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REVIEW ARTICLE

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Zirconia compared to titanium dental implants in preclinical studies—A systematic review and meta-analysis

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Abstract

Objectives: To evaluate whether zirconia implants demonstrate differences in hard and soft tissue integration compared to titanium implants in preclinical studies.

Material and Methods: In March 2017, electronic (MEDLINE, EMBASE) and hand search was performed to identify preclinical studies comparing zirconia and titanium implants. Primary outcomes were bone-to-implant contact (BIC) and removal torque out (RTQ), respectively, push-in (PI) measurements. Secondary outcomes included biologic width (BW) dimensions.

Results: A total of 37 studies were included for data extraction after screening of 91 from 1,231 selected titles. Thirty-seven experimental studies using six different species were identified. The follow-up periods ranged between 0.4 and 56 weeks. For titanium, mean values of 59.1% (95% CI: 53.3 – 64.8), 102.6 Ncm (95% CI: 81.5 – 123.6), and 25.1 N (95% CI: 20.2 – 30.0) for BIC, RTQ, and PI were estimated, respectively. The mean values for zirconia were 55.9% (95% CI: 51.6 – 60.1), 71.5 Ncm (95% CI: 51.1 – 91.9), and 22.0 N (95% CI: 13.2 – 30.7) for corresponding parameters. Confounding factors such as animal species, implant material, loading protocol, and study or loading duration significantly influenced the outcomes. Similar qualitative soft tissue integration was reported for zirconia and titanium implants. However, faster maturation processes of epithelial and connective tissues around zirconia implants were assumed. Quantitatively, similar BW dimensions were evaluated for titanium (3.5 mm; 95% CI: 2.9 – 4.2) and zirconia (3.2 mm; 95% CI: 2.7 – 3.7), whereas the loading protocol significantly influenced the outcomes.

Conclusions: Zirconia and titanium implants demonstrate a similar soft and hard tissue integration capacity. However, titanium tended to show a faster initial osseointegration process compared to zirconia. Importantly, not only material characteristics but predominantly animal species and study protocols can significantly influence the outcomes.

KEYWORDS
bone remodeling, dental implants, osseointegration, soft tissue, titanium, yttria-stabilized tetragonal zirconia, zirconium oxide

1 | INTRODUCTION

Replacing missing teeth in partially and fully edentulous patients with dental implants has become an evidence-based treatment option in dentistry and relies on the structural and functional stabilization of the implant in the surrounding bone tissue, called osseointegration (Branemark et al., 1969; Schroeder, Pohler & Sutter, 1976). In this context, it has been reported that the implant surface is among the most critical factors for the achievement of a successful osseous integration (Albrektsson, Branemark, Hansson & Lindstrom, 1981). Since the beginning of the 1990s, preclinical studies have started to investigate the influence of the surface topography of titanium implants on the osseointegration process in detail. It has been demonstrated that roughening of the implant surface up to a certain degree led to an accelerated and increased osseous integration (Buser et al., 1991, 1999). Since then, commercially pure titanium or specific titanium–zirconium metal alloy implants have been scientifically well-investigated (Roehling, Meng & Cochran, 2015). Clinically, survival rates of more than 96% for titanium implants with micro-rough surfaces were reported after 10 years of follow-up (Buser et al., 2012; Roccuzzo, Bonino, Dalmasso & Aglietta, 2014). Apart from that, also disadvantages with regard to the material properties of the metal titanilike its gray color or unwanted chemical–biological interactions of titanium with the surrounding soft and hard tissues have been reported (Kohal, Att, Bächle & Butz, 2008; Tschernitschek, Borchers & Geurtsen, 2005). However, the clinical relevance of these material-related findings is rather controversial. Due to its color, ceramic implants have already attracted interests of clinicians since end of the 1960s. At this time, aluminum oxide (alumina, Al_2O_3) was used as material for the fabrication of ceramic dental implants. Experimental studies showed that alumina implants could directly integrate into osseous host tissue (Zetterqvist, Anneroth & Nordenram, 1991; Zetterqvist, Anneroth, Nordenram & Wroblewski, 1995). However, based on poor biomechanical properties, alumina implants were prone to fracture when loaded extra-axially and therefore showed rather poor clinical performances (De Wijs, Van Dongen, De Lange & De Putter, 1994; Schlegel, Jacobs & Leitenstorfer, 1994). Consequently, alumina implants were taken from the market in the early 1990s. Since the beginning of the 2000s, ceramic implants are made from zirconium dioxide (zirconia, ZrO_2). Based on superior biomechanical properties compared to other ceramics, zirconia has the ability to withstand oral forces (Silva et al., 2009). Potential biological material-related advantages such as significantly reduced bacterial biofilm formation, less inflammatory cells in the peri-implant soft tissues, and significantly increased microcirculation in the peri-implant soft tissues were reported for zirconia compared to titanium or other metals (Degidi et al., 2006; Kajiwara et al., 2015; Roehling et al., 2017; Welander, Abrahamsson & Berglundh, 2008). Concerning a successful and reliable osseointegration process of zirconia, the microstructure of the implant surface is as important as for titanium (Gahlert et al., 2007; Sennerby, Dasmah, Larsson & Iverhed, 2005). Based on material characteristics, creating a micro-rough surface on zirconia implants without compromising the biomechanical stability is a technical challenge and many clinicians are still very skeptical regarding the osseointegrative capacity of zirconia implants. Nowadays, not only successful osseous integration but also soft tissue integration and pink esthetic outcomes have become important factors from a surgical point of view. Moreover, since gingival tissues around implants have a similar barrier function as dento-gingival tissues, the soft tissue integration—represented by epithelial and connective tissue—is as important as bone integration (Cochran, Hermann, Schenk, Higginbottom & Buser, 1997). In this context, constant vertical dimensions of healthy periodontal soft tissues—represented by the biologic width—are very important for gingival esthetics (Hermann, Buser, Schenk, Schoolfield & Cochran, 2001). However, only few scientific data dealing with soft tissue integration around zirconia dental implants are available to date.

Previously published systematic reviews and meta-analyses on experimental studies did not focus on the comparison between zirconia and titanium implants or included exclusively data on osseous integration (Hafezeqoran & Koodaryan, 2017; Manzano, Herrero & Montero, 2014; Pieralli, Kohal, Hernandez, Doerken & Spies, 2018).

The objectives of the present review were to evaluate whether zirconia dental implants demonstrate differences in hard and soft tissue integration directly compared to established titanium implants in preclinical studies.

2 | MATERIAL AND METHODS

This systematic review was reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P; Moher et al., 2015) statement using the Population, Intervention, Comparison, and Outcome (PICO) method (Schardt, Adams, Owens, Keitz & Fontelo, 2007). The protocol for this systematic review was registered on PROSPERO (CRD42016049624).

2.1 | Focused question

For the present review, the focused (PICO) question to be addressed was as follows: “In preclinical studies, do zirconia implants demonstrate differences in hard and soft tissue integration when compared to titanium implants?”

2.2 | Search strategy

In March 2017, an electronic, systematic search of the MEDLINE via PubMed and EMBASE via Elsevier databases was performed. Articles in the English and German languages were included, and no restriction with regard to the publication year was applied. For the literature search, clinical as well as preclinical studies were included. However, only data from preclinical studies are included in the present review. The evaluation of the clinical data has been reported in a separate manuscript (Roehling, Schlegel, Woelfler & Gahlert, 2018). For the MEDLINE search, the following combinations of terms were applied:

> "Dental implants" [MeSH] OR "dental implantation" [MeSH] AND "zirconium oxide" [MeSH] OR "yttria-stabilized tetragonal zirconia" [MeSH] OR "zirconia" OR "zirconia implant*" OR "ceramic implant*" AND "osseointegration" [MeSH] or "bone-implant-interface" [MeSH] or "survival rate" [MeSH] or "success rate" or "marginal bone loss" or "soft tissue."

With regard to the EMBASE search, the following EMTREE words and combination were used without any filters:

> "tooth implant" OR "tooth implantation" AND "zirconium oxide."

In addition to that, the electronic search was complemented by a manual hand search of the reference list of all included full texts.

For the electronic MEDLINE search, a reference management software (Endnote X 7.7.1, Thomson Reuters) was used. The obtained publications from the EMBASE search were also imported into the reference management software and finally screened.

2.3 | Inclusion criteria

For the systematic review, the following inclusion criteria were defined:

- Animal studies investigating zirconia compared to titanium implants.
- Studies at all levels of evidence, except expert opinion.
- Reported details regarding bone-to-implant contact, removal torque out/push-in measurements, and quantitative soft tissue parameters.
- Language: English, German.

2.4 | Exclusion criteria

Studies not meeting the inclusion criteria were excluded from the present review. In addition to that, in vitro experiments or experimental studies investigating only zirconia implants were excluded.

2.5 | Selection of studies

After elimination of duplicates, two reviewers (SR and MG) independently screened titles, abstracts, and full texts meeting the selection criteria. Unclear titles were included in the abstract screening. If titles or abstracts did not provide enough information for selection, full texts were obtained. Any disagreement with regard to inclusion and exclusion was resolved by discussion between the reviewers. To evaluate the agreement between the two reviewers, Cohen′s kappa coefficient (κ) was calculated for title and abstract selection (Landis & Koch, 1977).

2.6 | Data extraction

Data extraction was independently performed on all included studies using data extraction tables. Disagreement with regard to data extraction was resolved by discussion. In case of missing or unclear information, the corresponding authors of the papers were contacted via email. If the information was still not sufficient for inclusion and evaluation, the study was excluded for the present review.

Soft tissue parameters were classified as follows by Cochran et al. (1997) and Igarashi, Nakahara, Haga-Tsujimura, Kobayashi and Watanabe (2015):

- Epithelial tissue length (ETL): distance between the gingival margin (GM) and the most apical point of the junctional epithelium (aJE).
- Connective tissue contact (CTC): distance between aJE and the first bone-to-implant contact (fBIC).
- Biologic width (BW): distance between GM and fBIC.

Implant loading protocols were classified as follows by Weber et al. (2009):

- Immediate loading: functional loading of implants earlier than 1 week subsequent to implant placement.
- Early loading: functional loading of implants between 1 week and 2 months subsequent to implant placement.
- Conventional loading: functional loading after more than 2 months subsequent to implant placement.

From the included studies, the following data were extracted: author(s), year of publication, animal species, implant location, number of included animals and implants, implant system, implant material (yttria-stabilized zirconia (YTZP) or alumina-toughened zirconia (ATZ)) and applied surface treatment procedure, surface topography characteristics (characterized by the arithmetic mean deviation of the surface roughness: Sa or Ra), follow-up and loading periods (weeks), mean bone-to-implant contact (BIC, %), mean removal torque out (RTQ, Ncm) and push in values (PI, N). Moreover, quantitative soft tissue parameters (ETL, CTC, BW, mm) were recorded.

2.7 | Summary measures

The primary outcomes evaluated in the present review were bone-to-implant contact (BIC), removal torque out (RTQ), and push-in (PI) measurements. As secondary outcomes, quantitative peri-implant soft tissue parameters (ETL, CTC, BW) were investigated.

In addition, the influence of the implant material (titanium compared to zirconia, YTZP compared to ATZ), animal model, loading protocol, and length of follow-up and loading period as confounding factors for primary and secondary outcomes were analyzed.

2.8 | Statistical analysis

For the experimental studies, unpaired (two-sample) t tests (assuming unequal variances) were conducted on the equality of means of titanium and zirconia for BIC, RTQ, PI, and BW separately for each species. Additionally, forest plots were used for graphical presentations of the different outcomes in each study with confidence intervals and the weights given to each study in the meta-analyses, along with the overall pooled prevalence. In the graphs, the weight of each study included in the meta-analyses is represented by the area of a box with a center representing the size of the effect estimated from that study. The confidence intervals for the effect from each study are also shown. The summary effect is indicated by the middle of a diamond with left and right extremes representing the corresponding confidence interval.

In case of evidence of heterogeneity between studies, meta-regressions were used to analyze associations between the various outcomes and study characteristics. The estimated effects yielded evidence for the effects of implant material (titanium compared to zirconia, YTZP compared to ATZ), animal model, loading protocol, and length of follow-up and loading period on BIC, RTQ, PI, and BW. The critical level of alpha for determining whether a result could be judged statistically significant was set at 0.05. Thus, the likelihood of concluding there is an effect when there is none (Type I error) cannot exceed 5%. All analyses were performed using STATA statistical software version 15.0 (StataCorp LLC, College Station, USA).

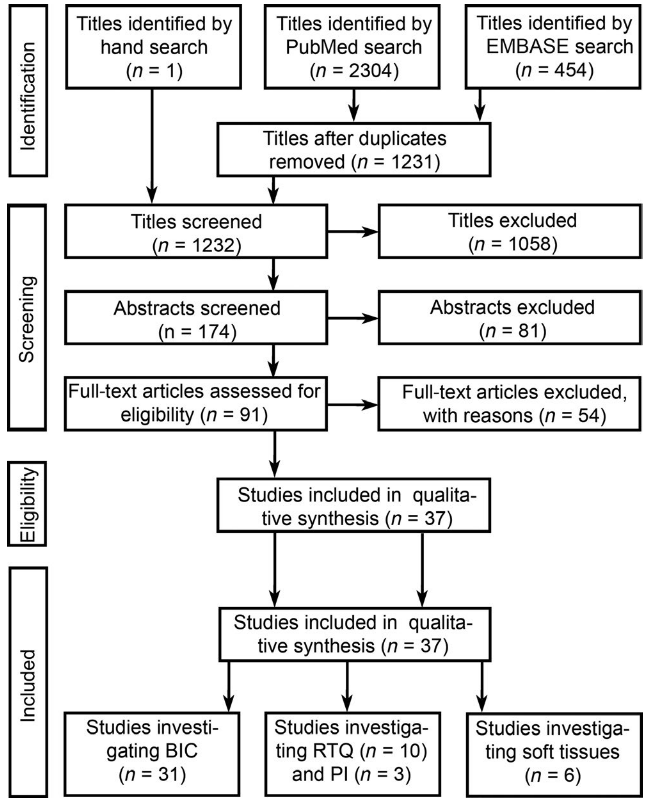

FIGURE 1 Search strategy and selection process of the included studies

3 | RESULTS

The electronic database search resulted in 2,758 publications (PubMed: 2304; EMBASE: 454, Figure 1). After removal of duplicates, 1,231 titles were available and one additional study was included after hand search. Thus, the two reviewers screened a total of 1,232 titles, whereas the inter-examiner agreement for title selection was $\kappa = 0.7$ resulting in 174 abstracts for further evaluation. After screening of the abstracts, 91 publications were selected for full-text evaluation (inter-examiner agreement $\kappa = 0.8$). After analysis of the included full-text articles, a total of 37 preclinical studies fulfilled the inclusion criteria and were included in the qualitative and quantitative analysis (Figure 1, Tables 1–7). Fifty-four reports had to be excluded with reasons (Table 8).

3.1 | Study characteristics

A total of 37 experimental studies using six different animal models were included in the present review (rats: $n = 3$, rabbits: $n = 8$, pigs: $n = 12$; canines: $n = 10$, sheep: $n = 2$, monkeys: $n = 1$, Tables 1–7).

In rats, implants were exclusively placed in the femur (Table 1), whereas in rabbits, the implants were either placed in the femur or placed in the tibia (Table 2). In pigs, maxilla, mandible, tibia, or os frontale and in canines mandible as well as humerus were reported as implant locations (Tables 3 and 4). With regard to sheep, femur and mandible or iliac bone were used as implant location, and in cynomolgus monkeys, implants were placed exclusively in the maxilla (Tables 5 and 6).

In rats, rabbits, and pigs, only unloaded implants were investigated after follow-up periods between 2 and 4 weeks, 2 and 12 weeks, and 1 and 13 weeks, respectively (Tables 1–3). In canines, unloaded (follow-up 0.4–20 weeks) as well as immediately, early, and conventionally loaded implants (follow-up 4–48 weeks, loading period 4–24 weeks) were evaluated (Table 4). In sheep, unloaded and immediately loaded implants after follow-up periods between 2 and 12 weeks (Table 5) and in cynomolgus monkeys implants that were conventionally loaded for 20 weeks after a follow-up period of 56 weeks were investigated (Table 6).

With regard to titanium and zirconia implant surface topographies, machined and micro-roughened implants were evaluated. For zirconia, additive and subtractive procedures as well as the manufacture process itself (e.g. sintering using rough pore formers or rough molds) were described for creating micro-rough implant surface topographies (Tables 1–6).

3.2 | Bone-to-implant contact

A total of 31 preclinical experiments investigating BIC fulfilled the inclusion criteria for the present review (Tables 1–6).

TABLE 1 Included experimental studies in rats

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/ Material	Surface top. (μm)		Follow-up (wk)	Mean BIC [%]		Mean PI [N]	
Kohal et al. (2016)	28	Femur	28	Nobel Biocare	Electrochemical anodization;	Sa	1.3	2	58.0		20.0	
					Ti-O			4	75.0		39.0	(Ti-O)
			28	Metoxit	Sintering with pore-building	Sa	1.5	2	24.0	(Ti-O)	10.0	(Ti-O)
					Polymers; ATZ-ZP			4	41.0		25.0	
Kohal et al. (2013)	56	Femur	28	Nobel Biocare	Machining; Ti-M	Sa	0.6	2	23.2		18.8	
								4	39.4		7.3	(Ti-O)
			28	Nobel Biocare	Electrochemical anodization;	Sa	1.3	2	36.2		26.5	
					Ti-O			4	56.1		49.0	
			28	Vita Zahnfabrik	Machining;, YTZP-M	Sa	0.2	2	30.9		18.9	
								4	46.6		9.3	(Ti-O)
			28	Vita Zahnfabrik	Sandblasting, acid etching;	Sa	1.0	2	17.6	(Ti-O)	25.8	
					YTZP-SE			4	33.5		30.6	(Ti-O, Ti-M, YTZP-M)
Kohal et al. (2009)	42	Femur	21	Nobel Biocare	Machining; Ti-M	Ra	0.1	2	23.2			
								4	39.4		7.3	(Ti-O, YTZP-P)
			21	Nobel Biocare	Electrochemical anodization;	Ra	0.3	2	36.4			
					Ti-O			4	55.2		34.0	
			21	Metoxit	Machining; ATZ-M	Ra	0.1	2	30.9			
								4	46.6		9.3	(Ti-O, YTZP-P)
			21	Nobel Biocare	Sintering with rough pore	Ra	0.4	2	45.3			
					Former; YTZP-P			4	59.4		45.8	

Notes. ATZ: alumina-toughened zirconia; NR: not reported; Ti: titanium; wks: weeks; YTZP: yttria-stabilized zirconia. Brackets show significant differences compared to subgroup.

TABLE 2 Included experimental studies in rabbits

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/Material	Surface top. (μm)	Follow-up (wk)	Mean BIC [%]	Mean RTQ [Ncm]
Aboushelib et al. (2013b)	40	Femur	20	Zimmer Dental	Sandblasting, acid etching; Ti-SE	NR	4	56.9 (YTZP-SIE)	NR
							6	68.3 (YTZP-SIE)	
			20	Toso Inc.	As sintered; YTZP	NR	4	53.3 (YTZP-SIE)	NR
							6	62.1 (YTZP-SIE)	
			20	Toso Inc.	Selective infiltration etching; YTZP-SIE	NR	4	65.4	NR
							6	75.0	
Park et al. (2013)	20	Tibia	26	Chaorum	Machining; Ti-M	Sa 0.3	4	42.5 (ZrO_2-SM, ZrO_2-RM)	10.56 (ZrO2-SM, ZrO2-RM)
			27	CetaTech	Injection molding, smooth mold; ZrO2-SM	Sa 0.5	4	61.6	44.27 (ZrO2-RM, Ti-M)
			27	CetaTech	Injection molding, rough mold; ZrO_2-RM	Sa 2.0	4	64.4	64.35
Salem et al. (2013)	30	Femur	30	Zimmer	Sandblasting, acid etching;	NR	4	62.8 (YTZP-FS)	43.58
				Dental	Ti-SE		8	82.9 (YTZP-FS)	74.26
							12	86.8	74.96
			30	Toso Inc.	Milling; YTZP-MI	NR	4	56.9 (YTZP-FS)	35.72 (YTZP-FS)
							8	70.4 (YTZP-FS)	63.1 (YTZP-FS)
							12	74.8	63.64 (YTZP-FS)
			30	Toso Inc.	Milling, fusion sputtering;	RA 14.0	4	69.7	46.24
					YTZP-FS		8	88.0	78.08
							12	89.1	78.7
Hoffmann et al. (2012)	48	Femur	24	NR	Acid etching; Ti-E	NR	6	34.2	39.82
							12	34.8	51.91
			24	Z-Systems	As sintered; YTZP	NR	6	33.0	35.41
							12	33.8	40.59
			24	Z-Systems	Laser modification;	NR	6	40.0	26.31
					YTZP-LM		12	43.9	39.71
			24	Z-Systems	Sandblasting; YTZP-S	NR	6	39.6	19.59 (Ti-E, YTZP)
							12	41.4	28.73 (Ti-E)

(Continues)

TABLE 2 (Continued)

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/Material	Surface top. (μm)		Follow-up (wk)	Mean BIC [%]		Mean RTQ [Ncm]
Shin, Blanchard, Ito and Chu (2011)	5	Tibia	10	NR	Machining; Ti-M		NR	6	35.8		10.9
			10	NR	NR; ZrO_2		NR	6	26.0		18.2
Rocchietta et al. (2009)	18	Tibia and	20	Nobel Biocare	Electrochemical anodization; Ti-O	Sa	1.3	4	54.7		NR
		Femur	41	Nobel Biocare	Sintering with rough pore former; YTZP-P	Sa	1.2	4	33.3		35.3
			41	Nobel Biocare	Sintering with rough pore former, HA-coating A; YTZP-PCA	Sa	NR	4	41.3		38.4
			41	Nobel Biocare	Sintering with rough pore former, HA-coating B; YTZP-PCB	Sa	NR	4	44.2		38.6
Lee et al. (2009)	40	Femur	20	Nobel Biocare	Electrochemical anodization; Ti-O	Ra	1.3	3	77.6		NR
								6	67.1		NR
			20	Nobel Biocare	Sintering with rough pore former; YTZP-P	Ra	1.0	3	70.5		NR
								6	69.7		NR
			20	Nobel Biocare	Sintering with rough pore former, Ca-P coating A;	Ra	1.0	3	64.6	(Ti-O)	NR
					YTZP-PCA			6	68.6		NR
			20	Nobel Biocare	Sintering with rough pore former, Ca-P coating C;	Ra	1.0	3	62.2	(Ti-O)	NR
					YTZP-PCC			6	64.5		NR
Hoffmann, Angelov, Gallez, Jung and Weber (2008)	4	Femur	4	Biomet 3i	Sandblasting, acid etching;		NR	2	47.7		NR
					Ti-SE			4	79.9		NR
			4	Z-Systems	Sandblasting; YTZP-S		NR	2	55.1		NR
								4	71.5		NR

Notes. ATZ: alumina-toughened zirconia; NR: not reported; Ti: titanium; wks: weeks; YTZP: yttria-stabilized zirconia; ZrO_2: zirconia bulk material not specified. Brackets show significant differences compared to subgroup at corresponding time points.

TABLE 3 Included experimental studies in pigs

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/Material	Surface top. (μm)	Follow-up (wk)	Mean BIC [%]	Mean RTQ [Ncm]
Chappuis et al. (2016)	7	Maxilla	14	Thommen	Sandblasting, acid etching;	Sa 2.2	4	82.3	NR
				Medical	Ti-SE		8	79.7	NR
			14	Dental-	Sandblasting, acid etching;	Sa 0.9	4	64.4 (Ti-SE)	NR
				Point	YTZP-SE		8	60.9 (Ti-SE)	NR
			14	Dental-	Sandblasting, acid etching;	Sa 0.7	4	70.0 (Ti-SE)	NR
				Point	ATZ-SE		8	57.0 (Ti-SE)	NR
Linares et al. (2016)	6	Mandible	9	Straumann	Sandblasting, acid etching, N2 protection; Ti-modSLA	NR	8	84.3	NR
			9	Straumann	Sandblasting and acid etching; YTZP-ZLA	NR	8	85.9	NR
Schierano et al. (2015)	16	Tibia	64	Nobel	Electrochemical	Sa 3.4	1	NR	NR
				Biocare	Anodization; Ti-O		2	NR	
							4	32.1	
							8	35.3 (ATZ-E)	
			64	NR	Acid etching; ATZ-E	Sa 5.4	1	NR	NR
							2	NR	NR
							4	45.4	NR
							8	53.3	NR
Bormann et al. (2012)	17	Maxilla	51	Straumann	Sandblasting, acid etching;	Sa 1.2	4	NR	131.6
					Ti-SLA		8	NR	132.6
							12	NR	177.6
			51	Straumann	Acid etching; YTZP-E	Sa 0.6	4	NR	109.9
							8	NR	97.4 (Ti-SLA)
							12	NR	139.6
Gahlert et al. (2012)	17	Maxilla	18	Straumann	Sandblasting, acid etching;	Sa 1.3	4	64.7	NR
					Ti-SLA		8	79.2	NR
							12	83.7	NR
			16	Straumann	Acid etching; YTZP-E	Sa 0.6	4	70.0	NR
							8	67.1	NR
							12	68.3	NR

(Continues)

TABLE 3 (Continued)

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/Material	Surface top. (μm)	Follow-up (wk)	Mean BIC [%]	Mean RTQ [Ncm]
Moller et al. (2012)	8	Os	32	Bredent	Sandblasting, acid etching;	NR	4	64.1	NR
		Frontale			Ti-SE		12	73.6	NR
			32	Bredent	NR; YTZP	NR	4	59.3	NR
							12	67.1	NR
Gahlert et al. (2010)	16	Maxilla	32	Straumann	Sandblasting, acid etching;	Sa 1.2	4	NR	42.1
					Ti-SLA		8	NR	75
							12	NR	73.1
			32	Straumann	Acid etching; YTZP-E	Sa 0.6	4	NR	42.4
							8	NR	69.6
							12	NR	69.3
Schliephake et al. (2010)	12	Mandible	24	Thommen	Sandblasting, acid etching;	Sa 2.6	4	69.3	244.5
				Medical	Ti-SE		13	78.9	221.9
			24	Thommen	Sandblasting, acid etching;	Sa 1.2	4	66.7	111.8 (Ti-SE)
				Medical	YTZP-SE		13	57.6 (Ti-SE)	100.3 (Ti-SE)
			24	Thommen	Sandblasting; YTZP-S	Sa 1.0	4	57.5	55.9 (YTZP-SE, Ti-SE)
				Medical			13	54.6 (Ti-SE)	99.4 (Ti-SE)
Stadlinger, Hennig, Eckelt, Kuhlisch and Mai (2010)	7	Mandible	7	Dentsply	Sandblasting, acid etching; Ti-SE-sub	Ra 2.8	4	53.0	NR
			7	Bredent	Sandblasting, YTZP-S-sub	Ra 1.0	4	53.0	NR
			7	Bredent	Sandblasting, YTZP-S-nsub	Ra 1.0	4	48.0	NR
Gahlert et al. (2009)	15	Maxilla	15	Straumann	Sandblasting, acid etching;	Sa 1.2	4	23.5	NR
					Ti-SLA		8	53.3	NR
							12	58.5	NR
			15	Straumann	Acid etching; YTZP-E	Sa 0.6	4	27.1	NR
							8	51.0	NR
							12	51.1	NR
Depprich et al. (2008b)	12	Tibia	24	Konus	Acid etching; Ti-E	Ra 1.8	1	47.7	NR
				Dental			4	58.6	NR
				Implants			12	82.9	NR
				Konus	Acid etching; YTZP-E	Ra 0.6	1	35.3	NR
				Dental			4	45.3	NR
				Implants			12	71.4	NR

(Continues)

TABLE 3 (Continued)

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/Material	Surface top. (µm)	Follow-up (wk)	Mean BIC [%]	Mean RTQ [Ncm]
Gahlert et al. (2007)	13	Maxilla	18	Straumann	Sandblasting, acid etching; Ti-SLA	Sa 1.2	4	NR	75.7
							8	NR	132.8
							12	NR	98.9
			30	Straumann	Sandblasting; YTZP-S	Sa 0.6	4	NR	32.3
							8	NR	43.1 (Ti-SLA)
							12	NR	31.3
			30	Straumann	Machining; YTZP-M	Sa 0.1	4	NR	27.2
							8	NR	24.0 (Ti-SLA, YTZP-S)
							12	NR	21.3 (Ti-SLA, YTZP-S)

Notes. ATZ: alumina-toughened zirconia; NR: not reported; nsub: non-submerged healing; sub: submerged healing; Ti: titanium; wks: weeks; YTZP: yttria-stabilized zirconia; ZrO_2: zirconia bulk material not specified.
Brackets show significant differences compared to subgroup at corresponding time point.

3.2.1 | Rats

In three studies, an early osseointegration period between 2 and 4 weeks of unloaded healing was investigated (titanium: BIC 23.2%–75.0%; ZrO_2: BIC 17.6 – 59.4%, Table 1). In comparison with zirconia, two experiments reported significantly higher values for titanium at single follow-up time points after 2 weeks, whereas significantly higher BIC values were not always associated with increased surface roughness, characterized by the arithmetic mean deviation of the surface roughness: Sa or Ra (Table 1). In detail, significantly higher values were evaluated for electrochemically anodized titanium implants (Sa = 1.3 µm) compared to zirconia implants with a sandblasted and acid-etched surface (Sa = 1.0 µm) or compared to zirconia implants that were sintered with pore-building polymers (Sa = 1.5 µm; Kohal et al., 2013; Kohal, Bachle, Renz & Butz, 2016).

Different zirconia implant surfaces were evaluated in two studies and increased surface roughness characteristics were associated with decreased (Kohal et al., 2013) as well as with increased BIC values (Kohal et al., 2009), whereas the differences were statistically not significant ($p > 0.05$).

The evaluated mean BIC values were 47.7% (CI: 35.9–59.4) and 39.0% (CI: 28.3–49.6) for titanium and zirconia, respectively. For the evaluated studies, a high degree of heterogeneity was estimated (titanium: $I^2 = 97.1\%$, $p < 0.01$; zirconia: $I^2 = 98.2\%$, $p < 0.01$, Figure 2). The difference between both materials was statistically not significant ($p = 0.33$).

3.2.2 | Rabbits

Unloaded implants placed in tibias and femurs were investigated in eight studies. After healing periods ranging from 2 to 12 weeks, mean values between 34.2% and 86.8% and between 26.0% and 89.1% were evaluated for titanium and zirconia, respectively (Table 2). In four studies, significant differences between both materials were reported at single follow-up time points and the reported differences were related to surface roughness characteristics. In detail, significantly increased BIC values after 4 and 6 weeks of healing were observed for zirconia implants with a micro-roughened surface created by selective infiltration etching compared to titanium implants with a sandblasted and acid-etched surface. However, quantitative surface characteristics were not provided (Aboushelib, Salem, Taleb & El Moniem, 2013b). In addition, significantly increased values after 4 weeks were reported for zirconia implants that were sintered using a smooth (Sa = 0.5 µm) or a rough mold (Sa = 2.0 µm) compared to machined titanium implants (Sa = 0.3 µm; Park, Chung & Shon, 2013). Moreover, Salem, Abo Taleb and Aboushelib (2013) evaluated significantly higher BIC values for milled zirconia implants with a micro-roughened surface created using "fusion-sputtering technique" compared to sandblasted and acid-etched titanium implants after 4 and 8 but not after 12 weeks of healing. Unfortunately, implant surface characteristics were not provided (Salem et al., 2013). In contrast to that, only one experiment found significantly increased values for

TABLE 4 Included experimental studies in canines

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/Material	Surface top. (µm)		Follow-up (wk)	Loading (wk)	Mean BIC [%]	Mean RTQ [Ncm]
Janner et al. (2018)	5	Mandible	30	Straumann	Sandblasting, acid etching; Ti-SLA	Sa	1.3	10	4	76.9	NR
								22	16	69.8	NR
			30	Straumann	Sandblasting, acid etching;	Sa	0.7	10	4	75.6	NR
					YTZP-ZLA			22	16	71.2	NR
Mihatovic et al. (2017)	9	Mandible	18	Straumann	Sandblasting, acid etching; Ti-SLA	Ra	3.2	0.4	0	42.3	NR
								2	0	62.2	NR
								10	0	58.6	NR
			18	3M ESPE	Sandblasting grit 1; ZrO_2-S1	Ra	1.3	0.4	0	25.1	NR
								2	0	42.4	NR
								10	0	49.7	NR
			18	3M ESPE	Sandblasting grit 2; ZrO_2-S2	Ra	2.1	0.4	0	30.0	NR
								2	0	44.5	NR
								10	0	39.0	NR
			18	3M ESPE	Sandblasting grit 3; ZrO_2-S3	Ra	4.1	0.4	0	29.0	NR
								2	0	61.3	NR
								10	0	69.6	NR
Calvo-Guirado et al. (2015)	6	Mandible	24	Bredent	Sandblasting, acid etching; Ti-SE		NR	4	4	51.4	NR
								12	12	61.7	NR
			24	Bredent	Laser modification; YTZP-LM		NR	4	4	44.7	NR
								12	12	47.9	NR
Igarashi et al. (2015)	5	Mandible	6	Nanto	NR; Ti	Ra	0.1	12	12	68.9	NR
			6	Nanto	NR; YTZP	Ra	0.1	12	12	62.7	NR
			6	Nanto	NR; CeTZP	Ra	0.1	12	12	58.7	NR
Montero et al. (2015)	8	Mandible	16	Microdent	NR; Ti	Ra	1.6	20	0	56.5	NR
			16	Metoxit	NR; ATZ	Ra	0.9	20	0	57.0	NR
Oh et al. (2015)	3	Humerus	5	Megagen	Blasting with resorbable media; Ti-RBM	NR	1.6	12	0	57.9	NR
			5	NR	Injection molding; YTZP	NR	0.7	12	0	72.0	NR
			5	NR	Injection molding, sandblasting; YTZP-SB	NR	1.2	12	0	58.3	NR

(Continues)

TABLE 4 (Continued)

Author (Year)	Animals (n)	Location	Impl. (n)	Company	Surface treatment/Material	Surface top. (µm)		Follow-up (wk)	Loading (wk)	Mean BIC [%]	Mean RTQ [Ncm]
Thoma et al. (2015)	6	Mandible	12	Straumann	Sandblasting, acid etching, Ti-SLA		NR	48	24	87.9	NR
			12	BPI Implantate	NR; ZrO_2		NR	48	24	84.2	NR
			12	Vita Zahnfabrik	NR, YTZP		NR	48	24	87.7	NR
			12	Ziraldent	NR, ATZ		NR	48	24	78.6	NR
Delgado-Ruiz et al. (2014a)	6	Mandible	8	Bredent	Sandblasting, acid etching; Ti-SE	Sa	3.1	12	12	57.0	NR
			8			Sa	3.1	12	0	43.0	NR
			8	Bredent	Sandblasting; YTZP-SB	Sa	2.7	12	12	48.0	NR
			8			Sa	2.7	12	0	36.0	NR
			8	Bredent	Sandblasting, laser modification	Sa	8.9	12	12	78.0	NR
			8		Total implant length; YTZP-LM	Sa	8.9	12	0	47.0	NR
Delgado-Ruiz et al. (2014b)	12	Mandible	26	Bredent	Sandblasting, acid etching; Ti-SE	Ra	1.8	4	4	NR	71.3
								8	8	NR	99.9
								12	12	NR	227.0
			26	Bredent	Sandblasting; YTZP-SB	Ra	1.3	4	4	NR	64.1 (YTZP-LM2, Ti-SE)
								8	8	NR	78.2 (YTZP-LM2, Ti-SE)
								12	12	NR	199.2 (YTZP-LM2, Ti-SE)
			26	Bredent	Sandblasting, laser modification	Ra	2.4	4	4	NR	69.2 (YTZP-LM2)
					Implant neck; YTZP-LM1			8	8	NR	88.8 (YTZP-LM2)
								12	12	NR	215.1 (YTZP-LM2)
			26	Bredent	Sandblasting, laser modification	Ra	9.5	4	4	NR	85.0
					Total implant length; YTZP-LM2			8	8	NR	127.0
								12	12	NR	240.2
Koch et al. (2010)	6	Mandible	12	Zeiterion	Sandblasting; Ti-SB	Ra	2.3	16	0	40.9	NR
			12	Zeiterion	Sandblasting; YTZP-SB	Ra	2.3	16	0	59.1	NR
			12	Zeiterion	Sandblasting, coating with TiO_2 gel; YTZP-TO	Ra	2.3	16	0	55.8	NR
			12	NR	Sandblasting; PEEK	Ra	2.3	16	0	26.0	NR

Notes. ATZ: alumina-toughened zirconia; NR: not reported; Ti: titanium; wks: weeks; YTZP: yttria-stabilized zirconia; ZrO_2: zirconia bulk material not specified. Brackets show significant differences compared to subgroup at corresponding time points.

TABLE 5 Included experimental studies in sheep

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/Material	Surface top. (μm)	Follow-up (wk)	Loading (wk)	Mean BIC [%]	Mean RTQ [Ncm]
Siddiqi et al. (2016)	10	Femur	10	Southern	Acid etching, Ti-E	Ra 0.7	12	0	79.0 (YTZP-E)	NR
		Mandible	10	Implants		Ra 0.7	12	12	60.2	NR
		Femur	10	Southern	Acid etching, YTZP-E	Ra 0.7	12	0	85.5	NR
		Mandible	10	Implants		Ra 0.7	12	12	72.2	NR
Ferguson et al. (2008)	15	Iliac	18	Thommen	Sandblasting, acid	Sa 2	2	0	NR	73.3
		Bone		Medical	Etching; Ti-SE		4	0	NR	141.3
							8	0	NR	188.4
			18	Thommen	Sandblasting, acid	Sa 1.2	2	0	NR	66.0
				Medical	Etching, CaP coating;		4	0	NR	129.7
					Ti-CaP		8	0	NR	168.3
			18	Thommen	Sandblasting, anodic	Sa 1.5	2	0	NR	59.4
				Medical	Plasma-chemical		4	0	NR	77.9
					Modification; Ti-APC		8	0	NR	91.9 (Ti-SE, Ti-CaP, Ti-ALD, Ti-CS)
			18	Thommen	Sandblasting, acid	Sa 2.2	2	0	NR	87.3
				Medical	Etching, coating with		4	0	NR	143.8
					Alendronate; Ti-ALD		8	0	NR	183.5
			18	Thommen	Sandblasting, acid	Sa 1.7	2	0	NR	68.3
				Medical	Etching, coating with		4	0	NR	146.2
					Collagen and CS; Ti-CS		8	0	NR	159.3
			18	Thommen	Sandblasting, acid	Sa 1.1	2	0	NR	55.0
				Medical	Etching; YTZP-SE		4	0	NR	86.7
							8	0	NR	100.5 (Ti-SE, Ti-CaP, Ti-ALD, Ti-CS)

Notes. NR: not reported; Ti: titanium; wks: weeks; YTZP: yttria-stabilized zirconia.
Brackets show significant differences compared to subgroup at corresponding time points.

TABLE 6 Included experimental studies in monkeys

Author (Year)	Animals (*n*)	Location	Impl. (*n*)	Company	Surface treatment/Material	Surface top. (μm)	Follow-up (wk)	Loading (wk)	Mean BIC [%]
Kohal et al. (2004)	6	Maxilla	12	Custom made	Sandblasting and acid etching, Ti-SE	NR	56	20	72.9
			12	Custom made	Sandblasting, YTZP-S	NR	56	20	67.4

Note. NR: not reported; Ti: titanium; wks: weeks; YTZP: yttria-stabilized zirconia.

electrochemically anodized titanium implants (Ra = 1.3 μm) after 3 weeks compared to zirconia implants that were sintered using a rough pore former and subsequently coated with calcium phosphate (Ra = 1.0 μm). Interestingly, after 6 weeks of healing, the differences between both materials were not any longer statistically significant (Lee et al., 2009). Moreover, it was reported that coating of the zirconia implants' surfaces with hydroxyapatite (Rocchietta, Fontana, Addis, Schupbach & Simion, 2009) or with calcium phosphate (Lee et al., 2009) did not have any significant effect on the osseointegrative capacity.

In two studies, different surface treatment procedures or increased surface roughness characteristics were associated with significantly higher BIC values (Aboushelib, Osman, Jansen, Everts & Feilzer, 2013a; Park et al., 2013).

Meta-analysis estimation revealed a mean BIC value of 59.2% (CI: 51.8–66.7) for titanium and 58.4% (CI: 52.4–64.5) for zirconia. For the evaluated studies, a high degree of heterogeneity was evaluated (titanium: $I^2 = 99.6\%$, $p < 0.01$; zirconia: $I^2 = 99.1\%$, $p < 0.01$, Figure 3). The difference between both materials was statistically not significant ($p = 0.58$).

3.2.3 | Pigs

Nine studies in pigs investigated unloaded implants. For titanium, the mean value ranges were 23.7%–84.25% for implants placed in maxilla, mandible, tibia, or os frontale after follow-up periods between 1 and 13 weeks. The values for zirconia were 27.1%–86.0% for corresponding time points and implant locations (Table 3). Significant differences between both materials were reported in three studies, whereas significantly increased BIC values for one material were always associated with increased quantitative surface roughness. In detail, significantly higher values were observed for titanium implants with a sandblasted and acid-etched surface (Sa = 2.2 μm) compared to sandblasted and acid-etched ATZ (Sa = 0.7 μm) and YTZP (Sa = 0.9 μm) zirconia implants after 4 and 8 weeks of healing (Chappuis et al., 2016). Similar results were reported for sandblasted and acid-etched titanium implants (Sa = 2.6 μm) compared to sandblasted (Sa = 1.0 μm) and sandblasted and acid-etched YTZP zirconia implants (Sa = 1.2 μm) after 13 weeks of healing in the maxilla (Schliephake, Hefti, Schlottig, Gedet & Staedt, 2010). In contrast to that, significantly increased values were reported for acid-etched ATZ zirconia implants (Sa = 5.4 μm) placed in tibia compared to electrochemically anodized titanium implants (Sa = 3.4 μm) after 13 weeks (Schierano et al., 2015).

When different zirconia implant surface topographies were investigated, increased surface roughness parameters were correlated with significantly increased BIC values (Schliephake et al., 2010). In contrast to that, another study reported that increased surface roughness was associated with increased as well as with decreased BIC values (Chappuis et al., 2016).

The meta-analysis estimated a mean BIC value of 60.48% (CI: 50.0–71.0) for titanium and 56.1% (CI: 49.9–62.3) for zirconia. For

TABLE 7 Experimental studies reporting soft tissue parameters

Author (Year)	Animals (*n*)	Species/Location	Impl. (*n*)	Surface Treatment/Material	Follow-up (wk)	Loading (wk)	ETL (mm)	CTC (mm)	BW (mm)
Linares et al. (2016)	6	Pig/Mandible	9	Sandblasting, acid etching, N2 protection; Ti-modSLA (1-piece TL)	8	0	2.2	1.49	3.7
			9	Sandblasting and acid etching; YTZP-ZLA (1-piece TL)	8	0	2	1.62	3.62
Igarashi et al. (2015)	5	Dog/Mandible	6	NR; Ti (1-piece TL)	12	12	1.88	1.23	3.11
			6	NR; YTZP (1-piece TL)	12	12	2.19	1.09	3.28
			6	NR; CeTZP (1-piece TL)	12	12	2.29	0.49	2.78
Thoma et al. (2015)	6	Dog/Mandible	12	Sandblasting, acid etching, Ti-SLA (2-piece TL, bu)	48	24	1.41	NR	2.78
				Sandblasting, acid etching, Ti-SLA (2-piece TL, li)	48	24	2.03	NR	3.4
			12	NR, ZrO_2 (2-piece BL, bu)	48	24	1.41	NR	2.71
				NR, ZrO_2 (2-piece BL, li)	48	24	1.41	NR	3.07
			12	NR, YTZP (1-piece TL, bu)	48	24	1.44	NR	2.64
				NR, YTZP (1-piece TL, li)	48	24	1.65	NR	3.26
			12	NR, ZrO_2 (1-piece TL, bu)	48	24	1.44	NR	3.03
				NR, ZrO_2 (1-piece TL, li)	48	24	3.57[a]	NR	5.05[a]
Delgado-Ruiz et al. (2014a)	6	Dog/Mandible	8	Sandblasting, acid etching; Ti-SE (2-piece BL)	12	12	NR	NR	3.12
			8		12	0	NR	NR	3.07
			8	Sandblasting; YTZP-SB (1-piece TL)	12	12	NR	NR	2.78
			8		12	0	NR	NR	2.8
			8	Sandblasting, laser modification total implant length;	12	12	NR	NR	2.82
			8	YTZP-LM (1-piece TL)	12	0	NR	NR	2.83
Koch et al. (2013)	6	Dog/Mandible	6	Sandblasting; Ti-SB (1-piece TL, sub)	16	0	1.28	NR	NR
			6	Sandblasting; Ti-SB (1-piece TL, nsub)	16	0	1.97	NR	NR
			6	Sandblasting; YTZP-SB (1-piece TL, sub)	16	0	1.63	NR	NR
			6	Sandblasting; YTZP-SB (1-piece TL, nsub)	16	0	2.01	NR	NR
			6	Sandblasting, coating with TiO2 gel; YTZP-TO (1-piece TL, sub)	16	0	1.73	NR	NR
			6	Sandblasting, coating with TiO2 gel; YTZP-TO (1-piece TL, nsub)	16	0	1.65	NR	NR
			6	Sandblasting; PEEK (1-piece TL, sub)	16	0	1.48	NR	NR
			6	Sandblasting; PEEK (1-piece TL, nsub)	16	0	1.49	NR	NR
Kohal et al. (2004)	6	Monkey/Maxilla	12	Sandblasting and acid etching, Ti-SE (2-piece TL)	56	20	2.9	2.4	5.2
			12	Sandblasting, YTZP-S (2-piece TL)	56	20	2.9	1.5	4.5

Notes. ATZ: alumina-toughened zirconia; BL: bone-level implant design; bu: buccal; li: lingual; NR: not reported; nsub: non-submerged healing; sub: submerged healing; Ti: titanium; TL: tissue-level implant design; wks: weeks; YTZP: yttria-stabilized zirconia; ZrO_2: zirconia bulk material not specified.

[a]Significant differences compared to subgroups.

TABLE 8 Excluded studies

Reason for exclusion	Number	Studies
Experimental studies investigating zirconia implants not compared to titanium implants	18	Akagawa, Hosokawa, Sato and Kamayama (1998), Akagawa, Ichikawa, Nikai and Tsuru (1993), Calvo-Guirado et al. (2015), Chang, Oka, Nakamura and Gu (1996), Chung, Kim, Shon and Park (2013), Han et al. (2016), Hayashi, Inadome, Tsumura, Mashima and Sugioka (1993), Hayashi, Matsuguchi, Uenoyama and Sugioka (1992), Kim et al. (2015), Mai et al. (2012), Ratiu, Cavalu, Miclaus, Rus and Lazarescu (2015), Richardson, Klawitter, Sauer, Pruitt and Hulbert (1975), Saulacic, Erdosi, Bosshardt, Gruber and Buser (2014), Scarano, Di Carlo, Quaranta and Piattelli (2003), Schreiner, Schroeder-Boersch, Schwarz and Scheller (2002), Shon et al. (2014, 2015), Taniguchi, Kakura, Yamamoto, Kido and Yamazaki (2016)
Review articles	18	Andreiotelli and Khol (2009b), Apratim et al. (2015), Assal (2013), Bosshardt, Chappuis and Buser (2017), Buser, Sennerby and De Bruyn (2017), Chen, Moussi, Drury and Wataha (2016), Depprich et al. (2014), Elnayef et al. (2017), Hafezeqoran and Koodaryan (2017), Hisbergues, Vendeville and Vendeville (2009), Hobkirk and Wiskott (2009), Kohal et al. (2008), Kumar, Jain, Jayesh, Parthasaradhi and Venkatakrishnan (2015), Manzano et al. (2014), Ozkurt and Kazazoglu (2011), Prithviraj, Deeksha, Regish and Anoop (2012), Van Dooren et al. (2012), Wenz et al. (2008)
In vitro studies	5	Kirsten (2015), Oblak, Verdenik, Swain and Kosmac (2014), Zhu, Yang and Ma (2010), Andreiotelli, Wenz and Kohal (2009a), Delgado-Ruíz et al. (2011)
Data not clear for evaluation	5	Dubruille et al. (1999), Gredes, Kubasiewicz-Ross, Gedrange, Dominiak and Kunert-Keil (2014), Langhoff et al. (2008), Lee et al. (2013), Sennerby et al. (2005)
Animal/experimental studies not investigating BIC or RTQ/PI or quantitative soft tissue parameters	4	Delgado-Ruiz et al. (2015), Depprich et al. (2008a), Kim et al. (2016), Thoma et al. (2016)
Experimental studies investigating titanium implants with a zirconia collar	2	Bianchi et al. (2004), Tete, Mastrangelo, Bianchi, Zizzari and Scarano (2009)
Studies investigating alumina dental implants	1	Nordlund, Zetterqvist and Oden (1989)
Experimental studies investigating titanium implants coated with zirconia	1	Sollazzo et al. (2008)

the included studies in pigs, a high degree of heterogeneity was evaluated (titanium: I^2 = 99.9%, $p < 0.01$; zirconia: I^2 = 99.4%, $p < 0.01$, Figure 4). The difference between zirconia and titanium was statistically not significant ($p = 0.43$).

3.2.4 | Canines

Ten studies were included, and the follow-up periods ranged between 0.43 and 48 weeks. For unloaded and loaded titanium implants placed in the mandible, mean value ranges of 40.9%–68.9% and 51.4%–87.9%, respectively, were reported. Zirconia implants demonstrated comparable results between 25.1% and 69.6% for unloaded and between 44.7% and 87.7% for loaded implants. No statistically significant differences between both materials were reported (Table 4).

When quantitative surface topography parameters were provided, increased surface roughness was associated with increased (Delgado-Ruiz et al., 2014a; Mihatovic, Golubovic, Becker & Schwarz, 2017) as well as with decreased BIC values (Mihatovic et al., 2017; Oh et al., 2015), whereas the differences were statistically not significant ($p > 0.05$).

The meta-analysis estimated mean BIC values of 60.4% (CI: 52.8–68.0) and 60.3% (CI: 52.3–68.3) for titanium and zirconia, respectively. In addition, a high degree of heterogeneity was estimated for titanium (I^2 = 95.7%, $p < 0.01$) as well as for zirconia (I^2 = 95.2%, $p < 0.01$, Figure 5). The difference between both materials was statistically not significant ($p = 0.46$).

3.2.5 | Sheep

Only one study was included in the present review (Table 5). The authors reported significantly increased BIC values for acid-etched zirconia (85.5%, Ra = 0.7 μm) compared to acid-etched titanium implants (79.0%, Ra = 0.7 μm) after 12 weeks of unloaded healing in the femur ($p = 0.002$). Interestingly, after 12 weeks of loading in the mandible, the differences were statistically not significant (zirconia: 72.2%; titanium: 60.2%, $p = 0.087$; Siddiqi, Duncan, De Silva & Zafar, 2016).

3.2.6 | Monkeys

In cynomolgus monkeys, one study observed comparable results for both materials after 56 weeks of follow-up and 20 weeks of

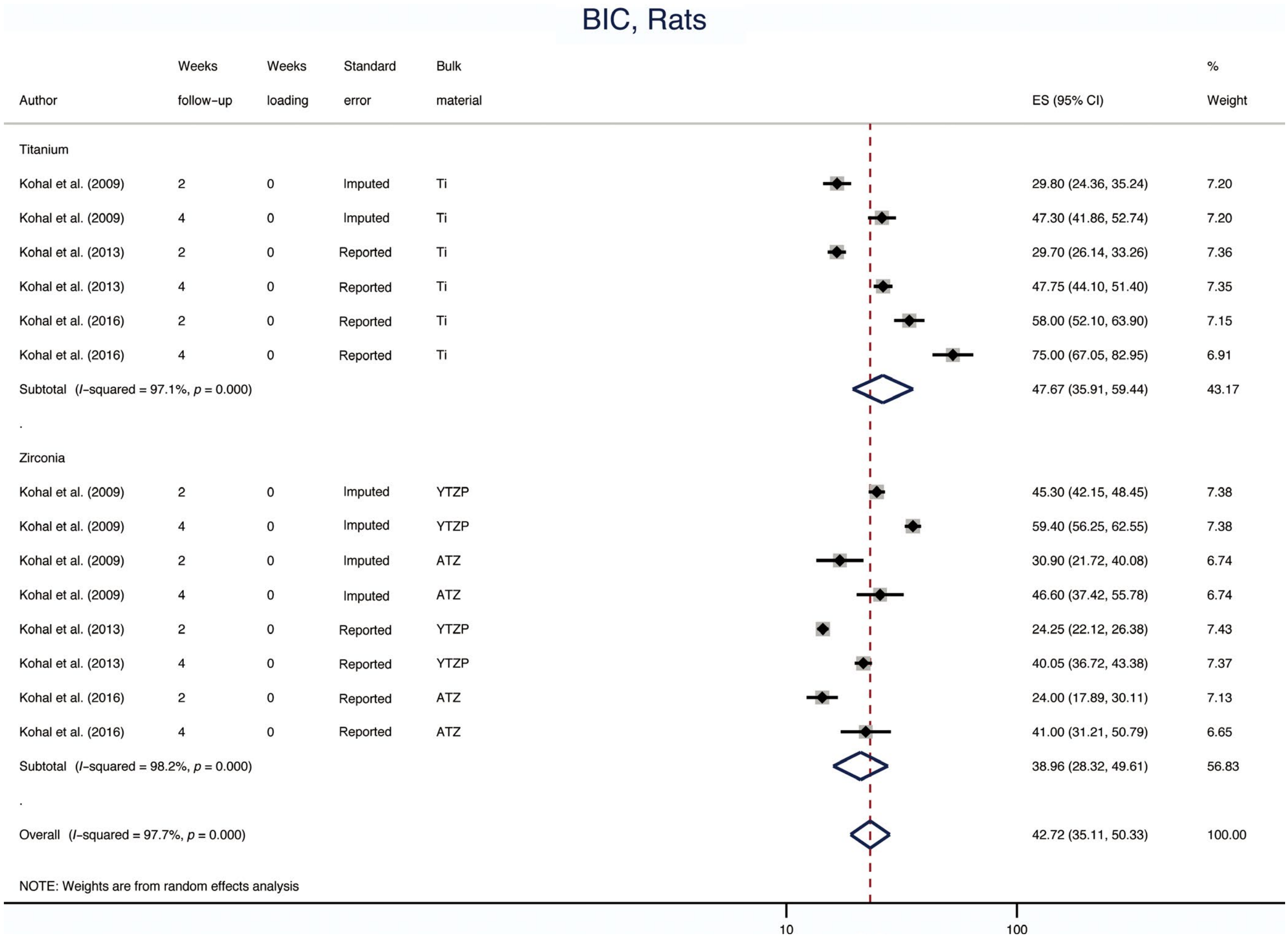

FIGURE 2 Forest plot of the BIC analysis of titanium and zirconia implants placed in rats

loading. The authors evaluated mean values of 72.9% and 67.4% for conventionally loaded, custom-made sandblasted and acid-etched titanium and sandblasted zirconia implants, respectively. The difference between both materials was statistically not significant ($p = 0.287$). However, no quantitative surface roughness characteristics were reported (Table 6; Kohal, Weng, Bachle & Strub, 2004).

3.2.7 | Meta-Regression for BIC including all animal models

Taking together all animal models, overall mean BIC values of 59.1% (CI: 53.3–64.8) and 55.9% (CI: 51.6–60.1) were evaluated for titanium and zirconia implants, respectively. The meta-regression showed that implant material (zirconia compared to titanium and YTZP compared to ATZ) did not have any significant effect on the evaluated BIC values ($p > 0.05$, Figure 6a). In contrast to that, a longer investigation and loading period was associated with a significant increase in BIC. Interestingly, conventionally loaded implants showed significantly increased BIC values compared to unloaded and immediately loaded implants. In addition, the statistical analysis revealed that the individual animal model significantly influenced the evaluated BIC outcomes ($p < 0.05$, Figure 6a,b).

3.3 | Removal torque out

A total of 10 experimental studies performed RTQ testing on titanium and zirconia implants (Tables 1–6).

3.3.1 | Rabbits

Four studies that performed RTQ measurements were included. For implants placed in tibia and femur, the mean values after unloaded healing between 4 and 12 weeks were 10.6–75.0 Ncm for titanium and 18.2–78.7 Ncm for zirconia (Table 2). Two studies reported significant differences between both materials. In detail, significantly decreased RTQ results were observed after 4 weeks of healing for machined titanium (Sa = 0.30 µm) compared to two types of micro-roughened injection molded zirconia implants that were sintered using a smooth (Sa = 0.5 µm) or a rough mold (Sa = 2.0 µm; Park et al., 2013). In contrast to that, significantly increased values were

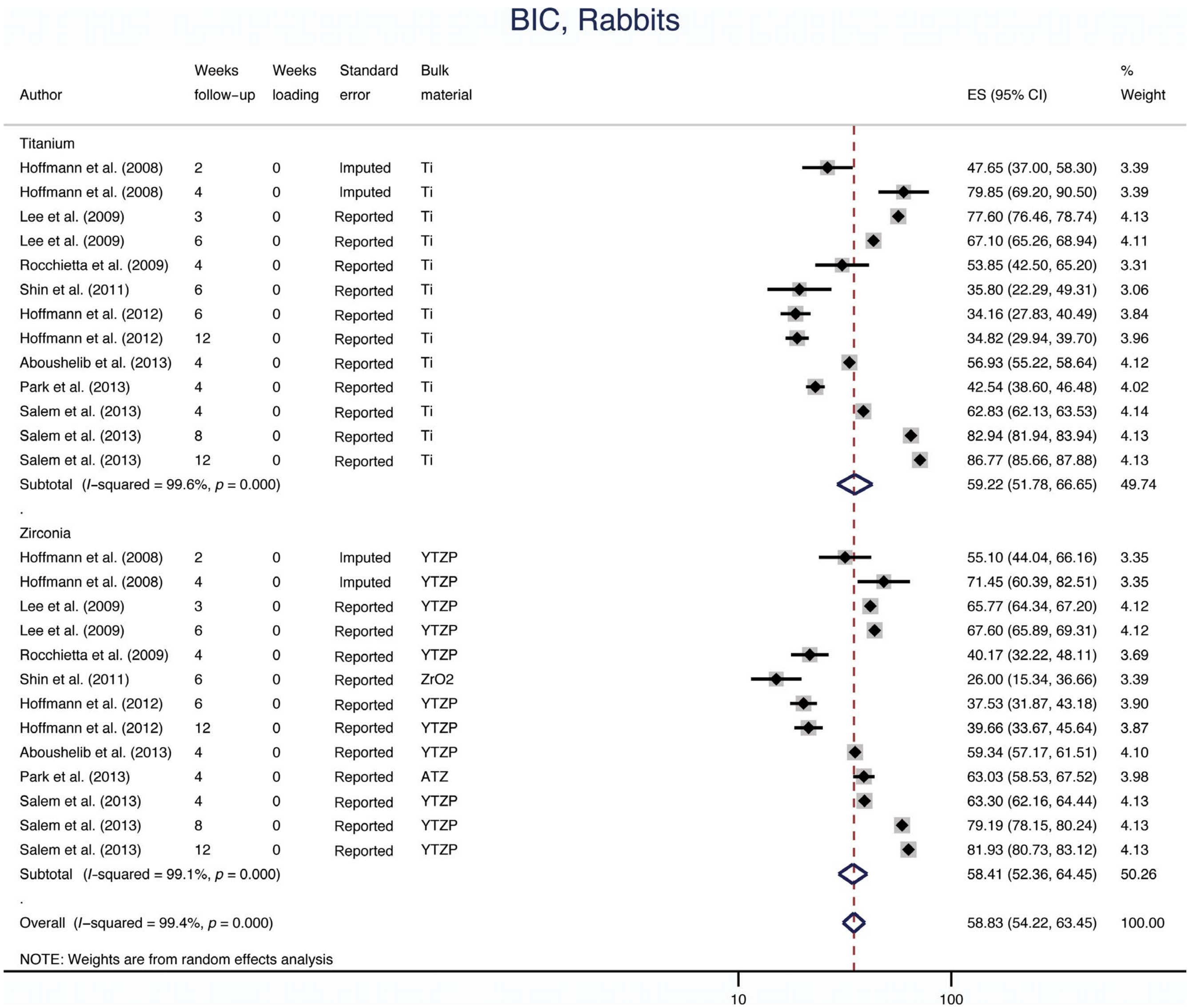

FIGURE 3 Forest plot of the BIC analysis of titanium and zirconia implants placed in rabbits

reported for acid-etched titanium in comparison with sandblasted zirconia implants after 6 and 12 weeks of healing. Interestingly, in the same study, the differences between the investigated titanium implants and zirconia implants with a laser-modified surface were statistically not significant. However, the authors of the latter study did not provide any quantitative surface roughness characteristics (Hoffmann, Angelov, Zafiropoulos & Andreana, 2012). When different types of zirconia implant surfaces were investigated, two studies found out that significantly increased RTQ values were associated with increased quantitative surface roughness values or surface treatment procedures (Park et al., 2013; Salem et al., 2013).

The meta-analysis estimated mean RTQ values of 43.8 Ncm (CI: 26.1–61.4) and 44.6 Ncm (CI: 29.5–59.7) for titanium and zirconia, respectively. In addition, a high degree of heterogeneity was estimated for both materials (I^2 = 99.9%, $p < 0.01$, Figure 7). The difference between both materials was statistically not significant (p = 0.88).

3.3.2 | Pigs

Altogether, four studies investigated unloaded implants (Table 3). For titanium, the mean value ranges for implants placed in maxilla and mandible were 42.1–177.6 Ncm and 221.9–244.5 Ncm, respectively, for healing periods between 4 and 13 weeks. With regard to zirconia, the values ranged between 21.3 and 139.6 Ncm (maxilla) and between 55.9 and 111.8 Ncm (mandible) for corresponding time points (Table 3). Three studies reported significantly increased values for titanium compared to zirconia at single follow-up time points, whereas significantly higher values for titanium were associated with increased quantitative surface roughness characteristics. In detail, compared to sandblasted and acid-etched titanium implants (Sa = 1.20 μm), significantly decreased values were observed for machined zirconia implants (Sa = 0.1 μm) after 8 and 12 weeks and for sandblasted zirconia implants (Sa = 0.6 μm) after 8 weeks of healing. Interestingly, after

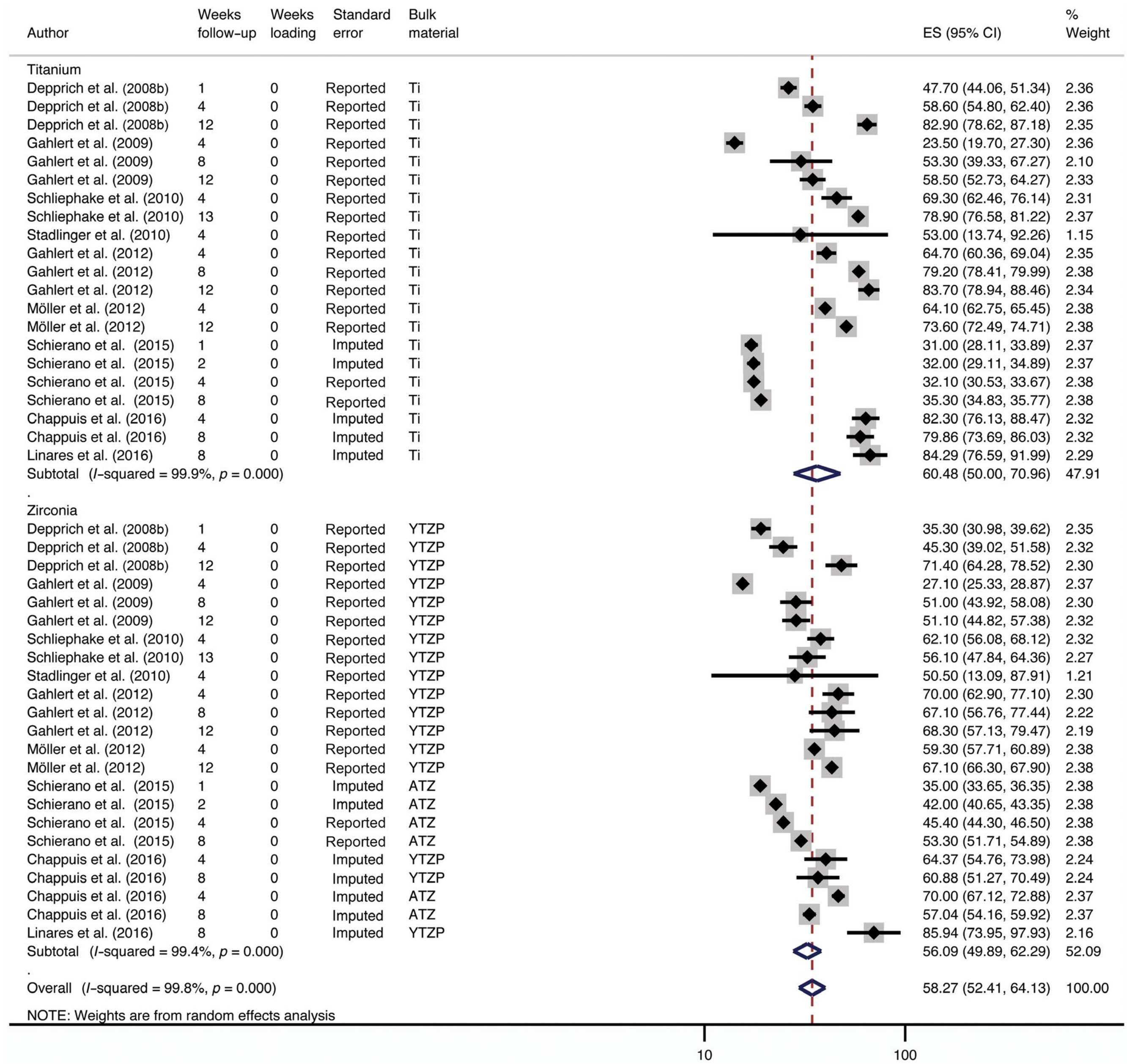

FIGURE 4 Forest plot of the BIC analysis of titanium and zirconia implants placed in pigs

4 weeks, the differences were statistically not significant (Gahlert et al., 2007). Similar results were observed by Schliephake et al. (2010) who evaluated significantly increased results for sandblasted and acid-etched titanium (Sa = 2.6 μm) compared to zirconia implants with a sandblasted (Sa = 1.0 μm) and with a sandblasted and acid-etched surface (Sa = 1.2 μm) after 4 and 13 weeks of healing in the mandible. In addition, significantly increased RTQ values were evaluated in another study for sandblasted and acid-etched titanium implants (Sa = 1.2 μm) compared to acid-etched zirconia implants (Sa = 0.6 μm) after 4 weeks of healing. However, after 8 and 12 weeks the differences were statistically not significant (Bormann et al., 2012). Moreover, two of the latter studies reported significant differences between the investigated zirconia implants, indicating higher RTQ values for implants with increased quantitative surface roughness (Gahlert et al., 2007; Schliephake et al., 2010).

The meta-analysis estimated a mean RTQ value of 127.8 Ncm (CI: 89.8–165.7) for titanium and 72.7 Ncm (CI: 52.6–92.7) for zirconia. For the included studies in pigs, a high degree of heterogeneity was evaluated (titanium: $I^2 = 99.2\%$, $p < 0.01$; zirconia: $I^2 = 98.1\%$, $p < 0.01$, Figure 8). The difference between zirconia and titanium was statistically significant ($p = 0.01$).

3.3.3 | Canines

Only one study evaluated RTQ on immediately loaded implants and the reported mean values ranged between 71.3 and 227.0 Ncm for titanium and between 64.1 and 240.2 Ncm for zirconia.

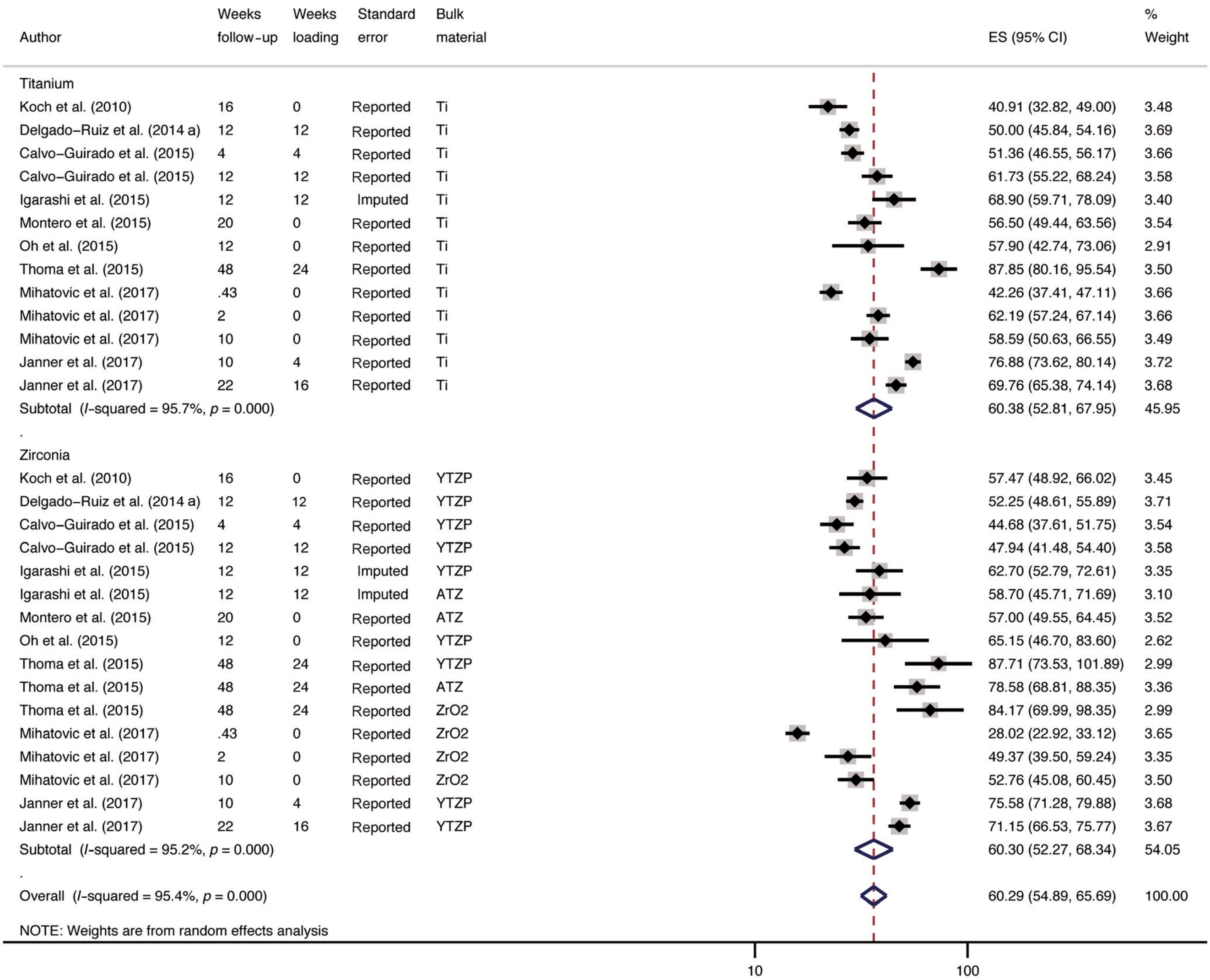

FIGURE 5 Forest plot of the BIC analysis of titanium and zirconia implants placed in canines

Significantly increased values for sandblasted and acid-etched titanium implants (Ra = 1.8 μm) compared to sandblasted zirconia implants (Ra = 1.3 μm) after 4, 8, and 12 weeks of immediate loading were observed. However, no significant differences were found in the same study between sandblasted and acid-etched titanium implants and zirconia implants with a laser-modified surface (Ra = 2.4 and 9.5 μm for titanium and zirconia, respectively). Higher quantitative surface roughness was associated with a statistically significant increase in RTQ for zirconia implants (Table 4; Delgado-Ruiz et al., 2014b).

3.3.4 | Sheep

Only one study was included in the present review. The authors reported significantly increased RTQ values for titanium implants with different surface topographies (Sa = 1.2–2.2 μm) compared to sandblasted and acid-etched zirconia implants (Sa = 1.1 μm) only after 8 but not after 2 and 4 weeks of unloaded healing ($p < 0.05$, Table 5, Ferguson et al., 2008).

3.3.5 | Meta-regression for RTQ including all animal models

Taking together all animal models, a mean overall RTQ value of 102.6 Ncm (CI: 81.5–123.6) was estimated for titanium and 71.5 Ncm (CI: 51.1–91.9) for zirconia. The meta-regression estimated that zirconia implants showed statistically significant reduced RTQ values compared to titanium implants ($p < 0.05$, Figure 9a). In contrast, zirconia implant bulk material (YTZP compared to ATZ) did not have any significant effect on RTQ. Moreover, a longer investigation and loading period was associated with a significantly increase in RTQ. Interestingly, conventionally loaded implants showed increased RTQ compared to unloaded implants. However, this difference was statistically not significant ($p > 0.05$, Figure 9a). In addition, the statistical

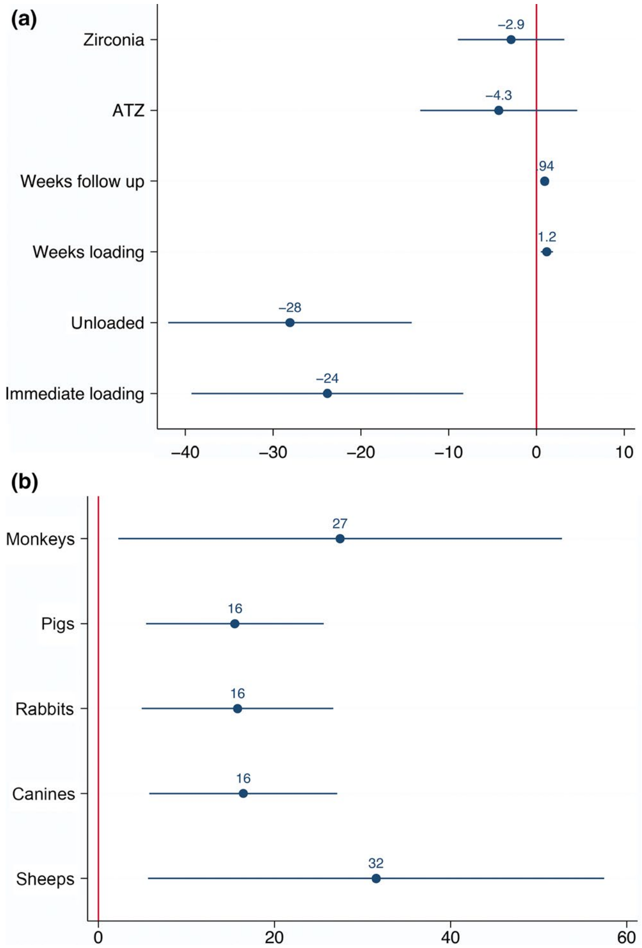

FIGURE 6 (a, b) Effects of single factors on BIC analysis of zirconia implants. Illustrated are the estimated coefficients, including 95% confidence intervals. Coefficients >0 imply a positive effect on BIC, and coefficients <0, a negative effect on BIC. All single 95% confidence intervals crossing the zero line imply no significant effect on BIC

analysis revealed that the individual animal model significantly influenced the evaluated RTQ outcomes ($p < 0.05$, Figure 9a,b).

3.4 | Push-in evaluation

Altogether, three studies in rats were included. For titanium, the values ranged between 7.3 and 49.0 N and between 9.3 and 45.8 N for zirconia after healing periods between 2 and 4 weeks (Table 1). In all included studies, significant differences between titanium and zirconia were reported at single follow-up time points. In two studies, titanium as well as zirconia implants with different surface characteristics were investigated. For both materials, increased surface roughness was correlated with increased PI values. In detail, significantly increased PI values after 4 weeks were observed for electrochemically anodized titanium (Ra = 0.3 μm) compared to machined zirconia implants (Ra = 0.1 μm). Interestingly, the difference between the same type of titanium implants compared to zirconia implants that were sintered using a rough mold (Ra = 0.4 μm) was statistically not significant (Kohal et al., 2009). In addition, significantly higher values were reported for electrochemically anodized titanium implants (Sa = 1.3 μm) compared to zirconia implants with a machined (Sa = 0.2 μm) or a sandblasted and acid-etched surface (Sa = 1.0 μm) after 4 weeks of healing. Interestingly, the sandblasted and acid-etched zirconia implants demonstrated significantly increased results compared to machined titanium implants (Sa = 0.6 μm; Kohal et al., 2013). In contrast to the findings of the latter study, in one investigation, significantly decreased PI values for zirconia implants sintered with pore-building polymers compared to electrochemically anodized titanium implants after 2 weeks of healing were associated with an increased surface roughness value (titanium: Sa = 1.3 μm; zirconia: Sa = 1.5 μm; Kohal et al., 2016).

Meta-analysis estimation revealed a mean PI value of 25.1 N (CI: 20.2–30.0) for titanium and 22.0 N (CI: 13.2–30.7) for zirconia. For the evaluated studies, a high degree of heterogeneity was evaluated (titanium: $I^2 = 81.6\%$, $p < 0.01$; zirconia: $I^2 = 98.5\%$, $p < 0.01$, Figure 10).

The meta-regression analysis showed that implant material (zirconia compared to titanium and YTZP compared to ATZ) did not have any significant effect on the evaluated PI values. In addition, a longer follow-up period was associated with an increase in PI. However, the differences were statistically not significant ($p > 0.05$, Figure 11).

3.5 | Soft tissue integration

With regard to quantitative and qualitative peri-implant soft tissue dimensions, six studies using three different animal models were included in the present review. Unloaded, immediately and conventionally loaded implants were investigated for follow-up periods between 8 and 56 weeks (Table 7).

Qualitatively, typical epithelial structures such as keratinized oral epithelium, not keratinized sulcular epithelium, and a thin layer of junctional epithelium in direct contact with the implant surface could be observed around zirconia implants. However, single observations reported a keratinized sulcular epithelium around unloaded tissue-level zirconia implants after 8 weeks of follow-up (Linares et al., 2016). Below the epithelial tissue, a connective tissue zone separates the bone tissue from the junctional epithelium (Igarashi et al., 2015; Koch, Weng, Kramer & Wagner, 2013; Kohal et al., 2004; Linares et al., 2016). In the connective tissue zone, collagen fibers are mainly aligned parallel to the zirconia implant surface (Igarashi et al., 2015).

Quantitatively, for zirconia, mean values of 1.4–3.6 mm, 0.5–1.6 mm, and 2.7–5.1 mm were reported for ETL, CTC, and BW dimensions. The mean values for titanium were 1.3–2.9 mm, 1.2–2.4 mm, and 2.8–5.2 mm, respectively, for corresponding parameters (Delgado-Ruiz et al., 2014a; Igarashi et al., 2015; Koch et al., 2013; Kohal et al., 2004; Linares et al., 2016; Thoma et al., 2015).

3.5.1 | Pigs

Only one study investigated unloaded implants after 8 weeks of healing. The authors evaluated comparable soft tissue parameters

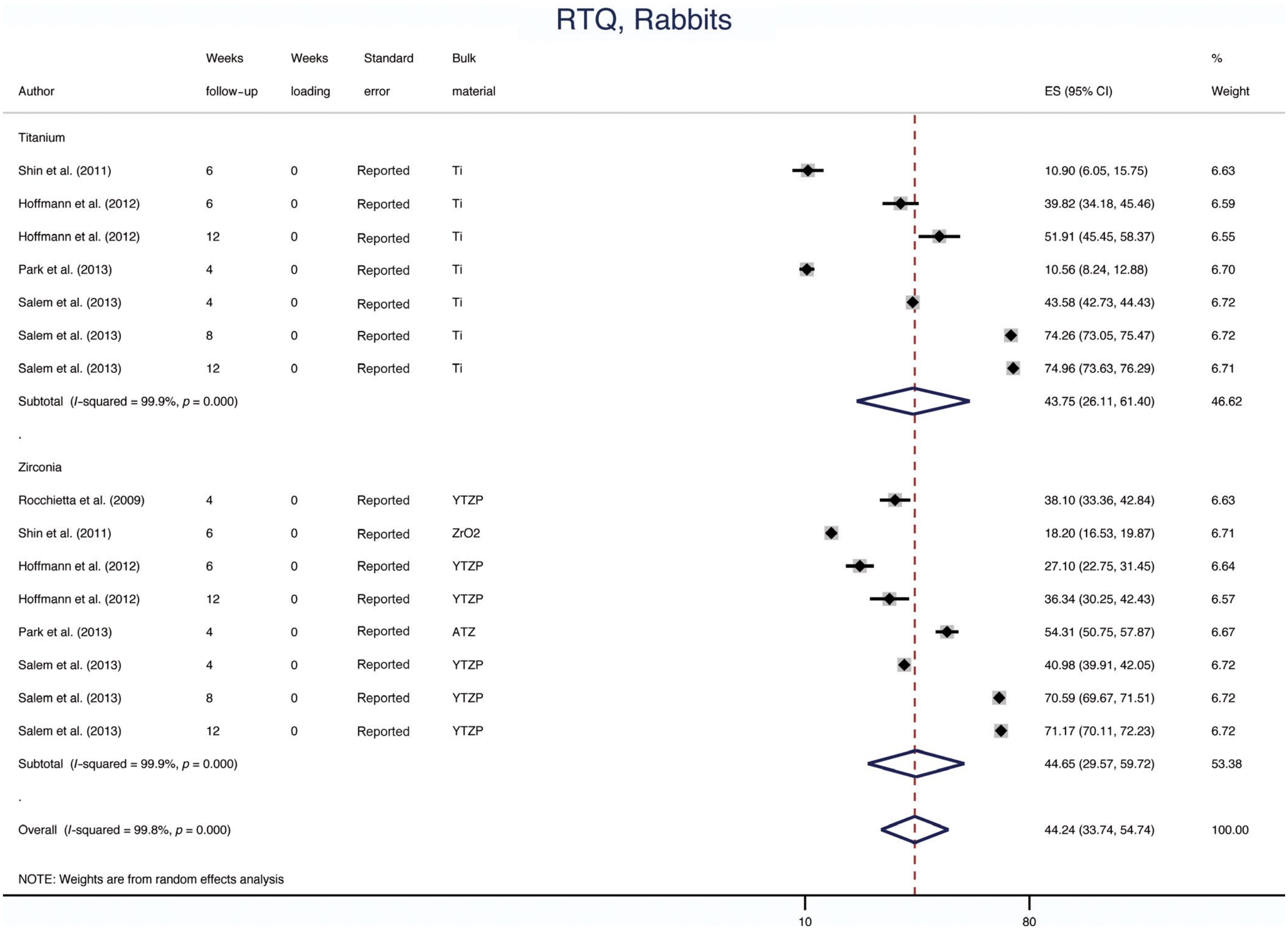

FIGURE 7 Forest plot of the RTQ analysis of titanium and zirconia implants placed in rabbits

resulting in similar ETL, CTC, and BW proportions for titanium (BW = 3.7 mm) and zirconia (BW = 3.6 mm). However, a significantly shorter sulcular and a longer junctional epithelium for zirconia (0.8 mm ± 0.3 and 1.2 mm ± 0.5, respectively) compared to titanium (1.4 mm ± 0.6 and 0.8 mm ± 0.5, respectively) were evaluated after 8 weeks. Moreover, the authors reported a significantly increased collagen organization on zirconia compared to titanium and concluded a more mature and pronounced soft tissue integration for this ceramic implant than for a standard titanium implant (Linares et al., 2016).

3.5.2 | Canines

Four studies evaluated unloaded as well as loaded implants. Comparable ETL, CTC, and BW values were reported for titanium and zirconia after follow-up periods between 8 and 56 weeks (Table 7). In detail, submerged or non-submerged healing did not have any significant effect on soft tissue integration and BW proportions of unloaded 1-piece tissue-level zirconia and titanium implants after 16 weeks of healing. Interestingly, the position of the micro-gap seemed to be relevant since the submerged implants that required a 0.5–1 mm deeper placement of the implant shoulder tended to have a lower mucosal height compared to non-submerged implants. However, this difference was statistically not significant ($p > 0.05$; Koch et al., 2013). In addition, unloading or immediate loading of non-submerged 1-piece tissue-level zirconia and 2-piece bone-level titanium implants did not have any significant effect ($p > 0.05$) on the total BW proportions after 12 weeks of healing. However, detailed information with regard to SD, JE, and CTC dimensions was not provided (Delgado-Ruiz et al., 2014a). Similar results were shown when different zirconia implant materials (yttria-stabilized zirconia implants compared to partially stabilized zirconia/alumina nanocomposite implants) were investigated and compared to titanium implants after 12 weeks of immediate loading in canines. No significant differences were reported between the evaluated implants with regard to ETL, CTC, and BW. Interestingly, increased epithelial tissue length was associated with decreased BW and CTC (Igarashi et al., 2015). Moreover, one study compared 1-piece tissue-level and 2-piece bone-level zirconia implants using 2-piece titanium tissue-level implants as control. Overall, after 48 weeks of follow-up and 24 weeks of loading, similar results with regard to ETL and BW were reported. However, the individual zirconia implant design had an effect on the peri-implant mucosal height (Thoma et al., 2015).

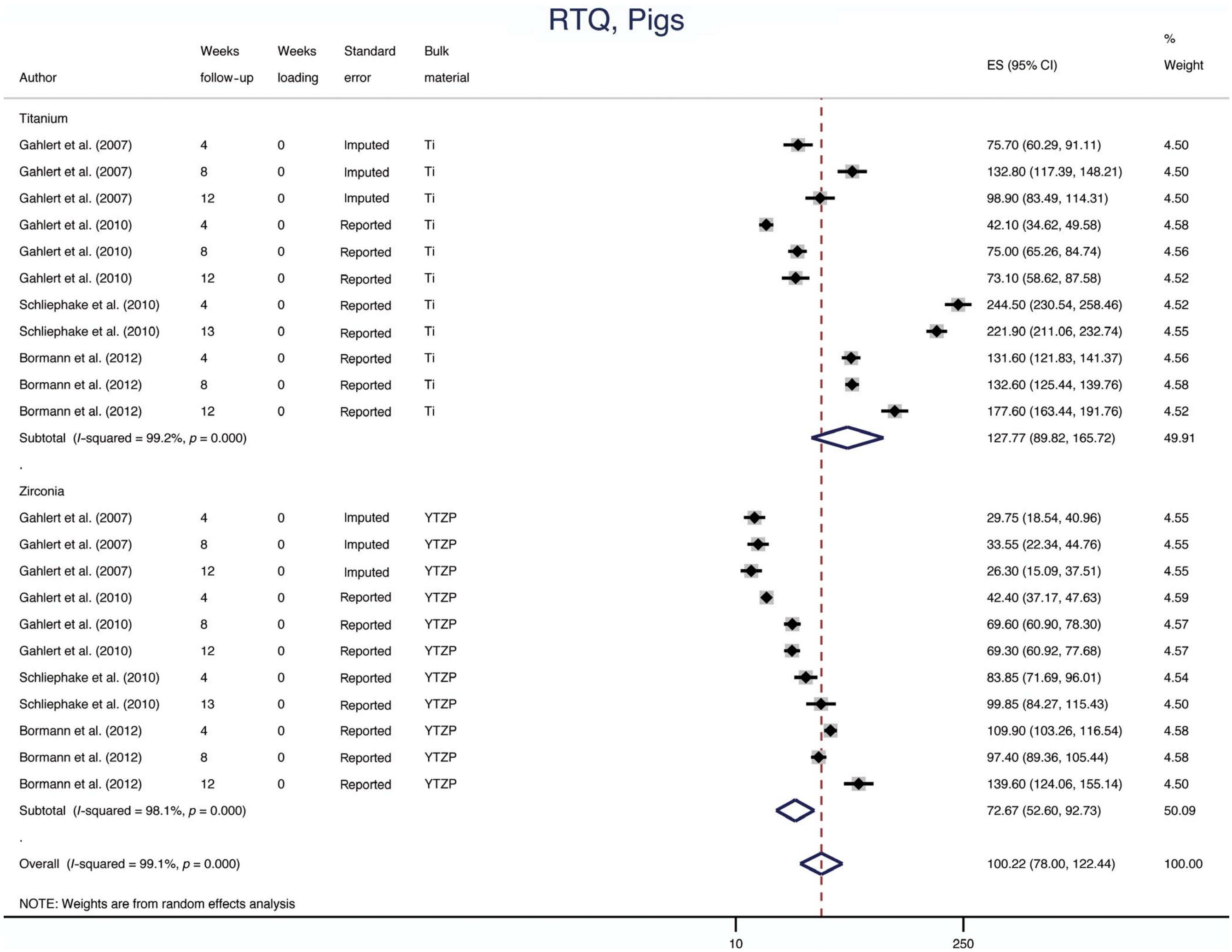

FIGURE 8 Forest plot of the RTQ analysis of titanium and zirconia implants placed in pigs

3.5.3 | Monkeys

One study investigated zirconia and titanium implants with a 2-piece tissue-level design, respectively. The authors reported no significant differences between both types of implants after 56 weeks of follow-up and 20 weeks of functional loading ($p > 0.05$). However, zirconia implants revealed decreased CTC (1.5 mm) and BW (4.5 mm) but similar ETL (2.9 mm) proportions compared to titanium (CTC: 2.4 mm; BW: 5.2 mm; ETL: 2.9 mm (Kohal et al., 2004)).

3.5.4 | Meta-analysis and meta-regression for BW including all animal models

The meta-analysis for BW proportions estimated mean values of 3.5 mm (CI: 2.9–4.2) and 3.2 mm (CI: 2.7–3.7) for titanium and zirconia, respectively. For the included studies, a high degree of heterogeneity was evaluated for titanium (I^2 = 92.9%, $p < 0.01$) and for zirconia (I^2 = 93.0%, $p < 0.01$, Figure 12).

The meta-regression showed that implant material (zirconia compared to titanium and YTP compared to ATZ) and time period of follow-up respectively loading period did not have any significant effect on the reported BW dimensions ($p > 0.05$, Figure 13). Moreover, unloaded and conventionally loaded protocols showed similar BW values. Interestingly, significantly increased BW dimensions were evaluated for immediately loaded compared to conventionally loaded implants ($p < 0.05$, Figure 13).

4 | DISCUSSION

BIC was evaluated as one of the primary outcomes. Statistically significant differences between titanium and zirconia were observed in only 10 out of the 31 included studies, whereas significantly higher values were reported for unloaded zirconia (Aboushelib et al., 2013b; Park et al., 2013; Salem et al., 2013; Schierano et al., 2015; Siddiqi et al., 2016) as well as for unloaded titanium implants (Chappuis et al., 2016; Kohal et al., 2013, 2016; Lee et al., 2009; Schliephake et al., 2010). Surprisingly, when directly comparing both materials, similar BIC values were not always associated with equivalent quantitative surface topography characteristics (Gahlert

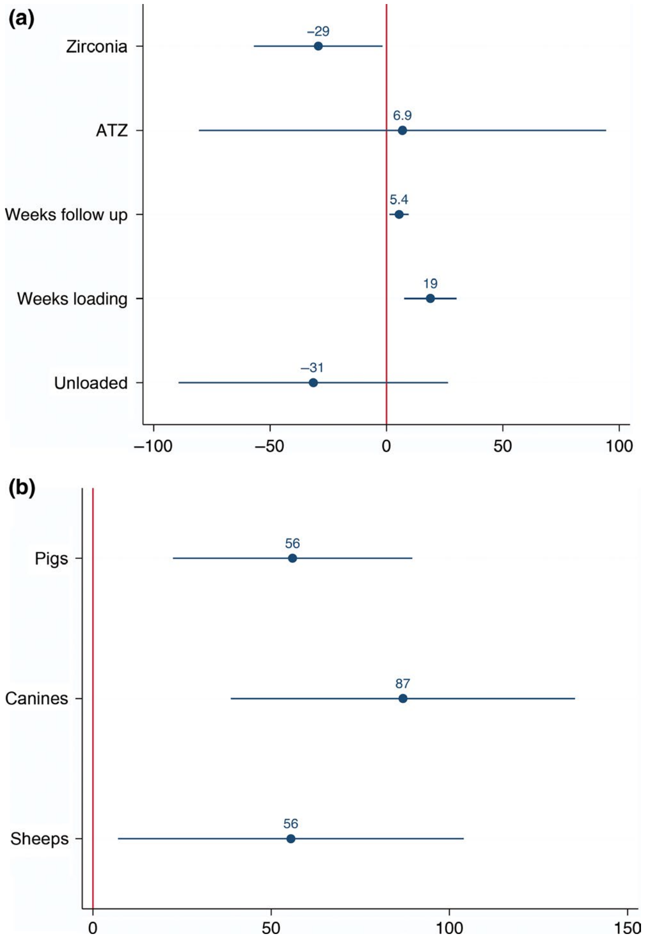

FIGURE 9 (a, b) Effects of single factors on RTQ analysis of zirconia implants. Illustrated are the estimated coefficients, including 95% confidence intervals. Coefficients >0 imply a positive effect on RTQ, and coefficients <0, a negative effect on RTQ. All single 95% confidence intervals crossing the zero line imply no significant effect on RTQ

et al., 2009, 2012; Janner et al., 2018). Thus, also zirconia implants with decreased surface roughness values compared to control titanium implants can reach similar BIC results. This finding may be based on a high osseointegrative/osseoconductive capacity of zirconia implants. The meta-analyses and meta-regressions revealed no significant differences between titanium and zirconia within the individually evaluated animal models as well as when the different animal models were combined (titanium: 59.1%, CI: 53.3–64.8; zirconia: 55.9%, CI: 51.6–60.1, Figures 2–6). Thus, both types of implant materials showed a similar osseous integration from a histomorphometrical point of view and not only quantitative surface roughness but also the manufacture processes creating micro-rough surface topographies seem to be important factors for the osseous integration process of zirconia implants. The evaluated results are in accordance with previously published systematic reviews, which reported similar mean BIC values for zirconia implants (Andreiotelli et al., 2009b; Pieralli et al., 2018; Wenz, Bartsch, Wolfart & Kern, 2008). Presently, the meta-regression showed that implant loading protocols, length of follow-up, respectively, loading period, and animal type had significant effects on the evaluated BIC outcomes. Thus, comparing results from experimental studies using different animal models is rather controversial. However, it should be noted that zirconia tended to demonstrate lower BIC values compared to titanium according to the results of the meta-regressions.

As additional primary outcomes, RTQ and PI were analyzed. Combining all animal models, the statistical analysis revealed significantly decreased RTQ values for zirconia compared to titanium. However, it must be noticed that the type of animal model and the length of the follow-up and loading period had significant effects on the RTQ outcomes. Regarding the individual animal models, contradictory results were evaluated, whereas significant differences between titanium and zirconia could only be evaluated for implants placed in pigs. In contrast, the differences between both materials were statistically not significant for implants placed in rabbits. Thus, the reported results might not just be based on material characteristics—titanium compared to zirconia—but also on the individual study protocol and animal species. Similar findings were reported in a previously published meta-analysis (Pieralli et al., 2018). Moreover, significant differences between both materials were also attributed to surface roughness and not to material characteristics, indicating reduced RTQ values for implants with decreased quantitative implant surface characteristics (Bormann et al., 2012; Delgado-Ruiz et al., 2014b; Ferguson et al., 2008; Gahlert et al., 2007; Park et al., 2013; Schliephake et al., 2010). Interestingly, contradictory results were evaluated in single studies. The authors reported that zirconia implants with decreased surface roughness could reach equivalent RTQ values compared to control titanium implants with increased surface roughness (Bormann et al., 2012; Gahlert et al., 2010). A previously published meta-analysis evaluated no significant differences between titanium and zirconia implants regarding RTQ combining different animal models. However, the individual animal models had significant effects on the reported outcomes (Pieralli et al., 2018).

With regard to PI evaluations, the presently performed meta-analysis estimated comparable results for unloaded titanium and zirconia implants, indicating similar biomechanical shear strength for both materials. A previously published meta-analysis reported mean values of more than 50 N (Pieralli et al., 2018). However, the latter review included more studies and did not exclusively focus on experiments directly comparing titanium and zirconia implants. In the present review, significant PI differences between titanium and zirconia were related to surface topography characteristics and not to material properties (Kohal et al., 2009, 2013). Moreover, one study reported that significantly decreased PI values for zirconia compared to titanium were associated with an increased surface roughness value (Kohal et al., 2016). However, this contradictory finding might be explained by a different push-in testing protocol that was used in the latter study and not by surface topography characteristics of the investigated implants.

The peri-implant soft tissue integration was evaluated as secondary outcome. For titanium implants, experimental studies

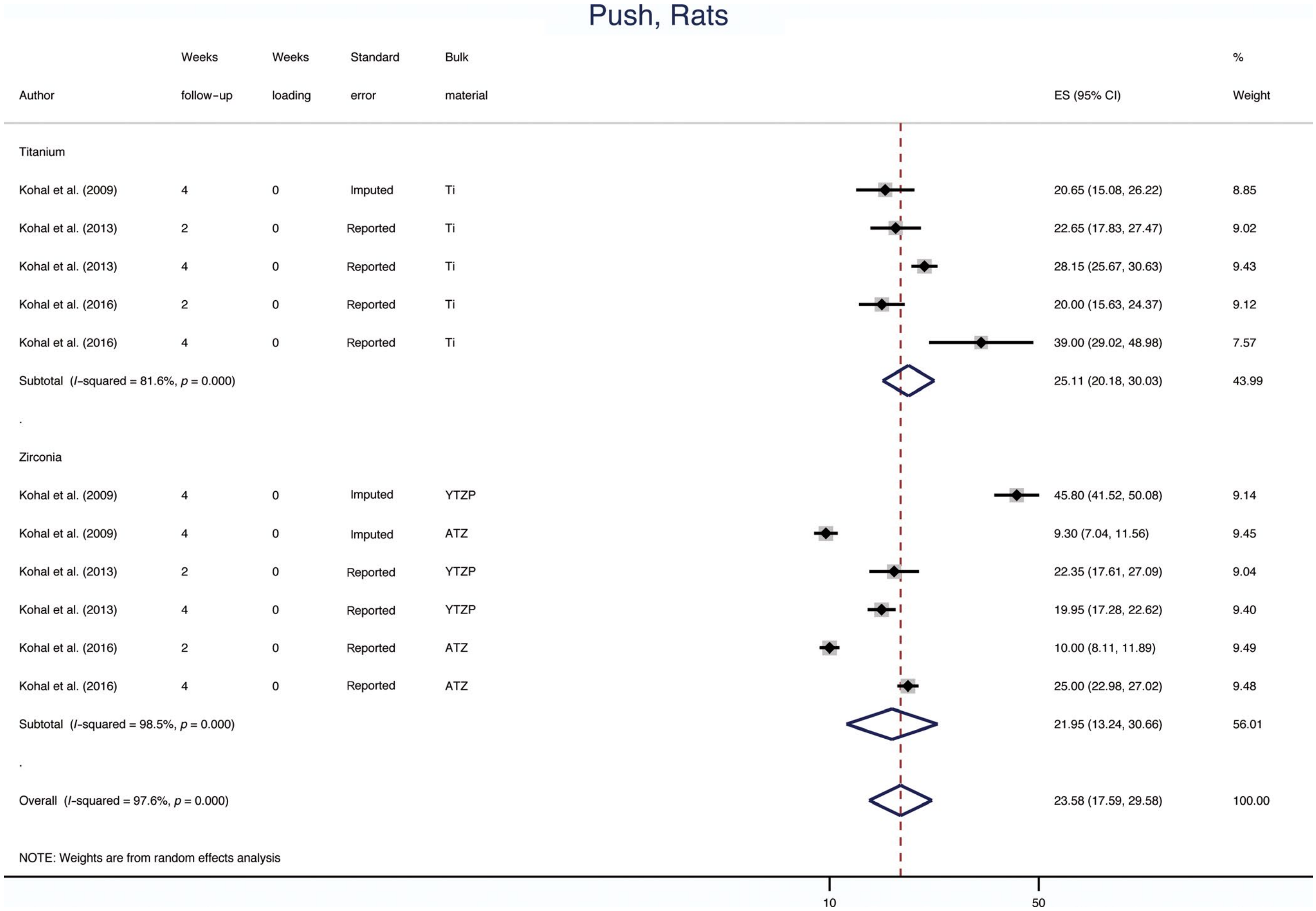

FIGURE 10 Forest plot of the PI analysis of titanium and zirconia implants placed in rats

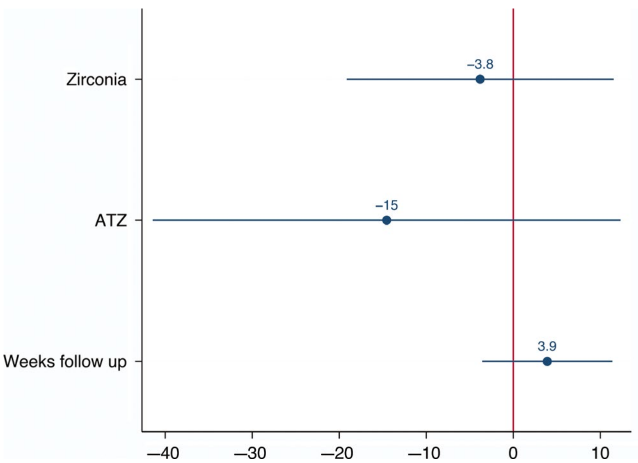

FIGURE 11 Effects of single factors on PI analysis of zirconia implants placed in rats. Illustrated are the estimated coefficients, including 95% confidence intervals. Coefficients >0 imply a positive effect on PI, and coefficients <0, a negative effect on PI. All single 95% confidence intervals crossing the zero line imply no significant effect on PI

have reported that the epithelial tissue consists of a keratinized oral epithelium, which turns into a not keratinized sulcular epithelium at the top of the papilla, and a junctional epithelium in direct contact with the implant surface. Below the junctional epithelium, there is a gingival connective tissue that separates bone from epithelium (Cochran et al., 1997). Same qualitative results were reported in the present review for 1- and 2-piece tissue-level zirconia implants, indicating similar qualitative soft tissue integration (Igarashi et al., 2015; Koch et al., 2013; Kohal et al., 2004; Linares et al., 2016). However, faster maturation processes of epithelial and connective tissues around zirconia implants were assumed in single observations indicated by a shorter sulcular epithelium and a higher grade of collagen organization (Linares et al., 2016). The presently performed meta-analysis estimated a similar quantitative soft tissue integration for zirconia compared to titanium implants. In addition, the meta-regression showed that implant material and an increased follow-up respectively loading period did not have significant effects on BW dimensions. Consequently, the BW is a stable structure that forms around both types of materials. Interestingly, immediate loading caused a statistically significant increase in BW compared to conventional loading and might be explained with a faster soft tissue maturation process for immediately loaded implants. However, it must be noticed that BW dimensions are not just dependent on material properties but also on implant design—tissue level compared to bone level (Hermann et al.,

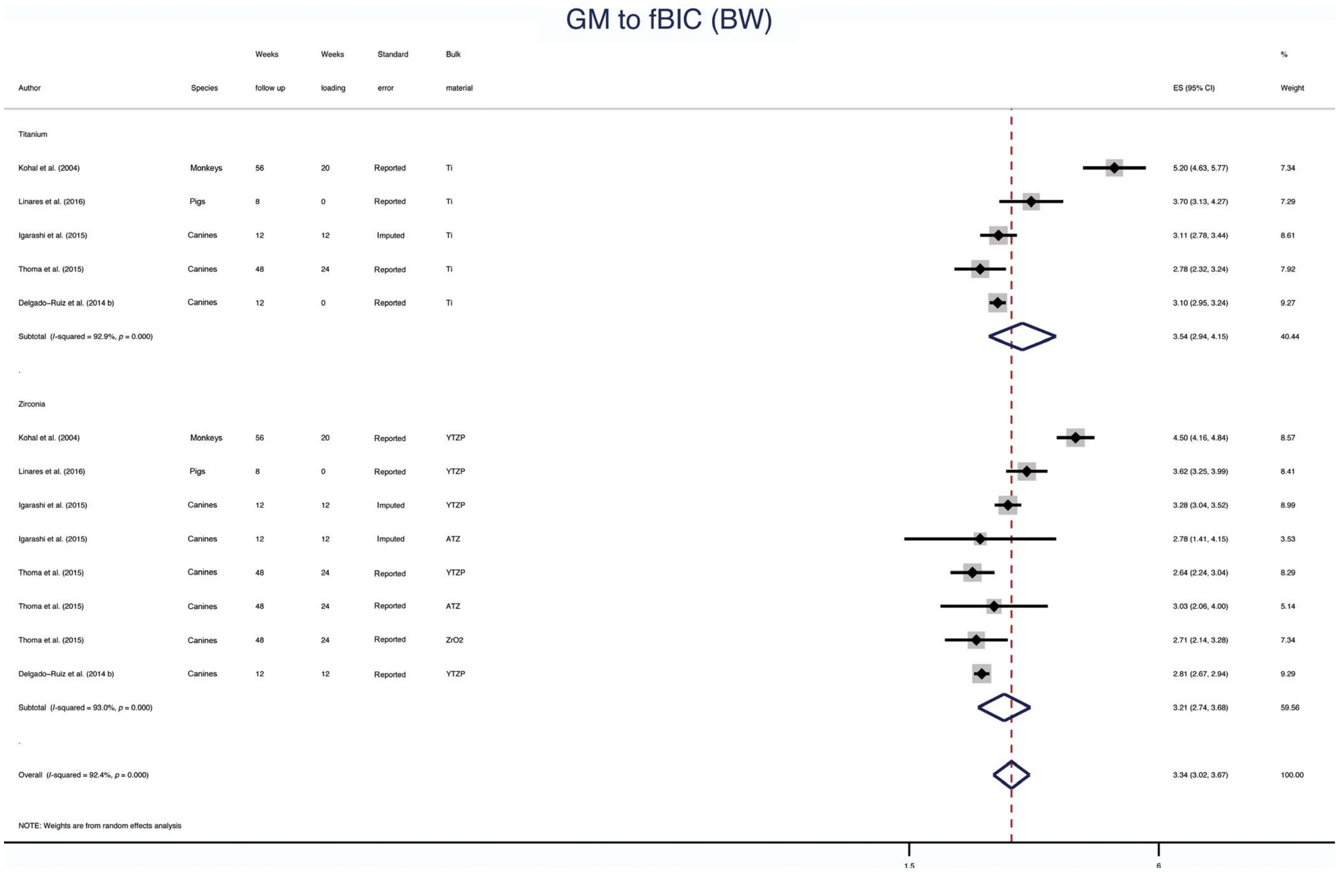

FIGURE 12 Forest plot of the BW analysis of titanium and zirconia implants placed in all included animal models [Colour figure can be viewed at wileyonlinelibrary.com]

2001). Additionally, the present review has shown that BW dimensions are independent from loading (unloading or immediate loading) and surgical protocol (submerged or non-submerged healing) but dependent on implant design and position of the micro-gap between implant and prosthetic suprastructure. Same observations were previously reported in experimental studies investigating titanium implants (Bakaeen, Quinlan, Schoolfield, Lang & Cochran, 2009; Hermann, Buser, Schenk, Higginbottom & Cochran, 2000; Hermann et al., 2001).

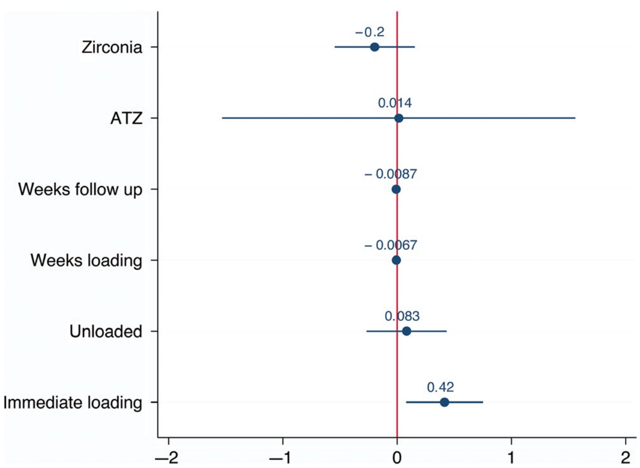

FIGURE 13 Effects of single factors on BW analysis of zirconia implants. Illustrated are the estimated coefficients, including 95% confidence intervals. Coefficients >0 imply a positive effect on BW, and coefficients <0, a negative effect on BW. All single 95% confidence intervals crossing the zero line imply no significant effect on BW

As limiting factor for the present review, it must be noticed that implant surface characteristics were not considered as confounding factors regarding the meta-analyses since quantitative surface roughness parameters were infrequently reported in the included studies. This lack of information with regard to the implant surface makes a comparison and interpretation of the results between specific experimental investigations hardly possible, since a machined surface in one study could be equivalent with a moderately roughened surface in another. Similar lack of information was reported in previous systematic reviews on the preclinical performance of zirconia implants (Hafezeqoran & Koodaryan, 2017; Manzano et al.,2014). Moreover, it must be noted that a comparison of single surface roughness parameters reported in different studies is not reasonable since standards and techniques of the used surface metrology may substantially vary and a successful osseointegration is not exclusively linked to one particular surface feature (Jarmar et al., 2008; Wennerberg & Albrektsson, 2010).

5 | CONCLUSIONS

Micro-rough zirconia implants demonstrate a similar osseointegrative capacity compared to micro-rough titanium implants under unloaded and loaded conditions. However, titanium tended to show a faster initial osseointegration process compared to zirconia. With regard to peri-implant soft tissues, qualitatively and quantitatively similar soft tissue integration was reported for zirconia compared to titanium implants. Thus, similar physiological processes might be supposed for both materials with regard to morphogenesis of peri-implant soft and hard tissues. Importantly, it must be considered that not only material characteristics—ceramics compared to titanium—but also predominantly the animal species and the study protocol can significantly influence the results from experimental studies.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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REFERENCES

Aboushelib, M. N., Osman, E., Jansen, I., Everts, V., & Feilzer, A. J. (2013a). Influence of a nanoporous zirconia implant surface of on cell viability of human osteoblasts. *Journal of Prosthodontics*, *22*, 190–195. https://doi.org/10.1111/j.1532-849X.2012.00920.x

Aboushelib, M. N., Salem, N. A., Taleb, A. L., & El Moniem, N. M. (2013b). Influence of surface nano-roughness on osseointegration of zirconia implants in rabbit femur heads using selective infiltration etching technique. *Journal of Oral Implantology*, *39*, 583–590. https://doi.org/10.1563/AAID-JOI-D-11-00075

Albrektsson, T., Branemark, P. I., Hansson, H. A., & Lindstrom, J. (1981). Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. *Acta Orthopaedica Scandinavica*, *52*, 155–170. https://doi.org/10.3109/17453678108991776

Bakaeen, L., Quinlan, P., Schoolfield, J., Lang, N. P., & Cochran, D. L. (2009). The biologic width around titanium implants: Histometric analysis of the implantogingival junction around immediately and early loaded implants. *The International Journal of Periodontics & Restorative Dentistry*, *29*, 297–305.

Bormann, K. H., Gellrich, N. C., Kniha, H., Dard, M., Wieland, M., & Gahlert, M. (2012). Biomechanical evaluation of a microstructured zirconia implant by a removal torque comparison with a standard tisla implant. *Clinical Oral Implants Research*, *23*, 1210–1216. https://doi.org/10.1111/j.1600-0501.2011.02291.x

Branemark, P. I., Adell, R., Breine, U., Hansson, B. O., Lindstrom, J., & Ohlsson, A. (1969). Intra-osseous anchorage of dental prostheses. I. Experimental studies. *Scandinavian Journal of Plastic and Reconstructive Surgery*, *3*, 81–100. https://doi.org/10.3109/02844316909036699

Buser, D., Janner, S. F., Wittneben, J. G., Bragger, U., Ramseier, C. A., & Salvi, G. E. (2012). 10-year survival and success rates of 511 titanium implants with a sandblasted and acid-etched surface: A retrospective study in 303 partially edentulous patients. *Clinical Implant Dentistry and Related Research*, *14*, 839–851. https://doi.org/10.1111/j.1708-8208.2012.00456.x

Buser, D., Nydegger, T., Oxland, T., Cochran, D. L., Schenk, R. K., Hirt, H. P., … Nolte, L. P. (1999). Interface shear strength of titanium implants with a sandblasted and acid-etched surface: A biomechanical study in the maxilla of miniature pigs. *Journal of Biomedical Materials Research*, *45*, 75–83. https://doi.org/10.1002/(ISSN)1097-4636

Buser, D., Schenk, R. K., Steinemann, S., Fiorellini, J. P., Fox, C. H., & Stich, H. (1991). Influence of surface characteristics on bone integration of titanium implants. A histomorphometric study in miniature pigs. *Journal of Biomedical Materials Research*, *25*, 889–902. https://doi.org/10.1002/(ISSN)1097-4636

Chappuis, V., Cavusoglu, Y., Gruber, R., Kuchler, U., Buser, D., & Bosshardt, D. D. (2016). Osseointegration of zirconia in the presence of multinucleated giant cells. *Clinical Implant Dentistry and Related Research*, *18*, 686–698. https://doi.org/10.1111/cid.12375

Cochran, D. L., Hermann, J. S., Schenk, R. K., Higginbottom, F. L., & Buser, D. (1997). Biologic width around titanium implants. A histometric analysis of the implanto-gingival junction around unloaded and loaded nonsubmerged implants in the canine mandible. *Journal of Periodontology*, *68*, 186–198. https://doi.org/10.1902/jop.1997.68.2.186

De Wijs, F. L., Van Dongen, R. C., De Lange, G. L., & De Putter, C. (1994). Front tooth replacement with tubingen (frialit) implants. *Journal of Oral Rehabilitation*, *21*, 11–26. https://doi.org/10.1111/j.1365-2842.1994.tb01120.x

Degidi, M., Artese, L., Scarano, A., Perrotti, V., Gehrke, P., & Piattelli, A. (2006). Inflammatory infiltrate, microvessel density, nitric oxide synthase expression, vascular endothelial growth factor expression, and proliferative activity in peri-implant soft tissues around titanium and zirconium oxide healing caps. *Journal of Periodontology*, *77*, 73–80. https://doi.org/10.1902/jop.2006.77.1.73

Delgado-Ruiz, R. A., Calvo-Guirado, J. L., Abboud, M., Ramirez-Fernandez, M. P., Mate-Sanchez de Val, J. E., Negri, B., & Rothamel, D. (2014a). Histologic and histomorphometric behavior of micro-grooved zirconia dental implants with immediate loading. *Clinical Implant Dentistry and Related Research*, *16*, 856–872. https://doi.org/10.1111/cid.12069

Delgado-Ruiz, R. A., Markovic, A., Calvo-Guirado, J. L., Lazic, Z., Piattelli, A., Boticelli, D., … Misic, T. (2014b). Implant stability and marginal bone level of microgrooved zirconia dental implants: A 3-month experimental study on dogs. *Vojnosanitetski Pregled.*, *71*, 451–461. https://doi.org/10.2298/VSP121003034D

Depprich, R., Zipprich, H., Ommerborn, M., Naujoks, C., Wiesmann, H. P., Kiattavorncharoen, S., … Handschel, J. (2008b). Osseointegration of zirconia implants compared with titanium: An in vivo study. *Head & Face Medicine*, *4*, 30. https://doi.org/10.1186/1746-160X-4-30

Ferguson, S. J., Langhoff, J. D., Voelter, K., von Rechenberg, B., Scharnweber, D., Bierbaum, S., … Schlottig, F. (2008). Biomechanical comparison of different surface modifications for dental implants. *International Journal of Oral & Maxillofacial Implants*, *23*, 1037–1046.

Gahlert, M., Gudehus, T., Eichhorn, S., Steinhauser, E., Kniha, H., & Erhardt, W. (2007). Biomechanical and histomorphometric comparison between zirconia implants with varying surface textures and a titanium implant in the maxilla of miniature pigs. *Clinical Oral Implants Research*, *18*, 662–668. https://doi.org/10.1111/j.1600-0501.2007.01401.x

Gahlert, M., Roehling, S., Sprecher, C. M., Kniha, H., Milz, S., & Bormann, K. (2012). In vivo performance of zirconia and titanium implants: A histomorphometric study in mini pig maxillae. *Clinical Oral Implants Research*, *23*, 281–286. https://doi.org/10.1111/j.1600-0501.2011.02157.x

Gahlert, M., Rohling, S., Wieland, M., Eichhorn, S., Kuchenhoff, H., & Kniha, H. (2010). A comparison study of the osseointegration of zirconia and titanium dental implants. A biomechanical evaluation in the maxilla of pigs. *Clinical Implant Dentistry and Related Research*, *12*, 297–305. https://doi.org/10.1111/j.1708-8208.2009.00168.x

Gahlert, M., Rohling, S., Wieland, M., Sprecher, C. M., Kniha, H., & Milz, S. (2009). Osseointegration of zirconia and titanium dental implants: A histological and histomorphometrical study in the maxilla of pigs. *Clinical Oral Implants Research*, *20*, 1247–1253. https://doi.org/10.1111/j.1600-0501.2009.01734.x

Hermann, J. S., Buser, D., Schenk, R. K., Higginbottom, F. L., & Cochran, D. L. (2000). Biologic width around titanium implants. A physiologically formed and stable dimension over time. *Clinical Oral Implants Research*, *11*, 1–11. https://doi.org/10.1034/j.1600-0501.2000.011001001.x

Hermann, J. S., Buser, D., Schenk, R. K., Schoolfield, J. D., & Cochran, D. L. (2001). Biologic width around one- and two-piece titanium implants. *Clinical Oral Implants Research*, *12*, 559–571. https://doi.org/10.1034/j.1600-0501.2001.120603.x

Hoffmann, O., Angelov, N., Gallez, F., Jung, R. E., & Weber, F. E. (2008). The zirconia implant-bone interface: A preliminary histologic evaluation in rabbits. *International Journal of Oral & Maxillofacial Implants*, *23*, 691–695.

Hoffmann, O., Angelov, N., Zafiropoulos, G. G., & Andreana, S. (2012). Osseointegration of zirconia implants with different surface characteristics: An evaluation in rabbits. *International Journal of Oral & Maxillofacial Implants*, *27*, 352–358.

Igarashi, K., Nakahara, K., Haga-Tsujimura, M., Kobayashi, E., & Watanabe, F. (2015). Hard and soft tissue responses to three different implant materials in a dog model. *Dental Materials Journal*, *34*, 692–701. https://doi.org/10.4012/dmj.2014-361

Janner, S. F. M., Gahlert, M., Bosshardt, D. D., Roehling, S., Milz, S., Higginbottom, F., … Cochran, D. L. (2018). Bone response to functionally loaded, two-piece zirconia implants: A preclinical histometric study. *Clinical Oral Implants Research*, *29*, 277–289. https://doi.org/10.1111/clr.13112

Jarmar, T., Palmquist, A., Branemark, R., Hermansson, L., Engqvist, H., & Thomsen, P. (2008). Characterization of the surface properties of commercially available dental implants using scanning electron microscopy, focused ion beam, and high-resolution transmission electron microscopy. *Clinical Implant Dentistry and Related Research*, *10*, 11–22. https://doi.org/10.1111/j.1708-8208.2007.00056.x

Kajiwara, N., Masaki, C., Mukaibo, T., Kondo, Y., Nakamoto, T., & Hosokawa, R. (2015). Soft tissue biological response to zirconia and metal implant abutments compared with natural tooth: Microcirculation monitoring as a novel bioindicator. *Implant Dentistry*, *24*, 37–41.

Koch, F. P., Weng, D., Kramer, S., Biesterfeld, S., Jahn-Eimermacher, A., & Wagner, W. (2010). Osseointegration of one-piece zirconia implants compared with a titanium implant of identical design: A histomorphometric study in the dog. *Clinical Oral Implants Research*, *21*, 350–356. https://doi.org/10.1111/j.1600-0501.2009.01832.x

Koch, F. P., Weng, D., Kramer, S., & Wagner, W. (2013). Soft tissue healing at one-piece zirconia implants compared to titanium and peek implants of identical design: A histomorphometric study in the dog. *The International Journal of Periodontics and Restorative Dentistry*, *33*, 669–677. https://doi.org/10.11607/prd.1043

Kohal, R. J., Bachle, M., Att, W., Chaar, S., Altmann, B., Renz, A., & Butz, F. (2013). Osteoblast and bone tissue response to surface modified zirconia and titanium implant materials. *Dental Materials*, *29*, 763–776. https://doi.org/10.1016/j.dental.2013.04.003

Kohal, R. J., Bachle, M., Renz, A., & Butz, F. (2016). Evaluation of alumina toughened zirconia implants with a sintered, moderately rough surface: An experiment in the rat. *Dental Materials*, *32*, 65–72. https://doi.org/10.1016/j.dental.2015.10.008

Kohal, R. J., Weng, D., Bachle, M., & Strub, J. R. (2004). Loaded custom-made zirconia and titanium implants show similar osseointegration: An animal experiment. *Journal of Periodontology*, *75*, 1262–1268. https://doi.org/10.1902/jop.2004.75.9.1262

Kohal, R. J., Wolkewitz, M., Hinze, M., Han, J. S., Bachle, M., & Butz, F. (2009). Biomechanical and histological behavior of zirconia implants: An experiment in the rat. *Clinical Oral Implants Research*, *20*, 333–339. https://doi.org/10.1111/j.1600-0501.2008.01656.x

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*, 159–174. https://doi.org/10.2307/2529310

Lee, J., Sieweke, J. H., Rodriguez, N. A., Schupbach, P., Lindstrom, H., Susin, C., & Wikesjo, U. M. (2009). Evaluation of nano-technology-modified zirconia oral implants: A study in rabbits. *Journal of Clinical Periodontology*, *36*, 610–617. https://doi.org/10.1111/j.1600-051X.2009.01423.x

Linares, A., Grize, L., Munoz, F., Pippenger, B. E., Dard, M., Domken, O., & Blanco-Carrion, J. (2016). Histological assessment of hard and soft tissues surrounding a novel ceramic implant: A pilot study in the minipig. *Journal of Clinical Periodontology*, *43*, 538–546. https://doi.org/10.1111/jcpe.12543

Mihatovic, I., Golubovic, V., Becker, J., & Schwarz, F. (2017). Bone tissue response to experimental zirconia implants. *Clinical Oral Investigations*, *21*, 523–532. https://doi.org/10.1007/s00784-016-1904-2

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., … Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015 statement. *Systematic Reviews 4*, 1. https://doi.org/10.1186/2046-4053-4-1

Moller, B., Terheyden, H., Acil, Y., Purcz, N. M., Hertrampf, K., Tabakov, A., … Wiltfang, J. (2012). A comparison of biocompatibility and osseointegration of ceramic and titanium implants: An in vivo and in vitro study. *International Journal of Oral & Maxillofacial Surgery*, *41*, 638–645. https://doi.org/10.1016/j.ijom.2012.02.004

Montero, J., Bravo, M., Guadilla, Y., Portillo, M., Blanco, L., Rojo, R., … Lopez-Valverde, A. (2015). Comparison of clinical and histologic outcomes of zirconia versus titanium implants placed in fresh sockets: A 5-month study in beagles. *International Journal of Oral & Maxillofacial Implants*, *30*, 773–780. https://doi.org/10.11607/jomi.3668

Oh, G. J., Ban, J. S., Lim, H. P., Yun, K. D., Lee, K. M., Vang, M. S., … Fisher, J. G. (2015). Analysis of removal torque of injection molded zirconia implants; an experimental study on beagles. *Journal of Nanoscience and Nanotechnology*, *15*, 339–341. https://doi.org/10.1166/jnn.2015.8376

Park, Y. S., Chung, S. H., & Shon, W. J. (2013). Peri-implant bone formation and surface characteristics of rough surface zirconia implants manufactured by powder injection molding technique in rabbit tibiae. *Clinical Oral Implants Research*, *24*, 586–591. https://doi.org/10.1111/j.1600-0501.2012.02468.x

Pieralli, S., Kohal, R. J., Hernandez, E. L., Doerken, S., & Spies, B. C. (2018). Osseointegration of zirconia dental implants in animal investigations: A systematic review and meta-analysis. *Dental Materials*, *34*, 171–182. https://doi.org/10.1016/j.dental.2017.10.008

Rocchietta, I., Fontana, F., Addis, A., Schupbach, P., & Simion, M. (2009). Surface-modified zirconia implants: Tissue response in rabbits. *Clinical Oral Implants Research*, *20*, 844–850. https://doi.org/10.1111/j.1600-0501.2009.01727.x

Roccuzzo, M., Bonino, L., Dalmasso, P., & Aglietta, M. (2014). Long-term results of a three arms prospective cohort study on implants in periodontally compromised patients: 10-year data around sandblasted and acid-etched (sla) surface. *Clinical Oral Implants Research*, *25*, 1105–1112. https://doi.org/10.1111/clr.12227

Roehling, S., Astasov-Frauenhoffer, M., Hauser-Gerspach, I., Braissant, O., Woelfler, H., Waltimo, T., … Gahlert, M. (2017). In vitro biofilm formation on titanium and zirconia implant surfaces. *Journal of Periodontology*, *88*, 298–307. https://doi.org/10.1902/jop.2016.160245

Roehling, S., Meng, B., & Cochran, D. (2015) Sandblasted and acid etched implant surfaces with or without high surface free energy – experimental and clinical background In A. Wennerberg, T. Albrektsson &

R. Jimbo (Eds.), *Implant surfaces and their biological and clinical impact* (pp. 93–136). Berlin, Heidelberg: Springer Verlag.

Roehling, S., Schlegel, K. A., Woelfler, H., & Gahlert, M. (2018). Performance and outcome of zirconia dental implants in clinical studies—A meta-analysis. *Clinical Oral Implants Research*, *29*(Suppl. 16), 135–153. https://doi.org/10.1111/clr.13352

Salem, N. A., Abo Taleb, A. L., & Aboushelib, M. N. (2013). Biomechanical and histomorphometric evaluation of osseointegration of fusion-sputtered zirconia implants. *Journal of Prosthodontics*, *22*, 261–267. https://doi.org/10.1111/j.1532-849X.2012.00940.x

Schardt, C., Adams, M. B., Owens, T., Keitz, S., & Fontelo, P. (2007). Utilization of the pico framework to improve searching pubmed for clinical questions. *BMC Medical Informatics and Decision Making*, *7*, 16. https://doi.org/10.1186/1472-6947-7-16

Schierano, G., Mussano, F., Faga, M. G., Menicucci, G., Manzella, C., Sabione, C., … Carossa, S. (2015). An alumina toughened zirconia composite for dental implant application: In vivo animal results. *BioMed Research International*, *2015*, Article Number: 157360.

Schlegel, K. A., Jacobs, K., & Leitenstorfer, B. (1994). Beurteilung des tsi implantes nach zehnjähriger Anwendung. *Zeitschrift für Zahnärztliche Implantologie*, *IX*, 67–70.

Schliephake, H., Hefti, T., Schlottig, F., Gedet, P., & Staedt, H. (2010). Mechanical anchorage and peri-implant bone formation of surface-modified zirconia in minipigs. *Journal of Clinical Periodontology*, *37*, 818–828. https://doi.org/10.1111/j.1600-051X.2010.01549.x

Schroeder, A., Pohler, O., & Sutter, F. (1976). [tissue reaction to an implant of a titanium hollow cylinder with a titanium surface spray layer]. *Schweizerische Monatsschrift fur Zahnheilkunde = Revue Mensuelle Suisse D'odonto-Stomatologie/SSO 86*: 713–727.

Shin, D., Blanchard, S. B., Ito, M., & Chu, T. M. (2011). Peripheral quantitative computer tomographic, histomorphometric, and removal torque analyses of two different non-coated implants in a rabbit model. *Clinical Oral Implants Research*, *22*, 242–250. https://doi.org/10.1111/j.1600-0501.2010.01980.x

Siddiqi, A., Duncan, W. J., De Silva, R. K., & Zafar, S. (2016). One-piece zirconia ceramic versus titanium implants in the jaw and femur of a sheep model: A pilot study. *BioMed Research International*, *2016*, 6792972.

Silva, N. R. F. A., Coelho, P. G., Fernandes, C. A. O., Navarro, J. M., Dias, R. A., & Thompson, V. P. (2009). Reliability of one-piece ceramic implant. *Journal of Biomedical Materials Research – Part B Applied Biomaterials*, *88*, 419–426. https://doi.org/10.1002/jbm.b.31113

Stadlinger, B., Hennig, M., Eckelt, U., Kuhlisch, E., & Mai, R. (2010). Comparison of zirconia and titanium implants after a short healing period. A pilot study in minipigs. *International Journal of Oral & Maxillofacial Surgery*, *39*, 585–592. https://doi.org/10.1016/j.ijom.2010.01.015

Thoma, D. S., Benic, G. I., Munoz, F., Kohal, R., Sanz Martin, I., Cantalapiedra, A. G., … Jung, R. E. (2015). Histological analysis of loaded zirconia and titanium dental implants: An experimental study in the dog mandible. *Journal of Clinical Periodontology*, *42*, 967–975. https://doi.org/10.1111/jcpe.12453

Tschernitschek, H., Borchers, L., & Geurtsen, W. (2005). Nonalloyed titanium as a bioinert metal–a review. *Quintessence International*, *36*, 523–530.

Weber, H. P., Morton, D., Gallucci, G. O., Roccuzzo, M., Cordaro, L., & Grutter, L. (2009). Consensus statements and recommended clinical procedures regarding loading protocols. *International Journal of Oral & Maxillofacial Implants*, *24*(Suppl), 180–183.

Welander, M., Abrahamsson, I., & Berglundh, T. (2008). The mucosal barrier at implant abutments of different materials. *Clinical Oral Implants Research*, *19*, 635–641.

Wennerberg, A., & Albrektsson, T. (2010). On implant surfaces: A review of current knowledge and opinions. *International Journal of Oral & Maxillofacial Implants*, *25*, 63–74.

Zetterqvist, L., Anneroth, G., & Nordenram, A. (1991). Tissue integration of al2o3-ceramic dental implants: An experimental study in monkeys. *International Journal of Oral & Maxillofacial Implants*, *6*, 285–293.

Zetterqvist, L., Anneroth, G., Nordenram, A., & Wroblewski, R. (1995). X-ray microanalytical and morphological observations of the interface region between ceramic implant and bone. *Clinical Oral Implants Research*, *6*, 104–113. https://doi.org/10.1034/j.1600-0501.1995.060206.x

List of excluded full-text articles

Akagawa, Y., Hosokawa, R., Sato, Y., & Kamayama, K. (1998). Comparison between freestanding and tooth-connected partially stabilized zirconia implants after two years' function in monkeys: A clinical and histologic study. *The Journal of Prosthetic Dentistry*, *80*, 551–558. https://doi.org/10.1016/S0022-3913(98)70031-9

Akagawa, Y., Ichikawa, Y., Nikai, H., & Tsuru, H. (1993). Interface histology of unloaded and early loaded partially stabilized zirconia endosseous implant in initial bone healing. *Journal of Prosthetic Dentistry*, *69*, 599–604. https://doi.org/10.1016/0022-3913(93)90289-Z

Andreiotelli, M., & Kohal, R. J. (2009). Fracture strength of zirconia implants after artificial aging. *Clinical Implant Dentistry and Related Research*, *11*, 158–166. https://doi.org/10.1111/j.1708-8208.2008.00105.x

Andreiotelli, M., Wenz, H. J., & Kohal, R. J. (2009). Are ceramic implants a viable alternative to titanium implants? A systematic literature review. *Clinical Oral Implants Research*, *20*(Suppl 4), 32–47. https://doi.org/10.1111/j.1600-0501.2009.01785.x

Apratim, A., Eachempati, P., Krishnappa Salian, K. K., Singh, V., Chhabra, S., & Shah, S. (2015). Zirconia in dental implantology: A review. *Journal of International Society of Preventive and Community Dentistry*, *5*, 147–156. https://doi.org/10.4103/2231-0762.158014

Assal, P. A. (2013). The osseointegration of zirconia dental implants. *Schweizerische Monatsschrift für Zahnmedizin*, *123*, 644–654.

Bianchi, A. E., Bosetti, M., Dolci, G. Jr, Sberna, M. T., Sanfilippo, S., & Cannas, M. (2004). In vitro and in vivo follow-up of titanium transmucosal implants with a zirconia collar. *Journal of Applied Biomaterials & Biomechanics*, *2*, 143–150.

Bosshardt, D. D., Chappuis, V., & Buser, D. (2017). Osseointegration of titanium, titanium alloy and zirconia dental implants: Current knowledge and open questions. *Periodontology 2000*, *73*, 22–40. https://doi.org/10.1111/prd.12179

Buser, D., Sennerby, L., & De Bruyn, H. (2017). Modern implant dentistry based on osseointegration: 50 years of progress, current trends and open questions. *Periodontology 2000*, *73*, 7–21. https://doi.org/10.1111/prd.12185

Calvo-Guirado, J. L., Aguilar-Salvatierra, A., Delgado-Ruiz, R. A., Negri, B., Fernandez, M. P., Mate Sanchez de Val, J. E., … Romanos, G. E. (2015). Histological and histomorphometric evaluation of zirconia dental implants modified by femtosecond laser versus titanium implants: An experimental study in fox hound dogs. *Clinical Implant Dentistry and Related Research*, *17*, 525–532. https://doi.org/10.1111/cid.12162

Chang, Y. S., Oka, M., Nakamura, T., & Gu, H. O. (1996). Bone remodeling around implanted ceramics. *Journal of Biomedical Materials Research*, *30*, 117–124. https://doi.org/10.1002/(ISSN)1097-4636

Chen, Y. W., Moussi, J., Drury, J. L., & Wataha, J. C. (2016). Zirconia in biomedical applications. *Expert Review of Medical Devices*, *13*, 945–963. https://doi.org/10.1080/17434440.2016.1230017

Chung, S. H., Kim, H. K., Shon, W. J., & Park, Y. S. (2013). Peri-implant bone formations around (ti, zr)o(2) -coated zirconia implants with different surface roughness. *Journal of Clinical Periodontology*, *40*, 404–411. https://doi.org/10.1111/jcpe.12073

Delgado-Ruíz, R. A., Calvo-Guirado, J. L., Moreno, P., Guardia, J., Gomez-Moreno, G., Mate-Sánchez, J. E., … Chiva, F. (2011). Femtosecond laser microstructuring of zirconia dental implants. *Journal of Biomedical Materials Research – Part B Applied Biomaterials*, *96B*, 91–100. https://doi.org/10.1002/jbm.b.31743

Delgado-Ruiz, R. A., Abboud, M., Romanos, G., Aguilar-Salvatierra, A., Gomez-Moreno, G., & Calvo-Guirado, J. L. (2015). Peri-implant bone organization surrounding zirconia-microgrooved surfaces circularly polarized light and confocal laser scanning microscopy study. *Clinical Oral Implants Research*, *26*, 1328–1337. https://doi.org/10.1111/clr.12461

Depprich, R., Zipprich, H., Ommerborn, M., Mahn, E., Lammers, L., Handschel, J., … Meyer, U. (2008a). Osseointegration of zirconia implants: An sem observation of the bone-implant interface. *Head & Face Medicine*, *4*, 25. https://doi.org/10.1186/1746-160X-4-25

Depprich, R., Naujoks, C., Ommerborn, M., Schwarz, F., Kubler, N. R., & Handschel, J. (2014). Current findings regarding zirconia implants. *Clinical Implant Dentistry and Related Research*, *16*, 124–137. https://doi.org/10.1111/j.1708-8208.2012.00454.x

Dubruille, J. H., Viguier, E., Le Naour, G., Dubruille, M. T., Auriol, M., & Le Charpentier, Y. (1999). Evaluation of combinations of titanium, zirconia, and alumina implants with 2 bone fillers in the dog. *International Journal of Oral & Maxillofacial Implants*, *14*, 271–277.

Elnayef, B., Lazaro, A., Suarez-Lopez Del Amo, F., Galindo-Moreno, P., Wang, H. L., Gargallo-Albiol, J., & Hernandez-Alfaro, F. (2017). Zirconia implants as an alternative to titanium: A systematic review and meta-analysis. *International Journal of Oral & Maxillofacial Implants*, *32*, e125–e134. https://doi.org/10.11607/jomi.5223

Gredes, T., Kubasiewicz-Ross, P., Gedrange, T., Dominiak, M., & Kunert-Keil, C. (2014). Comparison of surface modified zirconia implants with commercially available zirconium and titanium implants: A histological study in pigs. *Implant Dentistry*, *23*, 502–507.

Han, J. M., Hong, G., Lin, H., Shimizu, Y., Wu, Y., Zheng, G., … Sasaki, K. (2016). Biomechanical and histological evaluation of the osseointegration capacity of two types of zirconia implant. *International Journal of Nanomedicine*, *11*, 6507–6516. https://doi.org/10.2147/IJN

Hafezeqoran, A., & Koodaryan, R. (2017). Effect of zirconia dental implant surfaces on bone integration: A systematic review and meta-analysis. *Biomed Research International*, *2017*, 9246721.

Hayashi, K., Inadome, T., Tsumura, H., Mashima, T., & Sugioka, Y. (1993). Bone-implant interface mechanics of in vivo bioinert ceramics. *Biomaterials*, *14*, 1173–1179. https://doi.org/10.1016/0142-9612(93)90163-V

Hayashi, K., Matsuguchi, N., Uenoyama, K., & Sugioka, Y. (1992). Re-evaluation of the biocompatibility of bioinert ceramics in vivo. *Biomaterials*, *13*, 195–200. https://doi.org/10.1016/0142-9612(92)90184-P

Hisbergues, M., Vendeville, S., & Vendeville, P. (2009). Zirconia: Established facts and perspectives for a biomaterial in dental implantology. *Journal of Biomedical Materials Research. Part B, Applied Biomaterials*, *88*, 519–529. https://doi.org/10.1002/jbm.b.31147

Hobkirk, J. A., & Wiskott, H. W. A. (2009). Ceramics in implant dentistry (working group 1). *Clinical Oral Implants Research*, *20*, 55–57. https://doi.org/10.1111/j.1600-0501.2009.01779.x

Kim, H. K., Woo, K. M., Shon, W. J., Ahn, J. S., Cha, S., & Park, Y. S. (2015). Comparison of peri-implant bone formation around injection-molded and machined surface zirconia implants in rabbit tibiae. *Dental Materials Journal*, *34*, 508–515. https://doi.org/10.4012/dmj.2015-024

Kim, D. G., Elias, K. L., Jeong, Y. H., Kwon, H. J., Clements, M., Brantley, W. A., … Han, J. S. (2016). Differences between buccal and lingual bone quality and quantity of peri-implant regions. *Journal of the Mechanical Behavior of Biomedical Materials*, *60*, 48–55. https://doi.org/10.1016/j.jmbbm.2015.12.036

Kirsten, A. (2015). Bioactive and thermally compatible glass coating on zirconia dental implants. *Journal of Dental Research*, *94*, 297–303. https://doi.org/10.1177/0022034514559250

Kohal, R. J., Att, W., Bächle, M., & Butz, F. (2008). Ceramic abutments and ceramic oral implants. An update. *Periodontology 2000*, *47*, 224–243. https://doi.org/10.1111/j.1600-0757.2007.00243.x

Kumar, J. V., Jain, A. R., Jayesh, R., Parthasaradhi, T., & Venkatakrishnan, (2015). Biomaterials in implant dentistry: A review. *Biomedical and Pharmacology Journal*, *8SE*, 139–143. https://doi.org/10.13005/bpj

Langhoff, J. D., Voelter, K., Scharnweber, D., Schnabelrauch, M., Schlottig, F., Hefti, T., … von Rechenberg, B. (2008). Comparison of chemically and pharmaceutically modified titanium and zirconia implant surfaces in dentistry: A study in sheep. *International Journal of Oral & Maxillofacial Surgery*, *37*, 1125–1132. https://doi.org/10.1016/j.ijom.2008.09.008

Lee, B. C., Yeo, I. S., Kim, D. J., Lee, J. B., Kim, S. H., & Han, J. S. (2013). Bone formation around zirconia implants combined with rhbmp-2 gel in the canine mandible. *Clinical Oral Implants Research*, *24*, 1332–1338. https://doi.org/10.1111/clr.12004

Mai, R., Kunert-Keil, C., Grafe, A., Gedrange, T., Lauer, G., Dominiak, M., & Gredes, T. (2012). Histological behaviour of zirconia implants: An experiment in rats. *Annals of Anatomy*, *194*, 561–566. https://doi.org/10.1016/j.aanat.2012.09.004

Nordlund, A., Zetterqvist, L., & Oden, A. (1989). A comparative experimental investigation in monkeys between three different implant materials. *International Journal of Oral & Maxillofacial Surgery*, *18*, 373–377. https://doi.org/10.1016/S0901-5027(89)80037-2

Oblak, C., Verdenik, I., Swain, M. V., & Kosmac, T. (2014). Survival-rate analysis of surface treated dental zirconia (y-tzp) ceramics. *Journal of Materials Science: Materials in Medicine*, *25*, 2255–2264.

Ozkurt, Z., & Kazazoglu, E. (2011). Zirconia dental implants: A literature review. *Journal of Oral Implantology*, *37*, 367–376. https://doi.org/10.1563/AAID-JOI-D-09-00079

Manzano, G., Herrero, L. R., & Montero, J. (2014). Comparison of clinical performance of zirconia implants and titanium implants in animal models: A systematic review. *International Journal of Oral & Maxillofacial Implants*, *29*, 311–320. https://doi.org/10.11607/jomi.2817

Prithviraj, D. R., Deeksha, S., Regish, K. M., & Anoop, N. (2012). A systematic review of zirconia as an implant material. *Indian Journal of Dental Research*, *23*, 643–649.

Ratiu, C. A., Cavalu, S. D., Miclaus, V., Rus, V., & Lazarescu, G. I. (2015). Histological evidence of novel ceramic implant: Evaluation of tolerability in rabbit femur. *Romanian Journal of Morphology and Embryology*, *56*, 1455–1460.

Richardson, W. C. Jr, Klawitter, J. J., Sauer, B. W., Pruitt, J. R., & Hulbert, S. F. (1975). Soft tissue response to four dense ceramic materials and two clinically used biomaterials. *Journal of Biomedical Materials Research*, *9*, 73–80. https://doi.org/10.1002/(ISSN)1097-4636

Saulacic, N., Erdosi, R., Bosshardt, D. D., Gruber, R., & Buser, D. (2014). Acid and alkaline etching of sandblasted zirconia implants: A histomorphometric study in miniature pigs. *Clinical Implant Dentistry and Related Research*, *16*, 313–322. https://doi.org/10.1111/cid.12070

Scarano, A., Di Carlo, F., Quaranta, M., & Piattelli, A. (2003). Bone response to zirconia ceramic implants: An experimental study in rabbits. *Journal of Oral Implantology*, *29*, 8–12. https://doi.org/10.1563/1548-1336(2003)029<0008:BRTZCI>2.3.CO;2

Schreiner, U., Schroeder-Boersch, H., Schwarz, M., & Scheller, G. (2002). [Improvement of osseointegration of bio-inert ceramics by modification of the surface–results of an animal experiment]. *Biomedizinische Technik (Berl)*, *47*, 164–168. https://doi.org/10.1515/bmte.2002.47.6.164

Sennerby, L., Dasmah, A., Larsson, B., & Iverhed, M. (2005). Bone tissue responses to surface-modified zirconia implants: A histomorphometric and removal torque study in the rabbit. *Clinical Implant Dentistry & Related Research*, *7*(Suppl 1), S13–S20. https://doi.org/10.1111/j.1708-8208.2005.tb00070.x

Shon, W. J., Chung, S. H., Kim, H. K., Han, G. J., Cho, B. H., & Park, Y. S. (2014). Peri-implant bone formation of non-thermal atmospheric pressure plasma-treated zirconia implants with different surface

roughness in rabbit tibiae. *Clinical Oral Implants Research*, *25*, 573–579. https://doi.org/10.1111/clr.12115
Shon, W. J., Woo, K. M., Kim, H. K., Kwon, H. B., Shin, S. Y., & Park, Y. S. (2015). Time-dependent periimplant bone reaction of acidic monomer-treated injection molded zirconia implants in rabbit tibiae. *Implant Dentistry*, *24*, 287–293.
Sollazzo, V., Pezzetti, F., Scarano, A., Piattelli, A., Bignozzi, C. A., Massari, L., … Carinci, F. (2008). Zirconium oxide coating improves implant osseointegration in vivo. *Dental Materials*, *24*, 357–361. https://doi.org/10.1016/j.dental.2007.06.003
Taniguchi, Y., Kakura, K., Yamamoto, K., Kido, H., & Yamazaki, J. (2016). Accelerated osteogenic differentiation and bone formation on zirconia with surface grooves created with fiber laser irradiation. *Clinical Implant Dentistry & Related Research*, *18*, 883–894. https://doi.org/10.1111/cid.12366
Tete, S., Mastrangelo, F., Bianchi, A., Zizzari, V., & Scarano, A. (2009). Collagen fiber orientation around machined titanium and zirconia dental implant necks: An animal study. *International Journal of Oral & Maxillofacial Implants*, *24*, 52–58.
Thoma, D. S., Ioannidis, A., Cathomen, E., Hammerle, C. H., Husler, J., & Jung, R. E. (2016). Discoloration of the peri-implant mucosa caused by zirconia and titanium implants. *International Journal of Periodontics and Restorative Dentistry*, *36*, 39–45. https://doi.org/10.11607/prd.2663
Van Dooren, E., Calamita, M., Calgaro, M., Coachman, C., Ferencz, J. L., Pinho, C., … Dooren, E. V. (2012). Mechanical, biological and clinical aspects of zirconia implants. *The European Journal of Esthetic Dentistry*, *7*, 396–417.
Wenz, H. J., Bartsch, J., Wolfart, S., & Kern, M. (2008). Osseointegration and clinical success of zirconia dental implants: A systematic review. *International Journal of Prosthodontics*, *21*, 27–36.
Zhu, J., Yang, D. W., & Ma, F. (2010). Feasibility study of a partially hollow configuration for zirconia dental implants. *Journal of Oral & Maxillofacial Surgery*, *68*, 399–406. https://doi.org/10.1016/j.joms.2009.10.001

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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