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Review

Current status of zirconia implants in dentistry: preclinical tests

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ABSTRACT

Purpose: This systematic review aimed to provide an overview of zirconia implants as well as regarding the outcome of the implant-restorative complex in preclinical studies.
Study selection: An electronic search of the literature prior to July 2017 was performed to identify all articles related to preclinical research on zirconia implants. The search was conducted using MEDLINE (National Library of Medicine) and PubMed without restrictions concerning the date of publication. The search terminology included: zirconia implant, osseointegration, bone-to-implant contact, soft tissue, histology, histomorphometry, surface modification, surface roughness, surface characteristics, and restoration (connecting multiple keywords with AND, OR).
Results: Fifty-seven studies were finally selected from an initial yield of 654 titles, and the data were extracted. The identified preclinical studies focused on several aspects related to zirconia implants, namely biocompatibility, mechanical properties, implant design, osseointegration capacity, soft tissue response, and restorative options. Due to heterogeneity of the studies, a meta-analysis was not possible. The most frequently used zirconia material for the fabrication of implants is yttria-stabilized tetragonal zirconia polycrystal. The resistance-to-fracture for zirconia implants ranged between 516–2044 N. The mostly investigated parameter was osseointegration, which is compared to that of titanium. A lack of evidence was found with other parameters.
Conclusions: Due to its good biocompatibility as well as favorable physical and mechanical properties, zirconia implants are a potential alternative to titanium implants. However, knowledge regarding the implant-restorative complex and related aspects is still immature to recommend its application for daily practice.

1. Introduction

Since the introduction of dental implants for clinical application, titanium has been considered the standard material of choice. The selection of titanium is based on its excellent biocompatibility, good physical and mechanical properties, and versatility for fabrication of dental implants and components. Clinical studies have clearly validated the long-term success of titanium dental implants for the treatment of edentulous and partially edentulous jaws [1,2]. Although titanium has been in use for more than 40 years, a number of criticisms regarding its clinical application have been raised [3,4]. Basically, there are two types of titanium implant designs available: one- and two-piece implant designs. A one-piece titanium implant denotes that the transmucosal portion of the implant is manufactured together with the implant body as a single unit [5,6]. On the other hand, a two-piece implant necessitates the use of an abutment as a foundation for the prosthetic rehabilitation [7]. One-piece implants have been suggested to offer several advantages over two-piece implants from biologic, clinical and technological point of view [8]. However, the literature does not provide evidence that favors a specific implant design in terms of long-term clinical performance [6,7]. Regardless of the design, it is well known that titanium implants may lead to a dull greyish background of the soft tissue in cases with a thin peri-implant mucosa or recession. This discoloration may become an esthetic disadvantage in the anterior visible region, especially with a high lip line [9]. A further concern relates to possible adverse reactions against the metal titanium. Although convincing evidence remains to be introduced, a number of reports concluded that exposure to titanium could lead to hypersensitivity [10–13]. Additionally, discussions about the existence of titanium in a wet organic milieu, i.e., bone and soft tissue, suggested that the material's resistance to corrosion degrades over time [14–16]. With such disadvantages, and in

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conjunction with the notably growing number of patients rejecting metallic components in their bodies (so-called metal-free body concept), an increasingly critical attitude in recent years toward titanium as an implant material, especially in some European countries, has been observed. This drove for the search for an alternative implant material. Hence, a number of materials were used in efforts to develop ceramic implants. The very first attempts to introduce ceramic implants were not successful; following market withdrawal of existing products and fear of further clinical failure, the further development of ceramic implants was slowed [17]. A very good example here is the failure of alumina implants, often ascribed to its fracture susceptibility due to its brittleness, low tensile strength, and long-term aging [18]. On the other hand, yttria-stabilized tetragonal zirconia polycrystal (Y-TZP) is being used by a number of manufacturers as the main material for ceramic implant fabrication. Zirconia's exceptional mechanical properties, namely high flexural strength, favorable fracture toughness and suitable Young's modulus, as well as its white color, low susceptibility to plaque formation, and excellent biocompatibility encouraged the use of this material for the fabrication of dental implants and related components [19–21]. Today, zirconia implants are marketed by a significant number of manufacturers. Interestingly, the majority of zirconia implant manufacturers are located in the countries where concerns about titanium safety are being discussed. Similar to titanium implants, available zirconia implant systems differ in many aspects, such as material, design, indications, and restorative options. Hence, clinicians are often overwhelmed when selecting zirconia implants for clinical application. The decision tree becomes even more complex when selecting the restorative material onto zirconia implants. An overview of available zirconia implants, as well as implant-restoration complex would enhance the knowledge of clinicians and provide them with useful information regarding their applicability. Therefore, the aim of this paper was to provide a comprehensive overview about zirconia implants and the implant-restoration complex. To ease understanding for the reader, the paper is focusing on the basic background of zirconia implants and the implant-restoration complex in terms of preclinical outcomes, namely material properties, implant design, osseointegration capacity, soft tissue integration and restorative options.

2. Material and methods

An electronic search of the literature prior to July 2017 was performed to identify all articles related to preclinical research on zirconia implants. The search was conducted using MEDLINE (National Library of Medicine) and PubMed without restrictions concerning the date of publication. The search terminology included: zirconia implant, osseointegration, bone-to-implant contact, soft tissue, histology, histomorphometry, surface modification, surface roughness, surface characteristics, and restoration; the various keywords were connected with AND; OR. The bibliographies of all full-text articles and related reviews selected from the electronic search were also hand-searched. The literature search was limited to English-language articles. References appraised in related systematic reviews were also considered. In addition; hand-searching was conducted in the following journals; *Clinical implant dentistry and related research*; *Clinical Oral Implants Research*; *European Journal of Implantology*; *Implant Dentistry*; *International Journal of Oral and Maxillofacial Implants*; *International Journal of Oral and Maxillofacial surgery*; *International Journal of Periodontics & Restorative Dentistry*; *International Journal of Prosthodontics*; *Journal of Clinical Periodontology*; *Journal of Dental Research*; *Journal of Oral Rehabilitation*; *Journal of Periodontology*; *Journal of Prosthetic Dentistry*; *Journal of Prosthodontics*; *Journal of Oral Surgery*; *Oral Medicine*; *Oral Pathology and Quintessence International*; *Dental Master*; *Key Engineering Materials*; *Biomaterials*; *Dental materials*; *Jouranal of Dental Materials and Journal of Dental Research*.

The research was followed by a manual search and references were used to identify relevant articles. Initially, two reviewers (HN, MH) further screened titles and abstracts of all identified papers to eliminate irrelevant articles. Full-text analysis of selected studies was performed against the inclusion criteria. Disagreements regarding data extraction were resolved by discussion.

2.1. Inclusion criteria

- Animal studies reporting the bone-implant contact, strength of osseointegration, and/or soft tissue response to zirconia implants.
- Laboratory studies reporting the mechanical properties of zirconia implants and the implant-restoration complex.

2.2. Exclusion criteria

- Cell culture studies.
- *Ex vivo* studies.
- Clinical studies, case reports, and case studies.

Due to the heterogeneity of the data in preclinical tests and different variables/parameters identified via the initial search, the first part of this review did not formulate a PICO question. Rather, a conventional approach for systematic reviews was followed.

3. Results

A total of 654 studies were identified in the literature, of which 83 were selected for full-text screening. 26 studies were excluded and a total of 57 articles were finally selected (Fig. 1). The identified preclinical studies focused on several aspects related to zirconia implants, namely biocompatibility of the material zirconia, mechanical properties, implant design, osseointegration capacity, soft tissue response, and restorative options. To simplify understanding, each of the above-mentioned aspects will be presented separately.

3.1. Classification of zirconia-based implant materials

Today, Y-TZP is the most commonly used material for zirconia implants [18]. In addition, alumina-toughened zirconia (ATZ) and zirconia-toughened alumina (ZTA) were reported as possible material combinations for zirconia-based implants [22]. The available products and their mechanical properties are listed in Tables 1 and 2.

3.2. Zirconia-based implant materials and low thermal degradation (LTD)

Despite the stability and resistance of Y-TZP zirconia, a major drawback remains, namely low thermal degradation (LTD) or zirconia aging. LTD is an irreversible transformation from the tetragonal to the monoclinic phase (t–m transformation) of Y-TZP zirconia in the presence of water or water vapor [19,23]. LTD leads to grain transformation, increasing the number of microporosities, microcracks, surface uplift, grain pull out, and delamination [24]. The transformation is induced by stress starting from the surface and proceeding inward. This transformation is associated with surface roughening and micro-cracking, which subsequently facilitate water penetration into the bulk material directly under the surface [24,25].

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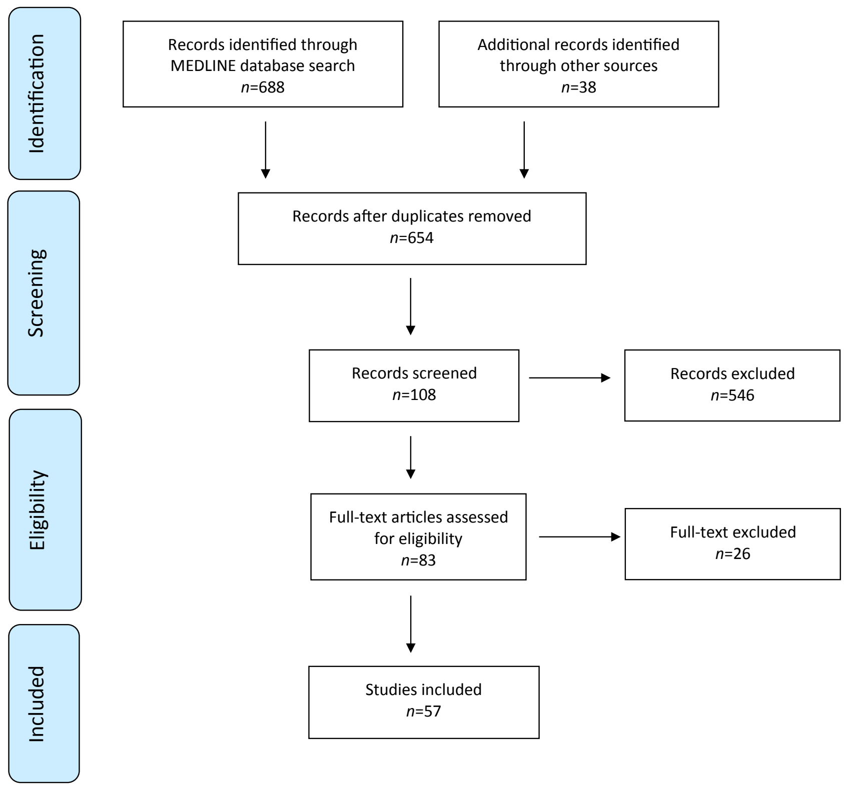

Fig. 1. Search strategy used for the review to identify studies.

While the clinical impact of LTD is unknown, a limited number of *in vitro* studies have evaluated it. In an *in vitro* study, the depth of grain transformation was limited between 1–4 μm after 30–60 years of accelerated aging; the effect of aging was considered minimal for zirconia implants [24]. However, the authors did not apply a load onto the samples to simulate masticatory forces, which would definitively accelerate the LTD process and likely yield a different outcome.

Several factors have been suggested to play a role in LTD resistance. These include but are not limited to: surface roughness and porosity, the amount and type of stabilizers, and grain size [23,26]. For example, porous surfaces showed higher susceptibility to accelerated aging than polished dense surfaces [27,28]. Also, grain size and stabilizer are strongly correlated and not easy to discuss separately: while a larger grain size leads to higher local stress, increasing stabilizer content induces a reduction in grain size [29,30]. Regarding stabilizer, zirconia materials commonly used for implants contain 3 mol% of yttrium to increase resistance to LTD and improve mechanical properties [31–33]. Moreover, while this results in a large amount (50 %) of cubic phase, leading to the high resistance to LTD, the fracture strength is decreased [34,35]. Apparently, the effect of LTD on the long-term stability of peri-implant tissues around zirconia implants remains unexplored.

3.3. Zirconia implant design

Several implant manufacturers, mainly from Europe, offer zirconia implants in their product portfolio (Table 1). As titanium implant, there are two types of zirconia implant designs available: one- and two-piece implant designs. Currently, the most frequently implemented implant design by manufacturers is the one-piece implant. This is mainly due to the favorable mechanical properties of one-piece implants, as well as technical difficulties in the fabrication of two-piece zirconia implants. The resistance of zirconia implants has been shown to be sufficient for application in the posterior region (Table 3). In *in vitro* studies, one-piece zirconia implants showed a fracture strength over 1000 N after preparation and thermomechanical fatigue loading [36–38]. On the other hand, two-piece zirconia implants showed a fracture strength between 187–398 N after thermomechanical fatigue loading. Average clinical forces for implants are 140–200 N in the anterior region and 250–450 N in the posterior region [39,40]. However, one-piece implants also have several limitations. Implants are not always placed in the ideal position to meet the prosthetic requirement; therefore, angulation should be corrected [36]. Moreover, one-piece implants might be immediately subjected to forces from the tongue and mastication after positioning [41]. Thus, there is a certain level of demand for two-piece implants. Currently, only few implant manufacturers offer two-piece zirconia implants. However, there is a lack of studies and clinical evidence regarding two-piece zirconia implants. *In vitro* studies established that most two-piece zirconia implants demonstrated higher fracture rates and lower resistance-to-fracture than two-piece titanium implants and one-piece zirconia implants [42,43]. Similar to two-piece titanium implants, the implant-abutment connection with zirconia implants can be either cement- or screw-retained. Studies using cemented abutments on zirconia implants indicated no fracture during a period of accelerated aging and showed a similar fracture resistance relative to titanium implants [43,44]. Nevertheless, a certain degree of failure was observed in the screw-retained group, with the majority of failures located around the screw [43].

3.4. Implant surface modification

Unlike titanium implants, modifying the surface of zirconia implants is considered challenging. Most surfaces of commercially-available zirconia implants are modified to include micro-roughness

Table 1. Commercially available zirconia implant systems.

Company	Product name	Form	Type	Material	Surface modification	Implant abutment connection
Argon Medical Productions	Konus K3Pro ZirKon Implantsystem	Conical	One-piece, two-piece	ZrO_2	OsteoActive Etching	Clamp fit
Bredent medical	Whitesky	Cylinder, conical	One-piece	HIP zirconia	Blasting	NA
CeraRoot S.L	CeraRoot	Cylinder	One-piece	Y-TZP	Acid etching (ICE surface)	NA
Dentalpoint AG	ZERAMEX (P)lus	Cylinder	Two-piece	ATZ	Blasting (alumina 250–500 μm, 3.5 bar) Etching	Screw (carbon fiber reinforced plastic)
	ZERAMEX (T)apered	Cylinder, conical	Two-piece	TZP	Blasting Etching	Cementation
Fairimplant	FairWhite™	Cylinder	One-piece	ATZ	ZircaPore (microporous)	NA
General Implants	Easy Kon	Conical	Two-piece	ZrO2	Coating (ultraviolet radiation type c) Blasting	Screw (titanium)
Moje Keramik-Implantate GmbH&Co.KG	ICX-White	Parallel and root-form	One-piece	Y-TZP	Micro-roughness	NA
Metoxit	Bio-Z Ziraldent	Parallel and root-form	One-piece	Ziraldent	ZircaPore (microporous)	NA
Natural Dental Implant AG	REPLICATE™System	Root-form	One-piece	Y-TZP	Blasting Enossal etching Machining	NA
SDS Swiss Dental Solutions AG	SDS 1.0 DT (Dynamic Thread)	Parabol	One-piece	ATZ	ZircaPore (microporous)	NA
	SDS 1.0 RD (Root Design)	Root-form	One-piece	ATZ	ZircaPore (microporous)	NA
	SDS 1.2 Monkey	Conical, parabol	One-piece, two-piece	ATZ	Blasting with ZrO_2	Screw (titanium, gold, PEKK) Cementation
	SDS 2.2	Conical, parabol	Two-piece	ATZ	Blasting with ZrO_2	Screw (titanium, gold, PEKK) Cementation
Straumann	Straumann PURE Ceramic Implantat	Cylinder	One-piece	Y-TZP	Blasting Etching	NA
VITA Zahnfabrik	Ceramic implant	Cylinder and conical	One-piece	Zirkonoxid tooth color	Polished neck	NA
ZV3-ZirconVison GmbH	ZV3 (S)andard, one-piece and two-piece	Cylinder, conical	One-piece, two-piece	zirconiaoxid TZP	Blasting before sintering	Cementation
	ZV3 (I)ndividual, one-piece and two-piece	Cylinder, conical	One-piece, two-piece	zirconiaoxid TZP	Blasting before sintering	Cementation
Z-systems AG	Z5m (one-piece)	Cylinder, parallel	One-piece	Zirkolith, HIP	Blasting Laser	NA
	Z5c (two-piece)	Cylinder, parallel	Two-piece	Zirkolith, HIP	Blasting Laser	Cementation
	Z5m(t) (one-piece)	Conical, rootform	One-piece	Zirkolith, HIP	Blasting Laser	NA
Camlog system	Ceralog	Cylinder	One-piece	Y-TZP	CIM (Ceramic Injection Molding)	NA
	Ceralog	Cylinder	Two-piece	Y-TZP	CIM (Ceramic Injection Molding)	Titanium or gold

Table 2. Mechanical properties of available material for zirconia implant.

Material	Composition	Flexural strength (MPa)	Fracture toughness (Mpa/m)	Elastic modulus (Gpa)	Hardness (VHN)
Y-TZP (yttrium-stabilized tetragonal zirconia polycrystals)	98 % tetragonal grains (0.2–0.5 %) 3 mol % yttria Y_2O_3	1000–1300	8.0–10	210	1200
ZTA (glass-Infiltrated zirconia-toughened alumina)	Matrix of alumina Al_2O_3 In-Ceram alumina 33 vol% of 12 mol% ceria-stabilized zirconia (12Ce-TZP)	500	4–4.5	280	1120
ATZ (alumina toughened Zirconia)	20 wt% alumina 80 wt% zirconia containing 3 mol%yttria	450–700	4.0–5.0	370–420	1700
Ce-TZP/Al_2O_3 (ceria paratially stabilized zirconia/ alumina nanocomposite)	Ce-TZP 10 mol% with 30 vol% Al2O3	1500	15–18	245	1160

features. These can be obtained by sandblasting and/or acid-etching (Table 1). Here, it is noteworthy to mention that conventional methods employed for modification titanium implant surfaces, such as acid-etching, are not effective on zirconia implant surfaces [45]. It has been shown that air-borne particle abrasion increased the surface roughness of zirconia dental implants [18,45]. However, this modification may negatively affect zirconia implant surface properties. In other words, it may induce t–m transformation and reduce resistance to LTD, subsequently weakening the mechanical properties of the zirconia implants [23,36]. In addition to subtractive techniques, such as acid-etching or sandblasting, additive techniques to modify zirconia implant surfaces have been suggested, e.g. an implant surface coating modification with slurry containing zirconia powder and an organic pore-former. While sintering the coating, the

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Table 3. Mechanical properties without crown.

	Type of device	Type of test	Group	Value					
Andreiotelli et al. [36]	Ti implant Zr implant	Chewing simulation + fracture sturength	Zr implant with preparation Zr implant without preparation	725–850 N 539–609 N					
Kohal et al. [38]	Ti implant Zr implant	Chewing simulation + fracture strength	ATZ without preparation ATZ with preparation TZP with preparation	0 cycle	1734 N 1220 N 578 N	1.2 million cycles	1489 N 1064 N 607 N	5 million cycles	1358 N 1098 N 516 N
Kohal et al. [127]	Zr implant	Chewing simulation + fracture strength	White sky with prep White sky without prep	0 cycle	1928 N 1221 N	1.2 million cycles	2044 N 967 N	5 million cycles	1364 N 884 N
Silva et al. [37]	Zr implant	Chewing simulation + fracture strength	Y-TZP with prep Y-TZP without prep	1111 N 1023 N					
Spies et al. [128]	Zr implant	Chewing simulation + fracture strength	One-piece Y-TZP with cyclic loading One-piece Y-TZP without cyclic loading Screw-retained two-piece Y-TZP with cyclic loading Screw-retained two-piece Y-TZP without cyclic loading Cement-retained two-piece Y-TZP with cyclic loading Cement-retained two-piece Y-TZP without cyclic loading	362 N 399 N 398 N 346 N 380 N 252 N					

pore-former is burned away, leaving behind a porous surface [46]. Moreover, there are other modifications, such as laser and bioactive coating [47–49]. These modifications increase surface roughness, wettability, and cell adhesion, spreading, and migration [50]. However, these modifications are still under investigation and not yet commercialized.

3.5. Osseointegration capacity of zirconia implants

Osseointegration is one of the most important factors determining implant treatment success [51]. It is well known that surface topography, chemistry, and micro-roughness are important factors not only for titanium but also for zirconia implants, as they influence the rate and quality of new tissue formation [52,53]. There are two methods to for investigating osseointegration: biomechanical strength and histomorphometry. In the existing investigations, biomechanical strength was investigated mostly by the removal torque (RT) and push-in tests. In contrast, histological evaluation is assessed by bone-implant contact (BIC), bone volume, and bone density. 42 of the studies identified for final selection evaluated these parameters (Table 4). BIC values ranged from 25–88 % for titanium and 24–85 % for zirconia, respectively. RT values ranged from 7–74 N for titanium and 9–78 N for zirconia, respectively. No significant differences were reported in most animal studies with respect to BIC and RT values between zirconia and titanium implants, independent from surface modification (Table 4).

Regardless of material choice, the interaction between cells and the implant surface plays an important role in enhancing osseointegration [54,55]. The previous study established the positive impact of the microtopography of rough surfaces on osteoblast-associated gene expression and on mineralization [56]. Additionally, with respect to the influence of various degrees of surface roughness on osteoblast activity, zirconia surfaces were reported to have a more positive effect on adhesion and proliferation than titanium surfaces [57,58].

3.6. Soft tissue response to zirconia implants

Soft tissue also plays an important role in achieving long-term implant success. However, only five studies investigated soft tissue parameters (Table 5). Soft tissues around the dental implant neck and on the orientation of peri-implant collagen fibers influence mucosal barrier. For instance, mucosal barriers around the implant defend against bacteria invading areas between the oral cavity and bone [59]. Similar to titanium implants, the mucosal barrier around zirconia implant are divided into epithelial mucosa and connective tissue, which determine the biological width [60]. The dimensions of the mucosal and connective tissue attachments seem to be similar between titanium and zirconia implants [61–66]. One *in vivo* study observed the soft tissue around zirconia and titanium implants with machined necks. It was investigated that collagen fibers in the connective tissue are similarly oriented in zirconia and titanium implants [60]. Peri-implant epithelia were investigated around one-piece zirconia and titanium implants in dogs. It was established that the epithelium length was not significantly different, irrespective of the material type and healing modality [62]. This finding is in agreement with previous studies [64,65]. In addition to the studies about zirconia implant, the length of epithelium around healing titanium/zirconia abutments was 1.83 mm (titanium) and 1.75 mm (zirconia) at 5 months. Still, a smaller extent of leukocytes were observed in the barrier epithelium around zirconia abutments compared with titanium abutments in this study [67]. Regarding inflammatory response, higher microvessel density, the expression of vascular endothelial growth factor and nitric oxide synthase were observed in the mucosa around titanium healing caps compared with zirconia healing caps [68]. In addition to this study, correlation and level of interleukin-1 receptor antagonist, interleukin-8, granulocyte colony-stimulating factor, macrophage inflammatory protein-1beta, tumor necrosis factor-alpha around zirconia implant and titanium implant were investigated in several studies. The results established that level of interleukin-1 receptor antagonist, interleukin-8, granulocyte colony-stimulating factor, macrophage inflammatory protein-1beta, tumor necrosis factor-alpha were similar with zirconia implants and titanium implants [69–72].

More, a recent study observed a long biological width and high density of collagen fiber around one-piece zirconia implants compared to titanium [66]. Furthermore, an experimental study in a canine model showed that the soft tissue dimensions around one-piece zirconia implants (loaded and unloaded) did not differ significantly among implant group, as had been observed in other

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Table 4. Evaluation of osseointegration around zirconia implant.

Author	Animal model	Type of device	Type of test	Group	Value			
Linares et al. [66]	Minipig	Zirconia implant(one-piece)	BIC	Ti Zr	84.0 % 86.2 %			
Mihatovic et al. [92].	Dog	Experimental zirconia implant Three difference roughness(Z1 < Z2 < Z3)	BIC	Ti Z1 Z2 Z3	14 days	62.2 % 42.4 % 44.5 % 61.3 %	10 weeks	58.6 % 49.7 % 39.0 % 69.6 %
Kohal et al. [86]	Rat	Miniature implants	BIC	ATZ (pore-building polymers sintered) TiUnite (electrochemically anodized titanium)	14 days	24 % 58 %	28 days	41 % 75 %
			Push-in	ATZ TiUnite	14 days	10 N 20 N	28 days	25 N 39 N
Thoma et al. [65]	Dog	Two/one-piece zirconia implants (ZD, VC) Two-piece zirconia implant (BPI) One-piece titanium implant (STM)	BIC	STM (one piece Ti) BPI (two piece Zr) VC (one piece Zr) ZD (one piece Zr)	88 % 84 % 88 % 79 %			
Shon et al. [93]	Rabbit	External hex-type zirconia implants	BIC	Zirconia (no treatment) zirconia (MDP-treated)	2 weeks	29.67 % 43.53 %	4 weeks	55.76 % 61.42 %
			RT	Zirconia (no treatment) zirconia (MDP-treated)	2 weeks	23.10 N/cm 29.87 N/cm	4 weeks	55.07 N/cm 54.51 N/cm
Montero et al. [94]	Dog	Zirconia implants Titanium implants	BIC	Ti Zr	5 month		57 % 56.5 %	
Kohal et al. [95]	Human	Implants (ZiUnite, NobelBiocare, Gothenburg, Sweden)	BIC	ZiUnite	76.5 %			
			Bone density (the bone area within the implant threads)	ZiUnite	84.8 %			
Kim et al. [96]	Rabbit	External hex threaded type implants with a similar macro-design Machined-surface zirconia implants	BIC	Group 1 (milled Zr) Group 2 (PIM Zr)	4 weeks		32 % 58 %	
			RT	Group 1 (milled Zr) Group 2 (PIM Zr)	4 weeks		19 N/cm 58 N/cm	
			Topographic analyses of the implant surface roughness	Group 1 (milled Zr) Group 2 (PIM Zr)	4 weeks		0.58 µm 1.67 µm	
Calvo-Guirad et al. [97]	Dog	Titanium implants; Zirconium dioxide implants	BIC	Ti Zr	1 month	51 % 45 %	3 months	62 % 48 %
Calvo-Guirados et al. [98]	Rabbit	Titanium implants; zirconium dioxide implants	BIC	Ti implant microgroovedZr implant Ti implant with melatonin Zr implant with melatonin	1 week	25 % 23 % 30 % 29 %	4 weeks	38 % 38 % 39 % 48 %
Shon et al. [99]	Rabbit	Threaded external hex implants	BIC	Group 1 (Zr) Group 2 (rough Zr) Group 3 (Plasma Zr) Group 4 (Plasma rough Zr)	58 % 57 % 71 % 72 %			
			RT	Group 1 (Zr) Group 2 (rough Zr) Group 3 (Plasma Zr) Group 4 (Plasma rough Zr)	40 N/cm 59 N/cm 47 N/cm 61 N/cm			
			Topographic analyses of the	Group 1 (Zr) Group 2 (rough Zr)	0.54 µm 1.98 µm			

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Table 4 (*Continued*)

Author	Animal model	Type of device	Type of test	Group	Value			
			implant surface roughness	Group 3 (Plasma Zr) Group 4 (Plasma rough Zr)	0.54 μm 1.99 μm			
			BV (bone volume)/ TV (tissue volume)	Group 1 (Zr) Group 2 (rough Zr) Group 3 (Plasma Zr) Group 4 (Plasma rough Zr)	42.75 % 43.51 % 51.24 % 58.28 %			
Saulacic et al. [100]	Mini pigs	Zirconia implants	BIC	Sandblasted Sandblasted and alkali etched Sandblasted and acid etched	1 week	0 % 0 % 0 %	2 weeks	6 % 2 % 20 %
Gredes et al. [101]	Pigs	Zirconia implants (sandblasted) Titanium implants (sandblasted + acid-etched)	BIC	Zirconia (blasted) Zirconia (etched) Zirconia (blasted/ etched) Zirconia Titanium	90 days		49.6 % 43.7 % 42.1 % 56 % 35 %	
Delgado-Ruiz et al. [87]	Dog	Control:Ti Test A: Zr (sandblasted) Test B: Zr (microgrooves, sandblasted)	CBL (cristal bone loss)	Tianium Zirconia (sandblasted) Zirconia (microgrooves, sandblasted)	Immediate loaded	1.2 mm 1.25 mm 1.19 mm	Unloaded	1.19 mm 1.24 mm 1.18 mm
			Bone density	Tianium Zirconia (sandblasted) Zirconia (microgrooves, sandblasted)	Immediate loaded	63.35 % 59.52 % 73.46 %	Unloaded	59.87 % 56.32 % 69.47 %
			BIC	Tianium Zrconia (sandblasted) Zirconia (microgrooves, sandblasted)	Immediate loaded	57 % 48 % 78 %	Unloaded	43 % 36 % 48 %
Calvo-Guirado et al. [102]	Dog	Zirconia implants	BIC	Immediate loading Non-immediate loading	30 days	39 % 32 %	90 days	65 % 58 %
Salem et al. [103]	Rabbit	Threaded custom-made zirconia implants	BIC	Fusion sputtered zirconia Ti Control Zr	4 weeks	70 % 63 % 57 %	8 weeks	88 % 83 % 70 %
			Bone density analysis	Fusion sputtered zirconia Ti Control Zr	4 weeks	46 % (BD-bt), 50 % (BD-ot) 44 % (BD-bt), 47 % (BD-ot) 38 % (BD-bt), 43 % (BD-ot)	8 weeks	54 % (BD-bt), 61 % (BD-ot) 53 % (BD-bt), 59 % (BD-ot) 47 % (BD-bt), 53 % (BD-ot)
			RT	Fusion sputtered zirconia Ti Control Zr	4 weeks	46 N/cm 44 N/cm 36 N/cm	8 weeks	78 N/cm 74 N/cm 63 N/cm
Park et al. [104]	Rabbit	External hex threaded type	Surface analysis	Group 1 (Machined Ti) Group 2 (Untreated Zr) Group 3 (Rough Zr)	0.27 μm 0.53 μm 2.0 μm			
			BIC	Group 1 (Machined Ti) Group 2 (Untreated Zr) Group 3 (Rough Zr)	43 % 62 % 65 %			

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Table 4 (*Continued*)

Author	Animal model	Type of device	Type of test	Group	Value			
			RT	Group 1 (Machined Ti) Group 2 (Untreated Zr) Group 3 (Rough Zr)	11 N 44 N 64 N			
Lee et al. [105]	Dog	Experimental Ti implants (grade 4) and zirconia (alumina-toughened yttria and niobia co-doped tetragonal zirconia polycrystalline	Topographic analyses of the implants' surface roughness	Ti implant ATZ implant	1.64 μm 1.76 μm			
Kohal et al. [106]	Rat	Commercially pure titanium and yttria-stabilized tetragonal zirconia polycrystal (Y-TZP) disks	Surface analysis	TiUnite Machined Ti Sandblasted and Acid-etched Zr Machined Zr	1.31 μm 0.58 μm 0.95 μm 0.19 μm			
			BIC	TiUnite Machined Ti Sandblasted and Acid-etched Zr Machined Zr	14 days	36 % 23 % 18 % 31 %	28 days	56 % 39 % 34 % 47 %
			Push-in	TiUnite Machined Ti Sandblasted and Acid-etched Zr Machined Zr	14 days	27 N 19 N 26 N 19 N	28 days	49 N 7 N 31 N 9 N
Chung et al. [107]	Rabbit	External hex-threaded type implants	BIC	Group 1 (smooth Zr) Group2 (rough Zr) Group3 (coated smooth Zr) Group 4 (coated rough Zr)	60 % 62 % 73 % 70 %			
			Surface analysis	Group 1 (smooth Zr) Group 2 (rough Zr) Group 3 (coated smooth Zr) Group 4 (coated rough Zr)	0.53 μm 1.98 μm 1.05 μm 2.56 μm			
			RT	Group 1 (smooth Zr) Group 2 (rough Zr) Group 3 (coated smooth Zr) Group 4 (coated rough Zr)	45.6 N/cm 64.99 N/cm 54.33 N/cm 63.21 N/cm			
Aboushelib et al. [108]	Rabbit	Zirconia implants Titanium implants	BIC	SIE zirconia As-sintered zirconia Titanium	4 weeks	65.38 % 53.30 % 56.93 %	8 weeks	75.01 % 62.14 % 68.31 %
			BD-bt	SIE zirconia As-sintered zirconia Titanium	4 weeks	47 % 38 % 40.8 %	8 weeks	54 % 41.8 % 41 %
			BD-ot	SIE zirconia As-sintered zirconia Titanium	4 weeks	51 % 42 % 44 %	8 weeks	52 % 48 % 49 %
Möller et al. [109]	Pig	Zirconia implants Titanium implants	BIC	Ti Zr	4 weeks	64 % 59 %	12 weeks	73 % 67 %
Hoffmann et al. [110]	Rabbit	Cylindrical screw-type implants of Zr and Ti	BIC	Laser Ref-T Ref-Z Sintered	28 days	40 % 34 % 40 % 33 %	56 days	44 % 35 % 41 % 34 %
Gahlert et al. [111]	Mini pig	Cylindrical low-pressure injection molded zirconia (ZrO_2) implants Titanium implants with identical shape	Surface analysis	Ti-SLA (control) Zirconia (test material)	1.26 μm 0.63 μm			
			Peri-implant bone density values	Ti-SLA (control) Zirconia (test material)	4 weeks	61.1 % 60.4 %	8 weeks	63.6 % 65.4 %

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Table 4 (*Continued*)

Author	Animal model	Type of device	Type of test	Group	Value			
			BIC	Ti-SLA (control) Zirconia (test material)	4 weeks	64.7 % 70 %	8 weeks	79.2 % 67.1 %
Shin et al. [112]	Rabbit	Screw-shaped threaded implants of Ti and Zr	BIC	Ti Zr	6 weeks		35.8 % 26 %	
			RT	Ti Zr	6 weeks		10.9 N/cm 18.2 N/cm	
Stadlinger et al. [113]	Mini pig	Zirconia implants Titanium implants	BIC	Titanium Zirconia (submerged) Zirconia (non-submerged)	53.08 % 52.63 % 47.95 %			
Schliephake et al. [114]	Mini pig	Implants	BIC	Sandblasted ZrO_2 Sandblasted and etched ZrO_2 Sandblasted and etched Ti	4 weeks 58 % 67 % 69 %		13 weeks 55 % 58 % 79 %	
Maccauro et al. [115]	Rabbit	Cylindric implant ZTA	Bone-ceramic contact	Alumina Zirconia ZTA	1 month	38.3 % 41.7 % 41.9 %	12 months	69.3 % 67.3 % 69.5 %
Koch et al. [116]	Dog	One-piece zirconia Titanium implants	BIC	Uncoated zirconia Coated zirconia Synthetic material (PEEK) Titanium implants	10 weeks		59.2 % 58.3 % 26.8 % 41.2 %	
Rocchietta et al. [117]	Rabbit	Zirconia implant modified in 3 different surfaces	BIC	ZrO_2 ZiUnite ZrO_2 Promimic ZrO_2 CoAT sputtered TiUnite	3 weeks		27.5 % 42.5 % 36.1 % 58.3 %	
			RT	ZrO_2 ZiUnite ZrO_2 Promimic ZrO_2 CoAT sputtered	3 weeks		28.9 Ncm 35 Ncm 36.8 Ncm	
Lee et al. [46]	Rabbit	Zirconia implant	BIC	ZrO_2(ZiUnite): ZrO_2 nanomodified surface A ZrO_2 nanomodified surface B TiUnite	3 weeks	70.5 % 64.6 % 62.2 % 77.6 %	6 weeks	69.7 % 68.6 % 64.5 % 67.1 %
Kohal et al. [118]	Rat	Zirconia implant	BIC	ZrO_2 modified Ti Unite	14 days	45.3 % 36.4 %	28 days	59.4 % 55.2 %
Gahlert et al. [119]	Pig	Zirconia implant	BIC	ZrO_2 SLA Ti	4 weeks	51.1 % 55.1 %	8 weeks	53.7 % 70.4 %
Langhoff et al. [120]	Sheep	Titanium implants Zirconium implants	BIC	Ti (sandblast + acid etched) Ti (calcium phosphate) Ti (Plasma anodized) Ti (collagen I + chondroitin sulfate) Ti (bisphosphonate) zirconia	2 weeks	57 % 59 % 62 % 60 % 59 % 77 %	4 weeks	73 % 57 % 77 % 72 % 74 % 81 %
Hoffmann et al. [121]	Rabbit	Zirconia implant	BIC	ZrO_2 (Y-TZP)	2 weeks	55.40 and 54.80 %	4 weeks	62.20 and 80.70 %
Depprich et al. [122]	Mini pig	Zirconia implant	BIC	ZrO_2 (Y-TZP) Ti	1 week	35 % 48 %	4 weeks	45 % 99 %
Sennerby et al. [46]	Rabbit	ZrO_2 implants	BIC	ZrO_2 control group ZrO_2-A	6 weeks (Femur)	46 % 60 %	6 weeks (Tibia)	19 % 31 %

Table 4 (*Continued*)

Author	Animal model	Type of device	Type of test	Group	Value			
				ZrO_2-B Ti-oxidized		70 % 68 %		22 % 24 %
Kohal et al. [61]	Monkey	Zirconia implant (sandblasted) Titanium implant (sandblasted + acid-etched)	BIC	Zr Ti	9 months		67.4 % 72.9 %	
Scarano et al. [123]	Rabbit	ZrO_2 implants	BIC	ZrO_2	4 weeks		68 %	
Schreiner et al. [124]	Mini pig	Alumina implants Zirconia implants	BIC Cortical bone Cancelous bone	Smooth, macro-structured, corundum-blasted, porous	Smooth and macro structured, no bone ingrowth 20.5 % and 41.7 % (cancellous bone) between 26.0 % and 52.8 % (cortical bone).			
Akagawa et al. [125]	Monkey	ZrO_2 implants	BIC	Single freestanding Connected Implant-tooth-supported	12 months loaded	54–71 % 58–77 % 70–75 %	24 months loaded	66–81 % 66–77 (freestanding) 66–82 %
Akagawa et al. [126]	Dog	ZrO_2 implants	BIC	Loaded Non-loaded	69.8 % 81.9 %			

Table 5. Soft tissue response to zirconia implants.

Author	Animal model	Type of device	Type of test	Group	Value
Linares et al. [66]	Minipig	One-piece zirconia implant	F-BIC (implant shoulder to most coronal implant contact)	Ti Zr	3.97 mm 3.95 mm
Thoma et al. [65]	Dog	Two/one-piece zirconia implants	Peri-implant mucosa	VC (onepiece Zr) ZD (onepiece Zr)	2.64 mm 3.03 mm
Igarashi et al. [64]	Dog	One-piece dental implant (Ti, Y-TZP, Ce-TZP/Al_2O_3)	Epithelial tissue length	Ti Y-TZP Ce-TZP/Al_2O_3	1.88 mm 2.19 mm 2.29 mm
			Connective tissue contact	Ti Y-TZP Ce-TZP/Al_2O_3	1.23 mm 1.09 mm 0.49 mm
			Biological width	Ti Y-TZP Ce-TZP/Al_2O_3	3.11 mm 3.28 mm 2.78 mm
Delgado-Ruiz et al. [87]	Dog	Tapered screw implants	Topographic analyses of the implants' surface roughness	Ti Zr (sandblasted) Zr (microgrooves, sandblasted)	3.05 μm 2.71 μm 8.9 μm
		Test A: Zr (sandblasted) Test B: Zr (microgrooves, sandblasted)	Soft tissue	Test A Immediately loaded Unloaded Test B Immediately loaded Unloaded	2.78 mm 2.80 mm 2.82 mm 2.83 mm
Koch et al. [62]	Dog	Dental implant	Barrier epithelium value	Uncoated zirconia Nonsubmerged Submerged Coated zirconia Nonsubmerged Submerged Titanium Nonsubmerged Submerged Synthetic Nonsubmerged Submerged	2.01 mm 1.63 mm 1.65 mm 1.73 mm 1.97 mm 1.28 mm 1.49 mm 1.48 mm
Kohal et al. [61]	Monkey	Zirconia implant (sandblasted) Titanium implant (sandblasted + acid-etched)	Soft tissue (first bone-to-implant contact to the apical end of the junctional epithelium)	Zr Ti	4.5 mm 5.2 mm

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studies [63,64]. Investigation of the soft tissue dimensions around one- and two-piece zirconia implants in canine mandibles showed very similar characteristics (the extent of the peri-implant epithelium and the peri-implant mucosa) compared to titanium implants [65]. In this study, it was also reported that one- and two-piece zirconia implants demonstrated similar peri-implant soft tissue dimensions to titanium implants [65]. Apparently, no significant differences were observed between zirconia and titanium implants in most studies [61,62,64].

3.7. Restorative options on zirconia implants

Studies describing the restoration of zirconia implants are scarce. The current reviews identified only three experimental studies (Tables 5 and 6). In one study, various all-ceramic crowns were tested on one-piece zirconia implants. Empress (Ivoclar Vivadent AG, Schaan, Liechtenstein) and Procera (Nobel Biocare Services AG, Kloten, Switzerland) were used, and Procera demonstrated sufficient fracture strength in the anterior region, while Empress demonstrated significantly low fracture values to justify clinical use [73]. Moreover, there is an evaluation of two-piece zirconia implants and ceramic restorations. This investigation showed no significant difference between crown materials [74]. In these studies, Panavia 21 (KURARAY Co., Ltd., Tokyo, Japan) and Panavia F 2.0 (KURARAY Co., Ltd.) were used for ceramic restorations and conventional cements (as glass-ionomer) were used for porcelain fused metal (PFM) [42,73,74].

4. Discussion

While zirconia has been proposed, and introduced over 30 years ago as an alternative material to fabricate dental implants, the scientific evidence seems to be far behind that of titanium implants. Several factors, such as manufacturing difficulties and surface modification, ideal material-stabilizer combination, long-term surface stability, selection of restorative material, and clinical experience have all contributed to the limited implementation of zirconia implants. In this context, the stability and durability of zirconia implants is a most interesting topic. LTD influences the stability of zirconia and clearly reduces its fracture resistance. A decrease in fracture resistance was only observed when more than 50% of the zirconia surface was in m-phase [75]. It would be challenging to maintain mechanical properties and improve LTD resistance at the same time. Generally, while improving LTD resistance is considered worthwhile, mechanical properties and stability would be decreased [76]. However, several manufacturers are working on solutions by controlling stabilizer type, grain size, and phase composition. The most common stabilizer beside yttria, which is well investigated in studies, is ceria. Ce-TZP with 12–14% showed a very high toughness and resistance to LTD in comparison to Y-TZP [77,78]. However, the mechanical properties of Ce-TZP are lower than those of Y-TZP. To improve the mechanical properties of Ce-TZP, current studies are focusing on 12 mol% Ce-TZP/Al_2O_3 composites [79]. Ce-TZP/Al_2O_3 has higher fracture resistance and 3-fold higher toughness [80,81]. Moreover, Ce-TZP/Al_2O_3 showed high resistance to LTD and long-term stability in an *in vivo* study [82]. In this review, the differences between different zirconia implant materials used lead to variations in the results. Therefore, it is difficult to provide clear information about the effect on zirconia implant material on its performance in experimental settings.

Apparently, surface modification strongly affects long-term surface stability. It is well known that sandblasting and grinding induce t–m transformation on zirconia surface, which would accelerate LTD [83,84]. Accordingly, laser or coating are developed to prevent such damage to the zirconia implants. For instance, ultraviolet light treatment of roughened zirconia surfaces changed their physical and chemical properties and accelerated initial cell adhesion and spreading [85]. However, there is a lack of information regarding the potential disadvantages of these modifications. Thus, limited information is available for long-term stability and durability of treated zirconia materials. More knowledge regarding these surface modifications must be acquired before their clinical use.

Surface modification is performed in order to enhance osseointegration. Regardless of surface modification, zirconia implants showed comparable or higher levels of osseointegration than titanium implants [51,65,86]. On the other hand, little information is available on the soft tissue response. Most parameters depend on organization or the length of each part. Most studies concluded that zirconia implants showed similar or favorable soft tissue responses when compared to titanium implants [64,65,87].

Table 6. Mechanical properties with crown.

Author	Type of device	Type of cement	Type of crown	Type of test	Group	Value
Kohal et al. [74]	Ti implant Zr two-piece implant	Panavia 21	DCS/Triceram (DC-zircon coping veneered with Triceram) Empress PFM	Chewing simulator	ALLC without chewing simulator ALLC with chewing simulator PFM without chewing simulator PFM with chewing simulator	303 N 278 N 595 N 166 N
Kohal et al. [73]	Ti implant Zr implant	Panavia 21	Procera Empress PFM	Chewing simulator ± fracture strength	PFM without chewing simulator PFM with chewing simulator Empress without chewing simulator Empress with chewing simulator Procera without chewing simulator Procera with chewing simulator	531 N 668 N 512 N 410 N 575 N 555 N
Rosentritt et al. [42]	Onepiece Zr implant Twopiece Zr implant Threepiece Zr implant	Panavia F 2.0	Zr crown	Chewing simulator ± fracture strengh	Two-piece Zr implant with screw retain Two-piece Zr implant with cement retain Two-piece Ti implant with screw retain One-piece Zr implant One-piece Zr implant	269 N 297 N 377 N 372 N 524 N

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Regarding hard and soft tissue responses, there is a limitation of generalization due to the heterogeneity, i.e., differences among animal models used in the studies, loading duration, and location of implant insertion. Therefore, direct comparison of the results from investigations with different protocols should be avoided. Further work on soft and hard tissues should be performed with a unified protocol which will permit more thorough cross-study comparisons.

As to the implant design, one-piece implants are the main products today, due to their favorable mechanical properties, as well as fabrication difficulties of two-piece zirconia implants. However, there is a certain amount of demand for two-piece implants. Unfortunately, evidence is lacking for two-piece implants regarding their mechanical properties and the inter-abutment connections [43]. Well-designed studies will be necessary to indicate the ideal connection type for zirconia implants.

Independent of implant type (one- or two-piece), all investigations related to zirconia implants' mechanical strength are carried out in the anterior region. There is little knowledge regarding the use of zirconia implants in posterior regions. Moreover, the abutment screw is the weakest point in the implant and the area around the screw head receives the highest force [88]. Prior to abutment or implant body fracture, reduction of screw tension and screw loosening occurred, due to micro-movements, repeated bending, and torsion [89]. Furthermore, micro-movements were related to insufficient fit of the abutment [90]. However, precision of the milled zirconia abutment is lower than that of titanium abutments. In a previous study, the authors observed that higher accuracy of zirconia abutment fittings reduced the fracture frequency [91]. Thus, *in vitro* studies focusing on the posterior region, as well as connection type, will be necessary.

Subsequently, we consider the effect of material selection for restoration and cementation on zirconia implants. According to previous studies, all-ceramic restorations cemented with adhesive cement are compatible with zirconia implants [73,74]. However, these studies did not focus on the type of the cement and methods. The influence of the cementation on zirconia implants is not clear. As described for the soft tissue response, functional sealing around zirconia implants is lower than around natural teeth. This may result in difficulties eliminating the cement and lead to peri-implantitis. Clearly, there is a need for studies and well-defined protocols to investigate the best material for superstructures and cementation methods on zirconia implants. Here, *in vitro* investigations with larger samples sizes are necessary to substantiate the combination of rehabilitation. In addition to larger sample size, further studies should focus on comparing combinations between different superstructure materials (e.g. zirconia, lithium disilicate, hybrid ceramics, composites, etc.) and different cements onto zirconia implants. To draw clinically-relevant data, it is important to implement study designs that simulate clinical conditions. These can be best achieved by subjecting the test samples to thermomechanical fatigue that simulates clinical service. Subsequently, a clinical evaluation demonstrates whether favorable *in vitro* results can be confirmed clinically.

In review of the obtained results, it is important to highlight that the current research about zirconia implants is exclusively sponsored by manufacturers, with a clear focus on "what is needed" to launch/introduce the product. Here, and despite well performed investigations, a bias regarding a specific implant product cannot be excluded. Unbiased long-term randomized clinical trials are the ultimate tools to provide sufficient data about the outcome of zirconia implants and related superstructures.

5. Conclusion

Despite the fact that zirconia can be used as an alternative implant material, many questions remain unanswered regarding ideal material composition, long-term stability, implant design, the implant-abutment interface, implant-restorative complex, and soft tissue responses. Carefully designed preclinical studies are required to validate the outcome of various zirconia materials and implants before recommending them for clinical application.

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