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Ich bedanke mich bei den unten aufgeführten Kolleginnen und Kollegen für ihre wertvolle Mitarbeit, die sie in den vergangenen zwei Jahren geleistet haben.

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The Osseointegration of Zirconia Dental Implants

Key words: ZrO_2, metal-free, ceramics, biocompatibility

Summary Zirconia is currently extensively used in medicine, especially in orthopedic surgery for various joint replacement appliances. Its outstanding mechanical and chemical properties have made it the "material of choice" for various types of prostheses. Its color in particular makes it a favored material to manufacture dental implants.

A literature search through Medline enables one to see zirconia's potential but also to point out and identify its weaknesses. The search shows that zirconia is a biocompatible, osteoconductive material that has the ability to osseointegrate. Its strength of bonding to bone depends on the surface structure of the implant.

Although interesting, the studies do not allow for the recommendation of the use of zirconia implants in daily practice. The lack of studies examining the chemical and structural composition of zirconia implants does not allow for a "gold standard" to be established in the implant manufacturing process. Randomized clinical trials (RCT) are urgently needed on surface treatments of zirconia implants intended to achieve the best possible osseointegration.

Part 1: Zirconia as a biomaterial

Discovery and origin

Zirconia is a material that is increasingly used in dental medicine. Despite the growing enthusiasm for this tough material, most clinicians know very little about the actual characteristics and properties of zirconia.

Zirconium is a chemical element with the symbol Zr and atomic number 40. It is a lustrous, grey-white, strong transition metal that resembles titanium. The name of the metal zirconium comes from the Arabic "zargun" (golden in color), which in turn derives from the two Persian words "zar" (gold) and "gun" (color). It is never found in nature as a native metal, but rather is obtained mainly from the mineral zircon. Zircon is found in alluvial deposits such as streambeds, ocean beaches or old lake beds. These are the only commercial sources of zirconium. In its pure state, zirconium exists in two forms: a) the crystalline form – a soft, white, ductile metal, and b) the amorphous form – a bluish-black powder. Zirconium ranks 18th in abundance among the elements in the crust of the Earth. Commercial grade zirconium contains 1 to 3% hafnium – a metal with properties similar to those of zirconium. Zirconia, the metal dioxide (ZrO_2), was identified as such in 1789 by the German chemist Martin Heinrich Klaproth in a reaction product obtained after heating some gems. The first to isolate zirconium in an impure form was Jöns Jakob Berzelius in 1824. Pure zirconium was not produced until 1914. The current process to obtain zirconium is by gathering it from coastal waters. The solid mineral zircon is purified by spiral concentrators to remove excess sand and gravel, and then by magnetic separators to remove ilmenite and rutile. The by-products can then be returned to the water safely, as they are all natural components of beach sand. The refined zircon is first purified into pure zirconium by chlorine or other agents and then "sintered"until sufficiently ductile for metalworking. Zirconium and hafnium are both contained in zircon and are quite difficult to separate due to their extremely similar chemical properties. Usually, an ion exchange process is used to separate them. Due to its outstanding resistance to corrosion, zirconium is often used as an alloying agent in materials that are exposed to corrosive agents – materials such as those used in surgical appliances, explosive primers, vacuum tube getters and filaments.

Properties

Zirconium dioxide is used in laboratory crucibles, metallurgic furnaces and as a refractory material. Zirconium dioxide is one of the most studied ceramic materials.

Zirconium dioxide is a white crystalline oxide of zirconium. The most abundant naturally occurring monoclinic crystalline form is the rare mineral baddeleyite. The initial interest in using zirconia as a ceramic biomaterial derived from its good chemical and dimensional stability as well as from its mechanical strength and toughness, coupled with a Young's modulus (200 GPa) of the same order of magnitude as stainless steel alloys. It was introduced in medicine and dentistry as a potentially ideal replacement for metal.

Effect of temperature on zirconia

Pure zirconia has a monoclinic crystal structure at room temperature and transitions to tetragonal and cubic at increasing temperatures. The volume expansion caused by the cubic to tetragonal to monoclinic transformation induces severe stresses and causes pure zirconia to crack upon cooling from high temperatures. Pure zirconia can break into pieces at room temperature (Christel et al. 1989). To prevent this phenomenon, several different oxides are added to zirconia to stabilize the tetragonal and/or cubic phases. Specifically, magnesium oxide (MgO), yttrium oxide (Y_2O_3), calcium oxide (CaO) and cerium oxide (Ce_2O_3) are used to generate partially stabilized zirconia (PSZ). PSZ's microstructure at room temperature generally consists of cubic zirconia as the major phase and monoclinic and tetragonal zirconia precipitates as the minor phase. In the presence of a small amount of stabilizing additive, tetragonal particles (provided they are small enough) can be maintained in a metastable state at temperatures below the transformation temperature from the tetragonal to monoclinic phase. The transformation of small tetragonal grains, which should result in a volume increase, is prevented by the compressive stresses applied on these grains by their neighbors. In the ZrO_2-MgO or ZrO_2-CaO systems, materials are "sintered" in the cubic state and small tetragonal precipitates are formed during the cooling as a result of partial transformation of the cubic phase. In the ZrO_2-Y_2O_3 system, it is also possible to obtain ceramics formed at room temperature with only a tetragonal phase called tetragonal zirconium polycrystal (TZP). As a result, using Y_2O_3 as a stabilizing agent, it is possible to produce a special case of zirconium dioxide ceramic made of 100% small metastable tetragonal grains.

Zirconia is mostly used in this "stabilized" state. The tetragonal phase is metastable. If sufficient quantities of the metastable tetragonal phase are present, an applied stress – magnified by the stress concentration at a crack tip – can cause the tetragonal phase to convert to monoclinic with the associated volume expansion. This phase transformation can then put the crack into compression, retarding its growth and enhancing the fracture toughness. This martensitic-like mechanism is known as transformation toughening (fig. 1) and significantly extends the reliability and lifetime of products made with stabilized zirconia, especially yttria-tetragonal zirconia polycrystal (Y-TZP).

Single crystals of the cubic phase of zirconia are commonly used as a substitute for diamond in jewelry (diamond simulant). Like diamond, cubic zirconia has a cubic crystal structure and a high index of refraction. Discerning a good quality cubic zirconia gem from a diamond is difficult. Most jewelers possess a thermal conductivity tester to identify cubic zirconia by its low thermal conductivity (diamond is a very good thermal conductor) (tab. I). This state of zirconia is commonly called cubic zirconia (CZ) or zircon by jewelers, however, this last name is not chemically accurate. Zircon is actually the mineral name for naturally occurring zirconium silicate ($ZrSiO_4$). Its transparent form is used as a gemstone and its opaque form as a refractory material.

Degradation of the material

The mechanical properties of zirconia relate to its fine-grained, metastable microstructure. The stability of this structure during the lifetime of TZP components is the key characteristic needed to attain the expected performances. Under certain manufacturing conditions or severe environmental conditions of moisture and stress, the resulting zirconia may transform more aggressively to the monoclinic phase with catastrophic results. Such a "high metastability" is clearly undesirable for medical implants. This mechanical property degradation in zirconia (due to the progressive spontaneous transformation of the metastable tetragonal phase into the monoclinic phase) is known as "ageing" of the material.

The low-temperature degradation has a maximum rate at 250°C. The transformation is enhanced in water or in vapor, while the most critical enhancing effects of temperature are in the range of 200–300°C. The tetragonal to monoclinic transition starts from the surface and progresses into the material bulk. Resistance to transformation is increased by a small grain size (< 1 µm), a density as close as possible to the theoretical

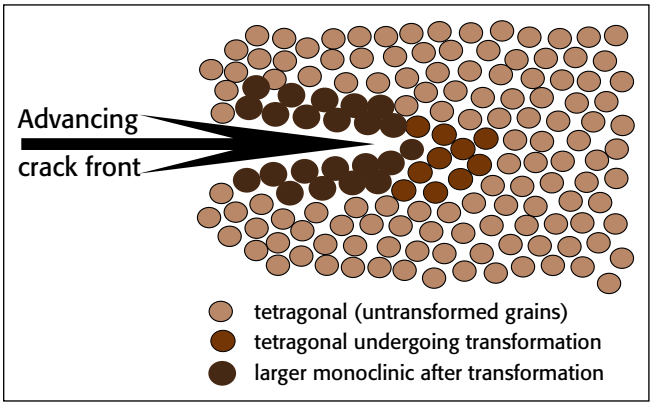

Fig. 1 **"Transformation toughening"** of an advancing crack in a block of stabilized zirconia. The phase transformation of the zirconia crystals from tetragonal to monoclinic with the associated volume expansion can put the crack into compression, retarding its growth and enhancing the fracture toughness of the material.

Tab. I Main differences between diamond and cubic zirconia

	Diamond	Cubic zirconia
Thermal conductivity	High	Low
Weight	1	1.7
Color	Almost never colorless	Can be made colorless. Very intense colors are possible
Origin	Natural	Synthetic
Refractive index	2.417	2.176
Hardness (Mohs scale)	10	8
Dispersion power	0.044	0.060 (more prismatic fire)
Effect of Temperature	Oxydizes (burns) in air over 700°C	Melting point 2750°C

($d = 6.1\ g/cm^3$) and yttrium oxide content as close as possible to 3 mol% (5.1 wt%). The increase in monoclinic phase leads to a reduction in strength, toughness and density, and is always followed by micro-macro-cracking. The growth of the transformed zone leads to extensive microcracking and surface roughening. In aqueous environments, this offers a path for the water to penetrate into the specimen, creating corrosion effects on the Zr-O-Zr bonds. The growth stage depends on several microstructural patterns: porosity, residual stresses and grain size (Deville et al. 2006). Reduction in grain size and/or increase in concentration of stabilizing oxides can reduce the transformation rate. However, reducing the size of grains too much may lead to the loss of metastability; the resulting increase in concentration of stabilizing oxide above 3.5 mol% may allow the nucleation of significant amounts of the stable cubic phase. This aspect of the Y-TZP implant ceramic was studied extensively and this ceramic was considered to be stable under normal body conditions (Ardlin 2002).

Manufacturing process and manufacturers

The manufacturing process of zirconia implants is very strict but varies for each implant company. The basic steps and phases of manufacturing a zirconia implant are: a) raw material formulation, b) pressing, c) sintering, d) HIP (hot isostatic pressing)-post-compaction, e) oxidizing, f) grinding and g) quality control. There are actually five known companies commercializing zirconia dental implants. However, only two reveal details about the chemical composition of their implants (Andreiotelli & Kohal 2009). The two companies that provide details about the manufacturing of their zirconia implants are:

- Y-TZP BIO-HIP Sigma® Implants (Incermed, CH-Lausanne): The crystalline products are processed into powder by grinding and compressed by an isostatic process at high temperature up to approximately 2000°C. The pure powder of zirconium (for which the granulometric spectrum has been defined) is processed through pressure in high temperature molds. This results in homogenous implants of exact dimensions. The chemical composition is >99.9% $ZrO_2+HfO_2+Y_2O_3$, out of which 5.2% is Y_2O_3 and 0.1% are other oxides.
- Y-TZP-A BIO-HIP® Implants (Metoxit AG, CH-Thayngen): The main steps of the manufacturing process for dental HIP Y-TZP-A implants are: a) material compaction, b) sintering, c) HIP, d) reoxidizing followed by e) machining (grinding), f) measurement proof testing and g) quality control. The chemical composition is >95.0% ZrO_2 (+HfO_2), 4.0% is Y_2O_3 and 0.25% is Al_2O_3.

This second company (Metoxit AG) claims that adding 0.25% of Al_2O_3 diminishes the rate of conversion from tetragonal to monoclinic by a factor 10 (Rieger et al. 2007). They also developed a new zirconia called Ziraldent® with a content of 25% of Al_2O_3 which, in combination with HIP process, should be the hardest ceramic material on the market.

These two companies do not provide extensive information about the surface characteristics of their implants. The only system that seems to add a porous surface on zirconia is ZiUnite® by Nobel Biocare® (ZiUnite implants, Nobel Biocare, SE-Gothenburg), though there is little or no information about the chemical structure of the implant. It is possible that the manufacturer adds a slurry containing zirconia powder as a pore-former on the surface of the not yet sintered implant. During sintering to full density, the pore-former burns off and leaves a porous surface.

Grey market

Since many companies provide the zirconia powder as a "raw material" and since each has its own formula for manufacturing, it is difficult to speak about zirconia as a single material. The implant companies manufacture their implants or other zirconia devices according to their own production protocol. The different and contrasting results concerning the performance of zirconia as a biomedical material highlight the need for zirconia biomaterials to be manufactured according to the guidelines of the existing ASTM (American Society for Testing and Materials) and ISO (International Organization for Standardization) standards.

Part 2: Literature review

Introduction

During an experiment in 1952, Professor Per-Ingvar Brånemark utilized a titanium implant chamber to study blood flow in rabbit bone and accidentally discovered that titanium could be completely integrated in bone in a way that meant the metal piece could not be removed from it. Brånemark called the discovery "osseointegration" and clearly saw the possibilities and applications for human use. The osseointegration capacity of titanium opened a new era that completely changed the treatment planning options in modern dental care.

Screw-shaped titanium dental implants have been widely used for over 40 years in implantology. Commercially pure grade 1 titanium has been accepted as the "material of choice" to fabricate dental implants. The material has been proven to be biocompatible (Brånemark 1985) and dental implant treatment has shown high long-term success rates in different indications (Attard & Zarb 2004, Ekelund et al. 2003, Andersson et al. 1998).

However, the grey color of the titanium may pose problems in esthetic areas, especially in non-optimal soft tissue situations. Moreover, due to peri-implant soft tissue recession, implant components may become visible over time. The demand for improved esthetics has become increasingly important in the general population. The increased preference for non-metal materials has motivated research toward tooth-colored ceramic implant materials. In the past, aluminium oxide has been used as dental implant material, e.g. the Tübingen Implant (Schulte 1981). Despite the good osseointegration of the implant, the biomechanical characteristics of the fixtures were not sufficient for long-term load. This resulted in the withdrawal of aluminum oxide from the market as a dental implant material.

After having been employed in orthopaedic surgery for approximately 30 years (Piconi et al. 1998), zirconia ceramics have recently been introduced into dentistry as a metal replacement for crowns, bridges and implant abutments. The flexural strength and fracture toughness of zirconia is roughly twice as high as that of alumina – a quality that makes zirconia very resistant to masticatory forces. Furthermore, zirconia is very resistant to corrosion (Slonaker & Goswami 2004) and several investigations have proven its high biocompatibility (Ichikawa et al. 1992, Albrektsson et al. 1985).

The purpose of the present study is to evaluate the available literature about the osseointegration ability of dental implants made out of zirconia.

Material and methods

A search was performed in Medline and MedPilot to identify relevant papers concerning the subject. The last search was

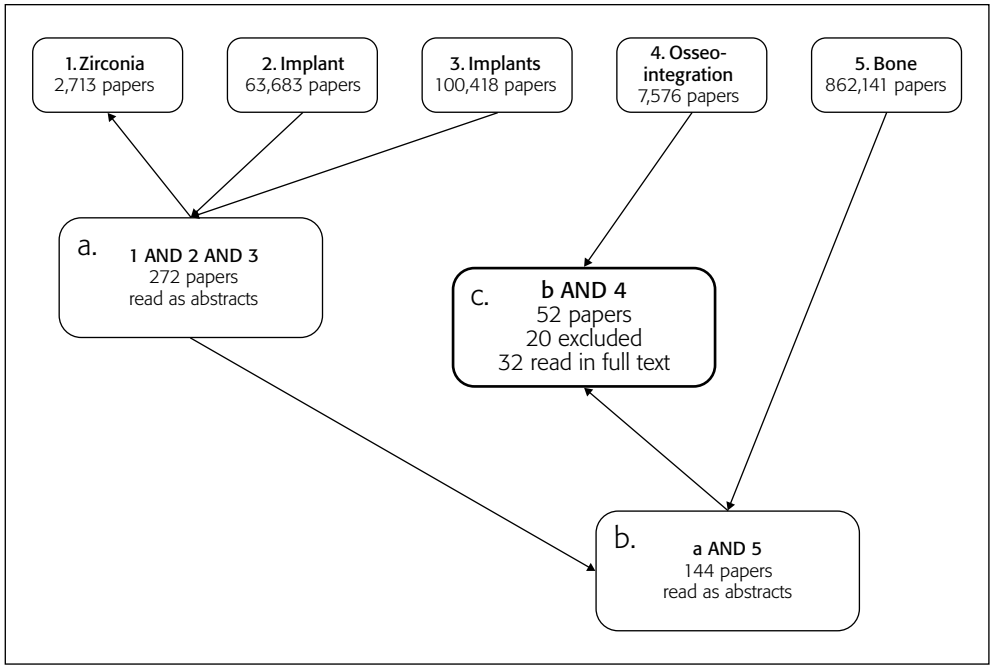

Fig. 2 Key words and combinations used to search the Medline Database. 1 to 5 are the key words used for the search. A, b and c are the combinations made to refine the search.

performed on December 31st, 2011. The single and fundamental inclusion criterion for this review was clinical or animal studies investigating osseointegration of zirconia dental implants. Studies of ceramic composites, zirconium oxide coatings on metallic implants or case reports or studies were not included in the review. Two in vitro studies addressing the topic were also included in the review.

Five key words (zirconia, implant, implants, osseointegration and bone) were used for the search, followed by three combinations. The papers obtained by the combined searches were read as abstracts. Out of the articles obtained by the last combination, 20 were excluded after reading the abstracts due to lack of relevance for this review or were concerning implant abutments. The remaining 32 articles were read in full (fig. 2).

Since this literature review was not limited to human trials, or RCTs, there did not appear to be any need to assess eligibility criteria according to the Delphi List (Verhagen et al. 1998).

Results

Literature search

Fifty-three articles were analyzed in detail after electronic (52 articles) or manual search (1 article): only 21 were included in this review. Thirty-two articles were excluded due to lack of relevance for this review or not directly addressing the subject. Only two studies addressing the reliability of zirconia dental implants could be identified, even if they did not give scientific evidence of reliability of zirconia implants. Eleven animal studies fulfilled the inclusion criterion, though one did not address osseointegration and will be mentioned in the discussion; one human study gave information about the topic, without being directly related to osseointegration of zirconia implants; three in vitro studies were also included, though one did not address osseointegration and will be mentioned in the discussion; four articles were reviews and are addressed in the discussion (tab. II + III).

In vitro studies

Two in vitro studies addressed the behavior of osteoblastic cells in contact with zirconia.

The first study (Depprich et al. 2008 a) was performed with 12 mm diameter disks made out three different materials: a) commercially pure titanium and b) zirconia (Y-TZP) as test groups, and c) polystyrene culture plates as a control. Primary bovine osteoblasts were put into culture in contact with the three materials. Both groups received a surface modification by acid etching. The disk surfaces were evaluated with a high-resolution field scanning electron microscope (SEM). The SEM showed noticeable differences between zirconia and titanium surfaces. The titanium surface was rough and contained many pores and grooves of different sizes, which were regularly distributed over the whole surface. In contrast, the zirconia surface appeared smooth with only a few pores.

Cell proliferation was found to be significantly higher on the zirconia surface than on titanium and polystyrene on days 3 and 5.

Tab. II Result of the literature search (number of studies). Last search performed on december 31st 2011.

	Animal	Human	Other	Total
In vitro studies	0	0	3	3
Studies on unloaded implant material	11	1	0	12
Studies on loaded implant material	0	2	0	2
Reviews				4
Total number of studies				21

Tab. III Results of the literature search

	Authors	Subject type: in vivo/vitro, review	Studied material	Control group or reference	Studied material	Surface treatment of studied material
1	Depprich et al. 2008 a	In vitro	12 mm ø disks	Yes, polystyrene and titanium	Commercially pure titanium, zirconia and polystyrene	Acid etching
2	Setzer et al. 2009	In vitro	20 mm ø disks, 1.5 mm thick	Titanium	Titanium, zirconia and alumina-toughened zirconia	All different Rough and smooth (TiUnite, ZiUnite…)
3	Scarano et al. 2004	Human	Unloaded implant material	Titanium	Commercially pure titanium and zirconia disks	Roughness "similar" for both materials
4	Scarano et al. 2003	Animal	Unloaded implants	No	Zirconia	No
5	Hoffmann 2008	Animal	Unloaded implants	Titanium	Titanium and zirconia implants	Zr: roughened Ti: sandblasted, acid etched
6	Depprich et al. 2008 b	Animal	Unloaded implants	Titanium	Titanium and zirconia implants	Acid etched
7	Langhoff et al. 2008	Animal	Unloaded implants	Yes, titanium SPI implant	Titanium and zirconia implants	Sandblasted, partially etched and coated with bisphosphonate or collagen
8	Gahlert et al. 2007	Animal	Unloaded implants	Yes, titanium SLA implant	Zirconia implants	Machined or sandblasted
9	Gahlert et al. 2011	Animal	Unloaded implants	Yes, titanium SLA implants	Zirconia implants	Acid etched and sandblasted
10	Sennerby et al. 2005	Animal	Unloaded implants	Yes, oxidized Ti implants	Zirconia implants	Machined and two different surface modifications
11	Rocchietta et al. 2009	Animal	Unloaded implants	Yes, oxidized titanium (TiUnite®) implants	Zirconia (ZiUnite®) implants with addition of two chemical surface modifications	Porous surface (ZiUnite®) with chemical surface modifications
12	Lee et al. 2009	Animal	Unloaded implants	Yes, zirconia (ZiUnite®) and Ti (TiUnite®) impl.	Zirconia (ZiUnite®) implants with addition of two chemical surface modifications	Porous surface (ZiUnite®) with chemical surface modifications
13	Aboushelib et al. 2011	Animal	Unloaded implants	Yes, as-sintered zirconia and titanium implants	Nano-porous selective infiltration etched zirconia implants	Nano-porous selective infiltration etched
14	Blaschke & Volz 2006	Human	Loaded implants	No	Zirconia implants	Sandblasted
15	Oliva et al. 2007	Human	Loaded implants	No	Zirconia implants of five different designs	Two surface roughnesses
16	Andreiotelli & Kohal 2009	In vitro	Loaded implants	Yes, titanium implants	Zirconia implants of two different qualities, with and without abutment preparation	Different surface topographies
17	Kohal et al. 2008	Literature review	Ceramic abutments and ceramic implants			
18	Wenz et al. 2008	Literature review	Zirconia dental implants			
19	Hisbergues et al. 2009	Literature review	Zirconia in dental implantology			
20	Tete et al. 2009	Animal	Unloaded implants	Titanium	Titanium implants with titanium or zirconia necks	
21	Andreiotelli et al. 2009	Literature review	Ceramic implants			

Result assessment method	Observation time	Observed and analyzed subject	Conclusion
Photograpy, select. washing, immuno-cytochemistry, SEM	1 to 5 days	Osteoblastic cells behavior	Zirconia can be considered biocompatible
Histology Gene behavior SEM	4 hours, 1, 7, 14 and 28 days	Cellular behavior of human fetal osteoblasts	Zirconia is comparable to titanium in regard to cell behavior. Cell behavior is affected by surface roughness
SEM	24 hours	Surface colonization by bacteria	Low colonization potential of zirconia
Histology	4 weeks	Cellular reactions and bone healing around zirconia implants	Bone to implant contact visible; no inflammation. Biocompatibility of zirconia
Histology	2 and 4 weeks	Early bone apposition around zirconia implants	Similar bone apposition around zirconia implants and around titanium implants
	1, 4 and 12 weeks	Osseous healing of implants	Osseointegration of zirconia similar to titanium
Histol. macro- and micro-radiological examination	2, 4 and 8 weeks	Osseointegration, bone to implant contact	No improvement of osseointegration by coated implant surfaces compared to control implant
Removal torque test Histology	4, 8 and 12 weeks	Removal torque values for two zirconia surfaces	Roughening the surface of zirconia implants has a beneficial effect on the interfacial shear strength
Histology, histomorphometrical analysis	4, 8 and 12 weeks	Direct bone-implant contact and peri-implant bone density	No detectable difference in osseointegration between test and control. Not directly applicable to humans
Bone tissue response	6 weeks	Removal torque test, histology, SEM	Resistance to torque force increased 4 to 5 times by surface modification of zirconia implants; similar to titanium
Removal torque test and histology	3 weeks	Removal torque test and bone to implant contact	No significant histological difference between test and control. Chemical surface modification is not beneficial to interfacial shear strength
Histology, SEM, histometric analysis	3 and 6 weeks	Bone density around implants, direct bone-implant contact	Addition of CaP nanotechnology to the ZiUnite® surface does not enhance the osteoconductivity displayed by the TiUnite® and the ZiUnite® implant surface
Histology, histometric analysis, SEM	4 and 6 weeks	Bone density around implants, direct bone-implant contact	The addition of this nano-porous selective infiltration etched surface improved osseous healing and bone apposition compared to as-sintered zirconia implants
Radiological	1 to 2 years	Crestal bone around implants	Good soft tissue response, feasible alternative to titanium
Panoramic X-ray at 12 months	1, 3, 6 and 12 months	Implant reconstruction stability	Zirconia implants may be an alternative for titanium implants
Survived or fractured	After exposure to artificial mouth	Survival rate and fracture strength of implants	One type of zirconia is more resistent than the other. Preparation of the abutment has a negative effect on fracture strength
			Due to lack of scientific support, cannot be recommended for clinical use
			Cannot be recommended for routine clinical use
			Need for consistent information on chemistry of zirconia
Histology clinical	3 months	Collagen fiber orientation around neck of implants	Collagen fiber orientation is the same for all materials
			Zirconia has the potential to be a successful implant material

The assessment of cell detachment from the surfaces showed significantly higher cell detachment rates from zirconia in comparison to titanium surfaces. There was no significant difference in cell detachment rate between zirconia and the control.

The immunocytochemical analysis showed no significant differences between titanium, zirconia and polystyrol. The present study showed that primary bovine osteoblasts were able to attach, proliferate and differentiate on modified zirconia surfaces in vitro, suggesting that the ceramic material might also have beneficial effects on biocompatibility and osseointegration when used in patients.

In the second study, researchers (Setzer et al. 2009) used human fetal osteoblasts to study their proliferation and adhesion on different materials. The investigated materials were: a) machined titanium disks (Nobel Biocare, Gothenburg, Sweden), b) titanium disks where the surface was treated with electrochemical anodization (TiUnite®, Nobel Biocare, Gothenburg, Sweden), c) machined yttrium-stabilized tetragonal polycrystal zirconia disks reinforced with 25% alumina (y-TZP-A-m, Metoxit, Thayngen, Switzerland), d) zirconia disks with a modified surface topography (ZiUnite®, Nobel Biocare, Gothenburg, Sweden), e) alumina-toughened zirconia with a machined surface (ATZ-m, Metoxit, Thayngen, Switzerland) and f) ATZ disks with a modified surface (ATZ-mod, Metoxit, Thayngen, Switzerland).

The different samples were all different in roughness, but divided into more or less two distinct groups: a) rough and b) smooth. The roughest surface was TiUnite® (Ra = 0.544 µm) and was followed in texture roughness by ZiUnite® (Ra = 0.489 µm).

The authors concluded that cell behavior was generally affected by surface roughness during the cell adhesion and proliferation stage before the cells established their pericellular environment. Similar cellular behavior could be observed on titanium and zirconia with respect to histology, gene expression and SEM.

The results of this in vitro study showed that the zirconia materials utilized were comparable to titanium – the classic implant material – with regard to cell behavior and could be recommended for further preclinical and clinical research.

Human study of unloaded implant material

The purpose of the next study (Scarano et al. 2004) was to quantify by SEM the percentage of surface covered by bacteria on commercially pure titanium and zirconium oxide disks after being in the human mouth for 24 hours. The authors concluded that zirconium oxide surfaces showed a significant reduction in the presence of bacteria compared to titanium. It seemed that zirconium oxide had a low colonization potential.

Animal studies of unloaded implants

The purpose of this investigation (Scarano et al. 2003) was to analyze in vivo cellular reactions and bone healing around zirconia implants inserted in rabbit tibiae. They placed 20 zirconia ceramic implants (Norton Desmarquest, Evreux, France) in the left and right tibiae of five male rabbits. They found an average bone-to-implant contact of 68.4% ± 2.4%. No gaps or fibrous tissue were present at the interface. No foreign-body reaction was found at the bone-implant interface. No epithelial downgrowth was observed at the interface. Wide marrow spaces were present, with some of them abutting on the implant surface. The newly formed bone showed many viable osteocytes. The study concluded that these implants were highly biocompatible and osteoconductive.

Subsequently, a histological examination of early bone apposition around zirconia dental implants at 2 and 4 weeks after insertion compared to surface-modified titanium implants was undertaken (Hoffmann et al. 2008). For this study, commercially available zirconia implants with a roughened surface (Z-Look 3 Implant, 3.25 × 10 mm, Z-systems AG, Constance, Germany) were used as test implants and commercially available titanium implants with a sandblasted, acid-etched surface (Osseotite, 3.25 × 8.5 mm, Biomet 3i, Palm Beach Gardens, FL, USA) were used as controls. One implant was placed in each distal condyle of the rear femur of each rabbit, 2 per rabbit (1 test and 1 control implant). Histologic specimens were harvested at 2 and 4 weeks after implant placement. The results of this limited histologic study demonstrated a similar rate of bone apposition on zirconia and surface-modified titanium implant surfaces during early healing.

A comparison between osseous healing of zirconia implants and titanium implants that had a roughened surface, but otherwise similar implant geometries, was also performed (Depprich et al. 2008 b). For this purpose, 24 screw-type zirconia implants (yttrium-stabilized tetragonal polycrystals) with modified (acid-etched) surfaces (Ra = 0.598 µm, according to manufacturer) were used and compared to 24 implants made of commercially pure titanium with acid-etched surfaces (Ra = 1.77 µm, according to manufacturer). Implants were supplied by Konus Dental Implants (Bingen, Germany). Implants were inserted into the tibia of 12 mini-pigs. Histological results showed direct bone contact on the zirconia and titanium surfaces, which demonstrated that zirconia implants with modified surfaces result in osseointegration comparable to that of titanium implants.

A hypothesis was proposed by some authors that chemical and pharmacological surface modifications of titanium would initiate a stronger bone response than an advanced sandblasted and acid-etched surface alone (Langhoff et al. 2008). They tested whether a surface-treated zirconia could compete with sophisticated titanium surfaces. The bone response to the implant modifications was tested on the identical established implant geometry using histomorphometry. All titanium and zirconia implants were sandblasted and partially etched prior to the surface treatments. The surface of the chemically modified implants was either plasma anodized or coated with calcium phosphate. The pharmacologically modified implants were either coated with bisphosphonate or collagen type I and chondroitin sulfate. An acid-etched and sandblasted implant made of titanium (grade 4, SPI®Element, Thommen Medical AG, Waldenburg, Switzerland) served as the reference and control for the surface modifications. The zirconia implants were manufactured out of yttrium partially stabilized medical grade zirconia. The zirconia implants were sandblasted and etched in an alkaline bath. The conclusions were: a) that bone-to-implant contact on zirconia implants was 20% better than all tested titanium implants after 2 weeks, and b) that bone-to-implant contact improved at 4 weeks and then it reduced at 8 weeks to below the level of the reference surface. In the end, the hypothesis could not be supported because all tested implants demonstrated good biocompatibility and osseointegration with only small differences compared to the reference implant surface.

The removal torque values for zirconia implants made with different surface designs were measured in another study (Gahlert et al. 2007). Zirconia implants with either a machined (smooth) or a sandblasted (rough) surface were manufactured with exactly the same cylindrical shape with the same

standard ITI thread configuration as the SLA titanium implants. The zirconia implants were manufactured by Metoxid AG (Thayngen, Switzerland) under the control of Straumann AG (Basel, Switzerland). The titanium implants were manufactured by Straumann AG. All implants had exactly the same design: a standardized diameter of 3.75 mm and a length of 10 mm. The zirconia implants were processed in the following way during manufacturing: a) isostatic dry pressing, b) sintering, c) HIP, d) shaping and e) polishing by a diamond tool. Half of the zirconia implants were sandblasted with particles of korund (Al_2O_3, Ø 250 µm) under 5 bars of pressure to generate a rough surface. The results of the study showed that rough zirconia implants had significantly higher removal torque values than smooth zirconia implants, although standard SLA titanium implants had significantly higher removal torque values than rough zirconia implants. The conclusion was that roughening the turned zirconia implants enhanced bone apposition and had a beneficial effect on the interfacial shear strength.

Later, a study was performed (Gahlert et al. 2012) to investigate the direct bone-implant contact (BIC) ratio and peri-implant bone density for zirconia implants with a rough acid-etched surface topography in comparison with equally shaped Ti-SLA implants in the maxilla of pigs. A total of 18 zirconia and 18 titanium implants were inserted in 18 mini-pigs. All implants had an identical shape and were all acid-etched and sandblasted. The results were taken after 4, 8 and 12 weeks of healing. The histomorphometric data obtained did not reveal statistically significant differences between test (zirconia) and control (Ti-SLA) implants for peri-implant bone density and BIC ratio. There were two exceptions: the mean peri-implant bone density and BIC values of the control implants were always higher than those of the tested zirconia implants. The conclusion was that no detectable difference in osseointegration could be observed between the two types of implants.

A study (Sennerby et al. 2005) was undertaken to perform a histological and biomechanical evaluation of the bone tissue response to zirconia implants with two different surface modifications in comparison with machined, non-modified zirconia implants and oxidized titanium implants. To accomplish this analysis, 72 threaded zirconia ceramic implants were used. They were manufactured by isostatically pressing cold zirconia powder (TZ-3YSB-E, Tosoh Corporation, Tokyo, Japan) into rods. These rods were pre-sintered and then turned into threaded implants. To achieve a porous surface, the implants were coated with a slurry containing zirconia powder and a pore former (ZiUnite®). For the study, two slurries each with a different pore former were used to create two different surface structures. After the coating was applied, the implants were sintered to full density under which the pore former burned off and left a porous surface. As a control, 24 non-coated implants treated in the same way, with the exception of the coating process, and 24 modified oxidized implants (TiUnite®) were also used. The study showed a strong bone tissue response to surface-modified zirconia implants after 6 weeks of healing. The non-modified zirconia implants showed statistically lower removal torque values than all other implants tested. All of the modified zirconia implants and the oxidized titanium implants showed similar resistance to torque forces. After removal torque testing, the SEM examination of the implant surfaces showed bone interface fracture rather than bone separation from the implant surface.

A study (Rocchietta et al. 2009) examined the benefit of chemical modification of an existing ZrO_2 implant surface (Zi-Unite®) as described in the previous article. The control group was comprised of titanium (Ti-Unite®) implants. A total of 143 implants (123 zirconia and 20 titanium) were used in 18 rabbits. The roughness value of the porous zirconia implants was $S_a = 1.24$ µm and of oxidized titanium implants was $S_a = 1.3$ µm. The addition to the zirconia surfaces involved the use of two types of hydroxyapatite nanoparticles. The removal torque test did not show any statistically significant difference between the three zirconia implant groups. The mean bone-to-implant contact showed no statistically significant difference between the three zirconia and the test titanium group. The conclusion was that chemical addition to zirconia implants does not seem to be beneficial.

Another study (Lee et al. 2009) compared zirconia implants with an advanced surface modification (ZiUnite®) versus two different nanoscale surface modifications. Non-modified zirconia (ZiUnite®) implants and titanium (TiUnite®) implants were used as controls. In total, 80 implants were placed in femoral sites of 40 rabbits. Results were taken at 3 and 6 weeks. ZiUnite® implants were surface modified by two nanoscale modifications: one with a CaP coating of < 50 nm and the other with a coating < 200 nm. The results showed that adding a coat of nanoscale particles to zirconia implants with the ZiUnite® surface does not enhance the osteoconductivity displayed by the TiUnite® and the ZiUnite® implant surfaces.

Recently, a group (Aboushelib et al. 2011) compared nanoporous selective infiltration-etched zirconia implants with as-sintered zirconia and titanium implants. Twenty rabbits received the test implants and a separate group of 20 rabbits received titanium implants as control. After 4 and 6 weeks, the results were taken and revealed a beneficial effect of the nanoporous selective infiltration-etched implant surface in comparison to the surface of as-sintered zirconia implants.

Human studies of loaded implants

The results of a 5-year study of zirconia implants in humans have now also been analyzed (blaschke & volz 2006). Sixty-six zirconia implants were placed (Volzirkon 1 or 2 and Z-Lock 3, Z-Systems AG, Constance, Germany). These implants were CAD/CAM-milled out of Bio-HIP A zirconia blocks produced by condensing ultrafine zirconium dioxide powder with a particle size of 0.2 µm under 1500 bars of pressure for several days. They were of a monoblock design with a sandblasted intraosseous portion and a polished gingival/abutment section. The implants were restored with zirconia superstructure between 4 and 6 months after fixture insertion. The implants were observed to be stable 1 to 2 years later. Therefore, the authors concluded that dental implants made out of zirconia 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. were the first to report on 100 restored zirconia implants placed in humans after a 1-year follow-up (Oliva et al. 2007). They placed 100 implants in 36 patients (34 in the esthetic zone, 46 in the posterior maxilla and anterior mandible). The implants were one-piece implants made in five different designs and two different degrees of surface roughness (CeraRoot, Barcelona, Spain). The manufacturing process consisted of pressing cold zirconia powder (TZ-3YSB-E, Tosoh Corporation, Tokyo, Japan) into rods. Rods were pre-sintered and then turned into threaded implants. Two different treatments were used to achieve a porous surface. In one group (the non-coated group) a special diamond wheel was used to mechanically roughen the surface. In the other group (the coated group), the implants were coated with a stable bioactive ce-

ramic material with the following composition: Na_2O-K_2O-MgO-Al_2O_3-CaO-SiO_2-P_2O_5-F. After the roughening process, the implants were sintered to full density. The average roughness (Ra) has been defined as the average distance from the profile to mean line over the length of the assessment. The roughness of the coated implants was Ra = 0.436 µm and of the non-coated implants was Ra = 0.293 µm. The patients had all-ceramic restorations installed between 4 and 8 months after implant insertion. Special attention was paid to occlusion and the definitive implant restorations were placed in slight infra-occlusion to compensate for the elasticity of the periodontal ligament of natural teeth. Contacts in the lateral excursions were avoided. 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.

Discussion

This literature review summarized the current relevant papers concerning the subject of osseointegration of zirconia implants. There is an enormous amount of information regarding the subject. The tentative conclusion from this mass of data and the various descriptions of manufacturing processes is that zirconia is a very complex material. It is totally different from titanium, which is a metal used in dentistry in its pure (or commercially pure) form. On the contrary, as explained in the introduction, zirconium in its pure form cannot be used in medicine. It has to be manufactured, following many different steps, to be usable in dentistry. This represents one part of the difficulty. Machined titanium implants have proven their osseointegration capacity even if not covered with a rough surface. The first screw-shaped implants placed by Brånemark over 40 years ago are still functional. It has been shown in the removal torque research that the obtained values for machined zirconia implants are very low, and it seems to be clear that zirconia without a rough surface cannot be considered as a good and reliable implant material.

The survival rate and fracture strength of unrestored and restored one-piece zirconia implants have also been evaluated after exposure to the artificial mouth (Andreiotelli & Kohal 2009). The results were compared to those of titanium implants. The ceramic implants were manufactured out of Y-TZP with two different chemical compositions and with different surface topographies and abutment preparation designs. A total of 120 screw-type ceramic and titanium implants were used for the experiment. The conclusions were unambiguous: the performance of one-piece implants made out of Y-TZP BIO-HIP® is not as good as the performance of the implants fabricated out of Y-TZP-A BIO-HIP®. They demonstrated a survival rate of only 50% after exposure to the artificial mouth, whereas the other groups had a survival rate of 87% to 100%. They also demonstrated that the preparation of the abutments has a negative influence on the fracture strength values of the implants.

A significant number of studies evaluate the ability of zirconia implants to osseointegrate. It has been shown in all studies that the biocompatibility of zirconia is good, even if the composition of the tested materials is always different. In every study, there is a brief description of the manufacturing process of the implants. It is more or less always the same since there are some steps that must be followed in zirconia manufacturing. However, a clear and accurate description is lacking both of the exact chemical composition of the implant material and of the manufacturing steps with exact timing, pressure and temperatures applied during the manufacturing process.

A literature review (Kohal et al. 2008) indicated that, since the clinical use of zirconia implants lacks scientific support, the authors do not currently recommend their use. Prospective clinical investigations are needed before these implant systems can be recommended for clinical use.

Another literature review (Wenz et al. 2008) concluded that Y-TZP implants may have the potential to become an alternative to titanium implants, but as no long-term clinical data is available, they cannot be recommended currently for routine clinical use.

Some interesting conclusions can be drawn from a review (Hisbergues et al. 2009) in which it was demonstrated from actual published data that zirconia: a) has proven to be biocompatible in vitro and in vivo, b) has very interesting microstructural properties and c) is osteoconductive. Physical and chemical treatments of zirconia were shown to largely influence its soft tissue interactions. Moreover, a few studies conclude and emphasise that zirconia and its derivatives (ZrN) have the capacity to reduce plaque on implant and surrounding tissues and, consequently, could be important in soft tissue healing and implant success at bone level. This perio-integration mechanism probably avoids the resorption of peri-implant bone as well. This mechanism has also been demonstrated in a study on collagen fibre orientation around titanium and zirconia implant necks placed into miniature pigs (Tetè et al. 2009). The study concluded that collagen fibre orientation was similar, regardless of implant material, and demonstrated a predominantly parallel or parallel-oblique pattern. Moreover, zirconia, which is used as a transgingival collar on some implants, showed connective tissue adhesion that was similar to that observed on a machined titanium surface. It also demonstrated limited plaque formation. Another systematic literature review (Andreiotelli et al. 2009) concluded that ceramic implants cannot be recommended for routine clinical use. Alumina implants did not perform satisfactorily and therefore were not recommended as a viable alternative to titanium implants. Zirconia, however, may have this potential but no clinical investigation can support this assumption yet. The authors deeply regret that zirconia implants are being offered on the market without any scientific support.

All studies indicate that zirconia has a genuine potential to become an effective implant material, however, it needs much more work to justify being recommended for daily use in dental practices. Even if one zirconia implant surface (ZiUnite®) seems to perform better than the others, an urgent need exists for more structured studies identifying the exact steps needed to be performed throughout the manufacturing process.

The first study should assess the mechanical capacities of different types of zirconia with their exact composition and sintering process. There is no point in re-visiting and re-analyzing the biocompatibility of zirconia; it has already widely been shown to be good. This research should not include removal torque resistance tests since these depend more on the surface structure, which should be evaluated in a later step. The first research should involve tests on ageing and chemical stability of the material over time. It should also be tested and verified if implant preparation (with diamond burs) leads to a weakening of those mechanical properties or not. Once a conclusive result from this study is obtained, namely, that one special type of zirconia is shown to be better than the others, it should be qualified or proposed as the standard. A further

study can at this point only evaluate different surface treatments in order to point out the best one. Some of the actual studies that compare titanium implants to zirconia implants try to create the same surface characteristics on both types of implant by sandblasting and acid-etching both surfaces. This has absolutely no relevance, since it has been previously shown that acid-etching has no effect on zirconia. It can be deduced from the outset that results will not be comparable. To conclude, research has to be conducted in order to discover the best way to manufacture the most reliable zirconia implants. Only at that time will there be scientific rigor possible in comparing the characteristics of zirconia implants and titanium implants.

Conclusions

To conclude this review of the current state of knowledge about osseointegration of zirconia implants, the following facts may be advanced:

- There is a lack of consistency in all publications. None of them gives the exact chemical structure of the tested zirconia implants. They are all of very short-term studies.
- Zirconia is proven to be biocompatible, osteoconductive and to have no adverse effect on the surrounding tissues.
- Zirconia implants have been shown to lead to, in general, an inferior degree of osseointegration (removal torque tests) compared to titanium implants.
- Some surface structures allow removal torque test values to come close to those obtained by existing titanium implants. The values depend more on the surface structure than on the implant material itself.

There is an urgent need for structured investigations on the chemical structure of the zirconia implant material. It is imperative to identify some standards in order to allow for consistency in the materials used and long-term stability. Research will then be able to proceed in the identification of the best surface structure for osseointegration.

Unfortunately, a great deal of further research and investigation is needed before zirconia implants can be recommended for daily practice with the same level of security as titanium implants.

Résumé

L'usage de l'oxyde de zirconium est actuellement très répandu en médecine, particulièrement pour la fabrication de prothèses orthopédiques. L'engouement pour ce matériau s'explique par son aspect, mais surtout par ses extraordinaires caractéristiques techniques. Ses propriétés chimiques et mécaniques en ont fait le «matériau de choix» pour divers types de prothèses. Sa couleur, en particulier, le rend très attractif pour la fabrication d'implants dentaires.

Le but de la présente revue de littérature est d'évaluer la capacité d'ostéointégration des implants en oxyde de zirconium. En préambule, une description détaillée des propriétés du matériau est proposée, de manière à expliquer les avantages, les inconvénients, les points forts et les faiblesses du zirconium.

La recherche de littérature sur Medline a permis de mettre en évidence le potentiel de l'oxyde de zirconium en tant qu'élément pour la fabrication d'implants dentaires et a démontré certaines faiblesses ainsi que le manque de rigueur et de logique des études actuelles sur ce matériau. En implantologie, le titane peut être valablement considéré comme la référence actuelle en matière d'intégration osseuse. Il est donc important que les nouveaux implants testés lui soient comparés. Le titane a prouvé sa capacité d'intégration osseuse même en étant lisse, mais pour qu'un implant en titane ait les caractéristiques souhaitées actuellement, il doit subir un certain nombre de traitements de surface, de manière à lui conférer une rugosité qui a prouvé son efficacité (sablage, mordançage, oxydation, etc.). L'oxyde de zirconium lisse, bien que toléré par l'os, ne s'intègre pas. C'est donc son traitement de surface qui va lui permettre d'avoir la résistance souhaitée une fois implanté. De nombreuses recherches comparent un même traitement de surface pour les implants en oxyde de zirconium et pour ceux en titane. Ces études ne sont pas fiables, puisque la réaction aux traitements des matériaux testés n'est pas comparable. Les surfaces obtenues n'ont donc pas la même rugosité. Cependant, le traitement de surface (ZiUnite®) semble être meilleur que les autres. Le titane est un élément qui existe en tant que tel, alors que l'oxyde de zirconium doit être fabriqué pour la réalisation d'un implant. Les études actuelles sur cette substance n'ont pas débouché sur un consensus quant à la description de la manière ou du processus de fabrication idéal de l'oxyde de zirconium à utiliser pour la réalisation d'implants dentaires. Ceci devrait pourtant être la première étape nécessaire et incontournable pour garantir la sécurité dans la conception des futurs implants en oxyde de zirconium. On sait actuellement que, selon la manière dont est fabriqué l'oxyde de zirconium, celui-ci peut être instable, soluble ou encore friable. Il est donc impératif que, préalablement à la recherche sur la surface et la forme de l'implant, un consensus soit trouvé sur le procédé de fabrication du matériau lui-même.

A l'heure actuelle, sur la base des études existantes, les implants en oxyde de zirconium ne peuvent pas être recommandés pour la pratique courante, puisqu'aucune étude clinique sérieuse n'a été réalisée. En conclusion, on ne peut pas affirmer que les implants en oxyde de zirconium offrent la même sécurité et la même fiabilité que les implants en titane.

Zusammenfassung

Der Gebrauch von Zirkonoxid ist zurzeit in der Medizin, besonders in der Orthopädie, weit verbreitet. Seine Farbe, aber auch seine ausserordentlichen Eigenschaften erklären die Begeisterung für dieses Material. Seine chemischen und mechanischen Eigenschaften zeigen es als «Material der Wahl» für verschiedene Prothesen. Seine Farbe sorgt für seine Attraktivität in der Herstellung zahnärztlicher Implantate.

Das Ziel dieser Arbeit ist es, die Fähigkeit der Implantate aus Zirkonoxid zur Osseointegration abzuschätzen. Als Einleitung dient eine ausführliche Beschreibung der Eigenschaften des Materials. Die Vorteile, Nachteile und auch Schwächen des Zirkonoxids werden unterstrichen.

Eine elektronische Literaturrecherche in Medline wurde durchgeführt, um das zukünftige Potenzial von Zirkonoxid als Herstellungsmaterial für zahnärztliche Implantate einzuschätzen und um Schwächen aufzuzeigen. In der Implantologie kann Titan als Goldstandard für Osseointegration angesehen werden. Es ist also wichtig, dass die getesteten Implantate damit verglichen werden. Im Gegensatz zu Titan, das sich auch mit einer polierten Oberfläche im Knochen integriert, müssen bei der Herstellung von Zirkonoxidimplantaten Schritte unternommen werden, damit es die zurzeit gewünschte raue Oberfläche erhält (Sandstrahlung, Säureätzung, Oxidierung). Glattes Zirkonoxid wird vom Knochen gut toleriert, integriert sich aber nicht. Es ist seine Oberflächenbehandlung, die ihm nach der

Implantation die gewünschte Stabilität im Knochen verleiht. Mehrere Untersuchungen vergleichen Titan- und Zirkonoxidimplantate mit derselben Oberflächenbehandlung. Diese Studien sind nicht verlässlich, da die Wirkung der Behandlungen auf den getesteten Materialien nicht die gleiche ist. Die entstandenen Oberflächen haben nicht die gleiche Rauheit. Eine Oberflächenbehandlung (ZiUnite®) scheint besser zu sein als die anderen. Die zur Verfügung stehenden Studien über dieses Material haben keine Einheitlichkeit gezeigt in der Beschreibung der Art und Weise des idealen Herstellungsprozesses des zur Implantatherstellung benötigten Zirkonoxids. Das sollte jedoch die erste unausweichliche Etappe sein, um Sicherheit in der Herstellung zukünftiger Zirkonoxidimplantate zu gewährleisten. Man weiss jetzt, dass Zirkonoxid, abhängig von seiner Herstellungsweise, unbeständig, wasserlöslich oder brüchig sein kann. Es ist also unbedingt notwendig, dass man sich auf eine einheitliche Herstellungsweise des Materials einigen kann, und zwar noch vor der Forschung über Oberfläche und Formgebung des Implantates.

Aufgrund der zur Verfügung stehenden Studien sowie wegen des Mangels an gut gemachten klinischen Studien können Zirkonoxidimplantate zur täglichen Anwendung derzeit nicht empfohlen werden. Als Schlussfolgerung kann man nicht behaupten, dass Zirkonoxidimplantate dieselbe Sicherheit und dieselbe Zuverlässigkeit wie Titanimplantate bieten.

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