J Periodontal Implant Sci. 2022 Apr;52(2):170-180
https://doi.org/10.5051/jpis.2104040202
pISSN 2093-2278·eISSN 2093-2286

JPIS
Journal of Periodontal & Implant Science

Research Article
Implant Science

Immediate implant placement in conjunction with guided bone regeneration and/or connective tissue grafts: an experimental study in canines

Hyun-Chang Lim [1,2,3], **Kyeong-Won Paeng** [4], **Myong Ji Kim** [4], **Ronald E. Jung** [1], **Christoph HF. Hämmerle** [1], **Ui-Won Jung** [4,*], **Daniel S. Thoma** [1,4]

[1]Clinic of Reconstructive Dentistry, Center of Dental Medicine, University of Zurich, Zurich, Switzerland
[2]Department of Periodontology, Periodontal-Implant Clinical Research Institute, School of Dentistry, Kyung Hee University, Seoul, Korea
[3]Department of Periodontology, Dental Hospital, Kyung Hee University Medical Center, Seoul, Korea
[4]Department of Periodontology, Research Institute for Periodontal Regeneration, Yonsei University College of Dentistry, Seoul, Korea

Received: Jul 17, 2021
Revised: Sep 29, 2021
Accepted: Oct 31, 2021
Published online: Nov 23, 2021

***Correspondence:**
Ui-Won Jung
Department of Periodontology, Research Institute for Periodontal Regeneration, Yonsei University College of Dentistry, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: drjew@yuhs.ac
Tel: +82-2-2228-3185
Fax: +82-2-392-0398

ORCID iDs
Hyun-Chang Lim
https://orcid.org/0000-0001-7695-1708
Kyeong-Won Paeng
https://orcid.org/0000-0001-7262-7345
Myong Ji Kim
https://orcid.org/0000-0001-7254-1883
Ronald E. Jung
https://orcid.org/0000-0003-2055-1320
Christoph HF. Hämmerle
https://orcid.org/0000-0002-8280-7347
Ui-Won Jung
https://orcid.org/0000-0001-6371-4172
Daniel S. Thoma
https://orcid.org/0000-0002-1764-7447

ABSTRACT

Purpose: This study was conducted to assess the effect of hard and/or soft tissue grafting on immediate implants in a preclinical model.
Methods: In 5 mongrel dogs, the distal roots of P2 and P3 were extracted from the maxilla (4 sites in each animal), and immediate implant placement was performed. Each site was randomly assigned to 1 of the following 4 groups: i) gap filling with guided bone regeneration (the GBR group), ii) subepithelial connective tissue grafting (the SCTG group), iii) GBR and SCTG (the GBR/SCTG group), and iv) no further treatment (control). Non-submerged healing was provided for 4 months. Histological and histomorphometric analyses were performed.
Results: Peri-implant tissue height and thickness favored the SCTG group (height of peri-implant mucosa: 1.14 mm; tissue thickness at the implant shoulder and ±1 mm from the shoulder: 1.14 mm, 0.78 mm, and 1.57 mm, respectively; median value) over the other groups. Bone grafting was not effective at the level of the implant shoulder and on the coronal level of the shoulder. In addition, simultaneous soft and hard tissue augmentation (the GBR/SCTG group) led to a less favorable tissue contour compared to GBR or SCTG alone (height of peri-implant mucosa: 3.06 mm; thickness of peri-implant mucosa at the implant shoulder and ±1 mm from the shoulder: 0.72 mm, 0.3 mm, and 1.09 mm, respectively).
Conclusion: SCTG tended to have positive effects on the thickness and height of the peri-implant mucosa in immediate implant placement. However, simultaneous soft and hard tissue augmentation might not allow a satisfactory tissue contour in cases where the relationship between implant position and neighboring bone housing is unfavorable.

Keywords: Alveolar ridge augmentation; Animal experimentation; Dental implantation

INTRODUCTION

Clinicians are confronted with several options when performing tooth extraction, ranging from ridge preservation techniques to a conventional protocol that awaits complete soft

Funding

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science, ICT & Future Planning) (No. NRF-2017R1A2B2002537).

Author Contributions

Conceptualization: Ronald E. Jung, Christoph HF. Hämmerle, Ui-Won Jung, Daniel S. Thoma; Formal analysis: Hyun-Chang Lim; Investigation: Kyeong-Won Paeng, Myong Ji Kim, Daniel S. Thoma; Methodology: Ronald E. Jung, Christoph HF. Hämmerle, Ui-Won Jung; Project administration: Kyeong-Won Paeng, Myong Ji Kim; Writing - original draft: Hyun-Chang Lim; Writing - review & editing: Ui-Won Jung, Daniel S. Thoma

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

and hard tissue healing. Among these options, immediate implant placement (IIP) has been proposed to offer advantages to patients and clinicians by minimizing the number of required interventions and reducing the overall treatment time. IIP was initially introduced to prevent changes in the ridge profile following tooth extraction using extraction socket-sized implant dimensions [1]. However, evidence has demonstrated that IIP cannot prevent shrinkage [2,3]. As a result, numerous studies have analyzed various IIP protocols [4,5].

Considering that the esthetic zone is the main target area for the IIP protocol, a facial mucosal recession above a certain threshold (>1 mm) and/or a loss of mucosal volume can be detrimental and can even be considered as treatment failure [6,7]. To overcome potential volume loss, simultaneous grafting with connective tissue grafts, with or without concomitant bone augmentation, has been suggested. This resulted in a more stable facial mucosal margin, greater mucosal volume, and a higher pink esthetic score [8-13]. Unfortunately, the relevant parameters leading to a successful outcome have not been systematically evaluated, and the majority of the studies on this topic had a case series design. Moreover, there is a lack of histologic and histomorphometric data regarding soft tissue dimensions and composition after soft and/or hard tissue grafting.

Therefore, this preclinical study aimed to assess the effect of hard and/or soft tissue grafting on immediate implants in a preclinical canine model.

MATERIALS AND METHODS

Animals

The present study was designed as a randomized controlled preclinical study that employed 5 mongrel dogs (>2 years old) weighing between 12 and 17 kg. All animals were kept in a purpose-designed room for experimental animals, provided a soft diet and access to water *ad libitum*, during the entire study period. The study protocol was approved by the Institutional Animal Care and Use Committee of Yonsei Medical Research Center, Seoul, South Korea (approval No. 2020-0085). This article was written in accordance with the ARRIVE guidelines [14].

Surgical procedures

All surgical procedures were performed under general anesthesia and sterile conditions in an operating room. General anesthesia was induced by an intravenous injection of atropine (0.04 mg/kg; Kwangmyung Pharmaceutical, Seoul, Korea) and an intramuscular injection of a combination of xylazine (Rompun®; Bayer Korea, Seoul, Korea) and ketamine (Ketara®; Yuhan Corporation, Seoul, Korea). Inhalation anesthesia (Gerolan®; Choongwae Pharmaceutical, Seoul, Korea) was maintained under monitoring of vital signs throughout the entire procedure. An intramuscular injection of antibiotics (20 mg/kg, cefazolin sodium; Yuhan, Seoul, Korea) was administered for 3 days post-surgery. Daily irrigation with 0.2% chlorhexidine solution (Hexamedin®; Bukwang Pharmaceutical, Seoul, Korea) was performed until suture removal.

Sulcular incisions were made around the maxillary premolars (P2 and P3) and buccolingual flaps were reflected. Subsequently, P2 and P3 were hemi-sectioned and the distal roots were carefully extracted with no bucco-palatal luxating force, in order to preserve the buccal/palatal bone plates. For the remaining mesial roots, pulpotomy was performed, and calcium hydroxide (Dycal®; Dentsply Sirona, York, PA, USA) was applied.

https://doi.org/10.5051/jpis.2104040202

JPIS
Journal of Periodontal & Implant Science

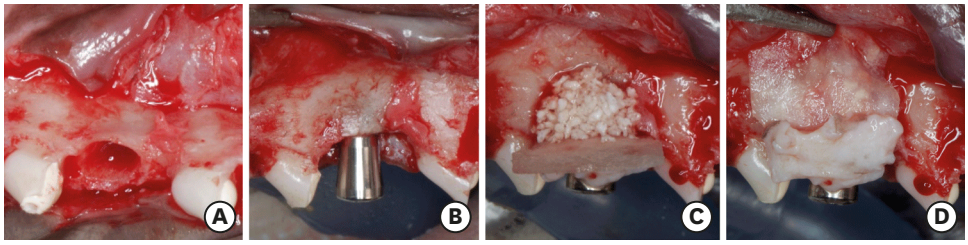

Figure 1. Clinical photographs of surgery. (A) Tooth extraction, (B) implant placement, (C) gap filling and guided bone regeneration, and (D) soft tissue augmentation.

Subsequently, in the areas of the distal root of P2/P3, 2-piece dental implants (NR line Ø3.2×7 mm [diameter × length]; Dentium, Suwon, Korea) were placed, which led to the implant shoulder being at the level of the palatal bone crest and there being approximately 0.5–1.0 mm of space between the implant and the buccal bone wall. The healing abutments were then connected to the implants. The following 4 treatment modalities were then randomly assigned: i) guided bone regeneration (GBR) only (the GBR group), ii) subepithelial connective tissue grafting (SCTG) only (the SCTG group), iii) GBR + SCTG (the GBR/SCTG group), and iv) no other treatment (control). In the GBR group, biphasic calcium phosphate (Osteon™ III; Genoss, Suwon, Korea) was applied in the socket and on the outer surface of the buccal alveolus (width: between proximal areas of two adjacent teeth, height: 3-4 mm). The augmented area was covered with a cross-linked collagen membrane (collagen membrane P; Genoss). In the coronal part of the membrane, a hole was made using a punch and the membrane was secured by the healing abutment (Ø3.7×3.5 mm [diameter × length]; Dentium). The apical part of the membrane was fixed to the bone using 2 membrane tacks (Membrane Pin; Dentium). In the SCTG group, a subepithelial connective tissue graft was harvested from the palate. The width of the graft was approximately twice the diameter of the implant, with a height of 5 mm and a thickness of at least 1.5 mm. The graft was immobilized by suturing it onto the palatal flap. In the GBR/SCTG group, the subepithelial connective tissue graft was placed on top of the collagen membrane and secured to the palatal flap. In the control group, no additional tissue augmentation procedures were performed. Finally, the flaps were sutured and transmucosal healing was performed for all implants (**Figure 1**). The sutures were removed 14 days later.

At 4 months of healing, all animals were sacrificed with an overdose of anesthesia. Maxillary segments with augmented sites were then harvested.

Histologic processing

The dissected tissue sections were fixed in 10% neutral-buffered formalin. Subsequently, the specimens were dehydrated in a series of ethanol solutions and embedded in methyl methacrylate. A central bucco-oral section for each implant site was prepared at a thickness of 40–50 μm [15]. All sections were stained with Masson-Goldner trichrome staining.

Histomorphometric measurements

All histological slides were scanned (Panoramic 250 Flash III; 3DHISTECH, Budapest, Hungary) and analyzed using a specific software (CaseViewer ver. 2.1; 3DHISTECH). The following references were marked: margo mucosae (MM), implant shoulder (IS), first bone-to-implant contact (fBIC), and buccal outline of the soft and hard tissue.

https://doi.org/10.5051/jpis.2104040202

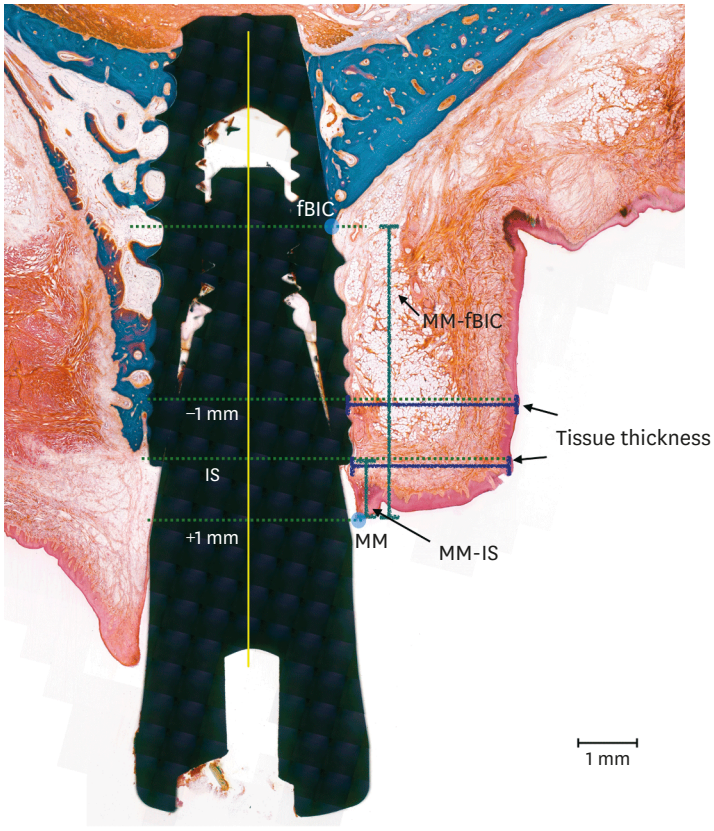

Figure 2. Histomorphometric measurements.
MM: margo mucosa, IS: implant shoulder, fBIC: first bone-to-implant contact.

The following measurements were performed (**Figure 2**):

Vertical measurements
- MM-IS (D1)
- MM-fBIC (D2)

Horizontal measurements
- Total tissue thickness (TT): distance between the outline of the soft tissue and implant surface
- Hard tissue thickness (HT): distance between the outline of the hard tissue and implant surface
- Soft tissue thickness (ST): distance between the outlines of the soft and hard tissues

Horizontal measurements were performed at 3 levels (at the level of the IS, 1 mm above and 1 mm below the IS).

Statistical analyses

Data are presented as mean ± standard deviation (SD), median, and quartiles. Due to the lack of HT in the majority of the specimens, statistical analysis was performed for MM-IS, MM-fBIC, and TT (SAS 9.4; SAS Institute, Cary, NC, USA). The sample size was too small for relevant statistical tests. The main goal was the description of the impact of the 4 treatments; however, to compare the parameters in the 4 treatment groups, parametric mixed linear models with the group as the impact factor were applied because of the clustered data within the dogs. Since all *P* values were quite large ($P>0.5$) and the sample size was small, we did not

https://doi.org/10.5051/jpis.2104040202

add confidence intervals of the mean differences. The threshold for statistical significance was set at $P<0.05$.

RESULTS

Clinical healing

All dogs remained healthy, and no local infections occurred during the entire study period. However, 2 implants were lost during follow-up (1 in the GBR/SCTG group and 1 in the GBR group).

Histologic observations

Due to the proximity of the maxillary sinus, the apex of all implants protruded into the sinus cavity to various extents. All implants included in the histological processing (except for 2 implants lost during the healing period) were osseointegrated. Generally, the buccal bone plate tended to undergo moderate resorption. The majority of the specimens exhibited no bone-to-implant contact more coronal than the third thread of the implants. In the GBR and the GBR/SCTG groups, no remnants of the collagen membrane were observed. Newly formed bone was interconnected with bone substitute particles, but the space occupied by bone substitute particles appeared to be collapsed in the majority of the specimens. The fibrous connective tissue layer tended to be thicker in the SCTG and GBR/SCTG group than in the other groups (**Figure 3**).

Histomorphometric outcomes

Height of the peri-implant mucosa (vertical measurements)

On the buccal aspect, the median level of the MM was located coronally with respect to the implant platform, with distances ranging between 1.99 mm (Q1: 1.83, Q3: 2.45) for the SCTG group (maximum) and 1.24 mm (Q1: 0.43, Q3: 2.05) for the GBR/SCTG group (minimum) (no statistically significant differences in mean values between the groups, mixed model: $P=0.72$) (**Table 1**, **Figure 4A**).

The median distance between the MM and the fBIC was in a similar range among the GBR, SCTG, and control groups (4.06 mm [Q1: 3.13, Q3: 5.09] for the GBR group and 3.86 mm [Q1: 3.19, Q3: 4.17] for the SCTG group). The GBR/SCTG group exhibited the shortest distance at 3.06 mm (Q1: 2.86, Q3: 4.21) (**Table 1**, **Figure 4B**), but there were no statistically significant differences between the mean values of groups (mixed model: $P=0.78$).

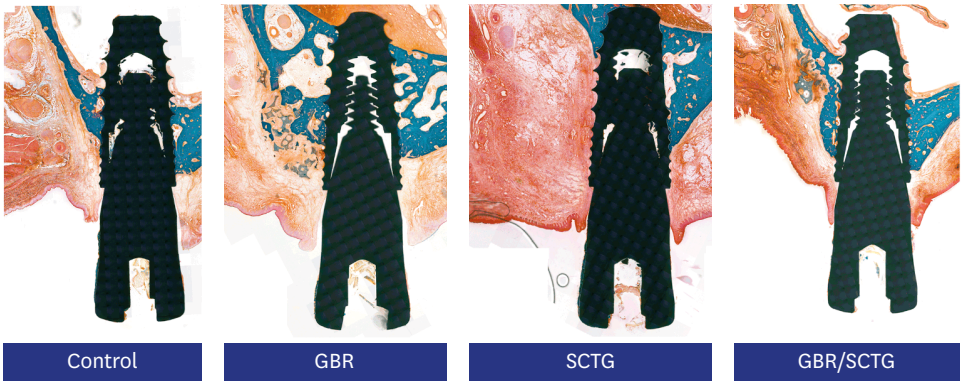

Figure 3. Representative histologic views of the groups.
GBR: guided bone regeneration, SCTG: subepithelial connective tissue grafting, Control: no other treatment.

https://doi.org/10.5051/jpis.2104040202

Table 1. Peri-implant soft tissue height (in mm)

Peri-implant soft tissue height	GBR group	SCTG group	GBR/SCTG group	Control
MM-IS (*P*=0.72)	1.45 (0.63, 2.58)	1.99 (1.83, 2.45)	1.24 (0.43, 2.05)	1.4 (1.38, 2.18)
	1.61±1.17	1.95±0.90	1.24±0.97	1.73±0.74
	n=4	n=5	n=4	n=5
MM-fBIC (*P*=0.78)	4.06 (3.13, 5.09)	3.86 (3.19, 4.17)	3.06 (2.86, 4.21)	3.97 (3.83, 4.19)
	4.11±1.47	3.93±1.23	3.37±0.73	4.20±1.32
	n=4	n=5	n=3	n=5

Data are presented as median (Q1, Q3) and mean ± standard deviation. There was no statistically significant difference between the means of the groups (*P* values of the mixed model).
GBR: guided bone regeneration, SCTG: subepithelial connective tissue grafting, Control: no other treatment, MM: margo mucosae, IS: implant shoulder, fBIC: first bone-to-implant contact.

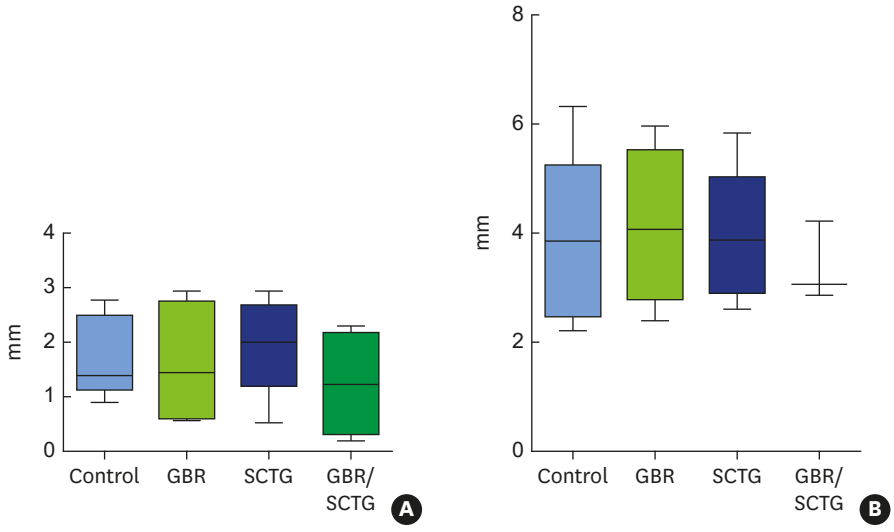

Figure 4. Bar graphs of the peri-implant soft tissue height. (A) Distance between margo mucosa and implant shoulder and (B) distance between margo mucosa and first bone-to-implant contact.
GBR: guided bone regeneration, SCTG: subepithelial connective tissue grafting, Control: no other treatment.

Thickness of the peri-implant mucosa (horizontal measurements)

All specimens, except for 1 in the GBR group, exhibited no mineralized tissue at the 1-mm level above the IS. However, the observed mineralized tissue in the GBR group was scattered and consisted of non-integrated bone substitute particles. The SCTG (0.78 mm [Q1: 0.77, Q3: 0.87]) and the GBR/SCTG (0.3 mm [Q1: 0, Q3: 0.92]) groups demonstrated the respective maximal and minimal median values in terms of total tissue thickness (mixed model: *P*=0.71) (**Table 2**, **Figure 5A**).

Table 2. Peri-implant tissue thickness (in mm)

Peri-implant tissue thickness	GBR group	SCTG group	GBR/SCTG group	Control
At the implant shoulder (*P*=0.71)	0.87 (0.57, 1.64)	1.14 (0.9, 1.93)	0.72 (0.62, 0.72)	1.17 (0.55, 1.5)
	1.11±0.73	1.29±0.72	0.81±0.31	1.26±0.82
	n=4	n=5	n=4	n=5
1 mm above the implant shoulder (*P*=0.80)	0.43 (0, 1.54)	0.78 (0.77, 0.87)	0.30 (0, 0.92)	0.57 (0.48, 0.67)
	0.77±1.06	0.83±0.62	0.46±0.59	0.51±0.31
	n=4	n=5	n=4	n=5
1 mm below the implant shoulder (*P*=0.56)	1.19 (0.91, 1.62)	1.57 (1.07, 2.50)	1.09 (0.56, 1.41)	1.05 (0.8, 1.39)
	1.26±0.51	1.69±0.85	0.99±0.54	1.25±0.86
	n=4	n=5	n=4	n=5

Data are presented as median (Q1, Q3) and mean ± standard deviation. There was no statistically significant difference between the means of the groups (*P* values of the mixed model).
GBR: guided bone regeneration, SCTG: subepithelial connective tissue grafting, Control: no other treatment.

https://doi.org/10.5051/jpis.2104040202

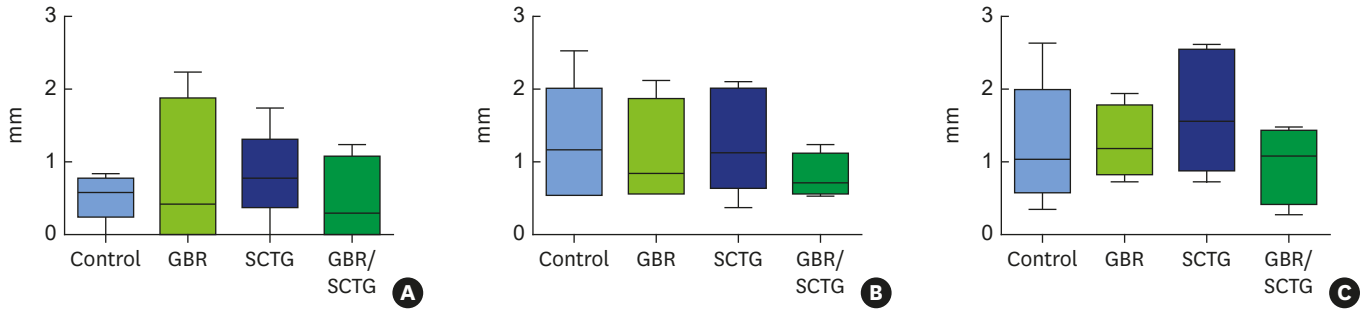

Figure 5. Bar graphs of tissue thickness on the buccal surface of the implant (A) at the 1 mm level above the implant shoulder, (B) at the level of the implant shoulder, and (C) at the 1 mm level below the implant shoulder.
GBR: guided bone regeneration, SCTG: subepithelial connective tissue grafting, Control: no other treatment.

At the level of the IS, mineralized tissue was not observed in any of the specimens. The TT in the SCTG and control groups exhibited similar median values (1.14 mm [Q1: 0.9, Q3: 1.93]) for the SCTG group and 1.17 mm [Q1: 0.55, Q3: 1.5] for the control group). The GBR/SCTG group demonstrated the smallest value (0.72 mm [Q1: 0.62, Q3: 1.0]) (mixed model: P=0.80) (**Table 2**, **Figure 5B**).

At 1 mm below the IS, the TT was greatest in the SCTG group (1.57 mm [Q1: 1.07, Q3: 2.5]), followed by the GBR group (1.19 mm [Q1: 0.91, Q3: 1.62]) (mixed model: P=0.56). Mineralized tissue was observed in only 5 specimens (2 in the GBR group, 1 in the SCTG group, 1 in the GBR/SCTG group, and 1 in the control group). The HT in specimens with mineralized tissue ranged between 0.28 mm (the GBR group) and 1.56 mm (the SCTG group) (**Table 2**, **Figure 5C**).

Despite some differences in the median values of the TT, there were no statistically significant differences between the mean values of the groups at any levels (P>0.05). Moreover, many specimens lacked hard tissue at the measured levels, making it impossible to conduct a proper-statistical analysis of the thickness of hard and soft tissues.

DISCUSSION

The present study investigated the effect of hard and/or soft tissue grafting on immediate implants and demonstrated that i) soft tissue augmentation alone (SCTG) resulted in a higher level of the MM and a greater overall tissue thickness compared to the control group and the groups with hard tissue augmentation, and was predominantly beneficial and more coronal than the IS; ii) hard tissue augmentation was predominantly effective below the IS; and iii) there was no benefit of simultaneous hard and soft tissue augmentation (SCTG/GBR) on the overall tissue thickness compared to hard tissue augmentation alone (GBR) or soft tissue grafting alone (SCTG).

IIP protocols are widely used by clinicians, offering benefits to both clinicians and patients in terms of fewer surgical interventions and a shortened overall treatment time. The drawbacks associated with IIP protocols are mainly due to an increased rate of early implant failure [4] and esthetic failure [16]. To minimize those risks and disadvantages, several preclinical and clinical studies have been performed to elucidate the factors involved in finding an optimal option [9-11,13,17-25]. The recommendations include proper implant position, soft/hard

https://doi.org/10.5051/jpis.2104040202

tissue grafting, and individualized abutment connection, but heterogeneity between studies was also found [4,10,11,13,19,24,26,27].

The use of SCTG to improve the buccal contour and minimize mucosal recession when applying IIP protocols has gained considerable attention. In clinical studies, the addition of SCTG increased the mucosal thickness and width of keratinized tissue, and prevented mucosal recession and marginal bone loss [11,21,27]. In the present study, the SCTG group exhibited more favorable tissue thickness than the other groups, indicating that SCTG alone can establish a sufficient tissue profile at the soft tissue level. Partially in line with this, a few studies have demonstrated the possibility of using SCTG as an alternative to bone augmentation for specific indications with delayed implant placement [28,29]. These studies demonstrated favorable mucosal thickness, keratinized tissue height, and stable periodontal parameters. However, it should be noted that SCTG alone cannot compensate for the resorption of the buccal bone following IIP, which was also demonstrated in another preclinical study [17].

Bone grafting procedures with IIP generally refer to filling the gap between the implant and the socket wall. In the past, the necessity of filling this gap was controversial (depending on the size of the gap), but gap filling with a slowly resorbing bone substitute material is currently recommended in order to compensate for the loss of the buccal bone plate and to prevent collapse of the buccal contour. Clinically, the size of the gap should be considered in conjunction with the thickness of the buccal bone plate. In the present study, a relatively small gap (≤ 1 mm) was present after implant placement because of the small ridge width and the presence of the maxillary sinus. In this situation, it was suspected that mere filling of the gap would jeopardize the integrity of the buccal plate after remodeling. This concern was noted in a clinical study emphasizing that the distance between the implant surface and external buccal graft side should be ≥ 4 mm [30]. Thus, both gap filling and buccal overbuilding were performed in groups with bone augmentation in the present study. However, the effect of bone grafting was not as satisfactory as that of SCTG, especially at or above the IS. This unfavorable outcome might have been influenced by several factors, including: i) augmentation outside of the bony envelope, and ii) possible compression at the IS area due to flap tension and suturing.

Simultaneous soft and hard tissue grafting did not appear to be beneficial in the present study, especially considering the efforts undertaken during surgery. In the GBR/SCTG group, the SCTG was positioned on top of the GBR area, where overbuilding using particulate bone graft material and a collagen membrane was performed. After flap closure, the sites in the GBR/SCTG group might have exhibited more tension and pressure than those at other sites due to the increased thickness of the augmentation under the flap. A clinical study also demonstrated that SCTG did not lead to a decrease in mucosal volume loss compared to sites without SCTG [13]. The authors of that study suspected that vascular damage caused by the surgical technique when inserting the SCTG induced more bone loss. However, the exact reason for this finding is unknown.

The present findings should be interpreted with caution. It is a rule of thumb that resorption makes it necessary to perform over-augmentation with a resorbable barrier membrane for GBR [31]. The implant position in relation to bone housing must be chosen to provide stability to the augmented hard tissue. Moreover, if soft tissue augmentation is added to hard tissue augmentation, one should realize that additional room for the augmented tissue is

https://doi.org/10.5051/jpis.2104040202

required. Additional care must be taken in situations where physiological bone remodeling is expected, such as IIP.

This study has several limitations, primarily its small sample size. Second, behavioral control was difficult in the experimental animals, unlike in human patients who became extremely careful after surgery. In a clinical prospective study, Chappuis and colleagues (2018) [32] performed simultaneous GBR and soft tissue volume augmentation using volume-stable collagen matrix, leading to 2.1 mm of tissue volume increase. Third, in the present canine study, the maxillary premolar region was chosen as the surgical site. This area provides less bone quantity and a shallower vestibulum on the oral side compared to a universal site for bone augmentation in dogs (i.e., the mandibular premolar region). These differences were due to the proximity of the maxillary sinus and location of the palate relative to the maxillary teeth. In the present study, implants with a narrow diameter were used to minimize the potential influence of the above factors.

In conclusion, careful case selection may be needed to implement soft and hard tissue augmentation when applying an IIP protocol. Preclinical studies using other defect models (such as box-type defects for favorable bone housing) and clinical studies are needed for further investigation.

ACKNOWLEDGEMENTS

The authors express their gratitude to the researchers in the Department of Periodontology, Yonsei University College of Dentistry, Seoul, Korea for supporting the experiment, and Dr. Kwang-Seok Lee in the Department of Periodontology, Kyung Hee University Dental Hospital for assisting with histomorphometry. The statistical support of Prof. Jürg Hüsler, University of Zurich is highly acknowledged.

REFERENCES

1. Gomez-Roman G, Schulte W, d'Hoedt B, Axman-Krcmar D. The Frialit-2 implant system: five-year clinical experience in single-tooth and immediately postextraction applications. Int J Oral Maxillofac Implants 1997;12:299-309.
PUBMED
2. Araújo MG, Sukekava F, Wennström JL, Lindhe J. Ridge alterations following implant placement in fresh extraction sockets: an experimental study in the dog. J Clin Periodontol 2005;32:645-52.
PUBMED | CROSSREF
3. Botticelli D, Berglundh T, Lindhe J. Hard-tissue alterations following immediate implant placement in extraction sites. J Clin Periodontol 2004;31:820-8.
PUBMED | CROSSREF
4. Cosyn J, De Lat L, Seyssens L, Doornewaard R, Deschepper E, Vervaeke S. The effectiveness of immediate implant placement for single tooth replacement compared to delayed implant placement: a systematic review and meta-analysis. J Clin Periodontol 2019;46 Suppl 21:224-41.
PUBMED | CROSSREF
5. Mello CC, Lemos CAA, Verri FR, Dos Santos DM, Goiato MC, Pellizzer EP. Immediate implant placement into fresh extraction sockets versus delayed implants into healed sockets: a systematic review and meta-analysis. Int J Oral Maxillofac Surg 2017;46:1162-77.
PUBMED | CROSSREF
6. Chen ST, Buser D. Clinical and esthetic outcomes of implants placed in postextraction sites. Int J Oral Maxillofac Implants 2009;24 Suppl:186-217.
PUBMED

7. Chen ST, Buser D. Esthetic outcomes following immediate and early implant placement in the anterior maxilla--a systematic review. Int J Oral Maxillofac Implants 2014;29 Suppl:186-215.
PUBMED | CROSSREF
8. Frizzera F, de Freitas RM, Muñoz-Chávez OF, Cabral G, Shibli JA, Marcantonio E Jr. Impact of soft tissue grafts to reduce peri-implant alterations after immediate implant placement and provisionalization in compromised sockets. Int J Periodontics Restorative Dent 2019;39:381-9.
PUBMED | CROSSREF
9. Kan JY, Rungcharassaeng K, Morimoto T, Lozada J. Facial gingival tissue stability after connective tissue graft with single immediate tooth replacement in the esthetic zone: consecutive case report. J Oral Maxillofac Surg 2009;67:40-8.
PUBMED | CROSSREF
10. Kolerman R, Nissan J, Mijiritsky E, Hamoudi N, Mangano C, Tal H. Esthetic assessment of immediately restored implants combined with GBR and free connective tissue graft. Clin Oral Implants Res 2016;27:1414-22.
PUBMED | CROSSREF
11. Noelken R, Moergel M, Pausch T, Kunkel M, Wagner W. Clinical and esthetic outcome with immediate insertion and provisionalization with or without connective tissue grafting in presence of mucogingival recessions: a retrospective analysis with follow-up between 1 and 8 years. Clin Implant Dent Relat Res 2018;20:285-93.
PUBMED | CROSSREF
12. Tsuda H, Rungcharassaeng K, Kan JY, Roe P, Lozada JL, Zimmerman G. Peri-implant tissue response following connective tissue and bone grafting in conjunction with immediate single-tooth replacement in the esthetic zone: a case series. Int J Oral Maxillofac Implants 2011;26:427-36.
PUBMED
13. van Nimwegen WG, Raghoebar GM, Zuiderveld EG, Jung RE, Meijer HJ, Mühlemann 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.
PUBMED | CROSSREF
14. Kilkenny C, Browne W, Cuthill IC, Emerson M, Altman DG; NC3Rs Reporting Guidelines Working Group. Animal research: reporting *in vivo* experiments: the ARRIVE guidelines. Br J Pharmacol 2010;160:1577-9.
PUBMED | CROSSREF
15. Donath K, Breuner G. A method for the study of undecalcified bones and teeth with attached soft tissues. The Säge-Schliff (sawing and grinding) technique. J Oral Pathol 1982;11:318-26.
PUBMED | CROSSREF
16. Cosyn J, De Bruyn H, Cleymaet R. Soft tissue preservation and pink aesthetics around single immediate implant restorations: a 1-year prospective study. Clin Implant Dent Relat Res 2013;15:847-57.
PUBMED | CROSSREF
17. Caneva M, Botticelli D, Viganò P, Morelli F, Rea M, Lang NP. Connective tissue grafts in conjunction with implants installed immediately into extraction sockets. An experimental study in dogs. Clin Oral Implants Res 2013;24:50-6.
PUBMED | CROSSREF
18. Cosyn J, Eghbali A, De Bruyn H, Collys K, Cleymaet R, De Rouck T. Immediate single-tooth implants in the anterior maxilla: 3-year results of a case series on hard and soft tissue response and aesthetics. J Clin Periodontol 2011;38:746-53.
PUBMED | CROSSREF
19. Cosyn J, Eghbali A, Hermans A, Vervaeke S, De Bruyn H, Cleymaet R. A 5-year prospective study on single immediate implants in the aesthetic zone. J Clin Periodontol 2016;43:702-9.
PUBMED | CROSSREF
20. Paolantonio M, Dolci M, Scarano A, d'Archivio D, di Placido G, Tumini V, et al. Immediate implantation in fresh extraction sockets. A controlled clinical and histological study in man. J Periodontol 2001;72:1560-71.
PUBMED | CROSSREF
21. Rungcharassaeng K, Kan JY, Yoshino S, Morimoto T, Zimmerman G. Immediate implant placement and provisionalization with and without a connective tissue graft: an analysis of facial gingival tissue thickness. Int J Periodontics Restorative Dent 2012;32:657-63.
PUBMED
22. Sanz M, Cecchinato D, Ferrus J, Pjetursson EB, Lang NP, Lindhe J. A prospective, randomized-controlled clinical trial to evaluate bone preservation using implants with different geometry placed into extraction sockets in the maxilla. Clin Oral Implants Res 2010;21:13-21.
PUBMED | CROSSREF

23. Sanz M, Lindhe J, Alcaraz J, Sanz-Sanchez I, Cecchinato D. The effect of placing a bone replacement graft in the gap at immediately placed implants: a randomized clinical trial. Clin Oral Implants Res 2017;28:902-10.
PUBMED | CROSSREF

24. Thoma DS, Jung UW, Gil A, Kim MJ, Paeng KW, Jung RE, et al. The effects of hard and soft tissue grafting and individualization of healing abutments at immediate implants: an experimental study in dogs. J Periodontal Implant Sci 2019;49:171-84.
PUBMED | CROSSREF

25. Wilson TG Jr, Schenk R, Buser D, Cochran D. Implants placed in immediate extraction sites: a report of histologic and histometric analyses of human biopsies. Int J Oral Maxillofac Implants 1998;13:333-41.
PUBMED

26. Kan JYK, Rungcharassaeng K, Deflorian M, Weinstein T, Wang HL, Testori T. Immediate implant placement and provisionalization of maxillary anterior single implants. Periodontol 2000 2018;77:197-212.
PUBMED | CROSSREF

27. 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.
PUBMED | CROSSREF

28. D'Elia C, Baldini N, Cagidiaco EF, Nofri G, Goracci C, de Sanctis M. Peri-implant soft tissue stability after single implant restorations using either guided bone regeneration or a connective tissue graft: a randomized clinical trial. Int J Periodontics Restorative Dent 2017;37:413-21.
PUBMED | CROSSREF

29. Stefanini M, Felice P, Mazzotti C, Marzadori M, Gherlone EF, Zucchelli G. Transmucosal implant placement with submarginal connective tissue graft in area of shallow buccal bone dehiscence: a three-year follow-up case series. Int J Periodontics Restorative Dent 2016;36:621-30.
PUBMED | CROSSREF

30. Capelli M, Testori T, Galli F, Zuffetti F, Motroni A, Weinstein R, et al. Implant-buccal plate distance as diagnostic parameter: a prospective cohort study on implant placement in fresh extraction sockets. J Periodontol 2013;84:1768-74.
PUBMED | CROSSREF

31. Naenni N, Schneider D, Jung RE, Hüsler J, Hämmerle CHF, Thoma DS. Randomized clinical study assessing two membranes for guided bone regeneration of peri-implant bone defects: clinical and histological outcomes at 6 months. Clin Oral Implants Res 2017;28:1309-17.
PUBMED | CROSSREF

32. Chappuis V, Shahim K, Buser R, Koller E, Joda T, Reyes M, et al. Novel collagen matrix to increase tissue thickness simultaneous with guided bone regeneration and implant placement in esthetic implant sites: a feasibility study. Int J Periodontics Restorative Dent 2018;38:575-82.
PUBMED | CROSSREF