the 2-week time point, but bone apposition was higher in titanium (68%–91%) than in zirconia (62%–80%) at 4 weeks.

Thus most of the in vitro studies and animal studies indicate similar biocompatibility and osseointegration for zirconium compared with titanium implants. A few human studies of loaded zirconia implants have been reported. Blaschke & Volz⁴² in a 5-year study of zirconia implants in humans have placed sixty-six zirconia implants (Volzirkon 1 or 2 and Z-Lock 3, Z-Systems AG, Constance, Germany) which were stable after 1 to 2 years. The authors concluded that zirconia dental implants were a feasible alternative to titanium dental implants and that their level of osseointegration and soft tissue response was superior to titanium dental implants. Oliva et al.⁴³ published the first report on 100 restored zirconia implants placed in humans after a 1-year follow-up. They placed one-piece implants made in five different designs and two different degrees of surface roughness (CeraRoot, Barcelona, Spain). The overall success rate for all the implants was 98%, and the authors concluded that zirconia implants with roughened surfaces might be a viable alternative for tooth replacement but that further follow-up was needed to evaluate long-term success rates of the studied implant surfaces. Pirker et al.⁴⁴ placed a zirconia implant to the maxillary first premolar region immediately and evaluated the clinical outcome of this implant. At 2-year follow-up, a stable implant and an unchanged peri-implant marginal bone level were observed.

Zirconia has also been used as a coating material and has shown success to various degrees.

Peri-implant soft tissues around zirconia and titanium implants

Holländer J⁴⁵ in his report on investigation of clinical parameters, patient satisfaction, and microbial contamination has confirmed the comparable low affinity of zirconia for plaque adhesion. Mellinghoff⁴⁶ stated that zirconia implants and abutments provide a very good peri-implant soft tissue interface that achieves an irritation-free attachment. Various other investigators like Pae A et al.⁴⁷, Rimondini L et al.⁴⁸, Scarano A et al.⁴⁹, Degidi M et al.⁵⁰ revealed comparable or even better healing response, less inflammatory infiltrate and reduced plaque adhesion on zirconium oxide discs compared to conventionally pure titanium.

In a study by Laranjeira MS⁵¹ the results indicated that microstructured bioactive coating seems to be an efficient strategy to improve soft tissue integration on zirconia implants, protecting implants from peri-implant inflammation and improving long-term implant stabilization. This new approach of micro patterned silica coating on zirconia substrates can generate promising novel dental implants, with surfaces that provide physical cues to guide cells and enhance their behavior. Cionca N et al.⁵² found that the correlation in the expression of five biomarkers at zirconia implants and teeth, and of four biomarkers at zirconia and titanium implants, is compatible with the existence of a patient-specific inflammatory response pattern. The peri-implant mucosa may be mechanically more fragile than the gingiva. Roehling S et al.⁵³ observed that zirconia implant surfaces showed statistically significant reduction in human plaque biofilm formation after 72 hours of incubation in an experimental anaerobic flow chamber model compared to titanium implant surfaces.

Disadvantages of zirconia

Mechanical and chemical type of failure has been reported.⁵⁴ Mechanical failure can occur either during the surgical placement of the implant⁵⁵ or subsequent functional loading.⁵⁶ To develop an optimal design for zirconia implants study of biomechanical properties of the material is imperative.⁵⁴ Considering the brittle nature of ceramics, all areas of excessive stress concentration should be avoided. This includes, but is not limited to, the configuration of the thread design. Sharp, deep and thin threads as well as sharp internal line angles represent areas of stress concentration that can enhance the likelihood of crack propagation and implant failure.⁵⁴ Contrary to titanium implants, manufacturing imperfections or flaws created during ceramic implant fabrication and subsequent surface treatment may compromise their strength⁵⁴.

Material flaws usually assume the form of pores or microcracks of a submillimetre scale⁵⁵. A reduced implant diameter of 3.25 mm, associated with a higher bending moment, has also been reported by Gahlert et al.⁵⁶ to be a contributing factor for implant fracture during functional loading. During surgical procedures, difficulties can be encountered when inserting the implants in dense hard-type bone. If hand torqueing is needed for final insertion of the implant and the applied forces are not purely rotational in nature, bending forces may be generated, resulting in implant failure⁵⁴. Ageing of zirconia. Slow surface transformation of the metastable tetragonal crystals to the stable monoclinic structure in the presence of water or water vapor causes low-temperature degradation (LTD), also known as ageing of zirconia. A certain degree of transformation actually improves the mechanical properties of Y-TZP. Studies have found that the degradation proceeds most rapidly at temperatures between 200 and 300 °C and is time dependent. Grain pull out, roughening of the surface,

increased wear and microcracking is seen with LTD.⁵⁷ Various methods to reduce LTD have been tried like addition of small amounts of silica⁵⁸, the use of yttria-coated rather than co-precipitated powder, the reduction of the grain size⁵⁹, an increase of the stabilizer content or even the formation of composites with aluminium oxide (Al₂O₃)⁶⁰. Alumina has to be very effective in slowing the ageing by changing the grain-boundary chemistry. Despite increased popularity of Zirconia dental implants, concerns have been raised regarding low temperature degradation (LTD) and its effect on micro-structural integrity. Monzavi M et al⁶¹ have studied the impact of in vitro accelerated aging, approximating 30 and 60 years in vivo, on commercially available zirconia dental implants and concluded that the depth of grain transformation remained within 1-4 μm from the surface. The effect of aging was minimal for all Zirconia implants.

IV. Conclusion

After going through all the available literature attempting to analyse zirconia as an upcoming dental implant material, it is thought that more randomised controlled trials in humans are certainly required to formulate exact treatment protocol for using zirconia dental implants. But we cannot ignore the important fact that zirconia is proven to be biocompatible, osteoconductive and to have no adverse effect on the surrounding tissues. As all the studies have noticed osseointegration especially when roughened zirconia was used suggests that slight difference in the manufacturing of YTZP may not have much bearing on the process. More studies should be directed towards finding a correct relationship between topography of the implants and the degree of osseointegration and improving the value of removal torque testing. A surface treatment is proposed for zirconia, which allowed a direct silanization of its surface and a higher cell attachment. The results of this research may open the possibility for the next generation of bioinert ceramic implants with more advanced tailored surfaces for increased osseointegration. Zirconia definitely deserves attention to become material of choice for manufacturing dental implant in recent future.

References

- [1]. Brånemark, P.I.; Hansson, B.O.; Adell, R.; Breine, U.; Lindström, J.; Hallén, O.; Ohman, A. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. *Scand. J. Plast. Reconstr. Surg.* 1977, 16, 1–132
- [2]. Smith, D.C. Dental implants: Materials and design considerations. *Int. J. Prosthodont.* 1993, 6, 106–117.
- [3]. Parr, G.R.; Gardner, L.K.; Toth, R.W. Titanium: The mystery metal of implant dentistry. *Dental materials aspect. J. Prosthet. Dent.* 1985, 54, 410–414.
- [4]. Heydecke G, Kohal R, Glaeser R. Optimal esthetics in singletooth replacement with the re-implant system: a case report. *Int J Prosthodont.* 1999;12:184–189.
- [5]. Stejskal J, Stejskal VD. The role of metals in autoimmunity and the link to neuroendocrinology. *Neuroendocrinol Lett.* 1999;20:351–364.
- [6]. Tschernitschek H, Borchers L, Geurtsen W. Nonalloyed titanium as a bioinert metal—a review. *Quintessence Int.* 2005;36:523–530.
- [7]. Valentine-Thon E, Schiwwara HW. Validity of MELISA for metal sensitivity testing. *Neuroendocrinol Lett.* 2003;24:57–64.
- [8]. Yamauchi R, Morita A, Tsuji T. Pacemaker dermatitis from titanium. *Contact Dermatitis.* 2000;42: 52–53.
- [9]. Lebedev KA, Poniakina ID, FiziolCheloveka. The center of pathological (toxic) action of metals in people organisms and a role of galvanic currents in its induction. 2011 Jul- Aug;37(4):90-7
- [10]. Chaturvedi TP. An overview of the corrosion aspect of dental implants (titanium and its alloys), *Indian J Dent Res.* 2009 Jan-Mar;20(1):91-8:
- [11]. Denry I, Kelly JR. State of the art of zirconia for dental applications. *Dent Mater* 2008; 24: 299-307
- [12]. Tsuge T. Radiopacity of conventional, resin-modified glass ionomer, and resin-based luting materials. *J Oral Sci*2009; 51:223-230
- [13]. Ban S. Reliability and properties of core materials for all ceramic dental restorations. *Jpn Dent Sci Rev* 2008; 44: 3-21
- [14]. Piconi C, Maccauro G. Zirconia as a ceramic biomaterial. *Biomaterials* 1999; 20: 1-25
- [15]. Porstendörfer J, Reineking A, Willert HC. Radiation risk estimation based on activity measurements of zirconium oxide implants. *J Biomed Mater Res* 1996; 32: 663-667
- [16]. Boothe GF, Stewart-Smith D, Wagstaff D, Dibblee M. The radiological aspects of zircon sand use. *Health Phys*1980; 38: 393-398
- [17]. Christel P, Meunier A, Dorlot JM, Crolet JM, Witvoet J, Sedel L, Boutin P. Biomechanical compatibility and design of ceramic implants for orthopedic surgery. *Ann N Y AcadSci*1988; 523: 234-256
- [18]. Chevalier J, Gremillard L, Virkar AV, Clarke DR. The tetragonal- monoclinic transformation in zirconia: Lessons learned and future trends. *J Am Ceram Soc*2009; 92: 1901–1920
- [19]. Suresh A, Mayo MJ, Porter WD, Rawn CJ. Crystallite and grain-size-dependent phase transformations in yttria-doped zirconia. *J Am Ceram* 2003; 86: 360-362
- [20]. Hjerpe J, Vallittu PK, Fröberg K, Lassila LV. Effect of sintering time on biaxial strength of zirconium dioxide. *Dent Mater* 2009; 25: 166-171
- [21]. Christel P, Meunier A, Heller M, Torre JP, Peille CN. Mechanical properties and short-term in-vivo evaluation of yttrium- oxide-partially-stabilized zirconia. *J Biomed Mater Res* 1989; 23: 45-61
- [22]. De Aza AH, Chevalier J, Fantozzi G, Schehl M, Torrecillas R. Crack growth resistance of alumina, zirconia and zirconia toughened alumina ceramics for joint prostheses. *Biomaterials* 2002; 23: 937-945
- [23]. Al Qahtani WM, Schille C, Spintzyk S. Effect of surface modification of zirconia on cell adhesion, metabolic activity and proliferation of human osteoblasts. *Biomed Tech (Berl).* 2016 Apr 23.
- [24]. Hirano T¹, Sasaki H, Honma S. Proliferation and osteogenic differentiation of human mesenchymal stem cells on zirconia and titanium with different surface topography. *Dent Mater J.* 2015;34(6):872-80

- [25]. Thoma DS¹, Benic GI¹, Muñoz F. Histological analysis of loaded zirconia and titanium dental implants: an experimental study in the dog mandible. *J ClinPeriodontol.* 2015 Oct;42(10):967-75
- [26]. Delgado-Ruiz RA¹, Gomez Moreno G², Aguilar-Salvatierra AH. Human fetal osteoblast behavior on zirconia dental implants and zirconia disks with microstructured surfaces. An experimental in vitro study. *Clin Oral Implants Res.* 2016 Nov;27(11):e144-e153
- [27]. Dubruille JH, Viguier E, Le Naour G, Dubruille MT, Auriol M, Le Charpentier Y. Evaluation of combinations of titanium, zirconia, and alumina implants with 2 bone fillers in the dog. *Int J Oral Maxillofac Implants* 1999;14:271–277.
- [28]. Schultze-Mosgau, S., Schliephake, H., Radespiel-Troger, M. & Neukam, F.W. (2000) Osseointegration of endodontic endosseous cones: zirconium oxide vs titanium. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 89: 91–98. Exclusion criteria: no bone-to-implant contact reported.
- [29]. Scarano, A., Di Carlo, F., Quaranta, M. & Piattelli, A. (2003) Bone response to zirconia ceramic implants: an experimental study in rabbits. *Journal of Oral Implantology* 29: 8–12.
- [30]. Sennerby, L., Dasmah, A., Larsson, B. & Iverhed, M. (2005) Bone tissue responses to surface-modified zirconia implants: a histomorphometric and removal torque study in the rabbit. *Clinical Implants Dentistry & Related Research* 7 (Suppl. 1): S13–S20.
- [31]. Gahlert, M., Gudehus, T., Eichhorn, S., Steinhäuser, E., Kniha, H. & Erhardt, W. (2007) Biomechanical and histomorphometric comparison between zirconia implants with varying surface textures and a titanium implant in the maxilla of miniature pigs. *Clinical Oral Implants Research* 18: 662–668.
- [32]. Alzubaydi, T. L., Alameer, S. S. Ismaeel, T. Alhijazi, A. Y. and Geetha, M. In vivo studies of the ceramic coated titanium alloy for enhanced osseointegration in dental applications. *J Mater Sci Mater Med.* 2009. 20(suppl 1):S35–S42.
- [33]. Ferguson, S.J.; Langhoff, J.D.; Voelter, K.; von Rechenberg, B.; Scharnweber, D.; Bierbaum, S.; Schnabelrauch, M.; Kautz, A.R.; Frauchiger, V.M.; Mueller, T.L.; et al. Biomechanical comparison of different surface modifications for dental implants. *Int. J. Oral Maxillofac. Implants* 2008, 23, 1037–1046.
- [34]. Langhoff J D, Voelter K, Scharnweber D, Schnabelrauch M, Schlottig F, Hefti T, Kalchofner K, Nuss K, Von Rechenberg B: Comparison of chemically and pharmaceutically modified titanium and zirconia implant surfaces in dentistry: a study in sheep. *Int J Oral Maxillofac Surg* 37: 1125–1132 (2008)
- [35]. Depprich R, Ommerborn M, Zipprich H, Naujoks C, Handschel J, Wiesmann H-P, Kübler N R, Meyer U: Behavior of osteoblastic cells cultured on titanium and structured zirconia surfaces. *Head Face Med* 4: 29 (2008 a)
- [36]. Depprich R, Zipprich H, Ommerborn M, Naujoks C, Wiesmann H P, Kiattavorncharoen S, Lauer H C, Meyer U, Kübler N R, Handschel J: Osseointegration of zirconia implants compared with titanium: an in vivo study. *Head Face Med* 4: 30 (2008 b)
- [37]. Akagawa Y, Ichikawa Y, Nikai H, Tsuru H. Interface histology of unloaded and early loaded partially stabilized zirconia endosseous implant in initial bone healing. *J Prosthet Dent* 1993;69:599–604. 58.
- [38]. Akagawa Y, Hosokawa R, Sato Y, Kamayama K. Comparison between freestanding and tooth-connected partially stabilized zirconia implants after two years' function in monkeys: A clinical and histologic study. *J Prosthet Dent* 1998;80:551–558. 59.
- [39]. Kohal RJ, Weng D, Bachle M, Strub JR. Loaded custom-made zirconia and titanium implants show similar osseointegration: An animal experiment. *J Periodontol* 2004;75:1262–1268.
- [40]. Kohal RJ¹, Schwinding FS², Bächle M¹, Peri-implant bone response to retrieved human zirconia oral implants after a 4-year loading period: A histologic and histomorphometric evaluation of 22 cases. *J Biomed Mater Res B Appl Biomater.* 2016 Nov;104(8):1622-1631.
- [41]. Hoffmann, O., Angelov, N., Gallez, F., Jung, R.E. & Weber, F.E. (2008) The zirconia implant–bone interface: a preliminary histologic evaluation in rabbits. *The International Journal of Oral & Maxillofacial Implants* 23: 691–695
- [42]. Blaschke C, Volz U: Soft and hard tissue response to zirconium dioxide dental implants – a clinical study in man. *Neuroendocrinol Lett* 27 (suppl 1): 69–72 (2006)
- [43]. Oliva J, Oliva X, Oliva J D: One year follow-up of first consecutive 100 zirconia dental implants in humans: a comparison of 2 different rough surfaces. *Int J Maxillofac Implants* 22: 430–435 (2007)
- [44]. Pirker W, Kocher A. Immediate, non-submerged, root-analogue zirconia implant in single tooth replacement. *Int J Oral Maxillofac Surg.* 2008;37:293–295.
- [45]. Holländer J, Lorenz J, Stübinger S, Hölscher W Zirconia Dental Implants: Investigation of Clinical Parameters, Patient Satisfaction, and Microbial Contamination. *Int J Oral Maxillofac Implants.* 2016 Jul-Aug;31(4):855-64
- [46]. Mellinghoff, J. Quality of the peri-implant soft tissue attachment of zirconia implants-abutments. *Z. Zahnärztl. Implants* 2010, 26, 62–71.
- [47]. Pae, A.; Lee, H.; Kim, H.S.; Kwon, Y.D.; Woo, Y.H. Attachment and growth behavior of human gingival fibroblasts on titanium and zirconia ceramic surfaces. *Biomed. Mater.* 2009, 2, 025005–025012.
- [48]. Rimondini, L.; Ceroni, L.; Carrassi, A.; Torricelli, P. Bacterial colonization of zirconia ceramic surfaces: An in vitro and in vivo Study. *Int. J. Oral Maxillofac. Implants* 2002, 17, 793–798.
- [49]. Scarano, A.; Piattelli, M.; Caputi, S.; Favero, G.A.; Piattelli, A. Bacterial adhesion on commercially pure titanium and zirconium oxide discs: An in vivo human study. *J. Periodontol.* 2004, 75, 292–296.
- [50]. Degidi, M.; Artese, L.; Scarano, A.; Perrotti, V.; Gehrke, P.; Piattelli, A. Inflammatory infiltrate, microvessel density, nitric oxide synthase expression, vascular endothelial growth factor expression, and proliferative activity in peri-implant soft tissues around titanium and zirconium oxide healing caps. *J. Periodontol.* 2006, 77, 73–80.
- [51]. Laranjeira MS, Carvalho Â, Pelaez-Vargas A, Hansford D. Modulation of human dermal microvascular endothelial cell and human gingival fibroblast behavior by micropatterned silica coating surfaces for zirconia dental implant applications. *SciTechnolAdv Mater.* 2014 Mar 7;15(2):025001.
- [52]. Cionca N¹, Hashim D², Cancela J², Giannopoulou C², Mombelli A². Pro-inflammatory cytokines at zirconia implants and teeth. A cross-sectional assessment. *Clin Oral Investig.* 2016 Nov;20(8):2285-2291.
- [53]. Roehling S^{1,2}, Astasov-Frauenhoffer M³, Hauser-Gerspach I³. In Vitro Biofilm Formation On Titanium And Zirconia Implant Surfaces. *J Periodontol.* 2016 Oct 7:1-16.
- [54]. Zhang, Y.; Sailer, I.; Lawn, B.R. Fatigue of dental ceramics. *J. Dent.* 2013, 41, 1135–1147.
- [55]. Osman, R.B.; Ma, S.; Duncan, W.; de Silva, R.K.; Siddiqi, A.; Swain, M.V. Fractured Zirconia implants and related implant designs: Scanning electron microscopy analysis. *Clin. Oral Implants Res.* 2013, 24, 592–597.
- [56]. Gahlert, M.; Burtscher, D.; Grunert, I.; Kniha, H.; Steinhäuser, E. Failure analysis of fractured dental zirconia implants. *Clin. Oral Implants Res.* 2012, 23, 287–293.
- [57]. Sanon, C.; Chevalier, J.; Douillard, T.; Cattani-Lorente, M.; Scherrer, S.S.; Gremillard, L. A new testing protocol for zirconia dental implants. *Dent. Mater.* 2015, 31, 15–25

- [58]. Samodurova, A.; Andraž, K.; Swain, M.V.; Tomaž, K. The combined effect of alumina and silica co-doping on the ageing resistance of 3Y-TZP bioceramics. *ActaBiomater.* 2014, 11, 477–487.
- [59]. Piconi, C.; Burger, W.; Richter, H.G.; Cittadini, A.; Maccauro, G.; Covacci, V.; Bruzzese, N.; Ricci, G.A.; Marmo, E. Y-TZP for artificial joint replacements. *Biomaterials* 1998, 19, 1489–1494.
- [60]. Lee, S.K.; Tandon, R.; Ready, M.J.; Lawn, B.R. Scratch damage on zirconia ceramics. *J. Am. Ceram. Soc.* 2000, 83, 1428–1432.
- [61]. Monzavi M, Noubissi S, Nowzari H. The Impact of In Vitro Accelerated Aging, Approximating 30 and 60 Years In Vivo, on Commercially Available Zirconia Dental Implants. *Clin Implant Dent Relat Res.* 2016 Nov 9. doi: 10.1111/cid.12462.