Primary bone augmentation leads to equally stable marginal tissue conditions comparing the use of xenograft blocks infused with BMP-2 and autogenous bone blocks: A 3D analysis after 3 years

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Abstract: OBJECTIVES To test whether or not primary bone augmentation using xenograft blocks infused with BMP-2 or autogenous bone blocks lead to similar results regarding the implant survival and 3D marginal soft tissue contours. METHODS Twenty-four patients with an insufficient ridge width for implant placement in need of primary augmentation were randomly assigned to either a block of deproteinized bovine bone mineral infused with rhBMP-2 (BMP) or an intraorally harvested block of autogenous bone (ABB). At 4 months, 1-4 dental implants were placed in the regenerated area. After crown insertion and at 3 years, peri-implant tissue parameters, two- and three-dimensional radiographic parameters, and soft tissue contour changes were evaluated. Explorative mixed model analyses were performed. The level of significance was set at 5%. RESULTS At the 3-year follow-up, 23 patients with 40 implants were evaluated. The implant survival rate was 100% in both groups. At baseline, the marginal hard tissue levels amounted to -0.4 ± 0.8 mm (mean ± standard deviation) in the BMP group and -0.7 ± 1.0 mm in the ABB group. At 3 years, these values were -0.2 ± 0.4 mm (BMP) and -0.6 ± 1.0 mm (ABB). At baseline, the thickness of the buccal hard tissue at the level of the implant shoulder measured 1.1 ± 1.1 mm (BMP) and 1.4 ± 1.0 mm (ABB). At 3 years, it measured 0.9 ± 0.9 mm (BMP) and 0.7 ± 0.6 mm (ABB). CONCLUSIONS The present study demonstrated excellent implant survival rates and stable marginal hard tissue levels in both augmentation groups, 3 years after crown insertion. In addition, the clinical stability of soft and hard tissues was demonstrated in both groups.

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ORIGINAL ARTICLE

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Primary bone augmentation leads to equally stable marginal tissue conditions comparing the use of xenograft blocks infused with BMP-2 and autogenous bone blocks: A 3D analysis after 3 years

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Abstract

Objectives: To test whether or not primary bone augmentation using xenograft blocks infused with BMP-2 or autogenous bone blocks lead to similar results regarding the implant survival and 3D marginal soft tissue contours.

Methods: Twenty-four patients with an insufficient ridge width for implant placement in need of primary augmentation were randomly assigned to either a block of deproteinized bovine bone mineral infused with rhBMP-2 (BMP) or an intraorally harvested block of autogenous bone (ABB). At 4 months, 1–4 dental implants were placed in the regenerated area. After crown insertion and at 3 years, peri-implant tissue parameters, two- and three-dimensional radiographic parameters, and soft tissue contour changes were evaluated. Explorative mixed model analyses were performed. The level of significance was set at 5%.

Results: At the 3-year follow-up, 23 patients with 40 implants were evaluated. The implant survival rate was 100% in both groups. At baseline, the marginal hard tissue levels amounted to −0.4 ± 0.8 mm (mean ± standard deviation) in the BMP group and −0.7 ± 1.0 mm in the ABB group. At 3 years, these values were −0.2 ± 0.4 mm (BMP) and −0.6 ± 1.0 mm (ABB). At baseline, the thickness of the buccal hard tissue at the level of the implant shoulder measured 1.1 ± 1.1 mm (BMP) and 1.4 ± 1.0 mm (ABB). At 3 years, it measured 0.9 ± 0.9 mm (BMP) and 0.7 ± 0.6 mm (ABB).

Conclusions: The present study demonstrated excellent implant survival rates and stable marginal hard tissue levels in both augmentation groups, 3 years after crown insertion. In addition, the clinical stability of soft and hard tissues was demonstrated in both groups.

KEYWORDS
autogenous bone block, bone morphogenetic protein 2, bone regeneration, cone beam-computed tomography, dental implants, follow-up, guided bone regeneration

1 | INTRODUCTION

Dental implants placed in pristine bone render high survival rates over 10 years and more (Chappuis et al., 2013; Jemt, 2016; Simion et al., 2018). In the presence of a severely resorbed ridge or a complex three-dimensional defect, primary implant stability often times cannot be obtained. For these indications, an array of different techniques has been proposed to regenerate the missing hard tissue and allows for staged implant placement (Maiorana et al., 2005; Nevins & Mellonig, 1994; Sanz-Sánchez et al., 2015). Autogenous bone blocks are considered to be the gold standard for the treatment of these defects, rendering sufficient bone quantity and quality for dental implant placement (Naenni et al., 2019; Stern & Barzani, 2015). Interestingly, some studies have observed favorable marginal bone levels during the follow-up period (Chappuis et al., 2017; Mordenfeld et al., 2017), whereas other studies have reported higher marginal bone loss compared to the implants placed in the native bone (Thoma et al., 2019).

Limitations of the technique are the additional morbidity resulting from the harvesting procedure, including post-operative pain and sensory disturbances (Nkenke & Neukam, 2014; Raghoebar et al., 2007). In order to overcome the disadvantages of autogenous bone grafts, additional regenerative procedures have been proposed for primary ridge augmentation. Data obtained applying various combinations of bone substitute materials, membranes and biologic mediators demonstrated high graft stability and high implant survival rates (Briguglio et al., 2019; Jung et al., 2009; Meloni et al., 2019; Wessing et al., 2017).

Mid- to long-term outcomes are of key importance when it comes to the selection of a specific treatment modality. However, the number of studies reporting long-term outcomes of implants placed in previously augmented bone is strikingly low. The studies available are usually hampered either by study design, or by the number of patients, or by the length of the follow-up (Chappuis et al., 2017; Dasmah et al., 2013; Meijndert et al., 2017; Mordenfeld et al., 2017; Thoma et al., 2019; Urban et al., 2011). In addition, dental implants having been placed into augmented ridges should be assessed not only by traditional methods (e.g. periapical X-rays), but also by more modern methods such as three-dimensional X-rays and surface scans. This will then allow to assess the volume differences of the regenerated soft and hard tissues over time.

The aim of the present study was, therefore, to test whether or not primary bone augmentation using xenograft blocks infused with BMP-2 or autogenous bone blocks leads to similar results regarding implant survival and 3D marginal soft tissue contours.

2 | MATERIAL AND METHODS

The present clinical study reports a 3-year data of a prospective, randomized, controlled clinical trial comparing two different treatment modalities for primary ridge augmentation and staged implant placement. The study was performed at the Clinic of Reconstructive Dentistry, University of Zurich, Zurich, Switzerland (14 patients) and at the Department of Oral Surgery and Radiology, School of Dentistry, Medical University Graz, Graz, Austria (10 patients). Partially edentulous patients in need of implant therapy were consecutively enrolled from April 2012 to December 2013. All participating patients gave their informed written consent. The local ethical committee of Zurich (KEK-ZH-Nr. 2010-0213/5) and Graz (24-372 ex 11/12) approved all the procedures and materials.

2.1 | Patients

Twenty-six female or male patients of at least 18 years of age were initially screened (Figure 1). The edentulous areas encompassed 1–4 sites in the posterior maxilla or mandible with an insufficient ridge width to placed dental implants. Further inclusion criteria were: Bleeding on probing and plaque control record <25%, no probing depth values exceeding 4 mm, smoking ≤10 cigarettes per day, tooth extraction at the defect site at least 3 months before without any augmentation procedures at the time and at least one natural tooth adjacent to the defect site(s). Specific exclusion criteria were pregnancy, breastfeeding, previous administration of InductOs®, skeletal immaturity, any active malignancy, hypersensitivity, or allergy to the class of drugs and products under investigation.

2.2 | Procedure

The detailed procedure of the primary augmentation was described earlier (Thoma et al., 2018). In brief, at the time of the surgery, a sealed envelope was opened indicating the treatment modality. Twelve patients were treated with a primary augmentation with a block of deproteinized bovine bone mineral (DBBM) (Bio-Oss Spongiosa Block®; Geistlich Pharma AG) infused with rh-BMP-2 (InductOs®; Medtronic BioPharma, rhBMP-2 concentration 1.5 mg/ml) and covered with a native collagen membrane (Bio-Gide®; Geistlich Pharma AG) (group BMP). Due to varying dimensions of the defects, the effectively applied dose ranged between 0.2 mg and 0.6 mg of rh-BMP-2. Another 12 patients received an intraorally harvested autogenous bone block, covered with DBBM particles (Bio-Oss Granules®; Geistlich Pharma AG) and a native collagen membrane (Bio-Gide®; Geistlich Pharma AG) (group ABB). One patient lost the autogenous block following 3 weeks of healing and was replaced (Thoma et al., 2018). At 4 months, the area was anesthetized (Ultracain® D-S; Hoechst-Pharma AG) and a full-thickness flap elevated. Forty-two (BMP = 22; ABB = 20) dental implants were placed in the prosthetically ideal position according to the manufacturer's recommendation (Astra Osseospeed TX, Astra Tech Implant System; Dentsply Sirona). Additional guided bone regeneration (GBR) procedures were performed on buccal implant surfaces whenever necessary (at 14 implants in group BMP, at 11 implants in group ABB, Figure 1), using DBBM granules (Bio-Oss®; Geistlich Pharma AG) and a native collagen membrane (Bio-Gide®; Geistlich Pharma AG). After a healing

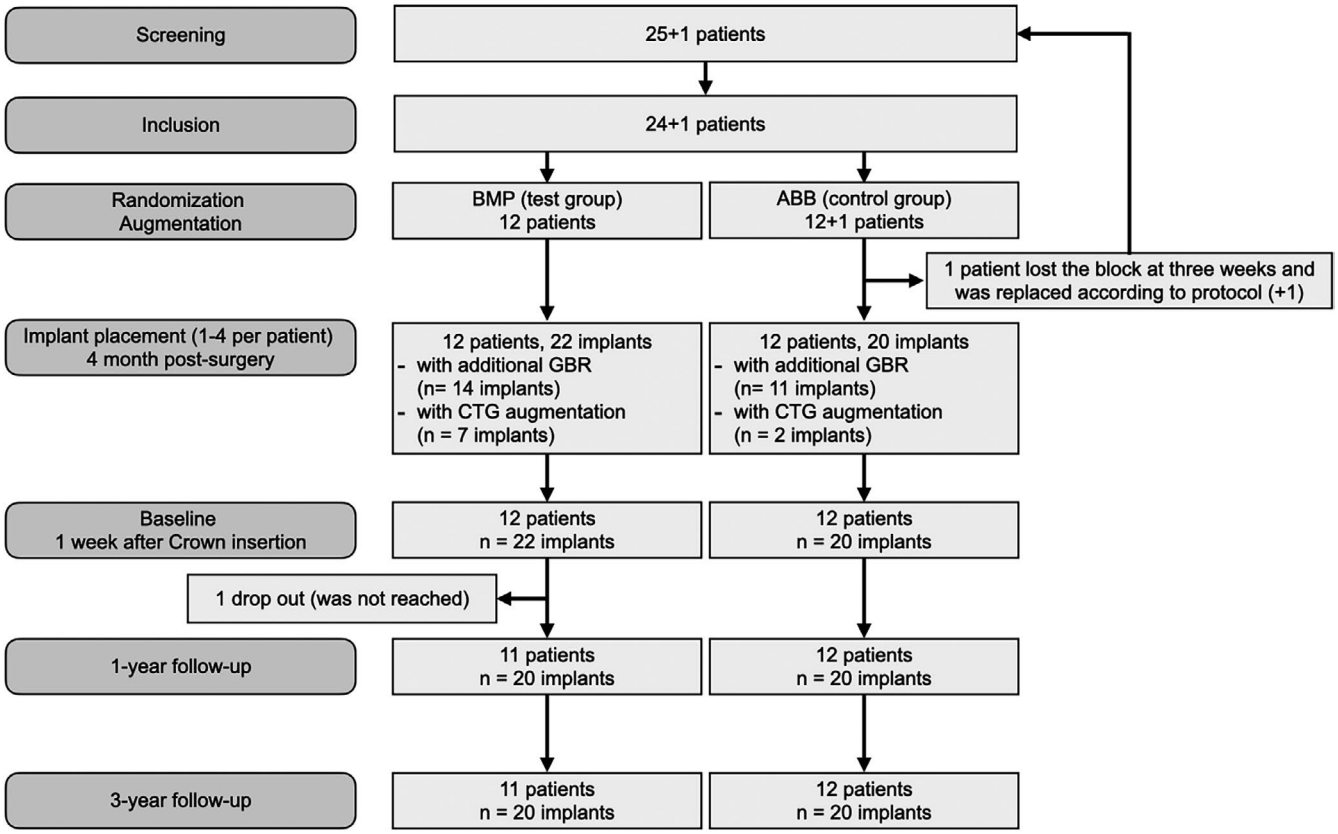

FIGURE 1 Patient flow of both study groups since initiation of the trial. ABB, primary augmentation with an autogenous bone block; BMP, primary augmentation with a xenogeneic block and rhBMP-2; CTG, connective tissue graft; GBR, guided bone regeneration

period of 3 months, a second-stage surgery was performed. Prior to the second-stage surgery, soft tissue augmentations by means of a connective tissue graft were performed depending on the soft tissue quality and esthetic indication (at seven implants in group BMP, at two implants in group ABB, Figure 1). After a healing period of at least 3 months following the implant placement, the second stage surgery was performed. Final impressions were taken and cement- or screw-retained restorations were inserted.

2.3 | Follow-up examinations

Baseline examinations were conducted 4–6 weeks after the insertion of the final reconstructions. Study-specific adverse events were recorded. These events included: General or local allergic reactions, fracture of the jaw, paresthesia, implant mobility, implant loss, implant fracture, formation of sequestrums, swelling, and pain. Plaque control record (PCR), probing depth (PD), and bleeding on probing (BOP) were evaluated at six sites around each implant and at the neighboring teeth. The amount of keratinized tissue (KT) was measured at the midfacial aspect of each implant and neighboring tooth. A partial arch, a-silicone impression, was taken of the reconstruction and the adjacent soft tissue contour. Single tooth x-rays were performed with the long-cone paralleling technique directing the central beam to the alveolar crest (Hawe X-ray film holder; Kerrhawe SA). Furthermore, cone beam-computed tomography (CBCT) scans were taken using two different scanners: a Kavo 3D eXam scanner (Kavo Dental GmbH) at center 1 and a Planmeca Romexis scanner (Planmeca Oy) at center 2. The settings in center 1 were 160 × 40 mm for the field of view, 5 mA and 120 kV with a voxel size of 0.25 mm. The settings in center 2 were 160 × 80 mm for the field of view, 12 mA and 84 kV with a voxel size of 0.2 mm.

Similar measurements were performed at 1 year and at 3 years (Figure 2a-f). In addition to the study-related follow-up visits, patients were enrolled in an individual maintenance care program.

2.4 | Measurements

An image analysis software (ImageJ; National Institutes of Health) was used to measure the mesial and distal marginal hard tissue levels of each implant (MBL^{m+d}) based on the single tooth X-rays. The implant shoulder (IS) served as a reference and the thread pitch of 0.6 mm was used to adjust the scale. Mesial and distal values were averaged and the differences, i.e. changes between the time-points, were obtained (Figure 3a-c).

The DICOM data were imported into a digital implant planning software program (SMOP; Swissmeda AG). The buccal marginal hard tissue level of each implant (MBL^{b}) was assessed at the center of the implant measuring the distance between the IS and the first hard tissue to implant contact (Figure 4a). In addition, the thickness of the buccal hard tissue was measured at the level of the implant

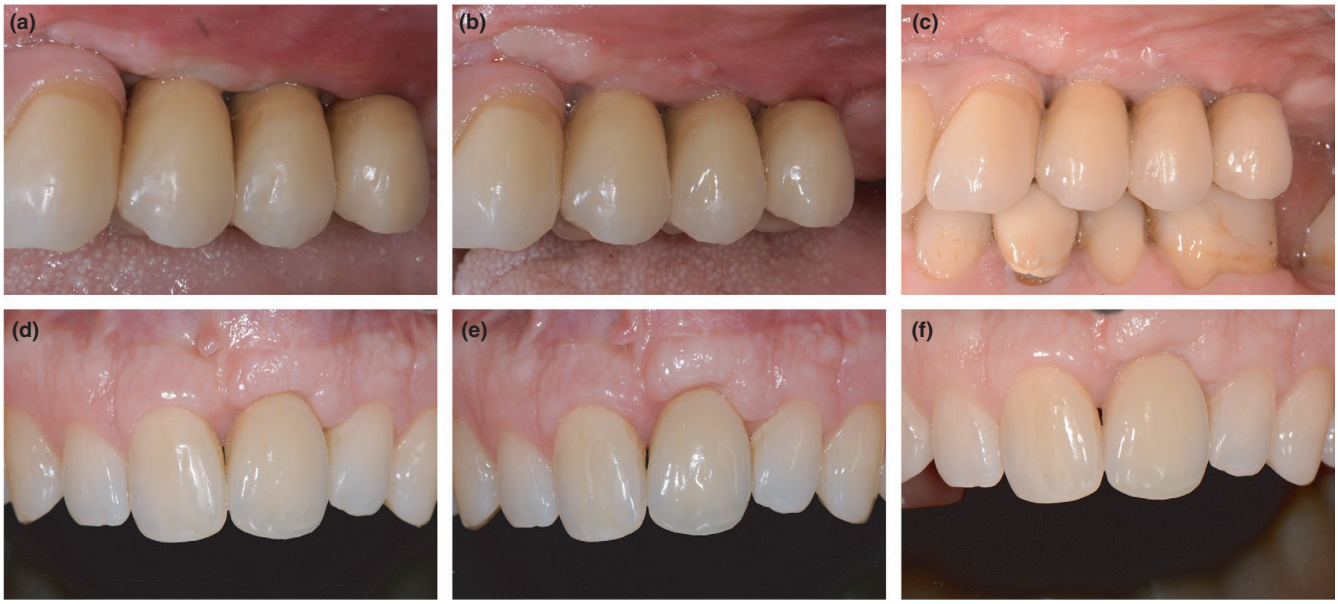

FIGURE 2 (a-f) Clinical pictures of a patient in group primary augmentation with a xenogeneic block and rhBMP-2 (BMP) at baseline (a), at 1 year (b), at 3 years (c), and for a patient treated in group primary augmentation with an autogenous bone block (ABB) (d-f)

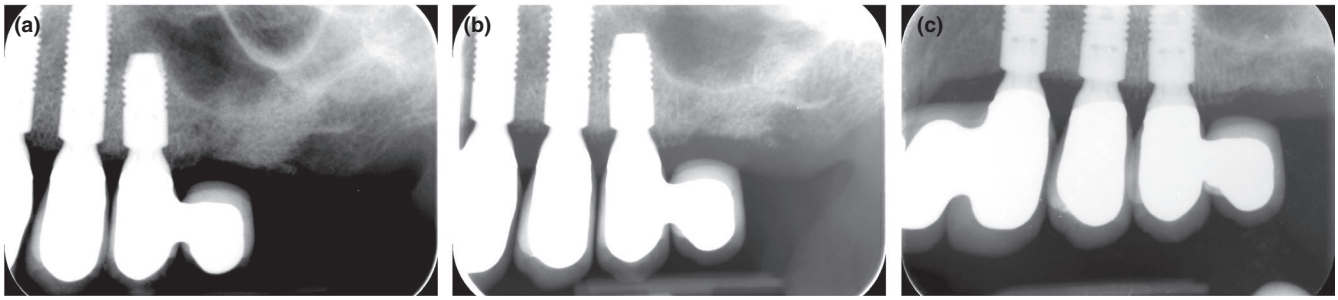

FIGURE 3 (a-c) Two-dimensional x-rays used for the evaluation of the marginal bone levels of the patient (BMP) are shown in Figure 2, with implants replacing maxillary premolars. (a) Baseline after crown insertion. (b) 1-year follow-up. (c) 3-year follow-up

shoulder BT^0, and at 1, 2 and 3 mm below (BT^1, BT^2, BT^3). For the above-mentioned analyses, the first hard tissue to implant contact was defined as the mineralized tissue being in direct contact with the implant surface. Due to prior augmentation procedures, anorganic bovine bone or mineralized structures of unclear histologic quality were included in this measurement.

Dental casts were fabricated based on the silicon impressions and digitized with a desktop scanner (Imetric 3D). The obtained standard tessellation language files (STL) were imported into the implant planning software and merged with the CBCTs. The following measurements of the overall tissue thickness were made using the implant as a fixed reference (performed for each implant): horizontally MT^h, vertically MT^v, and of the soft tissue contour MT^c (Figure 4b).

2.5 | Statistical analysis

Data were collected in a spreadsheet (Excel; Microsoft Corporation) and statistical analysis was conducted with a statistical analysis program (SAS 9.4; SAS Corp.). Mean, median, standard deviation, and interquartile range were used to describe continuous variables, whereas counts and percentages were used for categorical variables. The primary endpoint was the clinically evaluated ridge width at 4 months following the primary augmentation (Thoma et al., 2018). The present study reports data up to 3 years post insertion of final restorations and all analyses are explorative. For the present analysis, the statistical unit was the implant, not the patient. For each time point, mixed models with groups as an independent factor were performed for the analysis of primary and secondary endpoints, taking within-subject dependencies into account. From these analyses, the 95% confidence intervals for the group mean differences were derived and presented in Tables 2 and 3 and in Appendix S1. As a result of the smaller sample sizes, also mixed model analyses with the two independent factors group and time with interaction term were considered as well. These two approaches did not always reveal the same results. For several models, data were categorized and dichotomized because the model assumptions were not satisfactory. The level of significance was set at $p < .05$. No correction of the multiple testing of the parameters was applied, up to the mixed models with the two factors group and time.

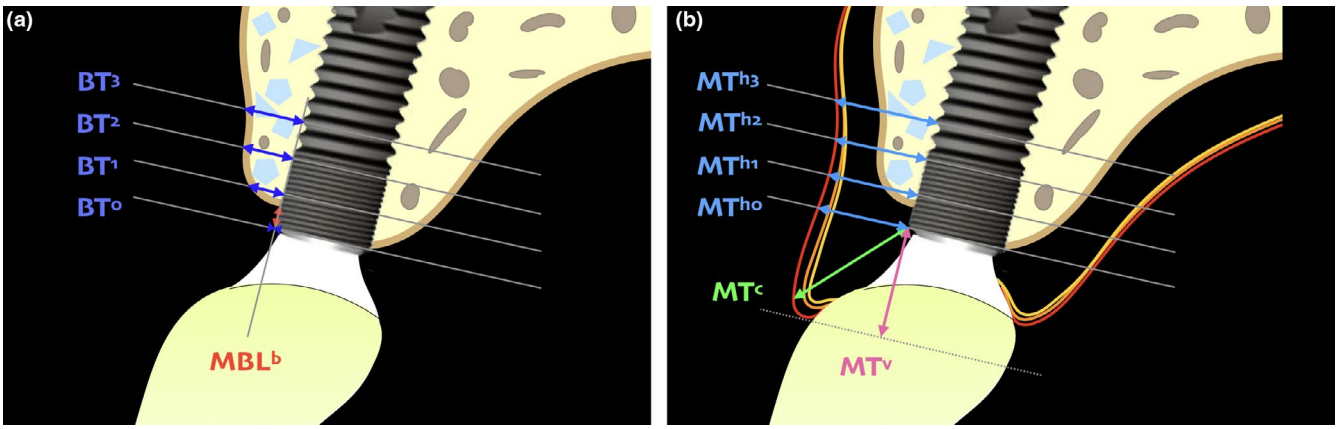

FIGURE 4 (a) Baseline cross-section of an implant at a lateral incisor position as evaluated in the CBCT scan. The midfacial marginal bone level (MBL^b) was measured on two-dimensional images. The buccal horizontal thickness of the bone (BT) was measured at the level of the implant shoulder (IS), and at 1, 2, 3 mm below. Measurements were repeated at 1 and at 3 years. (b) 3-year cross-section of the same implant, but in addition, the soft tissue contours were merged (red = baseline, orange = 1-year, yellow = 3-year). (c) According to the measurements on the level of the bone, the overall buccal tissue thickness (MT) was measured at the level of the implant shoulder (IS), and at 1, 2, 3 mm below and for each soft tissue contour. Moreover, a vertical and a 45° soft tissue contour measurement with the implant shoulder as a reference point was performed

TABLE 1 Characteristics of each group and overall, at the baseline visit (following the crown insertion), with patient-based and implant-based data

	BMP		ABB		Total	
Group	Patients	Implants	Patients	Implants	Patients	Implants
Number	12	22	12	20	24	42
Age						
Years (Mean ± SD)	56.3 ± 12.1		47.5 ± 17.7		52.1 ± 15.4	
Gender						
Female	4 (33.3%)		6 (50.0%)		10 (41.6%)	
Male	8 (66.7%)		6 (50.0%)		14 (58.4%)	
Center						
Zurich	8 (66.7%)	13 (59.1%)	6 (50.0%)	10 (50.0%)	14 (58.4%)	23 (54.8%)
Graz	4 (33.3%)	9 (40.9%)	6 (50.0%)	10 (50.0%)	10 (41.6%)	19 (45.2%)
Jaw						
Maxilla	5 (41.7%)	9 (40.9%)	8 (66.7%)	12 (60.0%)	13 (54.2%)	21 (50.0%)
Mandible	7 (58.3%)	13 (59.1%)	4 (33.3%)	8 (40.0%)	11 (45.8%)	21 (50.0%)
Site						
Incisor		8 (36.4%)		9 (45.0%)		17 (40.5%)
Canine		2 (9.1%)		2 (10.0%)		4 (9.5%)
Premolar		8 (36.4%)		7 (35.0%)		15 (35.7%)
Molar		4 (18.2%)		2 (10.0%)		6 (14.3%)

Abbreviations: ABB, primary augmentation with an autogenous bone block; BMP, primary augmentation with a xenogeneic block and rhBMP-2; SD, standard deviation.

3 | RESULTS

Twenty-six patients were initially screened and 23 completed the 3-year follow-up visit (Table 1, Figure 1). All implants survived, rendering a 100% survival rate for the BMP and ABB group, respectively. Two patients reported partial paresthesia at the recipient site, one from each group. The patient in group ABB reported that the paresthesia persisted over the 3-year period. The patient in group BMP was lost to follow-up. No other study-specific adverse events were reported for up to 3 years. Additional GBR procedures were performed in 7 patients at 16 sites in the BMP group and in 7 patients at 11 sites in the ABB group.

3.1 | Clinical parameters

All clinical findings are summarized in Appendix S1, including the confidence intervals of the mean group differences 1. PCR remained low throughout the observation period with mean values ranging from 0.0 ± 0.0% to 14.1 ± 18.6% (± = standard deviation). Mean PD values ranged from 2.8 ± 0.6 mm to 3.3 ± 0.7 mm. BOP amounted to 0.0 ± 0.0% (BMP) and to 3.4 ± 7.2% (ABB) at baseline, and to 22.0 ± 24.8% (BMP) and to 21.6 ± 21.0% (ABB) at 3 years. KT decreased from 2.6 ± 1.0 mm (BMP) and 2.1 ± 0.8 mm (ABB) to 2.3 ± 1.3 mm (BMP) and 1.6 ± 1.0 mm (ABB) over time. For KT, the mixed model analysis with group and time as factors revealed significantly higher values for the BMP group at 3 years ($p = .001$) and a significant reduction over time in both groups (from crown insertion to 3 years; $p = .001$), but no significant results in the single factor mixed model (group only).

3.2 | Hard tissue analysis (x-rays, CBCTs)

The mean marginal hard tissue levels (MBL^{m+d}) amounted to −0.4 ± 0.8 mm (BMP) and −0.7 ± 1.0 mm (ABB) at baseline and to −0.2 ± 0.4 mm (BMP) and −0.6 ± 1.0 mm (ABB) at 3 years. The changes over time were minimal within the groups: 0.0 ± 0.2 mm (BMP) and 0.0 ± 0.4 mm (ABB). The confidence intervals (Table 2) did not reveal relevant differences in the group means. Mean marginal hard tissue levels on the buccal side (MBL^{b}) were −0.2 ± 0.3 mm (BMP) and −0.3 ± 0.9 mm (ABB) at baseline and −0.3 ± 0.5 mm (BMP) and −0.4 ± 0.9 mm (ABB) at 3 years. The changes amounted to −0.1 ± 0.2 mm (BMP) and −0.2 ± 0.4 mm (ABB). Mixed model analyses with group and time as factors revealed no statistically significant group or time effect ($p > .10$). All MBL values are shown in Figure 5.

The thickness of the buccal hard tissues at the level of the implant shoulder (BT^{0}) was 1.1 ± 1.1 mm (BMP) and 1.4 ± 1.0 mm (ABB) at baseline. These values decreased to 0.9 ± 0.9 mm (BMP) and 0.7 ± 0.6 mm (ABB) at 3 years. The reduction from crown insertion to 3 years amounted to −0.3 ± 0.3 mm in group BMP and −0.6 ± 0.9 mm in group ABB and the reduction over time was statistically significant ($p \leq .04$), but the groups did not differ statistically significantly. The thickness of the buccal hard tissue was greater at more apical levels. Changes over time at BT^{3} amounted to −0.4 ± 0.6 mm in the BMP group and −0.4 ± 0.3 in the ABB group (all intergroup comparisons $p > .05$). Data are depicted in Table 2.

3.3 | Contour analysis (STL surface files)

Measurements are shown in Table 3. At baseline, the vertical soft tissue thickness (MT^{v}), measured from the implant shoulder, amounted to 3.1 ± 1.3 mm in the BMP group and to 2.8 ± 1.2 mm in the ABB group. The changes during the 3 years amounted to −0.3 ± 0.6 mm (BMP) and to −0.3 ± 0.5 mm (ABB). Mixed model analysis with the two factors revealed a statistically significantly thicker MT^{v} in the BMP group at 3 years ($p = .03$) and a decrease over time in both the groups ($p < .0001$); however, the models with a single factor (group) did not show significantly different group means. The changes of the buccal contour MT^{c} amounted to −0.4 ± 0.4 mm (BMP) and −0.2 ± 0.4 mm (ABB). The decrease from crown insertion to 3 years was demonstrated to be statistically significant in both groups ($p \leq .005$), but the group means are not significantly different.

The overall tissue thickness (hard and soft tissue; horizontal measurements) revealed more favorable results for the group BMP. The distance between the implant and the buccal contour amounted to 2.8 ± 1.0 mm (BMP) vs. 2.4 ± 1.5 mm (ABB) at baseline and to 2.5 ± 1.2 mm (BMP) vs. 2.1 ± 1.5 mm (ABB) at 3 years (MT^{h0}). MT^{h0} was statistically significantly thicker in the BMP group at 3 years ($p = .035$), whereas the decrease from crown insertion to 3 years was statistically significant for both groups ($p = .0005$). The absolute values at MT^{h3} were 4.1 ± 1.2 mm (BMP) and 2.9 ± 1.4 mm (ABB) at baseline and 3.1 ± 1.3 mm (BMP) and 2.1 ± 1.5 mm (ABB) at 3 years.

3.4 | Combined analysis of hard and soft tissues

The implant shoulder was the reference point for several hard and soft tissue measurements. The difference between the hard tissue analysis and the overall tissue contour reveals the changes in the

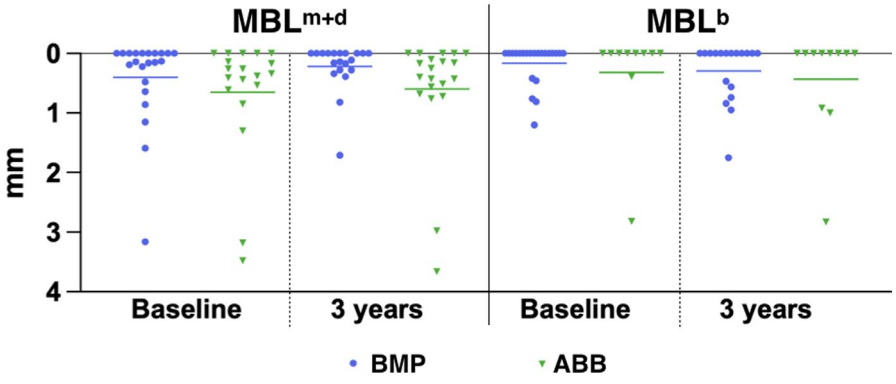

FIGURE 5 Scatterplot with combined mesial and distal marginal bone levels as well as buccal bone levels at baseline and at three years; ABB, primary augmentation with an autogenous bone block; BMP, primary augmentation with a xenogeneic block and rhBMP-2; MBL^{b}, buccal marginal bone levels; MBL^{m+d}, combined mesial and distal marginal bone levels

TABLE 2 Hard tissue parameters

Variable	Time point	Group	*N* (implant)	Mean	SD	Min	Median	IQR	Max	95% c.i. (BMP – ABB)
MBL^{m+d} (mm)	Baseline	BMP	22	−0.4	0.8	−3.2	0.1	0.5	0.0	(−0.38, 0.79)
		ABB	19	−0.7	1.0	−3.5	0.3	0.6	0.0	
	1 year	BMP	18	−0.3	0.3	−1.0	0.2	0.3	0.0	(−0.17, 0.97)
		ABB	16	−0.7	1.0	−3.3	0.4	0.6	0.0	
	3 years	BMP	20	−0.2	0.4	−1.7	0.1	0.3	0.0	(−0.18, 0.72)
		ABB	20	−0.6	1.0	−3.7	0.3	0.6	0.0	
	Baseline – 3 years	BMP	20	0.0	0.2	−0.6	0.0	0.2	0.6	(−1.28, 0.03)
		ABB	19	0.0	0.4	−1.1	0.0	0.3	0.7	
MBL^{b} (mm)	Baseline	BMP	22	−0.2	0.3	−1.2	0.0	0.0	0.0	(−0.29, 0.38)
		ABB	10	−0.3	0.9	−2.8	0.0	0.0	−2.8	
	1 year	BMP	20	−0.2	0.5	−1.8	0.0	0.2	−1.8	(−0.47, 0.29)
		ABB	9	−0.1	0.2	−0.7	0.0	0.0	−0.7	
	3 years	BMP	18	−0.3	0.5	−1.8	0.0	0.6	−1.8	(−0.28, 0.60)
		ABB	11	−0.4	0.9	−2.8	0.0	0.9	−2.8	
	Baseline – 3 years	BMP	18	−0.1	0.2	−0.1	0.0	0.1	0.8	(−0.37, 0.03)
		ABB	8	−0.2	0.4	0.0	0.0	0.3	1.0	
BT^{0} (mm)	Baseline	BMP	22	1.1	1.1	0.0	1.0	1.6	3.5	(−1.25, 0.41)
		ABB	10	1.4	1.0	0.0	1.5	1.7	2.7	
	1 year	BMP	20	1.2	1.1	0.0	1.1	1.7	4.1	(−0.92, 0.84)
		ABB	9	1.2	0.7	0.0	1.4	0.4	2.5	
	3 years	BMP	18	0.9	0.9	0.0	0.5	1.5	3.0	(−0.79, 0.72)
		ABB	10	0.7	0.6	0.0	0.6	1.3	1.6	
	Baseline – 3 years	BMP	18	−0.3	0.4	0.0	−0.2	0.5	−1.2	(−0.76, 0.26)
		ABB	6	−0.6	0.9	0.0	−0.2	1.2	−2.4	
BT^{3} (mm)	Baseline	BMP	22	2.1	1.1	0.9	1.9	1.2	5.8	(−0.41, 1.00)
		ABB	12	1.7	0.7	0.3	1.8	0.8	2.7	
	1 year	BMP	20	2.0	1.0	1.1	1.8	1.0	5.4	(−0.19, 0.98)
		ABB	10	1.7	0.6	0.9	1.6	0.9	2.5	
	3 years	BMP	18	1.9	1.1	0.6	1.6	1.2	5.4	(−0.24, 1.09)
		ABB	11	1.3	0.6	0.4	1.2	0.7	2.4	
	Baseline – 3 years	BMP	18	−0.4	0.6	0.0	−0.4	0.3	−1.4	(−0.50, 0.29)
		ABB	9	−0.4	0.3	0.1	−0.4	0.3	−0.9	

Note: Same uppercase letters indicate a statistically significant difference ($p < .05$) according to the mixed model analyses.

Abbreviations: ABB, primary augmentation with an autogenous bone block; BMP, primary augmentation with a xenogeneic block and rhBMP-2; BT^{0}, thickness of the bone at the level of the implant shoulder; BT^{3}, thickness of the bone 3 mm beneath the implant shoulder; c.i., confidence interval; IQR, interquartile range; Max, maximum; MBL^{b}, buccal marginal bone levels; MBL^{m+d}, combined mesial and distal marginal bone levels; Min, minimum; *N*, number; SD, standard deviation.

soft tissue thickness. Vertically, the soft tissue changes at the buccal aspect were minimal: −0.1 ± 0.6 mm ($n = 18$; BMP) and 0.0 ± 0.4 ($n = 8$; ABB). Horizontally, the soft tissue changes at the level of the implant shoulder amounted to −0.1 ± 0.4 mm ($n = 12$; BMP) and 0.5 ± 0.8 mm ($n = 8$; ABB). In group ABB, the hard tissue loss of −0.6 ± 1.0 mm was, therefore, compensated and the overall contour remained almost unchanged. No satisfactory model could be calculated due to a limited number of measurements available.

4 | DISCUSSION

The present randomized-controlled clinical trial revealed at 3 years of follow-up: (i) A 100% survival rate of 40 implants in 23 patients; (ii) stable marginal hard tissue levels at proximal and buccal sites in both groups; (iii) a higher tissue thickness at the level of the implant shoulder in group BMP compared to group ABB; (iv) a clinically negligible loss buccal contour of 0.2–0.4 mm over 3 years in both groups.

TABLE 3 Soft tissue contour parameters

Variable	Time point	Group	*N* (implant)	Mean	SD	Min	Median	IQR	Max	95% c.i. (BMP – ABB)
MT^{v} (mm)	Baseline	BMP	20	3.1[b]	1.3	1.5	2.8	2.1	6.4	(−0.43, 1.63)
		ABB	19	2.8[c]	1.2	1.4	2.6	1.7	5.8	
	1 year	BMP	16	3.0	1.3	1.3	2.6	1.5	6.2	(−0.99, 1.48)
		ABB	16	2.8	1.4	0.7	2.9	2.2	5.8	
	3 years	BMP	19	3.0[a,b]	1.4	1.2	2.8	1.6	6.5	(−0.46, 1.87)
		ABB	20	2.4[a,c]	1.3	0.7	2.1	2.1	5.4	
	Baseline – 3 years	BMP	19	−0.3	0.6	1.3	−0.1	0.7	−1.6	(−0.25, 0.29)
		ABB	19	−0.3	0.5	0.4	0.0	0.9	−1.1	
MT^{c} (mm)	Baseline	BMP	20	2.7[d]	1.0	1.4	2.6	1.7	4.8	(−0.61, 1.02)
		ABB	19	2.5[e]	1.4	1.2	2.2	1.5	7.0	
	1 year	BMP	17	2.5	1.0	1.0	2.5	1.2	4.3	(−0.74, 0.97)
		ABB	16	2.5	1.5	0.6	2.2	1.5	7.1	
	3 years	BMP	17	2.2[d]	1.0	0.9	2.0	1.7	4.0	(−0.89, 1.15)
		ABB	20	2.2[e]	1.4	0.4	1.9	1.8	6.7	
	Baseline – 3 years	BMP	17	−0.4	0.4	0.2	−0.4	0.6	−1.2	(−0.50, 0.04)
		ABB	19	−0.2	0.4	0.1	−0.1	0.4	−1.1	
MT^{h0} (mm)	Baseline	BMP	17	2.8[g]	1.0	1.4	2.9	1.2	5.2	(−1.56, 0.19)
		ABB	19	2.4[h]	1.5	0.9	1.8	1.3	6.8	
	1 year	BMP	15	2.8	1.0	1.1	2.8	1.3	5.1	(−1.28, 0.03)
		ABB	15	2.0	1.2	0.4	1.9	1.7	4.7	
	3 years	BMP	16	2.5[f,g]	1.2	1.0	2.3	1.9	5.4	(−0.28, 0.56)
		ABB	20	2.1[f,h]	1.5	0.4	1.7	1.5	6.6	
	Baseline – 3 years	BMP	14	−0.5	0.6	0.0	−0.3	0.6	−1.8	(0.01, 0.58)
		ABB	19	−0.2	0.3	0.0	−0.1	0.3	−0.7	
MT^{h3} (mm)	Baseline	BMP	10	4.1	1.2	2.8	3.9	1.1	6.3	(−1.81, 0.23)
		ABB	16	2.9	1.4	1.3	2.4	1.8	6.2	
	1 year	BMP	12	3.9	1.5	1.2	3.7	2.4	6.3	(−2.56, −0.70)
		ABB	13	2.2	1.1	1.0	1.9	1.2	4.6	
	3 years	BMP	9	3.1	1.3	1.5	3.5	1.7	5.3	(−2.20, 0.20)
		ABB	15	2.4	1.2	0.7	2.2	2.3	4.4	
	Baseline – 3 years	BMP	7	−0.7	0.7	0.1	−0.7	0.9	−1.7	(−0.35, 0.77)
		ABB	12	−0.3	0.4	0.2	−0.2	0.5	−1.2	

Note: Same uppercase letters indicate a statistically significant difference ($p < 0.05$) according to the mixed model analyses.

Abbreviations: ABB, primary augmentation with an autogenous bone block; BMP, primary augmentation with a xenogeneic block and rhBMP-2; c.i., confidence interval; IQR, interquartile range; Max, maximum; Min, minimum; MT^{c}, buccal soft tissue contour measured from the implant shoulder; MT^{h0}, tissue thickness at the level of the implant shoulder; MT^{h3}, tissue thickness 3 mm beneath the implant shoulder; $MT^{v,}$ vertical soft tissue thickness above the implant shoulder; *N*, number; SD, standard deviation.

Stable marginal hard tissue-level changes have been reported in several studies with implants placed following the primary augmentation. However, comparisons between studies might be hampered due to varying baseline time points and differences in implant systems used. In this context, a recent study reported marginal bone levels of implants placed following primary augmentation with changes of −0.2 mm in a short follow-up of 2 years (Mordenfeld et al., 2017). Baseline measurements were performed at delivery of the prosthetic reconstruction and the same implant system as in the present study was used. In line with these findings, another study reported a loss of −0.1 mm to −0.2 mm after 10 years (Chappuis et al., 2017). Here, the baseline was performed 6 months following the insertion of the prosthetic work, and a different implant system was used. The respective changes in marginal hard tissue levels in the present study were slightly higher compared to the above-mentioned studies. A review article has reported 5-year results on the implant system used in the present study, on implants placed in pristine bone (Laurell & Lundgren, 2011). Stable mean marginal bone levels were reported with an overall change of −0.25 mm. Again, the measurements in the present study were minimally higher.

There is a significant lack of studies reporting buccal bone level changes after primary augmentation. A clinical study investigated the buccal bone levels following the implant placement with a simultaneous GBR procedure. The marginal bone level change was amounted to be −0.32 mm on the buccal aspect during the first year after the implant placement (De Bruyckere et al., 2018). Second study was reported on a 15-year follow-up (Benic et al., 2017). The buccal bone level change amounted to 2.19 ± 1.29 mm for implants placed in pristine bone and 1.98 ± 0.98 mm for implants having undergone simultaneous GBR. In the present study, the buccal marginal hard tissue loss was minimal (−0.3 mm [BMP] and −0.4 mm [ABB]) and no difference was found between the two groups within the first 3 years. Interestingly, this hard tissue loss predominantly took place during the first year. It is important to bear in mind that in the present analysis, the obtained levels also describe anorganic bovine bone or mineralized structures of unclear histologic quality.

Three-dimensional radiographic imaging to assess marginal hard tissue levels around the implants is associated with shortcomings. Cone beam computer tomography and concomitant software do not allow precise imaging around dental implants and their suprastructure (Benic et al., 2013). An ex-vivo study demonstrated imprecise readings within a zone of about 0.45 mm in the immediate proximity of the implant (Vanderstuyft et al., 2019). In the case of thin bone plates of less than 0.45 mm, readings will not be fully reliable. In the present study, DBBM sites were more often eligible for evaluation. A potential reason might have been that the DBBM block (group BMP) as a material is more radiopaque and hence better visible in CBCTs. Consequently, more ABB sites could not be evaluated. Furthermore, the merging of dicom files obtained by computer tomographies in combination with STL files obtained from surface scans is less accurate as compared to the merging of STLs only (Flügge et al., 2017; Windisch et al., 2007). In order to keep the increased error as minimal as possible, the merging of several STL files has been performed based on the follow-up dicom file only, and the implant shoulder was used as a reference point. In addition, after adjusting the baseline STL file, the follow-up STL files have been adjusted to the baseline STL. Besides the lower accuracy in merging, this methodology also offers advantages. The present analysis was able to describe the change in thickness of the soft and of the hard tissues, not only the overall contour change.

Most of the soft tissue contour measurements revealed a significant decrease over time in both groups. The majority of these outcomes exhibited a loss of 0.3 mm over 3 years. Other studies have been analyzing contour changes with a similar methodology (Bienz et al., 2017; Sapata et al., 2018). However, these reports focused on different tissue augmentations. Interestingly, the changes at contralateral teeth revealed a certain amount of contour loss as well, amounting to −0.1 mm over 5 years (Sapata et al., 2018). When looking at the vertical soft tissue, the thickness was slightly higher in the BMP group, and the changes over time were similar in both groups. In other words, 5 sites (3 BMP, 2 ABB) out of 40 (12.5%) exhibited a recession of more than 1 mm. Overall, the tissue contour changes can be considered minimal over 3 years.

A significantly greater horizontal tissue thickness was found at the level of the implant shoulder in the BMP group. When looking at the groups individually, an interesting finding was made in the group ABB. The horizontal tissue thickness remained relatively stable in the group ABB, however, there was a reduction of horizontal bone thickness. The reduction was compensated by an increase in soft tissue thickness, resulting in a new ratio of soft and hard tissue but a stable overall contour. Similar findings with soft tissues partially compensating for missing hard tissue were reported earlier (Benic et al., 2012). A very small number of studies have assessed the buccal soft tissue contour. One study evaluated the changes over 3 years and reported a loss of 0.28 mm, for both, resorbable and non-resorbable membranes used for GBR (Basler et al., 2018). A second study reported larger changes within the first year following the GBR, amounting to 1.59 mm (De Bruyckere et al., 2018). In contrast to the present study, the baseline examination was 2 weeks after surgery. At this time point, postsurgical tissue dynamics may have prevented a recording of stable baseline measurements. In addition, the studies existing have looked at different indications and treatment regimens, time-points as well as different measurement techniques.

The main limitation of this study was the small sample size. Only 24 patients were included and this number was further reduced by missing clinical baseline data and of CBCT assessments. Moreover, the study is of an entirely explorative nature, in regards to the present data, but also in regards to the primary endpoint, which was the clinically evaluated ridge width at 4 months following the primary augmentation. Another important aspect is that the present report does not compare the growth factor vs. no growth factor or autogenous bone vs. DBBM. It does compare two treatment modalities, and autogenous bone blocks with additional DBBM coverage were considered the gold standard and served as a control.

Currently, regulatory restrictions and high production costs hamper the widespread availability of rhBMP-2 in dental medicine. The growth factor is available for more than two decades now (Schimandle et al., 1995), and the osteo-inductive potential is scientifically proven (Fujioka-Kobayashi et al., 2017). Nevertheless, the admission of rhBMP-2 varies from country to country and is often limited to ridge preservation procedures and sinus grafting procedures. In contrast to this, the effect of adding a growth factor to current procedures might be more relevant in the more challenging dental indications. Currently, the growth factor is mainly distributed for spine surgery (Liu, et al., 2020) and it appears that there is a lack of commercial interest to make rhBMP-2 widespread available in the dental field.

5 | CONCLUSIONS

The present randomized-controlled clinical trial demonstrated excellent implant survival rates and stable marginal hard tissue levels in both augmentation groups 3 years after the crown insertion. In addition, the clinical stability of soft and hard tissues was demonstrated in both groups.

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CONFLICT OF INTEREST

Dres Hammerle, Jung and Thoma report further grants from the Osteology Foundation outside of the submitted work. Dres. Bienz, Hammerle, Jung, and Thoma report further research commitments with Geistlich Pharma AG and Dentsply Sirona outside of the submitted work.

AUTHOR CONTRIBUTIONS

Stefan Bienz: Data curation (equal); Investigation (equal); Project administration (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Michael Payer:** Data curation (equal); Investigation (equal); Project administration (equal). **Jenni Hjerppe:** Data curation (equal); Investigation (equal); Validation (equal); Visualization (equal). **Christoph H.F. Hämmerle:** Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Ronald Ernst Jung:** Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Daniel S Thoma:** Conceptualization (equal); Data curation (equal); Funding acquisition (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal); Writing-original draft (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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