KEY WORDS
Post-extractive implant, Aesthetics, Soft tissue substitute

Randomized controlled trial

SOFT TISSUE SUBSTITUTES AT IMMEDIATE POST-EXTRACTIVE IMPLANTS TO REDUCE TISSUE SHRINKAGE – 3-YEAR RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

ADRIANO AZARIPOUR, DMD, MSc, PhD
Associate Professor, Department of Oral and Maxillofacial Surgery and Department of Periodontology and Restorative Dentistry, University Medical Hospital, Mainz, Germany, and Centre of Microinvasive Dentistry, Bad Soden, Germany

JACOPO BUTI, DDS, PhD, MPerio RCSEd
Associate Professor, Unit of Periodontology, UCL Eastman Dental Institute, London, UK

KEYVAN SAGHEB, DMD, MD, PhD
Associate Professor, Department of Oral and Maxillofacial Surgery, University Medical Hospital, Mainz, Germany

LARA STOCK, DMD, MSc
Private Practice, Dreikönigstraße. 12, 79102, Freiburg, Germany

BILAL AL NAWAS, DMD, MD, PhD
Director of Department of Oral and Maxillofacial Surgery, University Medical Hospital, Mainz, Germany

MARCO ESPOSITO, DDS, PhD
Freelance researcher and Associate Professor, Department of Biomaterials, The Sahlgrenska Academy at Göteborg University, Göteborg, Sweden

Correspondence to:
Adrian Azaripour
Centre of Microinvasive Dentistry
Sulzbacher Str. 1c, 65812 Bad Soden, Germany
E-mail: adrianoasso@hotmail.com

PURPOSE. The aim of this parallel randomized controlled trial (RCT) was to evaluate whether placement of a soft tissue graft substitute (STGS) could decrease peri-implant tissue shrinkage at immediate post-extractive implants.

MATERIALS AND METHODS. Twenty patients with one missing tooth between two adjacent healthy teeth in aesthetic areas and at least 4 mm of bone apically to the tooth apex were randomly allocated after tooth extraction to receive or not a subepithelial buccal STGS. Implants were inserted with a torque of at least 30 Ncm and sites were grafted with a cancellous particulate allograft. Ten patients received a buccal STGS and 10 patients did not (control group). All patients were restored with non-occluding immediate provisional screw-retained crowns, replaced after 6 months by definitive metal-ceramic crowns, and were followed to 3-year after grafting/loading.

RESULTS. Three-year after loading, no drop-out, crown or implant failure or complication occurred. No statistically significant difference or trends in aesthetics (difference = 0.2, 95% CI: -0.81 to 1.21; P = 0.97), peri-implant marginal bone loss (difference = 0.14 mm; 95% CI: -0.27 to 0.57; P = 0.58) and keratinized mucosa heights (difference = 0.8 mm; 95% CI: -1.79 to 3.39; P = 0.57) between the two groups were observed.

CONCLUSIONS. Acknowledging that the sample size was small, no clinical benefits could be observed using a soft tissue graft substitute at immediate post-extractive implants up to 3-year after grafting.

CONFLICT OF INTEREST STATEMENT. The manufacturer (BEGO Implant Systems, Bremen, Germany) of the implants used in this investigation, partially supported this trial, however data belonged to the authors and by no means the sponsor interfered with the conduct of the trial or the publication of its results.

INTRODUCTION

Immediate post-extractive implants are placed immediately after tooth extraction in fresh extraction sockets. This procedure shortens treatment times but may be associated to higher failure and complication rates compared to delayed implant placement[1,2]. Even though immediate implants may reduce the natural tissue resorption at extraction sockets[1], some shrinkage of the peri-implant tissues still takes place and could compromise the final aesthetic result, causing social discomfort and embarrassment.
A controlled study[3] suggested that augmenting thickness of thin soft tissues at the crestal aspect with a soft tissue graft substitute (STGS) at implant placement could reduce crestal

Doi: 10.36130/CTD.03.2021.04

bone loss of about 1 mm over the first year in function. However, several properly designed randomized controlled trials (RCTs)[4-8], did not report any differences in bone loss when grafting or not at implant sites. Nevertheless, some of those studies suggested that grafting with autogenous soft tissue or with a STGS can lead to increased keratinized mucosa heights[4], increased soft tissue thickness[4,9], increased marginal soft tissue levels[4,5,7], better aesthetics at soft tissue grafted sites[4]. By using a STGS it is not needed to harvest a graft from the palate, thus decreasing post-operative discomfort.

It would be useful to know whether a better clinical outcome could be obtained by augmenting soft tissues when placing immediate implants. The aim of this RCT was to evaluate the efficacy of STGS at single immediate post-extractive implants in aesthetic areas. Data at 1 year after loading/grafting were previously published[10].

MATERIALS AND METHOD

This was a single-center RCT of parallel group design with balanced randomization and blind assessment and was reported according to the CONSORT statement (http://www.consort-statement.org/).

Any patient requiring one single immediate post-extractive implant in the aesthetic area (from second to second premolar of both jaws), between two healthy teeth, being at least 18 years old and able to sign an informed consent form was eligible for inclusion.

Inclusion criteria were sufficient bone allowing placement of single implants with a length of at least 8.5 mm and with a diameter of at least 3.75 mm. In addition, the socket had to have at least 4 mm of bone apically to the tooth apex. Missing of buccal bone was not an exclusion criterion if after implant placement a horizontal space of at least 3 mm between the buccal side of the implant and the adjacent buccal bone was present. Finally, included implants had to be inserted with a torque of at least 30 Newton per centimeter (Ncm).

Exclusion criteria were:

- general contraindications to implant surgery;
- systemic diseases;
- immunosuppressed or immunocompromised;
- irradiation in the head or neck area;
- pregnancy or lactation;
- wish for pregnancy;
- full mouth bleeding and plaque score more than 15%;
- addiction to alcohol or drugs;
- psychiatric disorders;
- unable to commit to 3-year follow-up post-loading;
- under treatment or previous treatment with intravenous amino-bisphosphonates;
- smoking;
- lack of stable posterior occlusion;
- acute infection in the site intended for implant placement.

Patients were recruited and treated by one single operator (AA) at the University Medical Hospital of Mainz, following identical and standardized procedures. All patients signed a written informed consent. A presurgical cone-beam computed tomography (CBCT) was made for all potentially eligible patients to evaluate bone volumes at future implant sites and for planning a proper implant rehabilitation. Oral arches of all patients were scanned using an intraoral scanner (Carestream cs 3600, Rochester, NY, USA). Implant insertion was planned fully digital, matching the scan data with the CBCT data.

Patients received a single dose of antibiotic 1 hour prior to tooth extraction (1 g of amoxicillin or 600 mg of clindamycin, if allergic to penicillin). The keratinized mucosa height was measured with a graduated periodontal probe. Patients rinsed with 0.12% chlorhexidine mouthwash for 1 minute prior to the intervention. Patients were treated under local anesthesia using articaine with adrenaline 1:100.000. Teeth were extracted as atraumatically as possible attempting to preserve the buccal alveolar bone without flap elevation. Sockets were carefully cleaned from any remains of granulation tissue. The integrity of the socket walls was evaluated. Each patient provided one implant site. Three-dimensional printed surgical templates were used for guided surgery. Sites were prepared using drills with increasing diameters. In brief, a lance drill was used to mark the exact implant entrance point on the palatal wall of the socket, followed by a twist drill of 2.5 or 3 mm diameter. All implant sites were underprepared to ensure adequate implant primary stability with a drilling speed of 800 rpm. To ensure that the implants followed the planned direction and not the natural shape of the socket, they were inserted using the template with the motor set at a speed of 20 rpm. Semados microstructured shoulder RSX (Bego, Implant Systems, Bremen, Germany) titanium grade 4, self-tapping, conical implants with internal conical hexagon connection and 3.75 mm diameter were used. The operator was free to choose implant lengths (8.5, 10, 11, 13 and 15 mm) which were planned digitally prior to surgery. The motor was set with a torque of 30 Ncm. Implant heads were placed in touch with the palatal wall and about 1 to 2 mm below the most coronal palatal bone peak.

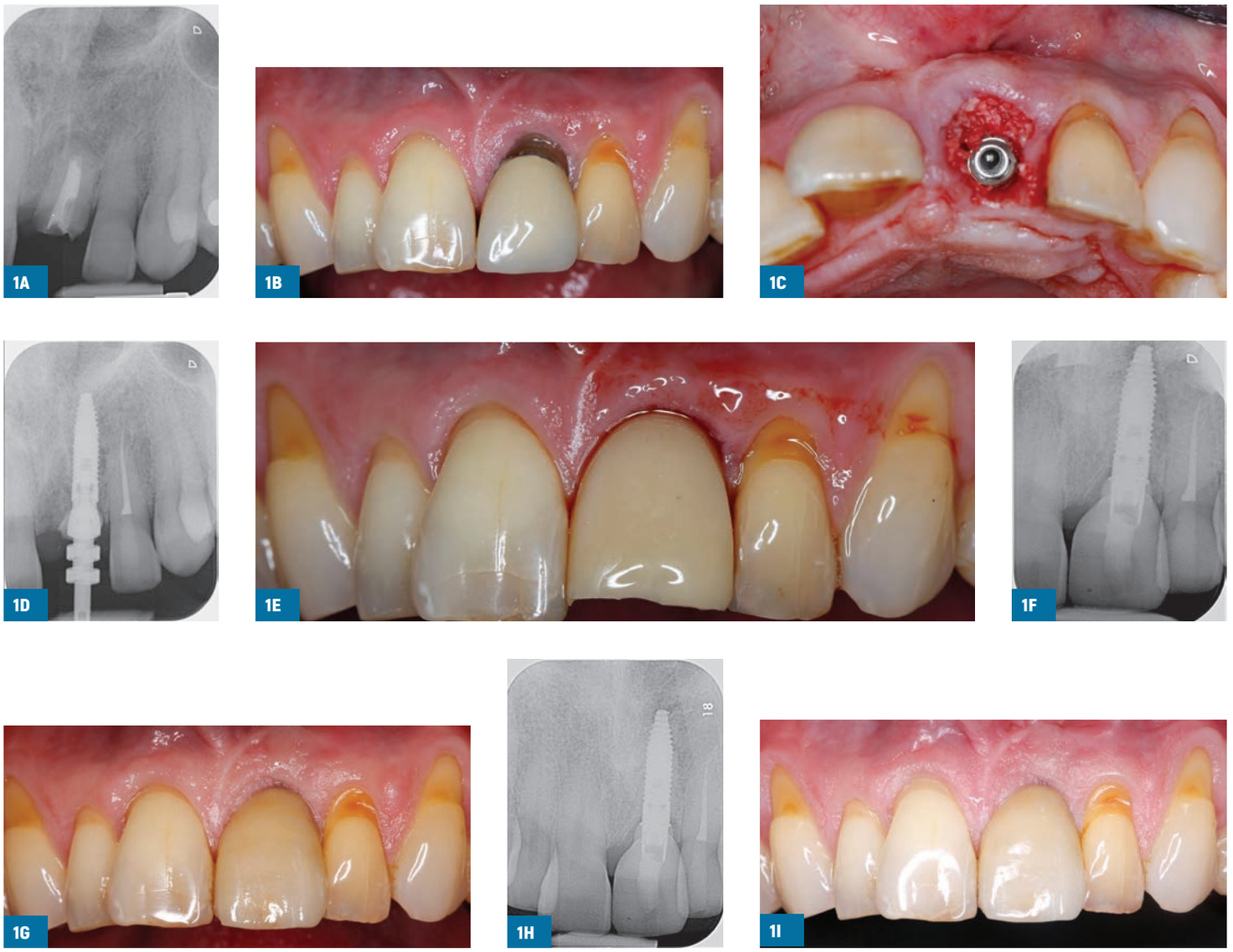
Patients whose implants were placed with a torque of at least 30 Ncm, were finally included in the study and randomly allocated to receive (**FIGS. 1A-I**) or not (**FIGS. 2A-I**) a buccal STGS composed of a porcine-derived acellular dermal collagen matrix (Mucoderm, Botiss, Zossen, Germany) 1.2 to 1.7 mm thick, by opening the corresponding sealed envelope. The collagen matrix was hydrated in sterile saline solution for 10 minutes, a vestibular flap was performed using a modified tunnel technique. Intra-sulcular incisions on the mesial and distal adjacent tooth were performed. A full-thickness flap was elevated in the first 2 mm apical to the cemento-enamel junction of the adjacent teeth. A partial thickness tunnel was performed in the papillary regions. In order to create a tunnel, the pouch preparations of the adjacent teeth were connected with each other. A split thickness incision was performed apically to the muco-gingival junction until the flap was tension free. The collagen matrix was inserted into the tunnel with a packing instrument, and no sutures were placed. Finally, residual gaps between the vestibular tissue and implants were loosely packed with granules of a human derived bone substitute (Puros allograft spongiosa, particle size: 0.25 to 1 mm, Zimmer Biomet, Palm Beach Garden, FL, USA).

Provisional screw-retained crowns, non in static or dynamic occlusion, were delivered within two hours after surgery on provisional abutments screwed with a torque of 15 Ncm. Baseline periapical radiographs and occlusal and vestibular pictures of the study implants were taken.

Ibuprofen 600 mg was prescribed to be taken three times a day for three days. Patients were instructed to rinse with 0.12% chlorhexidine for one minute three times a day for one week. Antibiotics were prescribed: Amoxicillin 1 g (or in case of allergy, clindamycin 600 mg) twice a day for 5 days. After 1 week, oral hygiene instructions were delivered.

Six months after surgery, implant level digital impressions were taken, screw-retained metal-ceramic crowns were fabricated on customized titanium abutments within 2 weeks. Patients were recalled for maintenance every 3 months.

At 3, 6 and 12 months post-loading follow-ups, intraoral scans, periapical radiographs, occlusal and vestibular pictures of the study implants were taken, and oral hygiene instructions rein-



FIGS. 1A-I: *Treatment sequence of one of the patients randomly allocated to the STGS group: preoperative radiograph (A) and clinical view (B); bone grafting (C); radiograph at impression taking (D); clinical view at delivery of the at delivery of the provisional crown (E); radiograph (F) and clinical (G) view at 1-year after loading; radiograph (H) and clinical (I) view at 3-year after loading.*

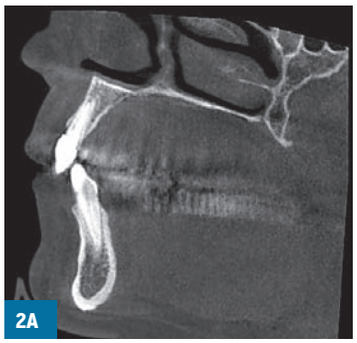
forced. At 3-year post-loading the same procedures were implemented with the exception of the intraoral scans that were not taken.

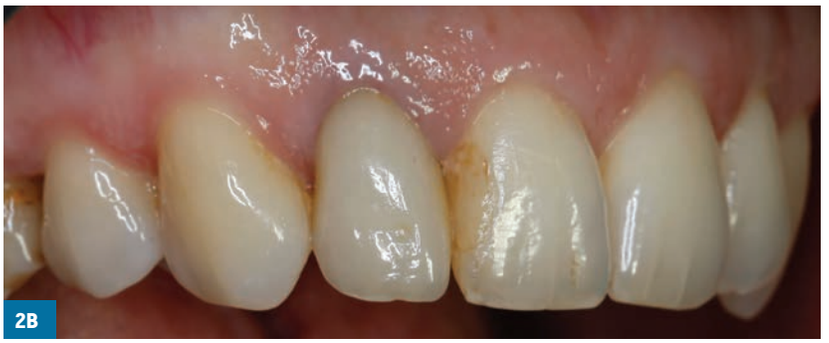
Outcome measures

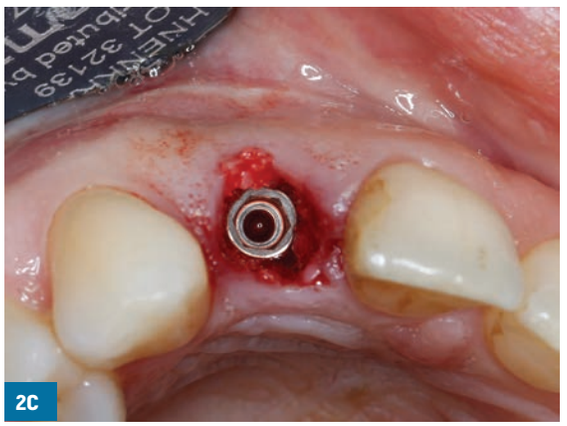
Implant/crown failures: implant mobility, removal of stable implants dictated by progressive marginal bone loss or infection, and any mechanical complications rendering the implant not usable (e.g. implant fracture) were considered as implant failures. If a definitive crown had to be replaced for any reason, it accounted as a crown failure.

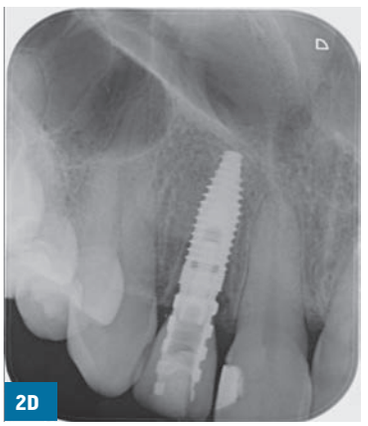
Any biological or biomechanical complication.

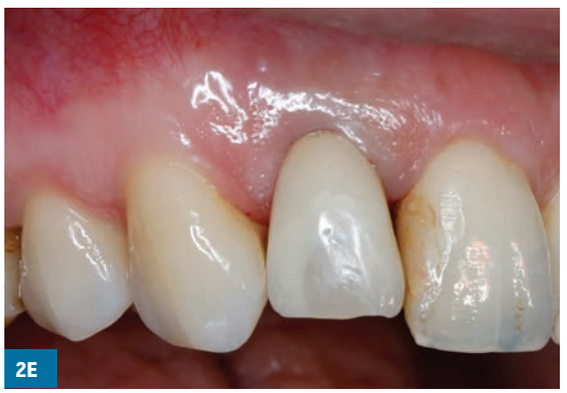
Peri-implant marginal bone level changes evaluated on digital periapical radiographs taken with the paralleling technique at immediate loading, 3, 6, 12 and 36 months after initial loa-

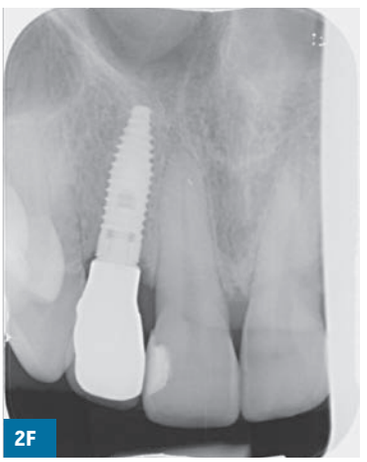

2A


2B

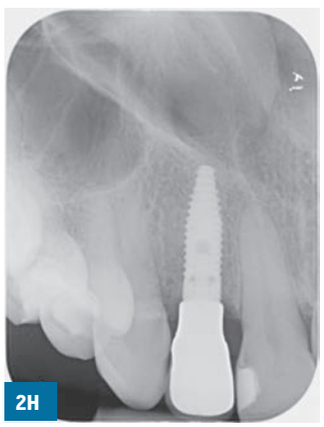

2C

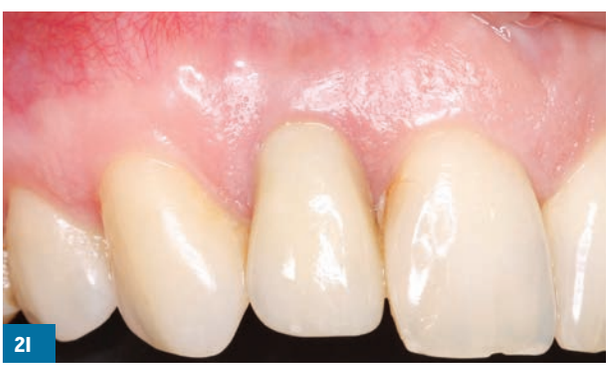

2D


2E


2F


2G


2H


2I

FIGS. 2A-I: *Treatment sequence of one of the patients randomly allocated to the non-grafted group: preoperative radiograph (A) (the upper lateral incisor had a deep horizontal fracture) and clinical (B) view; bone grafting (C); radiograph at delivery of the provisional crown (D); clinical view at delivery of the at delivery of the provisional crown (E); radiograph (F) and clinical (G) view at 1-year after loading; radiograph (H) and clinical (I) view at 3-year after loading*

ding. In case of an unreadable radiograph, a second radiograph was obtained. Peri-implant marginal bone levels were measured using the Planmeca software (Helsinki, Finland). The software was calibrated for every single image using the known implant diameter. Measurements of the mesial and distal bone crest level adjacent to each implant were made to the nearest 0.01 mm. Reference points for the linear measurements were the coronal margin of the implant collar and the most coronal point of visible bone-to-implant contact. The measurements at mesial and distal sides of each implants were averaged at implant level and then at group level.

Tissue volume changes from intraoral scans (Carestream cs 3600) taken before the surgical intervention. The volume scanned was delimitated superiorly by the buccal crown margin, inferiorly by an horizontal line 5 mm below the crown margin and laterally by the vertical lines from the center of both adjacent papillae. The baseline scan data as Standard Triangle Language (STL) format were compared with the 3, 6 and 12 months postsurgical scans to measure buccal soft tissue alterations using the GOM Inspect software (Braunschweig, Germany). The adjacent teeth of the extracted tooth were used to superimpose and match (pre- and post-operative scan) the 3D datasets. Thereafter the buccal soft tissue alteration as described above was precisely measured over time. It was not planned to collect this information at 3-year after loading.

Aesthetic evaluation of the vestibular and occlusal clinical pictures, including the two adjacent teeth at 3, 6, 12 and 36 months after loading, and performed on a computer screen. The aesthetic evaluation was carried out using the pink esthetic score (PES)[11]. In brief, seven variables were evaluated: mesial papilla, distal papilla, soft tissue level, soft tissue contour, alveolar process deficiencies, soft tissue color and texture. A 0-1-2 scoring system was used, 0 being the lowest and 2 being the highest value, with a maximum achievable score of 14 per implant.

Keratinized mucosa height was measured vestibularly in the middle of the long axis of the tooth/implant using a graduated periodontal probe before tooth extraction and 1 and 3 years after grafting/loading.

No sample size calculation was performed and it was agreed to recruit 20 patients, to be randomly allocated. One computer generated restricted randomization list was created. Only one investigator, who was not involved in the selection and treatment of the patients, knew the random sequence and had access to the random list stored in a pass-word protected portable computer. The randomized codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. After placement of the implant with a torque of at least 30 Ncm, the patient was finally entered in the study and the envelopes were sequentially opened. Therefore, treatment allocation was concealed to the investigators in charge of enrolling and treating the patients.

A blind outcome assessor (LS), not involved in the treatment of the patients, measured aesthetic, marginal bone levels, tissue shrinkage and keratinized mucosa heights without knowing group allocation, therefore the outcome assessor was blind. Complications were treated by the main operator (AA) in a non-blinded mode.

Statistical methods

All data analysis was performed according to a pre-established analysis plan by a clinician with expertise in statistics (JB) analyzing the data without knowledge of the group codes. The patient was the statistical unit of the analyses. Differences in the proportion of patients with implant failures and complications (dichotomous outcomes) were to be compared between the groups using the Fisher's exact probability test. Differences of means at patient level for

continuous outcomes (PES, keratinized mucosa height, bone levels, and volumetric changes) between groups were compared by Mann-Whitney-U test. The Wilcoxon signed-rank test was used to assess marginal bone level and keratinized mucosa changes and volumetric alterations within each group. All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

Twenty-five patients were screened and 20 patients were consecutively enrolled. Five patients were excluded after radiological evaluation because of lack of sufficient bone for implant placement. All patients were treated according to the allocated interventions and received a bone graft substitute.

No patient dropped out and no data was missed or lost. Therefore data of all patients were evaluated in the statistical analyses. No deviation from the protocol was reported. Patients received post-extractive implants from December 2016 until October 2017. The follow-up of all patients was to 3 year after loading. Patient demographics are presented in **TABLE 1**. There were no apparent significant baseline imbalances between the two groups.

No implant failed, no crown had to be remade, and no complication occurred during the entire follow-up period.

Marginal peri-implant bone level changes (**TABLE 2**). At implant placement, the average bone levels was 0 for both groups. At 3-year, the average bone level changes around grafted implants was 0.29 (0.53) mm *versus* 0.15 (0.31) mm at non-grafted implants, the difference being not significantly different (difference = 0.14 mm; 95% CI: -0.27 to 0.57; P = 0.58).

Pink Esthetic score (PES) (**TABLE 3**). Three years after loading, the average PES score was 13.1 (1.29) for the grafted group and 13.3 (0.83) for the non-grafted group, the difference being not significantly different (difference = 0.2 in favor of the non-grafted group, 95% CI: -0.81 to 1.21; P = 0.97; **TABLE 3**).

TABLE 1 PATIENT AND INTERVENTION CHARACTERISTICS

	Grafted (n = 10)	Non-grafted (n = 10)
Females	5	5
Males	5	5
Mean age at implant insertion (range)	45.2 ± 10.3 (28 to 61)	51.8 ± 14.3 (25 to 74)
Implants in upper incisor position	7	7
Implants in upper premolar position	2	2
Implants in lower premolar position	1	1
Implants of length 11 mm	1	1
Implants of length 13 mm	4	3
Implants of length 15 mm	5	6
Sites augmented with bone substitute at implant placement	10	10
Mean preoperative keratinized mucosa height (mm)	5.2 ± 1.4	6.0 ± 2.1
Baseline radiographic peri-implant marginal bone levels (mm)	0	0

TABLE 2 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVELS AND LEVEL CHANGES BETWEEN GROUPS AND TIME PERIODS UP TO 3-YEARS AFTER LOADING

	Implant placement	3 months	6 months	1 year	3 years
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Grafted = 10	0 (0)	0.32 (0.55)	0.35 (0.56)	0.23 (0.41)	0.29 (0.53)
Non-grafted = 10	0 (0)	0.08 (0.24)	0.19 (0.34)	0.15 (0.26)	0.15 (0.31)
Difference [95% CI]	0	0.24 [-0.15 to 0.64]	0.16 [-0.28 to 0.59]	0.08 [-0.24 to 0.40]	0.14 [-0.27 to 0.57]
P-value	1.0	0.28	0.71	0.48	0.58

Intragroup p-values:
Grafted: 3-month P = 0.25; 6-month P = 0.25; 12-month P = 0.25; 36-month P = 0.25
Non-grafted: 3-month P = 1.00; 6-month P = 0.25; 12-month P = 0.13; 36-month P = 0.50

TABLE 3 PES SCORES AT 36 MONTHS BY GROUPS AND BY DIFFERENT AESTHETIC DOMAINS; STANDARD DEVIATION IS IN PARENTHESIS

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Grafted = 10	1.8 (0.42)	1.8 (0.42)	1.9 (0.32)	1.8 (0.42)	2 (0)	1.9 (0.32)	1.9 (0.32)	13.1 (1.29)
Non-grafted = 10	1.8 (0.42)	1.8 (0.42)	1.9 (0.32)	1.8 (0.42)	2 (0)	2 (0)	2 (0)	13.3 (0.83)
Difference (95% CI)	0 (-0.40 to 0.40)	0 (-0.40 to 0.40)	0 (-0.30 to 0.30)	0 (-0.40 to 0.40)	0 (0 to 0)	0.10 (-0.11 to 0.31)	0.10 (-0.11 to 0.31)	0.2 (-0.81 to 1.21)
P-value	1.00	1.00	1.00	1.00	1.00	0.37	0.37	0.97

Volumetric changes (**TABLE 4**). There were no statistically significant differences in volume changes from baseline to 1 year after loading between the two groups (difference = 1.05 ± 1.39 mm^3, 95% CI: -2.27 to 4.37; P = 0.65)

Keratinized mucosa height (**TABLE 5**). Prior to tooth extraction, the average keratinized mucosa height at implant to be grafted implants was 5.2 (1.48) mm *versus* 6 (2.16) mm at implants not to be grafted, the difference being not statistically different (difference = -0.8 mm; 95% CI: -2.54 to 0.94; P = 0.33). At 1 year, the average keratinized mucosa height at grafted implants was 5.3 (1.70) mm *versus* 5.9 (2.23) mm at non-grafted implants, the difference being not statistically different (difference = -0.6 mm; 95% CI: -2.47 to 1.27; P = 0.56). At 3 years, the average keratinized mucosa height at grafted implants was 5.6 (2.41) mm *versus* 5.6 (1.51) mm at non-grafted implants, the difference being not statistically different (difference = 0 mm; 95% CI: -1.89 to 1.89; P = 1.00). Mean keratinized mucosa height changes at 3-year were 0.4 (2.72) mm at grafted implants and -0.4 (2.80) mm at not-grafted implants, the difference not being statistically significant (difference = 0.8 mm; 95% CI: -1.79 to 3.39; P = 0.57).

TABLE 4 MEAN VOLUME CHANGES (SD) IN MM^3 AT 3, 6 AND 12 MONTHS FOR THE TWO GROUPS, AND FROM BASELINE WITHIN EACH GROUP

	3 months	6 months	1 year
	Mean (SD)	Mean (SD)	Mean (SD)
Grafted = 10	4.31 (2.7)	6.21 (2.9)	6.21 (3.0)
Non-grafted = 10	5.16 (3.4)	7.22 (3.9)	7.31 (3.9)
Difference [95% CI]	0.84 [-2.06 to 3.76]	1.01 [-2.30 to 4.32]	1.05 [-2.27 to 4.37]
P-value	0.59	0.67	0.65

TABLE 5 KERATINIZED MUCOSA HEIGHT CHANGES UP TO 3 YEARS BY STUDY GROUP (N = 10 PER GROUP)

	Grafted mean (SD)	No-grafted mean (SD)	Mean difference	95% CI of the difference	P-value (Mann–Whitney U test)
Prior to extraction	5.2 (1.48)	6.0 (2.16)	-0.8	-2.54 to 0.94	0.33
1 year post-loading	5.3 (1.70)	5.9 (2.23)	-0.6	-2.47 to 1.27	0.56
3 year post-loading	5.6 (2.41)	5.6 (1.51)	0	-1.89 to 1.89	1.00
Mean changes at 1 year	0.1 (0.57)	-0.1 (0.32)	0.2	-0.23 to 0.63	0.36
95% CI of the difference (1 year)	-0.31 to 0.51	-0.33 to 0.13			
P-value from Wilcoxon test to 1 year	1.00	1.00			
Mean changes at 3 years	0.4 (2.72)	-0.4 (2.80)	0.8	-1.79 to 3.39	0.57
95% CI of the difference (3 years)	-1.54 to 2.34	-2.40 to 1.60			
P-value from Wilcoxon test at 3 years	0.61	0.66			

DISCUSSION

This trial was designed to assess whether the placement of a soft tissue graft substitute at immediate post-extractive implants could reduce tissue shrinkage. It was decided to graft the extraction sockets with a human derived bone graft since it has been shown in a RCT[12] a better aesthetic outcome and marginal bone levels when compared to non-grafted sites.

All outcome measures suggested no statistically or clinically significant difference between the two procedures up to 3 years after loading, indicating doubts on the possible clinical benefits of grafting at implant placement, however, the main limitation of the present trial was the insufficient sample size.

Similar findings were reported by other RCTs comparing other types of soft tissue substitutes *versus* non-grafted controls[7,9]. All these findings taken together are indicative of lack of utility of soft tissue substitutes in the tested indications. Since some keratinized mucosa was present at all study sites, it remains unclear whether some advantages of STGS could have been obtained in absence of keratinized mucosa.

Even though this was not the aim of the present study, on one hand the scientific literature suggests that autogenous soft tissues grafts determined statistically significant better resul-

ts in terms of less buccal tissue collapse at immediate post-extractive implants[13,1], better aesthetic outcomes[13], even though the mid-facial gingival margin migrated in an apico-palatal direction similarly, as in the non-grafted group[13,14]. On the other hand, other studies yielded opposite results, showing no difference in buccal mucosa tissue collapse[15], similar aesthetic outcome[5,6,15] but higher mid-facial mucosa level associated with the autogenous graft procedure[5,6,15,16]. Other studies reported no clinically relevant statistically significant differences in favor of autogenous soft tissue grafting[8,17]. Finally one study[16], showed that the application of connective tissue grafts in the aesthetic zone of immediately placed and restored implants was associated with more loss of buccal bone thickness than no grafting. Interestingly, the arm of another RCT evaluating the effect of PRF (platelet-rich fibrin) inserted with a split-flap technique on soft tissue thickening and initial marginal bone loss around implants *versus* no treatment, had to be stopped due to an unexpected statistically and clinically significant loss of soft tissue thickness[18]. The inconsistencies of the results of all these RCTs require a properly conducted systematic review and, most likely, more trials using appropriate outcome measures and sample sizes.

Since in the present investigation both procedures were tested in real clinical conditions, results can be generalized with confidence to a wider population with similar characteristics.

CONCLUSIONS

Acknowledging that the sample size was very small, no advantage could be observed by using a soft tissue graft substitute at immediate post-extractive implants up to 3-years after grafting.

REFERENCES

1. Felice P, Barausse C, Buti J, Gessaroli M, Esposito M. Immediate, early (6 weeks) and delayed (4 months) single post-extractive implants: 3-year post-loading data from a randomised controlled trial. Clinical Trials in Dentistry 2019;1:5-53.
2. Esposito M, Barausse C, Bonifazi L, Piattelli M, Pistilli R, Ferri A et al. Wide-diameter immediate post-extraction implants *versus* socket preservation and delayed placement of normal-diameter implants in the molar region: 5-year post-loading outcome of a randomised controlled trial. Clinical Trials in Dentistry 2020;2:21-37.
3. Puisys A, Linkevicius T. The influence of mucosal tissue thickening on crestal bone stability around bone-level implants. A prospective controlled clinical trial. Clin Oral Implants Res 2015;26:123-9.
4. Wiesner G, Esposito M, Worthington H, Schlee M. Connective tissue grafts for thickening peri-implant tissues at implant placement. One-year results from an explanatory split-mouth randomised controlled clinical trial. Eur J Oral Implantol 2010;3:27-35.
5. Yoshino S, Kan JY, Rungcharassaeng K, Roe P, Lozada JL. Effects of connective tissue grafting on the facial gingival level following single immediate implant placement and provisionalization in the esthetic zone: a 1-year randomized controlled prospective study. Int J Oral Maxillofacial Implants 2014;29:432-40.
6. Zuiderveld EG, Meijer HJA, den Hartog L, Vissink A, Raghoebar GM. Effect of connective tissue grafting on peri-implant tissue in single immediate implant sites: a RCT. J Clin Periodontol 2018;45:253-64.
7. Baldi N, Buti J, Mensi M, Alfonsi F, Cinquini CPT et al. Xenogenic dermal matrix *versus* autologous connective tissue graft *versus* no grafts at abutment connection for improving aesthetics: 6-month outcomes of a randomised controlled trial. Clinical Trials in Dentistry 2020;2:49-62.
8. Zuiderveld EG, Meijer HJA, Vissink A, Raghoebar GM. The influence of different soft-tissue grafting procedures at single implant placement on esthetics: a randomized controlled trial. J Periodontol 2018;89:903-14.
9. Froum SJ, Khouly I, Tarnow DP, Froum S, Rosenberg E, Corby P et al. The use of a xenogeneic collagen matrix at the time of implant placement to increase the volume of buccal soft tissue. Int J Periodontics Restorative Dent 2015;35:179-89.
10. Azaripour A, Sagheb K, Stock L, Schiegnitz E, Al Nawas B, Esposito M. The use of a soft tissue substitute at immediate post-extractive implants to reduce tissue shrinkage – 1-year results

from a randomized controlled trial. Int J Periodontics Restorative Dentistry 2021;41: in press.
11. Fürhauser R, Florescu D, Benesch T, Haas R, Mailath G, Watzek G. Evaluation of soft tissue around single-tooth implant crowns: the pink esthetic score. Clin Oral Implants Res 2005;16:639-44.
12. De Angelis N, Felice P, Pellegrino G, Camurati A, Gambino P, Esposito M. Guided bone regeneration with and without a bone substitute at single post-extractive implants: 1-year post-loading results from a pragmatic multicentre randomised controlled trial. Eur J Oral Implantol 2011;4:313-25.
13. Migliorati M, Amorfini L, Signori A, Biavati AS, Benedicenti S. Clinical and aesthetic outcome with post-extractive implants with or without soft tissue augmentation: a 2-year randomized clinical trial. Clin Implant Dent Relat Res 2015;17:983-95.
14. Jiang X, Di P, Ren S, Zhang Y, Lin Y. Hard and soft tissue alterations during the healing stage of immediate implant placement and provisionalization with or without connective tissue graft: a randomized clinical trial. J Clin Periodontol 2020;47:1006-15.
15. van Nimwegen WG, Raghoebar GM, Zuiderveld EG, Jung RE, Meijer HJA, Muhlemann S. Immediate placement and provisionalization of implants in the aesthetic zone with or without a connective tissue graft: a 1-year randomized controlled trial and volumetric study. Clin Oral Implants Res 2018;29:671-8.
16. Zuiderveld EG, van Nimwegen WG, Meijer HJA, Jung RE, Muhlemann S, Vissink A et al. Effect of connective tissue grafting on buccal bone changes based on cone beam computed tomography scans in the aesthetic zone of single immediate implants: a 1-year randomized controlled trial. J Periodontol 2020:671-8.
17. Buyukozdemir Askin S, Berker E, Akincibay H, Uysal S, Erman B, Tezcan I et al. Necessity of keratinized tissues for dental implants: a clinical, immunological, and radiographic study. Clin Implant Dent Relat Res 2015;17:1-12.
18. Hehn J, Schwenk T, Striegel M, Schlee M. The effect of PRF (platelet-rich fibrin) inserted with a split-flap technique on soft tissue thickening and initial marginal bone loss around implants: results of a randomized, controlled clinical trial. Int J Implant Dent 2016;2:13.