

Zirconia dental implants: where are we now, and where are we heading?

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The notion of an alternative to titanium implants has been growing for almost 40 years. As shown in other chapters of this volume of *Periodontology 2000*, titanium dental implants demonstrate excellent biocompatibility and offer numerous treatment possibilities to improve patients' quality of life. Nevertheless, questions regarding sensitivity to titanium have been arising in recent years. One study (61) indicated that some patients could develop clinical signs of hypersensitivity to titanium, and the inadequacy of conventional epicutaneous patch tests in detecting such allergies has been established. An optimized version of the lymphocyte transformation test, also called the memory lymphocyte immunostimulation assay (MELISA[®]), seems to be more reliable than patch tests for detecting sensitivity to titanium (99). The prevalence of titanium allergy was estimated at 0.6% using this method (91). An animal study (107), in which titanium implants with a titanium plasma-sprayed coating were examined, showed accumulation of titanium particles in regional lymph nodes and other organs, notably the lungs and bones, after implant placement in the jaws. Moreover, a corrosion process was demonstrated when titanium was placed in contact with fluoride or metal alloys in the saliva (104). It has also been suggested that bacterial biofilms could induce oxidation on the surface of titanium implants in an acidic environment (97). Higher concentrations of corrosion products have been associated with the length of time that the implants are in place (8). However, the clinical relevance of these observations remains unclear (56). Furthermore, none of these studies revealed histological signs of

inflammation in association with titanium deposits. Another drawback of titanium is its grey color. When placed in esthetic areas with a thin gingival biotype, the dark shadow of titanium may be visible through the peri-implant tissues, thus impairing the esthetic outcome (105). The high esthetic standards demanded nowadays, accompanied by fears of sensitivity to titanium, has led to the growing demand for metal-free restorations. Consequently, ceramic materials were proposed as potential surrogates.

Implant material and design

Evolution of the material

The first generation of ceramic implants was made of aluminum oxide (82, 106). Several systems of aluminum oxide implants were produced, such as Cerasand (Incermed, Lausanne, Switzerland) and Tübingen implant (Frialit I; Friadent, Mannheim, Germany). Single-crystal alumina implants, such as Bioceram (Kyocera, Kyoto, Japan), have also been fabricated. Aluminum oxide implants can be osseointegrated but their biomechanical properties, as reflected by fracture toughness, are unsatisfactory. Clinical studies on these implants have shown long-term survival rates of between 65% and 92% (22, 26, 50, 98, 110). However, the heterogeneity of the results prevented clear recommendations for routine use. Consequently, aluminum oxide implants were withdrawn from the market in the early 1990s.

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Zirconium dioxide (zirconia) ceramics with improved properties have been introduced as an alternative material to aluminium oxide. They were first used for the fabrication of crowns and implant abutments (3, 62). Currently, tetragonal zirconia polycrystal, particularly 3 mol% yttrium oxide (yttria) -stabilized zirconia, is the ceramic of choice for dental implants (38). The white, opaque color of zirconia, along with early reports of good biocompatibility and low affinity to bacterial plaque, make it a material of interest in biomedical sciences. *In vitro* experiments provided no evidence for mutagenic or carcinogenic effects (21). Zirconia also exhibits several promising physical and mechanical properties, including low thermal conductivity, high flexural strength (900–1,200 MPa), favorable fracture resistance, as well as wear and corrosion resistance. A phenomenon termed phase transformation toughening gives zirconia its excellent properties (83). It stops crack propagation resulting from the transformation of zirconia from the tetragonal phase into the monoclinic phase and the consequent 4% volume expansion and induction of compressive stresses. However, one of zirconia's negative properties is its low-temperature degradation or aging. In the presence of water or water vapor, slow transformation from the tetragonal phase into the monoclinic phase leads to slow development of roughness, thus producing progressive deterioration of the material (53). Aging thus occurs as a result of compressive stresses and microcracking, and the degree of aging is dependent on the balance between these two factors'. It may be influenced by various aspects of the production process, such as the macroscopic shape and the surface characteristics of an implant, but this has not yet been fully elucidated.

One-piece vs. two-piece implants

Currently, the majority of zirconia implants produced are one-piece implants (43, 67, 71). However, such systems have several limitations. The surgical placement of the implant may not always meet the prosthodontic requirements, and angled abutments to correct misalignment are unavailable. Secondary corrections of the shape by grinding must be avoided as this severely affects the fracture strength of zirconia (6). Moreover, single-piece implants are immediately exposed to forces from the tongue or as a result of mastication (72). Loading forces would be applied on the implant, regardless of the temporization system (116).

Cementation is the only option for connecting prosthodontic elements to one-piece implants. While

the absence of a microgap between the implant and the abutment may seem to be of benefit (33–35), the correct vertical positioning of the implant may be more of a challenge (30). In the esthetic zone, implants are often inserted deeper to avoid visibility of the crown margin. This, however, increases the risk for inadvertently leaving excess luting cement in the submucosal area (111). Excess cement can be invisible, even on radiographs (52), and induces local infection, which occasionally instigates substantial tissue damage (48, 49). According to a recent systematic review (112), technical and biological complications are significantly more frequent if restorations are cemented rather than screw-retained.

At present, only a few ceramic systems offer two-piece implants. In two clinical studies (20, 73), prefabricated zirconia abutments were cemented on implants using a dual-cure resin cement. Another method was described in two other clinical studies (7, 13), in which a modifiable glass-fiber abutment was fixed adhesively to the implant. The challenge of this design remains in the quality and the strength of the connection between the abutment and the implant. None of these studies reported loss of abutment retention. Moreover, neither Brüll et al. (13) nor Payer et al. (73) reported fractures. Becker et al. (7) reported fracture of a glass-fiber abutment 23 months after loading, resulting in a technical complication rate of 2.1%. Cionca et al. (20) reported two fractured abutments in two patients at 10 days and 8 months. The technical complication rate was 4%. Additional issues with this type of connection are sealing and the removal of cement remnants. Only one study (73) mentioned the use of a rubber dam during abutment connection.

When combining the two designs of zirconia implants, the major technical complication appears to be fracture of the material. Concerning one-piece implants, two patterns of fracture were identified in an *in vitro* study (47). When the implants were not prepared, the fracture line was horizontal, at the limit of the embedding resin. In contrast, when the implants were modified by grinding, the fracture was vertically parallel to the long axis. Grinding significantly decreased the fracture strength (from 804 N when prepared to 2,084 N when not prepared). However, it must be noted that the simulated chewing forces in this experiment were higher than the values of physiologic occlusal function. Another *in vitro* experiment tested the fracture resistance of two-piece zirconia and titanium implant prototypes under forces representative of a period of 5 years of clinical loading (41). Thirty-two zirconia implants were used.

Sixteen were restored with zirconia crowns and 16 with lithium disilicate crowns. Zirconia abutments were cemented with dual-cure cement. Sixteen titanium implants were restored with screwed titanium abutments and porcelain-fused-to-metal crowns. When the implants were artificially loaded, the authors measured fracture strength of 277 N in the zirconia group and 165 N in the titanium group. However, neither aging nor the crown materials had any influence on the fracture strength of the zirconia implants in this experiment. Regarding the mode of failure after chewing simulation, the line of fracture went through the implant head in the zirconia group, whereas a bending/fracture of the abutment screw was observed in the titanium group. The same authors compared these latter results with the fracture values obtained in a previous study (42). They used the same protocol to measure the fracture strength of one-piece zirconia implants loaded with ceramic crowns made from Procera[®] Kloten, Switzerland (555 N) or Empress[®]-1 Saint-Jorioz, France (410 N), and compared them with titanium implants (668 N). The differences in fracture values were explained by the design of the implant, which had a root-like shape with increased thickness at the implant head.

An animal study in dogs (103) found a higher fracture rate for one-piece zirconia implants than for two-piece implants. Of the seven fractured implants, six were one-piece. The failures appeared during the period between the healing phase and 6 months after loading. The implant neck seemed to be the point of weakness and the fracture rate seemed to depend on the implant design. A clinical study (27) showed a marked tendency of one-piece implants with a narrow diameter to fracture. After a follow-up period of 36.75 ± 5.34 months, the overall fracture rate was 10%, and 92% of the fractured implants had reduced diameter (3.25 mm). A single implant of 4.0 mm diameter fractured in a patient with strong bruxism. This mechanical failure was caused by forced rupture. None of the implants was ground, but surface modification by sandblasting may have created small defects where stress concentrations would be induced. Abutment fractures were described in a clinical study on two-piece zirconia implants (20). The line of fracture was located at the base of the abutment connection. A type of decapitation of the abutment was observed. In these cases, the remnants of the fractured abutments could be removed from the implant and a new crown could be fitted without further complications.

Based on the available evidence, quality control and proper handling of the material seems to be of utmost importance. Surface modification of any kind, including grinding and sandblasting, and even notches and minor scratches, have an impact on the strength of zirconia. Therefore, implants have to be placed with an appropriate torque in order to prevent damage. Finally, the thread design of the implant could be another factor that may play a critical role in crack initiation and propagation (6, 70).

Biologic data

Osseointegration

Osseointegration is a major factor in the success of modern dental implants (12, 88). Titanium remains the material of choice for obtaining and maintaining this functional ankylosis (14). After establishing the mechanical properties (115) and excellent biocompatibility (36, 57) of zirconia implants, osseointegration of zirconia implants was examined in various animal studies. Two systematic reviews (54, 109) compared osseointegration of zirconia implants with that of titanium implants. The values of bone-to-implant contact and removal torque values were the two key parameters used to assess the quality of osseointegration. Most studies (45, 90) reported no significant differences in bone-to-implant contact and removal torque value between zirconia and titanium implants. Bone-to-implant contact values ranged from 26% to 71% for zirconia implants compared with 24–84% for titanium implants. Removal torque values ranged from 12 to 98 Ncm for zirconia implants, compared with 42–74 Ncm for titanium implants. In minipigs, regardless of the implant material, removal torque values decreased to a minimum 4–12 weeks after implant placement, and increased again afterwards. It has been highlighted (54) that studies differed regarding the animal model used (monkeys, Beagle dogs, minipigs, rats and rabbits), the time of loading and the location of implant insertion (maxilla, tibia or femur), and therefore the generalization of these results has limitations.

Certain studies revealed enhanced bone-to-implant contact and removal torque values for implants with a modified surface, notably if the roughness was increased. Regardless of the material, the initial interaction between the cells and the implant surface is fundamental for achieving osseointegration. An *in vitro* study (114) evaluated the influence of surface roughness on the initial attachment of

osteoblast-like cells to two different zirconia substrates. Specimens with a mean roughness average of $1.04\ \mu\text{m}$ demonstrated significantly higher numbers of cells attached in a shorter time period compared with specimens with a mean roughness average of $0.24\ \mu\text{m}$. The expression of integrins $\alpha 5$ and $\beta 1$ was also enhanced in the group with micro-rough surfaces. The integrin $\alpha 5\beta 1$ receptor plays an important role in cell adhesion, and later in spreading and migration. It constitutes a bridge between osteoblasts and proteins adsorbed on the implant surface. These results are in agreement with those of other studies (87) describing the impact of the micro-topography of rough implants on the osteoblast-gene expression and on mineralization. Different chemical and physical techniques were developed to modify the surface roughness. The influence, on osteoblast activity, of two different zirconia surfaces (sandblasted with alumina particles or sandblasted and acid-etched in a mixture of hydrofluoric acid and sulfuric acid) and one standard titanium surface (sandblasted and acid-etched) were evaluated (28, 32). Both zirconia substrates showed a better effect on adhesion and proliferation of osteoblasts compared with titanium. The osteoblast differentiation, reflected by the level of alkaline phosphatase activity, was slightly faster on sandblasted and acid-etched zirconia disks than on sandblasted zirconia.

Several animal studies (11, 28, 86, 90) showed improved performance of roughened zirconia implants, with values of bone-to-implant contact and removal torque values reaching those of titanium. These experiments confirmed the significance of surface texture on bone apposition. In a study performed on Beagle dogs (60), titanium and zirconia implants were placed in fresh extraction sockets. Implants were identical in dimension and shape, but different regarding the the surface topography. The roughness average for titanium was $1.59\ \mu\text{m}$ compared with $0.85\ \mu\text{m}$ for zirconia. Despite the lack of significant differences in bone-to-implant contact between zirconia (57%) and titanium (56.5%) implants, the failure rate was significantly higher for zirconia implants (44% for zirconia and 12% for titanium). The surface topography appeared to play a major role in the success of zirconia implants.

In an effort to minimize the physical damage induced by surface modification, different procedures have been evaluated. Selective infiltration-etching (1) is a technique used to roughen the surface of the implant by creating nanoscale porosities. A heated glass is infiltrated between the surface grains, causing reorganization of those grains. Only the surface grains

are exposed to the modification, which prevents deep structural changes. Twenty zirconia implants (10 selective infiltration-etching implants and 10 as-sintered implants) were compared with 20 titanium implants (sandblasted and acid-etched) in 40 rabbits (2). At 6 weeks, the selective infiltration-etching zirconia implants showed greater bone-to-implant contact (75%) than both the as-sintered zirconia (62%) and the titanium (68%) implants. Mature mineralized bone was observed histologically in direct contact with the surface of all studied implants. In another experiment, zirconia implants were roughened using powder injection moulding (17) and subsequently were coated with titanium zirconium oxide [(Ti,Zr)O₂]. Significantly better results, in terms of bone-to-implant contact values, were obtained for coated implants. However, removal torque values were significantly correlated to the surface roughness, not the type of coating. Moreover, the greyish color was an esthetic limitation of this coating. Other studies (40, 93) have also tested coated zirconia implants with success.

Defining osseointegration by bone-to-implant contact and removal torque values could be confusing. These values do not reflect the quality of the bone, the presence of inflammation or any foreign body reactions (40). Therefore, comparing bone-to-implant contact values between different animal models and studies should be avoided. Moreover, the production of zirconia implants is more constraining than that of titanium. A histomorphometric study in 12 minipigs compared the bone-to-implant contact and the multinucleated giant cells-to-implant contact for three different types of surface of zirconia implants (sandblasted and acid-etched; sandblasted and alkali-etched; and sandblasted) (84). Surface modification by acid-etching, but not by alkali-etching, increased the bone-to-implant contact of sandblasted implants. A higher number of multinucleated giant cells was found around the acid-etched and the alkali-etched sandblasted implants. However, no local inflammatory reaction was detected. Multinucleated giant cells were also observed in another study (16), in which osseointegration was compared between zirconia and titanium implants. The cells-to-implant contact was 3.9% for titanium and 17.5% for zirconia at 4 weeks, and 5.8% and 30.3% at 8 weeks for titanium and zirconia, respectively. The authors found no evidence of a foreign body reaction in the presence of multinucleated giant cells. It was suggested that this was a local cellular phenomenon restricted to the area of contact between the implant and the bone marrow' with no effect on the newly formed bone.

A particular phenomenon was described in a clinical study (20) involving 32 patients with 49 two-piece zirconia implants. Five of these implants were lost because of unexpected loosening within 3–10 months of loading. The patients experienced no pain or discomfort and there were no clinical signs of infection or inflammation. A sudden, aseptic mechanical breakdown of the osseointegration seemed to have occurred. The implants were simply unscrewed and the sites healed uneventfully. No additional implants were lost to this phenomenon for more than 5 years after. This failure pattern was thought to have a certain similarity to aseptic loosening described in hip replacement implantology (5, 100). Different mechanisms were explored to explain aseptic loosening in this field: genetic variation; high fluid pressure; particle disease; micromotion; stress shielding; and endotoxin. Another clinical study (44), involving 28 patients with 56 one-piece zirconia implants, described a different biological complication: after 1 year, 40% of the patients presented bone loss of > 2 mm, and 28% of the patients presented bone loss of > 3 mm. No peri-implantitis was diagnosed around these implants. In this study, the design of the implant could have been the reason for the bone loss.

Soft-tissue integration

The soft-tissue-to-implant interface is a complex structure that plays a major role in the maintenance of health in the peri-implant region. The quality of this mucosal barrier seems also to depend on implant surface characteristics (79). An *in vitro* study (113) related the behavior of human gingival fibroblasts to the characteristics of the surfaces on which they were grown. After 48 and 72 h of incubation, the proliferation of human gingival fibroblasts was significantly faster on smooth zirconia disks than on rough zirconia and on both smooth and rough titanium, with the fibroblasts spreading more evenly on smooth zirconia. Irrespective of the material, smooth surfaces also showed better cell alignment. The expression of integrin alpha2 at 3 h, and of integrin alpha5 and type I collagen at 48 h, was up-regulated on zirconia compared with titanium. Hence, it was concluded that the wettability of zirconia could promote the adsorption of protein and the attachment and spreading of fibroblasts (66).

Comparison of the mucosal seal around zirconia and titanium implants with machined necks in five adult pigs found that collagen fibers in the connective tissue had a similar orientation (parallel and parallel-

oblique) on both implant surfaces (102). Soft-tissue healing around abutments made of titanium or zirconia (108) was studied in another experiment in dogs. It was observed that the dimensions of the peri-implant mucosa were similar around titanium and zirconia abutments, and that they remained stable over a period of 5 months. The length of the epithelium was 1.83 and 1.75 mm for titanium and zirconia specimens, respectively. A smaller proportion of leukocytes was detected in the barrier epithelium around zirconia abutments compared with the barrier epithelium around titanium abutments. It was suggested that zirconia could enhance epithelial attachment during the healing phase. These findings are in agreement with the results of a previous study (45) in which the soft-tissue conditions were analyzed around one-piece custom-made zirconia and titanium implants in monkeys. The biological width was 5 mm around the titanium implants and 4.5 mm around the zirconia implants. The length of the epithelium was similar in both groups (2.9 mm). A difference was noted in the dimension of the connective tissue (2.4 mm around zirconia implants and 1.5 mm around titanium implants). The performance of a recently available one-piece zirconia implant (ZLA[®]) was tested and compared with the performance of a one-piece titanium implant (SLActive[®]) in six minipigs (51). A significantly higher content of collagen and a shorter length of the sulcular epithelium were observed around zirconia implants (0.76 mm, compared with 1.4 mm at titanium implants). The biological width was 2.3 mm for titanium implants and 2.85 mm for zirconia implants. It was hypothesized that the longer junctional epithelium and the higher density of collagen fibers could improve the soft-tissue seal and reduce the inflammatory infiltration around zirconia implants. Therefore, zirconia implants could result in a somewhat more mature soft-tissue integration. Figure 1 shows the soft-tissue healing 3 months after placement of a two-piece zirconia implant (20).

Microbiology

Inflammation of the peri-implant mucosa and peri-implantitis are not unusual at titanium implants (59). Meta-analyses of the prevalence of peri-implant diseases revealed weighted mean values of 43% (95% CI: 32–54) and 23% (95% CI: 14–30) for mucositis and peri-implantitis, respectively (24). Bacterial infection is the main aspect of those pathological conditions (58). Studies have confirmed causality between plaque accumulation on implants and inflammation of



Fig. 1. Soft-tissue healing 3 months after implant placement (two-piece zirconia implant).

the peri-implant mucosa (55, 75, 81, 118). It has been postulated that bacterial biofilm accumulates less easily on zirconia than on titanium and hence it can be hypothesized that peri-implant soft tissues around zirconia implants may be at low risk for inflammation and infection. Each implant material has a specific surface free-energy. It was noted that zirconia abutments had a low surface free energy and surface wettability resulting in reduced adhesion of bacteria (4). An *in vitro* and *in vivo* study compared oral bacterial colonization on the surface of disks made of machined grade 2 titanium and of tetragonal zirconia polycrystal stabilized with yttrium (77). The *in vitro* test demonstrated differences in adhesion of some microbial species on zirconia and titanium; while *Streptococcus mutans* adhered more to zirconia, *Streptococcus sanguis* adhered more to titanium surfaces. No differences were observed for *Actinomyces* spp. and *Porphyromonas gingivalis*. Early colonization in the *in vivo* experiment showed less accumulation of bacteria on zirconia disks compared with titanium disks, with a lower prevalence of rods. The bacterial plaque growing on zirconia surfaces was judged to be less mature compared with the bacterial plaque growing on titanium. In another study (80), 12 patients received two titanium implants each. After 3 months of healing, each implant was loaded with either a titanium or a zirconia abutment for 5 weeks. The results showed no statistically significant differences in the DNA counts of *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* for the two types

of abutments. However, these results were in contrast to two other studies (25, 63). Nascimento et al. (63) used the DNA checkerboard hybridization method to identify and quantify microbial species in 24-h biofilms on three disks of different material (machined titanium; cast and polished titanium; and zirconia). Cast and polished titanium showed the highest total count of bacteria (2.2×10^5 bacteria) compared with machined titanium (1.1×10^5 bacteria) and zirconia (0.7×10^5 bacteria). Moreover, cast and polished titanium presented with the highest incidence of bacteria, while zirconia showed the lowest. In the cast and polished titanium group, *A. actinomycetemcomitans* was detected in 100% of the samples and *P. gingivalis* in 95%. In the machined titanium group, *S. sanguinis* and *Veillonella parvula* were found in 58% of the samples. In an *in vivo* study comparing 24-h plaque accumulation on zirconia and titanium disks with similar surface roughness, placed in a removable device (85), a significant difference was found in the area covered by bacteria between zirconium ($12.1 \pm 1.96\%$) and titanium ($19.3 \pm 2.9\%$) disks. Titanium surfaces also displayed higher proportions of rods and filamentous bacteria and fewer cocci compared with zirconia surfaces. Another study (92) determined the emergence of *P. gingivalis*, *Tannerella forsythia* and *Staphylococcus aureus* in fully edentulous patients on titanium and zirconia implants. Six months after placement, the proportions of the three microorganisms remained below the detectable levels, irrespective of the implant material.

Inflammatory reactions

Since its introduction in dentistry, particularly in prosthodontics, zirconia has demonstrated excellent biocompatibility. In one study (23), gingival biopsies were harvested around titanium and zirconia healing caps placed on titanium implants in five patients. The inflammatory infiltrate around the titanium specimens was more prominent and there were signs of ulceration of the mucosa in one case. In addition, the micro-vessel density, the expression of vascular endothelial growth factor and the expression of nitric oxide synthase were all higher in the mucosa around titanium healing caps compared with the mucosa around zirconia healing caps.

We conducted a pilot study (19) to determine the presence of zirconium and titanium particles in the superficial layer of the peri-implant mucosa around zirconia and titanium implants. There were three groups of patients: five with one zirconia implant;

three with titanium implants; and five with no implants. Cytologic samples of the peri-implant mucosa were collected using microbrushes. The concentrations of the elements zirconium and titanium were determined on an inductively coupled plasma mass spectrometer. Zirconium and titanium elements were demonstrated in the peri-implant mucosa. Zirconium was only found in patients with zirconia implants, whereas titanium was detected even in individuals without titanium implants. Further investigations are in progress to determine the validity of these results. Regarding titanium, an earlier cytologic study (68) demonstrated the presence of titanium particles in the peri-implant mucosa. A higher level of metal-like particles was detected in patients with peri-implantitis lesions. No titanium was found in the marginal gingiva of the contralateral teeth. Intracellular particles were found in some epithelial cells and macrophages. Previously, the same authors (69) reported the presence of titanium particles in 63 (41%) of 153 samples from biopsies of mucosa covering submerged implants. The detection of metal particles could not only be explained by the electrochemical corrosion but also by mechanical disruption or wear (implant insertion, abutment connection, cover screw removal). When interpreting these findings, one should not forget that titanium dioxide can be found in numerous products of daily life, such as toothpastes, food products, medicine pills and sunscreens. The extent and the consequences of this phenomenon need further attention.

We assessed expression of proinflammatory cytokines in the peri-implant and gingival crevicular fluid in a clinical study (18). Samples were taken from the crevice of one, two-piece zirconia implant and the contralateral tooth of 36 subjects. Nine patients also presented one titanium implant for comparison. No peri-implant lesions were present around the implants. A correlation was observed in the expression of interleukin-1RA, interleukin-8, granulocyte colony-stimulating factor, macrophage inflammatory protein-1beta, and tumor necrosis factor-alpha at zirconia implants and teeth. The levels of interleukin-1beta and tumor necrosis factor-alpha were significantly higher at zirconia implants than at teeth. Implants with restoration that gradually transitioned from the circumferential design of the implant collar to the cervical tooth anatomy demonstrated higher levels of interleukin-1RA and significantly lower levels of interleukin-6 than did implants with restorations that did not gradually transition from the circumferential design of the implant collar, adjacent implants with connected supra-structures or with adjacent

over/under-contoured implant and/or tooth-supported restorations affecting accessibility for oral hygiene. Comparison of zirconia implants with titanium implants found that the levels of interleukin-1RA, interleukin-8, granulocyte colony-stimulating factor and macrophage inflammatory protein-1beta were correlated. These findings might reflect a patient-specific inflammatory pattern, irrespective of the material used. In a clinical study, Nickenig et al. (65) demonstrated lower expression of two specific cytokines (interleukin-6 and tumor necrosis factor-alpha) in soft tissues surrounding cover screws coated with ceramic than in soft tissues surrounding cover screws made of titanium.

So far, the limited clinical experience with zirconia implants indicates that peri-implantitis seems to be less of a problem with these type of implants than with titanium implants. In fact, peri-implantitis has either not been observed (20) or not reported, but further confirmation by longitudinal monitoring is required. Cases with peri-implantitis have thus far only been described in one single series of 34 patients with 45 zirconia implants (89). Radiographic evidence of bone loss with bleeding on probing and/or suppuration was interpreted to be peri-implantitis, and was observed at 21 implants in 17 patients. All implants in this case series had a two-piece configuration with fiberglass abutments and carried single crowns. The patients were reported to be free of periodontitis, not heavy smokers, to practice good oral hygiene and to attend regular maintenance care sessions.

Clinical studies

Numerous studies evaluating the clinical use of zirconia implants have been published during the past decade. A variety of implant systems with great diversity in surgical and clinical protocols were implemented utilizing a wide range of implant designs with different surface modifications. Prosthetic rehabilitation and loading protocols included both fixed and removable prostheses with immediate or delayed loading protocols. Figure 2 shows the clinical pictures and the radiographs of a premolar replaced with a two-piece zirconia system, at 1 and 4 years after loading (20). We recently published a systematic review and meta-analysis evaluating the available evidence regarding the clinical success and survival of zirconia implants (31). Studies examining at least five subjects with zirconia implant-supported reconstructions, with an observation period of at least 1 year, were



Fig. 2. (A) Clinical photograph (left image) and radiograph (right image), 1 year after loading (two-piece zirconia implant). (B) Clinical photograph (left image) and radiograph (right image), 4 years after loading (two-piece zirconia implant).

included. Fourteen papers were analyzed, including three randomized clinical trials, whereas 11 were case series with varying designs (Table 1). The meta-analysis was limited to survival of implants at 1 year as a result of the short-term observation period in most studies. The overall survival rate of zirconia one- and two-piece implants was 92% (95% CI: 87–95) after 1 year of function. Furthermore, the prevalence of zirconia implant failure was examined (Table 2). Early failure of one-piece zirconia implants ranged between 1.8% and 100%, with the overall early failure rate calculated at 77% (95% CI: 56–90). Meta-analysis could not be performed on the failure rate of two-piece implants as only two studies clearly reported failure rates. Cionca et al. (20) reported an overall failure rate of 12.2% with only one early failure (2%) and five (10.2%) late failures. Payer et al. (73) showed a 6.3% failure rate with only one implant failing after loading. On the other hand, Brüll et al. (13) only reported failure of three implants without details on the implant design (one- or two-piece).

Future perspectives with zirconia implants

In a sense, a novel approach should be taken when dealing with zirconia. Protocols used to design, manufacture and test titanium implants cannot simply be translated to produce and evaluate zirconia implants. New methods are required considering the biomechanical properties of zirconia in general, and aging in particular. The stability of zirconia can be

compromised by very small defects acquired during or after fabrication, and osseointegration depends on specific details in the chemical composition of the material, as well as texture and purity of the surface. Standardization of the manufacturing processes and quality control of the end products is therefore essential. One study (117) analyzed two commercially available zirconia-implant systems in detail. Both had their surfaces sandblasted and acid-etched and their sintering was performed by hot isostatic pressure. Spectroscopy revealed the presence of residual aluminium oxide particles on the surfaces of both implants. Contamination with carbon and with other contaminants, such as sodium, potassium and chlorine, was also reported. It was suggested that cleaning procedures, performed after surface characterization, were responsible for this phenomenon. Their influence on the biomechanical parameters is still unknown. Moreover, the monoclinic phase was present on the surface of both implants. This represented a weak point from where defects could develop. A high torque, created during the implant insertion, could generate small cracks at this level.

The aging related to the low temperature degradation of zirconia has a negative impact on the biomechanical properties. Zirconia ceramics also appear to be sensitive to the manufacturing processes, the autoclaving (39), the milling and the cyclic loadings. Different approaches are being studied to improve the physical and chemical properties of the material and new zirconia composite ceramics developed. One is known as ceria partially stabilized zirconia/

Table 1. Studies recording clinical success and survival of zirconia implants*

Implant design	Author (reference no.)	Observation period	No. of patients	No. of implants	Time point and technique of implant placement	Type of prosthetic reconstruction and healing time	Survival rate (%)	Success rate (%)	Mean MBL (mm)
One-piece	Blaschke & Volz (9)	2–5 years	34	66	Not recorded	Implants protected during the healing phase by splints or prosthesis, then single crown after: Mandible: 4 months Maxilla: 6 months	98% good osseointegration after 1–2 years	Not recorded	Not recorded
	Pirker & Kocher (74)	Mean: 18 months	18	Total: 18 Group A: 6 Group B: 12	1–8 days postextraction by tapping	Immediate limited functional loading Composite SC after 3–13 months	Group A: zero survival in 2 months Group B: 92	Not recorded	Not recorded
	Oliva et al. (67)	Mean: 40.8 months	378	Total: 831 Uncoated: 249 Coated: 249 Acid-etched: 333	Immediate, flapless, regeneration, sinus lifts, stages 1 and 2, or late implant placement, screwed or tapped-in implants	Vacuum stent or immediate provisionally cemented restoration for esthetic areas Computer-aided design/computer-aided manufacturing final restoration after 4–11 months (depending on type of implant placement and regenerative procedure)	Reported success rate only	Overall: 94.9 Uncoated: 92.77 Coated: 93.57 Acid-etched: 97.6	Not recorded
	Cannizzaro et al. (15)	12 months	40	Total: 40 Occlusal: 20 Nonocclusal: 20	Immediate implant placement: 10 (5 occlusal; 5 nonocclusal) Late placement: 30	Implant preparation and single immediate acrylic crowns Occlusal: immediately occlusally loaded Nonocclusal: nonocclusally loaded Ceramic crowns after 4–5 months	Overall: 87.5 Occlusal: 85 Nonocclusal: 90	Not recorded	Occlusal: 0.9 ± 0.48 Nonocclusal: 0.7 ± 0.59

Table 1. (Continued)

Implant design	Author (reference no.)	Observation period	No. of patients	No. of implants	Time point and technique of implant placement	Type of prosthetic reconstruction and healing time	Survival rate (%)	Success rate (%)	Mean MBL (mm)
	Kohal et al. (43)	12 months	65	66	Immediate implant placement or in healed sites using flapless, punch or flap techniques	Implant preparation and immediate temporization, then single crowns subsequently Mandible: minimum 6 weeks Maxilla: minimum 14 weeks	95.4	Success criteria Grade I: 66 Grade II: 86	1.31
	Kohal et al. (44)	12 months	28	56	Immediate implant placement or in healed sites using flapless, punch or flap techniques Bone augmentation without membranes when needed	Implant preparation and immediate temporization, then fixed dental prosthesis subsequently Mandible: minimum 6 weeks Maxilla: minimum 14 weeks	98.2	Success criteria Grade I: 60 Grade II: 72	1.95
	Borgonovo et al. (10)	48 months	13 (10 at follow up)	35 (28 at follow up)	Late implant placement with full-thickness flap reflection Regenerative procedures used when required	Immediate implant abutment preparation and temporary restorations Final computer-aided design/computer-aided manufacturing All-ceramic zirconia SC or fixed dental prosthesis 6 months afterwards	100	100	1.63

Table 1. (Continued)

Implant design	Author (reference no.)	Observation period	No. of patients	No. of implants	Time point and technique of implant placement	Type of prosthetic reconstruction and healing time	Survival rate (%)	Success rate (%)	Mean MBL (mm)
	Payer et al. (72)	24 months	20	20	Late implant placement with full-thickness flap reflection No bone augmentation	Immediate computer-aided design/computer-aided manufacturing provisional adhesively cemented restoration (out of occlusion) All-ceramic SC after 4 months of healing (provisional ground and used as a cap under the final restoration)	95	95	1.29
	Osman et al. (71)	12 months	24 (19 at follow up) Titanium: 12 (8 at follow up) Zirconia: 12 (11 at follow up)	Total: 129 Titanium: 56 Zirconia: 73	Late implant placement with full-thickness flap reflection except for palatal implants	Implant-supported overdentures 3-4 months after implant placement Maxilla: two implants in the premolar regions, one off-center and one palatal implant Mandible: two distal implants in the molar regions and one in the midline	Overall zirconium: 71.2 Overall titanium: 82.1 Mandible, zirconium: 90.9 Mandible, titanium: 95.8 Maxilla, zirconium: 55 Maxilla, titanium: 71.9	Not recorded	Zirconia: 0.42 ± 0.40 Titanium: 0.18 ± 0.47
	Spies et al. (94)	12 months	27	27	Late placement in healed sockets	SC immediate provisional restoration then computer-aided design/computer-aided manufacturing all-ceramic crowns in the mandible at 6 weeks and in the maxilla at 14 weeks	88.9	Success criteria (Ostman et al. 2007, 2008) Grade I: 91.7 Grade II: 100	0.77

Table 1. (Continued)

Implant design	Author (reference no.)	Observation period	No. of patients	No. of implants	Time point and technique of implant placement	Type of prosthetic reconstruction and healing time	Survival rate (%)	Success rate (%)	Mean MBL (mm)
	Roehling et al. (78)	Mean \pm SD: 5.94 \pm 0.09 years	71	Total: 161 3.25 mm diameter: 51 (31.7%) 4.0 mm diameter: 82 (50.9%) 5.0 mm diameter: 28 (17.4%)	At least 6 weeks postextraction	At least a 3-month healing period (implants immediately protected from premature loading) SC 69% Fixed dental prosthesis: 19.3% Removable hybrid dentures: 2.5%	Overall: 77.3 3.25 mm implants: 58.5 4.0 mm implants: 88.9 5.0 mm implants: 78.6	Overall: 77.6 3.25 mm implants: 58.8 4.0 mm implants: 89 5.0 mm implants: 78.6	0.97 \pm 0.07
Two-piece	Payer et al. (73)	24 months	22	Total: 31 Zirconia: 16 Titanium: 15	Minimum 6-month healing period	Abutments cemented at second-stage surgery under rubber dam isolation 4–6 months after implant placement All-ceramic single crowns	Zirconia: 93.3 Titanium: 100	Zirconia: 93.3 Titanium: 100	Zirconia: 1.48 \pm 1.05 Titanium: 1.43 \pm 0.67
	Cionca et al. (20)	Mean \pm SD: 588 \pm 174 days	32	49	Late placement in healed sockets	Mean \pm SD healing period 193 \pm 79 days, cemented all-ceramic SC	87	Not recorded	Not recorded
One-piece + two-piece	Brüll et al. (13)	Mean: 18 months	74	Total: 121 Two-piece: 66 One-piece: 55	Immediate or late placement	Mean healing period: 4.6 \pm 3–17 months SC: 82.6% Fixed dental prostheses: 17.4%	96.5	Not recorded	0.1 \pm 0.6

*Adapted from Hashim et al. (31). MBL, marginal bone loss; SC, single crown.

Table 2. Failure rate and the prevalence of early failure, late failure and implant fracture*

Implant design	Author (reference no.)	Observation period	No. of implants	Calculated failure rate (%)	No. (%) of early failures	No. (%) of late failures	No. (%) of fractured implants
One-piece implant	Blaschke & Volz (9)	2–5 years	34	2	1 (2.9)	0	1 (2.9)
	Pirker & Kocher (74)	Mean: 18 months	Group A: 6	Group A: 100	Group A: 6 (100)	0	0
			Group B: 12	Group B: 8	Group B: 1 (8.3)	0	0
	Oliva et al. (67)	Mean: 40.8 months	831	5	38 (4.6)	4 (0.5)	0
	Cannizzaro et al. (15)	12 months	40	13	5 (12.5) (3 occlusal and 2 nonocclusal)	0	0
	Kohal et al. (43)	12 months	66	5	3 (4.6)	0	0
	Kohal et al. (44)	12 months	56	2	1 (1.8)	0	0
	Borgonovo et al. (10)	48 months	28	0	0	0	0
	Payer et al. (72)	24 months	20	5	1 (5)	0	0
	Osman et al. (71)	12 months	73	29	15 (20.6)	3 (4.1)	3 (4.1)
	Spies et al. (94)	12 months	27	11	3 (11.1)	0	0
Roehling et al. (78)	Mean: 5.94 years	161	22	14 (8.7)	4 (2.5)	18 (11.2)	
Two-piece implants	Payer et al. (73)	24 months	16	6	0	1 (6.3)	0
	Cionca et al. (20)	Mean: 588 days	49	12	1 (2)	5 (10.2)	0
One-piece/Two-piece implants	Brüll et al. (13)	Mean: 18 months	121	3	1 (0.8)	1 (0.8)	1 (0.8)

*Adapted from Hashim et al. (31).

alumina nanostructured composite or NANOZR (64, 101). This composite exhibits a flexural strength twice that of yttria-stabilized tetragonal zirconia polycrystal and greater fracture toughness. In addition, it is less subject to low-temperature degradation. *In vitro* experiments demonstrate promising results in terms of cell adhesion, spreading and differentiation into bone-forming cells (29, 114). An animal study (37) presented similar histological and histomorphometric results for titanium, yttria-stabilized tetragonal zirconia polycrystal and NANOZR. The bone-to-implant contact reached almost 60% in all groups. The biological width measured 3 mm with a reduced connective tissue dimension for NANOZR (0.5 mm) compared with titanium and yttria-stabilized tetragonal zirconia polycrystal (1.1 mm).

Other modifications on zirconia implants have also been described. Yttria-stabilized tetragonal zirconia polycrystal was toughened by the addition of 20 weight per cent alumina (alumina-toughened zirconia). This reinforced zirconia was conceived to limit the effects of aging. It was demonstrated that this

toughening mechanism improves the stability of the tetragonal form of zirconia and increases its hardness. This zirconia composite should not be confused with yttria-stabilized tetragonal zirconia polycrystal doped with alumina (6), in which only a small amount of alumina (up to 0.25 wt%) is added to yttria-stabilized tetragonal zirconia polycrystal. Laboratory experiments have evaluated the fracture strength of alumina-toughened zirconia implant prototypes under different loading procedures (46). They reported no implant fracture during loading and significantly higher mean fracture strength for alumina-toughened zirconia implants (1,064–1,734 N) than for tetragonal zirconia polycrystal implants (516–607 N). When the abutment was ground, the fracture strength was reduced but still showed better values than nonprepared tetragonal zirconia polycrystal implants. However, an *in vitro* study on commercial alumina-toughened zirconia one-piece zirconia implants did not find a decrease in fracture resistance because of the modification of the abutment. Finally, this implant system was also evaluated in a clinical study

(96) in which 27 patients received one implant with immediate temporization. After initial sandblasting, the surface was coated with ceramic slurry to create a porous surface before the final sintering process. Three implants in three patients were lost during the healing phase. The cumulative survival rate was 88.9% at 1 year. The average bone loss during the first year after implant insertion amounted to 0.77 mm. Two implants lost more than 2 mm; none lost more than 3 mm of marginal bone. The periodontal parameters remained stable during the first year. Moreover, multinucleated giant cells were also detected on the surface of alumina-toughened zirconia implants (16). The presence of multinucleated giant cells was not related to a foreign body reaction. It seemed more of a local cellular phenomenon, which did not affect the new bone formation.

Concerning the two-piece zirconia implants, the trend seems to be toward a screwed solution. A recent *in vitro* study (95) compared the fracture resistance of two differently connected two-piece implant systems with one-piece (alumina-toughened zirconia) implants. In the group of two-piece implants, one subgroup had its abutment (Y-TZP-A) screwed onto the implant (Y-TZP-A) with a titanium screw; the other had its abutment (alumina-toughened zirconia) bonded into the implant (Y-TZP-A). The bending moment (Ncm) was calculated by multiplying the lever arm extension (cm) with the fracture load (N). After dynamic loading, one-piece implants showed an increase in fracture resistance, whereas two-piece implants showed a decrease in values. Nevertheless, bending moment values were largely higher than the maximum values measured in the mouth. Only debonding was noted for the group with abutments cemented into the implants. The authors concluded that these implant systems had sufficient fracture-resistance values to withstand physiological bite forces *in vivo*.

A recent *in vitro* study (76) investigated the performance of different abutment-implant connections in six groups of different two-piece zirconia implant systems. In one group, the abutments were cemented to an alumina-toughened zirconia implant. In a second group, the abutments were screwed with a carbon-fiber-reinforced polymer screw on an alumina-toughened zirconia implant. In the remaining four groups, the abutments were screwed with titanium screws on tetragonal zirconia polycrystal implants. A standard screw-retained titanium implant served as the control. At the end of the simulation of loading and aging, only the bonded abutment system and the titanium

system were free of mechanical failures. In the screwed abutment systems, all specimens presented with either fractures of the abutments partially combined with fracture of the implants or fractures of the screws. It was highlighted that porosities and impurities were observed in some zirconia implants, indicating the use of zirconia of lower quality. This is again a perfect example of the distinction between titanium and zirconia. The behavior of these two materials is different. Concerning the prosthetic parts (abutment connections, fitting of the suprastructure, screw material and fabrication process) the precision of the zirconia still does not equal that of titanium. The screw technology could be the new challenge for zirconia implants.

Conclusions

At present, the following conclusions can be drawn regarding zirconia dental implants:

- Through *in vitro* and *in vivo* studies, zirconia has managed to earn its place as a valuable alternative to titanium. From a biological point of view, zirconia presents with interesting assets. It has demonstrated a low affinity to bacterial plaque, small amounts of inflammatory infiltrate and good soft-tissue integration. These properties might lower the risk for peri-implant diseases.
- The biomechanical properties of zirconia implants were assessed in numerous experiments with success. However, early failure rates of zirconia implant systems developed and tested so far were generally higher compared with titanium implants. Solid data on long-term outcomes are scarce. Technical failure as a result of fracture of the material is a sensitive issue and a critical factor for usability and acceptance in daily practice.
- There is room for further technical progress of currently available zirconia implant systems. Two-piece implant systems with screw-retained abutments are desirable for several reasons, although are technically challenging because of limitations in the materials. Further innovation will undoubtedly lead to enhanced biomechanical characteristics, allowing use of new solutions that are presently too high-risk. Enhanced strength could enable novel designs of implants, reconstructions and the parts connecting the two.
- More clinical investigations need to be carried out to identify all relevant technical and biological factors with impact on success and patient satisfaction. At present, the evidence for a final verdict is

still incomplete, and the field is still changing in many ways. Patients are aware of the availability of zirconia implants on the market and we need to be ready to respond to their demands.

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