

Three-year analysis of zirconia implants used for single-tooth replacement and three-unit fixed dental prostheses: A prospective multicenter study

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Abstract

Aim: The aim of the present investigation was to evaluate clinically and radiographically the outcome of zirconia oral implants after 3 years in function.

Materials and methods: In 60 patients in need of either a single-tooth replacement or a three-unit fixed dental prosthesis (FDP), a total of 71 one-piece zirconia implants were placed and immediately restored with temporary fixed prostheses. After a period of at least 2 months in the mandible and at least 4 months in the maxilla, zirconia-based reconstructions were cemented. The implants were clinically and radiologically examined at implant insertion, prosthetic delivery, at 6 months and then yearly up to 3 years. A linear mixed model was used to analyze statistically the influence of prognostic factors on changes in the marginal bone level.

Results: Seventy-one implants (48 in the mandible, 23 in the maxilla) inserted in 60 patients were restored with 49 crowns and 11 FDP. One patient lost his implant after 5 weeks. Five patients with one implant each could not be evaluated after 3 years. Based on 55 patients with a total of 66 implants, the mean survival rate was 98.5% after 3 years in function. A statistically significant mean marginal bone loss (0.70 mm ± 0.72 mm) has been detected from implant insertion to the 3-year follow-up. The largest marginal bone loss occurred between implantation and prosthetic delivery (0.67 mm ± 0.56 mm). After delivery, no statistically significant bone level change was observed (0.02 mm ± 0.59 mm). None of the investigated prognostic factors had a significant influence on changes in the marginal bone level.

Conclusions: After 3 years in function, the investigated one-piece zirconia implant showed a high survival rate and a low marginal bone loss. The implant system was successful for single-tooth replacement and three-unit FDPs. Further investigations with long-term data are needed to confirm these findings.

KEYWORDS

bone, ceramic, clinical, dental implants, human, osseointegration, zirconia

1 | INTRODUCTION

Endosseous screw-type implants offer a good opportunity to restore missing or lost teeth. Nowadays, there are a variety of different

implant systems and implants made of different materials available on the dental market. Regarding the material, implants from commercially pure titanium present the largest group of the used implants in the last decades. Based on various systematic reviews, titanium implants

reveal high implant survival and success rates over a long time period. Jung, Zembic, Pjetursson, Zwahlen, and Thoma (2012) reported in a systematic review a survival rate of 97.2% at 5 years and 95.2% at 10 years for commercially available titanium implants supporting single crowns (Jung et al., 2012). The reported survival rate of implants supporting fixed dental prostheses (FDPs) was 95.6% after 5 years and 93.1% after 10 years (Jung et al., 2012).

However, there are a number of patients demanding for metal-free solutions for implants and prosthetics. In addition, a few preclinical studies showed that a certain amount of titanium could be found in the tissues around dental implants (Addison et al., 2012; Bianco, Ducheyne, & Cuckler, 1996). Moreover, there is some evidence that metals in the oral cavity undergo corrosion through an electrochemical redox reaction (Cadosch et al., 2010) and may provoke hypersensitivity reactions (Jacobi-Gresser, Huesker, & Schutt, 2013) or even allergic reactions (Tschernitschek, Borchers, & Geurtsen, 2005). Even though its estimated prevalence is low (0.6%), Ti allergy can be detected in dental implant patients (Sicilia et al., 2008).

To overcome these possible, unwelcomed reactions, zirconia implants have been investigated. They show a high biocompatibility, good physical characteristics and a tooth-like color. In vitro evaluations confirmed that zirconia is not cytotoxic and is not able to generate mutations of the cellular genome (Covacci et al., 1999). In vivo studies reported that the osseointegration of zirconia is similar to commercially pure titanium (Kohal, Weng, Bachle, & Strub, 2004; Manzano, Herrero, & Montero, 2014) and histological investigations have shown that particularly in the early wound healing, zirconia led to an increased proliferation of osteoblasts (Hisbergues, Vendeville, & Vendeville, 2009). Based on the excellent mechanical properties, in particular a high flexural strength (900–1200 MPa), a high fracture toughness (7–10 MPa m^{1/2}) and a fairly high hardness (1200 HV0.1), yttria-stabilized zirconia is an appropriate biomaterial for dental implants (Piconi & Maccauro, 1999).

Zirconia has proven its value as a preferred esthetic material in challenging gingival conditions. Jung, Sailer, Hammerle, Attin, and Schmidlin (2007) have shown that all-ceramic abutments led to less change in color in a thin gingival biotype than titanium abutments (Jung et al., 2007).

On the other hand, zirconia can show signs of aging under certain circumstances, which has been described as low temperature degradation (Kobayashi, Kuwajima, & Masaki, 1981). Furthermore, one study showed that zirconium can also be found around zirconia implants (Cionca, Hashim, Meyer, Michalet, & Mombelli, 2016). Whether or not this has an influence on the long-term outcomes of endosseous ceramic implants, remains to be clarified. Although ceramic implants are presently used for several indications, a recently published systematic review (Pieralli, Kohal, Jung, Vach, & Spies, 2017) stated that few clinical reports on zirconia ceramic implants are available with an investigation time of 3 years and more.

Therefore, the aim of the present investigation was to evaluate clinically and radiographically the long-term safety and efficiency of zirconia oral implants for single-tooth replacement and three-unit FDPs after 3 years in function.

2 | MATERIAL AND METHODS

2.1 | Study design

The study was designed as a prospective cohort investigation according to Dekkers, Egger, Altman, and Vandenbroucke (2012). It was performed at two investigation centers: at the Department of Prosthetic Dentistry, Center for Dental Medicine, Medical Center—University of Freiburg, Faculty of Medicine, Freiburg, Germany, and at the Clinic of Fixed and Removable Prosthodontics and Dental Material Science, Center of Dental Medicine, University of Zurich, Switzerland. Both local ethical committees (Ethics Commission, Medical Center—University of Freiburg, Freiburg (241/08) and (Ethics Committee of the Canton of Zurich (StV 08/10)) gave their approval, and the study was conducted in full accordance with the World Medical Association Declaration of Helsinki. All patients were thoroughly informed about the study protocol and have signed an informed consent form prior to their inclusion.

2.2 | Participants

Sixty patients in need of either exact one single-tooth replacement or exact one implant-supported three-unit fixed dental prosthesis were consecutively included. The detailed inclusion and exclusion criteria have been outlined already in a previous study (Jung et al., 2016). In brief, the patients were only included if they were between 20 and 70 years old and in good general condition. The implant site had to be free of infection or extraction remnants and had to contain sufficient bone for the placement of an implant with a diameter of at least 4 mm and a length of 8 mm. The patients were excluded if there were any general medical findings, which did not permit the surgical procedure. Further exclusion criteria were the intake of medication that is known to interfere with the objectives of the study, pregnancy, signs of severe bruxism, a reported alcohol or drug abuse or nicotine abuse of more than 15 cigarettes per day. Also, the need for primary bone augmentation at the implantation site was an exclusion criterion; however, a simultaneous minor bone augmentation procedure was allowed to cover any exposed rough surfaces of the implant.

2.3 | Materials

The presently investigated ceramic implant was a commercially available one-piece zirconia screw-type implant (ceramic.implant; vitaclinical, VITA Zahnfabrik, Bad Säckingen, Germany). The endosseous part is constructed in a cylindric-conical geometrical form. The available implant lengths were 8, 10, 12 and 14 mm, and the available diameters were 4.0, 4.5 and 5.5 mm.

Regarding the material composition, surface roughness and processing steps, please refer to Fischer, Schott, and Martin (2016).

2.4 | Interventions

A late implant insertion (3 months after tooth extraction) was recommended; under optimal circumstances, a delayed implant insertion

(6–8 weeks after extraction) was possible (Figure 1a). For the placement of the implants, a mucoperiosteal flap was raised as far as necessary under local anesthesia (Ubistesin™ forte) (Figure 1b). The implants were placed according to the manufacturer's recommendations in a prosthetically correct position and angulation (Figure 1c). If required, guided bone regeneration was performed with xenogeneic bone substitutes (Bio-Oss® Spongiosa Granules, particle size 0.25–1.0 mm; Geistlich Pharma AG, Wolhusen, Switzerland) (Figure 1d) and a collagen membrane (Bio-Gide® Membrane; Geistlich Pharma AG) to cover the rough implant surface or to compensate deficiencies in the bony contour (Figure 1e). The flap was sutured for a transmucosal healing, and the implants were immediately restored with prefabricated provisional reconstructions made from PMMA (Figure 1f). The occlusion and lateral articulation were carefully checked and adjusted. Contacts in static or dynamic occlusion were removed.

2.5 | Postoperative treatment

Patients were instructed not to mechanically clean the operation field but to rinse twice a day with 0.2% chlorhexidine aqueous

solution. They were given antibiotic prophylaxis on the day of surgery and thereafter three times a day for 5 days (750 mg Clamoxyl® in Zurich; 300 mg clindamycin in Freiburg) after implant placement. Analgesics (500 mg Mefenacid in Zurich; 400 mg Ibuprofen in Freiburg) were dispensed and taken according to the individual requirements. Sutures were removed 10 days after the surgical intervention.

2.6 | Prosthetic insertion and follow-ups

The final prosthetic restoration was inserted at the earliest 2 months after implant placement in the mandible and 4 months in the maxilla. Both types of restorations, the implant-supported SC and the implant-supported three-unit FDPs, were manufactured from a zirconia framework (VITA In-Ceram YZ), which was subsequently veneered (VITA VM9) and adhesively cemented with a dual-curing cement (RelyX Unicem Aplicap; 3M Espe) (Spies, Kohal, Balmer, Vach, & Jung, 2017) (Figure 1g).

The implants were examined at baseline (implant insertion), at the placement of the restoration, at 6 months and then yearly up to 3 years (Figure 2a–c).



FIGURE 1 Implant insertion and prosthetic delivery: (a) initial situation, (b) mucoperiosteal flap, (c) implant insertion, (d) guided bone regeneration, (e) collagen membrane, (f) immediate provisional reconstruction, (g) prosthetic delivery

2.7 | Analyses

2.7.1 | Clinical and radiographic examinations

At each visit, soft tissue parameters in terms of probing depth (PD), marginal soft tissue level (ML), clinical attachment level (CAL), plaque control record (Pcr) and bleeding on probing (BoP) were recorded at four positions of the implants and neighboring teeth. One examiner per investigation center performed the measurements. Examiner alignment and calibration have been performed prior to the examinations. PD, ML, CAL and the presence of plaque were recorded with a periodontal probe (PCP 12; Hu Friedy, Rotterdam, The Netherlands), and the reference for the assessment of CAL and ML was the margin of the implant-crown/cemento-enamel junction. For the analyses of PD, ML and CAL, the four implant/tooth sites (mesial, buccal, distal lingual) were averaged. The size of the gingival papilla (Index according to Jemt (1997)) was recorded between the implants and neighboring teeth.

Standardized periapical radiographs were taken at implant insertion, at the placement of the restoration, at 1 year and at 3 years with an individual acrylic radiographic film holder (Figures 3a–d and 4a–d). Radiographs were imported in an open-source image-processing program (ImageJ, National Institutes of Health, Bethesda, MD, USA) and calibrated to measure the peri-implant bone level at each time point. Marginal bone loss was calculated as difference between baseline (implant placement) and subsequent follow-ups.

During the evaluation of the radiographic outcome at the 3-year follow-up, the authors detected a calibration error (incorrect distance of implant threads) for the measurements up to the 1-year follow-up. This previously published data of the same cohort (Jung et al., 2016) were recalculated and subsequently corrected for the present publication.

2.7.2 | Statistical analysis

The statistical analysis was performed at the University of Freiburg, Center for Medical Biometry and Medical Informatics, Institute for Medical biometry and Statistics, Freiburg, Germany.

Sample size calculation has been performed as previously described in detail (Jung et al., 2016). For the analysis of the mean marginal bone level, linear mixed models with random intercept were used to take within-subject dependencies (i.e., two implants within one patient) into account. For the clinical parameters, Wilcoxon signed-rank tests were used to compare both results of implants and corresponding teeth per time point and results between 0 and 36 months within implants and teeth, respectively.

The calculations were performed with the statistical software STATA 14.2 (StataCorp LT, College Station, TX, USA). The probability level for statistical significance was set to $p < .05$.

3 | RESULTS

3.1 | Patient demographics and baseline characteristics

Pretreatment examination was performed at 63 patients at one of the two investigation centers. Three patients had at least one violation of inclusion/exclusion criteria and were therefore excluded from the analysis. Two of these three patients received more than exactly one single-tooth replacement, and in one patient, no implant could be placed due to insufficient bone volume.

The remaining 60 patients (30 male/30 female) had a mean age of 48.1 ± 13.0 at the pretreatment examinations. They received a total of 71 implants (23 in the upper jaw/48 in the lower jaw) (Tables 1 and 2) between November 2009 and April 2011. Five implants in the maxilla and six in the mandible were placed with a simultaneous guided bone augmentation procedure. As one patient lost his implant 5 weeks after implantation due to a missing osseointegration, the implants were restored with 48 SC and 11 FDPs.

At the 3-year follow-up after final prosthetic restoration, 54 patients with a total of 65 implants could be evaluated. Mean observation time was 42.73 ± 4.19 months after implantation and 36.6 ± 1.08 months after prosthetic delivery. Five patients with one implant each did not show up for different reasons (one moved away; one missed the appointment; three more patients refused further participation). As described above, one patient with one implant dropped out short time after implant placement.

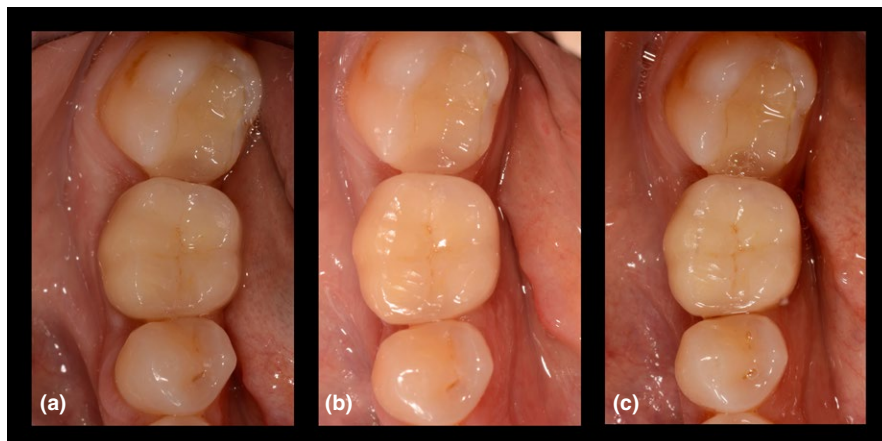


FIGURE 2 Follow-ups: (a) 1 year in function, (b) 2 years in function, (c) 3 years in function

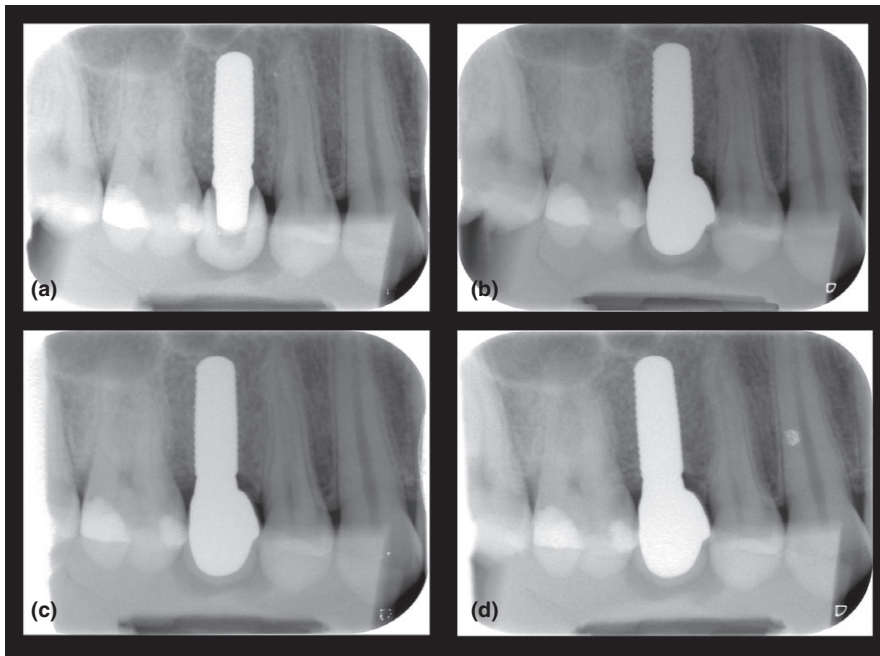


FIGURE 3 (a–d) Radiographic images (SC): (a) after implantation and provisional reconstruction, (b) at prosthetic delivery, (c) after 1 year in function, (d) after 3 year in function

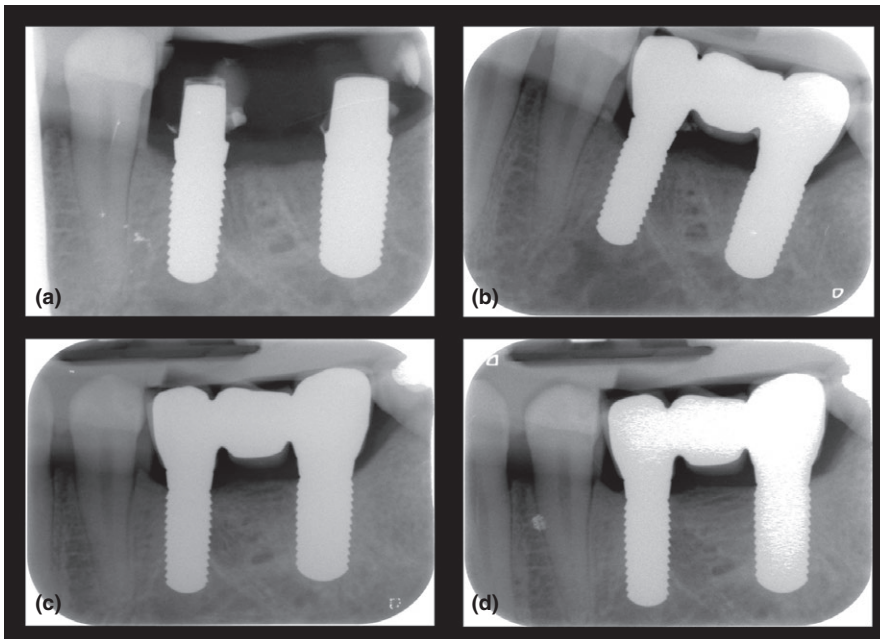


FIGURE 4 (a–d) Radiographic images (FDP): (a) after implantation and provisional reconstruction, (b) at prosthetic delivery, (c) after 1 year in function, (d) after 3 years in function

TABLE 1 Implant distribution

FDI	17	16	15	14	13	12	11	21	22	23	24	25	26	27	Total
Upper jaw	1	1	4	5	1	0	1	0	0	0	2	5	3	0	23
Lower jaw	4	11	4					1			2	7	13	6	48
FDI	47	46	45	44	43	42	41	31	32	33	34	35	36	37	71

3.2 | Analysis of the marginal bone loss (primary endpoint)

The mean marginal bone loss from implant insertion to the 3-year follow-up after the final prosthetic restoration was $0.70 \text{ mm} \pm 0.72 \text{ mm}$.

Table 3 shows the marginal bone loss from baseline to each evaluated time point. The change in mean marginal bone level was statistically significant ($p < .001$) between implantation and the 3-year follow-up. The largest marginal bone loss occurred between implantation and the insertion of the final restoration ($0.67 \text{ mm} \pm 0.56 \text{ mm}$). From delivery

TABLE 2 Implant characteristics

	Implant diameter			Implant length			
	4.0	4.5	5.5	8	10	12	14
Upper jaw	11	11	1	6	8	8	1
Lower jaw	15	21	12	6	31	11	0
Total	26	32	13	12	39	19	1

of the restorations to the 3-year follow-up, no further statistically significant bone loss was observed ($0.02 \text{ mm} \pm 0.59 \text{ mm}$; $p = .66$).

The frequency distribution for mean marginal bone level changes was as follows: 13% of the implants gained marginal bone, while 56% lost less than 1 mm, 22% 1–1.5 mm, 6% 1.5–2 mm and 3% more than 2 mm of marginal bone.

None of the investigated prognostic factors (center, jaw, type of reconstruction, implant diameter and length) had a significant influence on changes in the marginal bone level, except the baseline value of mean initial insertion depth of the implants ($p < .001$) (Table 4).

The estimator for “insertion depth” indicates that a change in insertion depth at implantation of 1 mm leads to a change of 0.695 mm marginal bone loss after 3 years. The estimated difference in mean marginal bone loss is about a value of 0.152 larger for Zurich than for Freiburg, about 0.390 units smaller for the upper jaw than for the lower jaw and 0.326 units smaller for a bridge than for a single tooth. For an implant diameter of 4.5 and 5.5 mm, the difference is about 0.065 and 0.275 units larger than for diameter 4.0 mm, respectively. For an implant length of 10 mm, the difference is about 0.156 units smaller and for an implant length of 12 and 14 mm about 0.226 and 0.282 units larger than for length of 8 mm, respectively.

3.3 | Analysis of secondary endpoint (survival rate of the implants)

During the observation time, one implant in the mandible failed 5 weeks after insertion. In addition, five implants in different patients could not

be evaluated because the patients did not show up to the 3-year follow-up. Based on 55 patients with a total of 66 implants, the mean survival rate was 98.5% (95% CI: 91.8%–99.9%) after 3 years in function.

3.4 | Clinical measurements

At each visit, plaque frequency was recorded at four sites of the implants and adjacent teeth (Table 5). At prosthetic insertion, the frequencies of plaque around implants (11.8%) and teeth (21.0%) were at the lowest level. This value increased for both groups between prosthetic insertion and the 6-month follow-up and remained on a relatively high level up to the 3-year follow-up (implants: 20.8%, teeth 41.4%). At each time point, plaque frequencies were significantly lower at implant sites compared to teeth $p < .05$.

At implant sites, the mean PD (Table 6) increased from 2.71 mm at prosthetic delivery to 3.52 mm after 3 years. Wilcoxon signed-rank test applied to the differences comparing 36 months with baseline showed significant changes in PD on patient level for implants ($p < .001$) but not for teeth. The mean PD at the adjacent teeth changed only from 2.53 mm to 2.54 mm during the observation period. The difference at each follow-up between implants and teeth was statistically significant ($p < .0001$).

The frequency of BoP (Table 7) was significantly higher during the whole observation time for implants compared to the neighboring teeth except at prosthetic insertion. The largest increase could be observed between prosthetic delivery and the 6-month follow-up for both groups. After 3 years, BOP for implants was 40.8%, which is about two times higher than for teeth (23.2%).

Mean marginal soft tissue level (Table 8) decreased from 0.7 mm to 0.65 mm at implants. At adjacent teeth, there was nearly no change in mean marginal soft tissue level (0.01 mm), but the Wilcoxon signed-rank test (baseline vs 36 month) showed significant changes in ML on patient level ($p = .047$).

The CAL (Table 9) around the implants at prosthetic insertion was 2.76 mm and 3.14 mm at the teeth. Until the 3-year follow-up, changes per patient in CAL were not significant at implant sites ($p = .523$) and around teeth ($p = .052$).

TABLE 3 Marginal bone loss from baseline (implant placement) to all evaluated time points

Treatment	Total	Missing	Total valid	Mean	SD	Min.	1. Quartile	Median	3. Quartile	Max
Marginal bone loss at prosthetic delivery										
SC	49	2	47	0.739	0.606	−0.41	0.34	0.64	1.09	2.78
FDP	22	1	21	0.534	0.425	−0.11	0.11	0.56	0.86	1.43
Total	71	3	68	0.676	0.561	−0.41	0.32	0.60	0.96	2.78
Marginal bone loss at 1-year follow-up										
SC	49	3	46	0.668	0.613	−0.45	0.19	0.58	1.01	2.33
FDP	22	3	19	0.438	0.425	−0.11	0.04	0.38	0.83	1.39
Total	71	6	65	0.601	0.571	−0.45	0.15	0.53	0.86	2.33
Marginal bone loss at 3-year follow-up										
SC	49	6	43	0.734	0.772	−0.44	0.18	0.55	1.09	3.21
FDP	22	1	21	0.638	0.616	−0.56	0.35	0.60	1.13	1.75
Total	71	7	64	0.702	0.721	−0.56	0.26	0.59	1.11	3.21

4 | DISCUSSION

The present multicenter prospective cohort investigations evaluated the mean marginal bone loss, survival rate and peri-implant soft tissue conditions of 71 zirconia implants placed in 60 healthy individuals

TABLE 4 Investigated prognostics factors on marginal bone loss

Variable	Estimate	95% CI	p-Value
Marginal bone level at implantation	−0.695	[−1.034, −0.356]	<.001
Center (Zurich/Freiburg)	0.152	[−0.236, 0.541]	.441
Jaw (maxilla/mandible)	−0.390	[−0.804, 0.024]	.065
SC/FDP	−0.326	[−0.818, 0.165]	.193
Implant diameter 4.5 relative to 4.0	0.065	[−0.195, 0.325]	.450
Implant diameter 5.5 relative to 4.0	0.275	[−0.153, 0.703]	
Implant length 10 relative to 8	−0.156	[−0.474, 0.160]	.064
Implant length 12 relative to 8	0.226	[−0.183, 0.635]	
Implant length 14 relative to 8	0.282	[−0.994, 1.559]	

after 3 years in function. Presently, only few clinical reports on zirconia ceramic implants are available with an investigation time of 3 years and more (Pieralli et al., 2017). Therefore, the present investigation adds to the scientific knowledge regarding these implants.

Long-term stable conditions of osseointegration around implants particularly with respect to marginal bone loss have been identified as success criteria for longevity for implants (Albrektsson, Zarb, Worthington, & Eriksson, 1986; Roos et al., 1997). The present investigation showed a mean marginal bone loss of 0.70 mm after 3 years with the maximum loss between the interval of implantation and prosthetic delivery (0.67 mm).

Another recently published prospective clinical trial with a similar study design (Spies et al., 2015) investigated 53 immediately temporized one-piece alumina-toughened zirconia implants over an observation time of 3 years after prosthetic delivery. The authors reported a similar mean marginal bone loss over the 3 years. As in the present study, they observed the greatest amount of bone loss between implantation and prosthetic insertion (0.70 mm): No further statistically significant bone loss up to the 3-year follow-up (0.79 mm) occurred. The finding of a pronounced MBL in the first 6 months after implant placement is in line with another study reporting on marginal bone loss over time for zirconia implants up to 4 years (Borgonovo et al., 2013).

In a recently published systematic review (Pieralli et al., 2017), the authors stated that no further meta-analysis for MBL of zirconia implants except for 12 months data could be performed due to the lack of long-term data. Their analysis after 12 months resulted in a MBL

TABLE 5 Comparison of the plaque frequency at implants and adjacent teeth (Δ shows the mean difference to baseline [0 month] in patients with both measurements. The *p*-values at the bottom refer to a Wilcoxon signed-rank test applied to the differences comparing 36 months with baseline)

	Total valid	Plaque in %				Signed-rank
		Implants	Δ	Teeth	Δ	
0 month	63	11.8 ± 25.8		21.0 ± 25.5		<i>p</i> = .0025
6 months	62	22.1 ± 30.8	10.1	37.5 ± 32.9	16.1	<i>p</i> < .0001
12 months	61	21.6 ± 29.8	0.9	41.6 ± 32.6	19.9	<i>p</i> < .0001
24 months	60	20.1 ± 27.9	7.8	47.3 ± 30.5	25.2	<i>p</i> < .0001
36 months	57	20.8 ± 26.7	8.5	41.4 ± 29.3	19.3	<i>p</i> < .0001
Signed-rank test (0 vs. 36)			<i>p</i> = .022		<i>p</i> < .0001	

TABLE 6 Comparison of the mean probing depth around implants and adjacent teeth (Δ shows the mean difference to baseline [0 month] in patients with both measurements. The *p*-values at the bottom refer to a Wilcoxon signed-rank test applied to the differences comparing 36 months with baseline)

	Total valid	PD in mm				Signed-rank test
		Implants	Δ	Teeth	Δ	
0 month	63	2.71 ± 0.62		2.53 ± 0.44		<i>p</i> = .111
6 months	62	3.24 ± 0.59	0.56	2.46 ± 0.48	−0.06	<i>p</i> < .0001
12 months	61	3.47 ± 0.67	0.78	2.43 ± 0.52	−0.10	<i>p</i> < .0001
24 months	60	3.60 ± 0.66	0.89	2.46 ± 0.45	−0.06	<i>p</i> < .0001
36 months	57	3.52 ± 0.66	0.81	2.54 ± 0.57	0.02	<i>p</i> < .0001
Signed-rank test (0 vs. 36)			<i>p</i> < .0001		<i>p</i> = .80	

TABLE 7 Comparison of bleeding on probing frequency at implants and adjacent teeth (Δ shows the mean difference to baseline [0 month] in patients with both measurements. The *p*-values at the bottom refer to a Wilcoxon signed-rank test applied to the differences comparing 36 months with baseline)

	Total valid	BoP %				Signed-rank test
		Implants	Δ	Teeth	Δ	
0 month	63	16.8 $\pm$ 27.5		13.5 $\pm$ 21.9		<i>p</i> = .909
6 months	62	43.5 $\pm$ 36.5	26.4	29.4 $\pm$ 42.8	16.1	<i>p</i> = .0052
12 months	61	57.5 $\pm$ 32.9	41.8	34.0 $\pm$ 48.9	20.5	<i>p</i> = .0001
24 months	60	48.9 $\pm$ 36.3	31.7	30.8 $\pm$ 38.9	17.1	<i>p</i> = .0013
36 months	57	40.8 $\pm$ 32.9	23.5	23.2 $\pm$ 33.0	9.6	<i>p</i> = .0045
Signed-rank test (0 vs. 36)			<i>p</i> < .0001		<i>p</i> = .137	

TABLE 8 Mean marginal soft tissue level at implant and adjacent teeth sites (Δ shows the mean difference to baseline [0 month] in patients with both measurements. The *p*-values at the bottom refer to a Wilcoxon signed-rank test applied to the differences comparing 36 months with baseline)

	Total valid	Marginal soft tissue level in mm			
		Implants	Δ	Teeth	Δ
0 month	63	0.70 $\pm$ 0.33		1.22 $\pm$ 0.80	
6 months	62	0.70 $\pm$ 0.48	-0.020	1.16 $\pm$ 0.77	-0.071
12 months	61	0.71 $\pm$ 0.24	0	1.22 $\pm$ 0.72	-0.029
24 months	60	0.66 $\pm$ 0.27	-0.033	1.23 $\pm$ 0.67	0.004
36 months	57	0.65 $\pm$ 0.27	-0.025	1.21 $\pm$ 0.59	0.057
Signed-rank test (0 vs. 36)			<i>p</i> = .526		<i>p</i> = .047

TABLE 9 Mean clinical attachment level around implants and adjacent teeth (Δ shows the mean difference to baseline [0 month] in patients with both measurements. The *p*-values at the bottom refer to a Wilcoxon signed-rank test applied to the differences comparing 36 months with baseline)

	Total valid	CAL in mm			
		Implants	Δ	Teeth	Δ
0 month	63	2.76 $\pm$ 0.68		3.14 $\pm$ 0.85	
6 months	62	2.88 $\pm$ 0.96	0.139	3.08 $\pm$ 0.85	-0.077
12 months	61	3.05 $\pm$ 0.92	0.258	3.11 $\pm$ 0.82	-0.053
24 months	60	2.81 $\pm$ 1.09	-0.029	3.15 $\pm$ 0.75	0.002
36 months	57	2.78 $\pm$ 1.00	-0.029	3.19 $\pm$ 0.74	0.118
Signed-rank test (0 vs. 36)			<i>p</i> = .523		<i>p</i> = .052

of 0.79 mm, which is slightly larger as observed in the present study (0.60 mm). However, other clinical studies analyzing MBL around zirconia implants reported results of 0.13 mm (Brull, van Winkelhoff, & Cune, 2014) and 0.79 mm after 3 years (Spies et al., 2015), of 1.63 mm after 4 years (Borgonovo et al., 2013) and of 1.23 mm after 5 years (Grassi et al., 2015). Considering the fact that after an initial remodeling, no further significant marginal bone loss could be detected, and based on MBL after 3 years in this present study, it can be concluded that marginal bone level around zirconia implants might be stable over a longer period of time.

Although in the present investigation the mean marginal bone loss amounted only to 0.70 mm, it has to be revealed that two of 65 implants had a MBL $\geq$ 2 mm and four implants showed a MBL between 1.5 and 2 mm.

In the present investigation, none of the evaluated prognostic factors (center, jaw, type of reconstruction, implant diameter and length) had a significant influence on MBL except for the baseline value insertion depth. The small *p*-value (*p* < .001) for marginal bone level at implantation in the mixed effect model should be interpreted cautiously. In this change from baseline analysis, the baseline value was only considered for adjustment according to EMA guidance "Points to consider on Adjustment for Baseline Covariates (European Agency for the Evaluation of Medical Products, CPMP/EWP/2863/99)."

One implant of 71 failed in our investigation 5 weeks after implantation due to a loss of osseointegration. As three implants could not be evaluated at the 1-year follow-up and five at the 3-year follow-up, the survival rate was 98.6% after 1 year and 98.5% after 3 years, respectively.

In a recently published systematic review (Hashim, Cionca, Courvoisier, & Mombelli, 2016), the one-year overall survival rate of (one- and two-piece) zirconia implants was calculated with 92% (95% CI: 87%–95%). Due to the limited observation periods of the included studies, no meta-analysis could be performed for later time points. The authors also reported a tendency toward early failure of one-piece implants with a calculated early failure rate at 77% (95% CI: 56%–90%). However, no further loss of implants could be detected up to the 3-year follow-up.

At each follow-up, soft tissue parameters were recorded of the implants and neighboring teeth. BoP was significantly more frequent after prosthetic delivery over the whole observation time for implants in comparison with teeth, although the plaque frequency was significantly lower at implant sites compared to teeth. As described in the literature, BOP is considered a clinical key measure to distinguish between disease and peri-implant health (Jepsen et al., 2015) and is always present with peri-implant disease (Zitzmann & Berglundh, 2008). Nevertheless, peri-implantitis is characterized by changes in the marginal bone level in conjunction with BoP with or without concomitant deepening of PD (Lang, Berglundh, & Working Group 4 of Seventh European Workshop on Periodontology, 2011). In this study, no significant changes in marginal bone level could be found after delivery of the restorations. However, the analyses showed significant changes in PD ($p < .001$) on patient level and an increase in mean PD at implant sites but not for teeth.

Interestingly, the analysis for CAL at implant sites demonstrated no significant differences to baseline after 3 years although PD increased over time and ML remained stable. A possible reason behind this is that PD, ML and CAL have been measured individually. CAL was not calculated as the mathematically sum of PD and ML which could lead to a small discrepancy to the measured value. However, the CAL did not change significantly over the 3 years, neither for implants nor for teeth, indicating stable soft tissue conditions around the investigated implants.

The present study was designed as a prospective cohort investigation without a control group. This might be a major limitation of the study and does not allow a direct comparison within the same cohort to titanium implants. However, it allowed us to collect more data and to gain clinical experience with a rather new implant material. An affirmative factor is that the study was performed in two investigational centers, which reduces the center effect on the results.

In addition, 11 of 71 implants of the present study were placed with a simultaneous bone augmentation procedure using a xenogeneic bone substitute. This can be another limitation of the present study because bovine bone substitute shows a radiopacity similar to human bone. It is therefore often difficult to distinguish from pristine bone and could have had an influence on the radiographical measurements. To ensure a standardized analysis of the peri-implant bone loss, we measured the highest bone-to-implant contact without differentiating between human bone and substitute.

In conclusion, the investigated one-piece zirconia implant showed a high survival rate and a low marginal bone loss after 3 years in function. Therefore, the implant can be regarded as successful for single-tooth replacement and three-unit FDPs. Nevertheless, further

investigations with long-term data are still needed to confirm these positive findings.

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