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HUMAN RANDOMIZED CONTROLLED TRIAL

Acellular dermal matrix for root coverage procedures: 9-year assessment of treated isolated gingival recessions and their adjacent untreated sites

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Abstract

Background: The long-term outcomes of acellular dermal matrix (ADM) for the treatment of isolated gingival recessions has not yet been evaluated. Thus, the aim of this study was to observe the root coverage outcomes of coronally advanced flap with ADM over time, and compare them with their adjacent untreated sites.

Methods: Twelve patients (from 20) were available at the 9-year recall. Clinical parameters (recession depth, mean root coverage [mRC], keratinized tissue width [KTW], and gingival thickness) were evaluated and compared with the 1-year results, and the ADM-adjacent untreated sites (on mesial and distal) via mixed-modeling regression analyses.

Results: From 1 to 9 years, the ADM-treated isolated recessions showed a relapse from 77% to 62% mRC (P <0.05). A similar pattern toward apical shift of the gingival margin was noticed for the ADM-adjacent untreated sites without baseline recession. However, ADM-adjacent untreated sites which had presented with recession at baseline but were not treated showed a significantly more apical shift of the gingival margin (almost two-fold). A significant increase in KTW was noted for all sites. Baseline KTW ≥2 mm was a significant predictor for the stability of the gingival margin at the ADM-treated, and the ADM-adjacent sites with baseline recession.

Conclusions: ADM-treated sites displayed recession relapse from 1 to 9 years. The untreated adjacent sites with a recession at baseline, showed a higher apical displacement of the gingival margin compared with the ADM-treated sites, and ADM-adjacent sites without a recession at baseline.

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

1 | INTRODUCTION

The long-lasting surgical outcomes obtained following a periodontal procedure has increasingly become a topic of interest among clinicians, patients, and across the scientific community.[1–4] In a recent study, Cortellini et al. demonstrated that the superiority of periodontal regeneration over traditional access flap surgery is

maintained over 20 years.[1] While a clear definition for "long-term" concerning root coverage procedures is not yet defined in the literature, a systematic review evaluating the progression of untreated gingival recessions (GRs) defined long-term studies as those with report outcomes at ≥24 months,[5] and another recent review defined long-term studies as those with a follow-up reaching at least 5 years.[6]

Clinical studies have also reported the outcomes of root coverage procedures at 3 and 5 years, referring to their period of observation as "long-term" as well.[7,8] Recently published follow-up studies of randomized clinical trials however, have also evaluated the behavior of GRs after a minimum follow-up of 10 years.[2–4,9,10] This raises the question whether studies with a shorter follow-up should still be considered in the long-term range.

The most investigated surgical technique for a root coverage procedure is the coronally advanced flap (CAF), whether with or without a connective tissue graft (CTG).[9,11–13] Therefore, it does not come as a surprise that many long-term follow-up studies have reported the outcomes of CAF and CAF + CTG.[2–4] However, in this era in which several CTG alternatives such as the acellular dermal matrix (ADM) and the collagen matrix, have also been introduced for minimizing patient discomfort and reducing the risk of complications at the donor site,[14–16] limited data are available regarding the long-term behavior of such graft substitutes.[17]

A recent study showed a significant relapse in the levels of the gingival margin over a period of 12 years for multiple GRs treated with ADM.[10] These results were in line with the drop in mean root coverage (mRC) shown by other authors when CAF alone, without a graft material, had been performed.[3,4] On the contrary, CTG-treated sites have displayed less susceptibility toward relapse of the gingival margin over time.[4,9,2] Additionally, when evaluating multiple adjacent GRs, it was suggested that not only do they pose more challenges in their treatment compared with single recessions,[18,13] but they are also more prone to recession relapse over time, as an entire quadrant of GRs may likely be due to a traumatic brushing habit that may be reassumed over time.[19,20] Therefore, whether treated GRs with CAF + ADM maintain their obtained results over a long period of time remains unknown. Moreover, while the progression/development of GRs has been documented overtime,[5,21,22] and even compared with contralateral sites receiving a free gingival graft (FGG),[23–25] no study has yet investigated the long-term behavior of the gingival margin of untreated teeth adjacent to those that received a root coverage procedure with ADM.

With this premise, the aim of the present article was to evaluate the long-term clinical and patient-related outcomes of GRs treated with CAF + ADM compared with their adjacent untreated sites and to investigate any possible factors that may have impacted the stability of the gingival margin.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study was designed as a follow-up investigation in which patients from the Michigan Center that participated in a previous multicenter randomized clinical trial (RCT) conducted from November 2009 to December 2010,[26] were invited for re-examination. Details of the study protocol, inclusion and exclusion criteria, data collection, and surgical intervention have been thoroughly described in the original article[26] (ClinicalTrials.gov Identifier NCT00881959). Briefly, patients presenting with a Miller Class I or II[27] GR defect ≥2 mm, located on the facial aspect of a maxillary incisor, canine, or premolar were recruited and randomly assigned to either receive CAF + freeze-dried acellular dermal matrix (FDADM)[*] or CAF + solvent-dehydrated acellular dermal matrix (SDADM).[†]

Participants were aged ≥18 years, able to understand and comply with all the instructions, and had to maintain good oral hygiene. Previous surgeries in the study area within 12 months, antibiotic use exceeding 2 weeks duration within the past 3 months, allergy to any of the study materials, and tobacco use within the previous year were among the exclusion criteria. The protocol of the follow-up study was approved by the Western Institutional Review Board (HUM00146261) and is in full accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consents were obtained from all subjects who participated in this study.

2.2 | Intervention

The patients were randomized into either of the two ADM groups before the surgery as the rehydration process for both ADM materials had to be initiated before the surgical procedure. The patients were not aware of which treatment they had been assigned to or had received. Each study participant received full-mouth supragingival scaling, polishing, and oral hygiene instructions 2 months before the scheduled surgery, and patients were instructed to maintain an optimal toothbrushing technique to correct wrong brushing habits related to the etiology of the GR.

[*] Alloderm, BioHorizons, Birmingham, AL.
[†] Puros Dermis, Zimmer Dental, Carlsbad, CA.

All surgical procedures that were conducted at the Michigan center were performed at the School of Dentistry, University of Michigan, Ann Arbor, by two experienced operators (HLW and RE) following a previously described protocol and strict calibration sessions.[28] Briefly, two diverging vertical releasing incisions were performed at the mesial and distal line angles of the tooth with the recession, starting at a distance equal to the recession depth (RECd) plus 1 mm from the adjacent papilla tip. A full-thickness mucoperiosteal flap was then elevated beyond the mucogingival junction. Adjacent gingival papillae were de-epithelialized using a scalpel blade. The exposed root was planed with rotary instruments, and 24% EDTA gel[29] was applied for 2 minutes. Periosteal scoring was performed for obtaining a tension-free flap. The rehydrated ADM (FDADM/SDADM) was then trimmed to cover the exposed root 3 mm beyond the lateral and apical root surfaces. The ADM graft was sutured at the level of the cemento-enamel junction (CEJ) using a single 5-0 fast-absorbing polyglycolic acid sling suture. The overlying flap was then advanced to a level 1- to 2-mm coronal to the CEJ using the sling and tag suture technique as previously described.[28,30] Postoperative instructions were provided for all subjects both verbally and in the written form. Postoperative medications included 600 mg ibuprofen over 6 to 8 hours, as needed, and 500 mg amoxicillin three times daily for 10 days, starting 1 hour before the surgery. After suture removal at 2 weeks, patients were instructed to resume an atraumatic brushing technique using a soft-bristle toothbrush. A session of clinical assessment, professional cleaning with oral hygiene instructions, was performed at 1, 3, 6, and 12 months.

2.3 | Study outcomes

The primary outcomes of the current follow-up study were to: 1) assess the long-term root coverage outcomes of isolated GRs treated with ADM, through comparing the clinical parameters at the 1-year follow-up to those obtained at the 9-year recall (changes in Recession, mRC, keratinized tissue width [KTW], gingival thickness [GT]); and 2) compare the ADM-treated sites, to their adjacent untreated sites (mesial and distal to the treated tooth) in terms of changes in the levels of the gingival margin from the 1-year follow-up to the 9-year recall, to observe the absence or progression of recession at the untreated sites.

Additionally, we explored the presence of possible correlations between any of the collected variables and the stability of the levels of the gingival margin over time and assessed the gathered patient-reported outcome measures.

2.4 | Clinical measurements

RECd, probing depth (PD), CAL, KTW, and GT were collected as described in the original protocol at each treated site using a periodontal probe[‡] by a calibrated examiner (RDG) who was masked to the treatments performed. The calibration process was conducted with the senior authors who took part in the original RCT, before the scheduling of patients. Additionally, the original customized acrylic resin stents used in the initial study were used for obtaining the measurements at the 9-year recall. The gingival phenotype at each treated site was also compared with the contralateral and opposing sites using a color-coded probe,[§31–33] and patients were asked to fill out a questionnaire which included dichotomous questions and a self-evaluation form regarding the stability of their obtained results using a visual analogue scale (VAS) of 100 mm.[34,35]

2.5 | Data management and statistical analysis

The data from the original study at the 1-year follow-up, and the previous intermediate timepoints, as well as the newly gathered clinical measures at the 9-year recall and their corresponding baseline records were entered into a pre-fabricated spread sheet and coded by an individual author (LT). The ADM-treated sites regardless of the type of ADM preparation (FDADM/SDADM) were merged under the same treatment group of ADM.[26]

The analyses were performed by a separate investigator with experience in biostatistics (SB) who had not participated in data collection or any of the measurements at the recall appointments and remained masked to the original raw data. Descriptive statistics were used to present the obtained data as means and standard deviations for continuous variables (RECd, RECw, PD, CAL, KTW, GT). Complete root coverage was expressed as a percentage of sites that achieved a complete root coverage at 1 year and those that maintained their complete coverage at the 9-year timepoint. To assess statistically significant changes strictly in the ADM-treated teeth for RECd, KTW, GT, and mRC, paired *t*-tests were used.

To evaluate and compare the changes in the ADM-treated sites relative to their untreated adjacent sites (mesial and distal) from the 1-year recall to the 9-year timepoint, we used mixed-modeling regression analyses. The models accounted for the fact that a single patient

[‡] PCP-UNC 15, Hu-Friedy, Chicago, IL.
[§] Colorvue Biotype probe, Hu-Friedy, Chicago, IL.

contributed to 3 sites (1 ADM-treated, and 2 untreated adjacent mesial and distal sites). The following mathematical formula represents the model where Rec_{itj} is the RECd (representing the level of the gingival margin in millimeters) for tooth j in subject i at time t, CR_{ij} is the indicator that tooth j in subject i is untreated with a recession at baseline, CN_{ij} is the indicator that tooth j in subject i is untreated with no recession at baseline, and AL_{ij} as the indicator that tooth j in subject i had been treated using FDADM (to control for any potential influence of the type of ADM):

$$Rec_{i1j} = \beta_0 + \beta_1 Rec_{i0j} + \beta_2 CR_{ij} + \beta_3 CN_{ij} + \beta_4 AL_{ij} + \theta_i + \varepsilon_{ij}$$

The random effect θ_i represents unique subject effects and the error term $\in_{ij}$ represents unexplained variation. Possible correlations between the 1- to 9-year changes in the levels of the gingival margin and the gathered patient-reported responses were also explored.

Line charts were produced to display the changes in the RECd and KTW over time with error bars representing SD. Confidence intervals (CI) were produced and a P value threshold of 0.05 was set for statistical significance. The analyses were performed using the lme4,[36] dplyr,[37] and stats[38] packages in Rstudio.[**]

3 | RESULTS

From the original 20 patients that completed the study at 1 year (11 females and nine males, with a mean age of 42.5 ± 12 years), 12 (seven females, five males) were available for the 9-year recall, demonstrating a response rate of 60% (seven in the FDADM-, and five in the SDADM-originally treated groups). Six of the patients received periodic professional cleaning or supportive periodontal therapy, at least twice a year at the University of Michigan School of Dentistry, and six were maintained at private practices.

3.1 | Clinical outcomes of acellular dermal matrix

Table 1 displays the root coverage outcomes of the ADM-treated teeth from baseline, to the 1-year, and the 9-year recall. From the 1-year timepoint to the 9-year recall, on average, the ADM-treated sites presented with an increase RECd of 0.37 ± 0.52 mm (P = 0.03), corresponding to 14.86% ± 20.19% decrease in mRC (P = 0.02) (from 76.94% at 1 year to 62.08% at the 9-year recall). There had been five cases with complete root coverage at 1 year, which was reduced to four at the 9-year recall. Additionally, there was an increase KTW of 0.71 ± 0.39 mm (P <0.01), and GT seemed to have remained stable since the 1-year results (mean changes of 0.08 ± 0.51, P = 0.58). When phenotypic changes were evaluated using a color-coded probe, at the 9-year recall, 83.3% of the ADM-treated sites (10 of 12) showed an increase in tissue thickness compared with their contralateral, opposing, and adjacent sites.

TABLE 1 Root coverage outcomes of ADM-treated sites at baseline and at the 1- and 9-year recall

Clinical parameter	Timepoint		
	Baseline (n = 12)	1 year (n = 12)	9 year (n = 12)
RECd	2.54 ± 0.49	0.58 ± 0.59	0.95 ± 0.83
mRC		76.94 ± 22.75	62.08 ± 34.15
KTW	2.16 ± 0.65	2.41 ± 0.59	3.12 ± 0.64
PD	1.04 ± 0.25	1.37 ± 0.43	1.5 ± 0.52
CAL	3.58 ± 0.41	1.95 ± 0.86	2.45 ± 0.81
GT	1.33 ± 0.44	1.79 ± 0.39	1.87 ± 0.43

RECd, recession depth; mRC, mean root coverage; KTW, keratinized tissue width; PD, probing depth; CAL, clinical attachment level; GT, gingival thickness

3.2 | Comparison of the ADM-treated sites to their adjacent untreated sites

The changes in the levels of the gingival margin and amount of KTW for the ADM-treated sites, and their immediately adjacent untreated sites (mesial and distal) are presented in Figure 1. Sixteen of the 24 ADM-adjacent sites had recession at baseline which was not treated, amounting to an average 1.4 ± 0.68 mm in RECd. The recession at these sites had remained qualitatively unchanged until the 1-year timepoint. Additionally, eight of the ADM-adjacent sites did not have baseline recession, which also remained unchanged until the 1-year timepoint.

Overall at the 9-year recall, the ADM-adjacent untreated sites presented with 2.25 ± 1.26 mm RECd (2.91 ± 0.89 mm for the adjacent untreated sites with baseline recession, and 0.93 ± 0.77 mm at the adjacent sites which did not have a gingival recession at baseline) (Figures 2 and 3). When comparing the changes in the levels of the gingival margin among the three groups (ADM, ADM-adjacent sites with, and without baseline recession), the mixed-modeling regression analysis demonstrated that with ADM-treated sites as the reference, the changes at the untreated sites

[**] Rstudio Version 1.1.383, Rstudio, Boston, MA.

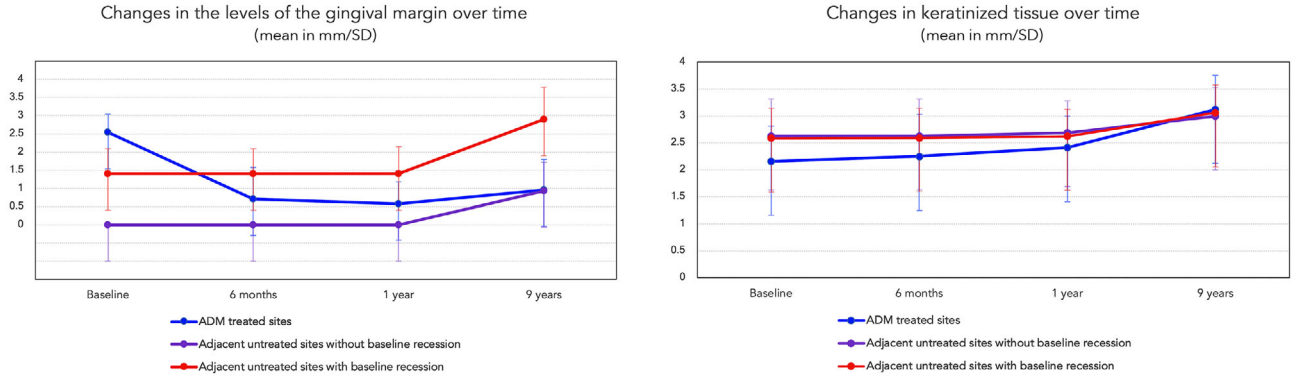

FIGURE 1 Changes in the levels of the gingival margin (left) and keratinized tissue (right) from pre-treatment (baseline) up to the 9-year recall for the ADM-treated sites and their adjacent untreated sites

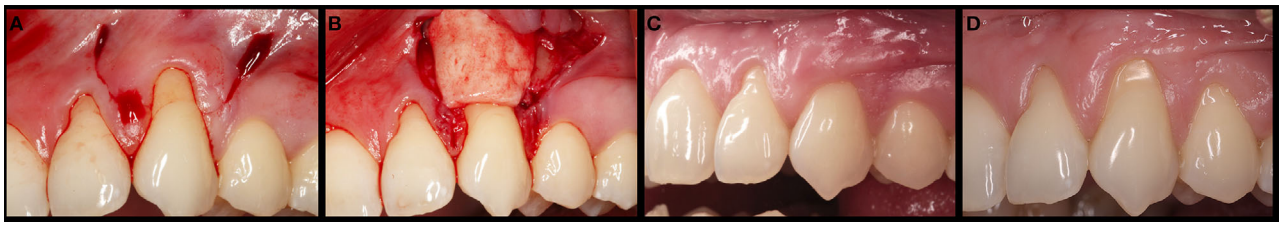

FIGURE 2 Root coverage outcomes of an isolated gingival recession treated with ADM. **A**) Baseline. **B**) Positioning of the ADM on the recipient bed. **C**) 1-year outcomes. **D**) 9-year outcomes. Note the relapse of the gingival margin in the ADM-treated sites and the apical shift of the gingival margin of the adjacent untreated teeth at the 9-year recall

with baseline recession (1.28 mm [95% CI: 0.59 to 1.97], $P = 0.001$) was significantly more than those without a recession at baseline (0.47 mm [95% CI: -0.31 to 1.25], $P = 0.23$). Additionally, RECd at 1 year presented as a significant predictor in the model (0.78 mm [95% CI: 0.39 to 1.16], $P < 0.001$) for the 9-year outcomes. The model illustrated that despite an average apical migration in the level of the gingival margin at all sites from 1 to 9 years, this apical shift was significantly more, and almost two-fold at sites which had presented with a gingival recession at baseline but were not treated (model estimates of 1.78 mm, versus 0.96 mm for the ADM-adjacent sites with, and without recession at baseline). Additionally, the changes in the gingival margin for the adjacent sites without baseline recession did not significantly differ from the ADM-treated sites.

Furthermore, despite a significant increase in KTW throughout time at all sites, when testing its effect at baseline and its interaction with the different groups, it was shown that KTW of <2 mm at baseline was significantly associated to RECd changes from 1 to 9 years for the ADM-treated sites (-0.4 [95% CI: -0.79 to -0.02], $P = 0.02$), and the untreated adjacent sites that presented with a baseline recession (-0.64 [95% CI: -1.27 to 0.01], $P = 0.01$).

3.3 | Patient-reported outcomes at the 9-year recall

Outcomes from the gathered responses of the patient questionnaires indicated a high satisfaction rate for the treatment of ADM, represented with VAS scores of 8.81 ± 1. Additionally, except for one patient that experienced post-surgical hematoma, all other patients stated that they would be willing to undergo the treatment again if needed (91.6%). Lastly, 40% of the subjects who presented with recession relapse (increase in RECd) at the 9-year recall were able to identify the apical shift of their gingival margin.

4 | DISCUSSION

The current article presents the 9-year outcomes of ADM-treated isolated GRs, and their untreated adjacent sites. This to the best of our knowledge, has not been reported yet in the literature. Several authors have assessed the long-term outcomes of untreated GRs.[21–24] A systematic review concluded that untreated GRs have a high tendency (78.1%) to progress over time (mean monitoring period of 8.9 years), with an incidence of 79.3% new recession

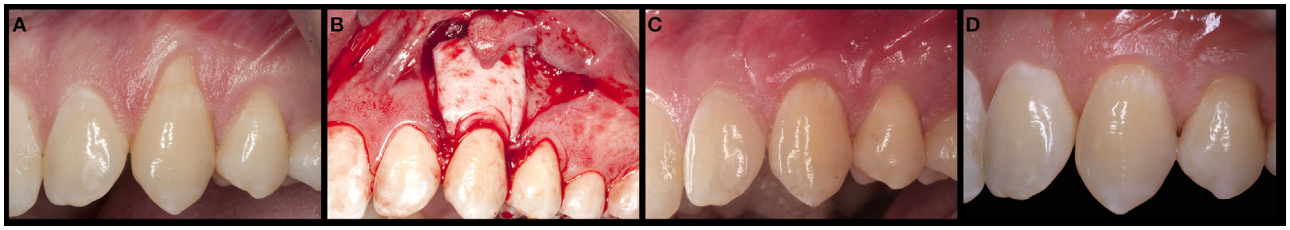

FIGURE 3 Root coverage outcomes of an isolated gingival recession treated with ADM. **A**) Baseline. **B**) Stabilization of the ADM on the root surface. **C**) 1-year outcomes. **D**) 9-year outcomes. Note the stability of the gingival margin at the ADM treated site from 1 to 9 years

defects.[5] Similarly, at 9 years, we observed an incidence of 75% for new GRs in the untreated sites, while no changes in the levels of the gingival margin had been observed at 1 year.

Regarding the progression of untreated GRs, we found that only 6.3% of sites remained stable at 9 years, while 93.7% of sites showed further apical shift in their gingival margin. The reason for the higher recession progression found in our study compared with the literature (ranging approximately from 23% to 87.4% in studies with at least 10 years of follow-up)[5,22,23] is open to speculations. One possible explanation for this difference could be resuming traumatic brushing techniques in areas with a thin gingival phenotype. Indeed, the ADM-treated sites showed a significantly lower relapse of the gingival margin compared with their adjacent untreated areas which had a recession at baseline. This may be due to the increased marginal soft tissue thickness that can be a protective factor from recession recurrence even in patients that may not be able to correct their traumatic brushing habits.[10,39] Additionally, a thin gingival phenotype has also been recognized as one of the most important etiological factors for the development of GRs.[40,41] Interestingly, the adjacent untreated sites with previous GRs at baseline showed a greater apical shift than sites without recession at baseline. It is reasonable to assume that at a site with a recession defect, the likelihood of having predisposing or precipitating factors[42] for the progression of GR is higher than sites without a recession. Among those, our analyses demonstrated that for sites presenting with an initial GR, having a baseline KTW $\geq$2 mm was a positive predictor for the stability of the gingival margin, which is in line with previous literature.[3,10,2]

Agudio et al. showed that FGG is able to maintain the level of the gingival margin over time or to provide some improvements (creeping attachment), compared with untreated contralateral sites that were associated with an increased RECd or development of new GRs.[23–25] The present article further confirms the advantage of adding a graft over untreated sites in terms of gingival margin stability is also valid for root coverage procedures with ADM.

Nonetheless, it has to be mentioned that ADM-treated sites showed a relapse of the gingival margin from 1 to 9 years. This is in line with the literature that shows that the recurrence of GR is a common finding.[10,43,44] A recent network meta-analysis from our group addressed the stability of root coverage outcomes over time, by comparing different surgical techniques head-to-head and analyzing potential influential factors, accounting for the effect of time in every comparison.[45] Interestingly, all root coverage procedures (flap alone, guided tissue regeneration, ADM-, collagen matrix-, and enamel matrix derivative-based approaches), except CTG, were found to have a tendency toward the apical shift of the gingival margin. The CTG was the only approach that showed a trend toward stability or even improvement in the level of the gingival margin over time.[45]

It has been suggested that the ADM is the graft material with the most similar outcomes to that of the CTG for root coverage procedures.[39,46] Harris was the first to report a significant relapse of ADM over time (up to 4 years) in the treatment of single and multiple GRs, while finding short-term results similar to the CTG.[47] Nevertheless, a 5-year RCT has shown a significant relapse in Complete root coverage and RECd in both ADM and CTG groups,[44] and another 5-year study reported greater recession reduction and KTW obtained in the CTG group, with comparable gain in tissue thickness.[48] A 12-year follow-up study showed a significant relapse of the gingival margin following ADM, with a drop in the mRC from ≈89% at 6 months to about 65% at the 12-year recall using ADM,[10] while the present study found a relatively lower drop in the mRC. This may have been due to different treated conditions (multiple versus single GRs), flap design (tunnel or envelope CAF versus CAF with vertical incisions), the different follow-up (12 versus 9 years), and the mRC obtained at 6 to 12 months (89% versus 76% in the present study).[10]

Lastly, our results also show an overall increased KTW from 1 to 9 years in both the ADM-treated and adjacent untreated sites. It can be speculated that this is due to the tendency of the mucogingival line to regain its genetically predetermined position.[41,49] In addition, it was

observed that ADM resulted in an increased GT, as also corroborated by the thickening in the gingival phenotype in 84% of cases compared with contralateral, opposite, and the adjacent sites. A similar increase in GT was also found in a previous article, where it was demonstrated that having GT ≥1.2 mm after 6 months was a predictor for the stability of the gingival margin.[10]

Among the limitations of the present study, the relatively high number of dropouts at the 9-year recall can be mentioned, which may have limited the power of our analyses, and hindered a direct statistical comparison between the two ADM groups. Furthermore, although masked and calibrated, a different examiner from the one in the original study performed the measurements at the 9-year recall. Nonetheless this change in the examiners is inherent to the long-term follow-up nature of such studies.[4,50] In addition, it would have been beneficial had we had information on GT at baseline for the adjacent untreated sites for further assessment of the effect of GT on the progression of recessions and its role in stability. The method for assessing GT may also have some limitations, including the possibility in needle bending and patient discomfort, which can be reduced with the use of contemporary non-invasive and more accurate technologies.[51] Lastly, it should be noted that although no changes in RECd at the untreated sites were noticed at the 1-year recall, originally some of the vertical releasing incisions had been performed close to the gingival margin of the untreated sites which could have induced a local trauma. This, and the fact that the original RCT only recruited maxillary GRs may limit the generalizability of our results and thus the conclusions of this report should be interpreted with caution.

5 | CONCLUSIONS

Within its limitations, the present investigation demonstrated that ADM-treated sites, while displaying a certain amount of recession relapse, presented a greater stability of the gingival margin compared with untreated adjacent sites with initial recession, from 1 to 9 years. Baseline KTW ≥2 mm was a significant positive predictor for the stability of the gingival margin in the ADM group and in the untreated ADM-adjacent sites that already presented with an initial recession defect.

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AUTHOR CONTRIBUTIONS

Dr. S. Barootchi assisted with the conception and design of the study; analysis, and interpretation of data; initial and final drafting of the work; final approval of the version to be published; and was accountable for all aspects of the work. Dr. L. Tavelli assisted with the design of the study, acquisition and interpretation of data, manuscript preparation and the initial draft and final reviewal of the work; and was accountable for all aspects of the work. Dr. Di Gianfilippo assisted with data acquisition and examination of clinical parameters at follow-up appointments; contribution to manuscript writing, critical review of the final draft, and was accountable for all aspects of the work. Dr. R. Eber contributed to study design; data interpretation; final approval of the version to be published and critical reviewal of the manuscript draft, and was accountable for all aspects of the work. Dr. M. Stefanini assisted with final approval of the version to be published, contribution to the writing, and critical reviewal of the drafted manuscript, and was accountable for all aspects of the work. Prof. G. Zucchelli contributed to the study design; data interpretation; final approval of the version to be published with critical manuscript reviewal; and was accountable for all aspects of the work. Prof. H-L Wang assisted with design of the study; critical review of the draft and contribution to the writing of the manuscript; final approval of the version to be published, and was accountable to the accuracy or integrity of the work.

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