








## ORIGINAL ARTICLE

# Recombinant human platelet-derived growth factor improves root coverage of a collagen matrix for multiple adjacent gingival recessions: A triple-blinded, randomized, placebo-controlled trial

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## Abstract

**Aim:** To evaluate the efficacy of recombinant human platelet-derived growth factor (rhPDGF)-BB combined with a cross-linked collagen matrix (CCM) for the treatment of multiple adjacent gingival recession type 1 defects (MAGRs) in combination with the coronally advanced flap (CAF).

**Materials and Methods:** Thirty patients were enrolled in this triple-blind, randomized, placebo-controlled trial and treated with either CAF + CCM + rhPDGF, or CAF + CCM + saline. The primary outcome was mean root coverage (mRC) at 6 months. Complete root coverage, gain in gingival thickness (GT), keratinized tissue width, volumetric and ultrasonographic changes, and patient-reported outcome measures were also assessed. Mixed-modelling regression analyses were used for statistical comparisons.

**Results:** At 6 months, the mRC of the CCM + rhPDGF and CCM alone groups were 88.25% and 77.72%, respectively ( $p = .02$ ). A significant gain in GT was consistently observed for both treatment arms, and more so for the patients receiving the matrix containing rhPDGF through time (0.51 vs. 0.80 mm, on average,  $p = .01$ ). The rhPDGF + CCM treated patients presented greater volume gain, higher soft tissue thickness, and a superior aesthetic score.

**Conclusion:** rhPDGF enhances the clinical, volumetric, and aesthetic outcomes of MAGRs above the results achieved with CAF + CCM alone (ClinicalTrials.gov NCT04462237).

## KEYWORDS

collagen matrix, gingival recession, platelet-derived growth factor, randomized clinical trial, root coverage

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### Clinical Relevance

*Scientific rationale for the study:* Different biomaterials have been investigated as alternatives to the autogenous connective tissue graft for root coverage. Their outcomes may be further enhanced with the addition of growth factors.

*Principal findings:* Recombinant human platelet-derived growth factor (rhPDGF) with a xenogeneic cross-linked collagen matrix (CCM) showed higher mean and complete root coverage, together with higher esthetic scores and a greater increase in gingival thickness compared to sites treated with CCM alone.

*Practical implications:* rhPDGF enhances the outcomes of CCM for root coverage procedures. Their combination therapy may be used as an alternative approach to the autogenous graft for multiple gingival recessions.

## 1 | INTRODUCTION

Gingival recession is a common condition that affects a significant portion of the population (Cortellini & Bissada, 2018; Romandini et al., 2020). Studies have demonstrated that among the variety of treatments available for the promotion of tooth root coverage, autogenous connective tissue graft (CTG)-based techniques are the most effective and predictable (Cairo et al., 2014; Barootchi, Tavelli, et al., 2020; Zucchelli et al., 2020). While most of the evidence on root coverage outcomes with the CTG or other techniques comes from treatment of isolated recession defects, gingival recession is more often a generalized condition (Zucchelli et al., 2019; Romandini et al., 2020). Therefore, it is not surprising that CTG substitutes, such as allogeneic dermal grafts and collagen matrices, have progressively gained popularity in the clinical arena for reducing patient morbidity, and due to their unlimited resources, making them strongly indicated for the treatment of multiple adjacent gingival recessions (MAGRs) (Tavelli et al., 2020b; Barootchi, Tavelli, Gianfilippo, et al., 2021).

A novel porcine, porous collagen matrix has recently been introduced for soft tissue augmentation (Thoma et al., 2016, 2017; Stefanini et al., 2020). This xenogeneic cross-linked collagen matrix (CCM) is characterized by a single porous layer, principally made of collagen type I and III, that has undergone chemical cross-linking for increasing its mechanical stability (Mathes et al., 2010; Asparuhova et al., 2021).

Based on the principle of tissue engineering of maxillofacial and periodontal tissues (Lynch et al., 1989; Lynch, 1999, 2009), it is reasonable to assume that this novel CCM may also serve as a viable scaffold for the ingrowth of cells following growth factor-mediated root coverage procedures. Agis et al. (2014) observed an increased cellular population and metabolic activity in the matrix when utilized as a scaffold for recombinant human platelet-derived growth factor (rhPDGF)-BB (Agis et al., 2014). A recent in vitro study demonstrated that rhPDGF can further enhance the effect of CCM on clot stabilization and regulation of the equilibrium between coagulation and fibrinolysis (Asparuhova et al., 2021). rhPDGF is known as a potent mitogen for fibroblasts and periodontal ligament cells (Hom & Maisel, 1992; Tavelli et al., 2020a). rhPDGF promotes angiogenesis by

stimulating the proliferation of pericytes, upregulating vascular endothelial growth factor (VEGF) and inducing macrophages to synthesize fibroblast growth factors and transforming growth factor beta. rhPDGF can also accelerate the rate of wound healing by enhancing fibroblast recruitment and activation and by increasing the wound breaking strength (Hom & Maisel, 1992; Tavelli et al., 2020a). Its combination with beta-tricalcium phosphate has been found to promote regeneration of Sharpey's fibres, new cementum, and new bone in teeth with isolated gingival recessions (McGuire, Scheyer, Nevins, & Schupbach, 2009; McGuire, Scheyer, & Schupbach, 2009). We speculate that rhPDGF can also enhance the properties of CCM in a clinical setting. Therefore, the aim of the present study was to investigate the effect of rhPDGF in combination with CCM for the treatment of MAGRs over a 6-month follow-up.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and trial registration

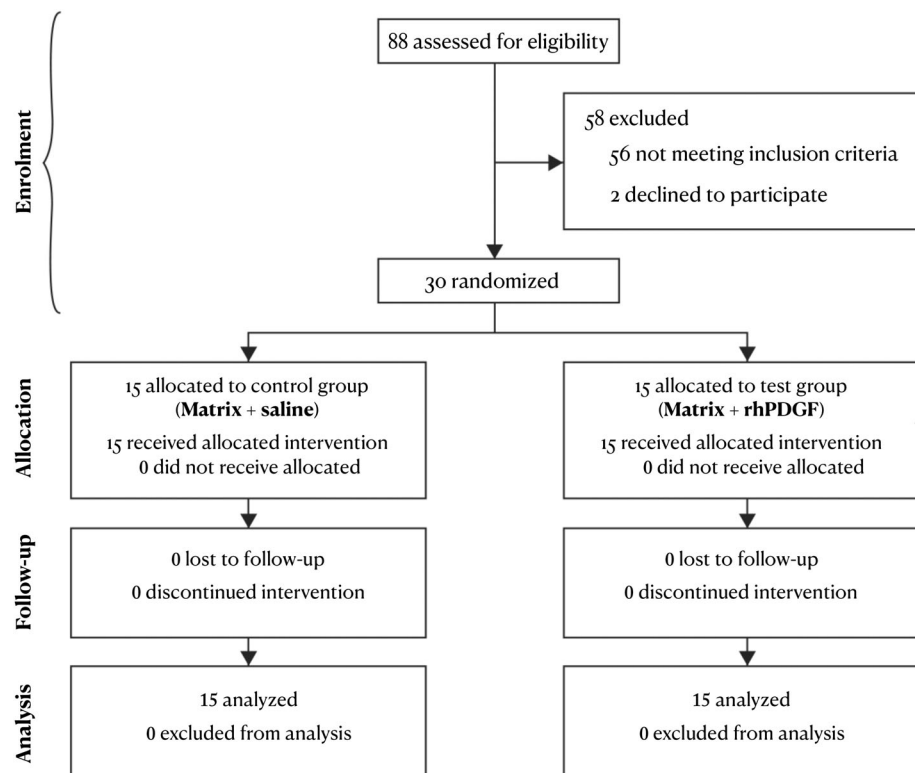
The present study was designed as a triple-blind, parallel-arm, randomized, placebo-controlled clinical trial to test the efficacy of rhPDGF in combination with a CCM (rhPDGF as the test group) versus CCM alone (scaffold matrix alone as the control group) for the treatment of MAGRs.

This human clinical trial was registered prior to initiation at ClinicalTrials.gov (NCT04462237) and follows the CONSORT statement (Schulz, Altman, Moher, & Fergusson, 2010; Schulz, Altman, Moher, & CONSORT Group, 2010) (Figure 1). The study protocol was approved by the Institutional Review Board of the University of Michigan Medical School (HUM00177214), in accordance with the Declaration of Helsinki of 1975, revised in Fortaleza in 2013.

### 2.2 | Participants

Participants were recruited based on the following inclusion criteria: (i) Periodontally and systemically healthy adults (age  $\geq$  18 years)

FIGURE 1 CONSORT flow chart



presenting with at least two adjacent sites exhibiting gingival recessions (at least one MAGR) classified as recession type 1 (RT1) (Cairo et al., 2011), associated with dental hypersensitivity or aesthetic concerns; (ii) self-reported smoking  $\leq 10$  cigarettes/day; (iii) full-mouth plaque and bleeding scores  $\leq 20\%$ ; (iv) presence of a least 2 mm depth on at least one recession; and (v) patients being able to maintain good oral hygiene.

The exclusion criteria included: (i) compromised general health; (ii) pregnancy or attempting to get pregnant (self-reported); (iii) untreated periodontal disease; (iv) persistence of uncorrected factitious gingival trauma from toothbrushing; (v) presence of severe tooth malposition, rotation, or super-eruption; (vi) presence of root caries or inadequate prosthetic restorations; (vii) previous periodontal plastic surgery at the experimental sites; and (viii) known allergy to collagen-based medical products.

### 2.3 | Interventions

Eligible patients received a session of dental prophylaxis, including oral hygiene instructions that aimed at eliminating possible traumatic toothbrushing habits at least 1 month before the surgery. The intervention consisted of coronally advanced flap (CAF) with a CCM (Geistlich Fibro-Gide, Geistlich Pharma AG, Wolhusen, Switzerland), either saturated with a sterile saline solution (control group) or with rhPDGF-BB (GEM 21S, Lynch Biologics, Franklin,

TN, test group) (Figure 2). Based on the location and distribution of the MAGRs, CAF was performed with a trapezoidal or envelope design, with horizontal or rotated papillae, with or without vertical incisions, as previously described (Zucchelli et al., 2009; Zucchelli & De Sanctis, 2000; Tonetti et al., 2018) (Appendix). After flap elevation and release, the root surfaces that were exposed to the oral cavity were scaled, planed, and chemically conditioned using 24% of EDTA for 2 min (Barootchi et al., 2018). For both groups, the CCM was first extraorally trimmed with a 15c blade, based on the characteristics of the recession defects. The matrices were then saturated with a micro-injection needle containing 1.5 cc of the solution that was prepared and provided by another study member through a sealed envelope. All envelopes similarly stated "Research Solution" with the patients' consecutively assigned identification (ID) numbers. The ID numbers were also marked on the injection needles. The scaffold constructs were left in the dappen dish for 15 min (Rubins et al., 2013, 2014). The solution was also applied onto the dried root surfaces before stabilizing the matrices. Simple interrupted sutures (6/0 and 7/0 PGA, AD Surgical, Sunnyvale, CA) engaging the matrix and the de-epithelialized anatomical papillae were performed for stabilizing the CCM at the recipient bed, approximately at the level of the cemento-enamel junction (CEJ) or 1 mm apical. Further stabilization of the matrix was also achieved, if necessary, with additional mattress sutures apical to the CCM, by engaging the periosteum. The flap was then coronally advanced and stabilized approximately 2 mm above the CEJ with sling sutures





**FIGURE 2** Surgical intervention in participants allocated to the test group. (a–c) Baseline. (d) Flap design. (e) Flap elevation and removal of the submucosal and muscular tissue. (f) Chemical root conditioning with 24% EDTA applied for 2 min. (g) Xenogeneic collagen matrix trimmed according to the dimension of the surgical site. (h) Collagen matrix after being soaked for 15 min in the liquid solution (recombinant human platelet-derived growth factor [rhPDGF] in this case). (i, j) The collagen matrix is applied on the recipient bed and sutured to the de-epithelialized anatomical papilla and the periosteum. (k, l) Flap advancement and suturing. (m–o) Six-month outcomes

and simple interrupted sutures (6/0 and/or 7/0 polypropylene [Ethicon, Johnson & Johnson, Somerville, MA]) at the level of the papillae, completely covering the CCM. Simple interrupted sutures were performed at the level of the vertical incisions, if any (7/0 polypropylene [Ethicon, Johnson & Johnson]).

A detailed description of the surgical intervention and the post-operative regimen is reported in the Supplementary Appendix.

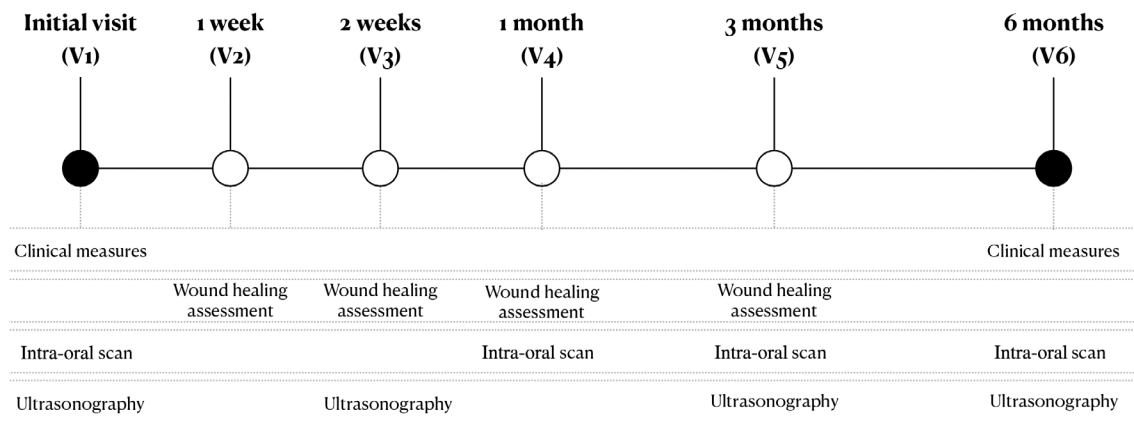
Patients returned at 1 week, 2 weeks, 1 month, 3 months, and 6 months after the surgery (Figure 3).

## 2.4 | Outcomes

The primary endpoint of this investigation was to test the efficacy of added rhPDGF onto the CCM, via comparison of the test and control groups in terms of the obtained mean root coverage (mRC) at 6 months, calculated as the percentage of defect coverage compared with baseline (Wang et al., 2001; Zucchelli et al., 2009).

The secondary outcomes that were analysed and compared within the two groups included:





**FIGURE 3** Study timeline from the initial visit (V1) to the 6-month follow-up visit (V6)

1. Frequency of complete root coverage (CRC) at 6 months, expressed in percentage.
2. Recession depth (Rec) reduction at 6 months.
3. Gingival thickness (GT) gain at 6 months, evaluated with the conventional method of transgingival probing.
4. Soft tissue volume changes using an intra-oral optical scanner, as changes relative to baseline (pre-operative measures).
5. Change in the augmented soft tissues/GT over time, evaluated using ultrasonography (longitudinally from baseline to 2 weeks, 3 months, and 6 months), referred to as ultrasonographic GT (UGT) at reference points 1.5 and 3 mm from the gingival margin.
6. Changes in keratinized tissue width (KTW) at 6 months.
7. Professionally evaluated aesthetics, with the root coverage aesthetic score (RES).

#### 2.4.1 | Clinical measures

The following clinical measurements were performed by a single masked and calibrated examiner (J.M.) at baseline and 6 months after the surgery on the mid-buccal aspect of all treated sites, using a periodontal probe (PCP UNC 15, Hu-Friedy, Chicago, IL) as previously described (Zucchelli et al., 2010; Cairo et al., 2016): (i) recession depth (Rec); (ii) probing depth (PD); (iii) clinical attachment level; and (iv) KTW. Rec and KTW were also assessed at 3 months.

GT was evaluated 1.5 mm apical to the gingival margin with an anaesthesia needle carrying a silicon disc stop and a digital calliper with 0.01 mm of accuracy (Zucchelli et al., 2010; Cairo et al., 2016). Gingival phenotype was classified at each site as thin, medium, thick, or very thick using colour-coded probes (Colorvue probes, Hu-Friedy). The RES (Cairo et al., 2009) was utilized at the last visit for the aesthetic assessment of the root coverage procedures. Examiner calibration consisted of two repeated measurements of Rec and KTW among 10 subjects who had not participated in the study (K coefficient of 0.89 for Rec and 0.88 for KTW, for obtaining measurements within 0.5 mm).

#### 2.4.2 | STL file acquisition and volumetric outcome assessment

An intra-oral optical scanner (Trios, 3Shape, Denmark) was utilized to generate digital models that were saved as STL files and imported into an image analysis software (GOM Inspect, GOM, Germany). A blinded and pre-calibrated examiner with experience in 3D volumetric analysis (L.M.) performed all the measurements. The calibration consisted of two repeated measurements of the volumetric outcomes of interest in 10 STL files from subjects not participating in the study that underwent treatment of MAGRs (intra-class correlation coefficient  $\geq .84$ ) (Parvini et al., 2021). A semi-automated alignment, based on the selection of reproducible points on the digital models and on a best-fit algorithm, was used to superimpose the STL files (Borges et al., 2020; Parvini et al., 2021). Each time point (1, 3, and 6 months) was superimposed with the baseline, which was used as the reference. The region of interest (ROI) was defined as previously described (Tavelli, Barootchi, Majzoub, Siqueira, et al., 2021) at each treated site. The volumetric outcomes of interest were volume change in cubic millimetres (Vol) and the mean distance between the surface/mean thickness of the reconstructed volume in millimetres ( $\Delta D$ ) (Schmitt et al., 2016; Tian et al., 2019; Fons-Badal et al., 2020; Tavelli, Barootchi, Majzoub, Siqueira, et al., 2021; Xue et al., 2021).

#### 2.4.3 | Ultrasound image acquisition

The ultrasound equipment set-up and the scanning procedures have been described in detail in previous reports (Chan, Wang, et al., 2017; Barootchi, Chan, et al., 2020; Chan & Kripfgans, 2020; Barootchi, Tavelli, Majzoub, et al., 2021; Tavelli, Barootchi, Majzoub, Chan, Giannobile, et al., 2021). Briefly, a commercially available ultrasound imaging device (ZS3, Mindray) was coupled with a 24 MHz (64  $\mu$ m axial image resolution) and miniature-sized (approximately 30 mm long  $\times$  18 mm wide  $\times$  12 mm thick) probe (L30-8) to generate ultrasound images. Single image frames ("still images") at the mid-facial

aspect of the site of interest were saved in “B-mode” in the Digital Imaging and Communications in Medicine (DICOM) format. “B-mode” generates 2D grey-scale images in which brightness is the result of the returned echo signal and its strength, which depends on the acoustical properties of the periodontal soft and hard tissues. The US probe was oriented perpendicular to the occlusal plane and parallel to the long axis of the tooth at its mid-facial aspect (Chan & Kripfgans, 2020; Tavelli, Barootchi, Majzoub, Chan, Giannobile, et al., 2021). A public-domain software package (Horos™, version 3.3.6, Horos Project) was utilized for evaluating GT (UGT) at 1.5- and 3-mm reference points from the gingival margin (Chan, Sinjab, et al., 2017; Tattan et al., 2019).

#### 2.4.4 | Patient-reported outcome measures

Post-operative morbidity was assessed using a questionnaire that was given to patients at the end of the surgical procedure and that included a 100-mm visual analogue scale (VAS) for each of the 15 post-operative days. Time to recovery was calculated as the time required to reach a VAS < 10 (Tonetti et al., 2018). Patient-reported aesthetics of the gingival recessions and dentin hypersensitivity (DH), assessed using the air spray approach (Meza-Mauricio et al., 2021), were obtained at baseline and 6 months using a 100-mm VAS. At the last follow-up visit, participants were also asked to rate the overall treatment satisfaction (SAT) using a 100-mm VAS.

### 2.5 | Sample size

This clinical trial was powered to detect a minimum clinically significant difference in root coverage (recession reduction) of 0.5 mm using  $\alpha = .05$ , a power ( $1-\beta$ ) of 80%, and a hypothesized within-group sigma of 0.4 mm (Cairo et al., 2016). Considering possible dropouts, the number of patients was increased by 15% for each arm. On the basis of these data, the minimum number of patients needed to be enrolled in this study was 30 in total, 15 for the test (CCM + rhPDGF) and 15 for the control group (CCM + saline).

### 2.6 | Stratified sequential randomization

Three sets of 10 patients were stratified by a computer software to obtain two equally balanced groups (of A and B) based on baseline characteristic of initial recession depth, arch, and smoking status. By the flip of a coin of the study coordinator, it would be decided which of the two groups would serve as test (CCM + rhPDGF) and which would be control (CCM + sterile saline solution, as placebo).

On the day of the surgery, the surgeon would receive a sealed envelope with the patient's ID number, containing a syringe with 1.5 cc of a clear solution, which could have either been sterile saline (control) or 0.3 mg/ml rhPDGF (test group). The test and control

envelopes and syringes appeared identical. The patients, the surgeon, and other study team members were unaware and remained uninformed of the test/control treatment allocation. All patients received treatment as they were assigned.

### 2.7 | Trial monitoring

An independent study monitor (L.K.) periodically assessed the progress of the clinical trial and observed aspects pertaining to recruitment, safety, data quality, and critical efficacy endpoints to ensure compliance with the study protocol, quality in patient enrolment, interventions, and data collection.

### 2.8 | Statistical methods and outcome assessment

The gathered data were entered into a prefabricated spreadsheet, as per patients' ID numbers and group identities (1 and 2). Means and SD were calculated for continuous measures (mRC, Rec, KTW, GT, Vol,  $\Delta D$ , etc.). CRC was calculated as the percentage of sites that achieved complete coverage at 6 months and expressed as a binary outcome.

Linear mixed-effects models were used to assess statistical differences for the primary outcome of mRC, as well as the other continuous secondary endpoints. Linear mixed-logistic regression models were utilized for binary outcomes, of which coefficients were exponentiated to produce odds ratios (ORs) from log odds. All models accounted for repeated measures and correlations induced by multiple sites per patient and multiple time points. The analysis of Rec and UGT was initially performed longitudinally, with the inclusion of Rec baseline and its interaction with the indicator of Rec being measured post-treatment initiation, to check for successful randomization, and similarly for baseline UGT, in their corresponding model. For the primary outcome (efficacy of rhPDGF relative to mRC at 6 months between the two groups) and to assess potential treatment-effect heterogeneity, baseline Rec was included as a fixed-covariate to investigate the influence of Rec baseline. In the event that a baseline variable was not significant, it was dropped from the final model (Supplementary Appendix).

Confidence intervals (CI) were produced and a  $p$  value of .05 was set for statistical significance. Descriptive statistics were utilized to show the gathered clinical data, displayed in tabular form with SDs. Line charts were also used for visualization of continuous means with corresponding SDs of outcomes of interest. The randomization as to which among the two groups (1 or 2) served as the test sites was revealed at the end of the analysis by the study coordinator (A.O.). All analyses were performed using a specified software (RStudio, Version 1.3.959), by a separate author (S.B.) with experience in biostatistical analyses who had not participated in the clinical measurements and was absent at the time of the surgical procedures.

### 3 | RESULTS

#### 3.1 | Participant flow, baseline data, and numbers analysed

Thirty subjects (19 female, 11 males, mean age  $38.4 \pm 11.5$  years), 15 per group, were randomized and received the allocated treatments. Each patient received a single (either test or control) treatment consisting of 2–5 MAGRs. Forty-four sites were allocated to the control group and treated with CCM + saline, while 47 teeth received CCM + rhPDGF. One patient in the control group was a light smoker (2–3 cigarettes/day), while no smokers were present in the test group. All subjects completed the follow-up visits and complied with the study recall appointments (Figure 1). Patient characteristics and baseline measurements of the study sites within groups are reported in the Supplementary Appendix and in Table 1, respectively.

#### 3.2 | Clinical and aesthetic outcomes

The CCM graft dimensions did not differ significantly between the test and control groups (Supplementary Appendix). The healing was uneventful for all treated sites, without any adverse events throughout the entire study.

Table 1 describes the obtained clinical and aesthetic measurements at 6 months.

For the primary outcome of mRC at 6 months, the results of the mixed models demonstrated that the test group (CCM + rhPDGF) obtained a significantly higher value of 88.25% versus 77.72% for control (CCM) (estimated coefficient of 10.47 [95% CI: 2.43 to 18.51,  $p = .02$ ]). CRC was also significantly higher at test sites (OR 11.35 [95% CI: 1.77 to 77.39],  $p < .01$ ). In addition, increase in GT was also

significantly in favour of test sites (0.22 mm [95% CI: 0.04 to 0.4],  $p = .01$ ). The changes in KTW only approached significance (0.39 mm [95% CI: -0.003 to 0.792],  $p = .058$ ) in favour of the test group. Analysis of Rec revealed a significantly superior Rec reduction in the test sites (-0.28 mm [95% CI: -0.53 to -0.02],  $p = .03$ ). All the sites in the test and control groups showed an increase in gingival phenotype when assessed with colour-coded probes. Professional aesthetic evaluation using the RES displayed a statistically significant better score in favour of the test group (1.14 [95% CI: 0.18 to 2.10],  $p = .02$ ) (Table 1 and Supplementary Appendix).

#### 3.3 | Volumetric outcomes

At 6 months, both groups and all treated sites showed a significant volumetric increase relative to baseline (pre-operative measures), which was significantly higher at the test sites, for the outcome of  $\Delta D$  (0.17 [95% CI: 0.03 to 0.31],  $p = .02$ ) and Vol (14.99 [95% CI: 0.11 to 29.87],  $p = .048$ ) (Figure 4 and Table 1, as well as additional data in the Supplementary Appendix).

#### 3.4 | Ultrasonographic assessment of GT changes

The analysis of UGT was performed longitudinally, to assess the rate of change in thickness with respect to time from baseline throughout the observed healing periods of 2 weeks, 3 months, and 6 months after the two interventions (Figures 5 and 6).

Based on the mixed model, it was found that the changes in thickness at 1.5 and 3 mm reference points below the gingival margin were significantly less for the test group over time (0.25 mm at 1.5 mm ref. point [95% CI: 0.09 to 0.418],  $p = .006$ ) and 0.32 mm at the 3 mm ref.

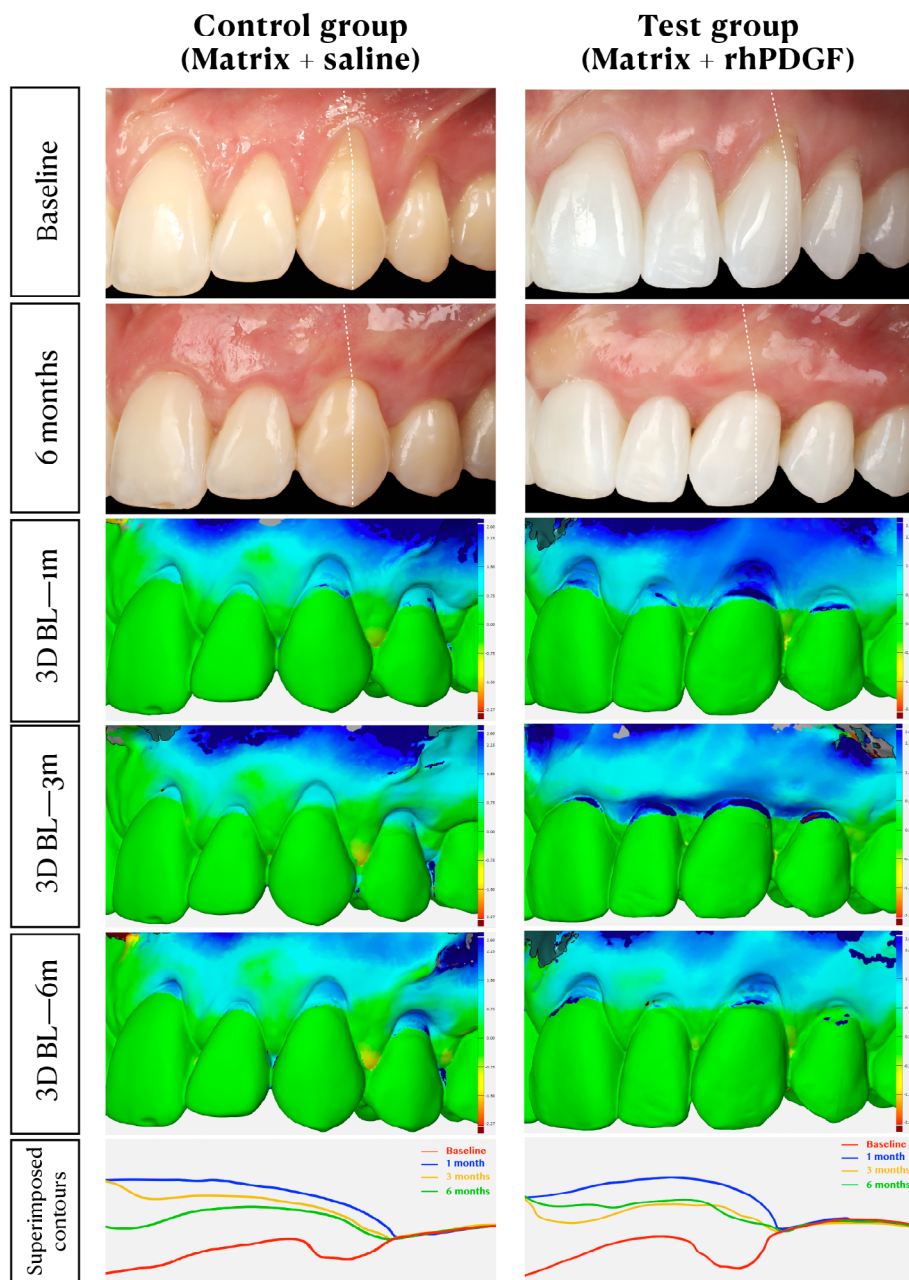
**TABLE 1** Clinical, volumetric, and aesthetic outcomes at baseline and 6-month follow-up visits

Outcome	Matrix + saline (N = 44)		Matrix + rhPDGF (N = 47)	
	Baseline	6 months	Baseline	6 months
Rec depth (mean $\pm$ SD) (mm)	3.05 $\pm$ 1.21	0.70 $\pm$ 0.50	2.87 $\pm$ 0.78	0.33 $\pm$ 0.49*
KTW (mean $\pm$ SD) (mm)	2.10 $\pm$ 1.28	2.34 $\pm$ 0.99	2.48 $\pm$ 0.87	2.81 $\pm$ 0.84
GT (mean $\pm$ SD) (mm)	0.84 $\pm$ 0.27	1.38 $\pm$ 0.33	0.92 $\pm$ 0.26	1.67 $\pm$ 0.31*
mRC (mean $\pm$ SD) (%)		77.72 $\pm$ 14.90		88.25 $\pm$ 16.31*
CRC (%)		20.45		59.57*
KTW gain (mean $\pm$ SD) (mm)		0.25 $\pm$ 1.08		0.32 $\pm$ 0.84
GT gain (mean $\pm$ SD) (mm)		0.51 $\pm$ 0.25		0.80 $\pm$ 0.39*
Vol (mean $\pm$ SD) (mm <sup>3</sup> )		58.67 $\pm$ 32.98		75.39 $\pm$ 24.76*
$\Delta D$ (mean $\pm$ SD) (mm)		0.73 $\pm$ 0.35		0.91 $\pm$ 0.19*
Final RES (mean $\pm$ SD) (points)		6.98 $\pm$ 1.41		8.17 $\pm$ 1.99*

Abbreviations:  $\Delta D$ , mean thickness of the reconstructed volume; CAL, clinical attachment level; CRC, complete root coverage; GT, gingival thickness; KTW, keratinized tissue width; mRC, mean root coverage; N, number of treated sites; PD, pocket depth; Rec, recession; RES, root coverage aesthetic score; rhPDGF, recombinant human platelet-derived growth factor; Vol, volumetric change in cubic millimetres.

\*Statistical significance based on  $p < .05$  threshold from the mixed model.





**FIGURE 4** 3D volumetric analysis between the two groups (1m, 1 month; 3m, 3 months; 6m, 6 months; BL, baseline)

point (95% CI: 0.091 to 0.55,  $p = .009$ ), indicating a less “shrinkage” of tissues at the test sites compared with the control, and thus a significantly greater UGT at the final study time point.

### 3.5 | Patient-reported outcome measures

Subjects allocated to the test group reported an overall lower morbidity during the first five post-operative days compared with the control group (mean VAS  $24.2 \pm 6.6$  vs.  $36.4 \pm 5.1$ , respectively). The mean VAS observed from Day 6 to Day 10 was  $9.5 \pm 3.8$  in the test group and  $13.7 \pm 2.3$  in the control group. From Day 11 to Day 15, the mean VAS for the test and control group was  $2.7 \pm 1.5$  and  $6.0 \pm 3.6$ , respectively. The mean time to recovery was  $8.1 \pm 1.6$  days

(8–9 days) for the subjects allocated to the test group, and  $11.4 \pm 1.5$  days (11–12 days) for the subjects allocated to the control group.

Both groups showed a substantial improvement in EST from baseline to 6 months (mean EST change of 61.9 and 61.8 VAS for the test and control group, respectively). The mean SAT reported at 6 months was 90.0 and 89.1 VAS for the test and control groups, respectively (Supplementary Table 5 of Appendix).

The intervention resulted in an average DH reduction of 25.8 and 26.8 VAS for the test and control group, respectively. Thirty-four percent of the subjects allocated to the test group showed no DH (VAS = 0) at the last follow-up, while 25% of subjects of the control group reported no DH (VAS = 0) at 6 months. The percentage of participants describing residual DH  $\leq 10$  VAS at 6 months was 61.4 and



**FIGURE 5** Ultrasonographic evaluation of gingival thickness (UGT) changes within the two groups (“Cr” identified the crown of the tooth and “R” the root. The soft tissue has been highlighted in blue). rhPDGF, recombinant human platelet-derived growth factor

63.8 for the sites treated with CCM + saline and sites treated with CCM + rhPDGF, respectively. Only one subject per each group reported a residual DH of  $\geq 50$  VAS at the last visit (Supplementary Table 5 and 6 of Appendix).

## 4 | DISCUSSION

### 4.1 | Main root coverage findings

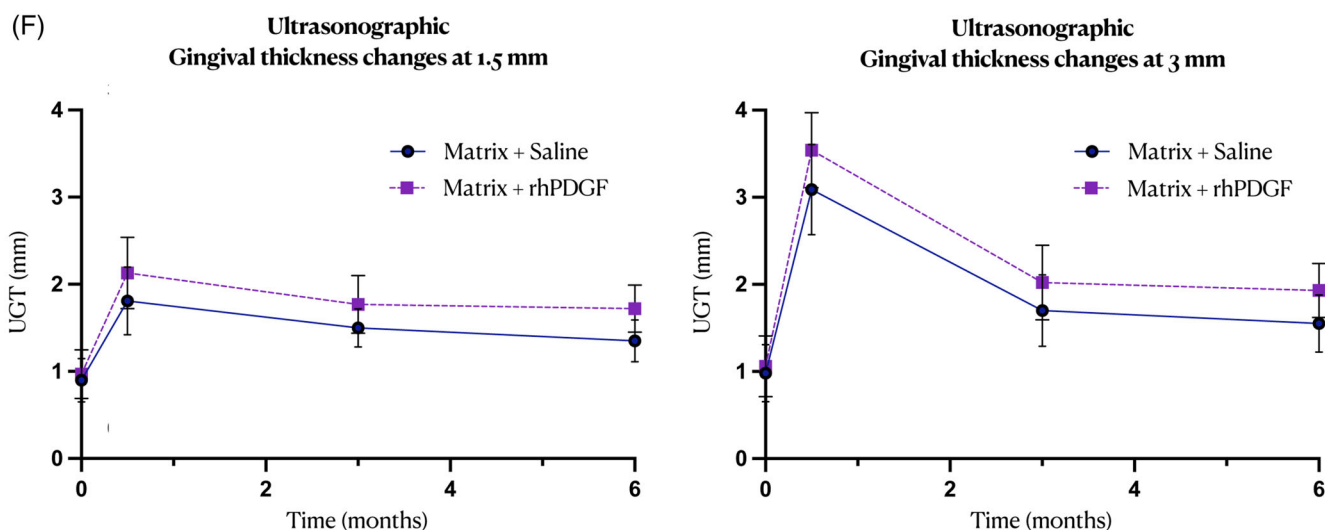
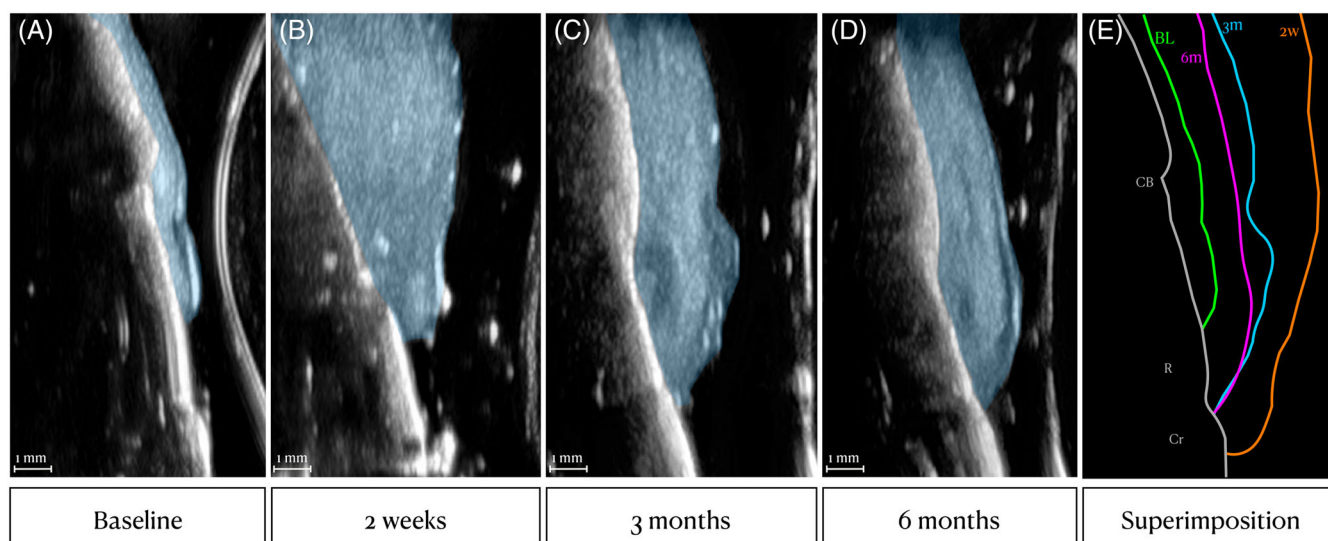
This clinical trial was designed to evaluate if the addition of rhPDGF to CCM would improve the clinical outcomes of treating MAGRs, compared with the use of a saline-hydrated CCM. The mRC at 6 months was set as the primary endpoint of the present investigation, and this analysis revealed that rhPDGF-treated sites achieved significantly higher mRC compared with sites allocated to the CCM + saline group (88.3% vs. 77.7%, on average, respectively). We also observed statistically higher Rec reduction and CRC at the 6-month follow-up for the test compared with the control group (CRC 59.6% vs. 20.5% favouring the test group, with an OR of 11.35).

These findings are consistent with the mechanism of action of rhPDGF in enhancing angiogenesis and accelerating the early stages of wound healing (Steed, 2006; Cheng et al., 2007; Kaltalioglu & Coskun-Cevher, 2015), which may have promoted a faster

revascularization and resolution of the inflammatory phase and more complete ingrowth of connective tissue, all leading to reduced soft tissue shrinkage. The growth factor has also been shown to accelerate fibroblast proliferation, production of the extracellular matrix, as well as the rate of re-epithelialization and wound closure (Cooke et al., 2006; Cheng et al., 2007; Sun et al., 2007; Jin et al., 2008; Kaltalioglu & Coskun-Cevher, 2015). It can therefore be assumed that rhPDGF enhances mRC and CRC of CCM by accelerating angiogenesis and vascular and cell invasion into the scaffold matrix, promoting a faster and better soft tissue healing.

One may question the clinical relevance of mRC between the test and control groups ( $\cong 10.5\%$ ). However, it should be noted that the estimated average mRC of the gold standard CTG and acellular dermal matrix, which has been defined as “the soft tissue substitute that may provide the most similar outcomes to those achieved by subepithelial CTG” by a recent Cochrane review (Chambrone et al., 2018), is 85% and 75%, respectively (Cairo, 2017). Therefore, it can be speculated that adding rhPDGF to a soft tissue graft substitute could be the determining factor for matching the root coverage outcomes of autogenous CTG. Nevertheless, future non-inferiority randomized controlled trials are needed to investigate this assumption.

Previous applications of rhPDGF for the treatment of gingival recessions have included the use of the growth factors with either synthetic bone graft, acellular dermal matrix or CTG (McGuire,



**FIGURE 6** Ultrasongraphic evaluation of gingival thickness (UGT) changes over time. (a–d) ultrasound scan of the same site at different time points where the soft tissue component has been highlighted in blue. (a) Ultrasound scan of a site allocated to the control group at baseline (BL). (b) Ultrasound scan 2 weeks after the intervention (2w). (c) Ultrasound scan 3 months after the intervention (3m). (d) Ultrasound scan 6 months after the intervention (6m). (e) Superimposition of the soft tissue profile at different time points. “Cr” identifies the crown of the tooth, “R” the root and “CB” the crestal bone. The grey line shows the profile of the buccal bone, the root and the crown, the green line highlights the soft tissue profile at baseline, while the orange, light blue line and purple lines identify the soft tissue profile 2 weeks, 3 months, and 6 months after the intervention, respectively. (f) Graphic representation of UGT changes over time between the two groups assessed 1.5 mm below the gingival margin and 3 mm below the gingival margin. Note that UGT was analysed longitudinally with respect to changes over time, for statistical inferences, the reader may refer to the text in the results section. rhPDGF, recombinant human platelet-derived growth factor

Scheyer, & Schupbach, 2009; Carney et al., 2012; Rubins et al., 2014; Parween et al., 2020), with an mRC ranging from 69% to 88.7%, as found in a recent review from our group (Tavelli, Ravida, Barootchi, Chambrone, & Giannobile, 2021). While a study by Carney et al. (2012) did not find differences in the root coverage outcomes of acellular dermal matrix with or without the growth factor, Parween et al. (2020) showed significantly higher mRC and CRC for the group in

which CTG was soaked with rhPDGF. Thus, one could assume that the properties of the scaffold material can play a key role in the final outcomes of biologic-mediated approaches and tissue-engineered grafting materials (Kuo et al., 2018; Tavelli et al., 2020a). A recent multicentre non-inferiority trial failed to demonstrate comparable mRC between CCM and CTG (70.7% vs. 90.5%, respectively) (McGuire et al., 2021). Interestingly, the mRC and CRC obtained in this trial at



the sites treated with CCM + rhPDGF are in line with the ones reported by McGuire and co-workers for CAF + CTG (90.5% and 66%) and, overall, with the expected outcomes of CAF + CTG described in the literature (mRC 84.7% and CRC 51.8%) (Cairo, 2017).

## 4.2 | GT assessment and outcomes

GT has been shown to be significantly associated not only with the early root coverage outcomes (Baldi et al., 1999; Huang et al., 2005) but also with the stability of the gingival margin over time (Tavelli, Barootchi, Di Gianfilippo, et al., 2019; Barootchi, Tavelli, et al., 2020). This parameter has been traditionally evaluated using the transgingival probing method. However, the need for a customized stent, the possibility of bending the needle/endodontic instruments, patient discomfort, and limited accuracy have led clinicians to explore new methods for assessing GT (McGuire, Scheyer, & Schupbach, 2009; Schulz, Altman, Moher, & Fergusson, 2010; Fons-Badal et al., 2020; Tavelli, Barootchi, Majzoub, Siqueira, et al., 2021). Digital scanning and superimposition of the obtained STL files have shown to be a valid tool for assessing soft tissue volumetric changes, although the actual value of GT at different time points cannot be measured. Ultrasonography has been proved to be a non-invasive and reliable technology for characterizing oral structures (Chan, Wang, et al., 2017; Tattan et al., 2019; Barootchi, Chan, et al., 2020; Siqueira et al., 2021; Tavelli, Barootchi, Majzoub, Chan, Giannobile, et al., 2021), and it has been recommended as the approach of choice for assessing longitudinal changes in soft tissue thickness and grafted biomaterials (Chan & Kripfgans, 2020; Tavelli, Barootchi, Majzoub, Chan, Stefanini, et al., 2021). In the present study, we investigated and described GT changes as a result of root coverage procedure, using transgingival probing (for facilitating comparisons with the existing literature), as well as digital scanning and ultrasonography. To the best of our knowledge, this is the first clinical report assessing GT changes following root coverage procedure with these three different analytical methods.

The mean GT gain at 6 months assessed with transgingival probing 1.5 mm apically to the gingival margin (0.51 and 0.80 mm in the control and test group, respectively) was in line with the measurements obtained from the ultrasound scans at the same level (mean UGT 0.45 and 0.75 mm, in the control and test group, respectively). The mean thickness of the ROI ( $\Delta D$ ) obtained from the superimposition of the digital impressions at baseline and 6 months was 0.73 and 0.91 mm, for the control and test groups, respectively.

The higher mean volume stability observed when the grafted CCM was combined with rhPDGF may be attributed to the enhanced migration and proliferation of fibroblasts promoted by the growth factor (Agis et al., 2014; Tavelli et al., 2020a). This property of the novel CCM—increasing GT—seems to be crucial when treating gingival recessions, as soft tissue phenotype modification plays a key role in the stability of the gingival margin over time (Tavelli, Barootchi, Di Gianfilippo, et al., 2019; Barootchi, Tavelli, et al., 2020).

The limited gain in GT and the inferior root coverage outcomes compared with the autogenous CTG, together with a high tendency towards recession recurrence in the long term (McGuire &

Scheyer, 2016; Tonetti et al., 2018; Tavelli, Barootchi, Cairo, et al., 2019; Barootchi, Tavelli, et al., 2020), have been the main drawback of the first-generation xenogeneic collagen matrices. The second-generation CCM—as utilized in this study and characterized by the cross-linking of collagen—may have a better propensity for promoting soft tissue phenotype modification as compared with the previous collagen matrix. In line with a previous study demonstrating that  $GT \geq 1.2$  mm and  $KT \geq 2$  mm 6 months after root coverage using a soft tissue graft substitute were predictors for the long-term stability of the gingival margin (Tavelli, Barootchi, Di Gianfilippo, et al., 2019), it may be speculated that several of the treated sites in our clinical trial will maintain the 6-month outcomes also in the long term. Nevertheless, limited evidence is available at the present moment on the root coverage outcomes with this recently introduced CCM, and the above-mentioned correlation among GT, KT, and the stability of the root coverage outcomes may not be valid for this novel graft material. In addition, it should be considered that the stability of gingival margin in the long term largely depends also on patient compliance with follow-up visits where oral hygiene procedures and toothbrushing techniques can be checked and reinforced, to avoid the re-assumption of traumatic toothbrushing (Moslemi et al., 2011; Pini Prato et al., 2011).

## 4.3 | KTW changes

Another interesting outcome of this study is the negligible change of KTW in both groups. Although it has been speculated that inducing keratinization of the alveolar mucosa is typically a prerogative of autogenous CTGs (Zucchelli et al., 2020), some authors have reported a considerable gain in KTW with graft substitutes (McGuire & Scheyer, 2010; Moslemi et al., 2011; Ayub et al., 2014; Cardaropoli et al., 2014; Stefanini et al., 2016). Nevertheless, a recent network meta-analysis further corroborated the superiority of CTG over acellular dermal matrix and collagen matrix for KTW gain, with collagen matrix that did not show a statistically significant change in KTW compared with flap alone (Barootchi, Tavelli, et al., 2020). In line with the findings of this study, Stefanini et al. (2020) obtained a mean KTW gain of 0.4 mm after 6 months when utilizing this second generation of collagen matrix. Similarly, no significant KTW alterations were observed over a 1-year observation period when CCM was used for peri-implant phenotype modification (Huber et al., 2018). Despite the scaffolding properties of facilitating fibroblast chemotaxis and ingrowth within the matrix, it appears that the CCM, even with the addition of rhPDGF, has limited potential to induce keratinization of the overlying alveolar mucosa, at least in the short term.

## 4.4 | Patient-reported outcome measures

The growth factor showed to promote a faster recovery and significantly less post-operative morbidity perceived during the first 5 days. This finding is consistent with the property of rhPDGF of encouraging

the migration of neutrophils and macrophages to the wound sites, resulting in a shorter inflammatory phase and quicker healing (Steed, 2006; Kaltalioglu & Coskun-Cevher, 2015; Kim et al., 2020).

The root coverage therapy was found effective in reducing DH, with the patients reporting an average reduction of 26–27 VAS points after 6 months. These results are in line with previous trials reporting similar VAS values for DH following root coverage, regardless of the treatment approach (Moreira et al., 2016; Rocha Dos Santos et al., 2017; Santamaria et al., 2017, 2022; Cairo et al., 2020). Nevertheless, it should be highlighted that, although a remarkable reduction in DH was observed in both groups, there were several subjects reporting residual DH at 6 months. Therefore, clinicians should keep in mind that root coverage procedure with CAF + CCM (either with or without rhPDGF) can reduce, but often not completely resolve, DH.

A substantial improvement in patient-reported aesthetics ( $\cong 62$  VAS) and overall treatment satisfaction (89–90 VAS) was found after the root coverage procedure. These results highlight a certain discrepancy between patients' subjective assessment and professional aesthetic evaluation using the RES. While professional VAS has the advantage of assessing the aesthetics of gingival recessions also at baseline, providing the magnitude of improvement after root coverage procedures, the RES is currently considered the gold standard for rating the final aesthetic outcome, and it is mainly determined by the position of the gingival margin and the achievement of CRC. The addition of a professional evaluation of the aesthetic outcomes using a VAS would have been beneficial for comparing patients' and operators' scores, and it is advocated in future studies.

#### 4.5 | Strength and limitations of the study

Among the strength of the present clinical investigation, a triple-blinded design, the evaluation of GT changes with traditional transgingival probing, digital scanning, and ultrasonography, as well as the utilization of an independent study monitor ensuring compliance with the study protocol and quality in data collection need to be highlighted.

On the other hand, it would have been interesting to evaluate the root coverage outcomes of an additional treatment arm, involving either CAF alone, as a negative control, or CAF in combination with CTG, as the standard of care. Readers should be aware that the present study describes short-term outcomes, and therefore caution is needed when interpreting our findings. Longer follow-up will be needed to assess the stability of the obtained results and whether the benefits observed at rhPDGF-treated sites are sustained also in the long term.

It should also be highlighted that using growth factors inevitably increases the cost of the surgical procedure, and that future studies with longer follow-up and cost-benefit analyses are needed to further evaluate the overall advantages of growth factor-mediated root coverage procedures. Health economics

should be carefully considered when choosing new treatments and technologies (Hammerle et al., 2014). Future studies may also include the assessment of other biomaterials for their ability to be utilized as scaffolds and suitable carriers for rhPDGF, or other biologic mediators, potentially within multi-arm studies to further determine their relative clinical efficacy, in the ultimate pursuit of less invasive and more patient-centred periodontal plastic reconstructive procedures.

## 5 | CONCLUSION

Within the limitations of the study, rhPDGF-BB enhances the 6-month root coverage outcomes of a xenogeneic collagen matrix in the treatment of MAGR defects with the CAF. Greater volumetric and esthetic outcomes were also observed in the sites that received rhPDGF. The use of the growth factor promoted a faster recover and less post-operative morbidity perceived during the first five days, while the other investigated patient-reported outcomes were similar between the two groups. Future studies are needed to investigate the long-term results and cost-effectiveness of recombinant human platelet-derived growth factor-BB when utilized with a collagen scaffold for root coverage procedure.

### AUTHOR CONTRIBUTIONS

Lorenzo Tavelli, Shayan Barootchi, Suncica Travan, Hom-Lay Wang, and William V. Giannobile involved in conception and design of the study. Lorenzo Tavelli involved in the surgical procedures. Maria Vera Rodriguez involved in patient recruitment, clinical procedures, and data collection. Shayan Barootchi involved in randomization, analysis, and interpretation of data. Jad Majzoub involved in clinical and ultrasound measurements. Leonardo Mancini involved in 3D superimposition and volumetric measurements. Jim Sugai involved in the release study, conception and design of the clinical study. Hsun-Liang Chan and Oliver Kripfgans involved in the ultrasonographic part of the study. Suncica Travan involved in patients recruitment. Lorenzo Tavelli, Shayan Barootchi, and William V. Giannobile involved in the initial and final drafting of the work. All the authors were involved in the critical manuscript reviewal, and are accountable for all aspects of the work.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board of the University of Michigan Medical School (HUM00177214), in accordance with the Declaration of Helsinki of 1975, revised in Fortaleza in 2013. Written consent was obtained from the patients.

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## REFERENCES

- Agis, H., Collins, A., Taut, A. D., Jin, Q., Kruger, L., Gorch, C., & Giannobile, W. V. (2014). Cell population kinetics of collagen scaffolds in ex vivo oral wound repair. *PLoS One*, 9, e112680. <https://doi.org/10.1371/journal.pone.0112680>
- Asparuhova, M. B., Stahli, A., Guldener, K., & Sculean, A. (2021). A novel volume-stable collagen matrix induces changes in the behavior of primary human oral fibroblasts, periodontal ligament, and endothelial cells. *International Journal of Molecular Sciences*, 22(8), 4051. <https://doi.org/10.3390/ijms22084051>
- Ayub, L. G., Ramos, U. D., Reino, D. M., Grisi, M. F., Taba, M., Jr., Souza, S. L., Palioto, D. B., & Novaes, A. B., Jr. (2014). A modified surgical technique for root coverage with an allograft: A 12-month randomized clinical trial. *Journal of Periodontology*, 85, 1529–1536. <https://doi.org/10.1902/jop.2014.140111>
- Baldi, C., Pini-Prato, G., Pagliaro, U., Nieri, M., Saletta, D., Muzzi, L., & Cortellini, P. (1999). Coronally advanced flap procedure for root coverage. Is flap thickness a relevant predictor to achieve root coverage? A 19-case series. *Journal of Periodontology*, 70, 1077–1084. <https://doi.org/10.1902/jop.1999.70.9.1077>
- Barootchi, S., Chan, H. L., Namazi, S. S., Wang, H. L., & Kripfgans, O. D. (2020). Ultrasonographic characterization of lingual structures pertinent to oral, periodontal, and implant surgery. *Clinical Oral Implants Research*, 31, 352–359. <https://doi.org/10.1111/clr.13573>
- Barootchi, S., Tavelli, L., Gianfilippo, R. D., Eber, R., Stefanini, M., Zucchelli, G., & Wang, H. L. (2021). Acellular dermal matrix for root coverage procedures: 9-year assessment of treated isolated gingival recessions and their adjacent untreated sites. *Journal of Periodontology*, 92, 254–262. <https://doi.org/10.1002/JPER.20-0310>
- Barootchi, S., Tavelli, L., Majzoub, J., Chan, H. L., Wang, H. L., & Kripfgans, O. D. (2021). Ultrasonographic tissue perfusion in peri-implant health and disease. *Journal of Dental Research*, 101, 278–285. <https://doi.org/10.1177/00220345211035684>
- Barootchi, S., Tavelli, L., Ravida, A., Wang, C. W., & Wang, H. L. (2018). Effect of EDTA root conditioning on the outcome of coronally advanced flap with connective tissue graft: A systematic review and meta-analysis. *Clinical Oral Investigations*, 22, 2727–2741. <https://doi.org/10.1007/s00784-018-2635-3>
- Barootchi, S., Tavelli, L., Zucchelli, G., Giannobile, W. V., & Wang, H. L. (2020). Gingival phenotype modification therapies on natural teeth: A network meta-analysis. *Journal of Periodontology*, 91, 1386–1399. <https://doi.org/10.1002/JPER.19-0715>
- Borges, T., Fernandes, D., Almeida, B., Pereira, M., Martins, D., Azevedo, L., & Marques, T. (2020). Correlation between alveolar bone morphology and volumetric dimensional changes in immediate maxillary implant placement: A 1-year prospective cohort study. *Journal of Periodontology*, 91, 1167–1176. <https://doi.org/10.1002/JPER.19-0606>
- Cairo, F. (2017). Periodontal plastic surgery of gingival recessions at single and multiple teeth. *Periodontology 2000*, 75, 296–316. <https://doi.org/10.1111/prd.12186>
- Cairo, F., Cortellini, P., Nieri, M., Pilloni, A., Barbato, L., Pagavino, G., & Tonetti, M. (2020). Coronally advanced flap and composite restoration of the enamel with or without connective tissue graft for the treatment of single maxillary gingival recession with non-carious cervical lesion. A randomized controlled clinical trial. *Journal of Clinical Periodontology*, 47, 362–371. <https://doi.org/10.1111/jcpe.13229>
- Cairo, F., Cortellini, P., Pilloni, A., Nieri, M., Cincinelli, S., Amunni, F., Pagavino, G., & Tonetti, M. S. (2016). Clinical efficacy of coronally advanced flap with or without connective tissue graft for the treatment of multiple adjacent gingival recessions in the aesthetic area: A randomized controlled clinical trial. *Journal of Clinical Periodontology*, 43, 849–856. <https://doi.org/10.1111/jcpe.12590>
- Cairo, F., Nieri, M., Cincinelli, S., Mervelt, J., & Pagliaro, U. (2011). The interproximal clinical attachment level to classify gingival recessions and predict root coverage outcomes: An explorative and reliability study. *Journal of Clinical Periodontology*, 38, 661–666. <https://doi.org/10.1111/j.1600-051X.2011.01732.x>
- Cairo, F., Nieri, M., & Pagliaro, U. (2014). Efficacy of periodontal plastic surgery procedures in the treatment of localized facial gingival recessions. A systematic review. *J Clin Periodontol*, 41(Suppl. 15), S44–S62. <https://doi.org/10.1111/jcpe.12182>
- Cairo, F., Rotundo, R., Miller, P. D., & Pini Prato, G. P. (2009). Root coverage esthetic score: A system to evaluate the esthetic outcome of the treatment of gingival recession through evaluation of clinical cases. *Journal of Periodontology*, 80, 705–710. <https://doi.org/10.1902/jop.2009.080565>
- Cardaropoli, D., Tamagnone, L., Roffredo, A., & Gaveglione, L. (2014). Coronally advanced flap with and without a xenogenic collagen matrix in the treatment of multiple recessions: A randomized controlled clinical study. *The International Journal of Periodontics & Restorative Dentistry*, 34(Suppl. 3), s97–s102. <https://doi.org/10.11607/prd.1605>
- Carney, C. M., Rossmann, J. A., Kerns, D. G., Cipher, D. J., Rees, T. D., Solomon, E. S., Rivera-Hidalgo, F., & Beach, M. M. (2012). A comparative study of root defect coverage using an acellular dermal matrix with and without a recombinant human platelet-derived growth factor. *Journal of Periodontology*, 83, 893–901. <https://doi.org/10.1902/jop.2011.110144>
- Chambrone, L., Salinas Ortega, M. A., Sukekava, F., Rotundo, R., Kalemaj, Z., Buti, J., & Pini Prato, G. P. (2018). Root coverage procedures for treating localised and multiple recession-type defects.



- Cochrane Database of Systematic Reviews, 10, CD007161. <https://doi.org/10.1002/14651858.CD007161.pub3>
- Chan, H. L., & Kripfgans, O. D. (2020). Ultrasonography for diagnosis of peri-implant diseases and conditions: A detailed scanning protocol and case demonstration. *Dento Maxillo Facial Radiology*, 49, 20190445. <https://doi.org/10.1259/dmfr.20190445>
- Chan, H. L., Sinjab, K., Chung, M. P., Chiang, Y. C., Wang, H. L., Giannobile, W. V., & Kripfgans, O. D. (2017). Non-invasive evaluation of facial crestal bone with ultrasonography. *PLoS One*, 12, e0171237. <https://doi.org/10.1371/journal.pone.0171237>
- Chan, H. L., Wang, H. L., Fowlkes, J. B., Giannobile, W. V., & Kripfgans, O. D. (2017). Non-ionizing real-time ultrasonography in implant and oral surgery: A feasibility study. *Clinical Oral Implants Research*, 28, 341–347. <https://doi.org/10.1111/clr.12805>
- Cheng, B., Liu, H. W., Fu, X. B., Sun, T. Z., & Sheng, Z. Y. (2007). Recombinant human platelet-derived growth factor enhanced dermal wound healing by a pathway involving ERK and c-fos in diabetic rats. *Journal of Dermatological Science*, 45, 193–201. <https://doi.org/10.1016/j.jdermsci.2006.11.014>
- Cooke, J. W., Sarment, D. P., Whitesman, L. A., Miller, S. E., Jin, Q., Lynch, S. E., & Giannobile, W. V. (2006). Effect of rhPDGF-BB delivery on mediators of periodontal wound repair. *Tissue Engineering*, 12, 1441–1450. <https://doi.org/10.1089/ten.2006.12.1441>
- Cortellini, P., & Bissada, N. F. (2018). Mucogingival conditions in the natural dentition: Narrative review, case definitions, and diagnostic considerations. *Journal of Clinical Periodontology*, 45(Suppl. 20), S190–S198. <https://doi.org/10.1111/jcpe.12948>
- Fons-Badal, C., Alonso Perez-Barquero, J., Martinez-Martinez, N., Faus-Lopez, J., Fons-Font, A., & Agustin-Panadero, R. (2020). A novel, fully digital approach to quantifying volume gain after soft tissue graft surgery. A pilot study. *J Clin Periodontol*, 47, 614–620. <https://doi.org/10.1111/jcpe.13235>
- Hammerle, C. H., Giannobile, W. V., & Working Group 1 of the European Workshop on, P. (2014). Biology of soft tissue wound healing and regeneration--consensus report of Group 1 of the 10th European Workshop on Periodontology. *Journal of Clinical Periodontology*, 41(Suppl. 15), S1–S5. <https://doi.org/10.1111/jcpe.12221>
- Hom, D. B., & Maisel, R. H. (1992). Angiogenic growth factors: Their effects and potential in soft tissue wound healing. *The Annals of Otolaryngology, Rhinology, and Laryngology*, 101, 349–354. <https://doi.org/10.1177/000348949210100411>
- Huang, L. H., Neiva, R. E., & Wang, H. L. (2005). Factors affecting the outcomes of coronally advanced flap root coverage procedure. *Journal of Periodontology*, 76, 1729–1734. <https://doi.org/10.1902/jop.2005.76.10.1729>
- Huber, S., Zeltner, M., Hammerle, C. H. F., Jung, R. E., & Thoma, D. S. (2018). Non-interventional 1-year follow-up study of peri-implant soft tissues following previous soft tissue augmentation and crown insertion in single-tooth gaps. *Journal of Clinical Periodontology*, 45, 504–512. <https://doi.org/10.1111/jcpe.12865>
- Jin, Q., Wei, G., Lin, Z., Sugai, J. V., Lynch, S. E., Ma, P. X., & Giannobile, W. V. (2008). Nanofibrous scaffolds incorporating PDGF-BB microspheres induce chemokine expression and tissue neogenesis in vivo. *PLoS One*, 3, e1729. <https://doi.org/10.1371/journal.pone.0001729>
- Kaltalioglu, K., & Coskun-Cevher, S. (2015). A bioactive molecule in a complex wound healing process: Platelet-derived growth factor. *International Journal of Dermatology*, 54, 972–977. <https://doi.org/10.1111/ijd.12731>
- Kim, N., Choi, K. U., Lee, E., Lee, S., Oh, J., Kim, W. K., Woo, S. H., Kim, D. Y., Kim, W. H., & Kweon, O. K. (2020). Therapeutic effects of platelet derived growth factor overexpressed-mesenchymal stromal cells and sheets in canine skin wound healing model. *Histology and Histopathology*, 35, 751–767. <https://doi.org/10.14670/HH-18-196>
- Kuo, S., Kim, H. M., Wang, Z., Bingham, E. L., Miyazawa, A., Marcelo, C. L., & Feinberg, S. E. (2018). Comparison of two decellularized dermal equivalents. *Journal of Tissue Engineering and Regenerative Medicine*, 12, 983–990. <https://doi.org/10.1002/term.2530>
- Lynch, S. E. (1999). *Tissue engineering, applications in maxillofacial surgery and periodontics*. Quintessence Publishing Co.
- Lynch, S. E. (2009). *Tissue engineering, applications in maxillofacial surgery and periodontics* (2nd ed.). Quintessence Publishing Co.
- Lynch, S. E., Williams, R. C., Polson, A. M., Howell, T. H., Reddy, M. S., Zappa, U. E., & Antoniadis, H. N. (1989). A combination of platelet-derived and insulin-like growth factors enhances periodontal regeneration. *Journal of Clinical Periodontology*, 16, 545–548. <https://doi.org/10.1111/j.1600-051x.1989.tb02334.x>
- Mathes, S. H., Wohlwend, L., Uebersax, L., von Mentlen, R., Thoma, D. S., Jung, R. E., Grolach, C., & Graf-Hausner, U. (2010). A bioreactor test system to mimic the biological and mechanical environment of oral soft tissues and to evaluate substitutes for connective tissue grafts. *Biotechnology and Bioengineering*, 107, 1029–1039. <https://doi.org/10.1002/bit.22893>
- McGuire, M. K., Janakievski, J., Scheyer, E. T., Velasquez, D., Gunsolley, J. C., Heard, R. H., & Morelli, T. (2021). Efficacy of a harvest graft substitute for recession coverage and soft tissue volume augmentation: A randomized controlled trial. *Journal of Periodontology*, 93, 333–342. <https://doi.org/10.1002/JPER.21-0131>
- McGuire, M. K., & Scheyer, E. T. (2010). Xenogeneic collagen matrix with coronally advanced flap compared to connective tissue with coronally advanced flap for the treatment of dehiscence-type recession defects. *Journal of Periodontology*, 81, 1108–1117. <https://doi.org/10.1902/jop.2010.090698>
- McGuire, M. K., & Scheyer, E. T. (2016). Long-term results comparing xenogeneic collagen matrix and autogenous connective tissue grafts with coronally advanced flaps for treatment of dehiscence-type recession defects. *Journal of Periodontology*, 87, 221–227. <https://doi.org/10.1902/jop.2015.150386>
- McGuire, M. K., Scheyer, E. T., & Schupbach, P. (2009). Growth factor-mediated treatment of recession defects: A randomized controlled trial and histologic and microcomputed tomography examination. *Journal of Periodontology*, 80, 550–564. <https://doi.org/10.1902/jop.2009.080502>
- McGuire, M. K., Scheyer, T., Nevins, M., & Schupbach, P. (2009). Evaluation of human recession defects treated with coronally advanced flaps and either purified recombinant human platelet-derived growth factor-BB with beta tricalcium phosphate or connective tissue: A histologic and microcomputed tomography examination. *The International Journal of Periodontics & Restorative Dentistry*, 29, 7–21.
- Meza-Mauricio, J., Cortez-Gianezzi, J., Duarte, P. M., Tavelli, L., Rasperini, G., & de Faveri, M. (2021). Comparison between a xenogeneic dermal matrix and connective tissue graft for the treatment of multiple adjacent gingival recessions: A randomized controlled clinical trial. *Clinical Oral Investigations*, 25, 6919–6929. <https://doi.org/10.1007/s00784-021-03982-w>
- Moreira, A. R. O., Santamaria, M. P., Silvério, K. G., Casati, M. Z., Nociti Junior, F. H., Sculean, A., & Sallum, E. A. (2016). Coronally advanced flap with or without porcine collagen matrix for root coverage: A randomized clinical trial. *Clinical Oral Investigations*, 20, 2539–2549. <https://doi.org/10.1007/s00784-016-1757-8>
- Moslemi, N., Mousavi Jazi, M., Haghghiati, F., Morovati, S. P., & Jamali, R. (2011). Acellular dermal matrix allograft versus subepithelial connective tissue graft in treatment of gingival recessions: A 5-year randomized clinical study. *Journal of Clinical Periodontology*, 38, 1122–1129. <https://doi.org/10.1111/j.1600-051X.2011.01789.x>
- Parvini, P., Galarraga-Vinueza, M. E., Obreja, K., Magini, R. S., Sader, R., & Schwarz, F. (2021). Prospective study assessing three-dimensional changes of mucosal healing following soft tissue augmentation using

- free gingival grafts. *Journal of Periodontology*, 92, 400–408. <https://doi.org/10.1002/JPER.19-0640>
- Parween, S., George, J. P., & Prabhuji, M. (2020). Treatment of multiple mandibular gingival recession defects using MCAT technique and SCTG with and without rhPDGF-BB: A randomized controlled clinical trial. *The International Journal of Periodontics & Restorative Dentistry*, 40, e43–e51. <https://doi.org/10.11607/prd.4505>
- Pini Prato, G., Rotundo, R., Franceschi, D., Cairo, F., Cortellini, P., & Nieri, M. (2011). Fourteen-year outcomes of coronally advanced flap for root coverage: Follow-up from a randomized trial. *Journal of Clinical Periodontology*, 38, 715–720. <https://doi.org/10.1111/j.1600-051X.2011.01744.x>
- Rocha Dos Santos, M., Sangiorgio, J. P. M., Neves, F., Franca-Grohmann, I. L., Nociti, F. H., Jr., Silverio Ruiz, K. G., Santamaria, M. P., & Sallum, E. A. (2017). Xenogenous collagen matrix and/or enamel matrix derivative for treatment of localized gingival recessions: A randomized clinical trial. Part II: Patient-reported outcomes. *J Periodontol*, 88, 1319–1328. <https://doi.org/10.1902/jop.2017.170127>
- Romandini, M., Soldini, M. C., Montero, E., & Sanz, M. (2020). Epidemiology of mid-buccal gingival recessions in NHANES according to the 2018 World Workshop Classification System. *Journal of Clinical Periodontology*, 47, 1180–1190. <https://doi.org/10.1111/jcpe.13353>
- Rubins, R. P., Tolmie, P. N., Corsig, K. T., Kerr, E. N., & Kim, D. M. (2013). Subepithelial connective tissue graft with growth factor for the treatment of maxillary gingival recession defects. *The International Journal of Periodontics & Restorative Dentistry*, 33, 43–50.
- Rubins, R. P., Tolmie, P. N., Corsig, K. T., Kerr, E. N., & Kim, D. M. (2014). Subepithelial connective tissue graft with purified rhPDGF-BB for the treatment of mandibular recession defects: A consecutive case series. *The International Journal of Periodontics & Restorative Dentistry*, 34, 315–321. <https://doi.org/10.11607/prd.1635>
- Santamaria, M. P., Neves, F., Silveira, C. A., Mathias, I. F., Fernandes-Dias, S. B., Jardini, M. A. N., & Tatakis, D. N. (2017). Connective tissue graft and tunnel or trapezoidal flap for the treatment of single maxillary gingival recessions: A randomized clinical trial. *Journal of Clinical Periodontology*, 44, 540–547. <https://doi.org/10.1111/jcpe.12714>
- Santamaria, M. P., Rossato, A., Viana Miguel, M. A., Fonseca, M. B., Gomez Bautista, C. R., Carvalho de Marco, A., Mathias-Santamaria, I. F., & Ferreira Ferraz, L. F. (2022). Comparison of two types of xenogeneic matrices to treat single gingival recessions. A randomized clinical trial. *Journal of Periodontology*, 93, 709–720.
- Schmitt, C. M., Matta, R. E., Moest, T., Humann, J., Gammel, L., Neukam, F. W., & Schlegel, K. A. (2016). Soft tissue volume alterations after connective tissue grafting at teeth: The subepithelial autologous connective tissue graft versus a porcine collagen matrix – A pre-clinical volumetric analysis. *Journal of Clinical Periodontology*, 43, 609–617. <https://doi.org/10.1111/jcpe.12547>
- Schulz, K. F., Altman, D. G., Moher, D., & Fergusson, D. (2010). CONSORT 2010 changes and testing blindness in RCTs. *Lancet*, 375, 1144–1146. [https://doi.org/10.1016/S0140-6736\(10\)60413-8](https://doi.org/10.1016/S0140-6736(10)60413-8)
- Schulz, K. F., Altman, D. G., Moher, D., & CONSORT Group. (2010). CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *Journal of Clinical Epidemiology*, 63, 834–840. <https://doi.org/10.1016/j.jclinepi.2010.02.005>
- Siqueira, R., Sinjab, K., Pan, Y. C., Soki, F., Chan, H. L., & Kripfgans, O. (2021). Comprehensive peri-implant tissue evaluation with ultrasonography and cone-beam computed tomography: A pilot study. *Clinical Oral Implants Research*, 32, 777–785. <https://doi.org/10.1111/clr.13758>
- Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and Reconstructive Surgery*, 117, 143S–149S; discussion 150S–151S. <https://doi.org/10.1097/01.prs.000022526.21512.4c>
- Stefanini, M., Jepsen, K., de Sanctis, M., Baldini, N., Greven, B., Heinz, B., Wennström, J., Cassel, B., Vignoletti, F., Sanz, M., Jepsen, S., & Zucchelli, G. (2016). Patient-reported outcomes and aesthetic evaluation of root coverage procedures: A 12-month follow-up of a randomized controlled clinical trial. *Journal of Clinical Periodontology*, 43, 1132–1141. <https://doi.org/10.1111/jcpe.12626>
- Stefanini, M., Mounssif, I., Barootchi, S., Tavelli, L., Wang, H. L., & Zucchelli, G. (2020). An exploratory clinical study evaluating safety and performance of a volume-stable collagen matrix with coronally advanced flap for single gingival recession treatment. *Clinical Oral Investigations*, 24, 3181–3191. <https://doi.org/10.1007/s00784-019-03192-5>
- Sun, W., Lin, H., Xie, H., Chen, B., Zhao, W., Han, Q., Zhao, Y., Xiao, Z., & Dai, J. (2007). Collagen membranes loaded with collagen-binding human PDGF-BB accelerate wound healing in a rabbit dermal ischemic ulcer model. *Growth Factors*, 25, 309–318. <https://doi.org/10.1080/08977190701803885>
- Tattan, M., Sinjab, K., Lee, E., Arnett, M., Oh, T. J., Wang, H. L., Chan, H. L., & Kripfgans, O. D. (2019). Ultrasonography for chairside evaluation of periodontal structures: A pilot study. *Journal of Periodontology*, 91, 890–899. <https://doi.org/10.1002/JPER.19-0342>
- Tavelli, L., Barootchi, S., Cairo, F., Rasperini, G., Shedden, K., & Wang, H. L. (2019). The effect of time on root coverage outcomes: A network meta-analysis. *Journal of Dental Research*, 98, 1195–1203. <https://doi.org/10.1177/0022034519867071>
- Tavelli, L., Barootchi, S., Di Gianfilippo, R., Modarressi, M., Cairo, F., Rasperini, G., & Wang, H. L. (2019). Acellular dermal matrix and coronally advanced flap or tunnel technique in the treatment of multiple adjacent gingival recessions. A 12-year follow-up from a randomized clinical trial. *Journal of Clinical Periodontology*, 46, 937–948. <https://doi.org/10.1111/jcpe.13163>
- Tavelli, L., Barootchi, S., Majzoub, J., Chan, H. L., Giannobile, W. V., Wang, H. L., & Kripfgans, O. D. (2021). Ultrasonographic tissue perfusion analysis at implant and palatal donor sites following soft tissue augmentation: A clinical pilot study. *Journal of Clinical Periodontology*, 48, 602–614. <https://doi.org/10.1111/jcpe.13424>
- Tavelli, L., Barootchi, S., Majzoub, J., Chan, H. L., Stefanini, M., Zucchelli, G., Kripfgans, O. D., Wang, H. L., & Urban, I. A. (2021). Prevalence and risk indicators of midfacial peri-implant soft tissue dehiscence at single site in the esthetic zone: A cross-sectional clinical and ultrasonographic study. *Journal of Periodontology*, 93, 857–866. <https://doi.org/10.1002/JPER.21-0402>
- Tavelli, L., Barootchi, S., Majzoub, J., Siqueira, R., Mendonca, G., & Wang, H. L. (2021). Volumetric changes at implant sites: A systematic appraisal of traditional methods and optical scanning-based digital technologies. *Journal of Clinical Periodontology*, 48, 315–334. <https://doi.org/10.1111/jcpe.13401>
- Tavelli, L., McGuire, M. K., Zucchelli, G., Rasperini, G., Feinberg, S. E., Wang, H. L., & Giannobile, W. V. (2020a). Biologics-based regenerative technologies for periodontal soft tissue engineering. *Journal of Periodontology*, 91, 147–154. <https://doi.org/10.1002/JPER.19-0352>
- Tavelli, L., McGuire, M. K., Zucchelli, G., Rasperini, G., Feinberg, S. E., Wang, H. L., & Giannobile, W. V. (2020b). Extracellular matrix-based scaffolding technologies for periodontal and peri-implant soft tissue regeneration. *Journal of Periodontology*, 91, 17–25. <https://doi.org/10.1002/JPER.19-0351>
- Tavelli, L., Ravida, A., Barootchi, S., Chambrone, L., & Giannobile, W. V. (2021). Recombinant human platelet-derived growth factor: A systematic review of clinical findings in oral regenerative procedures. *JDR Clin Trans Res*, 6, 161–173. <https://doi.org/10.1177/2380084420921353>
- Thoma, D. S., Naenni, N., Benic, G. I., Hammerle, C. H., & Jung, R. E. (2017). Soft tissue volume augmentation at dental implant sites using a volume stable three-dimensional collagen matrix – Histological outcomes of a preclinical study. *Journal of Clinical Periodontology*, 44, 185–194. <https://doi.org/10.1111/jcpe.12635>

- Thoma, D. S., Zeltner, M., Hilbe, M., Hammerle, C. H., Husler, J., & Jung, R. E. (2016). Randomized controlled clinical study evaluating effectiveness and safety of a volume-stable collagen matrix compared to autogenous connective tissue grafts for soft tissue augmentation at implant sites. *Journal of Clinical Periodontology*, 43, 874–885. <https://doi.org/10.1111/jcpe.12588>
- Tian, J., Wei, D., Zhao, Y., Di, P., Jiang, X., & Lin, Y. (2019). Labial soft tissue contour dynamics following immediate implants and immediate provisionalization of single maxillary incisors: A 1-year prospective study. *Clinical Implant Dentistry and Related Research*, 21, 492–502. <https://doi.org/10.1111/cid.12786>
- Tonetti, M. S., Cortellini, P., Pellegrini, G., Nieri, M., Bonaccini, D., Allegri, M., Bouchard, P., Cairo, F., Conforti, G., Fourmousis, I., Graziani, F., Guerrero, A., Halben, J., Malet, J., Rasperini, G., Topoll, H., Wachtel, H., Walkkamm, B., Zabalegui, I., & Zuh, O. (2018). Xenogenic collagen matrix or autologous connective tissue graft as adjunct to coronally advanced flaps for coverage of multiple adjacent gingival recession: Randomized trial assessing non-inferiority in root coverage and superiority in oral health-related quality of life. *Journal of Clinical Periodontology*, 45, 78–88. <https://doi.org/10.1111/jcpe.12834>
- Wang, H. L., Bunyaratavej, P., Labadie, M., Shyr, Y., & MacNeil, R. L. (2001). Comparison of 2 clinical techniques for treatment of gingival recession. *Journal of Periodontology*, 72, 1301–1311. <https://doi.org/10.1902/jop.2001.72.10.1301>
- Xue, F., Zhang, R., Cai, Y., Zhang, Y., Kang, N., & Luan, Q. (2021). Three-dimensional quantitative measurement of buccal augmented tissue with modified coronally advanced tunnel technique and de-epithelialized gingival graft: A prospective case series. *BMC Oral Health*, 21, 157. <https://doi.org/10.1186/s12903-021-01522-2>
- Zucchelli, G., & De Sanctis, M. (2000). Treatment of multiple recession-type defects in patients with esthetic demands. *Journal of Periodontology*, 71, 1506–1514. <https://doi.org/10.1902/jop.2000.71.9.1506>
- Zucchelli, G., Mele, M., Mazzotti, C., Marzadori, M., Montebugnoli, L., & De Sanctis, M. (2009). Coronally advanced flap with and without vertical releasing incisions for the treatment of multiple gingival recessions: A comparative controlled randomized clinical trial. *Journal of Periodontology*, 80, 1083–1094. <https://doi.org/10.1902/jop.2009.090041>
- Zucchelli, G., Mele, M., Stefanini, M., Mazzotti, C., Marzadori, M., Montebugnoli, L., & de Sanctis, M. (2010). Patient morbidity and root coverage outcome after subepithelial connective tissue and de-epithelialized grafts: A comparative randomized-controlled clinical trial. *Journal of Clinical Periodontology*, 37, 728–738. <https://doi.org/10.1111/j.1600-051X.2010.01550.x>
- Zucchelli, G., Tavelli, L., Barootchi, S., Stefanini, M., Rasperini, G., Valles, C., Nart, J., & Wang, H. L. (2019). The influence of tooth location on the outcomes of multiple adjacent gingival recessions treated with coronally advanced flap: A multicenter re-analysis study. *Journal of Periodontology*, 90, 1244–1251. <https://doi.org/10.1002/JPER.18-0732>
- Zucchelli, G., Tavelli, L., McGuire, M. K., Rasperini, G., Feinberg, S. E., Wang, H. L., & Giannobile, W. V. (2020). Autogenous soft tissue grafting for periodontal and peri-implant plastic surgical reconstruction. *Journal of Periodontology*, 91, 9–16. <https://doi.org/10.1002/JPER.19-0350>

## SUPPORTING INFORMATION

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