Received: 16 April 2021 | Revised: 8 November 2021 | Accepted: 18 November 2021

DOI: 10.1111/clr.13889

ORIGINAL ARTICLE

CLINICAL ORAL IMPLANTS RESEARCH WILEY

Informative title: Guided bone regeneration with and without rhBMP-2: 17-year results of a randomized controlled clinical trial

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Abstract

Objectives: To assess long-term outcomes of implants placed in conjunction with guided bone regeneration (GBR) with or without recombinant human bone morphogenetic protein-2 (rhBMP-2).

Materials and Methods: Eleven patients with at least two lateral bone defects (split-mouth design) received a total of 34 implants. The defects were treated with a xenogenic bone substitute with (test) or without (control) rhBMP-2 and covered with a collagen membrane. Eight patients could be reexamined after at least 17 years. Wilcoxon signed-rank tests were performed to assess differences between test and control groups.

Results: The implant survival rate was 100% for all test and control sites. Mean marginal bone levels were 2.51 mm (SD ±1.64) (mesial test), 1.83 mm (SD ±0.93) (mesial control) ($p = .055$), 2.36 mm (SD ±1.70) (distal test), and 2.13 mm (SD ±0.84) (distal control) ($p = 1.000$). Compared with the mean values at baseline, a mean bone loss of 1.16 mm (SD ±1.60) (test) and 0.70 mm (SD ±1.02) (control) was found. The mean buccal bone gain after 17 years was 5.38 mm (test) and 3.14 mm (control) based on the comparison between the measurements at the cone beam CT after 17 years and the data from the intraoperative measurements at baseline. Further, mean values for (i) bone thickness ranged from 1.36 to 3.09 mm (test) and 1.18 to 3.39 mm (control) and for (ii) mucosal thickness of 1.24 mm (test) and 1.26 mm (control).

Conclusion: Implants placed in conjunction with GBR applying a xenogenic bone substitute and a collagen membrane with and without the addition of rhBMP-2 demonstrate excellent clinical and radiographic results after at least 17 years.

KEYWORDS
bone graft, bone morphogenetic protein, bone regeneration, dental implants, deproteinized bovine bone, growth factor, human, membrane

1 | INTRODUCTION

Single-tooth implants show high survival rates for both implants and crowns and are thus considered to be a safe and predictable restoration method for single-tooth gaps (Jung et al., 2012). A lack of adequate bone quantity at implant sites, however, leads to increased failure rates (Chrcanovic et al., 2014).

Various techniques and materials have been described to reconstruct deficient alveolar ridges and to establish sufficient bone tissue to support implants (Hämmerle et al., 2002). Autogenous bone grafting (Cordaro et al., 2002; Simion et al., 1998), distraction osteogenesis (Chiapasco et al., 2007), bone splitting (Enislidis et al., 2006), and guided bone regeneration (GBR) (Hämmerle & Karring, 1998; Nyman, 1991) are among those techniques. GBR, in particular, is the best-documented and most prevalent bone regeneration technique and is used prior to or concomitantly with implant placement (Benic & Hämmerle, 2014; Jung et al., 2013). Implants placed in regenerated bone using GBR have been found to show similar survival rates as implants in non-regenerated bone (Aghaloo & Moy, 2007; Hämmerle et al., 2002).

The current research trends aim to reduce treatment time, enhance treatment predictability, and reduce surgical invasiveness by implementing growth factors. The intention is to increase the body's capability to regenerate lost tissue instead of just replacing it. Several growth factors, including but not limited to bone morphogenetic proteins, growth and differentiation factors, platelet-derived growth factor, vascular endothelial growth factor, and insulin-like growth factor, have been investigated for bone regeneration (for a comprehensive review see Benic & Hämmerle, 2014). In vitro as well as in vivo studies have shown that the utilization of growth factors increases tissue regeneration (Smith et al., 2015). Bone morphogenetic protein-2 (BMP-2), in particular, influences osteoblastogenesis and bone formation Lin et al., 2015; Smith et al., 2015) and could be shown—in its recombinant form rhBMP-2—in several clinical studies to improve the outcome of local bone augmentations (Benic & Hämmerle, 2014). The traditional absorbable collagen sponge (ACS) (Boyne et al., 2005), a compression-resistant matrix consisting of a ceramic/collagen composite (Herford et al., 2012), tricalcium phosphate (TCP) (Jung et al., 2008; Zétola et al., 2015), or xenogenic bone substitute (Jung et al., 2003) serve as carrier materials. Deproteinized bovine-derived bone mineral is currently the best-documented and most often used bone substitute in implant dentistry (Benic & Hämmerle, 2014; Thoma et al., 2019).

There is a lack of clinical long-term data on simultaneous implant placement and bone regeneration by means of GBR procedures with and without recombinant human bone morphogenetic protein-2 (rhBMP-2). So far, only studies with a follow-up period of 5.5 years are available (Jung et al., 2009; Kim et al., 2014; Noshchenko et al., 2014; Zétola et al., 2015).

The aim of the present long-term follow-up study was to evaluate the clinical and radiologic outcomes of implants placed in conjunction with GBR with or without rhBMP-2 at least 17 years after implant loading.

2 | MATERIALS AND METHODS

2.1 | Study population and study design

Eleven patients (seven women and four men) requiring implant therapy were included in the present prospective, controlled, and randomized study and were treated between December 1999 and March 2000 at the University of Zurich (Jung et al., 2003). All procedures and materials were previously approved by the local ethical committee (approval number 2018-00111). Written informed consent was obtained from all patients. Their median age was 53 years (ranging from 27 to 75 years), they were all in good general health, and all underwent comprehensive dental care at private offices. Each patient received at least two implants at different areas of the mouth with osseous defects (split-mouth study design). All test and control areas were situated in the same jaw and consisted of either single- or extended-tooth gaps.

The present study represents a follow-up of the previously published study on the effect of rhBMP-2 on GBR in humans (Jung et al., 2003) and also the previously published three- and five-year data (Jung et al., 2009).

2.2 | Dental implants

In total, 34 implants (Brånemark, Nobel Biocare) were inserted into sites with bony defects (18 at test sites and 16 at control sites). From each patient, one test and one control implant were included for data analysis. In cases of patients with three or more implants, two implants (one test and one control) were randomly chosen.

2.3 | Regeneration material

The defect sites were augmented with a xenogenic bone substitute mineral either containing or not containing rhBMP-2. The rhBMP-2 used in this study was produced in a licensed laboratory under good laboratory practice according to a method previously described (Weber et al., 2002). For loading, 0.5 g of the xenogenic bone substitute mineral (Bio-Oss® spongiosa granules 0.25–1 mm, Geistlich AG) was used. The material was removed from the original package and placed in a sterile tube. The test samples were evenly moistened with 1 ml of a 0.5 mg/ml rhBMP-2 solution and the control samples with 1 ml of 0.01% trifluoroacetic acid. After 1 h of equilibration, the tubes were put in sterile lyophilization containers and lyophilized under sterile conditions. The individual batches were prepared up to two weeks before implantation and stored at 4°C until use. The tubes with the bone substitute material were assigned to each patient. One tube containing rhBMP-2 to be used for the test site and one tube without rhBMP-2 to be used at the control site. On average, a dose of 0.18 mg (standard deviation [SD] ±0.13) of rhBMP-2 was used for the test sites. At no point during the study were the surgeons, examiners, or patients

aware if a particular tube contained rhBMP-2 or not, thus representing true, unbiased randomization.

2.4 | Surgical procedure

The surgical procedure is briefly summarized as follows: the patients received antibiotics and analgesics 1 h before surgery. Thereafter, a full thickness mucosa flap was raised and the implant site prepared; the surgery was performed according to the recommendations by the manufacturer (Brånemark implant system procedures).

Following implant insertion, the type of defect (dehiscence or fenestration) was noted for each defect. Using a calibrated periodontal probe, the following clinical measurements were determined in millimeters: defect height, infrabony defect, defect depth, and defect width.

The defect sites were treated with the demineralized bovine bone mineral with or without rhBMP-2. Each site was subsequently covered with a bioresorbable collagen membrane (Bio-Gide®, Geistlich AG). The membrane was trimmed and adapted to overlap the defect border by at least 2 mm and fixed by resorbable pins made of polylactic acid (Resor Pin®, Geistlich AG). After periosteal releasing incisions, the flap was repositioned and adapted using horizontal mattress and single interrupted sutures. The implants were left to heal in a submerged position.

2.5 | Reentry and prosthetic procedure

A reentry surgery was performed after an average healing period of 6 months (SD ±0.17) in order to measure the residual defects, to take bone biopsies, and to perform abutment connection. At this point, all the implants were stable (Jung et al., 2003). After a period of 6–8 weeks, implant impressions were taken. The prosthetic reconstructions were inserted 2–4 weeks later. Subsequently, periapical x-ray images using the parallel technique were made which served as the baseline radiographs.

2.6 | Follow-up examinations

The first two follow-up examinations were performed and published 3 and 5 years after insertion of the prosthetic restoration (Jung et al., 2009).

For the present follow-up, a total of eight (out of originally 11) patients could be recruited. Two of the patients of the original study were deceased, and one could not be called due to missing contact details. The examinations took place at the University of Zurich between March 2018 and January 2019. Hence, these follow-ups were conducted at least 17 years after insertion of the implants.

This present study largely followed the same set-up as the previous two follow-ups, namely all patients filled out questionnaires and were examined clinically and radiologically. Additionally, in the present study a cone beam computed tomography (CBCT) scan was performed for each patient to determine buccal bone and soft tissue levels around the study implants.

Unless otherwise stated, data of only these eight patients examined in this present study were used for analysis over time.

2.7 | Personal questionnaire

The impact of the treatment on the health of the periimplant tissues was assessed by the patients by filling out a questionnaire prior to the clinical and radiological examinations. This evaluation form consisted of both questions to be answered in written form and by visual analog scales (VAS). In particular, the condition of the soft tissues and the ability to perform oral hygiene were assessed by using the VAS. Therein, patients were asked to make a cross on the scale which ranges from "worse" (0%) to "better" (100%). There was also an evaluation of the patients' satisfaction regarding pain, swelling, color of the alveolar mucosa, inflammation, uncomfortable sensation, and differing sensation between the left and the right side. Further, the patients were asked whether they are in a steady recall program at a dentist or dental hygienist. Ultimately, they were also questioned about their prosthetic reconstruction, in particular about the loosening of the implant reconstruction or possible ceramic chippings.

In addition to the customized personal questionnaire, all patients were asked to complete the internationally standardized Oral Health Impact Profile questionnaire with 14 questions (OHIP-G 14).

2.8 | Clinical evaluation

The following clinical parameters were evaluated: (i) full-mouth plaque score (FMPS) (Lang et al., 1986), (ii) full-mouth bleeding score (FMBS) (O'Leary et al., 1972), and (iii) probing depth (PD). The PD was measured around each implant and its two adjacent teeth. For analysis, the mesial and distal values have been averaged to one proximal value. Additionally, the implants were checked for clinical signs of osseointegration by percussion test and tactile examination.

The prosthetic reconstructions were evaluated according to the US Public Health Service (USPHS) criteria (Ryge & Cvar, 1971) and included the following parameters: (i) frame fracture, (ii) veneer fracture, and (iii) occlusal abrasion.

2.9 | Radiographic evaluation

In order to assess the interproximal marginal bone level (MBL) around the implants, digital intraoral radiographs were taken using the long-cone paralleling technique with the central beam directed to the alveolar crest (Hawe x-ray film holder; Kerrhawe SA). Utilizing an image analysis program (Image J, Version 1.52a, Rasband, 1997–2018), the MBL (distance between the implant shoulder (IS) and the

first bone to implant contact) was measured at the mesial and distal aspect with a 10–15× magnification (Buser et al., 1996; Weber et al., 1992). The measured distance between three implant threads was used to determine the exact magnification and distortion of the images (Rodoni et al., 2005). All measurements were conducted by two examiners (M.N.K. and A.G.) to the closest 0.1 mm. In case of disagreement, the evaluation was redone and results discussed until an agreement was found.

To determine the buccal bone and the soft tissue levels, three-dimensional radiographs were taken and examined. A radio-opaque flowable composite material was applied onto the previously dried mucosa around the implants. The radiographs were taken using a 3D-Exam CBCT device (KaVo Dental). A digital imaging program (OsiriX Lite, Pixmeo SARL) was used for the analysis of the CBCT images. A centered bucco-oral cross-section perpendicular to the implant axis was used, and the following parameters measured: (i) distance between IS and most coronal bone-implant contact (BIC), (ii) horizontal bone thickness at the BIC and 1, 3, and 5 mm apically of the BIC, (iii) distance between IS and mucosal margin level (MML), and (iv) mucosal thickness 1 mm apically of the MML. The known implant length was utilized to distinctly determine the position of the IS. All measurements were again conducted by the two examiners (M.N.K. and A.G.) to the closest 0.1 mm. In case of disagreement, the evaluation was redone and results discussed until an agreement was found.

2.10 | Statistical analysis

The radiographic and clinical data were analyzed using R (R Core Team, 2019).

Mean values and SD were determined, and box plots were used to visualize the distribution of the data.

Wilcoxon signed-rank tests were performed to assess statistical differences between the test and control groups. The statistical significance level was set to $\alpha = .05$.

3 | RESULTS

3.1 | Follow-up outcomes

All eight patients stated that they had been in a regular recall schedule with their dentist and/or dental hygienist since implant insertion.

Implant survival at the follow-up examination was 100% for all test and control sites. The examined implants all showed clinical signs of osseointegration. The clinical examination revealed healthy periimplant tissues and only minimal marginal bone loss in most patients, except for one patient who showed signs of periimplantitis around the test implant (pus on probing and PD between 7 and 8 mm).

TABLE 1 Clinical conditions at test and control implant sites

	17-year reexamination		
	Buccal	Oral	Proximal
(a) Clinical conditions at test implants			
Plaque (number of sites)	1	2	22
BOP (number of sites)	6	2	18
Probing depth (mean) (mm)	3.1	2.4	3.8
PD ≤3 mm (%)	75	87.5	56.25
PD 4–5 mm (%)	12.5	12.5	28.13
PD ≥6 mm (%)	12.5	-	15.63
(b) Clinical conditions at control implants			
Plaque (number of sites)	3	3	18
BOP (number of sites)	3	3	18
Probing depth (mean) (mm)	2.8	2.6	3.5
PD ≤3 mm (%)	87.5	87.5	53.13
PD 4–5 mm (%)	12.5	-	40.63
PD ≥6 mm (%)	-	12.5	6.25

Abbreviations: BOP, bleeding on probing; PD, probing pocket depth.

3.2 | Personal questionnaire

The personal questionnaire reflects the patients' satisfaction and experiences since implant insertion at least 17 years prior. The condition of the gums was assessed on the VAS (0% = worse, 100% = better) at a mean of 48.8% (SD ±23.3) and the ability to maintain an adequate oral hygiene at a mean of 52.9% (SD ±24.9). Four patients reported sporadic swelling and pain of the gums around the implants (test and control implants). One patient perceived a dull feeling on all implants when chewing and one patient reported gum recession and food impaction in the region of the test implant.

On the OHIP-G 14 form, the patients evaluated their oral health-related quality of life in the past month generally very highly. Three patients reported occasional pain in the oral region, and two patients felt uncomfortable eating certain food items. Two patients perceived their lives to be generally less satisfactory, and one of them additionally reported an impaired sense of taste and difficulty to relax.

3.3 | Clinical examinations

3.3.1 | Full-mouth plaque score and full-mouth bleeding score

The mean FMPS was determined to be 39.7% (SD ±21.3) and the mean FMBS 26.6%. (SD ±12.4) The detailed results for the plaque score and bleeding score around test and control implants are listed in Table 1a and b.

3.3.2 | Probing pocket depth

The values for the PD can be found in Table 1a and b. The mean probing depths for the test implants were 3.1 mm (buccal) (SD ±1.46), 2.4 mm (oral) (SD ±0.92), and 3.8 mm (proximal) (SD ±1.74). For the control implants, the mean probing depths were 2.8 mm (buccal) (SD ±0.71), 2.6 mm (oral) (SD ±1.60), and 3.5 mm (proximal) (SD ±1.24).

3.3.3 | Prosthetic evaluation

Patient

Most patients did not report any damages of their prosthetic reconstructions. One patient remembered a screw loosening on a control implant shortly after insertion of the crown. Another patient reported a chipping on the crown of a control implant, which was subsequently polished by the respective private dentist.

Clinical prosthetic examination

The prosthetic reconstructions were examined according to the USPHS criteria and are listed in Table 2a and b. Only A- and B-rated reconstructions were found at the 17-year examination. In total, three polishable veneer fractures (12.5% of all test and 25% of all control crowns) were found and 12 crowns (100% of all test and 50% of all control crowns) showed occlusal wear (Figures 1 and 2).

3.4 | Radiographic examinations

3.4.1 | Periapical radiographs

The mean MBL is listed in Table 3a (test sites) and 3b (control sites) for baseline and the 17-year follow-up. Additionally, the data gathered for the eight reexamined patients at the 3- and 5-year follow-ups (Jung et al., 2009) are listed for comparison over time. No statistically significant differences were noticed between test and control implants at the 17-year follow-up (mesial $p = .055$, estimated difference = −0.487, 95% CI = [−1.90; 0.05]) (distal $p = 1.000$, estimated difference = 0.014, 95% CI = [−1.775; 0.775]) (Figures 3 and 4).

Table 4a (test sites) and 4b (control sites) describes mean changes of the MBL between periapical radiographs taken at baseline and at the 17-year examination. The mean changes of the MBL at test sites were −1.17 mm (mesial) (SD ±1.61) and −1.14 mm (distal) (SD ±1.69) and at control sites −0.57 mm (mesial) (SD ±1.03) and −0.82 mm (distal) (SD ±1.07), signifying a slight bone loss over time.

3.4.2 | Cone beam computed tomography

The mean values for buccal defect height (measured as the distance between IS and most coronal BIC) are listed in Table 5a (test sites) and 5b (control sites). Further, horizontal bone thickness was measured at four different levels, that is, at the very point of BIC and at

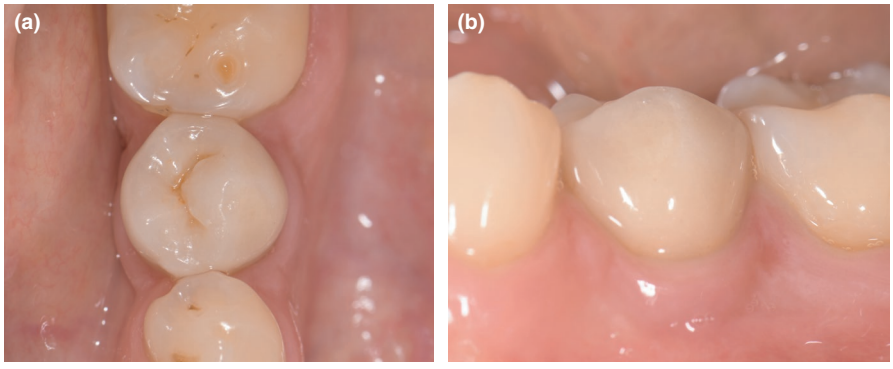

FIGURE 1 (a) Occlusal and (b) buccal view of test implant 35 at 17 years

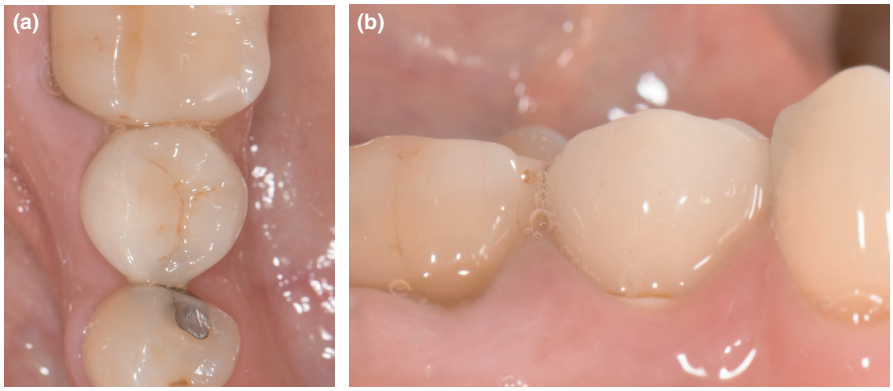

FIGURE 2 (a) Occlusal and (b) buccal view of control implant 45 at 17 years

1, 3, and 5 mm apically thereof. The mean values, ranging from 1.36 to 3.06 mm (test) and 1.18 to 3.39 mm (control), are also listed in Table 5a (test sites) and 5b (control sites). One control implant had to be excluded due to strong blurring of the implant–cortical bone interface in the CBCT.

Two mucosal variables (i) the distance between IS and MML and (ii) mucosal thickness 1 mm apically of the MML were also measured and are listed in Table 5a (test sites) and 5b (control sites).

Table 6a (test sites) and 6b (control sites) displays the mean change in defect height by comparing the intraoperative measurements taken at the time of implant placement with the CBCT results of the 17-year follow-up. At test sites, a mean bone gain of 5.38 mm was noted between implantation and reexamination after at least 17 years. At control sites, the mean bone gain between implantation and 17-year follow-up was 3.14 mm.

TABLE 2 Prosthetic reevaluation of the test and control sites according to the USPHS criteria

	17-year reexamination			
	Alpha	**Bravo**	**Charlie**	**Delta**
(a) Criteria of the USPHS index at test sites				
Frame fracture	8 (100%)	-	-	-
Veneer fracture	7 (87.5%)	1 (12.5%)	-	-
Occlusal wear	-	8 (100%)	-	-
(b) Criteria of the USPHS index at control sites				
Frame fracture	8 (100%)	-	-	-
Veneer fracture	6 (75%)	2 (25%)	-	-
Occlusal wear	4 (50%)	4 (50%)	-	-

Note: The absolute number of implants is given (percentage in parentheses).

Abbreviation: USPHS, US Public Health Service.

4 | DISCUSSION

The present long-term randomized controlled clinical trial (RCT) reveals promising results for implants placed in conjunction with GBR with or without the addition of rhBMP-2 after 17 years of prosthetic loading. For the first time, the long-term stability of sites treated with a xenogenic bone substitute mineral and a collagen membrane with or without the addition of rhBMP-2 could be shown, which confirms the predictability and reliability of these GBR procedures. The survival rates of all reexamined implants and the prosthetic reconstructions were 100% with only minor complications. Several systematic reviews found high implant survival rates between 95.5% and 100% for GBR procedures in general (Aghaloo & Moy, 2007; Khojasteh et al., 2017; Sanz-Sanchez et al., 2015). Regarding long-term outcomes of implants placed in bone augmented with GBR techniques specifically, a study found an implant survival rate of 91.9%–92.6% over an observation period of 12–14 years (Jung et al., 2013). A reason for the high survival rate in the present study might be the small sample size of eight split-mouth patients that were examined.

The level of oral care of the eight reexamined patients at 17 years after implantation was comparable to the 3-year and the 5-year follow-ups of all 11 original patients (Jung et al., 2009). The values for FMPS are also comparable to the ones found in another study on simultaneous implant placement with GBR. The FMBS in that study,

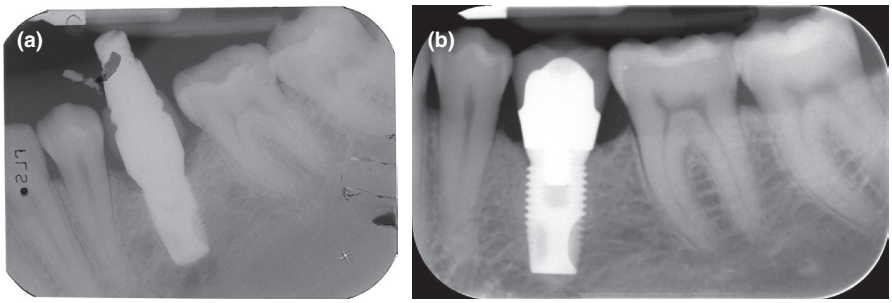

FIGURE 3 Periapical x-rays of test implant 35 at (a) baseline and (b) 17 years

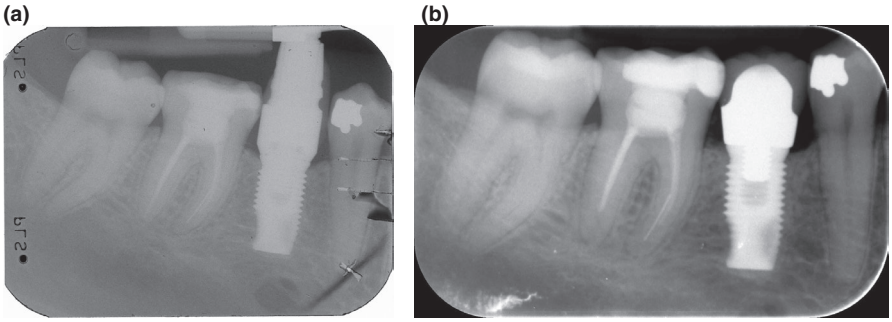

FIGURE 4 Periapical x-rays of control implant 45 at (a) baseline and (b) 17 years

TABLE 3 Mean distances from the first bone to implant contact to the implant shoulder, standard deviations (SD), min and max values (mm) at test and control sites

	Baseline mesial	Baseline distal	3 years mesial[a]	3 years distal[a]	5 years mesial[a]	5 years distal[a]	17 years mesial	17 years distal
(a) marginal bone level at test sites (mm)								
Mean	1.34	1.22	1.37	1.30	1.30	1.25	2.51	2.36
SD	0.41	0.25	0.36	0.35	0.41	0.36	1.64	1.70
Minimum	0.96	0.90	0.91	0.88	0.81	0.89	1.05	0.80
Maximum	2.22	1.67	1.96	1.79	1.93	1.75	6.20	6.20
(b) marginal bone level at control sites (mm)								
Mean	1.25	1.31	1.34	1.28	1.36	1.22	1.83	2.13
SD	0.35	0.46	0.28	0.24	0.54	0.52	0.93	0.84
Minimum	0.80	0.62	1.02	1.01	0.92	0.81	0.25	1.05
Maximum	1.79	1.95	1.78	1.65	2.50	2.34	3.20	3.35

[a](Jung et al., 2009).

TABLE 4 Mean changes of marginal bone level, standard deviations (SD), min and max values (mm) at test and control sites

	Baseline–17 years mesial	Baseline–17 years distal
(a) changes of the marginal bone level at test sites (mm)		
Mean	−1.17	−1.14
SD	1.61	1.69
Minimum	−4.89	−4.92
Maximum	+0.23	+0.48
(b) changes of the marginal bone level at control sites (mm)		
Mean	−0.57	−0.82
SD	1.03	1.07
Minimum	−2.17	−2.33
Maximum	+1.27	+0.90

Note: Negative values imply a bone loss and positive values a bone gain.

however, was notably higher (51% for test and 47% for control sites) (Benic et al., 2009). The oral hygiene levels could possibly be sustained over such a long period of time by the regular recall schedules all eight reexamined patients complied with.

The mean PD around the implants is comparable to the mean values determined in the 3-year and the 5-year follow-up examinations (Jung et al., 2009). Note that the mean values of the 3-year and 5-year follow-up include all 11 original patients. These data are also similar to the results of another study on GBR with a mean follow-up time of 4.3 years (Kolerman et al., 2014) and another implant study with a mean observation period of 7.2 years (Fenner et al., 2016).

The patients assessed the condition of their soft tissues slightly lower on the VAS than in the 5-year follow-up (Jung et al., 2009). Further, the ability to perform an adequate oral hygiene decreased from 64.5% in the 5-year follow-up (Jung et al., 2009) to 52.9% in the present study. This can potentially be explained by the increased age of the patients with a decreased ability to perform a proper oral hygiene.

In the personal questionnaire and the OHIP-G 14, only few mostly transient instances of adverse effects like swelling of the gums were reported and the patients rated their overall oral health and satisfaction very highly. This is in accordance with another implant study, where patients valued their satisfaction with a mean value of 9.7 on the VAS (Fenner et al., 2016). Unfortunately, to date only a few studies on long-term outcomes of implants have included personal questionnaires to assess patient-centered outcomes. Patients' satisfaction and oral health as well as the occurrence of adverse events are currently not well investigated, and comparisons between studies in this regard are, therefore, difficult.

For the purpose of comparison, the mesial and distal values of the mean MBLs are averaged to one proximal value, resulting in 2.44 mm for test and 1.98 mm for control sites. These values are comparable to the findings of another long-term study on GBR, in which the radiological bone level was 2.40 mm (test sites with collagen membrane), 2.53 mm (test sites with expanded polytetrafluorethylene membrane), and 2.36 mm (control sites) after a follow-up period of at least 12.5 years (Jung et al., 2013). Another study on GBR over an observation period of 1–7 years found similar results for test sites (Simion et al., 2004).

Compared with the mean values at baseline (1.28 mm for both test and control sites), a mean bone loss of 1.16 mm (test) and 0.70 mm (control) could be found in the 17-year follow-up. As the mean changes in bone level between baseline and 5-year follow-up were miniscule (0.03–0.13 mm) (Jung et al., 2009), no additional analysis of the mean bone level changes between the 5-year and the 17-year follow-ups was conducted. These findings are slightly better than the results of a GBR study in which a mean proximal bone loss of 2.37 mm after 8 years was reported (Tang et al., 2015) and the results of a long-term study on implants (without GBR), which found a mean bone loss of 2 mm after an observation period of 20 years (Attard & Zarb, 2004).

Comparing the mean buccal defect height determined by CBCT to the intraoperative measurement taken at implantation, an impressive mean bone gain was noted in this present study. These results

TABLE 5 Mean values for buccal defect height, horizontal bone thickness, distance mucosal margin level to implant shoulder and mucosal thickness at 17-year examination, standard deviations (SD), min and max values (mm) at test and control sites

	Defect height	Horizontal bone thickness				Mucosal margin. level to implant shoulder	Mucosal thickness
		0 mm	1 mm	3 mm	5 mm		
(a) test sites (mm)							
Mean	2.25	1.36	1.84	2.56	3.09	2.03	1.24
SD	0.69	0.61	0.73	1.10	1.50	1.08	0.31
Minimum	1.00	0.41	1.21	1.50	1.70	0.15	0.83
Maximum	3.13	2.12	3.06	4.47	5.86	3.47	1.79
(b) control sites (mm)							
Mean	3.11	1.18	1.77	2.57	3.39	1.79	1.26
SD	2.86	0.76	1.06	1.16	1.54	0.95	0.23
Minimum	1.02	0.44	0.56	1.06	1.55	0.11	0.99
Maximum	9.89	2.50	3.70	4.24	5.68	3.48	1.62

TABLE 6 Mean changes in defect height between the intraoperative measurements taken at implantation and 17-year follow-up, standard deviations (SD), min and max values (mm) at test and control sites

(a) test sites (mm)	
Mean	+5.38
SD	4.26
Minimum	+0.61
Maximum	+14.00
(b) control sites (mm)	
Mean	+3.14
SD	2.37
Minimum	−0.55
Maximum	+6.75

Note: Negative values imply a bone loss and positive values a bone gain.

are similar and, thus, confirm the findings of another study on GBR, where the values were also measured by CBCT 5 years after GBR and simultaneous implantation (Jung et al., 2015).

In order to gain more insights into alveolar ridge preservation, a recent systematic review analyzed the outcomes of rhBMP-2 in extraction sockets. In accordance with the present study, they did not find any association between the application of rhBMP-2 and alveolar ridge height preservation. They, however, stated a possible benefit in preserving alveolar ridge width using rhBMP-2 (Moslemi et al., 2018). Further studies on the subject are certainly needed.

In the original study, the maximal defect depth was measured at implant placement with a periodontal probe (Jung et al., 2003). Comparing these measurements to the CBCT data gathered at the 17-year follow-up, it can be noted that all reexamined implants were sufficiently covered with bone and no bone dehiscences could be found. These values, again, are similar to a study on GBR where horizontal bone thickness was also determined by CBCT (Jung et al., 2015).

In a 2014 conducted study where ridge expansion and GBR techniques were combined with simultaneous implantation, an average horizontal bone gain of 1.90 mm could be achieved at IS level after 6 months (Kolerman et al., 2014). These are slightly higher than the mean horizontal bone thickness at the same level measured in this present study. It has to be considered, however, that the observation periods and techniques are not directly comparable.

A meta-analysis showed that in general mean horizontal bone gains were slightly higher for simultaneous than for staged implantation (Sanz-Sanchez et al., 2015). Comparing the results of this present study to a study with a two-stage approach (de Freitas et al., 2013), this observation can be confirmed.

Two mucosal parameters were determined to assess esthetics around the implants in the present study. The distances between the MML and the IS were higher than the values found in another study on GBR procedures using CBCT imaging, while the values for mucosal thickness were similar (Jung et al., 2015). Due to artifacts around titanium implants in CBCT, periimplant tissues are notoriously difficult to evaluate and might, therefore, be imprecisely assessed (Benic et al., 2013). This and the comparison of CBCT data with intraoperative measurements taken at time of implantation might be limitations in the present study.

Further limitations to the study are certainly the small sample size of only eight patients and the rather high drop-out rate of 27%. As two of the originally 11 patients were deceased and one could not be called due to missing contact details, future long-term studies would profit from including more patients to cushion such losses.

In general, clinical trials in humans (Smith et al., 2015) and animals (Herford et al., 2012; Jung et al., 2008) showed a positive effect for BMP-2 on bone regeneration. It could be shown that the higher the dose of BMP-2 the more positive the effects on bone augmentation (Benic & Hämmerle, 2014). Studies quantified a positive effect on bone growth with a dose of rhBMP-2 of 1.5 mg/ml (Bianchi et al., 2004; Fiorellini et al., 2005). A systematic review stated that the optimal dose further depends on the type and location of bone as well as carrier binding properties (Kelly et al., 2016).

There seem to be differences in the efficacy of rhBMP-2 in different procedures. In lateral sinus floor augmentations, rhBMP-2 combined with ACS and xenogenic bone substitute mineral seems to show less new bone formation compared with xenogenic bone substitute mineral alone (Kao et al., 2012). This is confirmed by a recent review on the use of rhBMP-2 in craniofacial surgery (Ramly et al., 2019). In alveolar ridge augmentation procedures, however, rhBMP-2 is assessed to be superior to other bone substitutes and equivalent to an autogenous bone graft (Kelly et al., 2016; Ramly et al., 2019). The latter was recently confirmed by an RCT on ridge augmentation, in which a xenogeneic block loaded with rhBMP-2 yielded comparable results to an autogenous bone block (Thoma et al., 2019).

There are concerns about the safety of rhBMP-2 regarding its potential protumorigenicity. The cancer risk seems to be dose-dependent, and a cut-off point for an increased risk has thus far not been defined (Moslemi et al., 2018). A review article found a higher incidence of new malignancies in lumbar fusion procedures using a dose of 40mg rhBMP-2 (Carragee et al., 2011). In recent years, an increase in the use of rhBMP-2 in spinal surgery leads to an increase in reports on severe adverse events, including malignancies. No evidence of such events could be found in a recent review on the safety of rhBMP-2 in craniofacial surgery (Ramly et al., 2019). The reason might be that the mean doses of rhBMP-2 used in these procedures are generally much lower. Regarding immune responses, only transient reactions to rhBMP-2 could be found in 12% of patients in a study on sinus floor augmentation with rhBMP-2 (Boyne et al., 2005). The development of rhBMP-2 antibodies seems to be a rare event; patients mostly exhibit antibodies to bovine type I collagen from the carrier material (de Freitas et al., 2015).

The aim of the present study was to assess long-term outcomes of implants placed in conjunction with GBR with or without the addition of rhBMP-2. Although it could be shown for the first time that this procedure shows excellent long-term results, the addition of rhBMP-2 does not seem to have a positive or negative effect on the long-term stability.

5 | CONCLUSIONS

Despite the limitations of this study, especially its small sample size of eight split-mouth patients, it could be showed for the first time that implants placed in conjunction with GBR applying a xenogenic bone substitute and a collagen membrane with and without the addition of rhBMP-2 demonstrate excellent clinical and radiographic results after at least 17 years. However, there does not seem to be any long-term effect of adding rhBMP-2 to GBR procedures.

ACKNOWLEDGEMENTS

Daniel B. Wiedemeier, Alfonso Gil. Open Access Funding provided by Universitat Zurich.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Ronald Ernst Jung: Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal). **Marionna Kovacs:** Formal analysis (equal); Investigation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Daniel S Thoma:** Conceptualization (supporting); Funding acquisition (supporting); Methodology (supporting). **Christoph H.F. Hämmerle:** Conceptualization (supporting); Funding acquisition (supporting); Methodology (supporting); Resources (supporting).

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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How to cite this article: Jung, R. E., Kovacs, M. N., Thoma, D. S., & Hämmerle, C. H. F. (2022). Informative title: Guided bone regeneration with and without rhBMP-2: 17-year results of a randomized controlled clinical trial. *Clinical Oral Implants Research*, 33, 302–312. https://doi.org/10.1111/clr.13889