Clinical applications of concentrated growth factors membrane for sealing the socket in alveolar ridge preservation: a randomized controlled trial

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Abstract

The purpose of this study was to evaluate the efficacy of concentrated growth factor (CGF) membrane for the sealing of alveolar socket in alveolar ridge preservation (ARP). A total of 22 patients with 24 alveolar sockets were recruited and divided randomly into CGF group and Bio-Gide collagen membrane group. The soft tissue wound healing rate was calculated using intraoral scanner at 3, 7, and 14 days after ARP, and the bone resorption volume at 1, 3, and 5 mm below the alveolar ridge was measured by CBCT at 6 months postoperation. The keratinized gingival width was also measured before and 6 months after ridge preservation. In terms of soft tissue healing rate, the CGF group exhibited significant higher than that of Bio-Gide group at both 7 and 14 days after surgery ($P < 0.05$). However, there was no significantly different in bone resorption rate and the width of keratinized gingival after 6 months ($P > 0.05$). Therefore, the use of CGFs membranes for wound closure in ARP is a reliable method, but more clinical data are needed to prove it.

Keywords: Dental implant, Concentration growth factors, Alveolar ridge preservation, Soft tissue healing

Introduction

Alveolar ridge resorption is regarded as the common phenomenon after teeth extraction. It was reported that the buccal bone plate is less than 1 mm in thickness in most sites in the anterior maxilla. In addition, nearly half of the tested patients had a labial plate thickness of only 0.5 mm [1]. Extensive resorption of the alveolar ridge occurs in the first 3 months after tooth extraction [2]. Literature showed that vertical dimension decreased by 11–22% at 3 months, and horizontal dimension decreased by 32% at 3 months and 29–63% at 6–7 months [3]. Such bone resorption may cause the staged guided bone regeneration (GBR), which increases the surgical difficulty and potentially results in the occurrence of a hematoma and postoperative pain [4].

Alveolar ridge preservation (ARP) is considered as an effective method to reduce bone resorption and maintain alveolar bone morphology post-extraction, which includes the socket filling with different biomaterials [5] and sealing with closure materials to prevent the early loss of the underlying biomaterial [6]. Tight suturing of the wound will not only decrease the risk of wound infection, but also prevent early shedding of biomaterials, which possibly affect subsequent bone tissue contours.

Three sealing materials are frequently used in ARP: autogenous tissue, absorbable and non-resorbable collagen membranes [7]. Studies showed that there is no significant difference among them in ARP, but each has
drawbacks. Autogenous tissue is mainly derived from
tool’s palatal soft tissue which causes another surgical
damage, postoperative bone exposure, and additional pain [8].

The non-resorbable e-PTFE barrier (e-PTFE,
Gore-Tex®) membranes often give rise to soft tissue
dehiscence and need to be removed in time, which
increase the risk of infection [9]. Resorbable collagen
membranes are user-friendly, and have the advantage to
increase keratinized tissue thickness. Nevertheless, ani-
mal origin and high price limit their application in ARP
[10].

Growth factor (GF) is reserved in the alpha granules in
platelet, which contains high quantities of GFs, such as
vascular endothelial growth factor (VEGF), transforming
growth factor-β1 (TGF-β1) and β2 (TGF-β2), fibro-
blast growth factor (FGF), platelet-derived growth factor
(PDGF) and insulin-like growth factor (IGF) [11, 12]. GFs
play an important role in the modulation of healing after
dental implant placement, include stimulation of cell pro-
iferation, matrix remodeling and angiogenesis [13, 14].

Concentration growth factors (CGF) was developed
by Sacco in 2006, and is derived from the centrifuged
peripheral venous blood, contains blood-derived biomate-
rials and has much denser, larger, and richer in growth
factors fibrin matrix than platelet-rich plasma (PRP) and
platelet-rich fibrin (PRF) [15]. It has been found that CGF
is involved in the gingival regeneration by activation of
AKT/Wnt and YAP signaling pathway [16] and osteogen-
esis following tooth extraction [17]. However, few clinical
reports investigated the function of CGF on soft tissue
closure.

Therefore, the objectives of this study was to compare
the therapeutic effect of Bio-Gide® collagen membrane
and CGF membrane as sealing material in ARP.

**Materials and methods**

**Patient selection**

The study is a randomized RCT conducted in a man-
ner consistent with the 1975 Declaration of Helsinki
and its amendments since 2000. The study protocol was
approved by the ethical committee of The Affiliated
Stomatological Hospital of Xuzhou Medical University
(Approval Number: 2021-002), and registered in Chinese
Clinical Trial Registry (ChiCTR2100049442). Written
consent forms were signed by all patients and the poten-
tial risks of the study were made known to all patients.

The inclusion criteria were as follows: >15 years old;
no systemic diseases, no active periodontal disease, and
plan for a dental implant-supported restoration. The fol-
lowing criteria were used to exclude patients: an exces-
sive smoker (>5 cigarettes/day); periodontitis untreated
or poor oral hygiene; previous history of irradiation of
the head and neck area; pregnant; uncontrolled diabetes;
current or past treatment with bisphosphonate; inabili-
ty to complete the follow-up; at least half of the alveo-
lar buccal bone plate remained after tooth extraction.

The same specialist performed two surgical procedures
on selected patients: (1) minimally invasive tooth extrac-
tion and ARP; (2) placement of implants after 6 months
of ARP.

**CGF preparation**

Nine mL venous blood was collected from patients and
was stored in sterile vacuum tube (Greiner Bio-One,
GmbH, Kremsmunster, Austria) without any anticoagu-
latant. Then, the tube was immediately placed in centrifuge
(MediFuge, Silfradentsrl, Italy) with fixed process: accel-
eration for 30 s, 2700 rpm for 2 min, 2400 rpm for 4 min,
2700 rpm for 4 min, 3000 rpm for 3 min, deceleration to
a stop for 36 s. After this centrifugation process, the CGF
was composed of three sections including an upper layer
consisting of serum, light yellow gelatin in the middle
which consisted of lots of growth factors at the junction
with the lower layer, and a lower layer containing the red
blood cells (RBCs). Solid CGF was extracted from each
tube after centrifugation with sterile tweezers. The lower
RBCs were cut away, the fibrin layer and the junction
of the fibrin were then using gauze “squeezed” to form
CGFs membranes for cover tooth extraction wound.

**Surgical procedures**

Firstly, minimally invasive tooth extraction was per-
formed and attention should be paid to protect the alveo-
lar bone plate and surrounding soft tissues, rinsing the
extraction socket with sterile saline. After examining
the socket and debriding it, the inflammatory granula-
tion tissues should be completely removed. Patients were
randomly assigned to one of two groups. For the CGF
group, the sockets were grafted with collagen-enriched
deproteinized bovine bone mineral (Bio-Oss® Collagen,
Geistlich, Switzerland) and covered with CGF membranes,
stabilized with a suture. For the Bio-Gide group, the
wound was covered with collagen membranes (Bio-
Gide®, Geistlich, Switzerland) and the rest of the opera-
tions were the same as the CGF group.

Patients were instructed to take Roxithromycin and
Ornidazole (North China Pharmaceutical, China) twice a
day for 3 days and rinse with 0.2% chlorhexidine (Jiangsu
Chenpai Bond Pharmaceutical, China). All patients were
asked to follow up at 3,7,14 days and suture removal after
7 days. Six months after extraction, CBCT scans were
performed and dental implants were placed using a mini-
nally invasive technique. Meanwhile, the implant site
was initially prepared with a soft tissue punch. A trephine
(external diameter of 3 mm, internal diameter 2 mm)
for harvesting a soft tissue sample during the implant
surgery. If the initial stability of the implant was greater than 35 Ncm, the immediate repair will be considered (Fig. 1).

**Outcome measures**

**Soft tissue healing**

Area measurement is one of the most commonly used methods for assessing wounds in clinical and research settings. According to literature reports the 3D Wound Reconstruction System is the most precise and accurate device currently available for assessing wound size [18].

Follow-up visits were performed on 3, 7, 14 days after ARP, and digital oral scanning equipment (CS 3600 Carestream) was used to scan the patient’s operating area and adjacent dentition (the adjacent teeth will be used as reference landmarks for subsequent model registration) to obtain STL files (Fig. 2a). Then import the file into Geomagic Studio 2014 to measure the wound area (Fig. 2b), calculate the healing rate according to the calculation formula of healing rates reviewed by Jessup [19] for the wound healing rate:

\[
\frac{(\text{Area}_0 - \text{Area}_1)}{(\text{Area}_0)} \times 100\%.
\]

**Keratinized gingiva width**

The distance from the buccal central gingival margin to the mucogingival symphysis was measured preoperatively recorded as KGW1 (Fig. 3a), and the distance from the buccal central alveolar ridge to the mucogingival symphysis was measured 6 months after operation, it was recorded as KGW2 (Fig. 3b). Variation in keratinized gingiva width = KGW2-KGW1 [20].

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**Fig. 1** The process of ARP. a Clinical conditions at baseline; b 100 mg Bio-oss® Collagen was placed in both extraction sockets, 11 surfaces were covered with Bio-Gide® collagen membranes, 21 were covered with CGF membranes; c clinical conditions at the 6-month follow-up; d the soft tissue sample from implant surgery; e, f the initial stability of the two implants during the operation was greater than 35 Ncm, the immediate postoperative repair was selected.

**Fig. 2** The representative pictures of intraoral scanner. a Wounds are recorded using oral scanning software; b the area identified for assessment of area changes is demarcated in red.
CBCT analysis
In both groups, CBCT scans were conducted prior to the extraction and six months after the ARP procedure. Three measures were recorded for all preserved sites, before and after treatment. There were three horizontal ridge widths measured at three different levels located 1, 3 and 5 mm below the most coronal aspect of the bone crest, respectively (Fig. 4). Each level's bone loss was expressed as a linear difference between pre- and post-regeneration measurements.

Histologic analyses
Nascent soft tissue samples were adequately fixed in 4% paraformaldehyde. Routine dehydration-embedded sections, immunohistochemical staining with SP immunohistochemistry kit to observe the expression of the vascular marker CD31 in the gum tissue. Blood vessel density (MVD) count Light microscopy (Nikon Eclipse E100, Japan) to observe the expression of CD31 in each group of gum tissue sections.

Statistical analysis
The data were analyzed statistically with SPSS 22.0. The differences of means at the patient level for continuous outcomes (horizontal volumetric changes, soft tissue healing rate, change of keratinized gingiva width and micro-vessels density) between groups were compared by independent sample $t$-tests.

In order to estimate whether the data were normally distributed, Shapiro–Wilk was used, and homogeneity was assessed using the homogeneity of variance test. If the data follow a normal distribution with the same variance then the independent samples $t$-test is used. All data were averaged by the same person after three measurements. A significance level of $\alpha = 0.05$ was used for all analyses.

Results
Study population
A total of 22 patients (11 men and 11 women) with 24 sites. All patients met the requirements for implant surgery after 6 months of ARP. The patients’ average age was $30.46 \pm 10.58$ years (range 19–61 years). Patients experienced no complications during the surgery, and all had uneventful healing. The tooth extraction site information is described in detail in Table 1.
Soft tissue healing
All patients were followed up at the required time, and there were no cases of infection. And the soft tissue healing in the CGF group was significantly better than that in the Bio-Gide group (Fig. 5). The soft tissue healing rate of the CGF group was 21.71% ± 7.68% at 3 days, and the soft tissue healing rate of the Bio-Gide group was 18.19% ± 9.11%. There was no statistical difference between the two groups ($P = 0.317$). However, at 7 days after surgery, the soft tissue healing rate of the CGF group was 60.51% ± 18.41%, and the healing rate of the Bio-Gide group was only 38.38% ± 13.37%, with a statistically significant difference between the two groups ($P = 0.003$). At 14 days after the operation, the soft tissue healing rate in the CGF group was 89.1% ± 3.21%, and the healing rate in the Bio-Gide group was 61.73% ± 12.92%, and there was significant difference between the two groups ($P < 0.001$) (Fig. 6).

Change of keratinized gingiva width
Six months after alveolar ridge preservation of healing, the wounds of 22 patients were completely healed. The increase in keratinized gingiva width in the CGF group was 0.985 ± 0.6895. The change in the Bio-Gide group was 0.833 ± 0.4292. There was no statistical difference between the two groups ($P = 0.599$) (Fig. 7).
CBCT analysis
Alveolar ridge dimensions in all patients at 6 months were considered acceptable for implantation by minimally invasive surgery and does not require additional guided bone regeneration during surgery, which defining 100% clinical efficacy of ARP surgery. The labial and palatal plates were attached to a reference baseline prior to extraction, and the reference baseline was used as a standard for subsequent measurements.

After 6 months, the width change at 1 mm below the baseline was $-2.02 \pm 0.9$ mm in the CGF group and $-2.1 \pm 0.38$ mm in the Bio-Gide group. There was no statistical difference between the two groups ($P=0.917$). The absorption of 3 mm CGF under the alveolar ridge was $-1.77 \pm 0.8$ mm, and the absorption of the Bio-Gide group was $-1.43 \pm 0.62$ mm. There was no statistical difference between the two groups ($P=0.327$). The change in the width of 5 mm under the alveolar ridge in the CGF group was $-1.27 \pm 0.76$ mm, and the change in the Bio-Gide group was $-0.9 \pm 0.76$ mm, no statistical difference between the two groups ($P=0.327$) (Fig. 8).

Histological analyses
Immunohistochemical staining of gingival soft tissue specimens of CD31 expression positive cells is pale yellow or brownish-yellow (shown by the black arrow) (Fig. 9). The more positive signals, the more neovascularization of the gum soft tissue, the better the healing of the soft tissue. All vascular endothelial cells in both groups of specimens were positive for CD31 expression. Meanwhile, the density of new blood vessels was counted by CD31 immunohistochemical staining in the soft tissue obtained during the operation. The average number of new blood vessels in the CGF group was $35.32 \pm 3.47$, which was significantly higher than that in the Bio-Gide group which was $22.93 \pm 4.42$ ($P<0.001$) (Fig. 10).

Discussion
This study evaluated the healing rate of soft tissue and the change of alveolar bone which using different sealing materials in ARP. The literature shows that alveolar preservation techniques are more effective than natural healing [21, 22]. In order to compare only one variable, this study did not include natural healing group, and Bio-Oss Collagen was used in all patients. Results indicated that a complete preservation of the alveolar crest with ARP technique is unlikely and there was no significant differences between CGF groups and Bio-Gide groups.
concerning the alveolar height changes. Previous studies have reported the similar result [23].

Free gingiva, resorbable collagen membranes and non-resorbable collagen membranes are the most commonly used sealing materials in ARP. Previous studies have shown that there was no statistical difference among these three materials in terms of the effectiveness of extraction site preservation [24], but all of them have shortcomings: the use of free gingival closure requires the creation of a second operative area and the free tissue was prone to necrosis [25]; the use of non-absorbable collagen membranes requires secondary surgical removal and the use of absorbable collagen membranes was more expensive.

As an autologous blood extract, CGF has the advantages of low cost, convenient collection, and mild postoperative response. In recent years, CGFs membranes were used in guided bone regeneration to promote soft tissue healing [26]. In addition, the high concentration of anti-infection factors in CGF reduced the likelihood of postoperative infections [27]. It was found in several studies that researchers filled CGF in combination with bone grafting material in extraction sockets or put CGF alone for ARP. For example, Lin et al. [28] used CGF gels mixed with DBBM then filled this mixture in the socket and covered with CGF membranes in the test group, while filled DBMM alone and covered with Bio-Gide® collagen membranes in control group. Mixing CGF with DBBM makes it impossible to objectively evaluate the effect of CGF on wound closure. It can be seen that there is no research on the healing effect of CGFs membranes only on soft tissue in alveolar ridge preservation.

In this study, CGFs membranes were used to seal the socket and the wound healing rate was used to evaluate the effect of soft tissue closure. Many investigations on soft tissue healing have been performed by a modified version of the Masse healing index (HI) [29]. However, this method has the disadvantage of being highly subjective and not reflecting the rate of wound healing. Therefore, we used an intraoral scanner to obtain soft tissue information from patients at 3, 7, and 14 days in equal proportions, counted the wound area by Geomagic 2014 software and evaluated the wound healing effect by the soft tissue healing rate. These quantified data making the conclusions more accurate and reliable. The width of keratinized tissue may be important in maintaining periodontal health and preventing soft tissue recession [30], Chung et al. [31] reported that lack of keratinized mucosa predisposes to peri-implantitis. It can be seen that the width of the keratinized gingiva also has an important influence on implant surgery, so this study also measured the width of the keratinized gingiva. The width of the keratinized gingiva was increased in both groups of patients 6 months after alveolar ridge preservation. The amount of increase was not statistically different (P > 0.05), which proved that CGF and Bio-Gide membrane had the same effect on the healing of keratinized gingiva. Zhang et al. [32] came to the same conclusion.

Immunohistochemistry was used to observe neurovascular regeneration in soft tissue between the two groups 6 months after surgery to determine whether CGF could promote soft tissue healing. It can be seen that sites using CGFs membranes significantly increased the number of blood vessels positive for the vascular endothelial cell marker CD31. CGFs seem to have the potential to accelerate soft tissue healing earlier than Bio-Gide for the reason that most collagen membranes are known to release glutaraldehyde during healing, which probably led to cell death and dysfunction [33].

From the data obtained from CBCT, the amount of bone resorption with CGFs membranes was not statistically different from that with Bio-Gide after 6 months of ARP. According to Cardaropoli et al. [34] Bio-Oss® could be used to slow alveolar ridge resorption and stimulate new bone formation. Furthermore, the combination of DBBM with Bio-Gide® collagen membranes may significantly reduce the vertical and horizontal resorption of alveolar bone. This was similar to our findings: the use of CGF and Bio-Gide can play a good sealing effect and preserve the bone mass of alveolar ridge and provide favorable conditions for later implant surgery. This study also compared the ability of alveolar bone to resorb horizontally and both groups achieved similar effects. Silvio et al.[7] used porcine collagen matrix + DBBM, the horizontal bone resorption at 1, 3, and 5 mm at baseline was 0.67 ± 0.31 mm, 0.91 ± 0.38 mm, and 0.31 ± 0.18 mm after 5 months. In a systematic review that included 32 randomized controlled clinical trials, Jambhekar et al.[35] evaluated the ARP effect of DBBM filling analyzed the ARP effect of DBBM filling, which showed that the reduction in the horizontal width of the alveolar bone was 1.30 mm. These were similar to our results, but there was a certain difference in the amount of numerical change, which we think was due to the measurement method and the error caused by different CT imaging equipment.

Although CGF has many advantages, there are also shortcomings, such as easy to fall off and individual patient differences, and the next step is to increase the sample size to better evaluate the effect. We also need to develop a standardized procedure for CGF extraction and to improve the procedure for CGFs membranes fixation.
Conclusion
The application of CGFs membranes in ARP is a simple and cost-effective method, and has faster soft tissue healing speed and similar bone formation compared with Bio-Gide® membranes. Therefore, CGF could be recommended to patients with alveolar ridge preservation as a better choice considering economical and safe factors. However, our results need to be confirmed with larger sample sizes and longer follow-ups.

Acknowledgements
Not applicable.

Author contributions
CJ, YL carried out the collection of patients. CY and XL completed the alveolar ridge preservation surgery. YL, HG, GL, YH completed the follow-up of patients and data collection. All authors read and approved the final manuscript.

Funding
The study was funded by Xuzhou Municipal Health Commission (KC21236).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
The study is a randomized RCT conducted in a manner consistent with the 1975 Declaration of Helsinki and its amendments since 2000. The study protocol was approved by the ethical committee of The Affiliated Stomatological Hospital of Xuzhou Medical University (Approval Number: 2021-002), and registered in Chinese Clinical Trial Registry (ChiCTR2100049442).

Competing interests
The authors declare that they have no competing interests.

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Received: 27 June 2022 Accepted: 5 October 2022
Published online: 01 November 2022

References
1. Jung RE, Ioannidis A, Hämmerle CHF, Thoma DS. Alveolar ridge preservation in the aesthetic zone. Periodontol 2000. 2000;2008(77):165–75.
2. Farmer M, Darby I. Ridge dimensional changes following single-tooth extraction in the aesthetic zone. Clin Oral Implants Res. 2014;25:272–7.
3. Tan WL, Wong TLT, Wong MCM, Lang NP. A systematic review of post-extractional alveolar hard and soft tissue dimensional changes in humans. Clin Oral Implants Res. 2012;23(Suppl 5):1–21.
4. Mendoza-Azpurr G, de la Fuente A, Chavez E, Valdivia E, Khoul Y. Horizontal ridge augmentation with guided bone regeneration using particulate xenogenic bone substrates with or without autogenous block grafts: a randomized controlled trial. Clin Implant Dent Relat Res. 2019;21:521–30.
5. Majzoub J, Ravida A, Starch-Jensen T, Tattan M, Suárez-López del Amo F. The influence of different grafting materials on alveolar ridge preservation: a systematic review. J Oral Maxillofac Res. 2019;10.
6. Avila-Ortiz G, Chambrone L, Vignoletti F. Effect of alveolar ridge preservation interventions following tooth extraction: a systematic review and meta-analysis. J Clin Periodontol. 2019;46:195–223.
7. Meloni SM, Tallarico M, Lollis FM, Deledda A, Pisano M, Jovanovic SA. Post-extraction socket preservation using epidermal connective tissue graft vs. porcine collagen matrix 1-year results of a randomised controlled trial. Eur J Oral Implantol. 2015;8:39–48.
8. Silvestre R, de Velasco-Tarllonte AF, Beatriz B, Blanca R-C, Ana F-P. Complications in the use of deproteinized free gingival graft vs. connective tissue graft: a one-year randomized clinical trial. Int J Environ Res Public Health. 2021;18:4504.
9. Gielkens PFH, Schortinghuis J, de Jong JR, Rahoeber GM, Stegenga B, Bos RRM, Vissersorb®, Bio-Gide®, and Gore-Tex® as barrier membranes in rat mandibular defects: an evaluation by microangiography and micro-CT. Clin Oral Implants Res. 2008;19:516–21.
10. Aladmuswai MA, Natto ZS, Steffensen B, Levi P, Cheung W, Finkelman M, et al. A comparison between primary and secondary flap coverage in ridge preservation procedures: a pilot randomized controlled clinical trial. Biom Implant Dent Int. 2019;2019:1.
11. Mahendra J, Ari G. Case Report A Clinical and Histological Evaluation of Platelet—Rich Fibrin and CGF for Root Coverage Procedure using Coro-nally-Advanced Flap: A Split—Mouth Design. 2020.
12. Alturki A, Proietti R, Birnie DH, Essedag V. Management of antithrombotic therapy during cardiac implantable device surgery. J Arrhythmia [Internet]. 2016;32:163–9. https://doi.org/10.1016/j.joa.2015.12.003.
13. Grainger DJ, Mosedale DE, Metcalfe JC. TGF-β in blood: a complex problem. Cytokine Growth Factor Rev. 2000;11:133–45.
14. Choukroun J, Dass A, Simonperi A, Girard MO, Schoeffler C, Dohan SL, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part IV: clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol. 2006;101:56–60.
15. Rodella LF, Favouro G, Boninsegna R, Buffoli B, Labanca M, Scarì G, et al. Growth factors, CD34 positive cells, and fibrin network analysis in concentrated growth factors fraction. Micros Res Tech. 2011;74:772–7.
16. Qi L, Liu L, Hu Y, Li J, Li J, Gao N, et al. Concentrated growth factor promotes gingival regeneration through the AKT/Wnt/β-catenin and YAP signaling pathways. Artif Cells Nanomedicine Biotechnol [Internet]. 2020;48:920–32. https://doi.org/10.1080/21691401.2020.1773482.
17. Ma F, Lin Y, Sun F, Jiang X, Wei T. The impact of autologous concentrated growth factors on the alveolar ridge preservation after posterior tooth extraction: a prospective, randomized controlled clinical trial. Clin Implant Dent Relat Res. 2011;13:579–92.
18. St-Supery V, Tahir Y, Sampalis J, Brutus JP, Harris PG, Nikolis A. Wound healing assessment: does the ideal methodology for a research setting exist? Ann Plast Surg. 2011;67:193–200.
19. Jessup RL. What is the best method for assessing the rate of wound healing? A comparison of 3 mathematical formulas. Adv Skin Wound Care. 2006;19:138–47.
20. Huang JP, Liu JM, Wu YM, Dai A, Hu HJ, He FM, et al. Clinical evaluation of xenogenic collagen matrix versus free gingival grafts for keratinized mucosa augmentation around dental implants: a randomized controlled clinical trial. J Clin Periodontol. 2021;48:1293–301.
21. Avila-Ortiz G, Chambrone L, Vignoletti F. Effect of alveolar ridge preservation interventions following tooth extraction: a systematic review and meta-analysis. J Clin Periodontol. 2019.
22. Jung RE, Philipp A, Annen BM, Signorelli L, Thoma DS, Hämmerle CHF, et al. Radiographic evaluation of different techniques for ridge preservation after tooth extraction: a randomized controlled clinical trial. J Clin Periodontol. 2013;40:90–8.
23. Iocca O, Farcomeni A, Pardiñas Lopez S, Talib HS. Alveolar ridge preservation after tooth extraction: a Bayesian Network meta-analysis of grafting materials efficacy on prevention of bone height and width reduction. J Clin Periodontol. 2017;44:104–14.
24. López-Pacheco A, Soto-Peñaloza D, Gómez M, Peñarrocha-Oltra D, Alarcón MA. Socket seal surgery techniques in the esthetic zone: a systematic review with meta-analysis and trial sequential analysis of randomized clinical trials. Int J Implant Dent. 2021;7:13.
25. Thoma DS, Mühlemann S, Jung RE. Critical soft-tissue dimensions and data collation. All authors read and approved the final manuscript.
26. Wang X, Wang G, Zhao X, Feng Y, Liu H, Li F. Short-term evaluation of membrane guided bone reconstruction with titanium mesh membranes and CGF membranes in immediate implantation of anterior maxillary tooth. Biomed Res Int. 2021;2021:1.
27. Masuki H, Okudera T, Watanabe T, Suzuki M, Nishiyama K, Okudera H, et al. Platelet-rich fibrin and platelet-rich plasma for peri-implant mucosa augmentation around dental implants: a randomized clinical trial. J Clin Periodontol. 2021;48:1293–301.
28. Villela A, Mihara M, Christensen H, Siqueira J, Reitano F, Oikarinen A, et al. A comparison of bone loss and soft tissue healing in two surgical approaches for ridge preservation after tooth extraction. J Clin Periodontol. 2019;46:195–223.
plasma (PRP), plasma rich in growth factors (PRGF), advanced platelet-rich fibrin (A-PRF), and concentrated growth factors (CGF). Int J Implant Dent. 2016. https://doi.org/10.1186/s40729-016-0052-4.

28. Lin S, Li X, Liu H, Wu F, Yang L, Su Y, et al. Clinical applications of concentrated growth factors combined with bone substitutes for alveolar ridge preservation in maxillary molar area: a randomized controlled trial. Int J Implant Dent. 2021;7.

29. Mozzati M, Gallesio G, di Romana S, Bergamasco L, Pol R. Efficacy of plasma-rich growth factor in the healing of postextraction sockets in patients affected by insulin-dependent diabetes mellitus. J oral Maxillofac Surg. 2014;72:456–62.

30. Barone R, Clauzer C, Grassi R, Merli M, Prato GP. A protocol for maintaining or increasing the width of masticatory mucosa around submerged implants: a 1-year prospective study on 53 patients. Int J Periodontics Restorative Dent. 1998;18:377–87.

31. Chung DM, Oh T-J, Shotwell JL, Misch CE, Wang H-L. Significance of keratinized mucosa in maintenance of dental implants with different surfaces. J Periodontol. 2006;77:1410–20.

32. Zhang H, Li X. Effects of ridge preservation with different membrane techniques after extraction of severe periodontitis related teeth. J Oral Sci Res. 2020;36:962–7.

33. Yamada M, Kojima N, Att W, Minamikawa H, Sakurai K, Ogawa T. Improvement in the osteoblastic cellular response to a commercial collagen membrane and demineralized freeze-dried bone by an amino acid derivative: an in vitro study. Clin Oral Implants Res. 2011;22:165–72.

34. Cardaropoli G, Araújo M, Lindhe J. Dynamics of bone tissue formation in tooth extraction sites. An experimental study in dogs. J Clin Periodontol. 2003;30:809–18.

35. Jambhekar S, Kernen F, Bidra AS. Clinical and histologic outcomes of socket grafting after flapless tooth extraction: a systematic review of randomized controlled clinical trials. J Prosthet Dent United States. 2015;113:371–82.

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