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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

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Abstract

Aim: To evaluate the long-term outcomes of Acellular Dermal Matrix (ADM) with Coronally Advanced Flap (CAF) or Tunnel technique (TUN) in the treatment of multiple adjacent gingival recessions (MAGRs).

Material and methods: Nineteen of the original 24 patients contributing to a total number of 33 sites for CAF and 34 for TUN were available for the 12 years follow-up examination. Recession depth, mean root coverage (mRC), keratinized tissue width (KTW), gingival thickness (GT) were evaluated and compared with baseline values and 6-months results. Regression analysis was performed to identify factors related to the stability of the gingival margin.

Results: A highly significant drop in mRC was observed for both groups from the 6 months timepoint to the 12 years recall ($p < .001$). While there were no statistically significant differences between the two groups in terms of Clinical Attachment Level (CAL), KTW, GT changes and Root Coverage Esthetic Score at each timepoint ($p > .05$). KTW ≥ 2 mm and GT ≥ 1.2 mm at 6-months were two predictors for stability of the gingival margin ($p = .03$ and $p = .01$, respectively).

Conclusions: A significant relapse of the gingival margin of MAGRs treated with CAF or TUN + ADM was observed after 12 years.

KEYWORDS

acellular dermis, follow-up study, gingival recession, surgical flaps, tooth root

1 | INTRODUCTION

Gingival recession (GR) is the apical shift of the gingival margin with respect to the cementoenamel junction (CEJ) with the concomitant exposure of the root surface to the oral environment (Cortellini & Bissada, 2018). While most of the available literature focuses on the treatment of single GRs (Cairo, Nieri, & Pagliaro, 2014), recessions are most commonly observed as a generalized condition (Tonetti et al., 2018; Zucchelli & Mounssif, 2015; Zucchelli & De Sanctis, 2000). Several authors have suggested that multiple adjacent gingival recessions (MAGRs) should be treated at the same time, to minimize the number of surgeries and patient discomfort (Tonetti et al., 2018; Zucchelli & Mounssif, 2015; Zucchelli & De Sanctis, 2000).

A two-step procedure that involved a free gingival graft followed by a coronally advanced flap (CAF) was an approach that was first proposed for treating MAGRs (Bernimoulin, Luscher, & Muhlemann, 1975). Later on, Zucchelli & De Sanctis introduced a new flap design for MAGRs in the aesthetic zone that avoided vertical incisions and anticipated the rotational movement of

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the surgical papillae during the coronal advancement of the flap (Zucchelli & De Sanctis, 2000). Regardless of the vertical incisions (Skurska et al., 2015; Zucchelli et al., 2009), the CAF was proven to be an effective technique in the treatment of MAGRs, especially when combined with a connective tissue graft (CTG) (Cairo et al., 2016; Zucchelli et al., 2014).

To meet patients' high aesthetic demands, surgical procedures that avoided flap reflection and maintained the integrity of the papillae were proposed (Allen, 1994; Raetzke, 1985). Among these, a supraperiosteal envelope flap that was coronally positioned without opening the papillae ("tunnel", TUN) was proposed by Zabalegui (Zabalegui, Sicilia, Cambra, Gil, & Sanz, 1999) and later on further modified over the years (Aroca et al., 2010, 2013; Zuhr, Fickl, Wachtel, Bolz, & Hurzeler, 2007; Zuhr, Rebele, Schneider, Jung, & Hurzeler, 2014). It has been suggested that improved aesthetic outcomes, greater blood supply, faster healing and reduced patient morbidity are among the main advantages of the TUN (Allen, 1994; Aroca et al., 2013; Santamaria et al., 2017; Zabalegui et al., 1999). This may explain why this technique has slowly gained popularity among clinicians, especially in treating MAGRs.

The autogenous CTG has been the material of choice in root coverage procedures (Cairo et al., 2014; Chambrone & Tatakis, 2015). Nevertheless, several drawbacks have also been associated with harvesting a CTG, such as patient morbidity, prolonged intra- and post-operative bleeding, palatal sensory dysfunction, infection and an increased surgical time (Buff, Burklin, Eickholz, Monting, & Ratka-Kruger, 2009; Griffin, Cheung, Zavras, & Damoulis, 2006; Tavelli, Barootchi, Ravida, Oh, & Wang, 2018).

The acellular dermal matrix (ADM) is an allograft material obtained from the human skin that is chemically processed to remove all epidermal and dermal cells while preserving the extracellular dermal matrix (Bohac, Danisovic, Koller, Dragunova, & Varga, 2018; Scarano, Barros, Iezzi, Piattelli, & Novaes, 2009). Initially introduced for increasing the amount of attached gingiva (Shulman, 1996), nowadays the ADM is routinely used in soft tissue augmentation and for root coverage purposes around teeth and implants (Hutton, Johnson, Barwacz, Allareddy, & Avila-Ortiz, 2018; Ozenci, Ipci, Cakar, & Yilmaz, 2015; Scarano et al., 2009) especially for thickening gingival phenotype and reducing patient morbidity (Henderson et al., 2001; Joly, Carvalho, Silva, Ciotti, & Cury, 2007; Paolantonio et al., 2002). In a randomized clinical trial (RCT), Woodyard et al. showed that the addition of ADM to CAF resulted in a higher recession defect coverage and increased gingival thickness (0.4 vs. 0.3 mm, respectively) compared to CAF alone. Similarly, several authors have demonstrated favourable root coverage outcomes using ADM in combination of CAF or TUN, either for the treatment of isolated or multiple GRs (Barker et al., 2010; Cosgarea, Juncar, Arweiler, Lascu, & Sculean, 2016; Ozenci et al., 2015; Wang et al., 2014). Nevertheless, these studies reported the 6 or 12 months outcomes of ADM patients while its long-term behaviour is still unknown. Therefore, the aim of this study was to compare the long-term root coverage outcomes of CAF versus TUN with ADM in the treatment of MAGRs and to assess the stability of the obtained results over time.

Clinical Relevance

Scientific rationale for the study: To evaluate the long-term outcomes of CAF + ADM versus TUN + ADM in the treatment of multiple adjacent gingival recessions (MAGRs).

Principal findings: A highly significant drop in the mean root coverage was observed in both groups between 6 months and 12 years. CAF and TUN showed similar long-term clinical, aesthetic and patient-related outcomes. Baseline keratinized tissue width (KTW) ≥2 mm and gingival thickness (GT) ≥1.2 mm at 6-months were two predictors for stability of the gingival margin.

Practical implications: An apical shift of the gingival margin should be expected in the long-term when MAGRs are treated with ADM. KTW and GT seem to play a key role in the stability of the gingival margin over time.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study was designed as a follow-up investigation in which the patients that participated in a previous RCT between November 2005 and February 2007 (unpublished data), were invited for re-examination. The protocol, study population and clinical measurements of the original RCT are presented in detail in the Supplementary data (Data S1).

The protocol for the follow-up study was approved by the Western Institutional Review Board (HUM00146261), in accordance with the Helsinki Declaration of 1975, as revised in 2000. Additionally, an informed consent was obtained from all the subjects who participated in the follow-up study.

The present manuscript follows the CONSORT statement for improving the quality of reports of parallel-group RCT (http://www.consort-statement.org/) (Figure 1).

2.2 | Participants

Nineteen patients from the University of Michigan School of Dentistry completed the 12-year follow-up study. They were originally included in the original study if they presented with the following inclusion criteria: (a) Age ≥ 18 years, (b) Systemically healthy non-smokers, (c) Patients willing to provide an informed consent and attend the study, (d) No prior use of antibiotics within 3 months, (e) No known allergies to the materials used in the study, (f) No periodontal plastic surgery at the defect site within 12 months, (g) Full-mouth plaque score and full-mouth bleeding score ≤ 20%, (h) Miller Class I or II (RT1) (Cairo, Nieri, Cincinelli, Mervelt, & Pagliaro, 2011; Miller, 1985) MAGRs localized at the maxillary incisors, canines or premolars and (i) Recession depth of ≥2 mm on at least one of the MAGRs. The presence of one or multiple non-carious cervical lesions (NCCLs) was considered as an exclusion

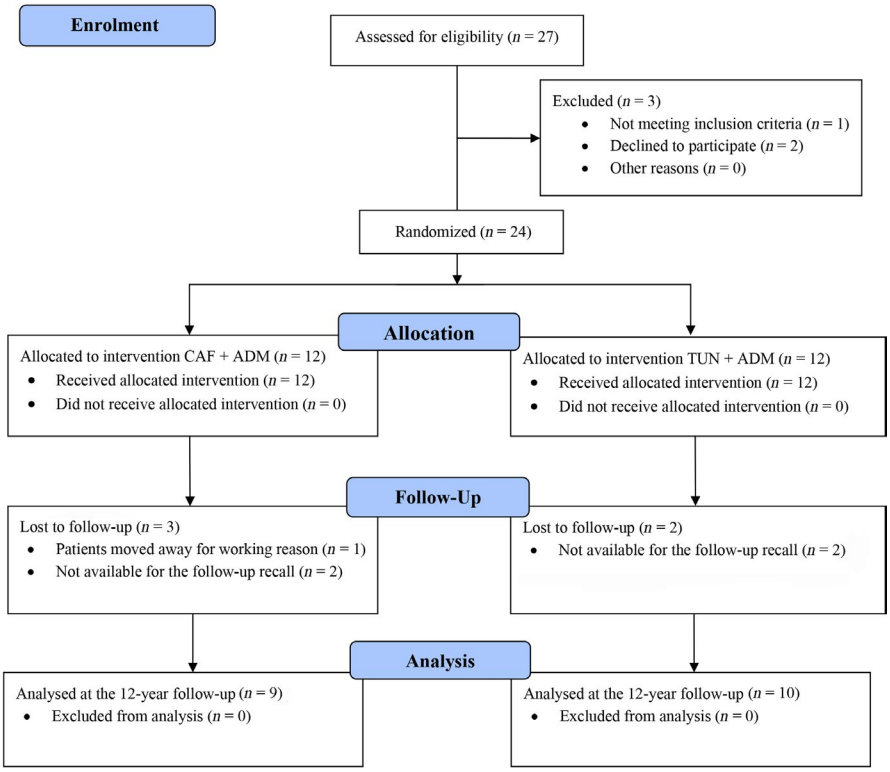


FIGURE 1 CONSORT flow chart of the study

criterion. Each patient contributed with a single experimental area consisting of 2–5 MAGRs.

2.3 | Intervention

All surgical procedures were performed at the University of Michigan, School of Dentistry by the same operator (MM). Each study participant received full-mouth supragingival scaling, polishing and oral hygiene instruction 2 months before the scheduled surgery. In particular, patients were instructed to maintain an optimal toothbrushing technique to correct improper habits related to the aetiology of the GRs. Patients were randomly assigned to the control (CAF) or the test group (TUN) prior to the surgery.

2.3.1 | ADM preparation

The ADM (Alloderm, BioHorizons, AL, USA) was rehydrated in saline for approximately 5 min in each of 2 successive washes. The average thickness of the ADM was approximately 1–1.5 mm, while the length was determined according to the size of the site that would be treated. For the CAF group, the graft was also trimmed interproximally for enhanced flap adaptation, however, this was not performed for the TUN group.

2.3.2 | Intervention – control group (CAF)

After performing local anaesthesia, the surgical procedure began preparation of the exposed root surfaces using curettes, burs and application of 24% EDTA root conditioning agent for two minutes (Barootchi, Tavelli, Ravida, Wang, & Wang, 2018). Intrasulcular incisions with two divergent vertical releasing incisions on the mesial and distal sides were placed extending beyond the mucogingival junction. The incisions were performed without involving the adjacent marginal gingiva or inter-dental papilla, as described by Bernimoulin et al. (1975) and Henderson et al. (2001). A partial thickness flap was elevated beyond the mucogingival junction, keeping the blade parallel to the external mucosal surface in order to eliminate muscle insertions. The flap was considered tension-free when it was possible to reposition 2 mm coronal to the CEJ. The ADM was prepared and trimmed in order to obtain a graft 8 mm in height that extended for all the length of the site. A double-back continuous sling suture (6/0 polyglyconate) was used to secure the ADM to the recipient site (Henderson et al., 2001). The flap was then sutured in order to completely cover the graft with individual sling sutures (6/0 polypropylene). In addition, vertical mattress sutures (6/0 polypropylene) were placed for each papilla and simple interrupted sutures (5/0 chromic gut) were performed for the vertical incisions (Figure 2).

2.3.3 | Intervention – test group (TUN)

In the test group, the tunnel technique adapted from the approach described by Allen (1994) and further modified by Allen and Cummings (2002) was performed. After a similar root preparation as that previously reported for the CAF group, intrasulcular incisions were made around each tooth, making sure to include the palatal and papillary sulci. A pouch was created by performing blunt dissection just past the mucogingival junction (MGJ). Then, sharp

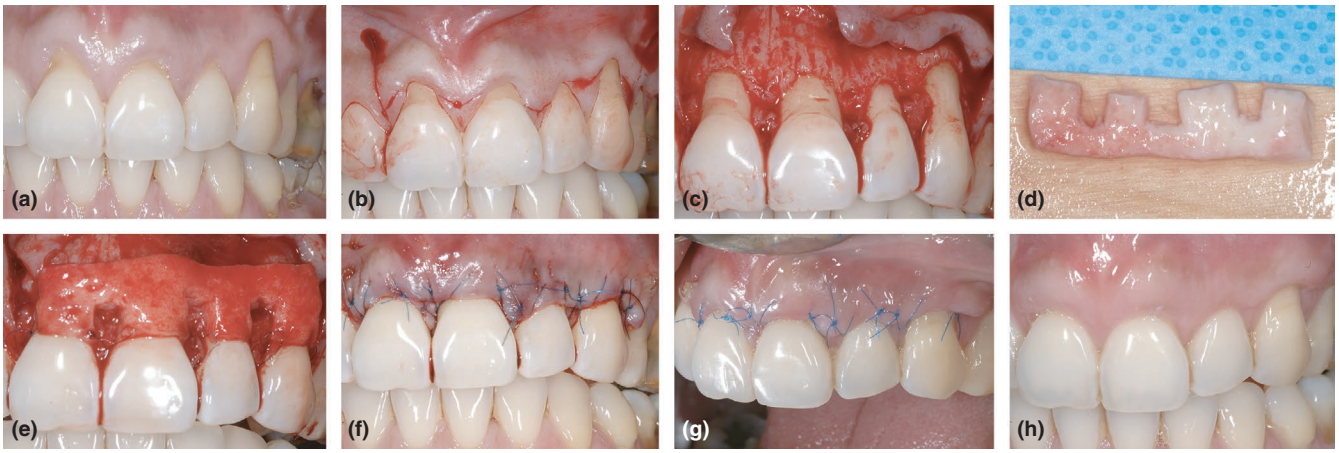


FIGURE 2 MAGRs treated with CAF + ADM. (a) Baseline; (b) Design of the CAF; (c) Flap elevation and papillae de-epithelialized; (d) ADM preparation; (e) ADM adaptation and suturing over the roots; (f) Flap coronally advanced and closed; (g) 2-week post-op; (h) 6-month results

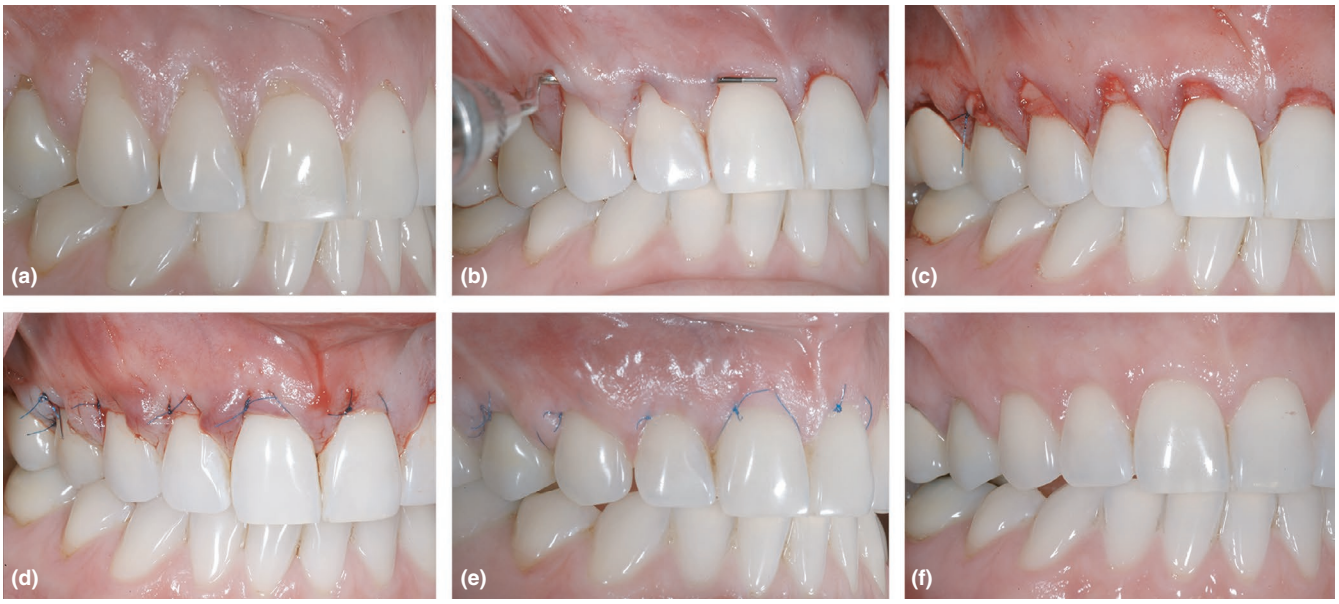


FIGURE 3 MAGRs treated with TUN + ADM. (a) Baseline; (b) Flap elevation; (c) ADM inserted in the tunnel and sutured; (d) TUN coronally advanced and sutured; (e) 2-weeks post-op; (f) 6-month results

supraperiosteal dissection was continued apically for an additional 10–12 mm. The palatal tissue was then elevated approximately 3 mm, and the papillary tissue was completely lifted from the bony crests. The dissection was continued as necessary to passively advance the pouch 2 mm coronal to the CEJs. The length required for the graft to extend to the site's adjacent line angles was measured and used to cut the ADM; a vertical dimension of 8 mm was used. The graft was placed into the pouch to cover the sites to be grafted. A subgingival double-back continuous sling suture (6–0 polypropylene) was used to secure the allograft to the teeth. Next, the graft was covered by the tension-free CAF and sutured with individual sling 6–0 polypropylene sutures (Figure 3).

Post-operative instructions are described in the Supplementary data (Data S2).

2.4 | Clinical measurements

At the 12-year recall, recession depth, pocket depth (PD), clinical attachment level (CAL), keratinized tissue width (KTW) and gingival thickness (GT) were collected (as described in the original protocol, Data S1) at each treated site using a periodontal probe (PCP UNC 15, Hu-Friedy) by an examiner (RDG) which was blinded to the treatments performed. In addition, the gingival phenotype in each treated site (at 12 years) was compared with the contra-lateral and opposing sites using a colour-coded probe (Rasperini, Acunzo, Cannalire, & Farronato, 2015). Aesthetic outcomes were evaluated using the Root Coverage Esthetic Score (Cairo, Rotundo, Miller, & Pini Prato, 2009). Lastly, patients were given a questionnaire including dichotomous questions and the self-evaluation of the stability of the results

over time using a visual analogue scale (VAS) of 100 mm (Cortellini et al., 2009; Tonetti et al., 2004).

2.5 | Outcomes

The primary endpoint of the present follow-up study was to compare the efficacy of TUN and CAF in terms of mean root coverage (mRC) and complete root coverage (CRC), after 12 years. The secondary outcome was to evaluate the changes of mRC, KTW and GT from 6 months to 12 years and from baseline to 12 years. In addition, another secondary endpoint of this investigation was identifying predictors for the stability of the gingival margin in the long-term. Patient-reported outcomes evaluating satisfaction of the treatment, willingness for retreatment (if needed) and the perceived grade of stability of the achieved results over time were collected at the 12 years recall with a questionnaire.

2.6 | Randomization and allocation concealment

Patients were randomly assigned to the control (CAF) or the test group (TUN) prior to the surgery by drawing a piece of paper (with T or C) from one of two identical brown bags presented to the operator's assistant at the time of the surgery (each with six Ts and six Cs); each paper was kept out of its bag once it had been drawn however both bags were simultaneously presented to the assistant. The assigned treatment was then communicated to the operator by the study coordinator right after the local anaesthesia using a sealed envelope. In addition, the patients were kept uninformed and were not aware of the treatment they had been randomly assigned to.

2.7 | Statistical analysis

The collected data from the RCT and from the follow-up appointments were transferred into pre-fabricated spreadsheet and coded by an author (LT). All the analyses were performed by a different author with experience in statistical analyses (SB) who had not taken part in the clinical measurements at recall or the surgical procedures and remained blinded to the original gathered data. Means and standard deviations (*SD*) were calculated for the continuous outcomes (recession depth, PD, CAL, KTW). Next, their changes were computed from baseline (time 0, prior to the surgery) to 6 months and to 12 years. Additionally, changes in all clinical parameters were also assessed from the initial recall appointment (at 6 months) to the final recall (12 years). CRC was calculated as the percentage of sites that achieved a complete coverage at 6 months and expressed as a binary outcome, this was also calculated for sites that maintained their complete coverage at the 12-year recall, and Fisher's exact test was used for the comparison of this independent outcome between each group (CAF vs. TUN) at every timepoint. Linear mixed-effects regression models were then conducted for evaluating the changes in clinical parameters, and to account for the fact that each subject may have contributed to more than one treated site (as the unit of analysis). Consequently, the effect of different variables (i.e. different baseline characteristics; keratinized tissue width at baseline and at 6 months, gingival thickness at baseline and at 6 months) was also assessed on the outcomes (recession depth and mRC changes from 6 months to 12 years). Particularly, the effect of keratinized tissue width ≥ 2 mm (Pini Prato, Magnani, & Chambrone, 2018) and gingival thickness ≥ 1.2 mm (Huang, Neiva, & Wang, 2005) on the gingival margin stability overtime was assessed. Confidence intervals (CI) were produced and a p value threshold of .05 was set for statistical significance. All analyses were performed in Rstudio (Rstudio Version 1.1.383, Rstudio, Inc), with the lme4 (Bates, Mächler, Bolker, & Walker, 2015) and the dplyr packages (Wickham, Francois, Henry, & Müller, 2017).

3 | RESULTS

Twenty-four patients (15 females and 9 males, with a mean age of 52.1 ± 9.2 years) completed the 6-months study. For the 12-year recall examination, 19 patients (contributing to a total number of 33 sites for CAF, and 34 for TUN) agreed to take part in the long-term evaluation, corresponding to a response rate of 79% (Figure 1). All enrolled subjects had received ≥ 2 periodontal supportive therapy throughout the 12 years, 16 receiving regular maintenance at the University of Michigan School of Dentistry, and three maintained at private practices. Details of patient characteristics at baseline and at the 12-year recall for CAF and TUN groups are presented in the Supplementary data (Data S3).

3.1 | Clinical outcomes

No significant differences were observed between the CAF and TUN groups for recession depth change, keratinized tissue width gain and gingival thickness change at 6 months and 12 years ($p > .05$) (Table 1). At the 12-year recall, the mRC dropped from 88.14 ± 16.91% to 65.77 ± 21.69% in the CAF-treated sites, and from 89.13 ± 15.19% to 63.64 ± 23.4% in the TUN group, without showing significance differences between the two groups (0.91 [−6.9, 8.89], $p = .8$). CRC decreased from 52.6% to 27.3% in CAF group and from 51.2% to 29.4% in TUN group, without showing significance differences between the two groups ($p = .32$) (Figure 4). Similarly, comparable clinical outcomes in terms of recession reduction, mRC and CRC were observed between Miller class I and II recession defects in the CAF and TUN groups at 6 month and the 12-year recall ($p > .05$).

The average gain in keratinized tissue width (compared to baseline) was 0.29 ± 1.58 mm, and 0.07 ± 1.96 mm for CAF and TUN, respectively ($p > .05$), and the changes in keratinized tissue width (compared to 6 months) was 0.5 ± 1.45 mm, and 0.6 ± 1.72 mm. Although a significant decrease in gingival thickness was observed from 6 months to 12 years ($p = .02$ for CAF and $p = .01$ for TUN), tissue thickness was found to be significantly

TABLE 1 Clinical parameters and their measurements at baseline, 6 months and 12 years, with the corresponding *p* values and confidence intervals when comparing the two treatment groups for each clinical parameter of interest at every time point

Time point	Parameter	CAF + ADM (mean ± *SD*) *N* = 33	TUN + ADM (mean ± *SD*) *N* = 34	EC [95% CI], *p* value
Baseline	REC (mm)	2.56 ± 1.4	2.29 ± 0.96	−0.26 [−0.85, 0.31], .36
	PD (mm)	1.11 ± 0.47	0.93 ± 0.41	−0.18 [−0.39, 0.03], .11
	CAL (mm)	3.67 ± 1.6	3.22 ± 1.02	−0.45 [−1.11, 0.21], .17
	KTW (mm)	3.09 ± 1.27	2.54 ± 1.16	−0.54 [−1.14, 0.05], .12
	GT (mm)	1.06 ± 0.45	1.15 ± 0.34	0.08 [−0.11, 0.28], .39
6 months	REC (mm)	0.41 ± 0.58	0.31 ± 0.57	−0.08 [−0.33, 0.17], .51
	mRC (%)	88.14 ± 16.91	89.13 ± 15.19	0.99 [−6.9, 8.89], .8
	CRC (%)	52.6	51.2	0.65
	PD (mm)	1.38 ± 0.46	1.29 ± 0.49	−0.29 [−0.66, 0.08], .12
	CAL (mm)	1.83 ± 0.64	1.59 ± 0.67	−0.39 [−0.86, 0.06], .16
	KTW (mm)	2.89 ± 1.12	2.01 ± 0.69	−0.87 [−1.79, 0.05], .18
	GT (mm)	1.46 ± 0.69	1.51 ± 0.61	0.04 [−0.27, 0.36], .77
12 years	REC (mm)	0.84 ± 0.57	0.91 ± 0.55	0.06 [−0.21, 0.34], .64
	mRC (%)	65.77 ± 21.69	63.64 ± 23.4	0.91 [−6.9, 8.89], .8
	CRC (%)	27.3	29.4	0.32
	PD (mm)	1.59 ± 0.54	1.42 ± 0.5	−0.16 [−0.42, 0.09], .19
	CAL (mm)	2.59 ± 0.87	2.33 ± 0.92	−0.25 [−0.69, 0.18], .24
	KTW (mm)	3.39 ± 0.89	2.62 ± 1.57	−0.76 [−1.62, 0.11], .31
	GT (mm)	1.28 ± 0.53	1.34 ± 0.47	0.06 [−0.18, 0.31], .059

Abbreviations: CAL, Clinical attachment level; CI, Confidence intervals; CRC (%), complete root coverage, comparison performed with Fisher Exact Test for independent group analysis; EC, Estimated coefficient from the regression model; GT, Gingival thickness; KTW, keratinized tissue width; mRC (%), mean root coverage percentage; *N*, number of treated sites; PD, Probing depth; REC, recession depth.

higher at the 12 years recall compared to baseline ($p = .02$ for CAF and $p = .03$ for TUN) (Table 2). When comparing gingival phenotype of each treated site with its contra-lateral and opposing sites, the CAF group presented a thickening of gingival phenotype at 8 treated sites (24.24%) while TUN group is 12 (35.29%) ($p > .05$). The aesthetic evaluation revealed that the CAF group exhibited an average 7.01 ± 1.43 RES score, while TUN achieved 6.93 ± 1.27 ($p > .05$). Table 1 depicts shows the collected parameters at baseline, 6 months and 12 years, and Table 2 reports their respective changes of over time.

3.2 | Patient-reported outcomes at the 12 years recall

The patient-reported outcomes demonstrated a high satisfaction of the overall treatment (8.67 ± 1.29 VAS scale for CAF and 8.31 ± 1.41 for TUN, $p > .05$) and a 100% willingness for re-treatment (if needed) in both groups. Patients were requested to indicate the perceived grade of stability of the root coverage procedures over time using a VAS scale. The subjects that had inquired about the treatment primarily for aesthetic purposes were the most accurate in detecting the level of their post-treatment stability over time, compared to ones who underwent the root coverage procedure for non-aesthetic demands (dental hypersensitivity, non-carious cervical lesion and fear of losing the teeth) ($p = .013$, $p = .022$, $p = .019$, respectively).

3.3 | Regression analyses

Regression analyses demonstrated that keratinized tissue width ≥ 2 mm at baseline was a significant predictor for both CAF and TUN-treated sites when correlated to the changes from 6 months to 12 years (EC: 5.32 (95% CI [0.9, 9.74], $p = .01$) (Data S4). Additionally, the presence of gingival thickness ≥ 1.2 mm at 6-months, was found to be a predictor for the stability of the gingival margin throughout the 12 years (EC: 6.62 95% CI [1.26, 11.97], $p = .01$) (Figure 5). In contrast, factors such as gender, patient age, tooth type and GT at baseline were not found to associate with the changes in the gingival margin throughout the follow-up period ($p > .05$).

4 | DISCUSSION

Several combinations of graft materials and surgical techniques have been investigated for treating MAGRs (Cairo et al., 2016; Pietruska,

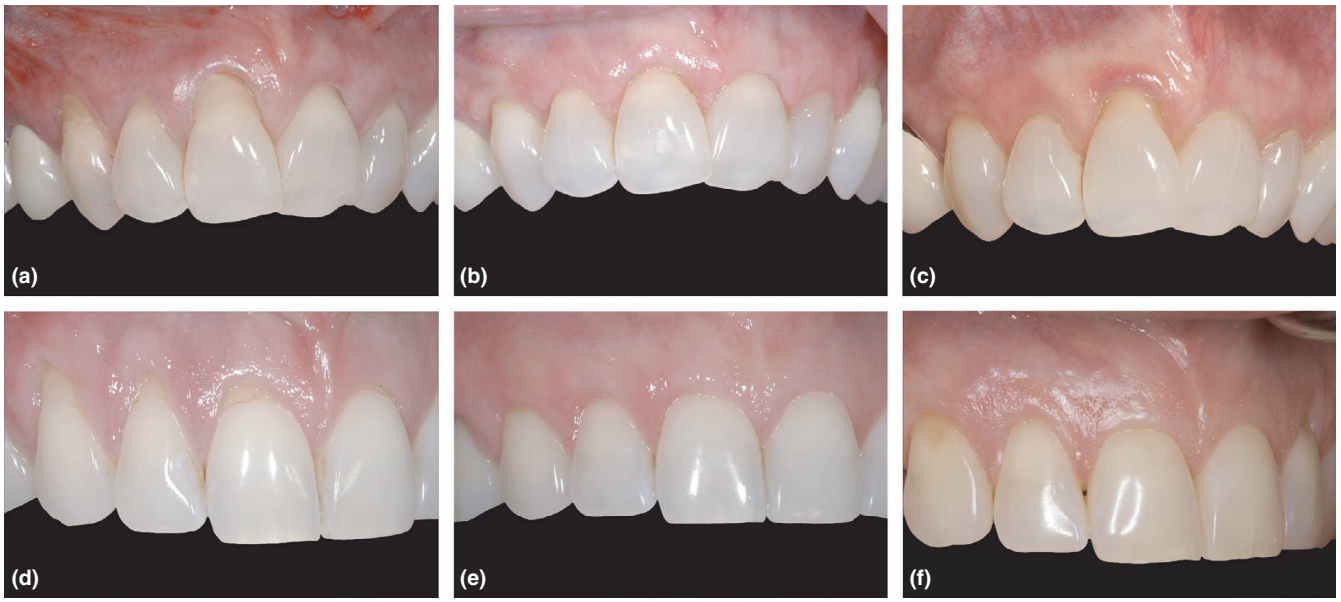


FIGURE 4 (a-c) Multiple adjacent gingival recessions (MAGRs) treated with coronally advanced flap + acellular dermal matrix; (a) Baseline MAGRs; (b) 6-month outcomes; (c) 12 years outcomes. (d-f) Multiple adjacent gingival recessions (MAGRs) treated with tunnel technique + acellular dermal matrix; (d) Baseline MAGRs (e) 6-months outcomes; (f) 12 years outcomes

TABLE 2 Changes in the clinical parameters between baseline and 12 years

Parameter	Baseline—6 months [mean (*SD*)]	*p* value	6 months—12 years [mean (*SD*)]	*p* value	Baseline—12 years [mean (*SD*)]	*p* value
mRC (%)						
CAF	–	–	−22.80 (27.18)	<.001*	–	–
TUN	–	–	−25.65 (26.61)	<.001*	–	–
KTW (mm)						
CAF	−0.2 (1.72)	.06	0.5 (1.45)	.01*	0.29 (1.58)	.13
TUN	−0.52 (1.36)	<.001*	0.6 (1.72)	.01*	0.07 (1.96)	.41
GT (mm)						
CAF	0.4 (0.84)	.001*	−0.18 (0.89)	.02*	0.21 (0.71)	.02*
TUN	0.36 (0.76)	.001*	−0.16 (0.85)	.01*	0.2 (0.57)	.03*

Note: Note that a negative value demonstrates reduction from the initial timepoint to the secondary timepoint.
Abbreviations: GT, Gingival thickness; KTW, keratinized tissue width; mRC (%): mean root coverage percentage.
*Statistically significant.

Skurska, Podlewski, Milewski, & Pietruski, 2019; Romanos, Abou-Arraj, Cruz, & Majzoub, 2017; Vincent-Bugnas, Borie, & Charbit, 2018). Our study reports on the long-term outcomes of the two most investigated approaches for treating MAGRs (CAF and TUN) (Cairo, 2017; Pietruska et al., 2019; Santamaria et al., 2017) which, to the best of our knowledge, have not been previously assessed.

Regardless of the graft material used, the advantages of CAF include increased access that facilitates periosteal dissection and the stabilization of the graft, along with the possibility of performing a split-full-split flap preparation (Santamaria et al., 2017; Tavelli, Barootchi, Nguyen, et al., 2018). Nevertheless, due to preservation of the integrity of the papillae, it has been reported that TUN has faster healing, provides enhanced blood supply, graft nutrition and superior aesthetic outcomes than CAF (Aroca et al., 2013; Zabalegui et al., 1999). While conflicting results are seen in the literature when comparing CAF to TUN in combination with autogenous connective tissue graft (Azaripour et al., 2016; Santamaria et al., 2017; Zuhr et al., 2014), a recent meta-analysis from our group demonstrated that CAF and TUN have similar clinical and aesthetic outcomes (Tavelli, Barootchi, Nguyen, et al., 2018). In line with this conclusion, the present study demonstrated that CAF and TUN are equally effective in treating MAGRs in the short- and long-term. Therefore, it may be reasonable to assume that other parameters (and not the surgical technique), such as the utilized graft material, the post-surgical keratinized tissue width, gingival thickness and patient maintenance, may have affected the long-term results and the recurrences of MAGRs.

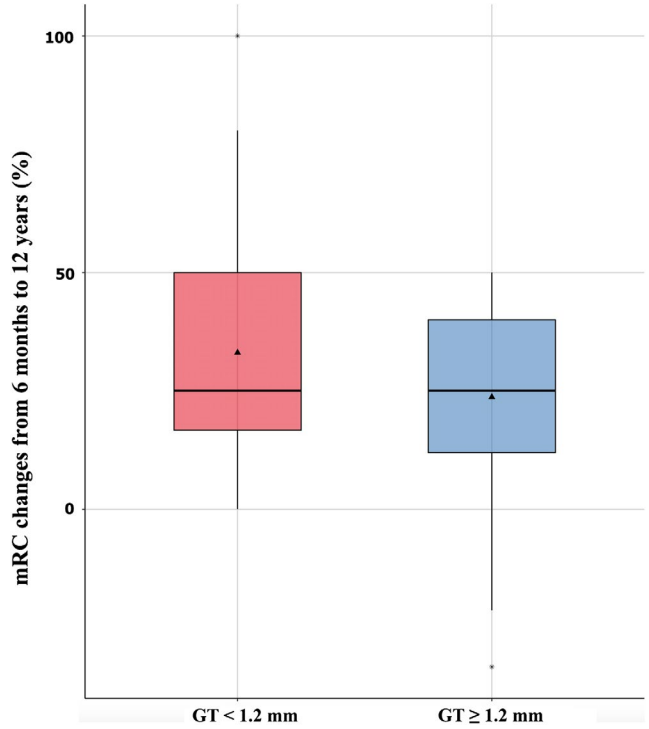


FIGURE 5 Box plot visualizing the influence of gingival thickness at 6 months (<1.2 mm vs. ≥1.2 mm) on the changes in mean root coverage from 6 months to the 12-year recall

It can be further speculated that reflection of the interproximal papillae, does not play a decisive role when treating several MAGRs, as the vascularization of the gingival margin largely depends on supraperiosteal vessels of the flap and not on the papillae. Therefore, the experience of the operator seems to be the main determinant in dictating which approach should be performed in treating MAGRs.

The long-term results of root coverage procedures have progressively gained interest among clinicians and practitioners (Nickles, Ratka-Kruger, Neukranz, Raetzke, & Eickholz, 2010; Pini Prato, Magnani, et al., 2018; Rasperini et al., 2018). Pini-Prato et al. reported the 20-year outcomes of CAF alone for the treatment of localized GRs (at a private practice), observing that the mRC decreased from 68.59% (at 1 year) to 56.11% (at 20 years) and the stability of the gingival margin was maintained in 56% of the treated sites (Pini Prato, Magnani, et al., 2018). Similarly, the same authors also reported on the 20-year outcomes of patients treated with CAF + CTG for isolated GRs. They found that the addition of a CTG seemed to provide benefits for maintaining the early obtained results, as minimal changes in the mRC were noted over the 20 years' timeframe (from 74.23% in the first year to 67.69% at the 20-year recall) (Pini Prato, Franceschi, Cortellini, & Chambrone, 2018). The 12-year result of the present study showed a drop in mRC from 88.14% to 65.77% in the CAF group and from 89.13% to 63.64% in the TUN group, respectively. The reason for the greater GRs reoccurrence in our study can be open to speculation. It may be possible that the different nature of the GRs [multiple defects in our study vs. localized in the study of Pini Prato et al. (Pini Prato, Franceschi, et al., 2018)] and the different clinical settings (University vs. private practice) could have contributed to this observed higher drop in our patients. A similar trend towards GRs recurrence following root coverage procedures has been reported in the literature (Moslemi, Mousavi Jazi, Haghighati, Morovati, & Jamali, 2011; Nickles et al., 2010; Pini Prato, Magnani, et al., 2018; Pini Prato et al., 2011). Nevertheless, it should be considered that sites with greater initial recession depth may be more prone to a relapse of the gingival margin over time, which might explain the relative higher drop in the mean root coverage found by some authors (Leknes et al., 2005; Nickles et al., 2010).

Large evidence is available in the literature when evaluating the efficacy of ADM in root coverage procedures in the short-term (Ayub et al., 2012; Ozenci et al., 2015; Wang et al., 2014), suggesting that the addition of ADM improves the outcomes of flap alone (Ahmedbeyli, Ipci, Cakar, Kuru, & Yilmaz, 2014; de Queiroz Cortes, Sallum, Casati, Nociti, & Sallum, 2006; Woodyard et al., 2004). Nevertheless, contradictory results are reported when ADM is compared to CTG (Barros, Macedo, Queiroz, & Novaes, 2015; Harris, 2004; Moslemi et al., 2011; de Souza et al., 2008). A recent systematic review by Chambrone et al. concluded that ADM as a graft substitute provides the most similar outcomes to the gold standard CTG (Chambrone et al., 2018). However, when evaluated in the long-term, clinical studies demonstrated a significant worsening in the root coverage outcomes obtained with ADM over time (Harris, 2004; Moslemi et al., 2011). Similar to our results, Harris reported a decrease in mRC from 93.4% at 3 months to 65.8% at 4 years (Harris, 2004). The authors concluded that while ADM was equally effective to CTG in treating single and multiple recession defects in the short-term, its outcomes present with a substantial worsening with time (Harris, 2004). The greater keratinized tissue width increase in the CTG- treated sites compared to ADM (Harris, 2004) may have affected the long-term outcomes, as the positive role of keratinized tissue width on the stability of the gingival margin has been proven by other studies (Pini Prato, Franceschi, et al., 2018; Pini Prato, Magnani, et al., 2018). In line with other previous studies (Harris, 2004; Moslemi et al., 2011), we did not observe a significant change in the KTW in either groups at 6 months or at the 12-year recall, suggesting that ADM may not have the capability of inducing keratinization of the overlying epithelium, which seems a prerogative of the CTG (Sculean, Gruber, & Bosshardt, 2014; Yu, Tseng, & Wang, 2018). It has been demonstrated that having keratinized tissue width ≥ 2 mm at the baseline is a positive predictor for the stability of the gingival margin over time (Pini Prato, Franceschi, et al., 2018; Pini Prato, Magnani, et al., 2018). Our regression analysis confirmed that keratinized tissue width has a positive effect on the long-term maintenance of root coverage outcomes. Having a wide band of keratinized tissue facilitates patients' own long-term maintenance and may reduce the risk of soft tissue relapse (Stefanini, Zucchelli, Marzadori, & Sanctis, 2018; Zucchelli et al., 2014). In addition, our results showed that gingival thickness ≥ 1.2 mm at the 6-month follow-up was a positive predictor for the stability of the gingival margin throughout the 12 years. The importance of gingival thickness on root coverage outcomes has been highlighted by several studies (Baldi et al., 1999; Cairo et al.,

2016; Huang et al., 2005; Rebele, Zuhr, Schneider, Jung, & Hurzeler, 2014). However, to the best of our knowledge, this is the first time that the obtained gingival thickness was demonstrated to have a positive effect on preventing GR reoccurrence. Several position papers have concluded that the risk of developing GRs is increased in sites with a thin gingival biotype (Cortellini & Bissada, 2018; Kim & Neiva, 2015; Scheyer et al., 2015). A recent study demonstrated a negative linear relationship between gingival thickness and gingival recession in young adults (Maroso, Gaio, Rosing, & Fernandes, 2015). It may be reasonable to assume that a thicker marginal soft tissue can also better tolerate traumatic toothbrushing in patients who may not be able to correct their brushing technique. The increase in GT is one of the main advantages that has been attributed to ADM compared to flap alone (Ahmedbeyli et al., 2014; de Queiroz Cortes et al., 2006). Because of its method of processing with the removal of the cellular component while preserving the extracellular matrix, ADM serves as a scaffold that promotes cellular migration and revascularization from the host tissue (Bohac et al., 2018). This leads to an increased gingival thickness that according to our findings, when ≥1.2 mm may be less prone to the apical shift of the gingival margin in the long-term. Among the factors affecting the long-term stability of the gingival margin, it has also been suggested that a stringent maintenance protocol where patient hygiene procedures are checked and re-instructed at each appointment is critical for preventing the resumption of traumatic toothbrushing and the recurrence of gingival recessions (McGuire, Scheyer, & Snyder, 2014; Pini Prato et al., 2011; Zucchelli et al., 2018). Indeed, in a 5-year RCT, Moslemi et al. found that returning to horizontal toothbrushing habits was the only parameter significantly related to the gingival margin relapse (OR = 11) (Moslemi et al., 2011).

Among the limitations of the present study, it has to be mentioned that the number of patients that were lost in the follow-up recall (5 out of 24) may have affected the results. The presence of different examiners at the baseline-6 months and the 12 years recall may introduce a limitation in the study. Only maxillary premolars, canines and incisors were included in the present study and therefore the short- and long-term root coverage outcomes may not be valid when applied to posterior or mandibular teeth. In addition, the original protocol involved the trimming of the ADM in the interproximal area for better adaptation to the recipient site only for the CAF group. It could be speculated that this may have had an influence on the short- and long-term outcomes. However, it has to be mentioned that the height and width of the ADM on the root surfaces of the treated sites was standardized within the two groups. Lastly, although no significant differences were found between the two groups, the method of randomization performed in the original protocol is considered to have a high risk of bias.

5 | CONCLUSIONS

The present investigation demonstrated a significant relapse of the gingival margin over time when MAGRs were treated with ADM, regardless of the surgical technique performed. Keratinized tissue width at baseline and gingival thickness at 6 months were found to be positive predictors for the long-term stability of the gingival margin.

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CONFLICT OF INTEREST

Dr. Giulio Rasperini did not participate in the data collection and data analysis and does declare a financial interest with the biotype probe produced by Hu-Friedy. Dr. Hom-Lay Wang received honorarium for speaking engagements with BioHorizons. No other author declares any conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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