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Zirconia implants restored with single crowns or fixed dental prostheses: 5-year results of a prospective cohort investigation

Balmer, Marc ; Spies, Benedikt C ; Kohal, Ralf-Joachim ; Hämmerle, Christoph Hans-Franz ; Vach, Kirstin ; Jung, Ronald E

Abstract: AIM: To evaluate the clinical and radiological outcomes of one-piece zirconia implants restored with single crowns (SCs) or fixed dental prostheses (FDPs) over an observation period of 5 years in function. **MATERIALS AND METHODS:** In a prospective cohort investigation with two investigational centers, one-piece zirconia implants were placed in anterior and posterior sites. After a healing period of at least 2 months in the mandible and 4 months in the maxilla with immediate provisional reconstructions, the final all-ceramic SCs or three-unit FDPs were cemented. Patients were followed for 5 years. Clinical parameters and radiological measurements of the implants and the neighboring teeth were assessed. For the statistical analysis, linear mixed models were applied. **RESULTS:** A total of 71 implants were placed in 60 patients. Sixty-three implants in 53 patients could be evaluated at the 5-year follow-up. Six patients with a total of seven implants were counted as dropouts. One implant did not achieve adequate osseointegration and had to be removed 5 weeks after implantation. The 5-year survival rate was calculated as 98.4% (95% CI 91.6, 99.9). The mean overall marginal bone loss from implant placement to the 5-year follow-up was 0.7 ± 0.6 mm. After an initial mean marginal loss before loading the implants (0.7 mm), no further statistically significant change in marginal bone level ($p = .458$) could be observed. **CONCLUSION:** The investigated one-piece zirconia implant showed a high survival rate, very stable marginal bone, and mucosal margin levels after 5 years in function. Therefore, it can be considered safe and reliable for the reconstruction of implant-supported SCs or FDPs over a mid-term period.

DOI: <https://doi.org/10.1111/clr.13581>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-187751>

Journal Article

Accepted Version

Originally published at:

Balmer, Marc; Spies, Benedikt C; Kohal, Ralf-Joachim; Hämmerle, Christoph Hans-Franz; Vach, Kirstin; Jung, Ronald E (2020). Zirconia implants restored with single crowns or fixed dental prostheses: 5-year results of a prospective cohort investigation. *Clinical Oral Implants Research*, 31(5):452-462.

DOI: <https://doi.org/10.1111/clr.13581>

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Article type : Original Research

Zirconia implants restored with single crowns or fixed dental prostheses:

5-year results of a prospective cohort investigation

(running title: 5-year analysis of zirconia implants)

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/CLR.13581](#)

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Keywords [MeSH]: bone, ceramic, clinical, dental implants, human, osseointegration, zirconia

Abstract

Aim: To evaluate the clinical and radiological outcomes of one-piece zirconia implants restored with single crowns (SCs) or fixed dental prostheses (FDPs) over an observation period of 5 years in function.

Material and Methods: In a prospective cohort investigation with two investigational centers one-piece zirconia implants were placed in anterior and posterior sites. After a healing period of at least 2 months in the mandible and 4 months in the maxilla with immediate provisional reconstructions, the final all-ceramic SCs or three-unit FDPs were cemented. Patients were followed for 5 years. Clinical parameters and radiological measurements of the implants and the neighboring teeth were assessed. For the statistical analysis linear mixed models were applied.

Results: A total of 71 implants were placed in 60 patients. 63 implants in 53 patients could be evaluated at the 5-year follow-up. Six patients with a total of 7 implants were counted as dropouts. One implant did not achieve adequate osseointegration and had to be removed 5 weeks after implantation. The 5-year survival rate was calculated as 98.4% (95% CI 91.6, 99.9). The mean

overall marginal bone loss from implant placement to the 5-year follow-up was 0.7 ± 0.6 mm. After an initial mean marginal loss before loading the implants (0.7 mm), no further statistically significant change in marginal bone level ($p=0.458$) could be observed.

Conclusion: The investigated one-piece zirconia implant showed a high survival rate, very stable marginal bone and mucosal margin levels after 5 years in function. Therefore, it can be considered safe and reliable for the reconstruction of implant-supported SCs or FDPs over a mid-term period.

Introduction

Ceramic implants are not a recent discovery in the field of oral implantology. They have been applied, as different publications have reported, already decades ago (Kawahara, 1984; Koth, McKinney, Steflik, Davis, 1988; Sandhaus, 1968). At that time, the majority of ceramic implants were produced from aluminum oxide. The material properties, in particular the high elastic modulus of about 340 GPa (Guess, et al., 2011), made it susceptible to bulk fractures.

Consequently, a safe and predictable clinical application could not be ensured and the alumina ceramic implants disappeared from the market. Meanwhile, significant advancements in the field of dental material science have made ceramics an attractive addendum to pure titanium or titanium alloys. Among the different available types of ceramics, yttria-stabilized zirconia exhibits appropriate mechanical properties with very high flexural strength (900-1200 MPa) and fracture toughness (7-10 MPa m^{1/2}) (Piconi, Maccauro, 1999).

Various zirconia implant systems are nowadays marketed, although their scientific evidence is still small. On the basis of a limited number of clinical studies on zirconia implants available in the recent literature, the available systematic reviews were only able to perform meta-analyses of survival rates after a period of two years and of marginal bone loss after one year (Hashim, Cionca, Courvoisier, Mombelli, 2016; Pieralli, Kohal, Jung, Vach, Spies, 2017; Roehling, Schlegel, Woelfler, Gahlert, 2018). Today, the use of zirconia implants is nonetheless justified by increased patient's specific requirements for metal-free implants and prosthetic solutions, and positive results from clinical and preclinical studies.

Animal investigations showed that failed titanium oral implants might be a result of substantial titanium release, which can be detected as particles in macrophages related to failed implants (Olmedo, Fernandez, Guglielmotti, Cabrini, 2003) and were even found in local lymph nodes (Frissen, Dandie, Lugowski, Jordan, 2002). Several studies demonstrated that osseointegration of zirconia implants is not inferior compared to titanium implants with well-documented rough surfaces (Bormann, et al., 2012; Hoffmann, Angelov, Zafiropoulos, Andreana, 2012; Kohal, Weng, Bachle, Strub, 2004; Pieralli, Kohal, Lopez Hernandez, Doerken, Spies, 2018; Thoma, et al., 2015). It was shown that biofilm formation was significantly reduced on zirconia surfaces compared to titanium surfaces in-vitro (Roehling, et al., 2017) as well as in-vivo (Scarano, Piattelli, Caputi, Favero, Piattelli, 2004). This possibility indicates that zirconia implants might be less susceptible to plaque-induced peri-implantitis. Furthermore, Nothdurft et al. demonstrated

that fibroblast cell response is influenced by both the material and surface topography and they could show significantly higher proliferation rates on zirconia compared to titanium alloy (Nothdurft, et al., 2015). This fibroblast cell response may be advantageous in a very early healing stage after implant placement.

If zirconia implants are to be successfully established in the market, their long-term safety and efficacy have to be proven in high-quality clinical trials including sufficient numbers of patients and with long observation periods.

Preliminary results of the current study were previously published after an observation time of 1 and 3 years (Balmer, et al., 2018; Jung, et al., 2016). However, long-term data after 5 or more years are still missing.

Therefore, the aim of the present study was to evaluate the clinical and radiological outcomes of one-piece zirconia implants restored with SCs or FDPs over an observation period of 5 years in function.

Material and Methods:

Study design:

The present study was performed at the University of Freiburg, Germany (Department of Prosthetic Dentistry, Center for Dental Medicine) and at the University of Zurich, Switzerland (Clinic of Fixed and Removable Prosthodontics and Dental Material Science, Center of Dental Medicine). This study was designed as a prospective cohort investigation (Dekkers, Egger, Altman, Vandenbroucke, 2012) and based on the requirements of the Declaration of Helsinki for ethical principles for medical research involving human subjects and according to the STROBE statement for observational studies. Prior to the start of the study, registration in the German Clinical Trials Register (ID: DRKS00000226) has been performed and approval of the study protocol by the two responsible local ethic committees was obtained. Patients to be included in the clinical trial were thoroughly informed and have given their informed written consent. Both centers underwent multiple calibration meetings before and during the course of the study.

Participants:

Patients were included if they were in need of exactly one implant for an implant-supported single crown (SC) or two terminal implants for a 3-unit implant-supported fixed dental prosthesis (FDP). The inclusion and exclusion criteria were described in detail in preliminary reports of the present study after 12 months (Jung, et al., 2016) and after 36 months (Balmer, et al., 2018). In brief, patients had to be in good general health, between 20 and 70 years old, non-smoker or only occasional smoker (max. 10 cigarettes per day) and had to show a good oral hygiene. Patients with active periodontitis were not included. Stabilized periodontitis measured by bleeding on probing, probing pocket depth and marginal bone levels was no criterion for exclusion. Anamnestic data or clinical signs of active bruxism were reasons for exclusion.

The recipient sites had to exhibit sufficient bone for a secure placement of an implant with a diameter of at least 4 mm and a length of 8 mm without the need of an increased bone augmentation. Simultaneous guided bone regeneration during implant placement was allowed to cover any exposed surfaces of the endosseous part of the implant or for contour augmentation in the esthetic area. Immediate implant placement was permitted, provided the osseous architecture ensured primary implant stability.

Intervention:

Six experienced operators of the two involved investigational centers performed the surgeries. For the insertion of the implants, the recipient area was anesthetized by local infiltration anesthesia (Ubistesin forte, 3M, Saint Paul, United States) and a mucoperiosteal flap was raised only to the extent necessary. A ceramic implant made of yttria-stabilized zirconia (Y-TZP) (ceramic.implant, vitaclinical, VITA Zahnfabrik, Bad Säckingen, Germany) was used in all patients. These implants were designed as screw-type, one-piece implants. The endosseous part had a cylindro-conical shape and an average surface roughness of 1.2 μm (Fischer, Schott, Martin, 2016). Implants were available in different lengths (8, 10, 12 and 14 mm) and different diameters (4.0, 4.5 and 5.0 mm) of the endosseous part. The preparation of the implant bed and the insertion of the implant were performed strictly according to the manufacturer's specifications. The protocol required a tapping with a thread cutter before implant insertion. The implants were prosthetically oriented placed and inserted until the rough-smooth borderline was located on the oral aspect at least epicrestally and the implant shoulder epimucosally. If indicated, guided bone regeneration was simultaneously performed with a deproteinized bovine bone material (BioOss® Spongiosa Granules, Geistlich Pharma, Wolhusen, Switzerland) and a collagen membrane (BioGide® Membrane, Geistlich Pharma). A transmucosal healing was chosen to allow an immediate provisional restoration with prefabricated SCs or FDPs made from PMMA. The provisional reconstructions were inserted with zinc-oxide-eugenol cement (Temp Bond, Kerr Corporation, Orange, United States). The occlusion of the inserted restorations was checked and if necessary adapted to avoid any extensive occlusal forces (Figure 1a-d). Patients received antibiotics for prophylactic purposes [3 times 750 mg Clamoxyl® (Zurich) or 3 times 300 mg Clindamycin (Freiburg) daily] during the following 5 days and were asked to rinse with a 0.2% chlorhexidine solution twice a day. Analgesics [500 mg Mefenacid (Zurich); 400 mg Ibuprofen (Freiburg)] were prescribed to reduce post-operative pain if necessary. Wound healing was controlled and sutures were removed after 7 to 10 days postoperatively.

Prosthetic insertion and follow-up:

After a healing period of at least 4 months in the maxilla and 2 months in the mandible, final SCs and FDPs were inserted. All reconstructions were produced with a zirconia framework (In-Ceram YZ, VITA Zahnfabrik), subsequently veneered (VM9, VITA Zahnfabrik) and adhesively cemented (RelyX Unicem 2 Aplicap, 3M Espe, Seefeld Germany)(Figure 1e). Detailed

information regarding manufacturing of the reconstructions, clinical prosthetic procedures and patient-reported outcome measures (PROMs) were published in separate publications with a special focus on analyses of the prosthetic outcomes (Spies, et al., 2017a; Spies, et al., 2019; Spies, Kohal, Balmer, Vach, Jung, 2017b). Patients were followed up annually from the first year to the fifth year after prosthetic insertions (Figure 1f-h). Aftercare included regular general dental checkups, professional dental hygiene and individual periodontal maintenance programs. The frequency of the check-ups was determined by the individual risk profile of each patient. Dental and periodontal assessments as well as supragingival cleaning were performed.

Examinations and analyses:

Baseline for the radiological analyses was implant placement. Radiographs were taken at implant placement, prosthetic insertion, 1-year, 3-year and 5-year follow-up. A paralleling device and a silicon registration material to reproduce the positioning allowed a standardized radiological recording. One single assessor evaluated marginal bone levels at the mesial and distal aspects of the implants and of the neighboring teeth (Figures 2a-e and 3a-e). Radiographs were calibrated using the distance between 5 implant threads. The distance between the implant shoulder and the first bone to implant contact was measured (ImageJ, National Institutes of Health, Bethesda, MD, USA). The difference in distance between implant placement (baseline) and the evaluated follow-up examination was calculated as marginal bone loss (primary outcome) for the respective period. Intra-examiner discrepancies when assessing marginal bone loss around implants have been shown (Walton, Layton, 2018). To take this into account, measurements were performed twice by the same assessor and mean values were used for analyses.

Baseline for the clinical analyses was prosthetic insertion. Clinical parameters were recorded mesially, distally, buccally and lingually at implants as well as at neighboring teeth by one examiner per investigational center. Distance to mucosal or gingival margin and clinical attachment level (CAL) were measured from implant crown margin, respectively from the cemento-enamel junction. Measurements were conducted with a periodontal-probe and rounded to the nearest millimeter. Furthermore, the Plaque Control Record (PCR) was performed and probing depth (PD) and bleeding on probing (BoP) were evaluated. The mean difference to baseline

(prosthetic insertion) was calculated in patients with data at baseline and the respective evaluated time-points.

Statistical Analysis

Sample size calculation was performed. The conditional probability of obtaining the desired precision given that the interval contains the true mean (mean marginal bone loss after 1, 3 and 5 years) was calculated. Using a standard deviation of 0.7 mm and a 2-sided 95% confidence interval, a total sample size of 60 patients was computed.

For the primary outcome (marginal loss bone) the mean, standard deviation and quartiles were calculated. Linear mixed models were used to statistically analyze changes in the mean marginal bone level between implant placement (baseline) and the 5-year follow-up and to evaluate the influence of several covariates (center, jaw, type of reconstruction and implant diameter). Within-subject dependencies (i.e. 2 implants within 1 patient) were taken into account (random intercepts). Survival rates of implants were calculated as proportions with exact confidence intervals.

Wilcoxon matched-pairs signed rank tests were applied to compare the clinical values between implants and adjacent teeth for each patient at all evaluation time-points. To analyze changes in clinical parameters on patient level between baseline and final follow up examination Wilcoxon signed-rank tests were applied.

For the statistical calculations, the statistical software STATA 14.2 (StataCorp LT, College Station, TX, USA) was used. The level of significance was set at $p < 0.05$.

Results

Demographics and baseline characteristics

A total of 60 patients (30 per investigational center) were consecutively recruited. 30 female and 30 male study participants with a mean age of 48.1 ± 13 years at pre-treatment examination were included. 71 implants were inserted between 11/2009 and 04/2011: 49 implants were intended to support 49 SCs and 22 implants to support 11 FDPs. Table 1 shows the details of the implant distribution. 11 implants (15.5%) were placed with a simultaneous bone augmentation procedure. One implant for a SC reconstruction in tooth region 36, did not osseointegrate and failed 5 weeks after implantation. As a result, 48 SCs and 11 FDPs were cemented after a mean healing period of 5.9 ± 4.4 months in the mandible and 6.4 ± 2.8 months in the maxilla.

At the 5-year follow up 53 patients with a total of 63 implants could be evaluated after a mean observation time of 5.6 ± 0.4 years after implantation. Six patients with a total of seven implants expressed that they no longer wished to participate in the trial for different reasons or without giving a reason for study withdrawal.

Marginal bone loss

Mean values, standard deviation and quartiles are listed in table 2. The mean overall marginal bone loss from implant placement to the 5-year follow-up (5.6 ± 0.4 years after implant placement) was 0.7 ± 0.6 mm. After an initial mean marginal loss before loading the implants (0.7 ± 0.6 mm), no further statistically significant change in marginal bone level ($p=0.458$) could be observed over the entire 5-year follow-up time period. In detail, after 5 years in function 57% ($n=36$) of the evaluated implants lost less than 1 mm of marginal bone, 22% ($n=14$) lost 1-1.5 mm, 10% ($n=6$) lost 1.5-2 mm and 2% ($n=1$) lost more than 2 mm. 10% ($n=6$) of the implants showed a stable marginal bone level or even gained some marginal bone.

Different prognostic factors on marginal bone loss during the 5 years of observation were evaluated. Table 3 lists all estimated regression coefficients and p-values of the evaluated prognostic factors according to the statistical analyses plan. Out of all evaluated prognostic factors, only the baseline value “marginal bone level at implantation” had a significant influence on marginal bone loss ($p=0.001$). In addition to the primary regression model, augmentation procedure was analyzed. Implant sites with grafting procedures showed non-significantly different marginal bone loss compared to sites without any bone augmentation procedures (0.1 mm (CI: [-

0.2, 0.5]) ($p=0.468$).

Implant survival

Seven implants in six patients could not be evaluated because the patients didn't show up for the 5-year follow-up and were counted as dropouts. Therefore, survival analysis was based on 64 implants in 54 patients. One implant had to be removed 5 weeks after implantation and was counted as failure. Implant survival rate after 5 years in function was calculated as 98.4% (95% CI 91.6, 99.9).

Clinical parameters

Table 4 shows appearance of plaque, bleeding on probing, probing depth, distance to the mucosal margin and clinical attachment level at zirconia implants and adjacent teeth at every evaluation time-point. Appearance of plaque increased for both, teeth and implants, within the first 6 months and was significantly higher for teeth at any time. Similarly, BoP showed an increase up to the 12-month follow-up and remained fairly high until the end of the investigation. BoP at tooth sites also increased from baseline to the 12-month follow-up with a second increase from 3 to 5 years. Bop was not significantly different at 48-month ($p=0.164$) and 60-month ($p=0.732$) follow-up examinations between implants and tooth sites.

No recession of the mucosal margin around implants could be evaluated from baseline to the end of the investigation. Distance from mucosal margin to implant crown margin did not increase significantly (0.1 mm; $p=0.189$). In contrast, the gingival margin around teeth showed a significant recession ($p<0.001$) with an increased distance to the cemento-enamel junction of 0.3 mm.

Except for the values at baseline, probing depth was significantly higher for implants ($p<0.001$) at every evaluation time-point. The probing depth showed a significant increase around implants over time ($p<0.001$), whereas it remained stable around teeth ($p=0.491$).

Measurements for clinical attachment increased significantly from 3.1 mm to 3.4 mm at teeth sites ($p=0.002$) but remained at a level of 2.8 mm at implants sites ($p=0.954$).

Based on the combination of the clinically evaluated parameters and the radiologically measured marginal bone loss, peri-implantitis was diagnosed only in one patient at one implant. This patient

was included in a cumulative peri-implantitis therapy with a stepwise approach, starting with non-surgical procedures.

Discussion

In the present prospective cohort investigation, 71 one-piece zirconia implants were placed in 60 patients and clinically and radiologically monitored over an observation period of 5 years in function. One implant was lost 5 weeks after implantation; thus, the survival rate of the investigated implants was 98.4%. The mean overall marginal bone loss from implant placement to the 5-year follow-up was 0.7 mm. After an initial mean marginal loss before loading the implants, no further statistically significant change in marginal bone level could be observed ($p=0.458$). The soft tissue conditions around implants showed stable conditions over the entire observation period. Mean marginal bone loss was analyzed as the primary outcome. Although radiological evaluation of marginal bone level around implants with standardized radiographs is used in numerous studies, it should be interpreted cautiously. Factors as level of accuracy of the measurements, radiograph brightness, experience of the examiners, recording angle and implant characteristics may have an influence on the measurements (Malloy, Wadhwani, McAllister, Wang, Katancik, 2017; Walton, Layton, 2018). This is a major limitation of the analyses of the current study.

In the present study, mean marginal bone loss was 0.7 ± 0.6 mm after a mean observation period of 5.6 ± 0.4 years. Besides mobility, pain and radiolucency, peri-implant bone loss is the most frequent criterion for success at implant level and together with BoP relevant for the diagnosis of peri-implantitis (Heitz-Mayfield, et al., 2018; Moraschini, Poubel, Ferreira, Barboza Edos, 2015). In dental literature multiple authors have considered a marginal bone loss of equal or less than 2 mm as a criterion for implant success (Misch, et al., 2008; Pjetursson, et al., 2018). The mean value for marginal bone loss in the present study is far below this generally suggested threshold and also slightly lower compared to studies reporting on marginal bone loss around zirconia implants with a similar observation period. A prospective study investigating 35 one-piece Y-TZP-implants in 13 patients reported a mean marginal bone loss of 1.6 mm after 48 months (Borgonovo, et al., 2013). Another prospective study evaluated marginal bone loss of

immediate and delayed placed one-piece Y-TZP-implants. Marginal bone loss was 1.3 mm for the immediate group and 1.2 mm for the delayed group after 61.2 months (Grassi, et al., 2015).

Studies with a longer observation period than 5 years described a mean marginal bone loss around one-piece zirconia implants of 1.0 mm after 71.3 months (retrospective study design including 161 Y-TZP-implants in 71 patients) (Roehling, Woelfler, Hicklin, Kniha, Gahlert, 2016) and 1.2 mm after 93.6 months (prospective study design including 83 Y-TZP-implants in 28 patients) (Lorenz, et al., 2019). Due to the lack of medium- to long-term data none of the existing systematic reviews on zirconia implants could perform a meta-analysis after 5 years (Haro Adanez, Nishihara, Att, 2018; Hashim, et al., 2016; Pieralli, et al., 2017; Roehling, et al., 2018).

However, the mean marginal bone loss in the present study is comparable to published data on titanium implants after 5 years (-0.2 – 0.8 mm) (Laurell, Lundgren, 2011).

The one-piece zirconia implants in the present study had a rough-smooth borderline located 2 mm apically from the implant shoulder and were surgically placed with this border epicrestally on the oral aspect. Guided bone regeneration was performed in cases with a buccal dehiscence. If neighboring teeth were present, the rough-smooth borderline at the mesial and distal aspects of the implants were often located considerably subcrestally due to the scalloped bone crest between implants and teeth. Radiological measurement evaluates only marginal bone levels mesial and distal of implants. Analysis of the radiological baseline values showed that the mean position of the rough-smooth border in the approximal area was 0.9 mm subcrestal. Previous investigations showed that implants with the rough-smooth border surgically placed below the crest showed a greater amount of remodeling within the first 6 months after implantation (Hartman, Cochran, 2004; Hermann, Cochran, Nummikoski, Buser, 1997). The mean marginal bone loss in the present study before loading the implants (0.7 mm) could be interpreted as the result of a similar remodeling process.

However, the mean bone loss is only the statistical average of all included implants and does not take into account single outliers with a value of 2 mm or more. Therefore, the present study additionally analyzed the distribution of the marginal bone loss. Despite individual periodontal maintenance programs and regular check-ups, one implant (SC; tooth position 45) exceeded this limit and must be judged as “satisfactory survival” (Misch, et al., 2008).

Based on the facts that after an initial remodeling process the marginal bone level remained stable over 5 years with no significant changes ($p=0.458$) and that only one implant exceeded the limit of

2 mm bone loss, it can be concluded that the presently investigated implant system showed promising results with a stable osseointegration.

None of the evaluated prognostic factors in relation to the marginal bone level – except of the baseline value “marginal bone level at implantation” - was statistically significant. This is in accordance with systematic reviews reporting that simultaneous bone augmentation and type of restoration (SC / FDP) had no significant influence on marginal bone loss around zirconia implants (Pieralli, et al., 2017; Roehling, et al., 2018). P-values for marginal bone levels should be interpreted with caution. In this change from baseline analysis according to scientific guidance of the European Agency for the Evaluation of Medical Products (CPMP/EWP/2863/99) baseline value (marginal bone level at implantation) was only considered for the adjustment for baseline co-variants.

In the present study, the implant survival rate was 98.4% (95% CI: 91.6, 99.9) after 5 years. One implant was lost 5 weeks after implantation without any signs of inflammation. The one-piece zirconia implants in the present study were immediately restored after implantation with a provisional reconstruction. The reconstructions had no occlusal contact, yet they were exposed to forces during masticatory function and during tongue movements. This could explain the early loss of the implant. In general, one-piece zirconia implants demonstrated a tendency towards early implant loss (Hashim, et al., 2016). Other studies on zirconia implants with similar observation periods reported survival rates of 100% after 48 months (Borgonovo, et al., 2013), 96.8% after 61.2 months (Grassi, et al., 2015), 77.3% after 71.3 months (Roehling, et al., 2016) and 100% after 93.6 months (Lorenz, et al., 2019). For comparison, the mean survival rates of titanium implants after 5 years reported in systematics reviews amounted 97.2% for implants supporting SCs (Jung, Zembic, Pjetursson, Zwahlen, Thoma, 2012) and 95.6% for implants supporting FDPs (Pjetursson, Thoma, Jung, Zwahlen, Zembic, 2012).

In the current study, the appearance of plaque at implants was constantly lower compared to the appearance at teeth. Interestingly, the constantly lower appearance of plaque did not result in a lower bleeding on probing. BoP was on a constantly high level during the whole observation period and permanently higher at implant sites. Partial explanations for BoP around the implants might be that many implant shoulders were submucosally located at the mesial and distal aspects during cementation. A submucosal cementation margin position increases the risk of undetected cement (Linkevicius, et al., 2013) and cement excess is identified as risk factor for peri-implant inflammation (Staubli, Walter, Schmidt, Weiger, Zitzmann, 2017). This might also explain the

increased probing depth around implants compared to baseline. The cementation process has to be considered as a major limitation of one-piece zirconia implants with an integrated abutment and may favor implants with screw-retained prostheses. However, although BoP is a positive predictive value for peri-implantitis (Hashim, Cionca, Combescure, Mombelli, 2018), no significant mean marginal bone loss could be observed in the present study.

Likewise, no reduction of the CAL or recession of the mucosal margin could be observed at implants sites during the entire observation period indicating stable soft tissue conditions around the implants. By comparison, the neighboring teeth showed during the same period a very small, but statistically significant recession of the gingival margin (0.3 mm, $p < 0.001$) and reduction in CAL (0.3 mm, $p = 0.002$). However, these very low values can hardly be regarded as clinically relevant.

One drawback of the present study is the missing control group in the form of a well-documented titanium implant system. Furthermore, zirconia implants with different lengths and diameters were placed by different operators, at different positions in the jaw und restored either with a SC or a FDP resulting in an inhomogeneous study population. This fact makes it difficult to identify a clear indication or specific risks of the presently investigated implant system.

Conclusion:

The investigated one-piece zirconia implant system showed a high survival rate, stable marginal bone and mucosal margin levels after 5 years in function. Therefore, it can be considered safe and reliable for the reconstruction of implant-supported SCs and FDPs over a mid-term period.

Acknowledgement: This investigation was supported by a grant from VITA Zahnfabrik H. Rauter GmbH & Co. KG, Bad Säckingen, Germany.

Disclosures Statement: Dr. Balmer, PD Dr. Spies, Prof. Dr. Kohal, Prof. Dr. Hämmerle and Prof. Dr. Jung report grants from Vita Zahnfabrik, during the conduct of the study. Outside the submitted work Dr. Balmer, PD Dr. Spies, Prof. Dr. Hämmerle and Prof. Dr. Jung report grants and personal fees from Vita Zahnfabrik and from PROSEC; Dr. Balmer, Prof. Dr. Hämmerle and Prof. Dr. Jung report grants and personal fees from Geistlich Pharma.

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Table 1: Implant distribution, number per implant lengths and diameters

FDI	17	16	15	14	13	12	11	21	22	23	24	25	26	27	Total	
n (maxilla)	1	1	4	5	1	0	1	0	0	0	2	5	3	0	23	71
n (mandible)	4	11	4					1			2	7	13	6	48	
FDI	47	46	45	44	43	42	41	31	32	33	34	35	36	37		
Implant Diameter	4.0 mm				4.5 mm				5.5 mm							
n	26				32				13				71			
Implant Length	8 mm			10 mm			12 mm			14 mm						
n	12			39			19			1			71			

FDI: tooth identification according the World Dental Federation

n: number of placed implants in the respective position or of respective diameter

Table 2: Marginal bone loss from baseline (implant placement) to the different follow-up time points. Positive values indicate a marginal bone loss, negative values a gain in marginal bone level. SCs = implant-supported-single crowns; FDPs = implant-supported fixed dental prostheses

	Marginal bone loss at prosthetic delivery (mm)									
Treatment	Total	Missing	Total valid	Mean	SD	Min.	1. Quartile	Median	3. Quartile	Max
SCs	49	2	47	0.7	0.6	-0.4	0.3	0.6	1.1	2.8
FDPs	22	1	21	0.5	0.4	-0.1	0.1	0.6	0.9	1.4
Total	71	3	68	0.7	0.6	-0.4	0.3	0.6	1.0	2.8
	Marginal bone loss at the 1-year follow-up (mm)									
Treatment	Total	Missing	Total valid	Mean	SD	Min.	1. Quartile	Median	3. Quartile	Max
SCs	49	3	46	0.7	0.6	-0.5	0.2	0.6	1.0	2.3
FDPs	22	3	19	0.4	0.4	-0.1	0.0	0.4	0.8	1.4
Total	71	6	65	0.6	0.6	-0.5	0.2	0.5	0.9	2.3
	Marginal bone loss at the 3-year follow-up (mm)									
Treatment	Total	Missing	Total valid	Mean	SD	Min.	1. Quartile	Median	3. Quartile	Max
SCs	49	6	43	0.7	0.8	-0.4	0.2	0.6	1.1	3.2
FDPs	22	1	21	0.6	0.6	-0.6	0.4	0.6	1.1	1.8
Total	71	7	64	0.7	0.7	-0.6	0.3	0.6	1.1	3.2
	Marginal bone loss at 5-year follow-up (mm)									
Treatment	Total	Missing	Total valid	Mean	SD	Min.	1. Quartile	Median	3. Quartile	Max
SCs	49	6	43	0.8	0.6	-0.5	0.4	0.7	1.2	2.7
FDPs	22	3	19	0.6	0.7	-0.9	0.3	0.6	1.1	1.6
Total	71	9	62	0.7	0.6	-0.9	0.4	0.7	1.1	2.7

Table 3: Evaluated prognostic factors on marginal bone loss at the 5-year follow-up: estimated regression coefficients (estimators) and p-values according to the statistical analyses plan. Estimators show the difference between the two groups at the 5-year follow-up. Positive values for estimators indicate a larger bone loss relative to the comparison.

Variable	Estimator (marginal bone loss at the 5-year follow-up)	95% CI	p-Value
Marginal bone level at implantation (per mm)	-0.6 mm	[-0.9, -0.2]	0.001
Zurich relative to Freiburg	0.2 mm	[-0.2, 0.5]	0.320
Maxilla relative to mandible	0.0 mm	[-0.4, 0.3]	0.911
Implant-supported fixed dental prostheses relative to implant-supported single crown	-0.2 mm	[-0.7, 0.3]	0.419
Implant diameter 4.5 relative to 4.0	0.0 mm	[-0.3, 0.3]	0.625
Implant diameter 5.5 relative to 4.0	0.2 mm	[-0.2, 0.6]	
Implant length 10 relative to 8	-0.2 mm	[-0.5, 0.1]	0.174
Implant length 12 relative to 8	0.1 mm	[-0.3, 0.5]	

Implant length 14 relative to 8	-0.2 mm	[-1.3, 0.9]	
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Table 4: Clinical parameters of implants and adjacent teeth. Number of valid patients, mean, standard deviation and difference to baseline (Δ) are listed. Wilcoxon signed-rank tests were applied to compare values between implants and adjacent teeth for each patient at all evaluation time-points and to analyze changes in clinical parameters on patient level between baseline and final follow-up examination.

Plaque in %	Total valid (patients)	Implants (mean $\pm$ SD)		Teeth (mean $\pm$ SD)		Signed-rank test
			Δ		Δ	
0 months	63	11.8 $\pm$ 25.8		21.0 $\pm$ 25.5		p=0.003
6 months	62	22.1 $\pm$ 30.8	10.1	37.5 $\pm$ 32.9	16.1	p<0.001
12 months	61	21.6 $\pm$ 29.8	9.3	41.6 $\pm$ 32.6	19.9	p<0.001
24 months	60	20.1 $\pm$ 27.9	7.8	47.3 $\pm$ 30.5	25.2	p<0.001
36 months	57	20.8 $\pm$ 26.7	8.5	41.4 $\pm$ 29.3	19.3	p<0.001
48 months	56	22.6 $\pm$ 24.9	9.9	45.8 $\pm$ 28.7	23.4	p<0.001
60 months	56	26.2 $\pm$ 27.5	13.5	42.2 $\pm$ 28.9	19.9	p=0.001
Signed-rank test (0 vs. 60)			p= 0.001		p<0.001	
BoP in %	Total valid (patients)	Implants (mean $\pm$ SD)	Δ	Teeth (mean $\pm$ SD)	Δ	Signed-rank test
0 months	63	16.8 $\pm$ 27.5		13.5 $\pm$ 21.9		p=0.909
6 months	62	43.5 $\pm$ 36.5	26.4	29.4 $\pm$ 42.8	16.1	p=0.005
12 months	61	57.5 $\pm$ 32.9	41.8	34.0 $\pm$ 48.9	20.5	p<0.001
24 months	60	48.9 $\pm$ 36.3	31.7	30.8 $\pm$ 38.9	17.1	p=0.001
36 months	57	40.8 $\pm$ 32.9	23.5	23.2 $\pm$ 33.0	9.6	p=0.005
48 months	56	52.8 $\pm$ 35.4	37.3	45.5 $\pm$ 47.2	32.1	p=0.164
60 months	56	48.0 $\pm$ 33.1	32.5	45.5 $\pm$ 42.4	32.1	p=0.732

Signed-rank test (0 vs. 60)			p<0.001		p<0.001	
PD in mm	Total valid (patients)	Implants (mean ± SD)	Δ	Teeth (mean ± SD)	Δ	Signed-rank test
0 months	63	2.7±0.6		2.5±0.4		p=0.111
6 months	62	3.2±0.6	0.6	2.5±0.5	-0.1	p<0.001
12 months	61	3.5±0.7	0.8	2.4±0.5	-0.1	p<0.001
24 months	60	3.6±0.7	0.9	2.5±0.5	-0.1	p<0.001
36 months	57	3.5±0.7	0.8	2.5±0.6	0.0	p<0.001
48 months	56	3.5±0.6	0.8	2.6±0.5	0.0	p<0.001
60 months	56	3.3±0.6	0.7	2.5±0.4	-0.1	p<0.001
Signed-rank test (0 vs. 60)			p<0.001		p=0.491	
distance to mucosal / gingival margin in mm	Total valid (patients)	Implants (mean ± SD)	Δ	Teeth (mean ± SD)	Δ	Signed-rank test
0 months	63	0.7±0.3		1.2±0.8		p<0.001
6 months	62	0.7±0.5	0.0	1.2±0.8	-0.1	p<0.001
12 months	61	0.7±0.2	0.0	1.2±0.7	0.0	p<0.001
24 months	60	0.7±0.3	0.0	1.2±0.7	0.0	p<0.001
36 months	57	0.7±0.3	0.0	1.2±0.6	0.1	p<0.001
48 months	56	0.8±0.3	0.1	1.4±0.7	0.3	p<0.001
60 months	56	0.8±0.4	0.1	1.5±0.7	0.3	p<0.001
Signed-rank test			p=0.189		p<0.001	

(0 vs. 60)						
mean CAL in mm	Total Valid (patients)	Implants (mean ± SD)	Δ	Teeth (mean ± SD)	Δ	Signed- rank test
0 months	63	2.8±0.7		3.1±0.9		p= 0.012
6 months	62	2.9±1.0	0.1	3.1±0.9	-0.1	p=0.321
12 months	61	3.1±0.9	0.3	3.1±0.8	-0.1	p=0.943
24 months	60	2.8±1.1	0.0	3.2±0.8	0.0	p=0.046
36 months	57	2.8±1.0	0.0	3.2±0.7	0.1	p=0.026
48 months	56	2.8±0.8	0.1	3.4±0.8	0.3	p<0.001
60 months	55	2.8±0.8	0.1	3.4±0.8	0.3	p<0.001
Signed- rank test (0 vs. 60)			p=0.954		p=0.002

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